First Enantioselective Catalyst for the Rearrangement of Allylic Imidates to Allylic Amides

Michael Calter,[1] T. Keith Hollis, Larry E. Overman,* Joseph Ziller, and G. Greg Zipp

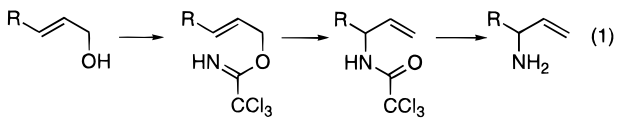
Department of Chemistry, 516 Physical Sciences 1, University of California, Irvine, California 92697-2025

Received November 8, 1996[⊗]

A series of Pd(II) complexes containing chiral diamine ligands were investigated as asymmetric catalysts for the rearrangement of allylic imidates to allyl amides. The best catalysts were cations obtained by dechlorination of dichloro[(*S*)-2-(isoindolinylmethyl)-*N*-methylpyrrolidine]palladium-(II) (**17**) with silver salts in CH_2Cl_2. Catalyst **18** was studied thoroughly and shown by ^{1}H NMR and X-ray crystallography analysis to be a C_1 symmetric dimer (Figure 1). A series of related catalysts **22**−**27** having various counterions and anionic ligands were also prepared and studied as asymmetric catalysts for the rearrangement of allylic *N*-(4-trifluorophenyl)benzimidate **29** to allylic benzamide **30** (eq 4). Rearrangement of **29** in CH_2Cl_2 (48 h at 40 °C) in the presence of 5 mol % of **18** affords (−)-**30** in 69% yield and 55% ee. Enantioselection is increased to 60% when an isomerically pure sample of **18** is employed. Chemical correlation of allylic benzamide **30** with (*R*)-norvaline established that (−)-**30** has the *R* absolute configuration (Scheme 3). A cyclization-induced rearrangement mechanism (Scheme 1) requires that in the major pathway the imidate nitrogen attacks the *re* face of the olefin with Pd coordinated to the *si* face. These studies constitute the first report of asymmetric catalysis of the rearrangement of allylic imidates to allylic amides. However, significant hurdles remain to be overcome before the enantioselective rearrangement of allylic imidates becomes a practical route to enantioenriched nitrogen compounds.

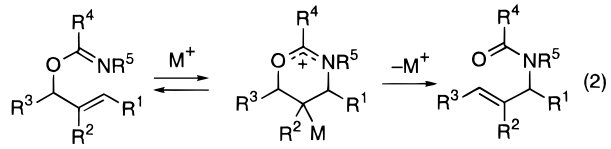
Introduction

The rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides with clean 1,3-transposition of the alkene moiety was first reported by one of us in 1974 (eq 1).[2] This rearrangement allows readily available allylic alcohols to be used as precursors of less available allylic amines and as such has been employed as a key element in the synthesis of a variety of nitrogen-containing molecules, including alkaloids, antibiotics, unnatural amino acids, and drug candidates.[3] In the original report, the rearrangement of allylic trichloroacetimidates was accomplished either thermally or by Hg(II) catalysis.[2a,b] This allylic transposition of oxygen and nitrogen functionality has been generalized to other allylic imidates, and soluble $PdCl_2$ complexes have emerged as optimal catalysts for the process.[2c,4−6]



(1)

The Pd(II)-catalyzed allylic imidate rearrangement tolerates considerable structural variation at all carbons including the internal alkene carbon (eq 2).[2c,4−6] There is substantial evidence that Hg(II)- and Pd(II)-catalyzed allylic imidate rearrangements occur by the mechanism outlined in eq 2, which we have termed cyclization-induced rearrangement catalysis.[5,6]



(2)

The development of an asymmetric Pd(II) catalyst for allylic imidate rearrangements would open up new opportunities for the synthesis of enantioenriched nitrogen compounds. Moreover, since palladium(II) complexes have been shown to catalyze a variety of allylic transpositions through cyclization-induced rearrangement mechanisms,[5,6] the possibility exists for evolving a catalytic process that would form a variety of allylic C−X bonds in asymmetric fashion. In this article we report our initial attempts to develop an enantioselective Pd(II) catalyst for the rearrangement of allylic imidates to allyl

⊗ Abstract published in *Advance ACS Abstracts,* February 15, 1997.

(1) Current address: Virginia Polytechnic Institute, Department of Chemistry, 104 Davidson Hall, Blacksburg, VA 24061-0212.

(2) (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597. (b) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901. (c) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218.

(3) Representative examples include: (a) Vyas, D. M.; Chiang, Y.; Doyle, T. W. *J. Org. Chem.* **1984**, *49*, 2037. (b) Hauser, F. M.; Ellenberger, S. R.; Glusker, J. P.; Smart, C. J.; Carrell, H. L. *J. Org. Chem.* **1986**, *51*, 50. (c) Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127. (d) Grigg, R.; Santhakumar, V.; Sridharan, V.; Thornton-Pett, M.; Bridge, A. W. *Tetrahedron* **1993**, *49*, 5177. (e) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829. (f) Saksena, A. K; Lovey, R. G.: Girijavallabhan, V. M.; Ganguly, A. K.; McPhail, A. T. *J. Org. Chem.* **1986**, *51*, 5024. (g) Isobe, M.; Fukuda, Y.; Nishikawa, T.; Chabert, P.; Kawai, T.; Goto, T. *Tetrahedron Lett.* **1990**, *31*, 3327. (h) Flynn, D. L.; Becker, D. P.; Nosal, R.; Zabrowski, D. L. *Tetrahedron Lett.* **1992**, *33*, 7283. (i) Takano, S.; Akiyama, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1984**, 770. (j) Mehmandoust, M.; Petit, Y.; Larchevêque, M. *Tetrahedron Lett.* **1992**, *33*, 4313. (k) Doherty, A. M.; Kornberg, B. E.; Reily, M. D. *J. Org. Chem.* **1993**, *58*, 795. (l) Gonda, J.; Helland, A.-C.; Ernst, B.; Bellus, D. *Synthesis* **1993**, 729. (m) Chen, A.; Savage, I.; Thomas, E. J.; Wilson, P. D. *Tetrahedron Lett.* **1993**, *34*, 6769. (n) Casara, P. *Tetrahedron Lett.* **1994**, *35*, 3049.

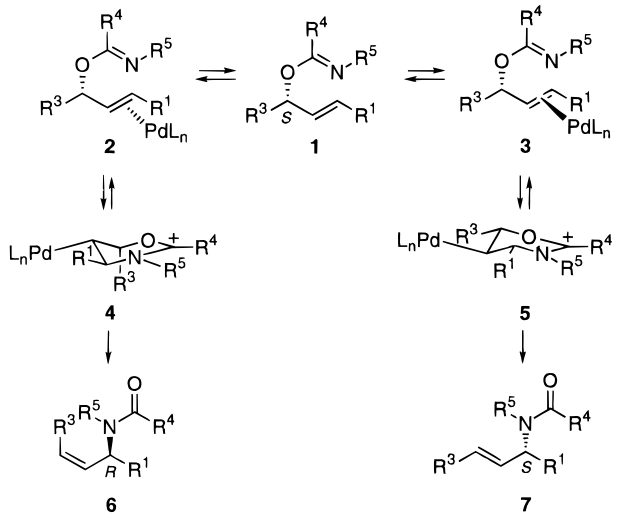
(4) (a) Ikariya, T.; Ishikawa, Y.; Hirai, K.; Yoshikawa, S. *Chem. Lett.* **1982**, 1815. (b) Metz, P.; Mues, C.; Schoop, A. *Tetrahedron* **1992**, *48*, 1071. (c) Mehmandoust, M.; Petit, Y.; Larchevêque, M. *Tetrahedron Lett.* **1992**, *33*, 4313. (d) Gonda, J.; Helland, A.-C.; Ernst, B.; Bellus, D. *Synthesis* **1993**, 729.

(5) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579.

(6) Schenck, T. G.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2058.

S0022-3263(96)02090-7 CCC: $14.00

Scheme 1



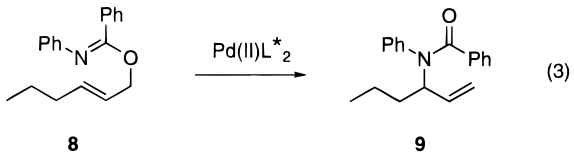
a: $R^1 = R^4 = R^5 = Ph$, $R^3 = Me$
b: $R^1 = Ph$, $R^3 = Me$, $R^4 = CCl_3$, $R^5 = H$

amides. To our knowledge, asymmetric catalysis of this rearrangement has not been reported previously.

Results and Discussion

Initial Studies. Before designing an asymmetric catalyst for the allylic imidate rearrangement, one would like to know which steps in the Pd(II)-catalyzed reaction are irreversible.[7] Unfortunately, no kinetic information is available about the elementary steps of the catalytic cycle depicted in Scheme 1. However, some insight is available from Bosnich's investigation of rearrangements of enantioenriched allylic imidates.[6] In this study, it was found that the $PdCl_2$-catalyzed rearrangement of (*S*)-*N*-phenylbenzimidate **1a** produces a 1:4 mixture of allylic amides **6a** and **7a**, while (*S*)-trichloroacetimidate **1b** gives **7b** as the sole product under similar conditions. A plausible, though not unique, rationalization of these results is the following. If stereochemistry in the catalyzed rearrangement of **1** is determined in the cyclization step, one would expect **7** to heavily predominate, since R^3 would be equatorial in cyclic intermediate **5**.[8,9] Apparently, cyclizations of Pd complexes **2a** and **3a** derived from the *N*-phenylbenzimidate are sufficiently fast that face selectivity in the alkene complexation step at least partially determines product composition. In the case of trichloroacetimidate **1b**, the imidate nitrogen is less nucleophilic, and cyclization becomes the first irreversible step.

The rearrangement of prochiral *N*-phenylbenzimidate **8** was chosen for our initial investigations based on the supposition that alkene complexation would likely be the enantiodifferentiating step in catalytic asymmetric rearrangements of this substrate (eq 3). Imidate **8** incorporated a trans alkene, since preliminary modeling had shown that this isomer would provide more opportunity for distinguishing the prochiral faces of the double bond. It would also be essential that the ligands of the Pd(II) catalyst not be strongly electron-donating or the ability of the catalyst to activate the alkene toward nucleophilic attack by the imidate nitrogen would be compromised. Not surprisingly, our initial investigations in this area had shown that phosphine-containing Pd(II) catalysts were unsatisfactory.[10] Consequently, the current investigation focused on Pd(II) catalysts containing less-donating diamine ligands.



(3)

The well-characterized achiral diamine complexes $[PdCl_2(bpy)]$ (**10**) and $[PdCl_2(TMEDA)]$ (**11**) were initially screened to evaluate ligands containing planar unsaturated nitrogen and saturated nitrogen donor atoms, respectively.[11] These dichloride catalysts were found to be catalytically inactive. In order to increase the lability of the Pd coordination sphere, one of the chlorides was exchanged for a more labile ligand to create a cationic complex. Thus, reaction of **10** with 1 equiv of $AgBF_4$ in DMF in the presence of 1 equiv of DMSO provided a product[12] that was catalytically active, yielding allylic benzamide **9** in 62% yield together with some *N*-phenylbenzamide resulting from elimination. Upon the basis of this observation, a series of enantiopure bis(oxazoline)-palladium cations were assayed; however, they provided **9** in moderate to poor yields (≤62%) and low enantioselectivities (≤10% ee).[13]

The cation prepared by allowing the saturated diamine complex **11** to react with 1 equiv of $AgBF_4$ in DMF in the presence of 2 equiv of DMSO was also catalytically inactive. Reasoning that the inactivity of this TMEDA catalyst resulted from steric hindrance preventing alkene coordination, $[PdCl_2(1,2\text{-ethylenediamine})]$[11] was dechlorinated with $AgBF_4$. The resulting cation (10 mol %, DMF, 25 °C, 40 h) was found to catalyze the rearrangement of allylic imidate **8** giving benzamide **9** in 56% yield together with only a trace of *N*-phenylbenzamide. Encouraged by this result, the chiral diamine (*R*,*R*)-*trans*-1,2-cyclohexyldiamine was treated with $[PdCl_2(MeCN)_2]$ to produce $[PdCl_2((R,R)\text{-}trans\text{-}1,2\text{-cyclohexyldiamine})]$ which was dechlorinated with $AgBF_4$. The resulting cationic complex (10 mol %) catalyzed the rearrangement of **8** in DMF or CH_2Cl_2 providing **9** in 13% ee and 74% yield (DMF) or 5% ee and 78% yield (CH_2Cl_2). The observed enantioselectivity stimulated us to prepare an analogous secondary amine complex based on (*R*,*R*)-*trans*-*N*,*N*′-diethyl-1,2-cyclohexyldiamine (**12**) that would

(7) In a catalytic asymmetric reaction, the first irreversible enantiodifferentiating step determines asymmetric induction, see: Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. For an exception, see: Zhang, W.; Lee, N. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 425.

(8) High selectivity for forming **7** is seen in related thermal rearrangements,[9] which are believed to proceed by a chair transition state related to intermediate 5.[2]

(9) Yamamoto, Y.; Shimoda, H.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3247.

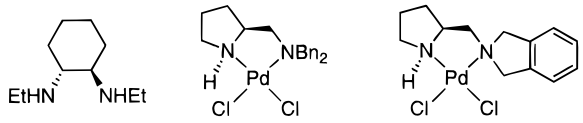
(10) Catalysts of composition $PdCl_2$(diphosphine) are inactive, while catalysts prepared from the reaction of diphosphines (1 equiv) with $Pd(MeCN)_4(BF_4)_2$ promoted elimination of allylic imidates. Unpublished studies of A. Renaldo, UCI, 1983.

(11) Wimmer, F. L.; Wimmer, S.; Castan, P. *Inorg. Synth.* **1992**, *29*, 185. The TMEDA complex was perpared analogously to the procedure for $[Pd(bpy)Cl_2]$.

(12) Annibale, G.; Cattalini, L.; Bertolasi, V.; Ferreti, V.; Gilli, G.; Tobe, M. L. *J. Chem. Soc., Dalton Trans.* **1989**, 1265.

(13) These experiments are summarized in the Supporting Information. For a recent review of oxazolidine-derived asymmetric catalysts, see: Ager, O. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

also be chiral at nitrogen.[14] Unfortunately, the palladium complex obtained from reaction of diamine **12** with $[PdCl_2(CH_3CN)_2]$ was a mixture of stereoisomers and this complex was not pursued further.

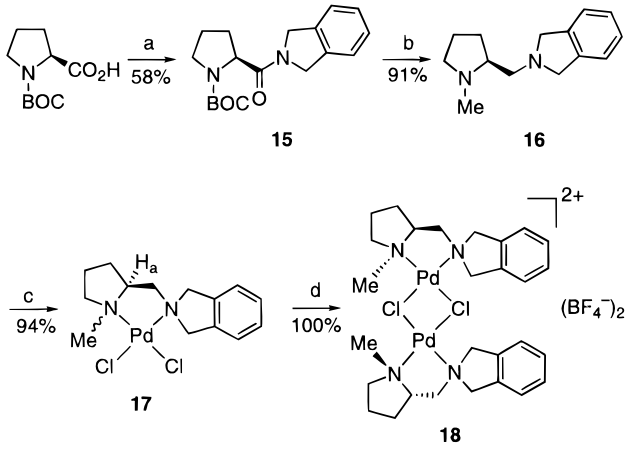


12 **13** **14**

An established method for obtaining a single diastereomeric chelate is to incorporate the coordinating atom(s) into a bicyclo[3.3.0]octane framework.[15] Several chiral diamine catalysts embodying this design feature were easily prepared from L-proline. Mono-dechlorination of dichloro[(*S*)-2-(*N*,*N*-dibenzylaminomethyl)pyrrolidine]-palladium(II) (**13**), however, provided a cation that was catalytically inactive. Based on the upfield ^{1}H NMR shifts of the *ortho* aromatic hydrogens of this complex, an agostic interaction was inferred as the cause of the inactivity.[16] In order to avoid an agostic interaction, dichloro[(*S*)-2-(isoindolinylmethyl)pyrrolidine]palladium-(II) (**14**) was prepared. Rearrangement of allylic imidate **8** in CH_2Cl_2 with 10 mol % of the cation formed from mono-dechlorination of **14** produced benzamide **9** in 80% yield, however, in only 16% ee. Assuming that enantioselection arose from alkene coordination to Pd cis to the chiral pyrrolidine unit, as opposed to coordination cis to the "meso" isoindole unit, increasing the size of the proximal nitrogen substituent from H to Me was expected to improve asymmetric induction. The preparation of these *N*-Me complexes and their evaluation as catalysts for the allylic imidate rearrangement is the subject of the remainder this report.

Preparation and Characterization of Palladium Diamine Complexes. *N*-Boc-(*S*)-proline was coupled to 1,3-dihydroisioindole yielding amide **15**, which was reduced to (*S*)-2-(isoindolinylmethyl)-*N*-methylpyrrolidine (**16**) as outlined in Scheme 2.[17] Diamine **16** was then complexed with $[PdCl_2(MeCN)_2]$ in MeCN at 50 °C (or with $Na_2[PdCl_4]$ in EtOH at rt) producing dichloro[(*S*)-2-(isoindolinylmethyl)-*N*-methylpyrrolidine]palladium-(II) (**17**) as a 5:1 (or 10:1) mixture of diastereomers. The major diastereomer was identified as the desired *cis*-bicyclo[3.3.0]octane chelate based on ^{1}H NOE experiments: irradiation of the *N*-Me group resulted in a 7% enhancement of H_a. Assignment of the minor diastereomer as the *trans*-bicyclo[3.3.0]octane complex seems reasonable due to the general observation that simple diamines form chelated palladium complexes, as opposed to a diamine bridged dimer or other structure.[18] A single crystal X-ray diffraction study confirmed the

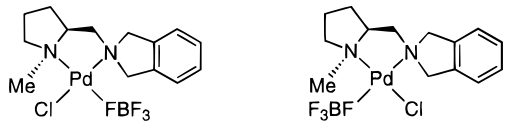
Scheme 2

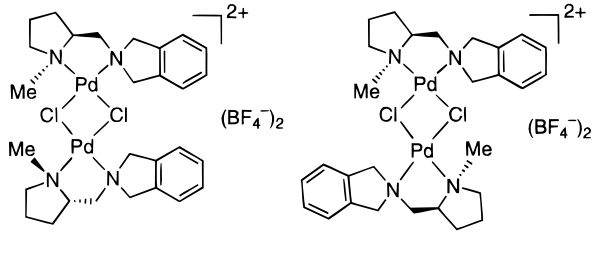


[a]Conditions: (a)1,3-dihydroisoindole, DCC, CH_2Cl_2; (b) $LiAlH_4$, THF, reflux; (c) Method A: $[PdCl_2(MeCN)_2]$, MeCN (ds = 5:1); Method B: Na_2PdCl_4, EtOH (ds = 10:1); (d) $AgBF_4$, CH_2Cl_2.

assignment of the *cis*-bicyclo[3.3.0]octane structure to the major isomer of **17**.[19]

Dechlorination of **17** with $AgBF_4$ in CH_2Cl_2 produced a microcrystalline orange solid **18** showing the expected elemental composition. This material displayed a complex ^{1}H NMR spectrum in CD_2Cl_2 or CD_3NO_2 showing two diagnostic methyl singlets in a 1:1 ratio. This latter observation could be consistent with several structures: (1) two monomeric palladium complexes in a 1:1 ratio where the chloride ligand occupies either of the unique coordination positions on palladium, depicted as **A** and **B**, (2) two different C_2 symmetric dimers, **C** and **D**, present in a 1:1 ratio, or (3) one of the dimers, **C** or **D**, could be C_1 symmetric placing the methyl groups in chemical shift inequivalent environments.





Of these explanations we favor the C_1 symmetric complex **C** for the structure of **18** in solution based on the solid state structure of **18** obtained by single crystal X-ray diffraction and on the strong dimer ions observed

(14) Diamine **12** was prepared by diacetylation of (*R*,*R*)-*trans*-1,2-cylclohexyldiamine followed by reduction with $LiAlH_4$: Lumma, W. C., Jr.; Wohl, R. A.; Davey, D. D.; Argentieri, T. M.; DeVita, R. J.; Gomez, R. P.; Jain, V. K.; Marisca, A. J.; Morgan, T. K., Jr.; Reiser, H. J.; Sullivan, M. E.; Wiggins, J.; Wong, S. S. *J. Med. Chem.* **1987**, *30*, 755.

(15) (a) Dokuzovic, Z., Roberts, N. K, Sawyer, J. F., Whelan, J., Bosnich, B. *J. Am. Chem. Soc.* **1986**, *108*, 2034. (b) Mukaiyama, T.; Asami. M. *Top. Curr. Chem.* **1985**, *127*, 133.

(16) Brookhart, M.; Green, M. L. H. *J. Organomet. Chem.* **1983**, *250*, 395. Crabtree, R. H.; Hamilton, D. G. *Adv. Organomet. Chem.* **1988**, *28*, 299.

(17) For other applications of this ligand, see, *inter alia*, Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805.

(18) A search of the Cambridge Crystallographic Data base revealed only one simple diamine that bridged two palladium atoms. This example involved a *trans*-2,3-norbornyldiamine that cannot form the simple chelate. Hatano, K.; Saito, R. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3818.

(19) Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

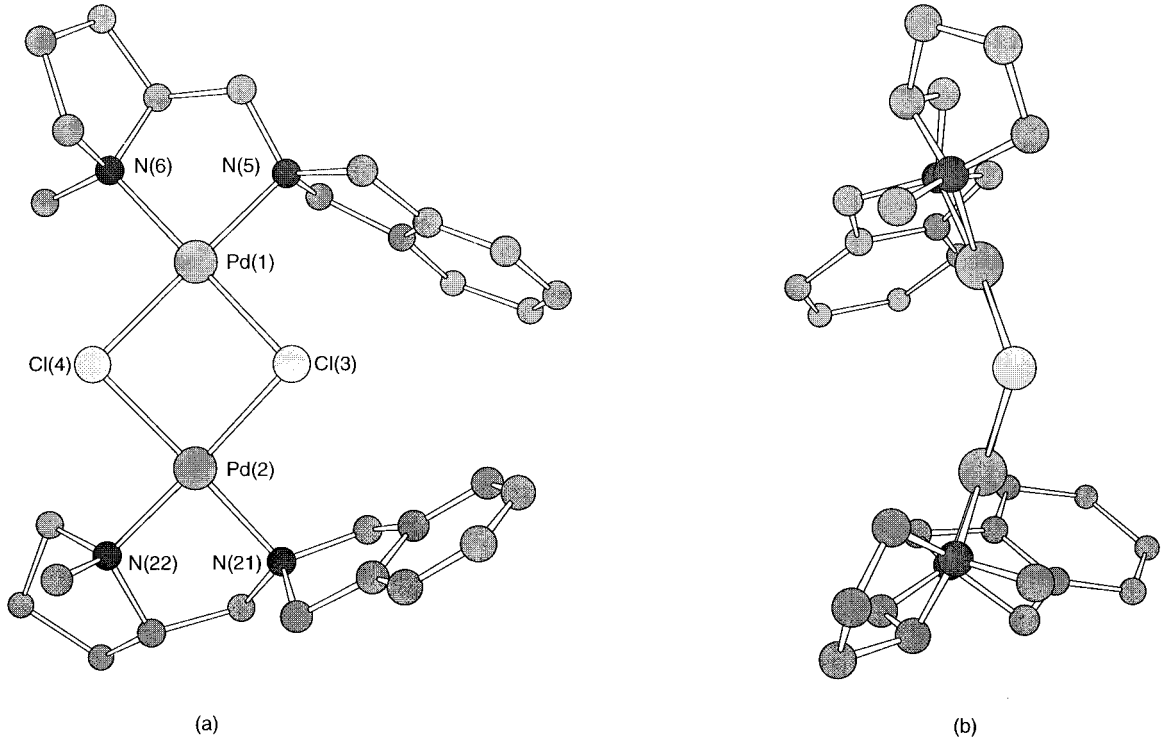
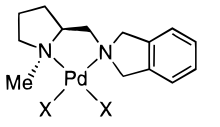


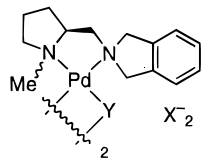
Figure 1.

by liquid secondary ion mass spectrometric analysis of **18** in 3-nitrobenzylalcohol. Figure 1 depicts two views of the crystal structure of **18**, together with selected bond lengths and angles.[19] The most obvious feature of the structure of **18** is the bend of the chloride bridges resulting in a C_1 symmetric structure. The Pd−N and Pd−Cl bond lengths are all in the lower quartile of a recent statistical analysis of crystal structures.[20] The reason for the short Pd−N bonds relative to other tertiary amine complexes is likely due to each nitrogen of **18** being part of a ring, which reduces steric congestion, and to the dicationic nature of this complex. The unusually short Pd−Cl bond lengths are also attributed to the complex being a dication. The Pd−Pd distance of 3.267 Å is well beyond that expected for a metal−metal interaction.[21] The bend at the μ-chloride bridges seems to be the result of electrostatic attraction since one of the tetrafluoroborate counterions is located in the "cupped" region formed by the bend. That the C_1 symmetric structure of **18** is retained in solution provides the simplest explanation for the observed ^{1}H NMR spectrum.

The bridging ligand and counter-ions in dication **18** were systematically varied to pursue what effects these structural changes would have on catalysis. The requisite precursors, dibromo[(*S*)-2-(isoindolinylmethyl)-*N*-methylpyrrolidine]palladium(II) (**19**), diiodo[(*S*)-2-(isoindolinylmethyl)-*N*-methylpyrrolidine]palladium(II) (**20**), and dithiocyanato[(*S*)-2-(isoindolinylmethyl)-*N*-methylpyrrolidine]palladium(II) (**21**), were prepared in standard fashion. The ^{1}H NMR spectra of complexes **19** and **20** indicates the presence of only a single isomer, which is assigned in each case as the *cis*-bicyclo[3.3.0]octane structure analogous to the major isomer of **17**. The ^{1}H NMR spectrum of complex **21** was much more complex, suggesting the possibility of four linkage isomers in the thiocyanato ligand.[22] Reaction of adducts **17** and **19**−**21** with the appropriate silver salt led to the isolation of a series of palladium cations, **22**−**27**. ^{1}H NMR spectra of complexes **22**−**27** are similar to that observed for **18**, and these complexes are likewise assigned as dimers. The ^{1}H NMR spectrum of **27** was more complex than the others, suggesting again linkage isomers of the thiocyanato ligand. Complex **28** was not pursued since it decomposed during isolation.[23]



19 X = Br
20 X = I
21 X = SCN

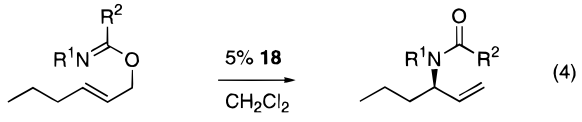


22 X = SbF_6, Y = Cl
23 X = PF_6, Y = Cl
24 X = BF_4, Y = Br
25 X = OTf, Y = Cl
26 X = OTf, Y = I
27 X = OTf, Y = SCN
28 X = BPh_4, Y = Cl

Catalysis with Palladium Diamine Cations. The rearrangement of *N*-phenylbenzimidate **8** was initially studied. Exposure of **8** to 10 mol % of the dimeric dication **18** at rt in CH_2Cl_2 provided benzamide **9** in 41% ee. However, the yield of **9** was only 18% after 72 h, with elimination to form *N*-phenylbenzamide being a major side reaction. On the assumption that the competing elimination reaction was triggered by coordination of the imidate nitrogen to the palladium cation, we examined three less basic (*E*)-2-hexenyl imidates: *N*-(4-trifluo-

(20) Orpen, A. G.; Brammer, L.; Allen, F. H.; Kennard, O.; Watson, D. G.; Taylor, R. *J. Chem. Soc., Dalton Trans.* **1989**, S1.
(21) Albeniz, A. C.; Espinet, P. In *Encyclopedia of Inorganic Chemistry*; King, R. B., Ed.; John Wiley & Sons: New York, 1994; Vol. 6, p 3010.
(22) Meek, D. W.; Nicpon P. E.; Meek,V. I. *J. Am. Chem. Soc.* **1970**, *92*, 5351.
(23) The transfer of phenyl from BPh_4 to Pd(II) has been described, see: (a) Crociani, B.; Di Bianca, F., Canovese, L.; Uguagliati, P. *J. Organomet. Chem.* **1990**, *381*, C17. (b) Garrou, P. E. *Chem. Rev.* **1985**, *85*, 171.

rophenyl)benzimidate **29**, trichloroacetimidate **31**,[2] and *N*-benzoylbenzimidate **32**[24] (eq 4). Exposure of **29** to 5 mol % of **18** at 40 °C in CH_2Cl_2 provided (−)-benzamide **30** in 55% ee and in an improved yield of 69% after 48 h. The products of [1,3] rearrangement, *N*-(2-hexenyl)-*N*-[(4-trifluoromethyl)phenyl)]benzamide, and elimination constituted the bulk of the remaining mass. Variation of the solvent for the rearrangement of **29** → **30** with 5 mol % **18** was also studied. However, no increase in enantioselectivity was observed: $CHCl_3$ (54% ee), DMF (35% ee), or CD_3NO_2 (55% ee). In marked contrast, hexenylimidates **31** and **32** did not undergo [3,3]-sigmatropic rearrangement efficiently when exposed to 5 mol % of **18** at 40 °C in CH_2Cl_2. In these latter cases, elimination to form trichloroacetamide or dibenzamide was the major reaction pathway.[25−27]



(4)

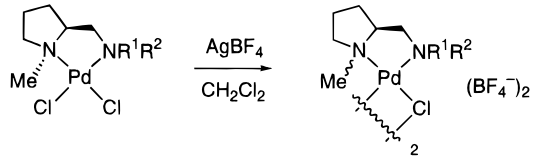
29 R^1 = 4-$CF_3C_6H_4$, R^2 = Ph
31 R^1 = H, R^2 = CCl_3
32 R^1 = COPh, R^2 = Ph

30 R^1 = 4-$CF_3C_6H_4$, R^2 = Ph

The related palladium diamine dications **22**−**27** were also examined as catalysts for the rearrangement of **29** → **30**. Representative results observed in forming **30** using 5% of the indicated catalysts are: **22** (CD_2Cl_2, 40 °C, 5 d, 48% ee, 68%), **23** (CD_2Cl_2, 40 °C, 5 d, 50% ee, 75%), **24** (CD_2Cl_2, rt, 18 d, 51% ee, 47%), **25** (CD_2Cl_2, 40 °C, 3 d, 56% ee, 66%; $PhNO_2$, 40 °C, 10 h, 50% ee, 68%); **26** (CD_2Cl_2, 40 °C, 8 d, 30% ee, 25%), **27** (CD_2Cl_2, 40 °C, 6 d, 28% ee, <20%). These results revealed no improvement in enantioselectivity with the structural modifications made thus far.[28] However, catalyst **25** does promote the rearrangement of **29** at a practical rate in nitrobenzene, affording **30** in 68% yield and 50% ee after 10 h at 40 °C.

The effect of the minor isomer present in **17** upon enantioselectivity was a concern throughout these studies. Therefore, a CD_2Cl_2 solution of **18** was treated with Et_4NCl (1.4 equiv) to produce an 8:1 mixture of diastereomers of **17**, which confirmed the presence of the dication derived from the minor isomer of **17** in the previous catalyses. Luckily when a sample of **17** was heated in MeCN at 50−70 °C for 24 h, the ^1H NMR spectrum indicated that none of the minor diastereomer remained. Isomerically pure **17** obtained in this way was dechlorinated to provide **18**. Rearrangement of allylic imidate **29** with this sample of "isomerically pure" **18** produced **30** in 60% ee (vs 55% ee with **18** formed from less stereoisomerically pure **17**), indicating that the minor diastereomer had little effect on the observed enantioselectivity.

We also briefly investigated two additional cationic palladium diamine catalysts, **34** and **36**, which differ from **18** and **22**−**27** in having the isoindolinyl group replaced by a piperidine or 1-naphthyl moiety. Catalysts **34** and **36** were prepared by dechlorination of the corresponding dichlorides **33** and **35** (eq 5), which in turn were prepared from *N*-Boc-(*S*)-proline using a sequence analogous to that of Scheme 2. While the 1-naphthyl catalyst **36** showed two diagnostic methyl signals in a 1:1 ratio in its ^1H NMR spectra and is presumed to be a C_1 symmetric dimer, the piperidyl catalyst **35**, surprisingly, displayed a single methyl signal. Since these cations were poorer catalysts for the **29** → **30** rearrangement than **18** (**35**: CD_2Cl_2, 40 °C, 2 d, 22% ee and 60% yield; **36**: CD_2Cl_2, 40 °C, 2 d, 44% ee and 63% yield), they were not pursued further.



(5)

33 R^1 = R^2 = $(CH_2)_5$
35 R^1 = H, R^2 = 1-napthyl

34 R^1 = R^2 = $(CH_2)_5$
36 R^1 = H, R^2 = 1-napthyl

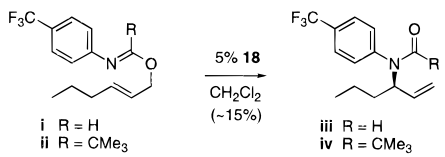
Determination of the Absolute Configuration of 30. A chemical correlation of allylic benzamide **30** with (*R*)-norvaline was carried out to establish the absolute configuration of (−)-**30** as depicted in Scheme 3. After protection of (*R*)-norvalinol[29] as the *tert*-butyl ether, amino ether **37** was subjected to Buchwald's aryl-amination procedure[30] to provide **38**. Cleavage of the *tert*-butyl group[31] yielded *N*-[4-(trifluoromethyl)phenyl]norvalinol (**39**), which showed a rotation at the Na line of +19.7. A sample of benzamide **30** ($[\alpha]^{23}_D$ −37.2, 55% ee) that was obtained by rearrangement of **29** with **18** was cleaved with ozone followed by reduction with $NaBH_4$ to produce **39**, which exhibited a rotation at the Na line of +9.7 establishing the *R* absolute configuration for the major enantiomer of **30** produced in the catalyzed rearrangement. A cyclization-induced rearrangement mechanism (Scheme 1) would then require that in the major pathway the imidate nitrogen attacks the *re* face of the olefin with Pd coordinated to the *si* face.

Conclusion. A series of cationic Pd(II) diamine complexes were prepared and shown to catalyze the rearrangement of prochiral allylic *N*-arylbenzimidate **29** to chiral *N*-arylbenzamide **30** with enantiomeric excesses

(24) Overman, L. E.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, in press.

(25) *N*-(1-ethenylbutyl)trichloroacetamide (5% ee by HPLC analysis using a Chiracel OD column) was isolated in 20% yield from rearrangement of **31** with **18**, while *N*-(1-ethenylbutyl)dibenzamide[24] (22% ee by HPLC analysis using a Chiracel OD column) was isolated in 30% yield from rearrangement of **32** with **18**.

(26) Catalytic rearrangements of *N*-[(4-trifluoromethyl)phenyl]-formimidate **i** and pivalimidate **ii** with 5 mol % of **18** at 40 °C in CH_2Cl_2 were also examined. The rearranged amides **iii** (37% ee by HPLC analysis using a Chiracel OD column) and **iv** (42% ee by HPLC analysis using a Chiracel AS column) were obtained in low yield and shown by chemical correlation to have the same absolute configuration as (−)-**30**.



i R = H
ii R = CMe_3

iii R = H
iv R = CMe_3

(27) The *Z* congener of **29** rearranged with 5 mol % of **23** (CH_2Cl_2, 40 °C, 48 h) to produce (+)-**30** in 86% yield and 63% ee. The rearrangement of other imidates has not been examined with catalyst **23**, since our current efforts focus on a more promising catalyst type (K. Hollis, unpublished results).

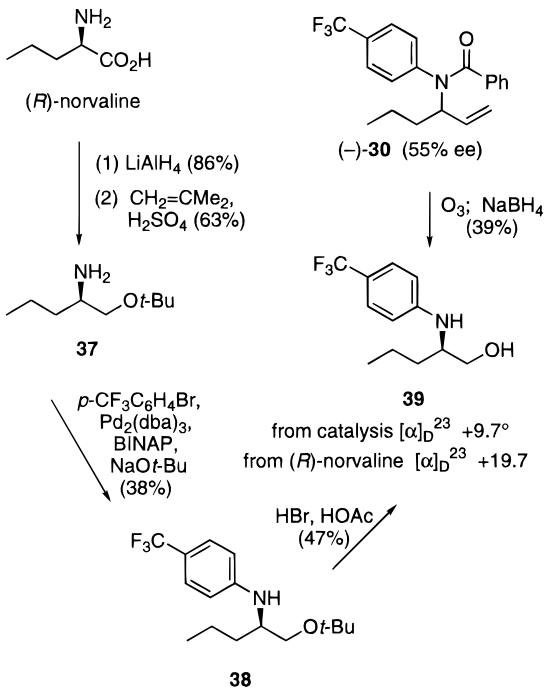
(28) Several achiral and chiral sulfoxides were used to modify the coordination sphere of **18** in an unsuccessful attempt to improve enantioselection in the rearrangement of allylic imidate **29**. Details are provided in the Supporting Information.

(29) Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Organic Syntheses*; Wiley, New York, 1990; Collect. Vol. VII, p 530. Rinaldi, P. L.; Wilk, M. J. *J. Org. Chem.* **1986**, *48*, 2141.

(30) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

(31) Callahan, F. M.; Anderson, G. W.; Paul, R.; Zimmerman, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 201.

Scheme 3



of up to 60%. To the best of our knowledge this is the first report of asymmetric catalysis of the rearrangement of allylic imidates to allylic amides. Clearly, significant hurdles remain to be overcome before enantioselective rearrangement of allylic imidates becomes a practical route to enantioenriched nitrogen compounds. Our continuing efforts to find improved asymmetric catalysts for allylic imidate rearrangements and other sigmatropic rearrangements will be reported in due course.

Experimental Section[32]

(*E*)-2-Hexenyl *N*-Phenylbenzimidate (8). A suspension of NaH (0.37 g, 60% dispersion in oil, 9.3 mmol) in THF (10 mL) was cooled to 0 °C, and (*E*)-2-hexen-1-ol (1.09 mL, 9.24 mmol) (>99% *E* by ^{1}H NMR analysis) was added dropwise over 5 min. After 30 min at 0 °C, the solution was warmed to rt, maintained at rt for 30 min, and then recooled to 0 °C. A solution of *N*-phenylbenzimidoyl chloride (2.00 g, 9.27 mmol)[6] and THF (5 mL) was added, and the reaction mixture was stirred at rt for 20 h. Water (10 mL) was then added slowly, the resulting mixture was diluted with EtOAc (20 mL), and the layers were separated. The aqueous phase was washed with EtOAc (2 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated to afford a light yellow oil, which was purified by silica gel chromatography (1:19 EtOAc−hexanes) to yield imidate **8** (2.50 g, 96%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.16 (m, 7H), 6.96 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.4 Hz, 2H), 5.95−5.76 (m, 2H), 4.84 (d, J = 5.6 Hz, 2H), 2.11 (q, J = 6.9 Hz, 2H), 1.55−1.40 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 148.5, 135.6, 131.5, 129.8, 129.3, 128.8, 127.9, 124.8, 122.5, 121.6, 67.3, 34.5, 22.2, 13.7; IR ($CDCl_3$) 1637 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.75; H, 7.61; N, 5.01.

(32) The procedure we employed to purify THF, CH_2Cl_2, and toluene has been recently described: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518. Hexanes were distilled from CaH_2 under nitrogen. High resolution mass spectra were measured on a MicroMass Analytical 7070E (EI or CI-isobutane); uncertainty (σ) in mass measurments is 1.0 millimass unit (molecular weight < 400) or 1.5 millimass units (molecular weight 400−1000). Other general experimental details have been detailed: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

***N*-(1-Ethenylbutyl)-*N*-phenylbenzamide (9).** Prepared according to the typical catalytic procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.10 (m, 9H), 7.01 (d, J = 6.6 Hz, 1H), 5.85 (ddd, J = 17.0, 11.8, 7.2 Hz, 1H), 5.3−5.2 (m, 1H), 5.27 (d, J = 17.0 Hz, 1H), 5.19 (d, J = 10.3 Hz, 1H), 1.74−1.40 (m, 4H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 140.9, 137.5, 137.0, 129.9, 129.0, 128.6, 128.3, 127.6, 127.1, 117.4, 59.7, 34.3, 19.8, 13.9; IR ($CDCl_3$) 1623 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.69; H, 7.59; N, 5.05.

(*S*)-2-(Isoindolinylmethyl)-*N*-methylpyrrolidine (16). A solution of DCC (2.30 g, 10.7 mmol) and CH_2Cl_2 (10 mL) was added dropwise at 0 °C to a solution of *N*-Boc-(*S*)-proline (2.10 g, 9.76 mmol), isoindoline (1.28 g, 10.7 mmol), and CH_2Cl_2 (50 mL). The ice bath was removed, and the reaction was stirred at rt. A white precipitate formed within 24 h, and after 48 h the reaction mixture was concentrated, slurried with Et_2O, filtered, and concentrated again to provide a pale pink oil (3.89 g). This oil was chromatographed on silica gel [200 g, packed with hexanes (200 mL) containing Et_3N (0.5 mL)], eluting with 75, 80, 85, and 90% EtOAc in hexanes (200 mL each) to afford amide **15** (1.8 g, 58%) as a colorless solid. A pure sample of **15** was obtained by recrystallization from 75% EtOAc in hexanes: mp 167−169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) (two rotamers) δ 7.35−7.2 (m, 8H), 5.19 (d, J = 13.6 Hz, 1H), 4.99 (d, J = 12.4 Hz, 1H), 4.93−4.73 (m, 6H), 4.59 (dd, J = 7.7, 3.6 Hz, 1H), 4.47 (dd, J = 8.0, 4.9 Hz, 1H), 3.68−3.41 (m, 4H), 2.29−2.06 (m, 4H), 2.05−1.81 (m, 4H), 1.45 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ171.7, 171.5, 154.5, 153.7, 136.3, 136.3, 136.1, 136.0, 127.9, 127.6, 127.6, 127.3, 123.0, 122.8, 122.6, 122.5, 105.3, 79.6, 79.5, 57.7, 57.4, 52.4, 52.3, 52.1, 46.8, 46.6, 30.3, 29.5, 28.4, 28.3, 24.4, 23.7; IR ($CDCl_3$) 1680, 1655 cm^{-1}; $[\alpha]^{25}_{D}$ +1.6, $[\alpha]^{25}_{577}$ −8.2, $[\alpha]^{25}_{546}$ −7.5, $[\alpha]^{25}_{435}$ −1.3, $[\alpha]^{25}_{405}$ −3.6, (*c* 0.5, CH_2Cl_2). Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.43; H, 7.68; N, 8.89.

A solution of $LiAlH_4$ (6.5 mL, 1.0 M in THF) was added dropwise to a solution of amide **15** (510 mg, 1.6 mmol) and THF (20 mL) at 0 °C. The ice bath was removed, and the reaction was heated at reflux overnight. After cooling to 0 °C, Na_2SO_4·$10H_2O$ was added until gas evolution ceased. The resulting slurry was filtered, and the filtrate was concentrated to a faintly pink oil (341 mg, 98%). A sample (232 mg) of this material was purified by bulb-to-bulb distillation (60−150 °C, 1 mmHg) to provide diamine **16**[17] as a colorless oil (212 mg, 91%):[33] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.15 (m, 4H), 3.96 (s, 4H), 3.07 (td, J = 9.1, 1.9 Hz, 1H), 2.93 (dd, J = 11.9, 4.6 Hz, 1H), 2.65 (dd, J = 11.8, 8.1 Hz, 1H), 2.44 (s, 3H), 2.38−2.29 (m, 1H), 2.25−2.16 (m, 1H), 2.12−2.00 (m, 1H), 1.88−1.61 (m, 3H); ^{13}C NMR(125 MHz, $CDCl_3$) 140.1, 126.5, 122.1, 64.7, 61.0, 59.8, 57.7, 41.4, 30.5, 22.5; MS (CI) *m*/*z* 217.1704 (MH, 217.1704 calcd for $C_{14}H_{20}N_2$).

Dichloro[(*S*)-2-(isoindolinylmethyl)-*N*-methylpyrrolidine]palladium(II) (17). Method A. A solution of diamine **16** (104 mg, 0.478 mmol) and MeCN (5 mL) was added to a 50 °C solution of $PdCl_2(MeCN)_2$ (118 mg, 0.455 mmol) and MeCN (20 mL). After stirring for 3 h at 50 °C, the reaction was concentrated to ~5 mL and Et_2O (15 mL) was added. The resulting orange solid was collected and dried under vacuum to give 168 mg (94%) of **17** as a 5:1 mixture of diastereomeric complexes: ^{1}H NMR (500 MHz, CD_3CN) signals for the major *cis*-bicyclo[3.3.0]octane isomer: δ 7.29−7.26 (m, 4H), 5.29 (d, J = 15.3 Hz, 1H), 5.02 (d, J = 14.6 Hz, 1H), 4.44 (d, J = 14.5 Hz, 1H), 4.04 (d, J = 15.0, 1H), 3.87−3.80 (m, 1H), 3.49−3.44 (m, 1H), 3.10−3.06 (m, 1H), 2.87 (dd, J = 13.1, 11.8 Hz, 1H), 2.77 (s, 3H), 2.64 (dd, J = 13.7, 4.7 Hz, 1H), 2.1−1.9 (m, 3H), 1.64−1.58 (m, 1H); diagnostic peaks of the minor isomer δ 5.16 (d, J = 14.4 Hz, 1H), 5.06 (d, 1H, overlapping with d of *cis*-isomer), 4.32 (d, J = 14.4, 1H), 4.27 (d, J = 14.4, 1H), 3.55−3.51 (m, 1H), 3.20 (ddd, J = 12.4, 8.5, 1.9 Hz, 1H), 3.04−3.01 (m, 1H), 2.65 (s, 3H, overlapping with m of *cis*-isomer), 2.60 (dd, J = 14.0, 1.2 Hz, 1H), 2.54 (dd, J = 13.9, 4.7 Hz, 1H),

(33) A racemic sample was prepared from racemic proline and analyzed on a Chiracel OD HPLC column (5% *i*-PrOH/hexane) giving two peaks; the diamine prepared from (*S*)-proline showed only a single peak.

1.55−1.46 (m, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 137.1, 135.6, 127.7, 127.5, 122.9, 122.5, 71.37, 67.0, 66.3, 63.7, 59.0, 49.1, 22.8, 21.2. Anal. Calcd for $C_{14}H_{20}N_2Cl_2Pd$: C, 42.72; H, 5.12; N, 7.12. Found: C, 42.73; H, 5.09; N, 7.03. An X-ray quality crystal was grown by slow evaporation of a MeCN solution.

Method B. A solution of diamine **16** (62.7 mg, 0.290 mmol) and EtOH (1 mL) was added to a red-brown suspension of Na_2PdCl_4 (82.5 mg, 0.280 mmol) and EtOH (1 mL), producing a yellow suspension. After rapidly stirring for 3 h, the solid was collected, dissolved in CH_2Cl_2, filtered through Celite, and concentrated again, and the residue was dissolved in CH_2Cl_2/hexanes (1:2, 12 mL) and slowly concentrated. Bright yellow crystals of **17** were collected and found to be the $0.5CH_2Cl_2$ solvate. ^{1}H NMR analysis indicated that this sample was a 10:1 mixture of diastereomeric complexes. Anal. Calcd for $C_{14}H_{20}N_2Cl_2Pd{\cdot}0.5CH_2Cl_2$: C, 39.94; H, 4.85; N, 6.42. Found: C, 39.84; H, 4.86; N, 6.36.

Di-μ-chloro-bis[(*S*)-2-(isoindolinylmethyl)-*N*-methylpyrrolidine]dipalladium(II) Bis(tetrafluoroborate) (18). A solution of **17** (51.4 mg, 0.131 mmol) and CH_2Cl_2 (6 mL) was added to $AgBF_4$ (98%, 260 mg, 0.131 mmol). The resulting suspension was stirred vigorously overnight, filtered through Celite, and then concentrated. The resulting solid was dissolved in CH_2Cl_2 (5 mL), filtered, and again concentrated. After drying under vacuum an orange powder was obtained (58.5 mg, 100%).[34,35] An X-ray quality crystal was obtained from CH_2Cl_2/Et_2O by vapor diffusion. ^{1}H NMR (500 MHz, CD_2Cl_2)[36] δ 2.8 (s, Me), 2.5 (s, Me). MS (LSIMS) *m/z* 803.0760 (M, 803.0741 calcd for $C_{28}H_{40}N_4BCl_2F_4Pd_2$) Anal. Calcd for $C_{14}H_{20}N_2BClF_4Pd$: C, 37.79; H, 4.53; N, 6.30. Found: C, 37.76; H, 4.68; N, 6.27.

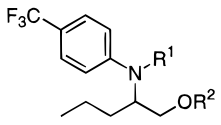
(*E*)-2-Hexenyl *N*-[4-(Trifluoromethyl)phenyl]benzimidate (29). Benzoyl chloride (0.62 mL, 4.4 mmol) was added dropwise to a solution of 4-trifluoromethylaniline (0.50 mL, 4.0 mmol), Et_3N (1.0 mL, 7.2 mmol), and CH_2Cl_2 (5 mL) at 0 °C, and the resulting mixture was stirred for 2 h. Saturated aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL) were added, and the mixture was stirred vigorously. The organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to yield a crude sample of amide **32** (1.1 g, 100%) as a colorless solid: ^{1}H NMR (500 MHz, CD_3NO_2) δ 8.74 (br s, 1H, N*H*), 7.94 (m, 4H), 7.70 (d, J = 8.4 Hz, 2H), 7.62 (m, 1H), 7.54 (m, 2H); MS (EI) *m/z* 265.0719 (MH, 265.0714 calcd for $C_{14}H_{10}F_3NO$).

A portion of this crude amide (0.790 g, 2.98 mmol) was combined with PCl_5 (0.620 g, 2.98 mmol) and heated at 85 °C for 1 h. Volatile materials were then removed under vacuum yielding *N*-[4-(trifluoromethyl)phenyl]benzimidoyl chloride (0.843 g, 100%) as an off-white solid that was >95% pure by ^{1}H NMR analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 7.7 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H), 7.54 (m, 3H), 7.10 (d, J = 8.2 Hz, 2H).

Following the procedure described for the preparation of **8**, (*E*)-2-hexen-1-ol (280 μL, 2.4 mmol), *N*-[4-(Trifluoromethyl)-phenyl]benzimidoyl chloride (0.68 g, 2.4 mmol), and NaH (0.11 g, 57% dispersion in oil, 2.6 mmol) yielded, after silica gel chromatography (column packed with 200:1 hexanes−Et_3N and eluted with 4:1 hexanes−CH_2Cl_2), allylic imidate **29** (0.629 g, 76%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2 H), 7.36−7.21 (m, 5 H), 6.78 (d, J = 8.2 Hz, 2 H), 5.93−5.72 (m, 2 H), 4.81 (d, J = 6.1 Hz, 2 H), 2.09 (q, J = 7.2 Hz, 2 H), 1.45 (sextet, J = 7.4 Hz, 2 H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 151.8, 136.0, 130.8, 130.2, 129.3, 128.1, 126.1, 124.4, 121.7, 67.7, 34.5, 22.2, 13.7; IR ($CDCl_3$) 1679 cm^{-1}. Anal. Calcd for $C_{20}H_{20}F_3NO$: C, 69.15; H, 5.80; N, 4.03. Found: C, 69.25.90; H, 5.77; N, 4.05.

***N*-(1-Ethenylbutyl)-*N*-[4-trifluoromethyl)phenyl]benzamide (30). A Typical Catalytic Procedure.** A solution of **29** (138 mg, 0.397 mmol), **18** (18 mg, 0.020 mmol), and CD_2Cl_2 (0.6 mL) was heated at 40 °C for 48 h, concentrated, and chromatographed on silica gel (4% EtOAc−hexanes) to yield **30** (95 mg, 69%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 8.3 Hz, 2 H), 7.29−7.16 (m, 7 H), 5.91 (ddd, J = 17.2, 10.2, 7.2 Hz, 1 H), 5.3−5.2 (m, 1 H), 5.30 (d, J = 18.4, 1 H), 5.25 (d, J = 11.4, 1 H), 1.79−1.58 (m, 2 H), 1.46 (sextet, J = 7.3 Hz, 2 H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 144.5, 137.1, 136.3, 129.9, 129.6, 129.1, 128.7, 128.3, 127.9, 125.7, 117.9, 60.1, 34.2, 19.7, 13.9; IR ($CDCl_3$) 1663 cm^{-1}; $[\alpha]^{25}_D$ −37.2 (*c* 0.5, CH_2Cl_2); 55% ee (Chiracel AS). Anal. Calcd for $C_{20}H_{20}F_3NO$: C, 69.15; H, 5.80; N, 4.03. Found: C, 68.90; H, 5.76; N, 4.05.

Determination of the Enantiomeric Excess of 30. The enantiomeric purity of **30** was determined by either of two methods. Benzamide **30** was treated with $O_3/NaBH_4$ in MeOH to provide amide **40** and/or ester **41**. The enantiomers of these derivatives were separated on a Chiracel OD HPLC column (3% *i*-PrOH/hexanes, 0.9 mL/min, UV detection). Alternatively, the enantiomeric excess of **30** could be determined directly on a Chiracel AS HPLC column (4% *i*-PrOH/hexanes, 1.0 mL/min, UV detection).



40 R^1 = Bz, R^2 = H

41 R^1 = H, R^2 = Bz

(*R*)-2-[*N*-[4-(Trifluoromethyl)phenyl]amino]-1-pentyl *tert*-Butyl Ether (38). A mixture of (*R*)-norvaline (2.0 g, 17 mmol), $LiAlH_4$ (1.0 g, 26 mmol), and THF (25 mL) was heated at reflux overnight to produce norvalinol (1.5 g, 86%) after bulb-to-bulb distillation (75 °C, 0.5 mmHg).[29] Isobutylene (5 mL) was condensed into a reaction vessel at −78 °C, and a solution of norvalinol (0.562 g, 5.45 mmol) and CH_2Cl_2 (10 mL) was added followed by dropwise addition of 0.3 mL of concentrated H_2SO_4. The reaction vessel was sealed, the −78 °C bath was removed, and the suspension was stirred vigorously overnight. Excess isobutylene was vented and NaOH (3 N) was added until the mixture was pH ≥10. This suspension was extracted with Et_2O (3 × 15 mL), and the organic layers were dried (K_2CO_3), filtered, concentrated, and the residue bulb-to-bulb distilled (100 °C, 3 mmHg) to afford ether **37** (416 mg, 63%) as a clear colorless liquid that was ∼85% pure by ^{1}H NMR (diagnostic 9H singlet at δ 1.2).

Following the procedure of Buchwald,[30] ether **37** (50 mg, 0.31 mmol) was coupled with 4-(trifluoromethyl)bromobenzene (44 μL, 0.35 mmol) to yield, after silica gel chromatography (hexanes then 1% EtOAc−hexanes), **38** in an unoptimized yield of 38% (36 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 4.25 (br d, J = 7.6 Hz, 1H, N*H*), 3.47 (m, 1H), 3.40 (m, 2H), 1.64 (m, 1H), 1.42 (m, 3H), 1.16 (s, 9H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 150.7, 126.4 (q, $^3J_{C,F}$ = 3.9 Hz), 125.2 (q, $^1J_{C,F}$ = 271 Hz), 117.4 (q, $^2J_{C,F}$ = 32.9 Hz), 111.9, 72.6, 62.7, 52.6, 34.0, 27.1, 19.3, 13.8; IR (film) 3425, 1617 cm^{-1}; MS (CI) *m/z* 303.1810 (M, 303.1810 calcd for $C_{16}H_{24}F_3NO$).

Preparation of *N*-[4-(Trifluoromethyl)phenyl]norvalinol (39) from 30. A solution of benzamide **30** (21 mg, 0.060 mmol, $[\alpha]^{25}_D$ −37.2, 55% ee) and MeOH (5 mL) at −78 °C was treated with O_3 until the blue color persisted. Excess $NaBH_4$ was added, and the −78 °C bath was removed. The resulting suspension was stirred at rt under a flow of N_2 until the solvent had been removed. MeOH (5 mL), H_2O (10 mL), HCl (1 N, 2 mL), and CH_2Cl_2 (10 mL) were added, and the resulting mixture was stirred vigorously for 20 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by silica gel chromatography (4:1 hexanes−EtOAc and then 2:1 hexanes−EtOAc) to yield

(34) LSIMS analysis of this compound in 3-nitrobenzyl alcohol produced ions of the dimer less one tetrafluoroborate ions, ions of the dimer less two tetrafluoroborate ions, and ions of the dimer less two tetrafluoroborate ions plus one fluorine. These ions exhibited the expected isotope pattern. This pattern of fragment ions from complexes having fluorine-containing anions has been observed previously.[35]

(35) Arana, C. R.; Abruna, H. D. *Inorg. Chem.* **1993**, *32*, 194.

(36) NMR spectra of this material are broad and complex; representative examples are provided in the Supporting Information.

39 (5.8 mg, 39%) as a clear colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 8.8 Hz, 2H), 3.75 (dd, J = 10.7, 4.0 Hz, 1H), 3.56 (m, 2H), 1.80−1.36 (m, 6H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 126.7 (q, $^3J_{C,F}$ = 3.9 Hz), 124.8 (q, $^1J_{C,F}$ = 269 Hz), 119.1 (q, $^2J_{C,F}$ = 32.9 Hz), 112.5, 64.3, 54.5, 34.0, 19.3, 14.0; IR (film) 3408, 1617 cm^{-1}; MS (EI) m/z 247.1180 (MH, 247.1184 calcd for $C_{12}H_{16}F_3NO$); $[\alpha]^{25}_D$ = +9.7 (c 0.51, $CHCl_3$).

Preparation of 39 from 38. A solution of ether **38** (30 mg, 0.099 mmol), HOAc (1 mL), and HBr (48%, 1 mL) was maintained at rt for 40 min. NaOH (3 N) was added until the solution was pH 11, and the aqueous layer was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated, and the residue was chromatographed (4:1 hexanes−EtOAc) to yield recovered starting material **38** (6.8 mg, 23%) and amino alcohol **39** (11.2 mg, 47%) each as a clear colorless oil that was homogenous by TLC analysis: $[\alpha]^{25}_D$ = +19.7, (c 0.56, $CHCl_3$).

Acknowledgment. This research was supported by NSF grant CHE 9412266. NMR spectra were determined at Irvine using instruments acquired with the assistance of NSF and NIH Shared Instrumentation Programs. We particularly thank Professor Steven Buchwald for providing experimental details for the arylation of amino alcohols, Professor Everly Fleischer for assistance with modeling, and Dr. John Greaves for his discussion and expert assistance with mass spectral analyses. M.C. thanks the American Cancer Society for a Postdoctoral Fellowship (PF 3994), T.K.H. thanks the NIH for an NRSA Postdoctoral Fellowship (F 32 GM17157), and G.G.Z. thanks the DOEd for a GAANN Predoctoral Fellowship.

Supporting Information Available: Preparation of the bis(oxazoline)-derived catalysts, table of catalytic results with the bis(oxazoline)-derived catalysts, table of catalytic results obtained in the presence of the chiral additives, experimental details for the preparation of **19**−**28**, **33**-**36**, **40**, and **41**, and ^{1}H NMR spectra of **16**, **18**, **21**−**27**, **34**, **36**, **38**, and **39** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO962090P