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Mechanism of Stereoinduction in Asymmetric Synthesis of Highly Functionalized 1,2-Dihydroquinolines and 2*H*-1-Benzopyrans via Nonracemic Palladacycles with a Metal-Bonded Stereogenic Carbon

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To establish the synthetic utility of palladacycles, a stable racemic benzannulated azapalladacycle featuring a palladium-bonded sp^3-hybridized stereogenic carbon was prepared and converted into a series of racemic 2,3,4-trisubstituted 1,2-dihydroquinolines via a regioselective insertion of activated alkynes (RC≡CCOOEt). Analogous diastereomerically enriched azapalladacyle (92% de) and oxapalladacycle (64% de) were synthesized from arylpalladium(II) iodo complexes possessing a nonracemic spectator ligand ((1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane) via an intramolecular displacement of the iodide by an ester enolate. Absolute configurations of the metal-bonded stereocenters in the diastereomerically enriched palladacycles were unequivocally assigned, and the efficiency of stereoinduction was systematically studied. On the basis of these experiments, a plausible mechanism for the transfer of chirality from the nonracemic auxiliary ligand to the palladium-bonded stereogenic carbon was proposed. A restricted rotation about the palladium-aryl bond in arylpalladium(II) iodo complexes giving rise to atropisomers, as well as the nature of the leaving group (iodide or acetate), were found to play a crucial role in the chirality transfer process. Diastereomerically enriched palladacycles underwent a ligand exchange with triphenylphosphine followed by regioselective insertion of unsymmetrical alkynes to afford nonracemic 1,2-dihydroquinolines (six examples) in excellent 80−91% ee and 2*H*-1-benzopyrans (four examples) in 32−56% ee.

Introduction

Transition-metal-mediated reactions have achieved a prominent position among the tools available for the synthesis of complex organic molecules.[1] For most practical purposes, intermediates with transition-metal-bonded sp^2-hybridized carbons have been involved in the key carbon−carbon bond-forming events.[2] If analogous transformations could be realized with chiral nonracemic complexes featuring metal-bonded sp^3-hybridized stereogenic carbons generated from achiral or racemic organic substrates, a powerful new approach to asymmetric synthesis would arise. Catalytic asymmetric cross-coupling of secondary alkylmagnesium or zinc-reagents,[3] and asymmetric arylation and vinylation of ketone, ester and amide enolates[4] highlight the potential of such methodologies. Although the outcome or the kinetic behavior of catalytic reactions may differ from the stoichiometric processes,[5a,b] numerous well-known metal-catalyzed transformations evolved from prior studies with stable organometallics.[5c−e] Surprisingly, reports on the preparation and reactivity of nonracemic organometallics with a metal-bonded sp^3-hybridized stereogenic carbon still remain rare.[6] Recently, palladacycles have been proposed as key intermediates in several palladium-catalyzed cascade reactions,[7] and preparations of stable palladacycles have been described.[8] Aiming to establish a foundation for the use of palladacycles as intermediates in catalytic asymmetric synthesis, we initiated a program exploring the reactivity of stable palladacycles.[9] We reasoned that racemic oxa- and azapalladacyclopentanes **II** could be generated from achiral aryl iodides **I** and

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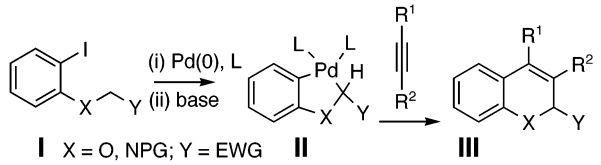

FIGURE 1. General outline of the synthetic strategy.

subsequently serve as templates for the introduction of the metal-bonded stereogenic center into heterocycles **III** via insertion of alkynes.[10] Accordingly, preparation of racemic 2*H*-1-benzopyrans **III** (X = O, Y = COOEt, $CONEt_2$) was recently reported from our laboratories (Figure 1).[9]

Elucidation of pathways for the transfer of stereochemical information to the metal-bonded stereogenic carbon represents a key goal of our studies. Stereoinduction from chiral nonracemic bidentate phosphine ligands L* (e.g., L* = (*S*,*S*)-DIOP) in palladium complexes **IV** permitted the preparation of palladacycles **V** in a high diastereomeric excess.[11] Treatment of palladacycle **V** (L* = (*S*,*S*)-DIOP, X = O, Y = $CONEt_2$) with dimethyl acetylenedicarboxylate afforded an enantiomerically enriched (88% ee) 2*H*-1-benzopyran **VI** (Figure 2).[11] However, palladacycles **V** bearing the (*S*,*S*)-DIOP ligand[11] failed to react with less activated unsymmetrical alkynes.

Herein, we report an extension of the strategy outlined in Figure 1 for the preparation of a series of racemic 1,2-dihydroquinolines **III** (X = NTf, Y = COOEt), and

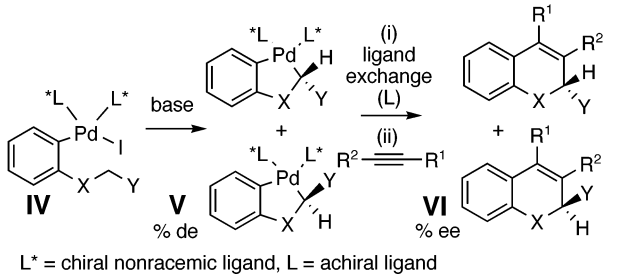

FIGURE 2. An approach to asymmetric synthesis.

describe a new dual ligand system (L*, L) capable of mediating asymmetric synthesis of an entire series of heterocycles **VI** (Figure 2). Exploiting asymmetric induction from (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane ligand (L*), followed by ligand exchange with triphenylphosphine (L = Ph_3P), alkyne insertion into chiral nonracemic palladacycles **V** yielded highly functionalized 1,2-dihydroquinolines **VI** (X = NTf) in 80−91% ee, and 2*H*-1-benzopyrans **VI** in 32−56% ee. Examination of factors that control diastereoselectivity of the ring closure (**IV** → **V**) led us to propose a plausible mechanism of stereoinduction revealing the significance of the atropisomeric composition of complexes **IV**.

Traditional methods for the construction of pharmaceutically significant[12] 1,2-dihydroquinolines and 2*H*-1-benzopyrans include condensation reactions,[13] nucleophilic additions to *N*-alkylquinolinium salts,[14] ring-closing methathesis,[15] or hydroarylation,[16] and usually require incorporation of the C-2 stereogenic center into

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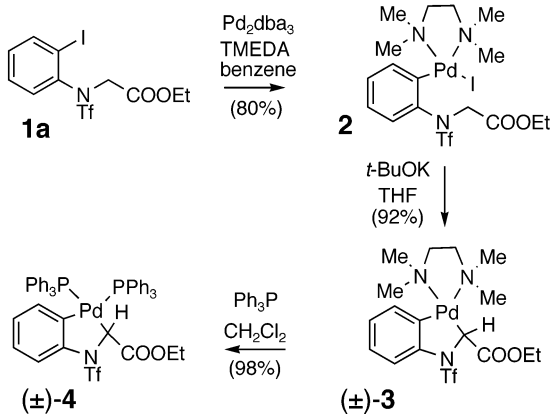
the substrates prior to cyclization,[17] or the use of covalently bonded chiral auxiliaries.[14] A catalytic asymmetric Reissert reaction represents a rare exception to these limitations.[18] In contrast, the convergent strategy described herein allows for functionalization of three carbons (C-2, C-3, and C-4) with concomitant formation of the C-2 stereogenic center, an approach that is amenable to a rapid generation of diversity. Results described herein demonstrate a new method for asymmetric synthesis of densely functionalized 1,2-dihydroquinolines, providing a rational foundation for the future design of a catalytic variant of the process.

Results and Discussion

Synthesis of Racemic 2,3,4-Trisubstituted 1,2-Dihydroquinolines. Preparation of stable azapalladacycle (±)-**4** commenced with treatment of sulfonamide **1a** accessible via *N*-alkylation[19] of *N*-trifluoromethanesulfonyl-2-iodo-aniline,[20] with palladium(0) (Pd_2dba_3) and tetramethylethylenediamine (TMEDA)[9] to afford palladium(II) complex **2** (Scheme 1). An easy ring closure of complex **2** providing palladacycle (±)-**3** in 92% yield was achieved at room temperature via addition of *t*-BuOK (1 M solution in THF, 1.2 equiv).[9] Displacement of tetramethylethylenediamine with triphenylphosphine delivered palladacycle (±)-**4** in essentially quantitative yields.[9] Palladacycles (±)-**3** and (±)-**4**, generated in approximately 70% yields from aryl iodide **1a**, were isolated as moisture- and air-stable white crystalline solids. In contrast to earlier reports indicating a limited stability of structurally related achiral azapalladacycles,[21] complex

SCHEME 1



(±)-**4** proved more stable than the corresponding oxapalladacycle,[9] and could be purified by flash chromatography over silica. Azapalladacycle (±)-**4** reacted smoothly with activated symmetrical diethyl acetylenedicarboxylate in refluxing 1,2-dichloroethane to afford dihydroquinoline (±)-**5** in an excellent yield (entry 1, Table 1), comparable to the performance of the corresponding oxapalladacycle[9] and contrasting with a low yield reported for the insertion of dimethyl acetylenedicarboxylate into a known achiral azapalladacycle.[22] A variety of unsymmetrical alkynes possessing one electron-withdrawing substituent (COOR) and alkyl (Me, *n*-Pent), cycloalkenyl, trimethylsilyl, and aryl (Ph, *p*-$MeOC_6H_4$, *p*-FC_6H_4) groups also participated in the insertion reaction with azapalladacycle (±)-**4**, providing the corresponding dihydroquinolines (±)-**6**−(±)-**12** in good yields (55−70%) as oils or solids after chromatography (entries 2−8, Table 1). Formation of potentially synthetically versatile 4-trimethylsilyl-2,3-bis-(ethoxycarbonyl)-1,2-dihydroquinoline (±)-**9** in a good yield (63%, entry 5, Table 1) is notable considering that the analogous 2*H*-1-benzopyran could only be obtained in a modest 36% yield.[9] Under the standard conditions (1,2-dichloroethane, reflux) palladacycle (±)-**4** failed to react with alkynes lacking an activating substituent (e.g., PhC≡CPh).

Dihydroquinolines (±)-**6**, (±)-**7**, and (±)-**9** (entries 2, 3, and 5, Table 1) were isolated as single compounds, and analyses of crude reaction mixtures by ^{1}H NMR spectroscopy did not indicate formation of regioisomers. ^{1}H NMR spectroscopic analysis of dihydroquinoline (±)-**8** (entry 4, Table 1) detected the presence of less than 4% of a chromatographically inseparable isomer, presumably the regioisomeric dihydroquinoline. Regiochemical assignments in structures of dihydroquinolines (±)-**6**−(±)-**9** were based on HMBC 2D-NMR analyses that clearly established all of the expected long-range ^{1}H−^{13}C connectivities. Dihydroquinolines (±)-**10**−(±)-**12**, arising from the insertion of aromatic alkynes, were isolated as chromatographically inseparable mixtures of regioisomeric dihydroquinolines (±)-**10a**−**b**, (±)-**11a**−**b**, and (±)-**12a**−**b** in approximately 9:1 ratios as determined by ^{1}H NMR analyses (entries 6−8, Table 1). A single crystal-

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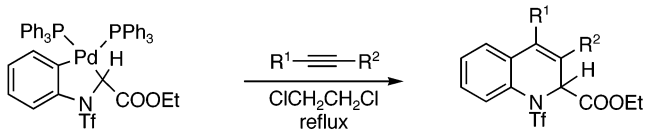
TABLE 1. Synthesis of Racemic 2,3,4-Trisubstituted 1,2-Dihydroquinolines



(±)-**4** (±)-**5**-(±)-**12**

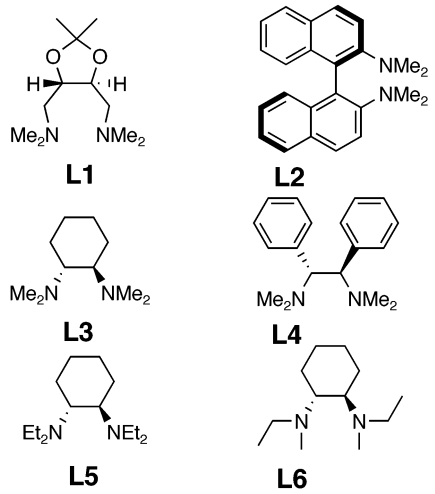
	alkyne[a]	time (h)	product	yield (%)	R^1	R^2	ratio of regioisomers
1	$EtO_2CC{\equiv}CCO_2Et$	1	(±)-**5**	89	CO_2Et	CO_2Et	na
2	$MeC{\equiv}CCO_2Et$	8	(±)-**6**	55	Me	CO_2Et	na
3	*n*-$PentC{\equiv}CCO_2Me$	7	(±)-**7**	61	*n*-Pent-	CO_2Me	na
4	$C_6H_9C{\equiv}CCO_2Me$[b]	9	(±)-**8**	62[c]	C_6H_9-[b]	CO_2Me	*d*
5	$TMSC{\equiv}CCO_2Et$	18	(±)-**9**	63	TMS	CO_2Et	na
6	$PhC{\equiv}CCO_2Et$	13	(±)-**10a**	64[c]	Ph	CO_2Et	**10a**:**10b**
			(±)-**10b**		CO_2Et	Ph	92:8
7	*p*-$MeOC_6H_4C{\equiv}CCO_2Me$	13	(±)-**11a**	59[c]	*p*-$MeOC_6H_4$-	CO_2Me	**11a**:**11b**
			(±)-**11b**		CO_2Me	*p*-$MeOC_6H_4$-	91:9
8	*p*-$FC_6H_4C{\equiv}CCO_2Me$	13	(±)-**12a**	70[c]	*p*-FC_6H_4-	CO_2Me	**12a**:**12b**
			(±)-**12b**		CO_2Me	*p*-FC_6H_4-	90:10

[a] 2.5−3.0 molar equiv of alkynes were used. [b] C_6H_9 = 1-cyclohexenyl. [c] Combined yield of both regioisomers. [d] Less than 4% of the regioisomeric 1,2-dihydroquinoline was present in the sample of product (±)-**8**.

lization of these mixtures afforded regioisomerically pure dihydroquinolines (±)-**10a**, (±)-**11a**, and (±)-**12a** as crystals suitable for X-ray crystallographic analyses, which confirmed the structures of dihydroquinolines (±)-**10a**, (±)-**11a**, and (±)-**12a**.

In contrast to previous limited studies with palladium-based metalacycles,[23] azapalladacycle (±)-**4**, much like its oxygen-containing counterpart,[9] showed an unexpectedly broad scope of reactivity toward alkynes (Table 1). However, slightly diminished regiocontrol in reactions with vinylic and aromatic alkynes was noted upon comparison of oxa- and azapalladacycles.[9] Nevertheless, insertion reactions of complex (±)-**4** with diverse unsymmetrical alkynes proceeded with synthetically useful regioselectivities (higher than 9:1) and in several cases with a complete regiocontrol, contrasting sharply with the reported 5:1 ($HC{\equiv}CCOOEt$)[23a] and 3:1 ($PhC{\equiv}CCOOEt$)[23b] selectivities in comparable systems. Presumably, electronic factors manifested in the interaction between frontier orbitals of the Csp^2-Pd bond[24] in palladacycle (±)-**4** and the C≡C bond of alkynes, control the regiochemistry of the insertion reaction.[25]

CHART 1



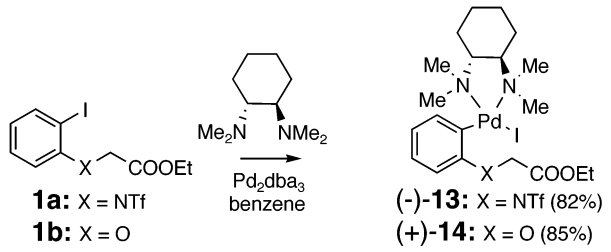
Diastereoselective Synthesis of Chiral Nonracemic Oxa- and Azapalladacycles. A Proposed Mechanism of Stereoinduction. With the goal to identify a ligand system that would allow for efficient stereoinduction and optimal reactivity of the resulting chiral nonracemic palladacycles with alkynes, the utility of several C_2-symmetrical bidentate diamine ligands[26] **L1**−**L6** (Chart 1) was surveyed. We envisioned that ligands **L1**−**L6** would function as the source of asymmetry (L*) in the conversion of complexes **IV** into palladacycles **V** (Figure 2). A subsequent ligand exchange with triphenylphosphine (L) would afford high-enantiopurity palladacycles **V** (L = PPh_3) (Figure 2) identical to palladacycles previously prepared in the racemic form and utilized in syntheses of diverse 2*H*-1-benzopyrans[9] and 1,2-dihydroquinolines (Table 1). Ligands **L1** and **L2** failed to provide the corresponding palladium(II) complexes **IV** as stable

(23) Depending on the spectator ligands, alkyne insertions to the known palladacycles are often limited to reactions with a highly activated dimethyl acetylenedicarboxylate; see: (a) Campora, J.; Lopez, J. A.; Palma, P.; del Rio, D.; Carmona, E.; Valerga, P.; Graiff, C.; Tiripicchio, A. *Inorg. Chem.* **2001**, *40*, 4116−4126. (b) Catellani, M.; Marmiroli, B.; Chiara-Fagnola, M.; Acquotti, D. *J. Organomet. Chem.* **1996**, *507*, 157−162.

(24) Studies on the reactions of various unsaturated molecules (e.g., NO_2, TsN_3, CS_2, COS, PhNSC) with benzannulated nickelacyclopentanes provided unequivocal evidence for the insertion occurring preferentially into the Csp^2-Ni (aryl-nickel) bond, most likely as the result of a chemoselective displacement of the more labile trialkylphosphine ligand positioned *trans* to the alkyl-Ni bond. However, no intermediates could be detected in the reactions of nickelacycles with alkynes, even at low temperatures. Exceptions to this regiochemical preference are known, e.g., in reactions with carbon monoxide or formaldehyde that preferentially insert into the Csp^3-Ni bond. See: (a) Koo, K.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1996**, *15*, 2669−2671. (b) Koo, K.; Hillhouse, G. L.; Rheingold, A. L. *Organometallics* **1995**, *14*, 456−460. (c) Koo, K.; Hillhouse, G. L. *Organometallics* **1995**, *14*, 4421−4423. (d) Campora, J.; Gutierrez, E.; Monge, A.; Palma, P.; Poveda, M. L.; Ruiz, C.; Carmona, E. *Organometallics* **1994**, *13*, 1728−1745. (e) Campora, J.; Llebaria, A.; Moreto, J. M.; Poveda, M. L.; Carmona, E. *Organometallics* **1993**, *12*, 4032−4038. (f) Carmona, E.; Gutierrea-Puebla, E.; Marin, J. M.; Monge, A.; Paneque, M.; Poveda, M. L.; Ruiz, C. *J. Am. Chem. Soc.* **1989**, *111*, 2883−2891.

(25) Conceivably, in a direct analogy to the conclusions of experimental and computational studies with comparable nickelacycles, the orientation of the alkyne during the insertion into the Csp^2-Pd bond in azapalladacycles (±)-**4** is controlled by the interaction of HOMO (Pd−C) orbitals in the Csp^2-Pd bond with LUMO orbitals of the alkyne. See: Bennett, M. A.; Macgregor, S. A.; Wenger, E. *Helv. Chim. Acta* **2001**, *84*, 3084−3104.

SCHEME 2



solids. Best diastereoselectivities in the ring-closure reactions (**IV** → **V**, Figure 2) of complexes **IV** (X = O, NTf, Y = COOEt) were achieved with the ligand **L3**,[27] which was selected for further development.

Treatment of aryl iodides **1a**−**b** with palladium(0) (Pd_2dba_3) and (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane (**L3**) accessible in one step from (1*R*,2*R*)-1,2-diaminocyclohexane,[28] afforded chiral nonracemic palladium(II) complexes (−)-**13** and (+)-**14** in excellent yields (82−85%) as stable yellow solids after chromatography (Scheme 2). ^{1}H NMR spectroscopic analyses of products (−)-**13** and (+)-**14** indicated the presence of two chromatographically inseparable isomeric species in variable ratios that were dependent on the solvent and the time of sample being dissolved prior to analysis, and the relative amount of silica used for chromatographic purification.[29] Furthermore, ^{1}H NMR analyses at elevated temperature (55 °C, $CDCl_3$) revealed sharpening of the signals for the methylenic protons (complex (−)-**13**), and a change in the observed ratio of isomers (complex (+)-**14**).[29] We hypothesized that a restricted rotation about the Csp^2-Pd bond in complexes (−)-**13** and (+)-**14** gave rise to atropisomers.[30] Reasoning that the observed equilibrium in complexes (−)-**13** and (+)-**14** may significantly influence the efficiency of stereoinduction (vide infra),[31] methods for reproducible preparations of complexes (−)-**13** and (+)-**14** with different ratios of atropisomers were sought. Treatment of complex (−)-**13** isolated in 42:58 ratio in methylene chloride (rt, 36 h) afforded the recovered complex (−)-**13** in a quantitative yield with 18:82 ratio of atropisomers. A solution of this material in ethyl acetate was treated with suspended silica (10 g SiO_2 per 1 g of (−)-**13**, 4 days, rt) to afford the recovered complex (−)-**13** in 98% yield and 2:98 ratio. When a $CDCl_3$ solution of this material (2:98) was kept for 1 day at room temperature, ^{1}H NMR analysis indicated a decrease to 12:88 ratio of atropisomers. The described protocols permitted a reproducible preparation of multigram quantities of complex (−)-**13** with 18:82 ratio of atropisomers, corresponding to the equilibrium ratio of atropisomers in a methylene chloride solution. Alternatively, complex (−)-**13** with 2:98 ratio of atropisomers could be conveniently obtained via the treatment with solid silica.[32] In contrast to these findings, ether-derived complex (+)-**14** could only be reproducibly isolated in 60:40 ratio of atropisomers achieved by equilibration in solution (methylene chloride or ethyl acetate). Although suspended silica also increased the ratio of atropisomers (to 80:20 from 60:40) for complex (+)-**14**, the experiments were poorly reproducible, as a rapid inversion of atropisomers (to 60:40 ratio) occurred during the solvent evaporation. A slow diffusion of hexane into methylene chloride solutions of complexes (−)-**13** and (+)-**14** afforded diffraction-quality crystals. Molecular structures of complexes (−)-**13** and (+)-**14** depicted in Figure 3 revealed an orthogonal orientation of the aryl ring with respect to the square planar coordination sphere of palladium, and suggested that the steric bulk of the trifluoromethanesulfonyl N-protecting group might be responsible for the apparently higher rotational barrier in complex (−)-**13**.

The diastereoselectivity of an intramolecular displacement of iodide in complexes (−)-**13** and (+)-**14** by in situ

(26) For a discussion of the applications of vicinal diamines and specifically *trans*-1,2-diaminocyclohexane in asymmetric synthesis, see: (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627. (b) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161−3195.

(27) Ring-closure reactions of palladium(II) iodo complexes **IV** (**L*** = **L3**-**L6**, X = O, Y = COOEt) performed under standardized conditions (*t*-BuOK, THF, rt, 1 h) afforded palladacycle **V** in 64% de from complex **IV** featuring ligand **L3**, in 50% de from complex **IV** with ligand **L4** and in 10% de from complex **IV** with ligand **L5**. Complex **IV** bearing ligand **L6** provided palladacycle **V** (X = O) as a complex mixture of several diastereomers apparently arising as a result of the creation of stereogenic palladium-bonded nitrogen atoms. For an application of ligand **L6**, see: Mahadevan, V.; Hou, Z.; Cole, A. P.; Root, D. E.; Solomon, E. I.; Stack, T. D. P. *J. Am. Chem. Soc.* **1997**, *119*, 11996−11997.

(28) Remenar, J. F.; Brett, B. L.; Column, D. V. *J. Am. Chem. Soc.* **1997**, *119*, 5567−5572.

(29) In the ^{1}H NMR ($CDCl_3$, 25 °C) spectra of palladium(II) complexes (−)-**13** and (+)-**14** integration of the signals for the two methylene protons (X-CH_2-COOEt) that *each* appeared as a set of two doublets, was used for determining the ratio of isomers (atropisomers). Signals for one methylene proton in complex (−)-**13** appeared at 6.41 ppm (d, J = 18.7 Hz) for the minor isomer, and at 5.51 ppm (d, J = 18.9 Hz) for the major isomer. Signals for one methylene proton in complex (+)-**14** appeared at 5.06 ppm (d, J = 16.1 Hz) for the major isomer, and at 5.00 ppm (d, J = 16.2 Hz) for the minor. Detailed ^{1}H NMR studies, including temperature-dependent experiments aimed at establishing the associated isomerization energy barriers are in progress and will be reported in due course.

(30) The existence of atropisomers arising from the hindered rotation about a transition metal-aryl bond (e.g., Pd−Ar or Pt−Ar) in square planar arylplatinum(II) iodo or arylpalladium(II) iodo complexes featuring bidentante phosphine ligands (achiral or chiral nonracemic) or the tetramethylethylenediamine ligand was detected via ^{1}H NMR spectroscopy; see: (a) Brown, J. M.; Perez-Torrente, J. J. *Organometallics* **1995**, *14*, 1195−1203. (b) Brown, J. M.; Perez-Torrente, J. J. *Organometallics* **1995**, *14*, 207−213. (c) Alster, P. L.; Boersma, J.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *Organometallics* **1993**, *12*, 1639−1647. The formation of distinct conformational isomers of copper complexes possessing bidentate diamine ligands (e.g., *N*,*N*,*N*′,*N*′-tetramethyl-*trans*-1,2-diaminocyclohexane) and two *ortho*-substituted σ-bonded aryl ligands, arising from the rotation about the Csp^2-Cu bond, was proposed to rationalize the observed regioselectivity of a copper-catalyzed cross-coupling reaction; see: (d) Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 7892−7897. Conformational isomers arising from two possible orientations of the quanine ligand (**G**) in platinum(II) complexes featuring *N*,*N*,*N*′,*N*′-tetramethyl-*trans*-1,2-diaminocyclohexane (Me_4DACH) [(*R*,*R*)-Me_4-DACH−Pt(H_2O)**G**] could be distinguished by ^{1}H NMR spectroscopy; see: (e) Benedetti, M.; Saad, J. S.; Marzilli, L. G.; Natile, G. *J. Chem. Soc., Dalton Trans.* **2003**, 872−879. A restricted rotation about palladium−nitrogen bonds of two heteroarenes (2,6-diazaanthracenes) bonded to palladium centers featuring chiral nonracemic bidentate phosphine ligands gave rise to a dynamic equilibrium between diastereomeric palladium(II) complexes, and the effect of asymmetric induction on the ratio of the atropisomers was studied; see: (f) Stang, P. J.; Olenyuk, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 732−736. (g) Stang, P. J.; Olenuyk, B.; Arif, A. M. *Organometallics* **1995**, *14*, 5281−5289.

(31) The ratio of atropisomers in complexes (−)-**13** and (+)-**14** would become a significant factor if the rates of the ring-closure reactions were faster than the rates of interconversion of the atropisomers. This principle was demonstrated in reactions involving a hindered rotation about the Csp^2-N bond in atropisomeric radical intermediates. See: (a) Curran, D. P.; Liu, W.; Chen, H.-T. C. *J. Am. Chem. Soc.* **1999**, *121*, 11012−11013. Analogous principle was exploited in a Michael-enol cyclization sequence applied to TpRe(CO)(MeIm)(3,4-η^2-naphthalene) complex undergoing a relatively slow interconversion of coordination diastereomers at room temperature in solutions; see: (b) Harman, W. D.; Keane, J. M.; Ding, F.; Sabat, M. *J. Am. Chem. Soc.* **2004**, *126*, 785−789.

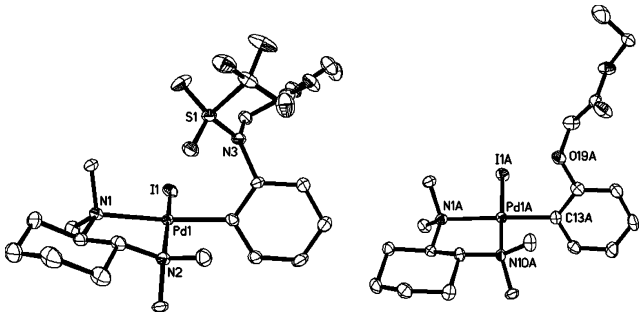
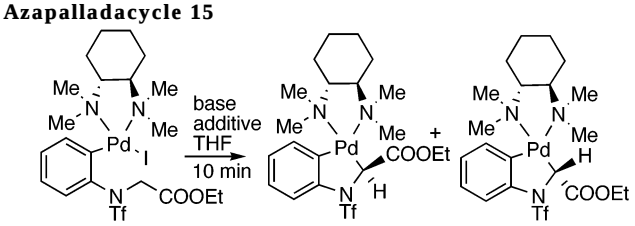


FIGURE 3. Thermal ellipsoid diagrams of complexes (−)-(*R*,*R*)-**13** (left) and (+)-(*R*,*R*)-**14** (right). The ellipsoids are drawn at the 50% probability level.

formed ester enolates yielding palladacycles (+)-**15** and (−)-**16** was dependent on the choice of bases and additives (Tables 2 and 3).[11] A series of experiments performed with palladium(II) complex (−)-**13** with 2:98 ratio of atropisomers (entries 1−8, Table 2) afforded palladacycle **15** as a white crystalline solid consisting of chromatographically inseparable mixtures of diastereomers (+)-**15a** (major) and **15b** (minor) in 10−92% de as established by ^{1}H NMR spectroscopy.[33] Crystallization of palladacycle **15a** (96:4 dr) via a slow diffusion of hexane into a methylene chloride solution afforded diffraction quality crystals of the pure major diastereomer (+)-**15a** as confirmed by ^{1}H NMR analysis of the crystalline material. X-ray crystallographic data permitted the assignment of the absolute configuration of the metal-bonded stereogenic carbon in the diastereomer (+)-**15a** as (*S*) (Figure 4).

Ring-closure reactions of complex (−)-**13** (ratio of atropisomers 98:2) induced by strong amide bases KHMDS and LDA, generating relatively sterically demanding highly associated enolates,[34] proceeded with significantly higher diastereoselectivities of 60% and 80% de (entries 1 and 3, Table 2) compared to the reaction mediated by *t*-BuOK (16% de, entry 5, Table 2). Only in one instance, with KHMDS base, an increase in diastereoselectivity (72% de, entry 2, Table 2) was achieved at subzero temperatures (compare entries 2, 4, and 6, Table 2). However, the addition of silver acetate (AgOAc, 3.0 equiv) along with *t*-BuOK (1.2 equiv) effected a dramatic improvement providing palladacycle (+)-**15a** in 86% de (compare entries 6 and 7, Table 2), and the same reagent mixture afforded palladacycle (+)-**15a** in an excellent 92% de at −78 °C (entry 8, Table 2). None of the other silver(I) salts tested ($AgNO_3$, Ag_3PO_4, Ag_2CO_3, and AgOTf) led

TABLE 2. Diastereoselective Preparation of Azapalladacycle 15

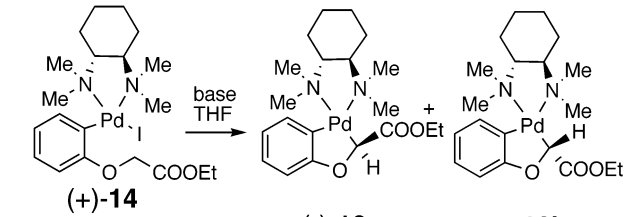


	conditions			diastereomeric ratio			
	base	additive	temp (°C)	**15a** (%)	**15b** (%)	de (%)	yield (%)
1	KHMDS		rt	80	20	60	89
2	KHMDS		−78	86	14	72	93
3	LDA		rt	90	10	80	61
4	LDA		−78	86	14	72	92
5	*t*-BuOK		rt	58	42	16	93
6	*t*-BuOK		−78	55	45	10	88
7	*t*-BuOK	AgOAc[b]	rt	93	7	86	94
8	*t*-BuOK	AgOAc[b]	−78	96	4	92	99

	conditions[c]	ratio of atropisomers in substrate **13** (%)		diastereomeric ratio **15a** (%)	diastereomeric ratio **15b** (%)	de (%)	yield (%)
9	*t*-BuOK/Ag(I)/−78 °C	43	57	69	31	38	97
10	*t*-BuOK/Ag(I)/−78 °C	13	87	86	14	72	100

[a] Substrates with the ratio of atropisomers 98:2 were used in entries 1−8. [b] Silver(I) acetate (3.0 equiv) was used. [c] Reaction conditions identical to conditions used in the entry 8 were employed for entries 9 and 10.

TABLE 3. Diastereoselective Preparation of Oxapalladacycle 16



	conditions				diastereomeric ratio **16a** (%)	diastereomeric ratio **16b** (%)	de (%)	yield (%)
	base	additive	temp (°C)	time (min)				
1	KHMDS		rt	15	77	23	54	59
2	LDA		−78	15	60	40	20	98
3	*t*-BuOK		rt	15	77	23	54	99
4	*t*-BuOK		rt	60	82	18	64	99
5	*t*-BuOK		−78	60	49	51	−2	100
6	*t*-BuOK	AgOAc[b]	rt	15	42	58	−16	89
7	*t*-BuOK	AgOAc[b]	−78	15	43	57	−14	88

[a] Substrates with the ratio of atropisomers 60:40 were used in entries 1−7. [b] Silver(I) acetate (3.0 equiv) was used.

(32) To investigate the nature of the effect of silica on the ratio of atropisomers in the recovered complex (−)-**13**, solutions of complex (−)-**13** (13:87 ratio of atropisomers) in ethyl acetate (0.1 g/15 mL) without an additive and with 5% and 10% of acetic acid (wt % per weight of **13**) were treated at room temperature under argon for 4 days. Complexes (−)-**13** were recovered from these experiments in excellent yields (97−98%) with the ratios of atropisomers 12:88 (no additive), 2:98 (5% AcOH), and 2:98 (10% AcOH) as established by ^{1}H NMR. Thus, the silica may have effected the pH-dependent equilibrium between the atropisomers of complex (−)-**13**; see: (a) Coogan, M. P.; Hibbs, D. E.; Smart, E. *Chem. Commun.* **1999**, 1991−1992. However, the potential involvement of a solid-phase phenomenon known as crystallization-induced asymmetric transformation (CIAT) by which one conformer or diastereomer can be selectively trapped in the solid state as a result of crystal packing forces and other intermolecular interactions could not be rigorously ruled out; see: (b) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447−456. (c) Kosmrlj, J.; Weigel, L. O.; Evans, D. A.; Downey, C. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 3208−3209. (d) Vedejs, E.; Donde, Y. *J. Org. Chem.* **2000**, *65*, 2337−2343. Examples of processes that utilize CIAT to provide a kinetically unstable diastereomer to control the selectivity of a subsequent chemical reaction occurring with a rate faster than interconversion of the diasteomers under the reaction conditions (see ref 31) are known; see: (d) Reference 31b (e) Ates, A.; Curran, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 5130−5131.

(33) The diastereomeric composition of palladacycle **15** was established by integration of ^{1}H NMR signals corresponding to the methine protons attached to the palladium-bonded sp^3-hybridized carbon: a singlet at 5.16 ppm (s) for diastereomer **15b** and a singlet at 4.81 ppm (s) for diastereomer **15a**.

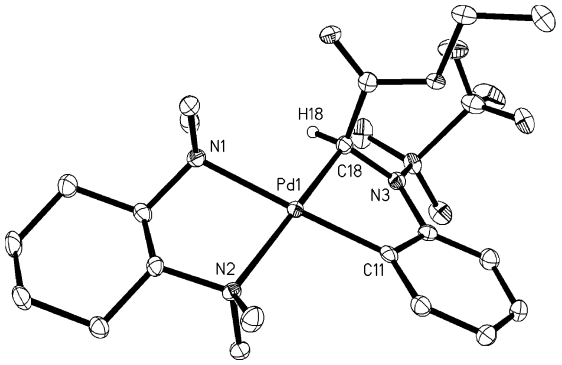


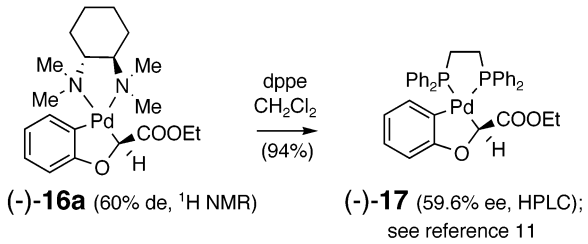
FIGURE 4. Thermal ellipsoid diagram of palladacycle (+)-(*S*,*R*,*R*)-**15a.** Ellipsoids are drawn at the 50% probability level.

to superior diastereoselectivities.[35] As anticipated,[31] when the optimized reaction conditions (*t*-BuOK, AgOAc, −78 °C) were applied to the ring closure of palladium(II) complexes (−)-**13** with the lower ratios of atropisomers 43:57 and 13:87, palladacycle (+)-**15a** was produced in 38% and 72% de, respectively, showing a strong correlation between the diastereoselectivity of the ring closure and the ratio of atropisomers in the substrate (entries 9 and 10, Table 2).

Interestingly, a distinct behavior was observed in the oxygen series (Table 3). Palladium(II) complex (+)-**14** with the ratio of atropisomers 60:40 afforded oxapalladacycle **16** as a pale yellow solid consisting of chromatographically inseparable mixtures of diastereomers (−)-**16a** (major) and **16b** (minor) in 2−64% de (entries 1−7, Table 3) as determined by ^{1}H NMR spectroscopy.[36] Limited stability of oxapalladacycles **16** in solution precluded the growth of diffraction quality crystals. Thus, the absolute configuration of the metal-bonded stereocenter was assigned via correlation of the signs of optical rotation with a known compound. Diastereomer (−)-**16a** (60% de) was treated with achiral 1,2-bis(diphenylphosphino)ethane (dppe) ligand to afford known palladacycle (−)-**17**[11] in 59.6% ee (by chiral-phase HPLC) with (*S*) configuration of the metal-bonded stereocenter (Scheme 3), indicating (*S*) configuration of the metal-bonded stereocenter in the palladacycle (−)-**16a** (Table 3 and Scheme 3).[37]

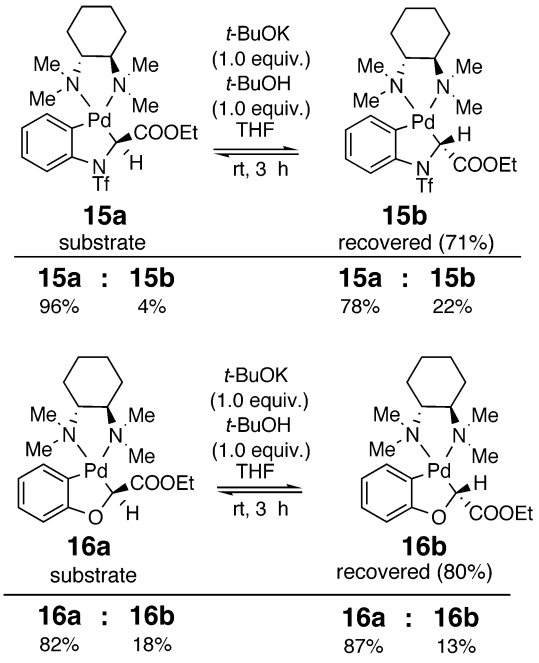
The ring closure of complex (+)-**14** (ratio of atropisomers 60:40) mediated by LDA or *t*-BuOK at subzero

SCHEME 3



(-)-**16a** (60% de, ^{1}H NMR) (-)-**17** (59.6% ee, HPLC); see reference 11

SCHEME 4



temperatures (entries 2 and 5, Table 3) led to poor diastereoselectivities of 20% and 2% de, respectively. An improvement to 54% de was noted in reactions induced by KHMDS and *t*-BuOK at ambient temperature (entries 1 and 3, Table 3). Synthetically useful results (64% de) were achieved when the *t*-BuOK-mediated reaction was allowed to proceed for an extended time (1 h) (compare entries 3 and 4, Table 3). However, addition of silver(I) acetate failed to raise the diastereoselectivity (entries 6 and 7, Table 3). To assess potential significance of a base-mediated epimerization of the palladium-bonded stereogenic carbon, the configurational stability of palladacycles (+)-**15a** (92% de) and (−)-**16a** (64% de) in the presence of excess *t*-BuOK at room temperature was studied (Scheme 4).

Whereas erosion of diastereoselectivity occurred in the recovered azapalladacycle (+)-**15a** (from 92% de to 56% de), enrichment from 64% de to 74% de was observed for oxapalladacycle (−)-**16a**. The data suggest that only negligible epimerization of metal-bonded stereogenic

(34) For a discussion of the differences in the structure and the aggregation state of enolate anions of lithium and potassium metals, in the presence of amine additives, see: (a) Smith, M. B. *Organic Synthesis*; McGraw-Hill: New York, 1994; Chapter 9, pp 865−869. The potassium enolate arising from the treatment of the substrate with KHMDS is expected to provide a more sterically demanding ion pair as a result of the association of the amine ($HN(SiMe_3)_2$) rather than THF with the potassium ion. Furthermore, presence of 1 equiv of *t*-BuOH in reactions mediated by *t*-BuOK would favor the formation of solvent-separated ion pairs; see: (b) Corset, J.; Froment, F.; Lautie, M.-F.; Ratovelomanana, N.; Seyden-Penne, J.; Strzalko, T.; Roux-Schmitt, M.-C. *J. Am. Chem. Soc.* **1993**, *115*, 1684−1694.

(35) A series of ring-closure experiments was performed with substrate (−)-**13** possessing the ratio of atropisomers 87:13 utilizing various Ag(I) salts under the optimized conditions (*t*-BuOK, 3.0 equiv AgX, THF, − 78 °C). Palladacycle (+)-**15a** was obtained in the following diastereomeric excesses: AgOAc (72% de), $AgNO_3$ (60% de), Ag_3PO_4 (58% de), Ag_2CO_3 (24% de) and AgOTf (−22% de, excess of **15b**).

(36) The diastereomeric composition of palladacycle **16** was established by integration of ^{1}H NMR signals corresponding to the methine protons attached to the palladium-bonded sp^3-hybridized carbon: a singlet at 5.69 ppm (s) for diastereomer **16a** and a singlet at 5.30 ppm (s) for diastereomer **16b**.

(37) The assignment is based on the assumption that the ligand exchange reaction proceeds without affecting the configurational integrity of the metal-bonded stereocenter. Stability of a Pd−C bond during a ligand exchange process has been previously established (see ref 6e), and used for the preparation of enantiomerically enriched transition metal complexes with achiral ligands; see ref 6i and: Ryabov, A. D.; Panyashkina, I. M.; Polyakov, V. A.; Howard, J. A. K.; Kuzmina, L. G.; Datt, M. S.; Sacht, C. *Organometallics* **1998**, *17*, 3615−3618.

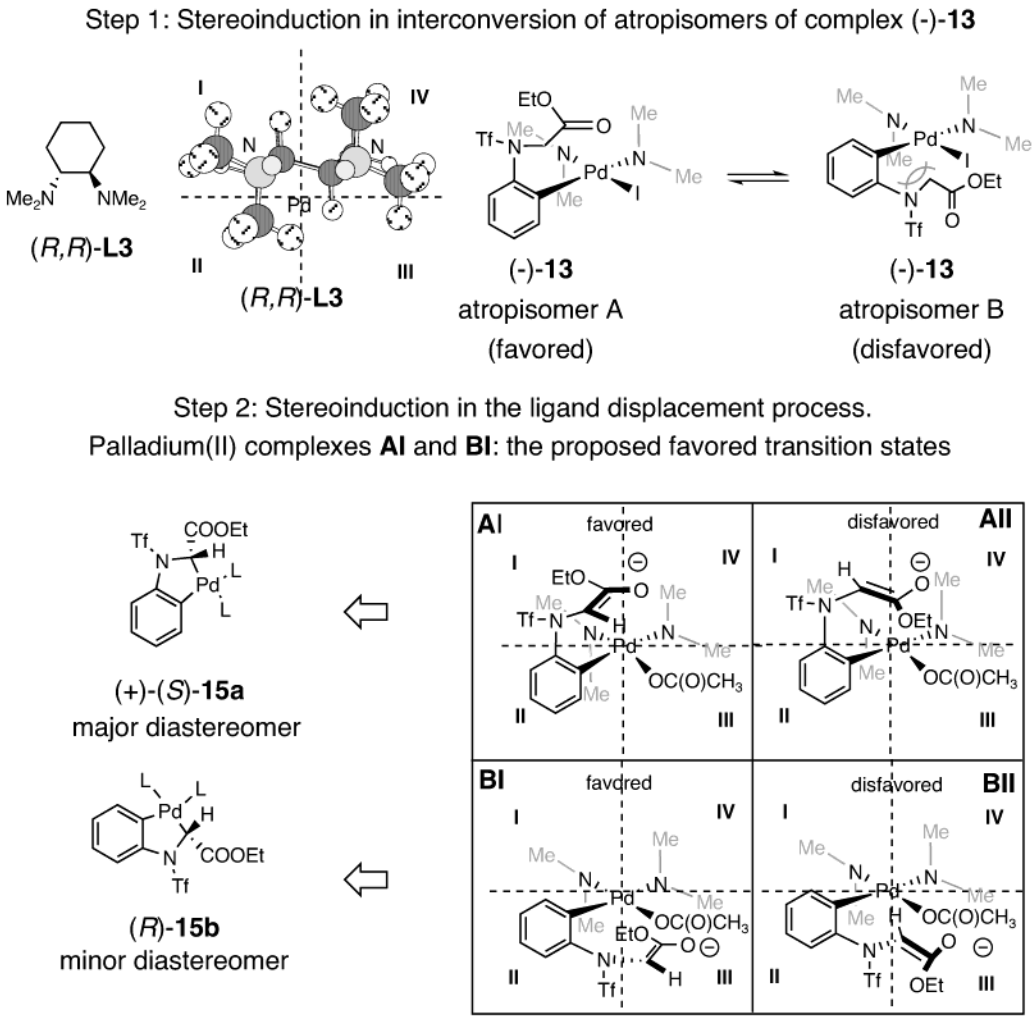


FIGURE 5. Proposed mechanism of stereoinduction in the formation of palladacycle (+)-**15a**.

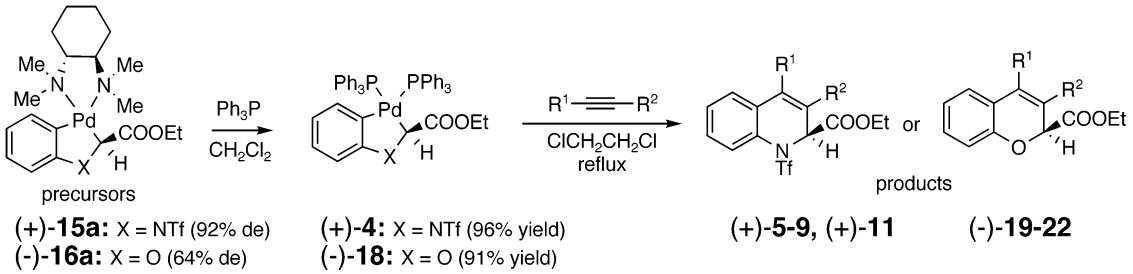
carbon in palladacycle (+)-**15a** could have occurred under the reaction conditions (entry 8, Table 2) following the facile and irreversible ring closure. In contrast, further enrichment in the content of the major diastereomer (−)-**16a** of oxapalladacycle **16** could have occurred via base-mediated epimerization of the metal-bonded stereogenic carbon under the reaction conditions following the irreversible ring closure[9,11] (compare entries 3 and 4, Table 3).

On the basis of the presented evidence, a plausible mechanism of stereoinduction in the formation of the palladacycle (+)-**15a** is proposed (Figure 5). The three-dimensional model of ligand (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane (**L3**) shows that the pseudoaxial methyl groups selectively block quadrants II and IV located above and below the plane defined by the two nitrogen atoms bonded to palladium within the square planar coordination sphere of the palladium complex (−)-**13**.[38] Consequently, the atropisomer **A** (Figure 5) of complex (−)-**13**, in which the sterically demanding *N*-alkyl side chain is located in quadrants I or III (equivalent as a result of the C_2-symmetry), would be favored over the atropisomer **B** (Figure 5), a notion supported by the crystal structure of complex (−)-**13** (Figure 3). We reasoned that the ligand exchange might proceed via an associative pathway involving four initial transition states **AI**, **AII**, **BI**, and **BII** represented by pentacoordinate square pyramidal palladium complexes featuring the enolate bonded in the apical position (Figure 5).[39] Under these circumstances, unfavorable steric interactions between the enolate and the leaving group (acetate) would occur in transition states **AII** and **BII** as a result of the coplanar orientation of the leaving group and the enolate side chain (Figure 5), favoring the reaction pathways proceeding via transition states **AI** and **BI**. Accordingly, the ring closure from the favored atropisomer **A** proceeding through the transition state **AI** would afford the observed major diastereomer (+)-**15a** with the

(38) For an approach to the assessment of structural features of a chiral ligand via "stereocartography", see: (a) Lipkowitz, K. B.; Kozlowski, M. C. *Synlett* **2003**, 1547−1565. The model of ligand **L3** shown in Figure 5 was constructed using CS Chem3D package and energy minimization via MM2 calculations.

(39) For examples of ligand exchange and geometrical isomerization reactions of palladium(II) complexes that were shown to proceed via associative pathways involving pentacoordinate palladium(II) intermediates, see: (a) Verstuyft, A. W.; Cary, L. W.; Nelson, J. H. *Inorg. Chem.* **1976**, *15*, 3161−3163. (b) Verstuyft, A. W.; Nelson, J. H. *Inorg. Chem.* **1975**, *14*, 1501−1505. (c) Poe, A. J.; Vaughan, D. H. *Inorg. Chim. Acta* **1967**, *1*, 255−164. For the synthesis and characterization of pentacoordinate complexes of palladium(II), see: (d) Garrone, R.; Romano, A. M.; Santi, R.; Milini, R. *Organometallics* **1998**, *17*, 5419−4522. (e) Albano, V. G.; Castellari, C. *Organometallics* **1990**, *9*, 1269−1276.

TABLE 4. Asymmetric Synthesis of 1,2-Dihydroquinolines and 2*H*-1-Benzopyrans



(+)-15a: X = NTf (92% de) **(-)-16a:** X = O (64% de)

(+)-4: X = NTf (96% yield) **(-)-18:** X = O (91% yield)

(+)-5-9, (+)-11 **(-)-19-22**

	precursor de (%)	alkyne[a]	product	ee[b] (%)	yield[c] (%)	R^1	R^2
1	**15a** (92)	$EtO_2CC{\equiv}CCO_2Et$	(+)-**5**	91	87	CO_2Et	CO_2Et
2	**15a** (92)	$MeC{\equiv}CCO_2Et$	(+)-**6**	91	54	Me	CO_2Et
3	**15a** (92)	*n*-$PentC{\equiv}CCO_2Me$	(+)-**7**	82	57	*n*-Pent	CO_2Me
4	**15a** (92)	$C_6H_9C{\equiv}CCO_2Me$	(+)-**8**[d]	86	56	C_6H_9[d]	CO_2Me
5	**15a** (92)	$TMSC{\equiv}CCO_2Et$[e]	(+)-**9**	80	57	TMS	CO_2Et
6	**15a** (92)	*p*-$MeOC_6H_4C{\equiv}CCO_2Me$	(+)-**11a**[f]	91	57	*p*-$MeOC_6H_4$	CO_2Me
7	**16a** (64)	$MeC{\equiv}CCO_2Et$[g]	(−)-**19**[h]	35	52	Me	CO_2Et
8	**16a** (64)	*n*-$BuC{\equiv}CCO_2Et$[g]	(−)-**20**	56	72	*n*-Bu	CO_2Et
9	**16a** (64)	$PhC{\equiv}CCO_2Et$[g]	(−)-**21**	40	59	Ph	CO_2Et
10	**16a** (64)	$PhC{\equiv}CCOMe$[g]	(−)-**22**	32	58	Ph	$COCH_3$

[a] Reaction conditions identical to the conditions used for the preparation of racemic products were employed (see Table 1) in entries 1−6. [b] Enantiomeric excess was established by HPLC chromatography on chiral stationary phases CHIRALPAK AD or CHIRACEL OD, except for compounds (+)-**8** and (+)-**9**, which were analyzed by ^{1}H NMR with a chiral shift reagents Eu(hfc)$_3$. [c] Yield is calculated per palladacycles (+)-**4** or (−)-**18**. [d] C_6H_9 = 1-cyclohexenyl. Dihydroquinoline (+)-**8** contained less than 4% of the regioisomeric dihydroquinoline. [e] Reaction proceeded for 12 h. [f] A 94:6 mixture of products **11a** and **11b** in overall 57% yield was isolated. [g] A solution of the appropriate alkyne (2.2−2.3 equiv) and the palladacycle (−)-**18** in 1,2-dichloroethane was heated to reflux for 6 h. [h] In contrast to a previous report on the synthesis of racemic (±)-**19** (ref 9), 2*H*-1-benzopyran (−)-**19** was produced as a pure single regioisomer.

(*S*) configuration (Figure 4) of the palladium-bonded stereocenter, while the minor atropisomer **B** would afford diastereomer **15b** via the transition state **BI** (Figure 5). The proposed mechanistic rationale is supported by the observed increase in diastereoselectivity in reactions involving bulky, associated enolates[34] (entries 1−4, Table 2), and the effect of the replacement of the iodide leaving group with a sterically more demanding palladium-associated acetate ligand prior to the ligand exchange[40] (entries 7 and 8, Table 2). The significance of the ratios of atropisomers of complex (−)-**13** (entries 9 and 10, Table 2) can be easily rationalized by contrasting the facile ring closure of complex (−)-**13** and a relatively slow interconversion of its atropisomers.[31] As a result of the relatively rapid inversion of atropisomers of the oxygen analogue (+)-**14**, the ring-closure reaction afforded oxapalladacycle **16** in a low diastereomeric excess, as seen from the experiments performed under conditions that limited a subsequent epimerization of the palladium-bonded stereogenic carbon (entries 2, 5, and 7, Table 3). In fact, the best stereoselectivity (64% de, entry 4, Table 3) was achieved under conditions that would allow for a subsequent base-mediated epimerization (extended reaction time at room temperature) of the diastereomers (−)-**16a** and **16b** (Scheme 4). The proposed mechanism of chirality transfer highlights the atropisomeric composition of substrate (−)-**13** as a key element that could play a role in a variety of asymmetric processes, involving both organic and organometallic intermediates.[30,31] Our data provide a support for the involvement of the anionic ligand (iodide or acetate leaving group) in the stereodifferentiating step of this intramolecular ligand exchange process.[40]

Asymmetric Synthesis of 2,3,4-Trisubstituted 1,2-Dihydroquinolines and 2*H*-1-Benzopyrans. Displacement of chiral nonracemic diamine ligands in palladacycles (+)-**15a** (92% de) and (−)-**16a** (64% de) with triphenylphosphine afforded palladacycles (+)-**4** and (−)-**18**[9] as stable solids in excellent yields (Table 4). Work is in progress toward developing a practical protocol for recovery of the chiral nonracemic diamine ligand from this operation for future recycle. The ligand displacement step was necessary since our previous studies revealed that palladacycles featuring bidentate diamine ligands (e.g., TMEDA) failed to react with alkynes.[9] Although we were unable to independently establish the enantiomeric purities of palladacycles (+)-**4** and (−)-**18**,[41] the assumption that no bond breaking and therefore no epimerization occurred at the palladium-bonded stereogenic carbons during a ligand-exchange reaction has ample precedent.[37]

Palladacycles (+)-**4** (presumably 92% ee) and (−)-**18** (presumably 64% ee)[42] were treated with activated

(40) Measurements of electric conductivity of acetone solutions of a (π-allyl)(PCy_3)PdOAc complex indicated minimum conductivity, suggesting that the complex had essentially an nonionic structure. See: (a) Yamamoto, T.; Saito, O.; Yamamoto, A. *J. Am. Chem. Soc.* **1981**, *103*, 5600−5602. In a related work, an intramolecular catalytic asymmetric arylation of an amide enolate was studied with aryl chloride, aryl bromide, and aryl iodide analogues of the substrate with the goal to establish whether the halide ligand is present on the intermediate organometallic complex in the key stereodifferentiating step. Inconclusive results were obtained indicating that both chloro and bromo analogues provided the product with similar enantioselectivity, while the iodo-analogue failed to provide products in an appreciable enantiomeric excess. See ref 4d.

(41) All attempts at resolving chromatographic signals for the enantiomers of complexes (+)-**4** and (−)-**18** on CHIRALPAK AD, AS and CHIRACEL OD chiral stationary phases failed. Furthermore, ^{1}H NMR and ^{31}P NMR of complexes (+)-**4** and (−)-**18** run in the presence of Eu(hfc)$_3$ chiral shift reagent did not provide a sufficient resolution to ascertain the enantiomeric excess.

alkynes under previously developed conditions (see Table 1 and ref 9) to afford a series of nonracemic heterocycles in good to excellent yields (52−87%, Table 4). The isolated 1,2-dihydroquinoline (+)-**8** (56% combined yield) contained less than 4% of the regioisomeric product, and 1,2-dihydroquinoline (+)-**11** (57% combined yield) consisted of a 94:6 ratio of the major regioisomer (+)-**11a** and the minor regioisomer **11b**. All remaining heterocycles were produced as single regioisomers as indicated by ^{1}H NMR analyses.[43] 1,2-Dihydroquinolines (+)-**5**−(+)-**9** and (+)-**11a** were obtained in high enantiomeric purities (80−91% ee) (entries 1−6, Table 4), and 2*H*-1-benzopyrans (−)-**19**−(−)-**22** were produced in moderate to modest enantiomeric excesses (32−56% ee) (entries 7−10, Table 4).[44] We were pleased to note that the metal-bonded stereocenter in azapalladacycle (+)-**4** was incorporated into the 1,2-dihydroquinolines (+)-**5**, (+)-**6**, and (+)-**11a** without any loss of the stereochemical information, and into 1,2-dihydroquinolines (+)-**9**, (+)-**7**, and (+)-**8** with only minimal 13%, 11%, and 6.5% racemization, respectively. However, the asymmetry transfer from the oxapalladacycle (−)-**18** proved less efficient. Although 2*H*-1-benzopyran (−)-**20** was produced with only 12% racemization, formation of 2*H*-1-benzopyrans (−)-**19**, (−)-**21**, and (−)-**22** occurred with 37−50% racemization. Absolute configurations of the 1,2-dihydroquinolines (+)-**5**−(+)-**9** and (+)-**11a**, and 2*H*-1-benzopyrans (−)-**19**− (−)-**22** were assigned as (*S*) in all cases, assuming a retention of configuration of the migrating stereogenic carbon center.[45] Surprisingly, dihydroquinolines (+)-**6** (91% ee) and (+)-**7** (81% ee) and 2*H*-1-benzopyrans (−)-**20** (56% ee) and (−)-**22** (32% ee) did not show any racemization when treated under simulated reaction (1,2-dichloroethane solution in light, 80 °C, 6 h) and workup (treatment with suspended silica in ethyl acetate solutions, rt, 1 h) conditions.[46] Thus, the disparity in the efficiency (0−50% racemization) of asymmetry transfer from the palladacycles (+)-**15a** and (−)-**16a** to the heterocycles (+)-**5**−(+)-**9**, (+)-**11a**, and (−)-**19**−(−)-**22** may be accounted for by the differences in the relative rates of racemization of palladacycles (+)-**4** and (−)-**18**, the rates of racemization of organometallic intermediates generated along the reaction coordinate, and the rates of formation of the heterocyclic products.

Conclusions

A conceptually new approach to a convergent assembly of highly substituted 1,2-dihydroquinolines from novel azapalladacycles with a metal-bonded stereogenic carbon has been described. In contrast to reactivity of other known palladacycles,[10,23] insertions of monoactivated unsymmetrical alkynes into azapalladacycle (±)-**4** proceeded with synthetically practical levels of regioselectivity (higher than 9:1) for aryl and cycloalkenyl alkynes, and with complete regiocontrol with alkyl- and trimethylsilyl-substituted alkynes. The protocol regenerates palladium(0), and work toward the development of a catalytic variant of this methodology, along with the design of a method for the recycle of palladium via solid-phase immobilized palladium(0) complexes, is in progress in our laboratories. Rare examples of stable diastereomerically enriched organometallics, palladacycles (+)-**15a** (92% de) and (−)-**16a** (64% de) featuring a palladium-bonded sp^3-hybridized stereogenic carbon, have been prepared, and the absolute configurations of the metal-bonded stereocenters were unequivocally assigned. Systematic studies of the parameters that control efficiency of asymmetric induction in the formation of diastereomerically enriched azapalladacycle (+)-**15a** revealed the significance of the content of atropisomers in the iodopalladium substrate (−)-**13**, and a crucial role played by the nature of the anionic ligand (iodide or acetate). A process for generating a highly enriched atropisomer of complex (−)-**13** via interaction with solid silica was discovered, providing a substrate for the preparation of a highly diastereomerically enriched palladacycle (+)-**15a** (92% de). These observations allowed us to propose a plausible mechanism of stereoinduction providing insights relevant to a variety of palladium-catalyzed transformations.[4,40] Stereoselective insertion of activated unsymmetrical alkynes into enantiomerically enriched azapalladacycle (+)-**4** and oxapalladacycle (−)-**18** provided nonracemic 1,2-dihydroquinolines (six examples) in excellent 80−91% ee and 2*H*-1-benzopyrans (four examples) in 32−56% ee. Despite the partial loss of the stereochemical information in the preparation of 2*H*-1-benzopyrans, the described method compares favorably with the rather limited number of protocols available for a direct enantioselective assembly of these heterocyclic systems.[14−18] Our results underscore the potential of nonracemic organometallics with a metal-bonded sp^3-hybridized stereocenter in asymmetric synthesis of valuable organic molecules. Further generali-

(42) However, a partial racemization of palladacycles (+)-**4** and (−)-**18** during the ligand exchange, or an alteration of the enantiomeric composition of palladacycle (−)-**18** during the high-yielding isolation via trituration could not be rigorously ruled out. Attempts at monitoring the stability of palladacycles (+)-**4** and (−)-**18** against racemization both at room temperature and at elevated temperatures via the measurements of specific rotations proved impractical because of the low absolute values of the specific rotations, $[\alpha]_D$ +17.6 and −13.0 for complexes (+)-**4** and (−)-**18**, respectively. For additional experiments see Supporting Information.

(43) In contrast to the reported[9] preparation of the racemic 2*H*-1-benzopyran (±)-**19** that yielded a 6:1 mixture of regioisomeric products, the enantiomerically enriched benzopyran (−)-**19** was isolated as a single regioisomer in 54% yield according to ^{1}H NMR analysis.

(44) (a) Enantiomeric excess of heterocycles (+)-**5**−(+)-**7**, (+)-**11a**, and (−)-**19**−(−)-**22** was measured by chiral phase HPLC analysis on CHIRACEL OD or CHIRALPAK AD chiral stationary phases. Enantiomeric purity of heterocycles (+)-**8** and (+)-**9** was determined by ^{1}H NMR analyses with a europium chiral shift reagent Eu(hfc)$_3$. (b) Enantiomeric purities of the minor regioisomers of heterocycles **8** and **11** could not be established by the corresponding analytical methods (HPLC for (+)-**11a** and ^{1}H NMR with Eu(hfc)$_3$ for (+)-**8**).

(45) It is generally accepted that migratory insertion reactions proceed with a retention of the absolute configuration at the metal-bonded carbon; see: (a) Flood, T. C. In *Topics in Inorganic and Organometallic Stereochemistry*; Geoffroy, G., Allinger, N. L., Eliel, E. L., Eds.; Willey-Interscience: New York, 1981; Vol. 12, pp 37−117. The original evidence for a net retention (80% efficiency) of absolute configuration at the migrating carbon was obtained in a study of insertion of dimethyl acetylenedicarboxylate into an iron−carbon bond in CpFe(CO)$_2$CH(D)CH(D)-*t*-Bu; see: (b) Bock, P. L.; Boschetto, D. J.; Rasmussen, J. R.; Demers, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 2814−2824. Retention of asymmetry, without establishing the absolute configurations of the organic products, at a palladium-bonded sp^3-hybridized stereogenic carbon in an alkyne insertion reaction has been demonstrated; see: (c) Spencer, J.; Pfeffer, M. *Tetrahedron: Asymmetry* **1995**, *6*, 419−426. To date, all attempts to produce a single crystal of the high-enantiopurity (91% ee) 1,2-dihydroquinoline (+)-**11a** to confirm the assigned (*S*) configuration via a X-ray crystallographic analysis failed.

(46) (a) For a light-induced racemization of 2*H*-1-benzopyrans, see ref 15a. (b) Van Gemert, B. In *Organic Photochromic and Thermochromic Compounds*; Crano, J. C., Guglielmetti, R. J., Eds.; Plenum: New York, 1999; Vol. 1, Chapter 3, p 111.

zation of this concept with respect to reaction types of the novel palladacycles is being pursued in our laboratories.

Experimental Section

Ethyl *N*-(2-Iodophenyl)-*N*-trifluoromethanesulfonyl-2-aminoacetate (1a). To a solution of *N*-trifluoromethanesulfonyl-2-iodoaniline[20] (3.00 g, 8.54 mmol) in DMF (8.5 mL) was added 60% NaH (0.444 g, 11.10 mmol) in small portions under argon at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 30 min. Ethyl bromoacetate (1.33 mL, 2.0 g, 11.96 mmol) was added dropwise, and the mixture was stirred for 8 h at room temperature. Methanol (2 mL) was added, and the mixture was poured into water (50 mL), extracted (EtOAc), and dried (Na_2SO_4) to afford a crude product, which was purified by flash chromatography over silica eluting with EtOAc/hexane (1:10) to yield anilide **1a** (3.10 g, 83%) as a colorless oil that solidified on standing at room temperature: mp 28−30 °C (EtOAc/hexanes 1:9); R_f = 0.44 (hexane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.9 Hz, 1.4 Hz, 1 H), 7.84 (dd, J = 8.0 Hz, 1.1 Hz, 1 H), 7.41 (td, J = 7.7 Hz, 1.4 Hz, 1 H), 7.12 (td, J = 7.7 Hz, 1.6 Hz, 1 H), 4.79 (d, J = 18.5 Hz, 1 H), 4.27−4.09 (m, 3 H), 1.27 (t, J = 7.13 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 140.4, 139.8, 133.2, 131.2, 129.3, 119.6 (q, $J(^{13}C-^{19}F)$ = 320.2 Hz), 99.7, 61.9, 53.1, 14.0; IR (KBr, cm^{-1}) 1756 (s), 1207 (s); HRMS (FAB) calcd for $C_{11}H_{12}F_3INO_4S$ (M + H$^+$) 437.9484, found 437.9489.

[(*N*-Ethoxycarbonylmethyl)-(*N*-trifluoromethanesulfonyl)-2-aminophenyl]iodo(tetramethylethylenediamine)-palladium (2). To a solution of tris(dibenzylideneacetone)-dipalladium(0) (Pd_2dba_3) (0.916 g, 1.00 mmol) in benzene (40 mL) at room temperature under argon was added tetramethylethylenenediamine (TMEDA) (0.45 mL, 0.349 g, 3.00 mmol) and aryl iodide **1a** (1.049 g, 2.40 mmol). The mixture was stirred at 55 °C for 1 h. The suspension was filtered through a plug of Celite, and solvents were removed under reduced pressure to afford a crude product. The crude product was purified by flash chromatography over silica eluting with EtOAc/hexane (1:10) to remove excess dibenzylideneacetone (dba) and subsequently with EtOAc/hexane (1:1) to afford palladium(II) complex **2** (1.059 g, 80%) as a yellow solid: mp 186−188 °C (CH_2Cl_2/hexane); R_f = 0.40 (hexane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.6 Hz, 1 H), 7.41 (d, J = 7.8 Hz, 1 H), 6.96 (t, J = 7.4 Hz, 1 H), 6.87 (t, J = 7.5 Hz, 1 H), 5.37 (t, J = 18.9 Hz, 1 H), 4.80 (d, J = 18.8 Hz, 1 H), 4.20−4.10 (m, 2 H), 3.07 (t, J = 8.9 Hz, 1 H), 2.75 (s, 6 H), 2.76−2.67 (m, 1 H), 2.62 (s, 3 H), 2.48−2.38 (m, 2 H), 2.09 (s, 3 H), 1.23 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 143.3, 141.7, 137.4, 130.0, 126.9, 123.9, 120.1 (q, $J(^{13}C-^{19}F)$ = 322.5 Hz), 61.8, 61.2, 58.5, 54.9, 51.7, 50.4, 49.1, 48.6, 14.1; IR (KBr, cm^{-1}) 1752 (s), 1384 (s), 1186 (s); HRMS (FAB) calcd for $C_{17}H_{31}F_3IN_4O_4PdS$ (M + NH_4^+) 677.0098, found 677.0104. Anal. Calcd for $C_{17}H_{27}F_3IN_3O_4PdS$: C, 30.95; H, 4.12; N, 6.37. Found: C, 31.02; H, 4.23; N, 6.37.

(±)-[(*N*-Ethoxycarbonylmethine)-(*N*-trifluoromethanesulfonyl)aza-1,2-phenylene] (tetramethylethylenediamine)palladium [(±)-3]. To a solution of complex **2** (0.330 g, 0.5 mmol) in THF (20 mL) was added dropwise *t*-BuOK (1.0 M solution in THF, 0.60 mL, 0.60 mmol). The mixture was stirred for 15 min at room temperature and filtered through a plug of basic alumina eluting with EtOAc/hexane (2:1). The solvent was removed under reduced pressure to afford palladacycle (±)-**3** (0.243 g, 92%) as a white solid: mp 190−192 °C (CH_2Cl_2/hexane); R_f = 0.29 (hexane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (s br, 1 H), 7.04 (dd, J = 7.5 Hz, 1.1 Hz, 1 H), 6.97 (td, J = 7.4 Hz, 1.4 Hz, 1 H), 6.85 (td, J = 7.4 Hz, 1.0 Hz, 1 H), 5.09 (s, 1 H), 4.05−3.97 (m, 2 H), 2.81 (s, 3 H), 2.78 (s, 3 H), 2.69−2.62 (m, 3 H), 2.66 (s, 3 H), 2.64 (s, 3 H), 2.55−2.47 (m, 1 H), 1.08 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 153.8, 141.3, 133.1, 124.8, 123.0, 120.2 (q, $J(^{13}C-^{19}F)$ = 325.1 Hz), 116.2, 61.2, 60.3 (br), 59.9, 59.5, 50.7, 49.8, 49.5, 48.8, 14.0; IR (KBr, cm^{-1}) 1706 (s), 1379 (m), 1178 (s); HRMS (FAB) calcd for $C_{17}H_{27}F_3N_3O_4PdS$ (M + H$^+$) 532.0709, found 532.0688. Anal. Calcd for $C_{17}H_{26}F_3N_3O_4PdS$: C, 38.39; H, 4.93; N, 7.90. Found: C, 38.52; H, 5.03; N, 7.81.

(±)-[(*N*-Ethoxycarbonylmethine)-(*N*-trifluoromethanesulfonyl)aza-1,2-phenylene] [bis(triphenylphosphine)]-palladium [(±)-4]. A solution of palladacycle (±)-**3** (0.537 g, 1.01 mmol) and Ph_3P (1.059 g, 4.04 mmol) in methylene chloride (25 mL) was stirred at room temperature for 1 h. The crude reaction mixture was purified by flash chromatography over silica eluting with EtOAc/hexane (1:20) to remove excess Ph_3P, and subsequently with EtOAc/hexane (1:1) to afford palladacycle (±)-**4** (0.929 g, 98%) as a white solid: mp 156−158 °C dec (CH_2Cl_2); R_f = 0.72 (hexane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, J = 9.0 Hz, 6 H), 7.45 (s br, 1 H), 7.31 (q, J = 7.4 Hz, 9 H), 7.24−7.18 (m, 9 H), 7.04 (t, J = 7.0 Hz, 6 H), 6.80 (t, J = 7.5 Hz, 1 H), 6.43 (td, J = 7.7 Hz, 3.6 Hz, 1 H), 6.19 (t, J = 7.4 Hz, 1 H), 5.20 (t, J = 10.0 Hz, 1 H), 4.08−4.01 (m, 1 H), 3.91−3.84 (m, 1 H), 0.99 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 153.2, 150.9 (d, br, $J(^{13}C-^{31}P)$ = 110.1 Hz), 140.6, (dd, $J(^{13}C-^{31}P)$ = 13.7 Hz, 3.0 Hz), 135.4 (d, $J(^{13}C-^{31}P)$ = 12.8 Hz), 134.5 (d, $J(^{13}C-^{31}P)$ = 12.7 Hz), 133.2, 132.9, 132.6, 132.3, 130.1 (d, $J(^{13}C-^{31}P)$ = 1.75 Hz), 129.9 (d, $J(^{13}C-^{31}P)$ = 1.6 Hz), 128.1 (d, $J(^{13}C-^{31}P)$ = 9.8 Hz), 127.8 (d, $J(^{13}C-^{31}P)$ = 9.7 Hz), 124.9, 122.8 (br), 120.4 (q, $J(^{13}C-^{19}F)$ = 325.8 Hz), 116.7 (br), 69.9 (d, br, $J(^{13}C-^{31}P)$ = 81.9 Hz), 59.3, 14.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ 32.19 (d, J = 30.7 Hz, 1 P), 25.6 (d, J = 30.8 Hz, 1 P); IR (KBr, cm^{-1}) 1711 (m), 1435 (s), 1384 (s); HRMS (FAB) calcd for $C_{47}H_{41}F_3NO_4P_2PdS$ (M + H$^+$) 940.1218, found 940.1206.

(+)-(*S*)-[(*N*-Ethoxycarbonylmethine)-(*N*-trifluoromethanesulfonyl)aza-1,2-phenylene] [bis(triphenylphosphine)]-palladium [(+)-4]. A solution of palladacycle (+)-**15a** (92% de) (vide infra) (1.222 g, 2.09 mmol) and Ph_3P (3.83 g, 14.60 mmol) in methylene chloride (25 mL) was stirred at room temperature for 24 h. The crude product was purified by flash chromatography over silica eluting with EtOAc/hexane (1:10) to remove excess Ph_3P and with EtOAc/hexane (1:1) to afford palladacycle (+)-**4** (1.884 g, 96%) as a white solid: mp 156−158 °C dec (CH_2Cl_2); $[\alpha]_D$ +17.6 (*c* 0.55 CH_2Cl_2).

General Procedure for the Synthesis of 1,2-Dihydroquinolines 5−12. To a solution of palladacycles (±)-**4** and (+)-**4** (1 mmol) in 1,2-dichloroethane (30 mL) at room temperature under argon was added the appropriate alkyne (2.5−3 mmol). The reaction mixtures were refluxed for the indicated time (oil bath at 85−90 °C). Solvent was removed under reduced pressure, and the crude product was separated by flash chromatography over silica eluting with ether/hexane mixtures to provide 1,2-dihydroquinolines **5**−**12** as colorless or light yellow oils or white solids.

(±)-2,3,4-Tris(ethoxycarbonyl)-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(±)-5] and (+)-(*S*)-2,3,4-Tris(ethoxycarbonyl)-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(+)-5]. Treatment of palladacycle (±)-**4** (0.180 g, 0.191 mmol) and diethyl acetylenedicarboxylate (0.097 mL, 0.097 g, 0.573 mmol) for 1 h according to the general procedure described above, eluting with hexane/ether (10:1) afforded 1,2-dihydroquinoline (±)-**5** (0.082 g, 89%) as a colorless oil: R_f = 0.39 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s br, 1 H), 7.49−7.44 (m, 2 H), 7.33 (t, J = 7.5 Hz, 1 H), 6.10 (s, 1 H), 4.41 (q, J = 7.1 Hz, 2 H), 4.38−4.30 (m, 2 H), 4.17−4.11 (m, 1 H), 4.08−4.02 (m, 1 H), 1.37 (t, J = 7.1 Hz, 3 H), 1.34 (t, J = 7.1 Hz, 3 H), 1.14 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 165.4, 162.5, 137.8, 132.9, 131.8, 127.8, 126.7, 125.0, 124.1, 122.9, 119.8 (q, $J(^{13}C-^{19}F)$ = 323.1 Hz), 62.7, 62.3, 62.2, 56.2, 14.1, 13.9, 13.8; IR (neat, cm^{-1}) 1739 (s), 1227 (s); HRMS (FAB) calcd for $C_{19}H_{21}F_3NO_8S$ (M + H$^+$) 480.0940, found 480.0924.

Preparation of (+)-5. Treatment of palladacycle (+)-**4** (generated from complex (+)-**15a** with 92% de) (0.207 g, 0.220 mmol) and diethyl acetylenedicarboxylate (0.11 mL, 0.112 g,

0.660 mmol) for 1 h according to the general procedure described above, eluting with hexane/ether (5:1) afforded 1,2-dihydroquinoline (+)-**5** (0.092 g, 87%) as a colorless oil in 91.3% ee (by HPLC): $[\alpha]_D$ +181.5 (*c* 0.80 CH_2Cl_2).

(±)-2,3-Bis(ethoxycarbonyl)-4-methyl-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(±)-6] and (+)-(*S*)-2,3-Bis(ethoxycarbonyl)-4-methyl-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(+)-6]. Treatment of palladacycle (±)-**4** (0.180 g, 0.191 mmol) and ethyl 2-butynoate (0.055 mL, 0.053 g, 0.477 mmol) for 8 h according to the general procedure described above, eluting with hexane/ether (10:1) afforded 1,2-dihydroquinoline (±)-**6** (0.043 g, 55%) as a colorless oil that crystallized on standing providing a white solid: mp 46−48 °C (hexane/ether 10:1); R_f = 0.50 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s br, 1 H), 7.56 (dd, J = 7.8 Hz, 1.3 Hz, 1 H), 7.41 (td, J = 7.7 Hz, 1.5 Hz, 1 H), 7.35 (td, J = 7.7 Hz, 1.0 Hz, 1 H), 6.10 (s, 1 H), 4.38−4.31 (m, 2 H), 4.11−4.08 (m, 1 H), 4.02−3.98 (m, 1 H), 2.56 (s, 3 H), 1.36 (t, J = 7.1 Hz, 3 H), 1.11 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 164.7, 141.8, 132.7, 130.5, 130.2, 127.5, 126.2, 124.7, 123.1, 119.9 (q, $J(^{13}C-^{19}F)$ = 322.5 Hz), 62.3, 61.4, 57.3, 16.2, 14.2, 13.8; IR (KBr, cm^{-1}) 1752 (s), 1713 (s); HRMS (FAB) calcd for $C_{17}H_{19}F_3NO_6S$ ($M + H^+$) 422.0885, found 422.0881.

Preparation of (+)-6. Treatment of palladacycle (+)-**4** (generated from complex (+)-**15a** with 92% de) (0.207 g, 0.220 mmol) and ethyl 2-butynoate (0.063 mL, 0.0617 g, 0.55 mmol) for 8 h according to the general procedure described above, eluting with hexane/ether (10:1), afforded 1,2-dihydroquinoline (+)-**6** (0.048 g, 54%) as a colorless oil in 91.3% ee (by HPLC): $[\alpha]_D$ +237.1 (*c* 1.75 CH_2Cl_2).

(±)-2-Ethoxycarbonyl-3-methoxycarbonyl-4-*n*-pentyl-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(±)-7] and (+)-(*S*)-2-Ethoxycarbonyl-3-methoxycarbonyl-4-*n*-pentyl-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(+)-7]. Treatment of palladacycle (±)-**4** (0.180 g, 0.191 mmol) and methyl 2-octynoate (0.080 mL, 0.074 g, 0.477 mmol) for 7 h according to the general procedure described above, eluting with hexane/ether (20:1), afforded 1,2-dihydroquinoline (±)-**7** (0.054 g, 61%) as a light yellow oil: R_f = 0.61 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s br, 1 H), 7.59 (dd, J = 7.9 Hz, 1.2 Hz, 1 H), 7.42 (t, J = 7.7 Hz, 1 H), 7.35 (t, J = 7.53 Hz, 1 H), 6.06 (s, 1 H), 4.11−3.99 (m, 2 H), 3.87 (s, 3 H), 3.35−3.23 (m, 1 H), 2.91−2.86 (m, 1 H), 1.46−1.30 (m, 6 H), 1.10 (t, J = 7.1 Hz, 3 H), 0.89 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 164.9, 147.3, 133.3, 130.6, 128.9, 127.5, 126.2, 124.9,121.9, 119.8 (q, $J(^{13}C-^{19}F)$ = 322.2 Hz), 62.3, 57.4, 52.3, 32.0, 29.3, 28.7, 22.4, 13.9, 13.8; IR (neat, cm^{-1}) 1752 (s), 1721 (s); HRMS (FAB) calcd for $C_{20}H_{25}F_3NO_6S$ ($M + H^+$) 464.1355, found 464.1326.

Preparation of (+)-7. Treatment of palladacycle (+)-**4** (generated from complex (+)-**15a** with 92% de) (0.207 g, 0.22 mmol) and methyl 2-octynoate (0.092 mL, 0.085 g, 0.55 mmol) for 7 h according to the general procedure described above, eluting with hexane/ether (20:1), afforded 1,2-dihydroquinoline (+)-**7** (0.058 g, 57%) as a light yellow oil in 81.9% ee (by HPLC): $[\alpha]_D$ +166.2 (*c* 0.66 CH_2Cl_2).

(±)-4-(1-Cyclohexenyl)-2-ethoxycarbonyl-3-methoxycarbonyl-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(±)-8] and (+)-(*S*)-4-(1-Cyclohexenyl)-2-ethoxycarbonyl-3-methoxycarbonyl-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(+)-8]. Treatment of palladacycle (±)-**4** (0.180 g, 0.191 mmol) and methyl 3-(1-cyclohexenyl)-2-propynoate[47] (0.078 g, 0.477 mmol) for 9 h according to the general procedure described above, eluting with hexane/ether (10:1), afforded 1,2-dihydroquinoline (±)-**8** (0.056 g, 62%) as a light yellow oil, containing less than 4% of a chromatographically inseparable regioisomeric product ((±)-3-(1-cyclohexenyl)-2-ethoxycarbonyl-4-methoxycarbonyl-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline). Analytical data for 1,2-dihydroquinoline (±)-**8**: (R_f = 0.60 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s br, 1 H), 7.49 (d, J = 7.4 Hz, 1 H), 7.40 (t, J = 7.9 Hz, 1 H), 7.31 (t, J = 7.5 Hz, 1 H), 6.02 (s, 0.96 H), 5.90 (s, 0.04 H), 5.55 (s, 0.96 H), 5.51 (s, 0.04), 4.07 (qd, J = 7.1 Hz, 1.8 Hz, 2 H), 3.82 (s, 2.88 H), 3.80 (s, 0.12 H), 2.23−2.16 (m, 2 H), 2.11−2.05 (m, 2 H), 1.84−1.77 (m, 2 H), 1.77−1.69 (m, 2 H), 1.11 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 164.5, 148.3, 133.7, 133.0, 130.7, 128.5, 128.1, 127.4, 126.8, 124.7, 120.3, 119.9 (q, $J(^{13}C-^{19}F)$ = 322.7 Hz), 62.2, 57.2, 52.1, 28.8, 25.1, 22.6, 21.8, 13.8; IR (neat, cm^{-1}) 1750 (s), 1702 (s); HRMS (FAB) calcd for $C_{21}H_{22}F_3NO_6S$ (M^+) 473.1120, found 473.1118.

Preparation of (+)-8. Treatment of palladacycle (+)-**4** (0.180 g, 0.191 mmol) (generated from complex (+)-**15a** with 92% de) and methyl 3-(1-cyclohexenyl)-2-propynoate[47] (0.078 g, 0.477 mmol) for 9 h according to the general procedure described above, eluting with hexane/ether (6:1), afforded 1,2-dihydroquinoline (+)-**8** (0.052 g, 56%) as a light yellow oil in 86% ee (by ^{1}H NMR with Eu(hfc)$_3$): $[\alpha]_D$ +123.9 (*c* 1.45 CH_2Cl_2).

(±)-2,3-Bis(ethoxycarbonyl)-4-trimethylsilyl-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(±)-9] and (+)-(*S*)-2,3-Bis(ethoxycarbonyl)-4-trimethylsilyl-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(+)-9]. Treatment of complex (±)-**4** (0.180 g, 0.191 mmol) and ethyl (3-trimethylsilyl)propynoate (0.109 mL, 0.097 g, 0.573 mmol) for 18 h according to the general procedure described above, eluting with hexane/ether (10:1), afforded 1,2-dihydroquinoline (±)-**9** (0.058 g, 63%) as a colorless oil that solidified at room temperature providing a white solid: mp 88−90 °C; R_f = 0.63 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 7.9 Hz, 1 H), 7.37−7.34 (m, 2 H), 7.28 (t, J = 6.9 Hz, 1 H), 5.99 (s, 1 H), 4.45−4.38 (m, 1 H), 4.29−4.22 (m, 1 H), 4.11−4.05 (m, 1 H), 4.00−3.90 (m, 1 H), 1.36 (t, J = 7.1 Hz, 3 H), 1.09 (t, J = 7.1 Hz, 3 H), 0.29 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 166.0, 146.8, 139.9, 132.7, 131.7, 129.4, 128.7, 126.9, 126.1, 120.0 (q, $J(^{13}C-^{19}F)$ = 323.2 Hz), 62.3, 61.9, 57.7, 14.1, 13.8, 1.0 (3 carbons); IR (KBr, cm^{-1}) 1752 (s), 1714 (s); HRMS (FAB) calcd for $C_{19}H_{25}F_3NO_6SSi$ ($M + H^+$) 480.1124, found 480.1104.

Preparation of (+)-9. Treatment of palladacycle (+)-**4** (generated from complex (+)-**15a** with 92% de) (0.180 g, 0.191 mmol) and ethyl (3-trimethylsilyl)propynoate (0.109 mL, 0.097 g, 0.573 mmol) for 12 h according to the general procedure described above, eluting with hexane/ether (6:1), afforded 1,2-dihydroquinoline (+)-**9** (0.052 g, 57%) as a colorless oil that solidified at room temperature providing a white solid in 80% ee (by ^{1}H NMR with Eu(hfc)$_3$): mp 88−90 °C; $[\alpha]_D$ +203.6 (*c* 1.24 CH_2Cl_2).

(±)-2,3-Bis(ethoxycarbonyl)-4-phenyl-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(±)-10a] and (±)-2,4-Bis(ethoxycarbonyl)-3-phenyl-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(±)-10b]. Treatment of palladacycle (±)-**4** (0.180 g, 0.191 mmol) and ethyl phenylpropiolate (0.070 mL, 0.069 g, 0.477 mmol) for 13 h according to the general procedure described above, eluting with hexane/ether (10:1), afforded a chromatographically inseparable mixture of two regioisomeric 1,2-dihydroquinolines (±)-**10a** and (±)-**10b** in 92:8 ratio (by ^{1}H NMR) (0.061 g, 64%) as a white solid: R_f = 0.47 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s br, 0.92 H), 7.64 (d, J = 6.8 Hz, 0.08 H), 7.56 (d, J = 7.3 Hz, 0.08 H), 7.46−7.42 (m, 4 H), 7.39 (t, J = 7.4 Hz, 1 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.20−7.07 (s br, 1 H), 6.90 (dd, J = 7.8 Hz, 1.06 Hz, 0.92 H), 6.20 (s, 0.92 H), 5.77 (s, 0.08 H), 4.29 (q, J = 7.1 Hz, 0.16 H), 4.18−4.10 (m, 2 H), 4.04 (q, J = 7.1 Hz, 1.84 H), 1.17 (t, J = 7.11 Hz, 2.76 H), 1.04 (t, J = 7.1 Hz, 0.24 H), 0.95 (t, J = 7.1 Hz, 2.76 H), 0.91 (t, J = 7.1 Hz, 0.24 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 164.1, 145.2, 136.3, 132.8, 130.8, 129.8, (129.4), 129.3, (128.9), 128.6 (two carbons), 128.1-(two carbons), 128.0, (127.7), 127.3, (125.6), 124.6, 122.8, 120.0 (q, $J(^{13}C-^{19}F)$ = 343.7 Hz), 62.5, (61.4), 61.1, 57.4, 13.9, (13.7),

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13.6, (13.5) (arbitrarily assigned signals for the minor regioisomer (±)-**10b** are shown in parentheses).

Crystallization via a slow diffusion of hexanes into an ether solution of the mixture of dihydroquinolines (±)-**10a** and (±)-**10b** afforded white crystals of pure 1,2-dihydroquinoline (±)-**10a**: mp 84−86 °C(ether/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s br, 1 H), 7.46−7.42 (m, 4 H), 7.39 (t, J = 7.4 Hz, 1 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.20−7.07 (s br, 1 H), 6.90 (d, J = 7.8 Hz, 1 H), 6.20 (s, 1 H), 4.18−4.10 (m, 2 H), 4.04 (q, J = 7.1 Hz, 2 H), 1.17 (t, J = 7.11 Hz, 3 H), 0.95 (t, J = 7.1 Hz, 3 H); IR (KBr, cm^{-1}) 1732 (s); HRMS (FAB) calcd for $C_{22}H_{21}F_3NO_6S$ (M + H$^+$) 484.1042, found 484.1032.

(±)-2-Ethoxycarbonyl-3-methoxycarbonyl-4-(4-methoxyphenyl)-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(±)-11a], (±)-2-Ethoxycarbonyl-4-methoxycarbonyl-3-(4-methoxyphenyl)-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(±)-11b], (+)-(*S*)-2-Ethoxycarbonyl-3-methoxycarbonyl-4-(4-methoxyphenyl)-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(+)-11a], and (*S*)-2-Ethoxycarbonyl-4-methoxycarbonyl-3-(4-methoxyphenyl)-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline (11b). Treatment of palladacycle (±)-**4** (0.180 g, 0.191 mmol) and methyl (*p*-methoxy)phenylpropiolate[47] (0.090 g, 0.477 mmol) for 13 h according to the general procedure described above, eluting with hexane/ether (3:1), afforded a chromatographically inseparable mixture of two regioisomeric 1,2-dihydroquinolines (±)-**11a** and (±)-**11b** in 91:9 ratio (by ^{1}H NMR) (0.056 g, 59%) as a white solid: R_f = 0.44 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s br, 0.91 H), 7.56 (dd, J = 7.74 Hz, 1.3 Hz, 0.09 H), 7.40 (td, J = 7.8 Hz, 1.3 Hz, 0.91 H), 7.37 (td, J = 7.8 Hz, 1.5 Hz, 0.09 H), 7.31 (t, J = 7.8 Hz, 0.09 H), 7.18 (t, J = 7.8 Hz, 0.91 H), 7.10 (s br, 2 H), 6.97 (d, J = 8.9 Hz, 2 H), 6.93 (d, J = 7.9 Hz, 1 H), 6.17 (s, 0.91 H), 5.75 (s, 0.09 H), 4.18−4.08 (m, 1.82 H), 4.03 (q, J = 7.1 Hz, 0.18 H), 3.88 (s, 2.73 H), 3.86 (s, 0.27 H), 3.67 (s, 2.73 H), 3.61 (s, 0.27 H), 1.16 (t, J = 7.1 Hz, 2.73 H), 1.03 (t, J = 7.1 Hz, 0.27 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (167.3), 167.1, (166.1), 164.4, (160.2), 159.6, 145.8, 136.7, 132.9, 130.8, 130.1, 129.5, 129.3, (129.2), 127.9, 127.3, 125.6, 124.5, 121.9, 120.0 (q, J(^{13}C−^{19}F) = 323.2 Hz), (114.1), 113.5, 62.5, 57.5, (55.3), 55.2, (52.3), 52.2, 13.9, (13.7) (arbitrarily assigned signals for the regioisomer (±)-**11b** are shown in parentheses).

Crystallization via a slow diffusion of hexanes into an ether solution of the mixture of dihydroquinolines (±)-**11a** and (±)-**11b** afforded white crystals of pure 1,2-dihydroquinoline (±)-**11a**: mp 116−118 °C (ether/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, br, 1 H), 7.39 (t, J = 7.4 Hz, 1 H), 7.18 (t, J = 7.7 Hz, 1 H), 7.04 (s, br, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 7.8 Hz, 1 H), 6.16 (s, 1 H), 4.20−4.05 (m, 2 H), 3.87 (s, 3 H), 3.63 (s, 3 H), 1.16 (t, J = 7.1 Hz, 3 H); IR (KBr, cm^{-1}) 1751 (s), 1726 (s); HRMS (FAB) calcd for $C_{22}H_{21}F_3NO_7S$ (M + H$^+$) 500.0991, found 500.0984.

Preparation of (+)-11a and 11b. Treatment of palladacycle (+)-**4** (generated from complex (+)-**15a** with 92% de) (0.180 g, 0.191 mmol) and methyl (*p*-methoxy)phenylpropiolate[47] (0.090 g, 0.477 mmol) for 13 h according to the general procedure described above, eluting with hexane/ether (3:1), afforded a mixture of two regioisomeric 1,2-dihydroquinolines (+)-**11a** and **11b** in 94:6 ratio (by ^{1}H NMR) (0.054 g, 57%) as a white solid in 90.6% ee for the major isomer (+)-**11a** (by HPLC) (chromatographic signal for the (*R*)-enantiomer of the minor regioisomer **11b** could not be detected**)**: $[\alpha]_D$ +91.9 (*c* 0.69 CH_2Cl_2).

(±)-2-Ethoxycarbonyl-3-methoxycarbonyl-4-(4-fluorophenyl)-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(±)-12a] and (±)-2-Ethoxycarbonyl-4-methoxycarbonyl-3-(4-fluorophenyl)-*N*-trifluoromethanesulfonyl-1,2-dihydroquinoline [(±)-12b]. Treatment of palladacycle (±)-**4** (0.180 g, 0.191 mmol) and methyl (*p*-fluoro)phenylpropiolate[47] (0.085 g, 0.4775 mmol) for 13 h according to the general procedure described above, eluting with hexane/ether (10:1), afforded a chromatographically inseparable mixture of two regioisomeric 1,2-dihydroquinolines (±)-**12a** and (±)-**12b** in 91:9 ratio (by ^{1}H NMR) (0.065 g, 70%) as a light yellow solid: R_f = 0.56 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s br, 0.9 H), 7.57 (d, J = 7.8 Hz, 0.1 H), 7.41 (td, J = 8.8 Hz, 1.4 Hz, 0.9 H), 7.33 (t, J = 7.7 Hz, 0.1 H), 7.20 (t, J = 7.8 Hz, 1 H), 7.22−7.02 (m, 4 H), 6.86 (dd, J = 7.9 Hz, 1.3 Hz, 1 H), 6.2 (s, 0.9 H), 5.71 (s, 0.1 H), 4.19−4.09 (m, 1.8 H), 4.03 (q, J = 7.1 Hz, 0.2 H), 3.63 (s, 2.7 H), 3.60 (s, 0.3 H), 1.17 (t, J = 7.1 Hz, 2.7 H), 1.04 (t, J = 7.1 Hz, 0.3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9 (166.8), (166.0), 164.1, [162.9 (d, J(^{13}C−^{19}F) = 248.4 Hz)], 162.7 (d, J(^{13}C−^{19}F) = 246.5 Hz), 144.9, 135.8, 132.8, 131.7 (d, J(^{13}C−^{19}F) = 3.5 Hz), 131.0, 130.5 (d, J(^{13}C−^{19}F) = 8.0 Hz), 129.9 (d, J(^{13}C−^{19}F) = 8.2 Hz), (129.6), 129.2, 127.4, (125.7), 124.7, 122.6, 120.0 (q, J(^{13}C−^{19}F) = 322.4 Hz), 116.0 (d, J(^{13}C−^{19}F) = 26.2 Hz), 115.3 (d, J(^{13}C−^{19}F) = 21.5 Hz), 62.5, (61.4), 57.4, (52.4), 52.3, 13.8 (13.7) (arbitrarily assigned signals for the regioisomer (±)-**12b** are shown in parentheses or brackets).

Crystallization via a slow diffusion of hexanes into an ether solution of the mixture of dihydroquinolines (±)-**12a** and (±)-**12b** afforded white crystals of pure 1,2-dihydroquinoline (±)-**12a**: mp 152−154 °C (ether/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, br, 1 H), 7.41 (t, J = 7.8 Hz, 1 H), 7.20 (t, J = 7.7 Hz, 1 H), 7.18−7.13 (m, 4 H), 6.86 (d, J = 7.3 Hz, 1 H), 6.17 (s, 1 H), 4,19−4.09 (m, 2 H), 3.63 (s, 3 H), 1.16 (t, J = 7.1 Hz, 3 H); IR (KBr, cm^{-1}) 1742 (s), 1731 (s); HRMS (FAB) calcd for $C_{21}H_{18}F_4NO_6S$ (M + H$^+$) 488.0791, found 488.0779.

(−)-[(*N*-Ethoxycarbonylmethyl)-(*N*-trifluoromethanesulfonyl)-2-aminophenyl]iodo[(1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane]palladium [(−)-13]. To a solution of *(1R,2R)-N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane (TMCDA)[28] (1.226 g, 7.20 mmol) in benzene (120 mL) at room temperature under argon were added tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) (2.747 g, 3.00 mmol) and aryl iodide **1a** (2.885 g, 6.60 mmol). The mixture was stirred at 55 °C for 1 h. The suspension was filtered through a plug of Celite, and solvents were removed under reduced pressure to afford a crude product. The crude product was purified by flash chromatography over silica eluting with EtOAc/hexane (1:10) to remove excess dibenzylideneacetone (dba), and subsequently with EtOAc/hexane (1:1) to afford palladium(II) complex (−)-**13** (3.50 g, 82%) as a light yellow solid, with ratios of atropisomers (by ^{1}H NMR) ranging from 42:58 to 8:92, depending on the reaction scale and amount of silica used: mp 190−192 °C dec (CH_2Cl_2/hexane); R_f = 0.63 (hexane/EtOAc 1:1). The products (−)-**13** with various ratios of atropisomers were converted into material with an uniform ratio of atropisomers 98:2 by the procedure(s) described below:

Protocol for Interconversion of Conformational Isomers (Atropisomers) of (−)-13. (a) A solution of complex (−)-**13** with the ratio of atropisomers 58:42 (3.40 g, 4.76 mmol) in methylene chloride (50 mL) was stirred at room temperature under argon for 36 h. Solvents were removed under reduced pressure to afford the recovered complex (−)-**13** (3.40 g, 100%) as a light yellow solid with the ratio of atropisomers 82:18 (by ^{1}H NMR).

(b) A suspension of complex (−)-**13** with the ratio of atropisomers 82:18 (3.00 g, 4.20 mmol) and silica (30 g) in EtOAc (300 mL) was stirred at room temperature under argon for 96 h. The suspension was filtered, and the silica was eluted with EtOAc to afford recovered complex (−)-**13** (2.95 g, 98%) as a light yellow solid with the ratio of atropisomers 98:2 (by ^{1}H NMR). A solution of the recovered complex (−)-**13** with 98:2 initial ratio of atropisomers was kept in $CDCl_3$ for 24 h at room temperature. Subsequent ^{1}H NMR analysis indicated that equilibration to 88:12 ratio of atropisomers occurred.

Analytical Data for (−)-13 with the Ratio of Atropisomers 12:88. $[\alpha]_D$ −43.3 (*c* 0.52 CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, J = 7.1 Hz, 2.5 Hz, 0.12 H), 7.45 (t, J = 7.4 Hz, 1.88 H), 7.25 (dd, J = 7.0 Hz, 1.9 Hz, 0.12 H), 7.00 (td, J = 7.5 Hz, 1.3 Hz, 0.88 H), 6.89 (t, J = 7.9 Hz, 1 H), 6.41 (d, J = 18.7 Hz, 0.12 H), 5.51 (d, J = 18.9 Hz, 0.88 H), 4.81 (d, J =

18.7 Hz, 1 H), 4.28−4.08 (m, 2 H), 2.98 (td, J = 11.5 Hz, 3.9 Hz, 1 H), 2.96 (s, 0.36 H), 2.90 (s, 2.64 H), 2.76 (s, 2.64 H), 2.72 (s, 2.64 H), 2.71 (s, 0.36 H), 2.70 (s, 0.36 H), 2.50 (td, J = 11.5 Hz, 3.7 Hz, 1 H), 2.45 (s, 0.36 H), 2.08−2.00 (m, 2 H), 2.00 (s, 2.64 H), 1.86 (d br, J = 10.7 Hz, 1 H), 1.77 (d, J = 10.6 Hz, 1 H), 1.42−1.24 (m, 2 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.20−1.07 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3 (167.8), 144.1, 143.2, (142.6), (140.6), (139.6), 136.9, 130.2, 127.2, 123.9, 123.6 (q, $J(^{13}C-^{19}F)$ = 512 Hz), (123.6), (118.8), (70.3), 69.3, 66.9 (66.7), 61.3, 54.7, (52.0), (50.3), 49.3, (49.2), 47.1, (43.0), 42.3 (42.1), 40.7, 24.9, (24.6), (24.5), 24.4, 23.8, (23.4), (23.2), 22.7, (14.1), 14.0 (signals for the minor atropisomer are indicated in parentheses); IR (KBr, cm^{-1}) 1759 (s); HRMS (FAB) calcd for $C_{21}H_{37}F_3N_4IO_4SPd$ ($M + NH_4^+$) 731.0567 found 731.0579. Anal. Calcd for $C_{21}H_{33}F_3IN_3O_4PdS$: C, 35.33; H, 4.66; N, 5.89. Found: C, 35.31; H, 4.75; N, 5.91.

(+)-[2-(Ethoxycarbonylmethoxy)phenyl]iodo[(1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane]palladium [(+)-14]. To a solution of *(1R,2R)-N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane (TMCDA)[28] (0.613 g, 3.60 mmol) and ethyl (2-iodophenoxy)acetate[19] **1b** (0.992 g, 3.24 mmol) in benzene (60 mL) at room temperature under argon was added tris(dibenzylidene)dipalladium (Pd_2dba_3) (1.374 g, 1.50 mmol). The mixture was stirred at 55 °C for 1 h. The suspension was filtered through a plug of Celite, and solvents were removed under reduced pressure to afford a crude product. The crude product was purified by flash chromatography over silica eluting with EtOAc/hexane (1:10) to remove excess dibenzylideneacetone (dba), and subsequently with EtOAc/hexane (1:1) to afford palladium(II) complex (+)-**14** (1.480 g, 85%) as a light yellow solid with the ratio of atropisomers (by ^{1}H NMR) of 60:40: mp 132−134 °C (CH_2Cl_2/hexane); R_f = 0.53 (hexane/EtOAc 1:1); $[\alpha]_D$ +9.6 (c 0.76 CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (dd, J = 7.2 Hz, 1.5 Hz, 0.4 H), 7.21 (dd, J = 7.3 Hz, 1.5 Hz, 0.6 H), 6.79 (q, J = 7.2 Hz, 1 H), 6.71 (t, J = 7.2 Hz, 1 H), 6.47 (d, J = 7.9 Hz, 1 H), 5.06 (d, J = 16.1 Hz, 0.6 H), 5.00 (d, J = 16.2 Hz, 0.4 H), 4.58 (d, J = 16.2 Hz, 0.4 H), 4.56 (d, J = 16.1 Hz, 0.6 H), 4.28−4.21 (m, 2 H), 2.91−2.86 (m, 0.6 H), 2.90 (s, 1.2 H), 2.87 (s, 1.8 H), 2.75 (td, J = 11.5 Hz, 4.0 Hz, 0.4 H), 2.65 (s, 1.8 H), 2.63 (s, 1.2 H), 2.60 (s, 1.2 H), 2.54−2.46 (m, 1 H), 2.52 (s, 1.8 H), 2.33 (s, 1.8 H), 2.30 (s, 1.2 H), 2.10−1.95 (m, 2 H), 1.85−1.75 (m, 2 H), 1.31−1.21 (m, 2 H), 1.30 (t, J = 7.1 Hz, 1.8 H), 1.29 (t, J = 7.1 Hz, 1.2 H), 1.15−1.03 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 160.6, (160.2), 139.5, 137.7, (133.6), (132.7), 123.7, (123.6), (121.8), 121.5, (114.2), 113.9, (70.2), 69.7, (67.2), 66.9, 66.8, (66.4), 60.6, (49.6), (49.1), 49.0, 47.7, (42.2), (41.7), 41.2, 41.1, 24.7, 24.6, (24.6), (23.3), 23.3, 23.2, (23.1), 14.2 (signals for the minor atropisomer are indicated in parentheses); IR (KBr, cm^{-1}) 1752 (s); HRMS (FAB) calcd for $C_{20}H_{37}N_3IO_3Pd$ ($M^+ + NH_4^+$) 600.0914, found 600. 0887. Anal. Calcd for $C_{20}H_{33}IN_2O_3PdS$: C, 41.22; H, 5.71; N, 4.81. Found: C, 41.21; H, 5.85; N, 4.85.

(+)-[(*S*)-(*N*-Ethoxycarbonylmethine)-(*N*-trifluoromethanesulfonyl)aza-1,2-phenylene][(1*R*,2*R*)-(*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane)]palladium [(+)-15a]. A suspension of AgOAc (0.501 g, 3.00 mmol) and palladium(II) complex (−)-**13** with the ratio of atropisomers 98:2 (0.714 g, 1.00 mmol) (by ^{1}H NMR) in THF (40 mL) was stirred at room temperature under argon for 10 min. The suspension was cooled to −78 °C, and stirring was continued for an additional 30 min. Then, *t*-BuOK (1 M solution in THF, 1.2 mL, 1.2 mmol) was added dropwise, and the reaction mixture was stirred for additional 10 min at −78 °C. Sodium bicarbonate ($NaHCO_3$, 0.336 g, 4.00 mmol) was added, and the reaction mixture was allowed to warm to room temperature before it was filtered through a plug of basic alumina eluting with EtOAc/hexane (2:1). Solvents were removed under reduced pressure to afford palladacycle (+)-**15a** (0.579 g, 99%) as a white solid in 92% de (**15a**:**15b** = 96:4 by ^{1}H NMR): mp 200−202 °C dec (EtOAc/hexane, 2:1); R_f = 0.30 (hexane/EtOAc 1:1); $[\alpha]_D$ +227.2 (c 0.47, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (s br, 0.96 H), 7.15 (d, J = 7.7 Hz, 0.04 H), 7.04 (d, J = 7.4 Hz, 1 H), 6.96 (td, J = 7.5 Hz, 0.9 Hz, 1 H), 6.87 (t, J = 7.4 Hz, 1 H), 5.16 (s, 0.04 H), 4.81 (s. 0.96 H), 4.12−3.80 (m, 2 H), 2.91 (s, 0.12 H), 2.87 (s, 0.12 H), 2.79 (s, 2.88 H), 2.76 (s, 2.88 H), 2.74 (s, 3 H), 2.70 (s, 3 H), 2.60 (td, J = 11.5 Hz, 3.8 Hz, 1 H), 2.52 (td, J = 11.5 Hz, 3.9 Hz, 1 H), 2.09 (t br, J = 10.9 Hz, 2 H), 1.84 (d br, J = 9.5 Hz, 2 H), 1.34−1.22 (m, 2 H), 1.16−1.06 (m, 2 H), 1.01 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 153.7, 143.2, 133.0, 124.7, 123.2, 120.2 (q, $J(^{13}C-^{19}F)$ = 324.8 Hz), 116.1, 69.1, (68.6), 67.4 (67.1), 60.8 (br), (59.6), 59.4, 48.7, 48.5, 41.5, 40.9, (38.7), (25.1), 24.7, 24.6, (24.5), (23.5), 22.7, 22.5, (21.9), 13.9 (signals for the minor diastereomer are indicated in parentheses); IR (KBr, cm^{-1}) 1717 (m), 1683 (s); HRMS (FAB) calcd for $C_{21}H_{33}F_3N_3O_4SPd$ ($M + H^+$) 586.1179, found 586.1166. Anal. Calcd for $C_{21}H_{32}F_3N_3O_4PdS$: C, 43.04; H, 5.50; N, 7.17. Found: C, 42.99; H, 5.56; N, 7.19.

Crystallization via a slow diffusion of hexanes into a methylene chloride solution of the palladacycle (+)-**15a** in 92% de (96:4 ratio of diastereomers **15a**:**15b**) afforded white crystals of pure diastereomer (+)-**15a**: mp 200−202 °C (ether/methylene chloride); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (s br, 1 H), 7.04 (d, J = 7.4 Hz, 1 H), 6.96 (td, J = 7.5 Hz, 0.9 Hz, 1 H), 6.87 (t, J = 7.4 Hz, 1 H), 4.81 (s. 1 H), 4.01−3.85 (m, 2 H), 2.79 (s, 3 H), 2.76 (s, 3 H), 2.74 (s, 3 H), 2.70 (s, 3 H), 2.60 (td, J = 11.5 Hz, 3.8 Hz, 1 H), 2.52 (td, J = 11.5 Hz, 3.9 Hz, 1 H), 2.09 (t br, J = 10.9 Hz, 2 H), 1.84 (d br, J = 9.5 Hz, 2 H), 1.34−1.22 (m, 2 H), 1.16−1.06 (m, 2 H), 1.01 (t, J = 7.1 Hz, 3 H).

(−)-[(*S*)-(Ethoxycarbonylmethineoxy-1,2-phenylene)]-[(1*R*,2*R*)-(*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane)]-palladium [(−)-16a]. To a solution of palladium(II) complex (+)-**14** (0.117 g, 0.200 mmol) in THF (8 mL) at room temperature under argon was added dropwise *t*-BuOK (1 M solution in THF, 0.24 mL, 0.24 mmol). The reaction mixture was stirred for 1 h at room temperature. The suspension was filtered through a plug of basic alumina eluting with EtOAc/hexane (2:1), and solvents were removed under reduced pressure to afford palladacycle (−)-**16a** (0.090 g, 99%) as a pale yellow solid in 64% de (**16a**:**16b** = 82:18 by ^{1}H NMR): mp 168−170 °C dec (EtOAc/hexane 2:1); R_f = 0.71 (hexane/EtOAc 1:3); $[\alpha]_D$ −153.7 (c 0.62 CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, J = 7.5 Hz, 1.2 Hz, 0.82 H), 6.99 (dd, J = 7.5 Hz, 1.2 Hz, 0.18 H), 6.92 (t, J = 7.7 Hz, 1 H), 6.67 (dd, J = 7.8 Hz, 1.1 Hz, 0.82 H), 6.67−6.65 (m, 0.18 H), 6.63−6.61 (m, 0.18 H), 6.62 (td, J = 7.4 Hz, 1.1 Hz, 0.82 H), 5.69 (s, 0.82 H), 5.30 (s, 0.18 H), 4.13−4.07 (m, 2 H), 2.96 (s, 2.46 H), 2.87 (s, 2.46 H), 2.81 (s, 0.54 H), 2.76 (s, 0.54 H), 2.75 (s, 0.54 H), 2.71 (td, J = 11.5 Hz, 4.1 Hz, 1 H), 2.68 (s, 0.54 H), 2.65 (s, 2.46 H), 2.54 (td, J = 11.6 Hz, 3.8 Hz, 1 H), 2.50 (s, 2.46 H), 2.09−2.04 (m, 2 H), 1.85−1.75 (m, 2 H), 1.36−1.21 (m, 4 H), 1.18 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, (178.1), 173.9, (172.9), (138.9), 137.7, 133.3, (133.2), 125.5, (125.2), (118.0), 117.5, 108.4, (108.3), 87.5, (86.9), (68.7), 68.5, (67.3), 67.3, 59.4, (59.1), 48.7, (48.53), (48.51), 47.6, 42.8, (41.6), (41.0), 38.1, 25.0, (24.8), (24.7), 24.4, 23.5, (22.7), (22.6), (22.3), 21.6, 14.3, (14.2) (signals for the minor diastereomer are indicated in parentheses); IR (KBr, cm^{-1}) 1712 (s); HRMS (FAB) calcd for $C_{20}H_{33}N_2O_3Pd$ ($M + H^+$) 455.1526, found 455.1537.

(−)-[(*S*)-Ethoxycarbonylmethineoxy-1,2-phenylene]-[1,2-bis(diphenylphosphino)ethane]palladium [(−)-17].[11] A solution of complex (−)-**16a** (0.045 g, 0.100 mmol) (60% de) and dppe (0.079 g, 0.199 mmol) in methylene chloride (3 mL) was stirred for 16 h at room temperature under argon. The crude reaction mixture was purified by flash chromatography over silica eluting with EtOAc/hexane (1:10), to remove excess dppe and with EtOAc/hexane (1:1) to afford palladacycle (−)-**17** (0.064 g, 94%) as a white solid in 59.6% ee (by HPLC): mp 214−216 °C dec (EtOAc/hexane, 1:1) (lit.[11] 213−214 °C); R_f = 0.70 (hexane/EtOAc 1:1); $[\alpha]_D$ −72.2 (c 0.54 CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94−7.90 (m, 2 H), 7.78−7.69 (m 6 H), 7.50−7.38 (m, 12 H), 6.95 (ddd, J = 7.9 Hz, 3.4 Hz, 1.3 Hz, 1 H), 6.91 (dd, J = 7.0 Hz, 1.3 Hz, 1 H), 6.89−6.85 (m, 1 H),

6.31 (dd, J = 9.9 Hz, 3.8 Hz 1 H), 6.26 (tt, J = 7.2 Hz, 1.6 Hz, 1 H), 3.86 (dq, J = 7.1 Hz, 3.4 Hz, 1 H), 3.22 (dq, J = 7.1 Hz, 3.6 Hz, 1 H), 2.64−2.48 (m, 1 H), 2.38−2.25 (m, 1 H), 2.06−1.99 (m, 1 H), 1.85−1.74 (m, 1 H), 0.76 (t, J = 7.1 Hz, 3 H).

(−)-[(*S*)-Ethoxycarbonylmethineoxy-1,2-diphenylene]-[bis(trisphenylphosphine)] palladium [(−)-18].[9] A solution of palladacycle **(−)-16a** (64% de) (0.426 g, 0.936 mmol) and PPh_3 (0.983 g, 3.75 mmol) in methylene chloride (9.4 mL) was stirred at room temperature for 16 h. Trituration of the crude product with small amounts of ether afforded palladacycle (−)-**18** (0.740 g, 91%) as a pale yellow solid: mp 172−174 °C dec (EtOAc/hexane) (lit.[9] 173−174 °C dec (ether)); R_f = 0.57 (hexane/EtOAc 1:1); $[\alpha]_D$ −13.0 (*c* 1.15 CH_2Cl_2); ^{1}H NMR (500 MHz) δ 7.50 (t, J = 9.1 Hz, 6 H), 7.35 (t, J = 8.6 H, 6 H), 7.27 (td, J = 7.3 Hz, 1.1 Hz, 3 H), 7.21 (t, J = 7.4 Hz, 3 H), 7.15 (td, J = 7.9 Hz, 1.7 Hz, 6 H), 7.05 (t, J = 7.5 Hz, 6 H), 6.85−6.77 (m, 2 H), 6.37 (td, J = 7.8 Hz, 3.3 Hz, 1 H), 6.02 (tt, J = 7.3 Hz, 1.7 Hz, 1 H), 5.43 (dd, J = 10.7 Hz, 7.7 Hz, 1 H), 4.25−4.12 (m, 1 H), 3.86−3.79 (m, 1 H), 1.01 (t, J = 8.8 Hz, 3 H).

General Procedure for Synthesis of Nonracemic 2*H*-1-Benzopyrans. To a solution of palladacycle (−)-**18** (generated from complex (−)-**16a** with 64% de) (1 mmol) in 1,2-dichloroethane (30 mL) at room temperature under argon was added the appropriate alkyne (2.2−2.3 mmol) as a neat liquid. The reaction mixtures were refluxed for the indicated time (oil bath at 80 °C). Solvent was removed under reduced pressure, and the crude product was separated by flash chromatography over silica eluting with ether/hexane mixtures (1: 6) to afford 2*H*-1-benzopyrans (−)-**19**−(−)-**22** as colorless oils. Preparation of racemic benzopyrans (±)-**19**−(±)-**22** was previously described.[9]

(*S*)-2,3-Bis(ethoxycarbonyl)-4-methyl-2*H*-1-benzopyran [(−)-19].[9] Treatment of palladacycle (−)-**18** (generated from complex (−)-**16a** with 64% de) (0.097 g, 0.120 mmol) and ethyl 2-butynoate (0.030 mL, 0.029 g, 0.269 mmol) for 6 h according to the general procedure described above, eluting with hexane/ether (6:1), afforded regioisomerically pure[43] benzopyran (−)-**19** (0.018 g, 52%) as a colorless oil in 35.4% ee (by HPLC): R_f = 0.32 (hexane/EtOAc 3:1); $[\alpha]_D$ −61.1 (*c* 0.57 CH_2Cl_2); ^{1}H NMR (500 MHz) δ 7.40 (dd, J = 7.8 Hz, 1.2 Hz, 1 H), 7.28 (td, J = 7.1 Hz, 1.4 Hz, 1 H), 7.02 (d, J = 7.1 Hz, 1 H), 6.98 (t, J = 7.4 Hz, 1 H), 5.84 (s, 1 H), 4.38−4.24 (m, 2 H), 4.17−4.03 (m, 2 H), 2.49 (s, 3 H), 1.35 (t, J = 7.1 Hz, 3 H), 1.15 (t, J = 7.1 Hz, 3 H).

(*S*)-4-*n*-Butyl-2,3-bis(ethoxycarbonyl)-2*H*-1-benzopyran [(−)-20].[9] Treatment of the palladacycle (−)-**18** (generated from complex (−)-**16a** with 64% de) (0.097 g, 0.120 mmol) and ethyl 2-heptynoate[47] (0.045 mL, 0.041 g, 0.264 mmol) for 6 h according to the general procedure described above, eluting with hexane/ether (6:1), afforded benzopyran (−)-**20** (0.029 g, 72%) as a colorless oil in 55.6% ee (by HPLC): R_f = 0.56 (hexane/EtOAc 3:1); $[\alpha]_D$ −32.6 (*c* 0.34 CH_2Cl_2); ^{1}H NMR (400 MHz) δ 7.42 (dd, J = 7.8 Hz, 1.4 Hz, 1 H), 7.28 (t, J = 7.6 Hz, 1 H), 7.03 (d, J = 8.4 Hz, 1 H), 6.98 (dd, J = 7.5 Hz, 1.0 Hz, 1 H), 5.83 (s, 1 H), 4.37−4.23 (m, 2 H), 4.14−4.03 (m, 2 H), 3.09−3.02 (m, 1 H), 2.94−2.87 (m, 1 H), 1.53−1.42 (m, 4 H), 1.35 (t, J = 7.1 Hz, 3 H), 1.15 (t, J = 7.1 Hz, 3 H), 0.94 (t, J = 7.1 Hz, 3 H).

(*S*)-2,3-Bis(ethoxycarbonyl)-4-phenyl-2*H*-1-benzopyran [(−)-21].[9] Treatment of the palladacycle (−)-**18** (generated from complex (−)-**16a** with 64% de) (0.150 g, 0.185 mmol) and ethyl phenylpropiolate (0.067 mL, 0.070 g, 0.406 mmol) for 6 h according to the general procedure described above, eluting with hexane/ether (6:1), afforded benzopyran (−)-**21** (0.038 g, 59%) as a colorless oil in 40.0% ee (by HPLC): R_f = 0.42 (hexane/EtOAc 3:1); $[\alpha]_D$ −32.8 (*c* 1.17 CH_2Cl_2); ^{1}H NMR (400 MHz) δ 7.44−7.37 (m, 5 H), 7.26 (td, J = 10.3 Hz, 1.6 Hz, 1 H), 7.06 (dd, J = 8.1 Hz, 1.0 Hz, 1 H), 6.83 (td, J = 7.8 Hz, 1.1 Hz, 1 H), 6.73 (dd, J = 7.8 Hz, 1.5 Hz, 1 H), 5.94 (s, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 4.02−3.92 (m, 2 H), 1.20 (t, J = 7.1 Hz, 3 H), 0.91 (t, J = 7.1 Hz, 3 H).

(*S*)-2-Ethoxycarbonyl-3-methylcarbonyl-4-phenyl-2*H*-1-benzopyran (−)-22.[9] Treatment of the palladacycle (−)-**18** (generated from complex (−)-**16a** with 64% de) (0.097 g, 0.120 mmol) and 4-phenyl-3-butyn-2-one (0.040 mL, 0.039 g, 0.275 mmol) for 6 h according to the general procedure described above, eluting with with hexane/ether (6:1), afforded benzopyran (−)-**22** (0.022 g, 58%) as a yellow oil in 31.6% ee (by HPLC): R_f = 0.37 (hexane/EtOAc 3:1); $[\alpha]_D$ −18.8 (*c* 0.50 CH_2Cl_2). ^{1}H NMR (500 MHz) δ 7.51−7.45 (m, 5 H), 7.27 (td, J = 7.7 Hz, 1.5 Hz, 1 H), 7.06 (d, J = 8.1 Hz, 1 H), 6.85 (t, J = 7.8 Hz, 1 H), 6.79 (dd, J = 7.8 Hz, 1.5 Hz, 1 H), 6.01 (s, 1 H), 4.19−4.10 (m, 2 H), 1.71 (s, 3 H), 1.20 (t, J = 7.1 Hz, 3 H).

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Supporting Information Available: Description of the analytical methods for determination of the enantiomeric excess of 1,2-dihydroquinolines (+)-**5**−(+)-**9** and (+)-**11a** and 2*H*-1-benzopyrans (−)-**19**−(−)-**22**, including chiral phase HPLC chromatograms and ^{1}H NMR spectra recorded in the presence of a chiral shift reagent; description of the structure elucidation of racemic 1,2-dihydroquinolines **6**−**9** via HMBC 2D NMR analyses; ^{1}H and ^{13}C NMR spectra for all new compounds prepared in this study; experimental protocols for experiments in Scheme 4 and the stability studies with 1,2-dihydroquinolines (+)-**6** and (+)-**7**, 2*H*-1-benzopyrans (−)-**20** and (−)-**22** and palladacycle (−)-**18**; and description of X-ray crystallographic studies on organometallic complexes (−)-**13**, (+)-**14**, and (+)-**15a** and 1,2-dihydroquinolines (±)-**10a**, (±)-**11a**, and (±)-**12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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