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Synthesis of Chiral 3-Substituted Indanones via an Enantioselective Reductive-Heck Reaction

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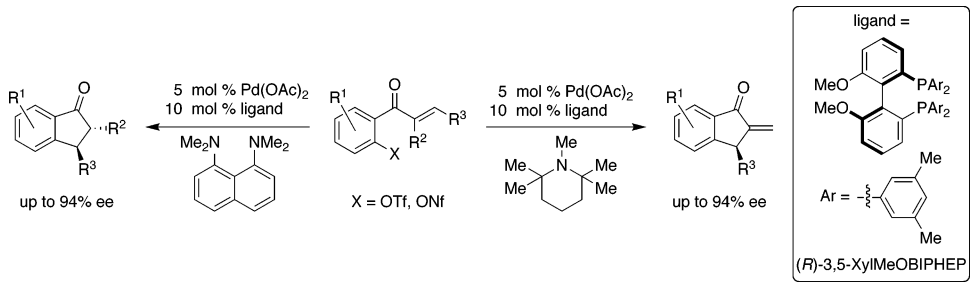
Received August 7, 2007



An efficient intramolecular palladium-catalyzed, asymmetric reductive-Heck reaction has been developed, which allowed for the synthesis of either enantiomerically enriched 3-substituted indanones or α-*exo*-methylene indanones depending on the base used.

Introduction

The indan framework is found in a large number of bioactive and pharmaceutically important molecules.[1] Further, chiral 3-substituted indanones serve as valuable intermediates for the synthesis of a variety of interesting compounds, or possess inherent biological activity themselves.[2] The introduction of chirality in position 3 of the indanone framework has been accomplished by using a number of different approaches.[3] Most recently, Morehead[4] and Hayashi[5] have shown that rhodium-(I)-catalyzed asymmetric intramolecular hydroacylation of 2-vinyl benzaldehyde systems and isomerization of racemic α-arylpropargyl alcohols represent very elegant ways to generate chiral 3-substituted indanones. Results described by Püschl attracted our attention, as racemic 3-arylindanones were obtained in moderate to good yields through a palladium-catalyzed intramolecular reductive cyclization of (*E*)-2′-bromochalcones by using high reaction temperatures (155 °C) or microwave conditions.[6]

Herein, we describe the development of a palladium-catalyzed asymmetric reductive-Heck cyclization[7] of 2′-perfluoroalkylsulfonated aryl α,*β*-unsaturated ketones for the synthesis of

* Address correspondence to this author. Phone: (+1) 617-253-1885. Fax: (+1) 617-253-3297.

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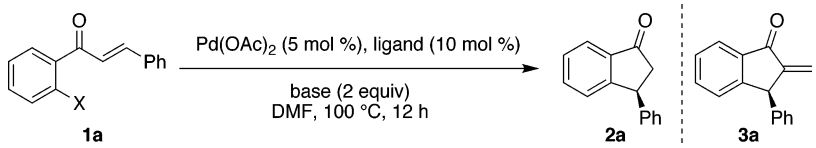
10.1021/jo701741y CCC: $37.00
Published on Web 10/30/2007

TABLE 1. Effect of the Amine and the Ligand on the Pd-Catalyzed Asymmetric Heck-Type Cyclization



entry	X	ligand	amine	**2a**:**3a**	yield [%][a]	ee [%][b]
1	OTf	(*R*)-BINAP	$MeNCy_2$	100:0	32	54
2	OTf	(*R*)-BINAP	NEt_3	100:0	40	53
3	OTf	(*R*)-BINAP	ps[c]	100:0	65	55
4	OTf	(*R*)-3,5-XylBINAP	ps	100:0	75	70
5	OTf	(*R*)-MeOBIPHEP	ps	100:0	81	73
6	OTf (ONf)	(*R*)-3,5-XylMeOBIPHEP	ps	100:0	88[d] (90)[d]	79 (78)
7	OTf	(*R*)-3,5-tButylMeOBIPHEP	ps	100:0	45	70
8	I	(*R*)-3,5-XylMeOBIPHEP	ps	100:0	25	76
9	Br	(*R*)-3,5-XylMeOBIPHEP	ps	100:0	30	77
10[e]	ONf	(*R*)-3,5-XylMeOBIPHEP	PMP[f]	0:100	74	80

[a] Determined by GC. [b] Determined by HPLC on a Chiracel OJ column. [c] ps = proton sponge. [d] Isolated yield. [e] Reaction conducted in 1,4-dioxane. [f] PMP = 1,2,2,6,6-pentamethylpiperidine.

chiral 3-substituted indanones using proton sponge and a related synthetic route for accessing α-*exo*-methylene indanones using 1,2,2,6,6-pentamethylpiperidine (PMP).[8]

Results and Discussion

After some preliminary screening studies, our initial reaction conditions for the cyclization of (*E*)-2′-triflylchalcone **1a** (X = OTf) employed a catalyst system comprised of 5 mol % of Pd(OAc)$_2$, 10 mol % of (*R*)-BINAP, and 2 equiv of Hünig's base in DMF at 100 °C (Table 1, entry 1). We observed that the cyclization provided the desired product **2a** in 32% yield with an enantiomeric excess of 54%.[9] Variation of the amine base revealed that proton sponge gave the highest yield, though no increase of the enantiomeric excess was observed (Table 1, entry 3). Subsequently, various phosphine ligands were tested and some representative examples are shown in Table 1. (*R*)-3,5-XylMeOBIPHEP was identified as the most effective ligand yielding product **2a** in 88% yield and 79% ee.[10] Variation of temperature, solvent, and/or palladium source did not improve the yield or the enantiomeric excess obtained for **2a**. The use of the sterically more hindered ligand (*R*)-3,5-*tert*-ButylMeO-BIPHEP had a deleterious effect on both yield and enantiomeric excess (Table 1, entry 7). This result supports the hypothesis that the extent of the "3,5-dialkyl-*meta*-effect" on enantioselectivity is substrate dependent.[11] The products derived from the corresponding (*E*)-2′-iodo and -bromo chalcone derivatives **1a** (X = I or Br) showed similar enantiomeric excesses under the optimized reaction conditions, though only moderate reactivity was observed (Table 1, entries 8 and 9). Interestingly, replacement of proton sponge with 1,2,2,6,6-pentamethylpiperidine (PMP) produced α-*exo*-methylene indanone **3a**, which under optimized reaction conditions was obtained in 74% yield and 80% ee (Table 1, entry 10).

Encouraged by these results, we sought to investigate the scope of this asymmetric reductive-Heck cyclization to chiral 3-substituted indanones **2** (Table 2). We found that electron-donating as well as electron-withdrawing substituents on the *β*-phenyl ring are tolerated, yielding the corresponding indanones in good yields and enantiomeric excesses (Table 2, **2c**−**f**). Additionally, using this method, we were able to prepare the enantiomerically enriched indanone **2e**, an intermediate in the total syntheses of chiral indatraline derivatives,[2e] as well as the 1,3-benzodioxole-substituted indanone **2f**, a framework found in various biologically active indan derivatives.[3c]

A significant increase of enantioselectivity was achieved by introducing an additional substituent in the position ortho to the leaving group. Thus, indanone **2g** was obtained in excellent yield and 94% ee. Indanone **2h** is of particular interest as the silyl-group allows for further functionalization, such as Hiyama cross-coupling,[12] iodination,[13] or fluorination.[14] Finally, we were able to apply our reaction conditions to the cyclization of a trisubstituted chalcone derivative, yielding *trans*-2-methyl-3-phenylindanone (**2m**) with excellent enantiomeric excess (94%) and good diastereomeric ratio (83:17), which could be increased to 91:9 after isomerization by treatment with HCl in a H_2O/THF solvent mixture. 2-Alkyl-3-phenyl-substituted indanones have proven to be potent inhibitors of tubulin polymerization and tumor and endothelial cell proliferation in vitro.[15] This is the first time that the introduction of two stereocenters in positions 2 and 3 of the indanone core in the same reaction sequence has been reported.

As mentioned before, the use of PMP in the palladium-catalyzed asymmetric reductive-Heck cyclization allowed for the synthesis of α-*exo*-methylene indanone **3a**. The scope of this reaction is shown in Table 3. The corresponding α-*exo*-methylene indanones **3a**−**h** were obtained in good yields and good to excellent enantioselectivities, up to 94%, with the

(8) This reaction type can formally be classified as a catalyzed asymmetric arylation reaction. For a review, see: Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem.* **2001**, *113*, 3382; *Angew. Chem., Int. Ed.* **2001**, *40*, 3284.

(9) The stereochemistry of the product was assigned to be (*S*) by comparison of the sign of the optical rotation value with the literature value.[3e]

(10) Although the results obtained with the nonaflate **1a** (X = ONf) and the triflate **1a** (X = OTf) were identical, the easier handling of the nonaflate made it the substrate of choice.

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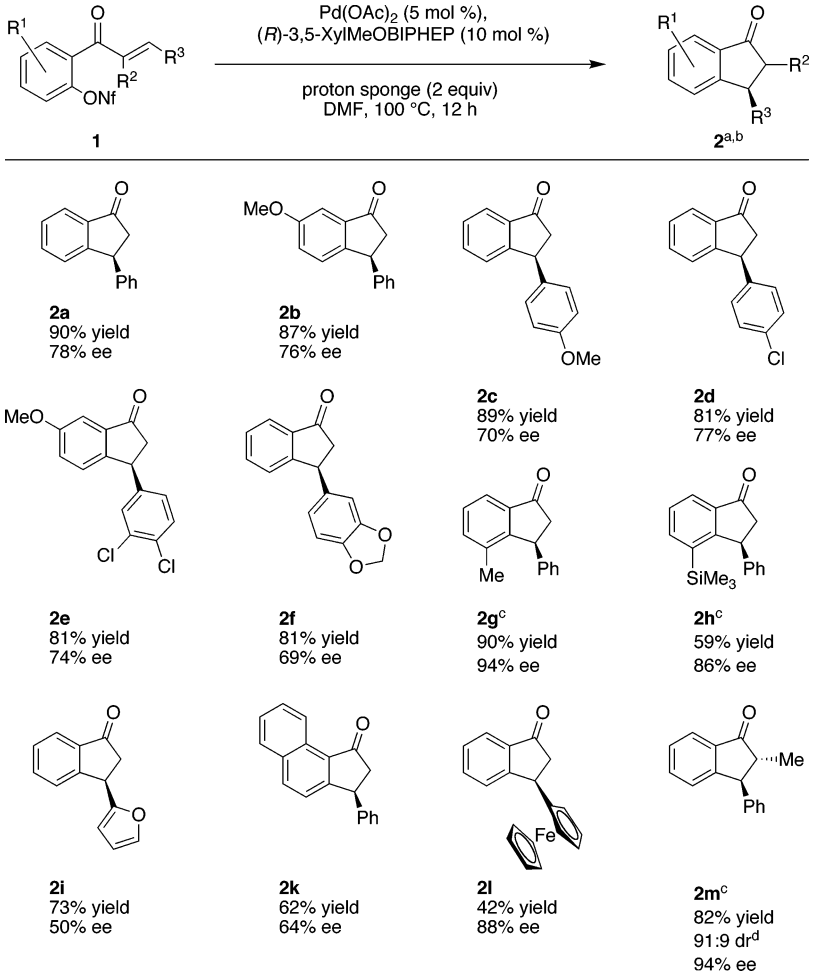
(14) de Meio, G. V.; Pinhey, J. T. *J. Chem. Soc., Chem. Commun.* **1990**, *15*, 1165.

(15) Aventis Pharma SA; Preparation of 3-arylindan-1-ones as inhibitors of tubulin polymerization and their composition for treatment of cancer. FR 2838432, A1, October 17, 2003.

TABLE 2. Scope of the Palladium-Catalyzed Asymmetric Synthesis of 3-Substituted Indanones 2



[a] Yields of the isolated products are the average of two runs. [b] Determined by HPLC on a chiral stationary phase. [c] The triflate was used instead of the nonaflate. [d] Dr = 91:9 after isomerization; the major diastereoisomer is shown.

exception of the *p*-chloro-substituted α-*exo*-methylene indanone **3d**, which was isolated in only 44% yield (80% ee) due to instability of the product. We observed that, in the case of (*E*)-2′-nonaflyl chalcone **1a**, the choice of solvent had a significant influence on the outcome of the reaction. In 1,4-dioxane indanone **3a** was obtained in 90% yield with 78% ee.[16] However, when the same reaction was carried out in DMF, the sole product observed was the achiral indenone **3i**, which was isolated in 70% yield. Synthesis of the later compound by palladium-catalyzed annulation of 2-iodobenzonitrile or 2-halobenzaldehyde with 1-phenyl-1-propyne results in low yields of inseparable 1:1 mixtures of the isomers, rendering our reaction protocol an attractive alternative.[17] 3-Furyl-2-methylindenone (**3k**) was predominantly formed regardless of the solvent employed.

Analogous to the intermolecular, palladium-catalyzed conjugate addition of aryl halides to α,β-unsaturated ketones, we propose the following reaction mechanism outlined in Scheme 1 for the formation of indanones **2**.[18] Oxidative addition of the aryl nonaflate **1** to the in situ formed Pd(0) phosphine complex results in the cationic Pd(II) complex **I**. Carbopalladation of the (*E*)-configured double bond in complex **I** occurs in a *syn*-fashion via a 5-*endo*-trig cyclization leading to the π-oxa-allyl palladium species **II**. Since β-hydride elimination is precluded by the initially formed cationic cyclic cis-configured C-bound Pd-enolate intermediate **II** (drawn as a η^3-oxoallyl Pd-complex), a hydride transfer from the α-proton of the proton sponge to palladium provides the iminium ion **III** and the Pd(II) hydride complex **IV**.[19] The Pd(II) hydride complex **IV** then collapses to provide **2** with reductive elimination to regenerate Pd(0). By using our standard reaction conditions with proton sponge as the amine base, no formation of the indenone type product was observed in any case (Table 2), which would arise from a classical Heck reaction. This is not surprising as β-hydride

(16) A single report on the generation of racemic **3a** in 1% yield by gas-flow thermolysis has been reported: Koller, M.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1986**, *69*, 560.

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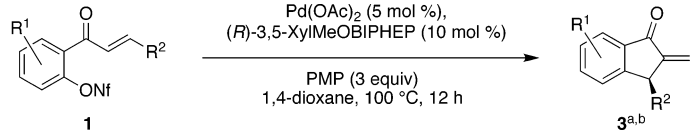
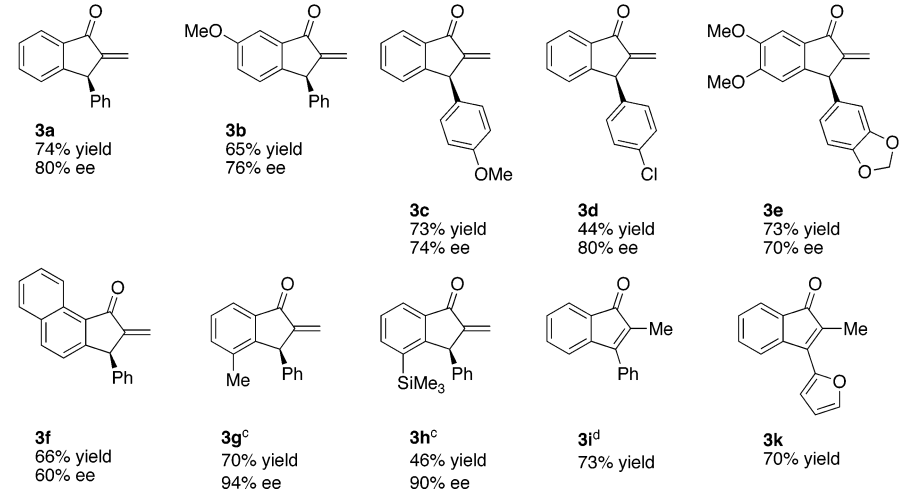
(18) (a) Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, *48*, 4236. (b) Amorese, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerrini, S.; Fedeli, W.; Ortar, G. *Tetrahedron* **1989**, *45*, 813. (c) Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1995**, *36*, 7047. (d) Hagiwara, H.; Eda, Y.; Morohashi, K.; Suzuki, T.; Ando, M.; Ito, N. *Tetrahedron Lett.* **1998**, *39*, 4055. (e) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813.

(19) Complexation of a tertiary amine with palladium(II) followed by metal insertion and subsequent β-hydride elimination has been described before: (a) Konopelski, J. P.; Chu, K. S.; Negrete, G. R. *J. Org. Chem.* **1991**, *56*, 1355. (b) Stokker, G. E. *Tetrahedron Lett.* **1987**, *28*, 3179. (c) Murahashi, S.-I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429.

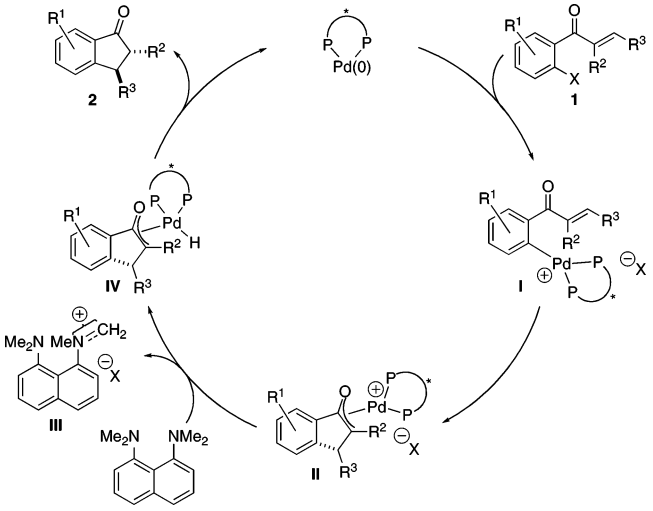
TABLE 3. Scope of the Palladium-Catalyzed Asymmetric Synthesis of 3-Substituted α-*exo*-Methylene Indanones 3





[a] Yields of the isolated products are the average of two runs. [b] Determined by HPLC on a chiral stationary phase. [c] The triflate was used instead of the nonaflate. [d] Reaction conducted in DMF.

SCHEME 1. Proposed Catalytic Cycle (X = OTf, ONf)



elimination to yield the 3-aryl-substituted indenone is possible only if isomerization of the cis-configured intermediate **II** to the trans-configured complex via a η^3-oxoallyl Pd-complex occurs.

We were able to obtain an X-ray crystal structure of the cationic palladium(II) complex **I** derived from racemic MeO-BIPHEP (Figure 2). The solid-state structure of the cationic complex shows the coordination of the carbonyl unit to the palladium(II) center. As a consequence the carbonyl double bond [1.264(8) Å vs 1.204(6) Å] and the α,β-unsaturated olefinic bond [1.344(7) Å vs 1.319(6) Å] are slightly elongated compared to those of free chalcone.[20] The fact that the Pd1−P1 bond [2.2357(1) Å] is shorter than the Pd1−P2 bond [2.3562 (7) Å] presumably reflects the higher trans influence of the aryl group compared with that of the *O*-carbonyl moiety.

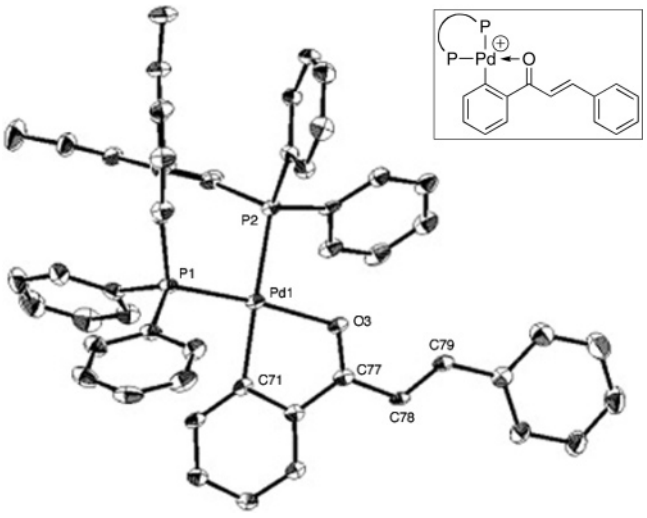


FIGURE 1. ORTTEP illustration of a cationic Pd(II) complex related to **I**. Thermal ellipsoids at 50% probability. Solvent and counterions removed for clarity. Selected bond lengths [Å] and angles [deg]: C77−O3 1.264(8), C77−C78 1.459(8), C78−C79 1.344(7), Pd1−C71 2.056(8), Pd1−O3 2.089(8), Pd1−P1 2.2357(7), Pd1−P2 2.3562(7), C71−Pd1−O3 81.3(4), O3−Pd1−P2 93.1(6), C71−Pd1−P1 94.3(3), P1−Pd1−P2 93.79(2)

The observed stereochemical outcome of the reaction with the C_2-symmetric, (*R*)-configured ligand can be rationalized based on the two diastereomeric intermediates **A** and **B** shown in Figure 2 for the formation of indanone **2g** as a representative example, assuming that the carbopalladation of the (*E*)-configured double bond (**I** → **II**) is the stereochemistry-determining step. Molecular mechanics calculations with MMFF force field were used to visualize the structures **A** and **B**. In the

(20) Rabinovich, D. *J. Chem. Soc. B* **1970**, 11.

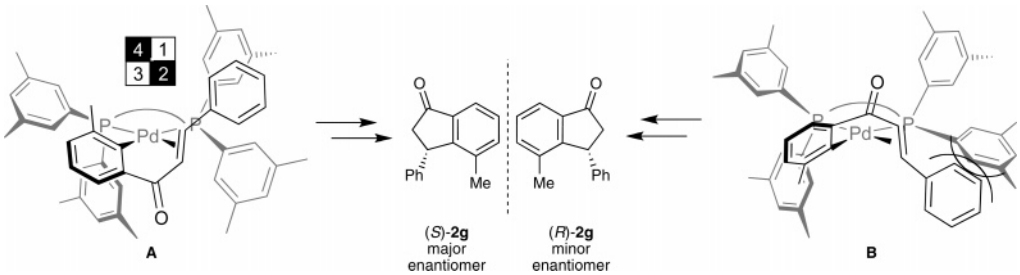
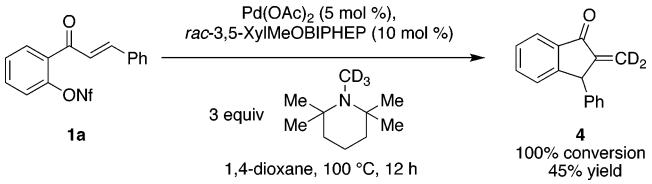


FIGURE 2. Proposed enantiofacial selection with (*R*)-3,5-XylMeOBIPHEP-Pd(II) template. The backbone of the ligand is omitted for clarity.

SCHEME 2. Deuterium-Labeling Experiment



favored structure **A**, the relatively uncrowded quadrants 1 and 3 are occupied by the substrate and the double bond is coordinating to palladium from its *si*-*re* face. Structure **B** is disfavored due to steric interactions in congested quadrant 2.

The origin of the α-*exo*-methylene group in indanones **3** was probed by using deuterium-labeled PMP. Using our otherwise standard reaction conditions, 45% of the α-*exo*-dideuteromethylene indanone **4** was obtained as the sole product (Scheme 2).

On the basis of this result, two possible reaction mechanisms can be proposed for the formation of indanones **3** (Scheme 3). Both pathways involve a Mannich-type reaction of the iminium ion **V** (Scheme 3), which is obtained after hydride transfer from PMP to Pd(II)-enolate **II** (Scheme 1).[21] The Eschenmoser salt **V**[22] can react either with the Pd(II)-enolate **IV** or with the already realeased indanone **2** to yield the final product **3**.[23] We assume that in the case of proton sponge the Mannich-type reaction with the Eschenmoser salt **III** (Scheme 1) is not favored as the positive charge on the iminium ion is stabilized by the lone pair electrons of the adjacent nitrogen atom, rendering it less electrophilic.

The methylene group in the conformationally restricted *s*-*cis* indanones **3** can undergo a variety of synthetic transformations as is known for related compounds bearing an α-*exo*-methylene group.[24] Performing a Michael-addition on the enantioenriched indanone **3a** or hydrogenation of the olefinic double bond generated an additional stereocenter in the α-position. The enantiomerically enriched 2-alkyl-3-phenyl-substituted indanones **5** and *cis*-**2m** were each obtained with excellent diastereoselectivity (Scheme 4). The latter result demonstrates that the synthetic approaches presented in Tables 2 and 3 are complementary as both *cis*- and *trans*-**2m** are readily accessible.

In conclusion, we have developed a highly efficient synthesis of chiral 3-aryl-substituted indanones and α-*exo*-methylene indanones based upon an asymmetric reductive-Heck reaction using (*R*)-3,5-XylMeOBIPHEP as the chiral ligand. Most important, the described catalyst system provides ready access to enantiomerically enriched *trans*-2-alkyl-3-aryl-substituted indanones or the corresponding cis-isomers by manipulation of the methylene group in the α-*exo*-methylene indanones.

Experimental Section

General Procedure for Table 2. An oven-dried screw-cap test tube equipped with a Teflon septum was charged with a magnetic stirbar, the corresponding nonaflate or triflate (1 equiv), $Pd(OAc)_2$ (5 mol %), (*R*)-3,5-XylMeOBIPHEP (10 mol %), and proton sponge (2 equiv). The tube was evacuated and backfilled with argon; this procedure was carried out two times. The solids were dissolved in DMF (4 mL/mmol nonaflate or triflate), the reaction tube was sealed, and the reaction mixture was stirred in a preheated oil-bath at 100 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (20 mL/mmol nonaflate), and washed with an aqueous solution of HCl (1 M, 20 mL/mmol nonaflate). The organic phase was separated, washed with brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude material was purified by column chromatography on silica gel. A representative example is given.

6-Methoxy-(3*S*)-phenylindan-1-one (2b). Compound **2b** was prepared according to the general procedure with (*E*)-4-methoxy-2-(3-phenylprop-2-enoyl)phenyl nonafluorobutanesulfonate **1b** (268 mg, 0.500 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), (*R*)-3,5-XylMeOBIPHEP (35 mg, 0.050 mmol), and proton sponge (214 mg, 1.00 mmol) in DMF (2 mL). The crude material was purified by column chromatography (hexane/ethyl acetate 5:1) to give the title compound as a white solid (104 mg, 87%, 76% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.34 (m, 4H), 7.17 (2H, J = 1.5 Hz), 7.13 (m, 2H), 4.53 (dd, 1H, J = 3.6, 7.8 Hz), 3.87 (s, 3H), 3.27 (dd, 1H, J = 7.8, 19.2 Hz), 2.71 (dd, 1H, J = 3.6, 19.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 159.7, 150.8, 143.9, 138.0, 128.8, 127.6, 127.5, 126.9, 124.5, 104.3, 55.6, 47.5, 43.7; IR (neat) ν 3400, 3027, 2940, 2836, 1709, 1613, 1489, 1331, 1282, 1243, 1045, 1026, 839, 760, 701 cm^{-1}; Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.36; H, 5.84. Mp 74−75 °C. The enantiomeric excess of **2b** was determined by HPLC analysis (Chiracel OJ column, *i*-PrOH/hexane 5:95; 1.0 mL/min, 254 nm); (3*R*) isomer (minor) t_R = 18.1 min and (3*S*) isomer (major) t_R = 22.3 min; $[\alpha]_D$ +43.3 (*c* 0.6, $CHCl_3$).

General Procdure for Table 3. An oven-dried Schlenk tube equipped with a Teflon screw seal was charged with a magnetic stirbar, the corresponding nonaflate or triflate (1 equiv), $Pd(OAc)_2$ (5 mol %), (*R*)-3,5-XylMeOBIPHEP (10 mol %), and pentamethylpiperidine (3 equiv). The tube was evacuated and backfilled with argon; this procedure was carried out two times. The solids were dissolved in the corresponding solvent (4 mL/mmol nonaflate or triflate), the reaction tube was sealed, and the reaction mixture was stirred in a pre-heated oil-bath at 100 °C for 12 h. The reaction

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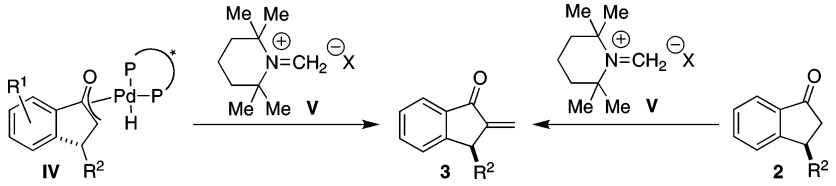
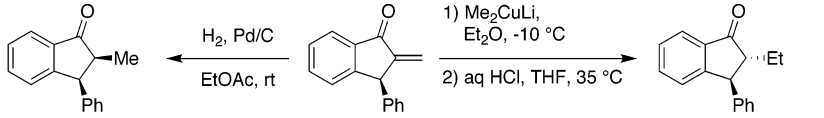
SCHEME 3. Mechanistic Proposal for the Formation of Indanones 3 via a Mannich−Eschenmoser Methylenation Pathway (X = OTf, ONf)



SCHEME 4. Synthesis of Enantiomerically Enriched 2-Alkyl-3-phenyl-Substituted Indanones



cis-**2m** (74%)
dr 93:7, major 80% ee

3a (80% ee)

5 (78%)
dr 94:6, major 80% ee

mixture was cooled to room temperature, diluted with ethyl acetate (20 mL/mmol nonaflate), and washed with an aqueous solution of HCl (1 M, 20 mL/mmol nonaflate). The organic phase was separated, washed with brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude material was purified by column chromatography on silica gel. A representative example is given.

6-Methoxy-2-methylene-(3*S*)-phenylindan-1-one (3b). Compound **3b** was prepared according to the general procedure with (*E*)-4-methoxy-2-(3-phenylprop-2-enoyl)phenyl nonafluorobutanesulfonate **1b** (268 mg, 0.500 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), (*R*)-3,5-Xyl-MeO-BIPHEP (35 mg, 0.050 mmol), and pentamethylpiperidine (270 μL, 1.5 mmol) in 1,4-dioxane (2 mL). The crude material was purified by column chromatography (hexane/ethyl acetate 5:1) to give the title compound as a white solid (82 mg, 65%, 76% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 1H), 7.20−7.29 (m, 3H), 7.15 (m, 2H), 7.07−7.09 (m, 2H), 6.36 (dd, 1H, J = 0.5, 2.2 Hz), 5.34 (dd, 1H, J = 0.4, 1.7 Hz), 4.89 (t, 1H, J = 1.9 Hz), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 160.0, 149.8, 146.6, 142.7, 138.9, 128.9, 128.3, 127.5, 127.2, 125.0, 121.0, 105.3, 55.75, 48.5; IR (neat) ν 3027, 2941, 2836, 1704, 1641, 1612, 1489, 1331, 1282, 1251, 1189, 1159, 1026, 1008, 837, 800, 762, 700 cm^{-1}; mp 90 °C; the enantiomeric excess of **3b** was determined by HPLC analysis (Chiracel OJ column, *i*-PrOH/hexane 5:95; 1.0 mL/min, 254 nm); (3*R*) isomer (minor) t_R = 11.8 min and (3*S*) isomer (major) t_R = 15.0 min; $[\alpha]_D$ +71.0 (*c* 0.86, $CHCl_3$); A copy of the NMR spectra is provided.

Acknowledgment. Generous financial support from the National Institutes of Health (GM 46059) is gratefully acknowledged. We thank Hoffmann-La Roche and Dr. R. Schmid for a generous gift of (*R*)-3,5-Xyl-MeOBIPHEP and BASF for Pd(OAc)$_2$. A.M. thanks the Alexander von Humboldt Stiftung for a postdoctoral Feodor Lynen Fellowship. We are indepted to Dr. T. E. Barder for measuring the X-ray crystal structure and Dr. P. Müller for refining the structure. We thank A. M. Hyde for assistance with the calculations. The Bruker Advance 400 MHz used in this work was purchased with funding from the National Institutes of Health (GM 1S10RR13886-01). The Varian NMR instruments used for this publication were supported by National Science Foundation (CHE 9808061 and DBI 9729592).

Supporting Information Available: Experimental procedures and characterization data for all new and known compounds and X-ray crystallographic data for complex **I**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701741Y