Stereochemistry at Carbon of the Cyclometalation of 8-(α-Deuterioethyl)quinoline by Palladium(II) Salts

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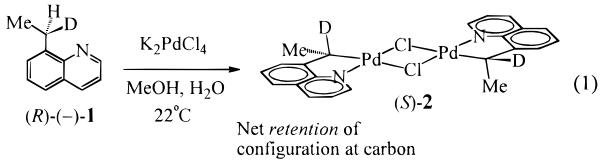
The stereochemistry at carbon of the known cyclometalation of 8-ethylquinoline by Pd(II) salts has been examined. The preparation of (*R*)-(−)-8-(α-deuterioethyl)quinoline ((*R*)-**1**-*d*, 91% d_1 and 40% ee) from (*R*)-(−)-mandelic acid is described. Cyclometalation of racemic **1**-*d* using K_2PdCl_4 in aqueous methanol affords the dimer {Pd(μ-Cl)[$\kappa^{C_\alpha,N}$-8-(CRMe)-quinoline]}$_2$ (**2**, R = H, D) with a kinetic isotope effect of >11 and no detectable isotopic scrambling. Cyclometalation of (*R*)-**1**-*d* using K_2PdCl_4, $PdCl_2$, or $Pd(OAc)_2$ affords **2** which is converted to PdCl[$\kappa^{C_\alpha,N}$-8-(CRMe)quinoline](NH_2R) (R = H, D; NH_2R = (+)-α-phenethylamine (**6a**) or (+)-*endo*-bornylamine (**6b**)) and to Pd[$\kappa^{C_\alpha,N}$-8-(CRMe)quinoline]($\kappa^{O,N}$-(+)-leucine) (**7a**, R = H, D). Analysis of **7a** shows 17−36% de (44−94% net stereospecificity), and comparison with the known absolute configuration of **7a** establishes that the C−H activation proceeds with retention of configuration at carbon.

Introduction

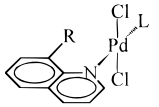
We report that the cyclometalation of (*R*)-(−)-8-(α-deuterioethyl)quinoline, (*R*)-**1**-*d*, by palladium(II) salts results in formation of the palladium−carbon bond in **2** with net retention of configuration at carbon as shown in eq 1.



(1)

Hydrogen−deuterium exchange of saturated hydrocarbons by soluble palladium and platinum complexes was first reported by Shilov in the late 1960's.[2] In recent years, there has been a revival of interest in this and related electrophilic activation reactions of saturated hydrocarbons[3] because of the continued need for controlled functionalization of feedstocks, including methane. The palladation of 8-alkylquinolines and many related substrates was studied years ago by Deeming and Rothwell,[4] and the electrophilic activation of the H−C_{sp^3} bond in **1** may be a model for the general electrophilic activation of alkanes by Pd^{II} and Pt^{II} in protic media (see Discussion).

One piece of information which is crucial to defining a mechanism is the stereochemical outcome of any changes in bonding at a saturated carbon. Most observers would immediately suggest that retention of configuration at carbon is the most probable outcome of C−H activation by a late transition metal, since such processes are usually envisaged as oxidative additions where the metal must simultaneously interact with both the carbon and hydrogen orbitals of the C−H bond. However, in the case of the 8-alkylquinoline activations, investigation of reactivity as a function of the structure of the 8-alkyl group introduced an intriguing ambiguity.[4] An isolable quinoline−Pd^{II} complex **3** was generated whether the 8-alkyl group was methyl, ethyl, or isopropyl, but only when R was methyl or ethyl did C−H activation product **2** form; 8-isopropylquinoline showed no activation.



3: R = Me, Et, Pr^i

That **3** (R = Pr^i) would not activate was a provocative observation, since, if the coordination complex would form, steric interactions would force the tertiary isopropyl C−H bond to lie tightly against the metal, as in **4a** in Scheme 1. This orientation should be ideal for a C−H activation reaction if it were to proceed by the conventionally assumed mechanism involving transition state **5a**, whether by front-side deprotonation as shown or via initial oxidative addition to palladium.

Alternatively, the activation of C−H might actually occur by a general-base-induced deprotonation of a carbon activated by back-side interaction with the electrophilic metal. As depicted in transition state **5b**, this type of reaction could result in inversion of configuration at the carbon center. It is possible that methyl and ethyl groups could achieve this back-side geometry, while for isopropyl the back-side orientation would be impossible, thus explaining the relative reactivity for C−H activation as a function of R. Either transition

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(1) (a) USC. (b) UOP.

(2) Goldshleger, N. F.; Tyabin, M. B.; Shilov, A. E.; Shteinman, A. A. *Zh. Fiz. Khim.* **1969**, *43*, 2174. Shilov, A. E; Shteinman, A. A. *Coord. Chem. Rev.* **1977**, *24*, 97.

(3) (a) Luinstra, G. A.; Wang, L.; Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Organometallics* **1994**, *13*, 755. (b) Sen, A.; Benvenuto, M. A.; Lin, M.; Huston, A. C.; Basickes, N. *J. Am. Chem. Soc.* **1994**, *116*, 998. (c) Periana, R. A.; Taube, D. J.; Evitt, E. R.; Loffler, D. G.; Wentrcek, P. R.; Voss, G.; Masuda, T. *Science* **1993**, *259*, 340. (d) Horvath, I. T.; Cook, R. A.; Millar, J. M.; Kiss, G. *Organometallics* **1993**, *12*, 8. (e) Olah, G. A. *Acc. Chem. Res.* **1987**, *20*, 422.

(4) Deeming, A. J.; Rothwell, I. P. *J. Organomet. Chem.* **1981**, *205*, 117 and references therein.

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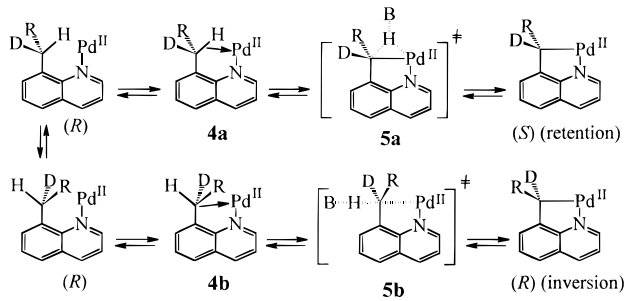
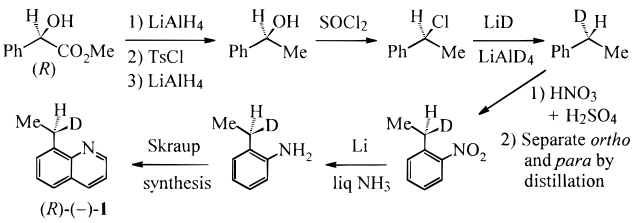
Scheme 1



Scheme 2



state **5a** (as written) or **5b** corresponds to C−H activation in one direction and protonolysis of the palladium−carbon bond in the other direction along the reaction coordinate. We are unaware of any example of either C−H activation to form or protonolysis to break a M−C bond which has been shown to proceed with inversion of configuration at carbon. There are, however a number of examples of heterolytic cleavages of metal−carbon bonds by electrophiles other than protons which do exhibit inversion of configuration at carbon and are believed to involve direct back-side attack by the electrophile.[5] Thus, the paucity of explicit stereochemical examples of C−H activation reactions and the (unrequited) possibility of uncovering an unusual mechanism in this particular case led us to investigate the stereochemistry of the cyclopalladation of 8-alkylquinoline.

Results

Syntheses. Several attempts to prepare (*R*)-(−)-8-(α-deuterioethyl)quinoline, (*R*)-**1**-*d*, were unsuccessful. One such attempt was based on the literature report of the resolution of 8-(α-bromoethyl)quinoline,[6] but several attempts to achieve this resolution failed in our hands. The synthetic path ultimately used is shown in Scheme 2 and began with commercially available, enantiomerically pure (*R*)-(−)-mandelic acid. The methyl ester was made by Fischer esterification of the acid, and the ester was reduced with $LiAlH_4$ in 1,2-dimethoxyethane at room temperature. Conversion of the diol in pyridine to the primary tosylate and then reduction again with $LiAlH_4$ gave (*S*)-(−)-α-phenethyl alcohol. Treatment of the alcohol with thionyl chloride according to the procedure of McKenzie and Clough,[7] which favors retention of configuration, yielded (*S*)-(−)-α-chloroethylbenzene. The chloride was reduced by the method of Eliel[8] to the known (*R*)-(−)-(α-deuterioethyl)benzene. Within the accuracy of ^{1}H NMR integration, the ethylbenzene was quantitatively α-monodeuterated, and the specific rotation of the neat liquid corresponded to 80% ee compared to the value of Elsenbaumer and Mosher.[9] Nitration of the ethylbenzene under standard conditions afforded ethylnitrobenzene as an *ortho*/*para* isomer mixture in an approximately one-to-one ratio. Pure *ortho* isomer was separated from the mixture by spinning-band distillation at reduced pressure. Lithium in liquid ammonia reduced the nitroaromatic[10] to *o*-ethylaniline, and this was used in a modification[11] of the Skraup synthesis to form the desired (*R*)-8-(α-deuterioethyl)quinoline, (*R*)-**1**-*d*. The overall yield from mandelic acid was 2%.

The deuterium content of (*R*)-**1**-*d* was assayed by ^{1}H NMR spectroscopy. The methylene quartet at δ 3.45 ppm, in comparison to the single-proton aromatic resonances at δ 6.80 and 8.80, integrated to 1.09 protons, corresponding to 91% deuteration at the α carbon. Since optically active ethylquinoline was not known, its optical purity was determined through the use of the optically active, paramagnetic, NMR shift reagent tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphorato]ytterbium(III), $Yb(hfc)_3$. A $CDCl_3$ solution $Yb(hfc)_3$ was added in small portions to an NMR sample of **1**-*d* until the optimum shift of the resonances of the chiral α-H was obtained. Although baseline separation of the enantiomer peaks was not achieved, the separation obtained was sufficient to establish the optical purity. The ratio was determined by peak deconvolution, and an average was taken of several measurements of peak areas at different shift reagent concentrations and from several data acquisitions. The average relative areas of the two diastereotopic α-CH resonances were 1.00 and 0.50. Taking account of the 91% α-d_1 label content (9% α-CH_2), optical purity was calculated to be 40% ee for the α-d_1 component. Thus, in the conversion from α-deuterioethylbenzene (∼100% d_1, 80% ee) to **1**-*d*, isotopic purity had dropped to 91% and the optical purity had diminished to 40%.

In an attempt to establish the origin of these decreases, the synthetic intermediates were examined more closely. Careful NMR integration of the (*R*)-(α-deuterioethyl)nitrobenzene revealed it to have 91% α-d_1 label content (9% α-CH_2), the same as the quinoline product. Thus, the label loss occurred in the electrophilic nitration step and not in the reduction or the Skraup reaction. Unfortunately, ethylnitrobenzene is not a strong enough Lewis base to give useful pseudocontact shifts with any of several NMR shift reagents that were tried. A new batch of the mixture of *ortho*- and *para*-(α-deuterioethyl)aniline isomers was prepared from the (*R*)-(α-deuterioethyl)benzene (∼100% d_1, 80% ee) and purified by a short-path distillation. The ethylaniline exhibited larger and more diastereotopically differentiated pseudocontact shifts with $Yb(hfc)_3$ than did 8-(α-deuterioethyl)quinoline. In addition, the pseudocontact shifts of the α-*d* resonances of the *ortho* isomer were substantially greater than those of the *para* isomer, so both isomers could be assayed in the same experiment. Integration of the shifted diastereotopic α-H resonances and correction for 9% α-CH_2 in each isomer (an assumption for the *para* isomer) revealed

(5) For examples of reactions thought to proceed by the S_E2-inversion mechanism, see: Flood, T. C. *Top. Stereochem.* **1981**, *12*, 37.
(6) Sokolov, V. I. *Inorg. Chim. Acta* **1976**, *18*, L9. Sokolov, V. I.; Bashilov, V. V.; Musaev, A. A.; Reutov, O. A. *J. Organomet. Chem.* **1982**, *225*, 57.
(7) McKenzie, A.; Clough, G. W. *J. Chem. Soc.* **1913**, *103*, 687.
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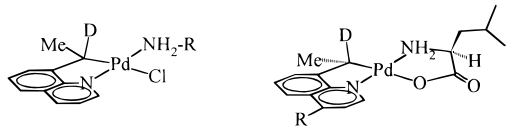
(10) Krapcho, A. P.; Collins, T. A. *Synth. Commun.* **1982**, *12*, 293.
(11) Bailey, J. R.; Glenn, R. A. *J. Am. Chem. Soc.* **1941**, *63*, 639.

optical purities of 65% ee for (*R*)-*ortho*-(α-deuterioethyl)-aniline and 77% ee for the *para*.

Since all of the deuterium loss occurred in the nitration and/or its workup and not in the subsequent Li/NH_3 reduction, it is most likely, although not obligatory, that the optical yield suffered in the same step. The fact that the spinning-band distilled *ortho* isomer had a much lower ee than the short-path distilled material (shorter time, lower temperatures) suggests that the racemization may have been incurred at higher temperatures rather than in strongly acidic (nitration) or basic (reduction) media. In any event, (*R*)-**1**-*d* of 40% ee was adequate to the task of examining the stereochemistry of the C−H activation, so alternate routes to material of higher optical purity were not sought.

The absolute configuration of optically active (α-deuterioethyl)benzene has been known for many years, and it is widely accepted that the (−)-rotating antipode has the (*R*) configuration.[9] Of course, this assignment is also consistent with the expected stereochemical outcome for the synthetic sequence from (*R*)-mandelic acid. Since the ethyl group is not altered in the conversion of ethylbenzene to 8-ethylquinoline, aside from the partial racemization discussed above, the absolute configuration of (−)-**1**-*d* must also be (*R*).

The Strategy, the Cyclometalation, and the Fate of the Deuterium. The strategy to determine the stereochemical path of the C−H activation was to prepare the optically active quinoline in such a way that its absolute configuration would be known. Cyclometalation of (*R*)-**1**-*d* would yield **2**-*d*, and then cleavage of the dimer using an enantiomerically pure resolving base, such as α-phenethylamine or *endo*-bornylamine, would generate $Pd(CDMeC_9H_6N)Cl(NH_2R)$, **6a**,**b**, as a pair of diastereomers. Crystallization of the dominant diastereomer and an X-ray structure determination should then allow assignment of the absolute configuration of the α-carbon center by reference to the known configuration of the resolving base.



6a, RNH_2 = (+)-α-phenethylamine
6b, RNH_2 = (+)-*endo*-bornylamine

7a, R = H
7b, R = methyl

Naturally, it was important to establish the feasibility of observing the stereochemical outcome of cyclometalation in the first place since it is easy to imagine mechanisms that would exchange deuterium from the α-position into the methyl group of **2** or into the solvent. Thus, before optically active **1**-*d* should be prepared, it was important to establish whether the deuterium would remain in place except when directly activated. An additional point of interest regarded the size of the kinetic isotope effect (KIE). If C−H activation were highly stereospecific but k_H/k_D were close to 1, then nearly racemic **2** would form, except that one enantiomer would be d_1 and the other d_0. This would necessitate the resolution of the two product enantiomers in the form of the two diastereomers **6** mentioned above in order to ascertain which isotopomer had which absolute configuration. If the measured KIE were small, then the product enantiomers must be resolvable to obtain an answer.

A variety of conditions for cyclometalation were examined with unlabeled **1**, including use of K_2PdCl_4 in methanol−water (3:2 by volume), $PdCl_2$ in the same solvent, and $Pd(OAc)_2$ in CH_2Cl_2. These produced the chloride-bridged dimer, **2**, in ∼100%, 88%, and 28% yields, respectively. The addition of several bases, such as Na_2CO_3, $NaHCO_3$, and NaOAc, to the reaction medium was tried, but they generally diminished the yield or prevented reaction altogether. Dimer **2** is rather insoluble, but sufficient material could be dissolved in $CDCl_3$ to obtain good ^1H NMR spectra. The dimer was generally contaminated with a small amount of what appeared to be the disubstituted but noncyclometallated $Pd(\mathbf{1})_2Cl_2$ which, because of its similar solubility properties, was difficult to separate. Nevertheless, the resonances were distinct and quantitation of any deuterium label in **2** was straightforward by integration of the α-CH−Pd resonance at δ 4.55 in comparison to the quinoline ring protons at δ 7.44 and 8.32.

Thus, reaction of racemic **1**-*d* (91% *d*) with K_2PdCl_4 under conditions of eq 1 afforded **2** which was 89% *d*. The label content of **2** corresponds to a k_H/k_D for cyclometalation of 89/(91 − 89) = 44. In this range of deuterium retention, the size of the kinetic isotope effect is very sensitive to the accuracy of the determination of the label content of both starting material and product. If one makes the conservative assumption of a standard error in the NMR determination of label content of ±3%, then an approximate lower limit of k_H/k_D for the cyclometalation is 86/(94 − 86) ∼ 11. Clearly, the isotope effect is very large.[12] This fortuitous result established that **1**-*d* should yield **2**-*d* with a high deuterium content in the α-position. If the reaction turned out to be highly stereospecific, it would mean that essentially a single enantiomer of product would form and no product resolution would be necessary; only crystallization of a single enantiomer of a single diastereomer of $Pd(CDMeC_9H_6N)Cl(NH_2R)$ would be required. The high percentage α-*d* also established that the label does not migrate to other locations in the ligand and it does not exchange into the medium.

At the point where the ligand synthesis was essayed and yielded (*R*)-(−)-**1**-*d* of only 40% ee, however, it appeared that some degree of resolution of $Pd(CDMeC_9H_6N)Cl(NH_2R)$ would be necessary after all in order to make the final assignment of absolute configuration by X-ray crystallography. Unfortunately, extensive efforts at resolution of both amine complexes **6a**,**b** failed in our hands.[13] At about this time, the preparation and resolution of leucine complexes **7a**,**b** (both nondeuterated; the (*S*,*S*) diastereomers are shown) were reported along with the crystal structure of (*S*,*S*)-**7b**.[14] This report obviated the need for further attempts to separate any of the diastereomers **6a**,**b** or even **7a**, since

(12) Kinetic isotope effects in excess of 10 are well-known for proton/deuteron transfer reactions and are generally attributed to tunneling through the reaction barrier by the lighter particle: Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman and Hall: New York, 1980. Precedents for hydrogen tunneling involving metal centers are also becoming more numerous: Rosenberg, E. *Polyhedron* **1989**, *8*, 383. For example, a hydrogen kinetic isotope effect of 27 at 32 °C has been reported for migration of a metal hydride to a nitrogen ligand in a triosmium cluster: Anslyn, E. V.; Green, M.; Nicola, G.; Rosenberg, E. *Organometallics* **1991**, *10*, 2600.

(13) Preparation of **6a** and separation of its diastereomers have been reported: Sokolov, V. I.; Sorokina, T. A.; Troitskaya, L. L.; Solovieva, L. I.; Reutov, O. A. *J. Organomet. Chem.* **1972**, *36*, 389.

(14) Spencer, J.; Maassarani, F.; Pfeffer, M.; DeCian, A.; Fischer, J. *Tetrahedron: Asym.* **1994**, *5*, 321.

Table 1. Stereochemistry of Cyclopalladation Reactions of (*R*)-(−)-8-(α-Deuterioethyl)quinoline, (*R*)-1-*d*,[a] at 25 °C Assayed as Pd[$\kappa^{C_\alpha,N}$-8-(CRMe)quinoline]($\kappa^{O,N}$-(+)-leucine) (7a, R = H, D)

reagent	conditions	% de of **7a**[b]	% net retention
$PdCl_2$	H_2O, MeOH	17	44
K_2PdCl_4	H_2O, MeOH	22	58
$Pd(OAc)_2$	CH_2Cl_2	36	94

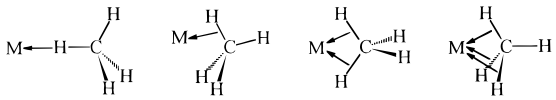
[a] (*R*)-**1**-*d* was 91% d_1, and the d_1 portion was of 40% ee. [b] Diastereomer ratio of **7a** corrected for 4.5% each of (*RS*)-d_0 and (*SS*)-d_0 which come from unlabeled (achiral) starting **1**.

correlations of the ^{1}H NMR resonances of **7a**-d_1 with the reported diastereomeric resonances of **7a**,**b** would establish the absolute configuration of its dominant diastereomer.

Cyclometalation of (*R*)-(−)-1-*d*. Reaction of (*R*)-**1**-*d* (91% d_1, 40% ee) was conducted under three sets of conditions, as shown in Table 1, using $PdCl_2$, K_2PdCl_4, and $Pd(OAc)_2$. The first two formed dimer **2** directly. An acetate-bridged dimer was the initial product from reaction of **1** with $Pd(OAc)_2$,[4] and this was then converted to the chloride dimer (**2**) by ligand metathesis with chloride ion. In each case, dimer **2** was cleaved with (+)-leucine according to the procedure of Pfeffer[14] and isomer analysis was conducted on the resulting **7a**. In particular, the resonances of the quinoline hydrogen *ortho* to nitrogen at δ 8.77 for the (*RS*) diastereomer and δ 8.82 for the (*SS*) isomer were baseline separated and readily integrated to provide the assay. The absolute configuration of the dominant isomer could be confirmed by several individual resonances in the proton spectrum in comparison with the assignments of Pfeffer *et al.*,[14] in particular, (*RS*) δ 1.25 (C*H*$_3$CDPd), 2.59, 4.18 (N*H*), 6.98 (H_m), 7.82 (H_p), and 8.81 (H_o) *versus* (*SS*) δ 1.17 (C*H*$_3$CDPd), 2.19, 4.87 (N*H*), 6.91 (H_m), 7.77 (H_p), and 8.70 (H_o). The **7a** diastereomer ratios were corrected by subtracting from each diastereomer $^1/_2$ of the amount of unlabeled (α-CH_2) (9%) in starting **1**. In the calculation of the percent net retention, the assumption was made that the degree of stereospecificity is the same for both the D abstraction and the H abstraction. Since only 2% of the material proceeds via D abstraction, this assumption is inconsequential in any event. The results are shown in Table 1. The fact that the percent diastereomeric excess of **7a** from cyclometalation by $Pd(OAc)_2$ is so high corroborates that there is no large loss of stereochemistry in either the conversion of the acetate dimer to chloride dimer **2** or the conversion of **2** to **7a**.

Discussion

The above results establish that the activation of the C−H bond in 8-ethylquinoline by Pd^{II} salts proceeds with net retention of configuration at carbon and with quite high stereospecificity in the case of $Pd(OAc)_2$. Retention would be the expected result from an oxidative addition pathway for the reaction or from a variation where the overt formation of Pd^{IV} would be avoided by deprotonation of the activated Pd(C−H) complex, **4a**, as shown in the transition state drawing **5a** in Scheme 1. Four possible geometries for alkane coordination to the vacant site of a metal complex are **8a**−**d**. Several recent theoretical calculations[15,16] have been carried out regarding alkane interactions with metals, particularly



8a **8b** **8c** **8d**

in the context of C−H oxidative addition.[15] Calculations of the fragment $RhCl(PH_3)_2$ reveal local energy minima for the interaction of Rh with CH_4 in the form of **8b**,**c**. The η^3-CH_4 complex **8d** was found not to be a minimum.[15b] On the other hand, the lowest energy geometry calculated for the interaction of methane with the electrophilic fragment $H_2M{=}NH$ (M = Ti, Zr, Hf) is **8d**.[16] In this case, the highest degree of charge transfer from a hydrogen to the metal is calculated to be for the hydrogen trans to the metal, which we believe implies that hydrogen might be labile toward abstraction by a base. Thus, the back-side geometry postulated in **4b** and **5b** seems feasible. Nevertheless, the observed retention of configuration clearly indicates that the hydrogen is removed from the front side of the carbon, either directly by base as in **5a** or by migration to palladium followed by metal deprotonation.

It is relevant to consider whether activation of this particular substrate is in any way an experimental precedent that is likely to have general implications for the stereochemical path of C−H activation by electrophilic metals. There are two circumstances that might render the present example unique and so devoid of general implications: (1) the forced propinquity of the C−H and Pd groups brought about by prior coordination of quinoline **1**; (2) the benzylic nature of the C−H bond in **1**. Obviously, definitive answers can be given to these questions only after the stereochemistry of the intermolecular activation of a non-benzylic substrate has been established. Nevertheless, we suspect that the benzylic nature of the activated C−H bond in **1** should have little bearing on the path of the activation, since the in-plane position of the metal imposed by its coordination requires that all interactions with the organic center in transition states **5** for Pd−C bond formation or C−H bond cleavage occur in or close to the plane of the rings. Thus there should be no large interaction of the π system of the ring with either the metal (other than as usual through the nitrogen) or the reacting bonds. The aryl group inductive effect would render the C−H bond less reactive toward an electrophile than that of a normal alkane, but what effect this variable should have on the stereochemistry is unclear. Several studies now adduce indirect but convincing evidence for the intermediacy of metal complexes of intact alkanes in C−H activation reactions.[17] The presumed major advantage offered by **1** is that prior

(15) (a) Ziegler, T.; Tschinke, V.; Fan, L.; Becke, A. D. *J. Am. Chem. Soc.* **1989**, *111*, 9177. (b) Koga, N.; Morokuma, K. *J. Phys. Chem.* **1990**, *94*, 5454−5462. (c) Song, J.; Hall, M. B. *Organometallics* **1993**, *12*, 3118. (d) Margl, P.; Ziegler, T.; Bloechl, P. E. *J. Am. Chem. Soc.* **1995**, *117*, 12625−12634. (e) Siegbahn, P. E. M.; Svensson, M. *J. Am. Chem. Soc.* **1994**, *116*, 10124.

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palladium−quinoline coordination stabilizes such an alkane complex so that the actual activation can be achieved in higher yield under milder conditions. Whether this stabilization might cause the selection of a mechanism which is not competitive in an intermolecular reaction is unclear, so one cannot unequivocally assert the relevance of the stereochemical outcome reported here to the general nonchelated case.

Table 1 shows that $PdCl_2$ or K_2PdCl_4 activates **1**-*d* with 40−60% stereospecificity, while $Pd(OAc)_2$ approaches complete stereoselection. Pfeffer *et al.*[14] found that treatment of **7b** with dilute HCl in MeOH (room temperature overnight) gave chloride-bridged dimer **2** as a 1:1 mixture of diastereomers in which the α-position had been totally epimerized. In contrast, cleavage with dilute acetic acid (MeOH, overnight, room temperature, followed by LiCl in acetone) gave **2** with essentially complete retention of configuration at the α-carbon. On the basis of Pfeffer's observations, we infer that reaction between **1**-*d* and $PdCl_2$ generates HCl in the reaction medium which causes partial racemization. The dilute acetic acid formed in the activation of **1**-*d* using $Pd(OAc)_2$, on the other hand, is not strong enough an acid to cause racemization. As mentioned above, however, use of weak buffering bases tended to quench the reaction, so this issue was not pursued further.

Experimental Section

General Methods. NMR chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane for ^1H and ^{13}C. All reactions, including those involving organometallic compounds, unless otherwise mentioned, were carried out in the air. When protection from air was necessary, reactions were carried out under an atmosphere of nitrogen or argon purified over reduced copper catalyst (BASF R3-11) and Aquasorb, in flamed out glassware using standard vacuum line, Schlenk, and inert-atmosphere glovebox techniques. Benzene, ether, hexanes, pentane, and THF were distilled from purple solutions of sodium benzophenone when necessary. Methylene chloride was distilled twice from CaH_2 when needed anhydrous. (*R*)-(−)-mandelic acid, (*R*)-(+)-*endo*-bornylamine, and (*R*)-(+)-α-phenethylamine were commercial samples. Elemental analyses were performed by the Microanalytical Laboratory, University of California, Berkeley, CA. The historical convention of *grams/100 mL* has been used in reporting concentrations of polarimeter samples.

Methyl (*R*)-(−)-Mandelate. A mixture of (*R*)-(−)-mandelic acid (100 g, 0.66 mol, $[\alpha]_D^{23}$ −153° (*C* = 2.5, H_2O)), methanol (53 mL, 1.3 mol), 2,2-dimethoxypropane (81 mL, 0.66 mol), and H_2SO_4 (3 mL, 0.06 mol) was heated at reflux for 4 h after which the solvent was removed by rotary evaporator. The red-brown residue was dissolved in 3.5 L of boiling hexanes, charcoal was added, the solution was filtered, and the filtrate was placed in the freezer overnight. The white precipitate was collected on a Büchner funnel and washed with cold pentane. Yield: 80% (87.5 g, 0.53 mol). ^1H NMR ($CDCl_3$): δ 3.55 (s, 3H), 3.73 (s, 1H), 5.16 (s, 1H), 7.3−7.5 (m, 5H).

(*R*)-1-Phenyl-1,2-ethanediol. To a stirred solution of lithium aluminum hydride (24.14 g, 0.64 mol) in 700 mL of 1,2-dimethoxyethane (DME, fresh bottle) in an ice bath was slowly added a solution of methyl (*R*)-mandelate (87.5 g, 0.53 mol) in 300 mL of DME. After addition, the ice bath was removed and the mixture was stirred for 12 h at room temperature. Then 150 mL of saturated NH_4Cl and 150 mL of 3 M HCl were added sequentially, carefully at first. The salts were removed by filtration, washed with 200 mL ether and then 100 mL of dilute HCl, and finally extracted with three 75-mL portions of ether. The solvent was removed from the combined ether/DME layers by rotary evaporator to give a yellow oil which was crystallized from benzene and hexanes to give a white solid. Yield: 88% (63.9 g, 0.46 mol). ^1H NMR ($CDCl_3$): δ 2.6 (broad, 2H), 3.70 (m, 2H), 4.78 (dd, 1H), 7.33 (m, 5H).

(*R*)-1-Phenyl-1,2-ethanediol 2-Tosylate. *p*-Tosyl chloride (92.1 g, 0.483 mol, recrystallized from $CHCl_3$ and petroleum ether) was slowly added to a stirred solution at 0 °C of (*R*)-1-phenyl-1,2-ethanediol (63.92 g, 0.46 mol) in 1.5 L of fresh pyridine. The ice bath was removed, and the solution was stirred for 24 h under an argon atmosphere. The mixture was poured onto an ice/acid mixture, and the solution was made acidic, as indicated by litmus paper. The solution was extracted with three 100-mL portions of ether. The ether was dried with $MgSO_4$ and concentrated on the rotary evaporator to give an off-white solid. Yield: 78% (106 g, 0.36 mol). ^1H NMR ($CDCl_3$): δ 2.42 (s, 3H), 2.70 (s, 1H), 4.05 (m, 2H), 4.95 (dd, 1H), 7.30 (s, d, 3H), 7.74 (d, 2H).

(*S*)-(−)-α-Methylbenzyl Alcohol. Lithium aluminum hydride powder (15 g, 0.395 mol) was added slowly to a stirred solution of (*R*)-1-phenyl-1,2-ethanediol 2-tosylate (106 g, 0.36 mol) in 1 L of fresh ether at 0 °C. The ice bath was removed, and the reaction was stirred for 3 h under an argon atmosphere. Water was carefully added to the mixture, and the separated salts were washed with water and then ether. The aqueous layer was extracted with three 50-mL portions of ether. The combined ether layers were dried with $MgSO_4$ and concentrated by rotary evaporator to give a yellow oil which was distilled (35 °C/10^{-5} mmHg) to give a clear, colorless oil. Yield: 77% (33.9 g, 0.28 mol). $[\alpha]_D^{23}$ = −44.4° (*C* = 5.0, EtOH); lit.[7] $[\alpha]_D^{23}$ −43.7°. ^1H NMR ($CDCl_3$): δ 1.46 (d, 3H), 4.9 (q, 1H), 7.35 (m, 5H).

(*S*)-(−)-α-Methylbenzyl Chloride.[7] (*S*)-(−)-α-Phenylethyl alcohol (33.37 g, 0.27 mol) was added slowly to distilled $SOCl_2$ (50.2 mL, 0.69 mol) with stirring, and the mixture was stirred for an additional 30 min at 25 °C. The excess $SOCl_2$ was removed by vacuum distillation, and the product was distilled at 28 °C/10^{-5} mmHg, to give a clear colorless oil. Yield: 77% (30 g, 0.21 mol). $[\alpha]_D^{23}$ = −45.4° (*C* = 5.4, EtOH); the best literature value of $[\alpha]_D^{23}$ is not clear.[18] ^1H NMR ($CDCl_3$): δ 1.86 (d, 3H), 5.1 (q, 1H), 7.37 (m, 5H).

(*R*)-(−)-α-Deuterioethylbenzene.[8] LiD (3.97 g, 0.095 mol) and $LiAlD_4$ (1.36 g, 0.036 mol) were suspended in 200 mL of dry THF. (*S*)-α-Phenethyl chloride (30 g, 0.21 mol) was added rapidly, and the solution was heated at reflux under argon for 24 h. Water was cautiously added, and the mixture was poured onto a dilute H_2SO_4−ice mixture. The product was extracted with three 20-mL portions of pentane, and the combined extracts were dried with $CaCl_2$. The solvent was removed by rotary evaporation to give a slightly yellow oil which was distilled at 130 °C to give a clear, colorless oil in 64% yield (14.7 g, 0.14 mol). ^1H NMR ($CDCl_3$): δ 1.27 (d, 3H), 2.57 (q, 1H), 7.30 (m, 5H). Within the accuracy of careful ^1H NMR integral measurements, the δ 1.27/δ 2.57 ratio was 3.00, indicating essentially quantitative monodeuteration; $[\alpha]_D^{23}$ = −0.648° (neat); lit.[9] $[\alpha]_D^{23}$ −0.81° (neat, 100% ee), implying 80% ee.

(*R*)-*o*- and -*p*-(α-Deuterioethyl)nitrobenzene. While the solution was being stirred, concentrated H_2SO_4 (13.1 mL, 0.257 mol) was slowly added to concentrated HNO_3 (11.7 mL, 0.292 mol). The temperature was kept below 50 °C with an ice bath. With continued stirring, (*R*)-α-deuterioethylbenzene (14.7 g, 0.14 mol) was slowly added to the acid mixture, with the temperature maintained at 20−25 °C. After completion of the addition, the mixture was heated at 60 °C for 30 min and then

(18) Values reported for $[\alpha]_D$ of enantiomerically "pure" α-phenethyl chloride have varied widely: Ott, E. *Chem. Ber.* **1928**, *61*, 2124; 50.3°. Reference 7, 50.6°. Reference 8, 103.9°. Burwell, R. L.; Shields, A. D.; Hart, H. *J. Am. Chem. Soc.* **1954**, *76*, 908; 109°. Streitweiser, A.; Reif, L. *J. Am. Chem. Soc.* **1964**, *86*, 1988; 117°.

poured into a beaker containing ice and water. The water was decanted from the ethylnitrobenzenes, and the water was extracted with three 25-mL portions of ether. The extracts were added to the ethylnitrobenzenes and washed with four 50-mL portions of water. The ether layer was dried with Na_2SO_4 and concentrated by rotary evaporation. The crude yield was 95% (19.9 g, 0.13 mol) of a light tan/orange oil. This material was not purified. ^{1}H NMR ($CDCl_3$): δ 1.25 (m, 6H), 2.72 (qq, 1H), 2.89 (qq, 1H), 7.33 (m, 4H), 7.55 (d, 1H), 7.85 (d, 1H), 7.95 (d, 2H).

Isomer Separation. The isomer mixture (19.94 g, 0.132 mol) was distilled using a platinum spinning band column. The spinning rate was set at 2000 rpm and the pressure at 16 mmHg. Distillation began with a pot temperature of 136 °C and a head temperature of 110 °C which was obtained after several hours of equilibration. The first and second fractions obtained were pure ortho material. The third and subsequent fractions all contained para isomer. The yield of pure ortho was 19% (3.7 g, 24 mmol) of light yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.24 (d, 3H), 2.85 (q, 1H), 7.3 (m, 2H), 7.5 (m, 1H), 7.85 (m, 1H). Within the accuracy of careful ^{1}H NMR integral measurements, the δ 1.24/δ 2.85 ratio was 2.75, indicating a level of monodeuteration of 91%.

(*R*)-*o*-(α-Deuterioethyl)aniline.[10] Ammonia (*ca.* 75 mL) was condensed into a Schlenk flask containing a small amount of sodium metal as a drying agent. The dry ammonia was then transferred by recondensation into a 500-mL three-neck, round-bottom flask with a −78 °C cold finger condenser and sitting in a −78 °C bath. A solution of (*R*)-*o*-(α-deuterioethyl)-nitrobenzene (3.64g, 24 mmol) in methanol (9.7 mL, 0.24 mol) was added slowly to the ammonia over 15 min. Hexane-washed lithium metal (1.33 g, 0.192 mol) was then carefully added to the ammonia solution as small pieces over a period of 30 min. The dry ice−acetone bath was removed, and the ammonia was allowed to reflux from the cold finger condenser for 2 h, after which the ammonia was allowed to evaporate. Then 20 mL of ether was added, followed by the careful addition of 20 mL of water. The ether layer was separated, and the aqueous layer was extracted with three 20-mL portions of ether. The ether extracts were dried over Na_2SO_4, and the solvent was removed by rotary evaporation to give an orange-tan oily material. Crude yield: 3.41 g (>100%). ^{1}H NMR ($CDCl_3$): δ 1.25 (d, 3H), 2.5 (q, 1H), 3.56 (s, 2H), 6.69 (m, 1H), 6.78 (m, 1H), 7.1 (m, 2H).

(*R*)-(−)-8-(α-Deuterioethyl)quinoline.[11] (*R*)-*o*-(α-Deuterioethyl)aniline (3.41 g, 30 mmol), $FeSO_4{\cdot}7H_2O$ (1.04 g, 4 mmol), and nitrobenzene (1.79 mL, 17 mmol) were combined in a 50-mL single-neck round-bottom flask with a stir bar and a condenser fitted with an ice water supply and connected to an argon bubbler. Next, a cold (ice bath) solution of boric acid (1.82 g, 29 mmol) in glycerol (8.8 mL, 0.12 mol) was added. Finally, concentrated H_2SO_4 (5.2 mL, 0.102 mol) was *slowly* added (*exothermic*) with stirring. Heat was applied *slowly* until a gentle reflux was maintained.

Caution! It is imperative that heat be applied slowly since the reaction becomes highly exothermic once it initiates. After 20 min the solution turned black and the mixture was heated at reflux for an additional 24 h. The mixture was allowed to cool, 50 mL of water was added, and any nitrobenzene was removed by steam distillation. The mixture was made basic with ammonium hydroxide (litmus paper) and again steam distilled to remove the product. The (*R*)-(−)-8-(α-deuterioethyl)quinoline was then extracted from the aqueous layer with three 20-mL portions of ether. The product was removed from the ether with dilute HCl and diazotized at 0 °C to remove any primary amines. This solution was neutralized with NaOH and extracted with three 10 mL portions of ether. Removal of the solvent using the rotary evaporator gave a dark orange oil. This oil was treated with nitric acid in an ethanol−ether solution to precipitate out the 8-(α-deuterioethyl)quinolinium nitrate salt as white crystals, mp 134−136 °C (lit.[11] mp 146 °C). Decomposition of the salt by treatment with NH_4-OH and extraction with three 10-mL portions of ether gave a clear, slightly yellow oil. The oil was Kugelrohr-distilled at 16 mmHg and at 75 °C/16 mmHg to give a clear, colorless oil. Yield: 53% (2.51 g, 16 mmol). ^{1}H NMR indicated that the product contained quinoline, so the mixture was submitted to column chromatography on activated neutral aluminum oxide (Brockmann I, standard grade, 150 mesh) and eluted with a 7:1 hexanes−ethyl acetate solvent mixture. The yield of pure 8-(α-deuterioethyl)quinoline as a clear, colorless oil was 2.0 g or 13 mmol (52% based on pure *o*-(α-deuterioethyl)nitrobenzene) and 2% overall from mandelic acid. ^{1}H NMR ($CDCl_3$): δ 1.42 (d, 3H), 3.45 (q, 1H), 6.80 (m, 1H), 7.22 (m, 1H), 7.32 (m, 2H), 7.55 (d, 1H), 8.80 (d, 1H). Integration of the ^{1}H NMR resonances gave relative integrals for δ 3.35, 6.67, and 8.7 of 1.09, 1.00, and 1.00, respectively, which corresponds to 91% deuteration at the α carbon. The specific rotation was corrected for the 9% α-CH_2 achiral material; $[\alpha]_D^{23} = -0.399°$ (3.9, EtOH).

Determination of Optical Purity of (*R*)-*o*- and -*p*-(α-Deuterioethyl)aniline. The synthetic isomer mixture (*ca.* 1:1) of (*R*)-*o*- and -*p*-(α-deuterioethyl)aniline (1 mg, 8 μmol) was dissolved in 0.5 mL of $CDCl_3$ in a 5 mm NMR tube. The commercial, optically active, paramagnetic, NMR shift reagent tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphorato]-ytterbium(III) (250 mg, 0.206 mmol) dissolved in 1.5 mL of $CDCl_3$ was added in 50 μL portions to the NMR sample until the optimum shift of the resonance of the chiral α-H was obtained. Complete separation of the enantiomer peaks of both the ortho and para isomers was achieved after the addition of only a small amount of the shift reagent solution. For example, the α-*H* resonance of *o*-(α-deuterioethyl)aniline at δ 2.49 was shifted and separated to δ 6.77 (smaller) and 7.70 (larger), by the addition of 150 μL of shift reagent solution, and to δ 7.71 and 10.72, by a total of 450 μL. For comparison, after addition of 150 μL of shift reagent solution, the *p*-(α-deuterioethyl)aniline α-*H* resonances appeared at δ 3.91 (larger) and 4.08 (smaller). An average was taken of several measurements of peak areas at different shift reagent concentrations and several data acquisitions. For the *ortho* isomer the relative peak areas were 1.00 and 0.30, and for the para isomer they were 1.00 and 0.22. Taking account of the 91% α-d_1 label content (9% α-H_2), optical purity was calculated to be 65% ee for the α-d_1 component of the ortho isomer and 77% ee for the para isomer.

Determination of Optical Purity of (*R*)-(−)-8-(α-Deuterioethyl)quinoline (1). (*R*)-8-(α-Deuterioethyl)quinoline (1 mg, 6 μmol) was dissolved in 0.5 mL of $CDCl_3$ in a 5 mm NMR tube. The commercial, optically active, paramagnetic, NMR shift reagent tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphorato]ytterbium(III) (250 mg, 0.206 mmol) dissolved in 1.5 mL of $CDCl_3$ was added in 50- and 100-μL portions to the NMR sample until the optimum shift of the resonance of the chiral α-H was obtained. For example, the α-*H* resonance of **1**-*d* at δ 3.35 was shifted and separated to δ 11.15 (larger) and 11.23 (smaller) by the addition of a total of 800 μL of shift reagent solution. Although complete separation of the enantiomer peaks was not achieved, the separation obtained after the addition of several hundred microliters was sufficient to determine the optical purity. The peak ratio was determined with the use of curve deconvolution software, and an average was taken of several measurements of peak areas at different shift reagent concentrations and from several data acquisitions. The average relative peak areas were 1.00 and 0.50. Taking account of the 91% α-d_1 label content (9% α-H_2), optical purity was calculated to be 40% ee for the α-d_1 component. A value of 40% ee for this material and the $[\alpha]_D^{23}$of −0.399° (C = 3.86, EtOH) together imply a value of $[\alpha]_D^{23} = -1.00°$ for optically pure and isotopically pure (*R*)-(−)-8-(α-deuterioethyl)quinoline.

Reaction of (*R*)-8-(α-Deuterioethyl)quinoline with K_2PdCl_4. K_2PtCl_4 (1.5 g, 4.6 mmol) was partially dissolved in 135 mL of methanol and 90 mL of water. (*R*)-8-(α-

Deuterioethyl)quinoline (1.4 g, 8.9 mmol) was added, and the mixture was stirred. After several hours a yellow precipitate began to form. The reaction was allowed to stir for an additional 24 h, after which the precipitate was collected on a fritted filter and washed with three 20-mL portions of water and three 50-mL portions of ether. The bright-yellow, vacuum-dried, powdery $[PdCl(C_{11}H_9ND)]_2$ (**2**) amounted to 1.5 g. Since this would correspond to 2.5 mmol (>100% yield), impurities were clearly present. ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 3H), 7.44 (dd, 1H), 7.54 (d, 1H), 7.64 (dt, 2H), 8.32 (dd, 1H), 9.0 (s, 1H); lit.[4] ^{1}H NMR spectrum of **2**. Because of the large isotope effect, the quartet at δ 4.55 was greatly reduced. See the Results section regarding determination of the isotope effect.

Reaction of (*R*)-8-(α-Deuterioethyl)quinoline with Palladium Acetate. $Pd(OAc)_2$ (1.0 g, 4.5 mmol) and (*R*)-8-(α-deuterioethyl)quinoline (740 mg, 4.7 mmol) were dissolved in 20 mL of CH_2Cl_2. After 17 h the solution was a deep brown color at which point it was filtered and the solvent was removed under vacuum to give an oily dark brown material, which was washed with three 20-mL portions of pentane, and the remaining solid was dried in vacuo. The solid was then dissolved in 100 mL of acetone, 0.95 g (22 mmol) of LiCl was added, and the mixture was gently heated on a hot plate almost to boiling until all of the initial yellow precipitate formed had dissolved or nearly so. The solution was filtered, and 100 mL of water was added in one protion, resulting in immediate precipitation of a yellow solid. The solid was collected on a fritted filter and washed with 20 mL of ether and 20 mL of pentane and dried in vacuo. A 28% yield (0.37 g, 0.62 mmol) of $[PdCl(C_{11}H_9ND)]_2$ (**2**) was obtained. The ^{1}H NMR spectrum in $CDCl_3$ matched that given above.

Reaction of (*R*)-8-(α-Deuterioethyl)quinoline with Palladium Dichloride. $PdCl_2$ (0.213 g, 1.2 mmol) and (*R*)-8-(α-deuterioethyl)quinoline (394 mg, 2.5 mmol) were dissolved in 23 mL of methanol and 15 mL of water. After 30 h, the bright-yellow solid was collected on a fritted filter, washed with three 20-mL portions of water and three 50-mL portions of ether, and dried in vacuo. An 88% yield (0.32 g, 0.53 mmol) of $[PdCl(C_{11}H_9ND)]_2$ was obtained. The ^{1}H NMR spectrum in $CDCl_3$ matched that given above.

Cleavage of the Chloride Dimer by (*R*)-(+)-α-phenethylamine.[13] A solution of $[PdCl(C_{11}H_{10}N)]_2$ (124 mg, 0.21 mmol) in 10 mL of CH_2Cl_2 was prepared, and to this was added *R*-(+)-α-phenethylamine (75.6 mg, 0.62 mmol). The resultant mixture turned yellow after several minutes. After *ca.* 75 min the solvent was removed in vacuo and the waxy material was washed with several portions of hexanes to give bright yellow solid **6a**. Yield: 56% (98 mg 0.23 mmol). ^{1}H NMR (resonances of a 1:1 diastereomer mixture) ($CDCl_3$): δ 1.17, 1.28 (2d, 2 × 3H, J = 7.4 Hz, C*H*$_3$CHPd), 1.83, 1.89 (2d, 2 × 3H, J = 6.9 Hz, C*H*$_3$CHN), 2.62 (br d, 1H, J = ∼10 Hz, N*H*), 2.68 (br t, 1H, J = ∼10 Hz, N*H*), 3.42 (br d, 1H, J = ∼10 Hz, N*H*), 3.66 (br t, 1H, J = ∼10 Hz, N*H*), 3.78 (q, 1H, J = 7.4 Hz, C*H*Pd), 3.88 (q, 1H, J = 7.4 Hz, C*H*Pd), 4.29 (br m, 1H, C*H*N), 4.60 (br m, 1H, C*H*N), 7.2−7.6 (m, 18H), 8.22 (2dd, 2 × 1H, $\Delta\delta$ = 12 ppb, J = 8.4, $^4J_{op}$ = 1.6 Hz, H_p), 9.45 (2dd, 2 × 1H, $\Delta\delta$ = 5.8 ppb, J = 5.0, $^4J_{op}$ = 1.6 Hz, H_o). Repeated attempts at separation of the two diastereomers[13] by crystallization under a variety of conditions failed.

Cleavage of the Chloride Dimer with (*R*)-(+)-Bornylamine. A solution of racemic $[PdCl(C_{11}H_{10}N)]_2$ (130 mg, 0.22 mmol) in 10 mL of CH_2Cl_2 was prepared, and to this was added (*R*)-(+)-*endo*-bornylamine (86.4 mg, 0.56 mmol). The resultant mixture turned yellow after several minutes. After *ca.* 90 min the solvent was removed in vacuo and the waxy material was washed with several portions of hexanes to give bright yellow solid **6b**. Yield: 46% (90 mg 0.20 mmol). ^{1}H NMR (resonances of a 1:1 diastereomer mixture) ($CDCl_3$): δ 0.876, 0.886, 0.897, 0.902, 0.910, 1.05 (6s, bornyl methyls), 1.26 (2d, 2 × 3H, $\Delta\delta$ = 8.5 ppb, J = 7.2 Hz, C*H*$_3$CHPd), 1−1.83 (br m, bornyl ring C*H*), 2.09 (br d, 1H, J = 10 Hz, N*H*), 2.27 (br dd, 1H, J = ∼10, ∼9 Hz, N*H*), 2.47 (br m, 2 × 1H, bornyl C$_{(3)}H_{endo}$), 3.20 (br m, 2H, C*H*N + N*H*), 3.37 (br dd, 1H, J = ∼10, ∼9, N*H*), 3.51 (m, 1H, C*H*N), 3.79 (q, 1H, J = 7.3 Hz, C*H*Pd), 3.91 (q, 1H, J = 7.3 Hz, C*H*Pd), 7.35 (2 dd, 2 × 1H, $\Delta\delta$ = 4.7 ppb, J_{mp} = 8.4, J_{mo} 5.0 Hz, H_m), 7.47 (2dd, 2 × 1H, $\Delta\delta$ = 9.8 ppb, J = 8.3, 6.8 Hz, H_6), 7.57−7.64 (m, 4H), 8.20 (2dd, 2 × 1H, $\Delta\delta$ = 6.1 ppb, J_{mp} = 8.4, $^4J_{op}$ = 1.5 Hz, H_p), 9.44 (2dd, 2 × 1H, $\Delta\delta$ = 3.9 ppb, J_{om} = 5.0, $^4J_{op}$ = 1.5 Hz, H_o). Repeated attempts at separation of the two diastereomers by crystallization under a variety of conditions failed. A ^{1}H NMR spectrum of the analytical sample in dry $CDCl_3$ clearly showed 0.5 equiv of H_2O of crystallization (br s, δ 1.60). Anal. Calcd for $C_{21}H_{29}N_2ClPd\cdot{}^1/_2H_2O$: C, 54.79; H, 6.57; N, 6.09. Found: C, 54.93; H, 6.37; N, 6.18.

Cleavage of the Optically Active Chloride Dimer (Formed from K_2PdCl_4) with (*S*)-(+)-Leucine.[14] $[PdCl(C_{11}H_9ND)]_2$ (105 mg, 0.18 mmol) was suspended in 15 mL of methanol, and to this was added first Na_2CO_3 (47 mg, 0.44 mmol) and then (*S*)-(+)-leucine (58 mg, 0.44 mmol) with stirring. After 2 h of stirring, water was added and the product was extracted with three 10-mL portions of CH_2Cl_2. The organic layers were combined and dried with Na_2SO_4, and the solvent was removed by rotary evaporation to give tan solid **7a**, which was washed with pentane. Yield: 45% (62 mg, 0.16 mmol). Data for the major (*SS*) isomer: ^{1}H NMR ($CDCl_3$) δ 0.95, 1.00 (2d, J = 6.5 Hz, (C*H*$_3$)$_2$CH), 1.25 (s, C*H*$_3$CDPd), 1.7−2.1 (m, 3H, C*H*Me$_2$, C*H*$_2$), 2.59 (br d, 1H, ^2J = 9.8 Hz, N*H*), 3.74 (m, 1H, C*H*N), 4.18 (br dd, 1H, ^2J = 9.8 Hz, ^3J = 4.8 Hz, N*H*), 6.98 (dd, J_{mp} = 4.9 Hz, J_{mo} = 8.4 Hz, H_m), 7.30−7.55 (m, 3H), 7.82 (dd, J_{mp} = 4.9 Hz, $^4J_{op}$ = 1.4 Hz, H_p), 8.81 (dd, J_{mo} = 8.4 Hz, $^4J_{op}$ = 1.4 Hz, H_o). Data for the minor (*RS*) isomer: ^{1}H NMR ($CDCl_3$) δ 0.93, 0.97 (2 d, J = 6.5 Hz, (C*H*$_3$)$_2$CH), 1.17 (s, C*H*$_3$CDPd), 1.7−2.1 (m, 3H, C*H*Me$_2$, C*H*$_2$), 2.19 (br d, 1H, ^2J = 10.0 Hz, N*H*), 3.74 (m, C*H*N), 4.87 (br dd, 1H, ^2J = 10.0 Hz, ^3J = 4.8 Hz, N*H*), 6.91 (dd, J_{mp} = 4.9 Hz, J_{mo} = 8.4 Hz, H_m), 7.30−7.55 (m, 3H), 7.77 (dd, $^4J_{op}$ = 1.6 Hz, H_p), 8.70 (dd, H_o). On the basis of integration of the peaks at δ 8.70 (*RS*) and 8.81 (*SS*) ppm, the mixture contained a 22% diastereomeric excess. The dominant structure was (*S*,*S*) based on Pfeffer's assignments as compared to the assignments given above.

Cleavage of the Optically Active Chloride Dimer (Formed from $Pd(OAc)_2$) with (*S*)-(+)-Leucine.[14] The same procedure as above was used with 69 mg (0.12 mmol) of $[PdCl(C_{11}H_9ND)]_2$, 30.5 mg (0.29 mmol) of Na_2CO_3, and 37.7 mg (0.29 mmol) of leucine. The yield of **7a** calculated to 133% due to the presence of water. ^{1}H NMR ($CDCl_3$) was as described above. On the basis of integration of the peaks at δ 8.70 (*RS*) and 8.81 ppm (*SS*), the mixture contained a 36% diastereomeric excess of (*S*,*S*).

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