Cyclopropanation with Diazomethane and Bis(oxazoline)palladium(II) Complexes

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Received January 7, 1997[⊗]

Studies toward the development of an enantioselective diazomethane-based cyclopropanation reagent derived from bis(oxazoline)palladium(II) complexes are reported. Several simple palladium chelates, **2** and **7**, in addition to the novel carbon-bound complexes **15** were synthesized and evaluated in the cyclopropanation of various electron-deficient olefins. The X-ray crystal structure of aryl−bis(oxazoline)palladium complex **15c** is described. Although all catalysts efficiently affected cyclopropanation, all products were racemic. An intriguing relationship between substitution on the oxazoline ring, particularly the commonly-derivatized 4-position, and catalyst efficiency was discovered. The results are rationalized by either partial or complete bis(oxazoline) decomplexation during the course of the reaction.

Introduction and Background

The design, evaluation, and understanding of catalysts for organic reactions is an active field of modern research.[1] Though many useful and highly selective transition metal catalysts are available in the organic chemist's repertoire, there are still formidable challenges in both the design and understanding of these most useful tools. One venue for the design and evaluation of asymmetric catalysis in recent years has been based on bis(oxazoline) and related ligands as first described by Pfaltz and co-workers in 1986.[2] Since the initial disclosure of semicorrin-based copper cyclopropanation catalysts, dozens of reports have appeared detailing the use of these and similar ligands in a number of synthetic transformations.[3] These ligands were initially chosen for their ease of preparation and intrinsic simplicity due to the chiral C_2-symmetric environment offered, and they continue to be investigated for these reasons and because of their proven effectiveness in asymmetric catalysis.

The field of catalytic asymmetric cyclopropanation has existed as long as asymmetric homogeneous catalysis, both being born of Nozaki's seminal communication in 1966.[4] Although the selectivity observed was poor, and little was understood about the reactivity of the copper catalyst utilized, the enormous potential for asymmetric synthesis was obvious. Several similar catalyst designs based on Nozaki's salicylaldiminatocopper(II) complex were forwarded in the 1970's, particularly by Aratani and co-workers,[5] although generality and enantiomeric purity of the products was moderate. Further progress in asymmetric cyclopropanation was reported by Nakamura and co-workers.[6] They found that using a dioximatocobalt(II) complex enantiomeric excesses (ee's) approaching

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1997.

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S0022-3263(97)00044-3 CCC: $14.00

90% could be generally obtained. In the late 1980's breakthroughs appeared on several fronts of asymmetric cyclopropanation, including chiral bis(sulfonamide)-promoted Furukawa−Simmons−Smith-directed cyclopropanations[7] and diazoacetate-based cyclopropanations with both chiral rhodium carboxamides[8] or bis(oxazoline)-copper[2] complexes as the catalysts. The modified Furukawa methods of Kobayashi,[7a−c] Charette,[7d,e] and later our own group[7f−i] provided good to excellent enantiomeric excesses of cyclopropanes, but the method is limited to allylic and homoallylic alcohols. The rhodium carboxamide systems pioneered by Doyle are generally useful and are the reagents of choice for intramolecular cyclopropanation[9] and C−H insertion reactions,[10] though the realm of intermolecular asymmetric cyclopropanation belongs to the methylene bis(oxazoline)copper(I) (and semicorrin) catalysts of Pfaltz,[11] Masamune,[12] and Evans,[13] and the pyridine bis(oxazoline)ruthenium(II) complex of Nishiyama.[14] These complexes promote the reaction of hindered diazoacetate esters and styrene with very good trans-selectivity and very high ee.

While the catalytic systems developed by Pfaltz, Masamune, Evans, and Nishiyama give exceptional enantiomeric excesses, there are several drawbacks in the general utility of these catalytic asymmetric cyclopropanations; primary among them is the use of diazoacetic esters as the carbene source. All of these methods rely on a copper or ruthenium catalytic center which transfers the diazocarbon, presumably via a fleeting metal−carbenoid intermediate, to a carbon−carbon double bond. Two inherent problems are immediately recognized. First, the products formed are cyclopropane carboxylates; if other functionality is required one must transform the ester as desired. Second, and more importantly, a mixture of cis- and trans-cyclopropanes is usually isolated. Although bulky diazoesters can enhance the trans selectivity, problems can arise in further transformation of such hindered esters. In addition, the diazoester-based methods are not effective at providing cis-cyclopropanes in high ee. These problems could be simultaneously addressed by changing the diazocarbon source from a diazoester to diazomethane. We felt that an asymmetric diazomethane-based cyclopropanation would be useful synthetically and complement the procedures already outlined in the literature for asymmetric cyclopropane formation.[15]

Many diazocarbonyl compounds are decomposed smoothly by a number of transition metal species (for example Cu, Ru, Rh, Pd, Pt, V, W, Cr, Ni),[16] but the only metal which reliably forms cyclopropanes using diazomethane as the carbene source is palladium. Our primary challenge was to select an appropriate chiral ligand to provide an asymmetric environment for palladium. We were attracted to the bis(oxazoline) ligands for the reasons mentioned above, and also because they had been used successfully in cyclopropanations previously. We therefore undertook the preparation and evaluation of bis(oxazoline)palladium complexes to be used as catalysts for diazomethane-based cyclopropanation.

Results

2,2′-Bis(oxazoline) Complexes. Synthesis. The initial ligand design was based on the simple 2,2′-bis-(oxazolines) **1**, which lead to five-membered palladacyclic complexes **2**. The synthesis of these ligands proceeded as described in the literature,[11c] and is summarized in Scheme 1. Treatment of commercially available oxamide with the indicated amino alcohols **3** (obtained by borane−methyl sulfide/boron trifluoride−etherate or lithium aluminum hydride reduction of the corresponding amino acids[17]) led cleanly to the bisamides **4**. Alternatively the amides **4** could be obtained by heating the amino alcohol and diethyl oxalate in toluene at reflux. Chloridation of the hydroxy amides **4** with thionyl chloride, followed by base-promoted cyclization led to the 2,2′-bis(oxazoline) ligands **1** in good overall yield. Initial attempts to form the palladium chelates with bis(triphenylphosphine)-palladium(II) dichloride quickly demonstrated that bis-(oxazoline) ligands could not compete with phosphines for coordination to palladium(II). Bis(acetonitrile)palladium(II) dichloride was also ineffective at the transformation due to a slow rate of ligand exchange. However, treatment of the ligands **1** with 1 equiv of bis(benzonitrile)palladium(II) dichloride in dichloromethane led rapidly to ligand exchange and the formation of the palladium chelates **2**. Complexation was obvious due both to significant shifts in the ^{1}H and ^{13}C NMR spectra of **2** relative to the free ligands **1** and to a distinct color

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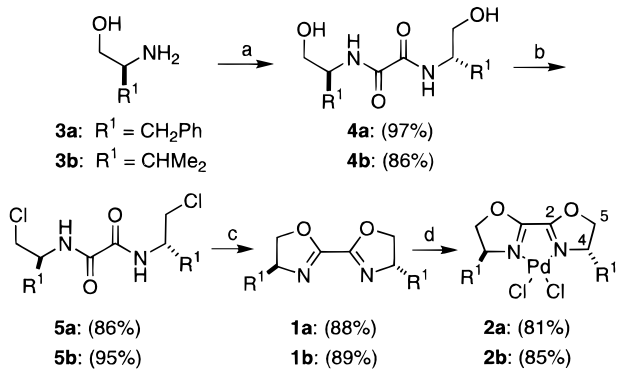
Scheme 1



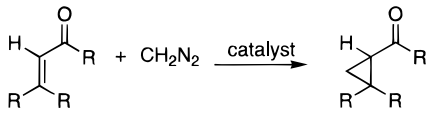
(a) oxamide/Δ, or diethyl oxalate/toluene/Δ. (b) $SOCl_2$/toluene/Δ. (c) KOH/MeOH/Δ. (d) $(PhCN)_2PdCl_2/CH_2Cl_2$.

change; the complexes range from medium orange to deep red-orange. Both five-membered chelates were quite stable to air, though both decomposed upon silica gel chromatography. Fast ligand exchange was taking place, however, as evidenced by combining **1a** and **2b** in deuteriochloroform and observing all four possible species, **1a**, **1b**, **2a**, and **2b**, in the ^{1}H NMR spectrum.[18]

Cyclopropanation. Several α,β-unsaturated carbonyl compounds were used as initial test substrates because electron-deficient olefins have been noted to be particularly good substrates for palladium-catalyzed cyclopropanations.[16] Addition of 2−4 equivalents of ethereal diazomethane to a chilled (0 °C) ca. 0.2 M (1 mmol) solution of olefin and 1 mol % palladium complex in 1/1 dichloromethane/diethyl ether led to quick and efficient formation of the corresponding cyclopropanes as monitored by GC. Concentration of the reaction solution, followed by silica gel chromatography of the residue, provided the pure cyclopropane products in good to excellent yield, Table 1. However, *all cyclopropanes formed were racemic*. This result was surprising given the success of similar ligands reported in the literature for similar reactions. In a control experiment it was demonstrated that diazomethane alone gave essentially no reaction with any of the olefins over a several hour period at 0 °C (the catalyzed reaction proceeded within minutes), demonstrating that palladium was indeed catalyzing the reaction, although with no observable selectivity. At this time several reports had already appeared on the effectiveness of the related six-membered-metal chelates so we shifted our attention to those systems for the palladium-catalyzed cyclopropanation.

Methylene−Bis(oxazoline) Complexes. Synthesis and Initial Cyclopropanation Studies. The methylene 2,2-bis(oxazoline) ligands **6** were formed as described in the literature,[3h,bb] Tables 2 and 3. As before, bis(benzonitrile)palladium(II) dichloride was the most effective palladium source. The complexes **7** (Chart 1) were highly colored, had characteristic shifts in both the ^{1}H and ^{13}C NMR spectra relative to the parent ligands, and were, in general, very stable. These complexes were also evaluated in combination with several olefins as described above, and the results are summarized in Table 4. As was observed for the five-membered ring complexes **2**, none of the complexes **7** induced a stereoselective cyclopropanation.

Table 1. Cyclopropanation with Complexes 2



substrate	catalyst	yield, %[a]	ee, %[b]
ethyl (*E*)-cinnamate	**2a**	89	≤2
ethyl (*E*)-cinnamate	**2b**	83	≤2
(*E*)-benzylideneacetone	**2a**	95	≤2
(*E*)-benzylideneacetone	**2b**	93	≤2
cyclohexenone	**2a**	96	≤2
ethyl tiglate	**2a**	0	

[a] Yield of purified (chromatographed) product. [b] Determined by chiral-phase (β-cyclodextrin) GC.

Oxazoline Substitution and Concentration Studies. As no asymmetric induction had yet been observed in our catalytic system, we thought that the ligand was having little effect on the reaction. To examine the effect of ligand substitution on reactivity of the catalyst, we also synthesized achiral ligands **7d**, **7e**, **7f,** and **7g** (Chart 1, Tables 2 and 3). We then studied the effect of **7a**, **7b**, **7d**, **7e**, **7g**, and **7h** on the rate of cyclopropanation of ethyl (*E*)-cinnamate by diazomethane at various initial concentrations. The standard conditions for the reaction involved treating a cold (0 °C) solution of ethyl *(E)*-cinnamate (0.25 M) and palladium complex (1 mol %) in dichloromethane with diazomethane (0.25 M in dichloromethane[19]). Four portions of diazomethane (each 1 equiv) were added in series: each equivalent over 3−4 min. The mixture was allowed to stir for 5 min and assayed by GC, and then the next equivalent of diazomethane was added. The results of this study are presented graphically in Figure 1.

Clearly there is a tremendous difference in catalyst efficiencies depending on the ring substitution pattern of the bis(oxazoline) ligands. With respect to the parent unsubstituted complex **7d**, it seemed that minimal substitution with sterically nondemanding groups (R^3 = benzyl, **7a**) at the 4-position slowed the reaction down, as did substitution at the 5-position, **7g**. However, the 4,4-disubstituted catalyst **7e** led to a much more rapid cyclopropanation. It seemed that a more sterically encumbered palladium complex was more efficient at methylene transfer. Two hypotheses were advanced to rationalize these results, namely an aggregation effect and the involvement of an inactive diazomethane adduct, both of which were tested as described below.

Aggregation Effect Studies. If this system involved a catalytically active monomer and an inactive aggregate, then forming a more hindered complex might disfavor self-aggregation and thereby increase the observed catalytic efficiency. The 4,4-diethyl-substituted complex **7f** was chosen as a model of a "more hindered" complex for this investigation. The requisite amino alcohol could be readily accessed by dialkylation of a glycine anion equivalent followed by cleavage of the benzophenone blocking group and lithium aluminum hydride reduction (Scheme 2).[20] Formation of the palladium complex (Tables 2 and 3) provided the more hindered catalyst **7f**. Cyclopropanation of ethyl *(E)*-cinnamate as before provided a reactivity profile essentially identical to that of

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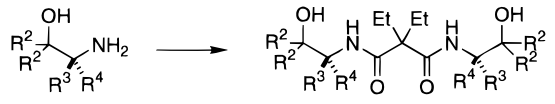
Table 2. Preparation of Bis(hydroxyamides) 8a−h[a]

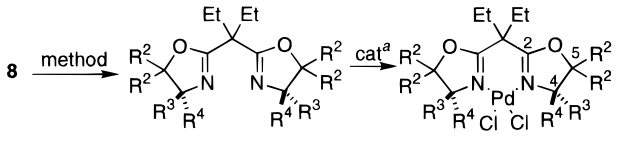


3 **8**

amino alcohol	R^2	R^3	R^4	hydroxy amide	yield, %[b]
3a	H	$PhCH_2$	H	**8a**	98
3b	H	Me_2CH	H	**8b**	97
3c	H	Me_3C	H	**8c**	86
3d	H	H	H	**8d**	86
3e	H	Me	Me	**8e**	93
3f	H	Et	Et	**8f**	95
3g	Me	H	H	**8g**	79
3h	Me	Me_2CH	H	**8h**	88

[a] Amino alcohol/diethylmalonyl dichloride/Et_3N/CH_2Cl_2. [b] Yield of analytically pure material.

Table 3. Preparation of Palladium Complexes 7[a]



6 **7**

hydroxy amide	ligand	method[b]	yield, %[c]	complex	yield, %[c]
8a	**6a**	A	78	**7a**	69
8b	**6b**	A	86	**7b**	87
8c	**6c**	A	75	**7c**	80
8d	**6d**	B	89	**7d**	78
8e	**6e**	B	90	**7e**	89
8f	**6f**	B	92	**7f**	78
8g	**6g**	C	92	**7g**	64
8h	**6h**	C	69	**7h**	85

[a] cat = $(PhCN)_2PdCl_2/CH_2Cl_2$. [b] Method A: (1) MsCl/Et_3N/CH_2Cl_2, (2) NaOH/MeOH/H_2O/Δ. Method B: (1) $SOCl_2$/toluene/Δ, (2) 5% NaOH/MeOH/Δ. Method C: $MeSO_3H/CH_2Cl_2$/Δ. [c] Yield of analytically pure material.

Chart 1

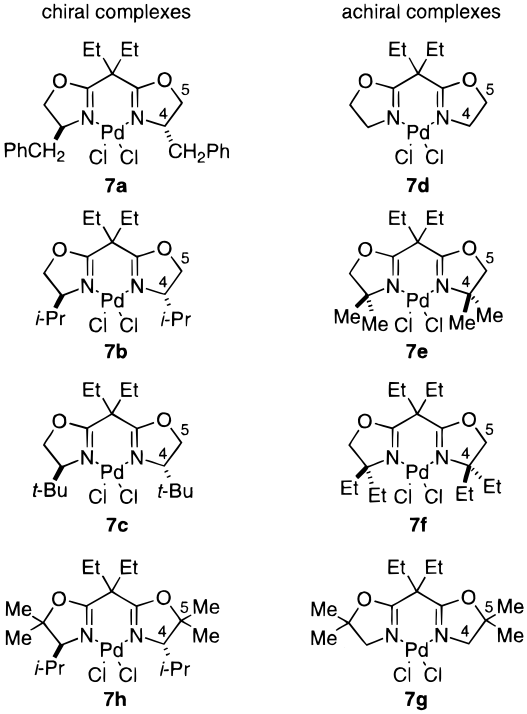
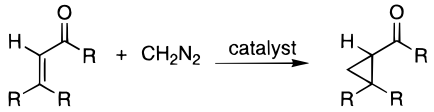


Table 4. Cyclopropanation with Complexes 7



substrate	catalyst	yield, %[a]	ee, %[b]
ethyl (*E*)-cinnamate	**7c**	45	≤2
ethyl (*E*)-cinnamate	**7a**	93	≤2
ethyl (*E*)-cinnamate	**7h**	96	≤2
(*E*-benzylideneacetone	**7a**	79	≤2
cyclohexenone	**7a**	71	≤2
ethyl tiglate	**7a**	0	

[a] Yield of purified (chromatographed) product. [b] Determined by chiral-phase (*β*-cyclodextrin) GC.

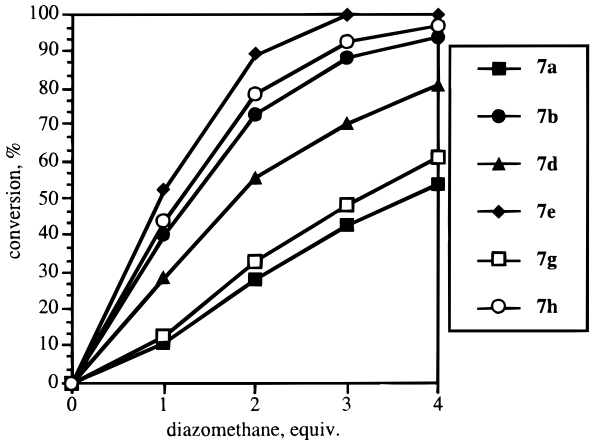
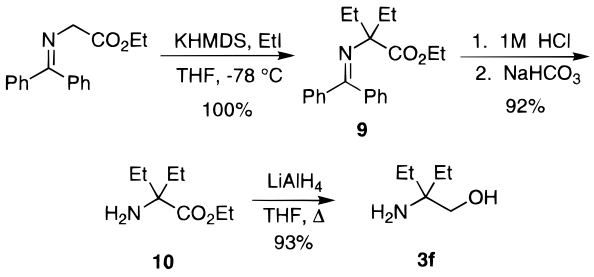


Figure 1. Plot of alkene conversion to cyclopropane versus added diazomethane at 0.25 M initial olefin concentration. Conversion determined by GC analysis.

Scheme 2



the 4,4-dimethyl analog **7e**, thus demonstrating that an increase in bulk at the 4-position did not measurably affect the reactivity. This may be due to the nominal increase in bulk of a *gem*-diethyl versus a *gem*-dimethyl substitution pattern. Alternatively, it may be that **7e** is already in the fully monomeric state as the reactive complex so that increasing bulk has no effect.

Performing the cyclopropanation over a 50-fold concentration range of olefin (0.5 M to 0.01 M) while keeping catalyst loading and diazomethane concentration constant showed little change in the reactivity profiles for most of the bis(oxazoline) complexes as depicted in Figure 2. In addition, bis(benzonitrile)palladium(II) dichloride and palladium(II) diacetate showed essentially no difference in cyclopropanation efficiency over this concentration range. The 5,5-dimethyl-substituted complex **7g** did show the largest concentration dependence, being less efficient at lower concentrations. This efficiency change is, however, opposite to what one would expect from the active-monomer inactive-aggregate proposal outlined

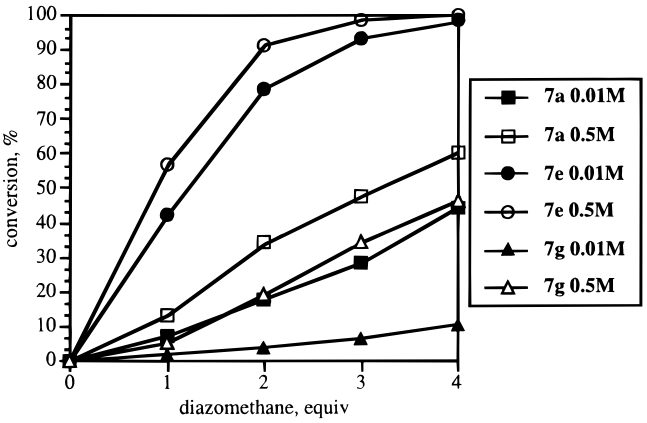


Figure 2. Plot of conversion to cyclopropane versus diazomethane added for 0.5 M initial substrate and 0.01 M initial substrate concentrations. Conversion was determined by GC analysis.

above. Consequently we considered the hypothesis that the catalysts may form unreactive adducts with diazomethane or otherwise become deactivated at different rates.

Catalyst Decomposition Studies. We envisioned that the less hindered complexes might form an unreactive adduct with diazomethane, most likely a chloromethyl palladium species similar to the ones reported by McCrindle and co-workers.[21] Attempts to observe such a species by ^{1}H or ^{13}C NMR spectroscopy were unsuccessful, although several interesting results should be noted. Treatment of complex **7e** with ca. 80 equiv of diazomethane (0.6 M in dichloromethane), followed by evaporation, provided a ≈1:3.5 ratio of starting complex: free ligand (**7e**:**6e**) by ^{1}H NMR spectroscopy. The presence and identity of both species was confirmed by their characteristic resonances in the ^{13}C NMR spectrum. When complex **7g** was similarly treated with diazomethane (ca. 80 equiv), signals initially assigned as both complex and free ligand (**7g** and **6g**) were observed in the ^{1}H NMR spectrum. However, inspection of the ^{13}C NMR spectrum demonstrated that, in fact, there was no starting complex **7g** present. Free ligand **6g** was detected in the ^{13}C NMR spectrum along with two other sets of signals that could not be fully assigned. It was apparent, however, that the unassigned signals were oxazoline derived: either two bis(oxazolines) in different environments, or one bis(oxazoline) in an environment such that C_2-symmetry was lost.

Exposure of either complex to ca. 80 equiv of diazomethane, as above, followed by standing at room temperature for 48 h led to, in both cases, mixtures of starting complex and free ligand. The unassigned signals in the **7g** example above were not present in this experiment. The complex **7e** led to a ratio of ≈1.5:1 complex:free ligand (**7e**:**6e**), and **7g** led to ≈1:1 complex: free ligand (**7g**:**6g**). From these results we became concerned about the possibility of total or partial ligand dissociation upon treatment of the complexes **7** with diazomethane.

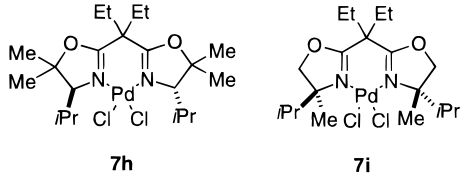


Figure 3. New asymmetric bis(oxazoline)palladium(II) complexes **7h** and **7i**.

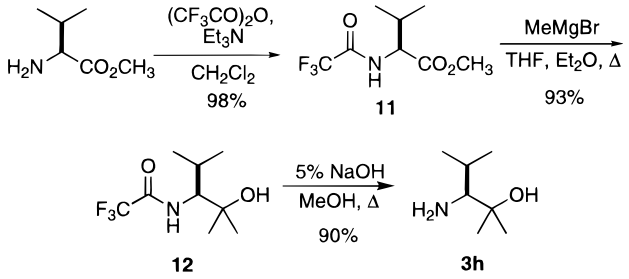
To further investigate the stability of the palladium complexes during the cyclopropanation reactions we attempted to recover and analyze the catalyst after reaction. Cyclopropanation was performed on large scale (25 mmol) with complex **7e**, and the palladium complex was recovered after the reaction by trituration with hexane and centrifugation. Although the recovered catalyst was not pure (as judged by ^{1}H NMR spectroscopy), a ca. 93% mass recovery of (primarily) the unchanged catalyst was obtained. Several unassigned signals were also present in the recovered material, which appeared to be oxazoline derived. Similar experiments performed on a smaller scale (6 mmol) with higher loading of catalyst **7e** led to similar results. Thus, while the reactions were not enantioselective, the ligands were clearly influencing the reaction rate, and the complexes were not undergoing wholesale decomposition in the presence of diazomethane or during the cyclopropanation event though transient decomplexation may be a problem.

New Asymmetric Designs. Although few concrete rationalizations could be made with the data thus far collected, one thing was certain: the substitution pattern of the bis(oxazoline) ligand dramatically affected the reactivity of the palladium complex toward diazomethane. We thus decided to pursue the synthesis of enantiomerically pure analogs of both complexes **7e** and **7g**. We hoped that since the reactivity was so varied, one end of the reactivity spectrum, whether fast or sluggish, would be due to cyclopropanation in the full ligand sphere and therefore lead to enantiomerically-enriched cyclopropanes. Toward this end, complex **7h**, in analogy to Corey's stabilized Diels–Alder catalyst,[3m] and complex **7i** which possessed a stereogenic quaternary center at the 4-position were proposed. For the synthesis of complex **7h**, the requisite amino alcohol **3h** was produced by adapting published procedures, as described in Scheme 3.[3m] Formation of the trifluoroacetamide **11** from L-valine methyl ester, followed by addition of methylmagnesium bromide and forcing deprotection of the trifluoroacetamide **12**, led to the appropriately substituted amino alcohol **3h** in excellent yield. The complex **7h** was then synthesized as before (Tables 2 and 3). Complex **7h** was a good catalyst (Figure 1), somewhat more efficient than the parent complex **7d**, and surprisingly more efficient than the sterically similar 4-benzyl-substituted complex **7a**. To further investigate this phenomenon, the simple 4-isopropyl complex **7b** was reevaluated. The reactivity of complex **7b** closely paralleled that of **7h** (Figure 1), suggesting that whatever decelerating effect is provided by substitution at the 5-position it was completely overridden by substitution at the 4-position, and that *any* substituent at the 4-position, except for benzyl, seemed to accelerate the reaction. In addition, it was found that

(21) (a) McCrindle, R.; Ferguson, G.; McAlees, A. J.; Arsenault, G. J.; Gupta, A.; Jennings, M. C. *Organometallics* **1995**, *14*, 2741. (b) McCrindle, R.; McAlees, A. J. *Organometallics* **1993**, *12*, 2445. (c) McCrindle, R.; Arsenault, G. J.; Farwaha, R.; McAlees, A. J.; Sneddon, D. W. *J. Chem. Soc., Dalton Trans.* **1989**, 761. (d) McCrindle, R.; Arsenault, G. J.; Gupta, A.; Hampden-Smith, M. J.; Rice, R. E.; McAlees, A. J. *J. Chem. Soc., Dalton Trans.* **1991**, 949. (e) McCrindle, R.; Sneddon, D. W. *J. Organomet. Chem.* **1985**, *282*, 413.

7h also produced racemic cyclopropane from ethyl (*E*)-cinnamate.

Scheme 3



Although the necessary amino alcohol for **7i** could be obtained from L-valine with Seebach's "self reproduction of chirality" methodology,[22] only small amounts of the complex could be prepared due to throughput problems. Initial results suggested that **7i** was indeed an excellent catalyst though it too produced cyclopropanes in racemic form and was therefore not pursued further.

At this point, we considered that perhaps this catalytic system required excess ligand to provide enantioselection. The use of 10 mol % of complex **7a** in the cyclopropanation of ethyl *(E)*-cinnamate led to little change in efficiency, and, again, racemic products. Interestingly, the use of 1 mol % of complex **7a**, with an additional 10 mol % of the corresponding ligand **6a**, also led to the formation of racemic cyclopropane, but was substantially slower that the system without excess free ligand.

"Two-Salvo" Experiments. Although ligand substitution had a demonstrable effect on the efficiency of cyclopropanation, the lack of enantioselectivity suggested that the palladium complexes themselves might be precatalysts. Thus, to probe the stability of such in-situ-generated catalytic species, we chose to examine the catalyst efficiency after some extent of cyclopropanation. This was accomplished by performing a cyclopropanation as described above, (1 mol % catalyst) waiting roughly 1 h after the final addition of diazomethane to ensure that the diazomethane had reacted or escaped, adding a second equivalent of olefin, and continuing the serial addition of diazomethane as before. Comparison of these "second-salvo" efficiencies with the corresponding first salvo efficiencies at the proper concentration (now 0.05 M) should provide some information on the nature of the active catalyst throughout the reaction. These results are summarized in Figure 4. Clearly there was a drop in efficiency after "one salvo" of cyclopropanation for most of the catalysts (that is, the "second-salvo" reaction curves are below the control 0.05 M reactions). It appeared that either the nature of the catalyst changed during the reaction, or that the amount of the catalytic species dropped over time (either scenario would account for the reduced efficiency after "one-salvo" of reaction). To test this, we performed the same two experiments, now with 10 mol % of **7e**. If new catalytic species were formed at some point during the reaction, then this experiment should have approximately the same rate profile as the 1 mol % **7e** experiment. However, if it is simply partial deactivation of the catalyst due to excess diazomethane, the effect should be attenuated due to the larger quantity of palladium complex present relative to other reactants.

(22) (a) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243. (b) Naef, R.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 135. (c) Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 144.

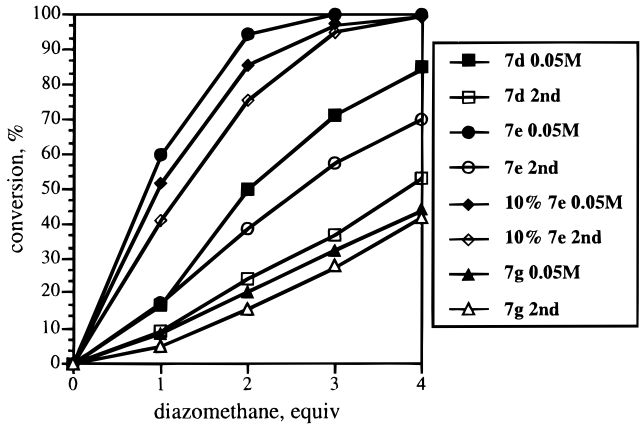


Figure 4. Plot of conversion to cyclopropane versus diazomethane added for "second salvo" experiments and 0.05 M substrate controls as determiend by GC analysis.

The results are also presented in Figure 4, and clearly show an attenuation of the efficiency drop-off, suggesting that the active species present in early stages of the reaction remains, though its concentration may well decrease.

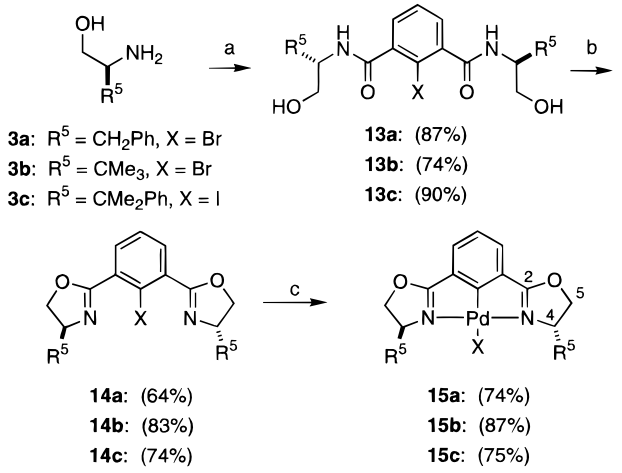
Aryl Bis(oxazoline) Complexes. The failure to observe enantioselectivity in the catalytic cyclopropanations as well as with the growing body of perplexing catalytic behavior led to the search for a fundamentally different catalyst structure. We felt that catalyst integrity could be a critical problem and sought to examine a more stable, covalently-linked palladium complex. The pybox ligands of Nishiyama provided the primary inspiration.[3g] Owing to the requirement of a C_2-symmetrical palladium(II) complex, however, the arene connecting the oxazolines together needed to present an anionic site to the palladium. Several related possibilities were considered, including anionic nitrogen and phosphorus atoms, which were rejected in favor of the carbon-bound complexes **15**. The carbon−palladium σ-bond was viewed as advantageous not only to stabilize these complexes, but also to situate the palladium deeper in the asymmetric environment provided by the ligand, now with a trans geometry in the square planar system.

Synthesis and Cyclopropanation. In view of the large number of examples of *ortho*-palladated complexes in the literature,[23] including several examples of aryl−oxazoline complexes of palladium(II),[24] we were confident that the synthesis of these complexes would be straightforward and that they would be stable, easy-to-handle

(23) Some examples include: (a) Holton, R. A *Tetrahedron Lett.* **1977**, *18*, 355. (b) Van der Poel, H.; van Koten, G. *J. Organomet. Chem.* **1981**, *217*, 129. (c) Grove, D. M.; van Koten, G.; Louwen, J. N.; Noltes, J. G.; Spek, A. L.; Ubbels, H. J. C. *J. Am. Chem. Soc.* **1982**, *104*, 6609. (d) Canty, A. J.; Minchin, N. J.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1987**, 1477. (e) Hiraki, K.; Fuchita, Y.; Matsumoto, Y. *Chem. Lett.* **1984**, 1947. (f) Ryabov, A. D. *Inorg. Chem.* **1987**, *26*, 1252. For reveiws see: (g) Omae, I. *Chem. Rev.* **1979**, *79*, 287. (h) Ryabov, A. D. *Synthesis* **1985**, 233. (i) Newkome, G. R.; Puckett, W. E.; Gupta, V. K.; Kiefer, G. E. *Chem. Rev.* **1986**, *86*, 451. For reviews on palladium−carbon bonds see: (j) Maitlis, P. M.; Espinet, P.; Russell, M. J. H. *Compounds with Palladium-Carbon σ-Bonds.* In *Comprehensive Organometallic Chemistry;* Wilkenson, G., Ed.; Pergamon Press: New York, 1982; Vol. 6. (k) Canty, A. J. Palladium-Carbon σ-Bonded Complexes. In *Comprehensive Organometallic Chemistry II*; Puddephatt, R. J., Ed.; Pergamon Press: New York, 1995; Vol. 9.

(24) (a) Izumi, T.; Watabe, H.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1711. (b) Balavoine, G.; Clinet, J. C.; Zerbib, P.; Boubekeur, K. *J. Organomet. Chem.* **1990**, *389*, 259. (c) Balavoine, G.; Clinet, J. C. *J. Organomet. Chem.* **1990**, *390*, C84. (d) Clinet, J. C.; Balavoine, G. *J. Organomet. Chem.* **1991**, *405*, C29. (e) Yang, H.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1993**, *12*, 3485. (f) Valk, J.-M.; Maassarani, F.; van der Sluis, P.; Spek, A. L.; Boersma, J.; van Koten, G. *Organometallics* **1994**, *13*, 2320.

Scheme 4



(a) 2-halo-isophthaloyl dichloride/Et_3N/CH_2Cl_2. (b) (1) $SOCl_2$/toluene/Δ, (2) 10% NaOH/H_2O. (c) $(dba)_3Pd_2 \cdot 2H_2O$/benzene/Δ.

compounds. The synthesis is described in Scheme 4, starting from 2-haloisophthaloyl dichloride (itself obtained by halogenating the organomercury compound derived from decarboxylation of 1,2,3-benzenetricarboxylic acid,[25] followed by treatment with thionyl chloride). Coupling with the appropriate amino alcohol and base-promoted cyclization led to the protio-ligands **14**. Treatment of these compounds with tris(dibenzylideneacetone)-dipalladium dihydrate[26] in degassed benzene led to clean oxidative addition across the carbon−bromine bond and formation of the carbon-bound palladium species **15** which were not only quite stable to air, but also to silica gel chromatography. Due to slow oxidative addition to the more hindered bromo-ligands, specifically the (dimethylphenyl)methyl substituted compound, the iodo-ligand **14c** was needed to accomplish this transformation at a reasonable rate.

To assure the assignment of structure, we turned to X-ray crystallographic analysis; an ORTEP projection of **15c** is shown in Figure 5. Several features of this structure are notable. First, the palladium is certainly covalently bonded to the aromatic ring of the ligand. Second, formation of the palladacycle via chelation through nitrogen rather than oxygen is confirmed.

Third, there is some deviation from the idealized square planar arrangement about the palladium, the inner C(1)−Pd−N bond angles being somewhat less than the expected 90° (78.9°) and the I−Pd−N angles somewhat greater than 90° (99.7, 102.5°). In addition, the palladium is slightly puckered from planarity, with dihedral angles C−N−Pd−C of 11.6° and 9.5°. To accommodate this distortion, the oxazoline rings are twisted out of plane with the aromatic ring by 6.8° and 8.8° respectively. The overall structure correlates well with solid state structures of other bis(oxazoline)metal complexes.[27]

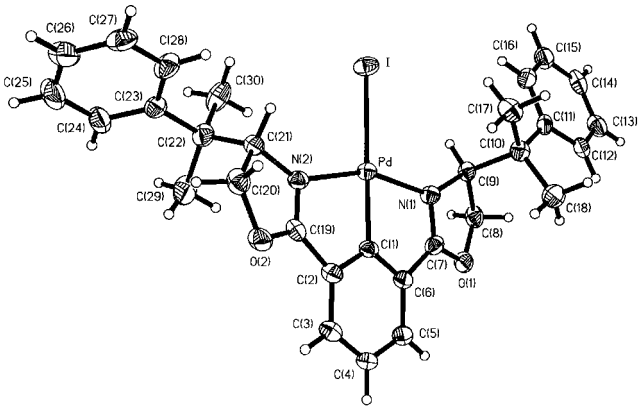
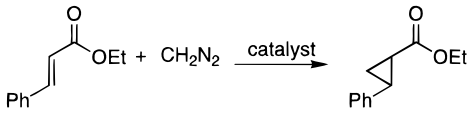


Figure 5. ORTEP projection of the X-ray crystal structure of complex **15c**.

Table 5. Cyclopropanation with Complexes 15



catalyst	additive	yield, %[a]	ee, %[b]
15a	none	92	≤2
15b	none	98	≤2
15b	AgOTf	ND[c]	≤2
15b	$AgPF_6$	ND	≤2
15b	$NaBPh_4$	ND	≤2
15c	none	ND	≤2

[a] Yield of purified (chromatographed) product. [b] Determined by chiral-phase (β-cyclodextrin) GC. [c] ND = not determined.

As in the simple chelated systems, these complexes were excellent catalysts for the cyclopropanation reaction. Cyclopropanation proceeded as previously described, and the results are summarized in Table 5. Disappointingly, however, they too provided only racemic cyclopropanes. Holding to our initial concern that an oxazoline nitrogen-donor was dissociating, thus leaving a less discriminating asymmetric environment behind, we sought to render the anionic ligand a more dissociable group. Initial efforts to prepare complexes of the type **15** by direct electrophilic attack on the unsubstituted ligand **14d** (X = H) with

(25) Whitmore, F. C.; Perkins, R. P. *J. Am. Chem. Soc.* **1929**, *51*, 3352.

(26) Initial attempts at oxidative addition with "$(dba)_3Pd_2$" were complicated by excess palladium(0) remaining after the reaction had gone to completion; in addition, the dibenzylideneacetone could not be recovered quantitatively. Elemental analysis indicated the starting material to be $(dba)_3Pd_2$-$2H_2O$. $C_{51}H_{46}O_5Pd_2$ requires C: 64.36; H: 4.87; Pd: 22.36. Found: C: 64.31; H: 4.83; Pd: 22.36. The use of this formula to calculate stoichiometry resulted in clean oxidative addition and recovery of dibenzylideneacetone.

(27) For other crystal structures of bis(oxazoline)metal complexes see: Cu: (a) Reference 11a. (b) Reference 13b. (c) Hall, J.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1. Pd: (d) Nesper, R.; Pregosin, P.; Püntener, K.; Wörle, M.; Albinati, A. *J. Organomet. Chem.* **1996**, *507*, 85. (e) Reference 3b. (f) Zehnder, M.; Neuburger, M.; von Matt, P.; Pfaltz, A. *Acta. Crystallogr.* **1995**, *C51*, 1109. Zn: (g) Reference 18c. Ni: W: (h) Lloyd-Jones, G. C.; Pfaltz, A. *Z. Naturforsch.* **1995**, *50b*, 361. Rh: (i) Reference 2i Ru: (j) Bennett, S.; Brown, S. M.; Conole, G.; Kessler, M.; Rowling, S.; Sinn, E.; Woodward, S. *J. Chem. Soc., Dalton Trans.* **1995**, 367. (k) Szczepura, L. F.; Maricich, S. M.; See, R. F.; Churchill, M. R.; Takeuchi, K. J. *Inorg. Chem.* **1995**, *34*, 4198. Zr: (l) Cozzi, P. G.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Inorg. Chem.* **1995**, *34*, 2921. For crystal structures of mono(oxazoline)metal complexes see: Cu, Ni, Zn: (m) Bolm, C.; Weickhardt, K.; Zehnder, M.; Glasmacher, D. *Helv. Chim. Acta* **1991**, *74*, 717. Pd: (n) Reference 23b. (o) Reference 23e. (p) Reference 23f. (q) Reference 3r. Pt: (r) Michelin, R. A.; Bertani, R.; Mozzon, M.; Bombieri, G.; Benetollo, F.; Angelici, R. J. *Organometallics* **1991**, *10*, 1751. (s) Michelen, R. A.; Bertani, R.; Mozzon, M.; Bombieri, G.; Benetollo, F.; Angelici, R. J. *J. Chem. Soc., Dalton Trans.* **1993**, 959. (t) Michelen, R. A.; Mozzon, M.; Berin, P.; Bertani, R.; Benetollo, F.; Bombieri, G.; Aneglici, R. J. *Organometallics* **1994**, *13*, 1341. Tc (u) Duatti, A.; Marchi, A.; Rossi, R.; Magon, L.; Deutsch, E.; Bertolasi, V.; Bellucci, F. *Inorg. Chem.* **1988**, *27*, 4208. (v) Wilcox, B. E.; Cooper, J. N.; Elder, R. C.; Deutsch, E. *Inorg. Chim. Acta* **1988**, *142*, 55. Al, Ga, In: (w) Hoveyda, H. R.; Karunaratne, V.; Rettig, S. J.; Orvig, C. *Inorg. Chem.* **1992**, *31*, 5408. Ti, Zr, V: Ref 27l. Re, Tc: (x) Shuter, E.; Hoveyda, H. R.; Karunaratne, V.; Rettig, S. J.; Orvig, C. *Inorg. Chem.* **1996**, *35*, 368.

palladium(II) acetate or palladium(II) trifluoroacetate in the presence of acetic acid or trifluororacetic acid led only to decomposition of the oxazoline ligands.[23a] Ortho lithiation followed by trapping with a palladium salt was not attractive, as the 2-lithiation of aryl 1,3-bis(oxazolines) of the type **14d** has been shown to require excess LDA and TMEDA, which would greatly complicate the metal coordination issue.[28] We therefore attempted to exchange counterions in a more classical manner utilizing silver or sodium salts. Treatment of the bromide complex **15b** in acetonitrile with silver triflate, silver hexafluorophosphate, or sodium tetraphenylborate, followed by filtration and concentration, provided a crude solid which was used directly in the cyclopropanation reaction as described previously (attempted purification proved fruitless). In all cases the crude solids catalyzed the cyclopropanation ethyl *(E)*-cinnamate, though with poor efficiency and no enantioinduction, Table 5.

Control Experiments. Several sources report that olefin coordination is important in palladium-catalyzed cyclopropanation. Therefore, we investigated the nature and extent of interaction between the substrate olefin and the palladium complexes by ^{1}H and ^{13}C NMR spectroscopy. Admixture of palladium(II) diacetate, **7e**, or **7g**, with ethyl vinyl ether, styrene, or ethyl *(E)*-cinnamate produced ^{1}H and ^{13}C NMR spectra that were identical to those of the unmixed compounds. Thus, though it is possible that a very small amount of complexed olefin exists in rapid equilibrium with uncomplexed olefin, it was undetected. A series of experiments reported by Doyle and co-workers[29] suggest that initial coordination is not necessary for (and may inhibit) palladium-catalyzed cyclopropanation with diazoesters. Thus, the lack of observable coordination may not be surprising; however, no similar experiments have been conducted with a diazomethane-based cyclopropanation system.

Although several substrates had been "successfully" cyclopropanated at this point, all were either *E*- or cyclic olefins, no acyclic *Z*-olefins had yet been attempted. When methyl *(Z)*-cinnamate was treated with diazomethane, no background reaction was observed. In addition, treatment of methyl *(Z)*-cinnamate with either palladium(II) diacetate or complex **7e** in dichloromethane led to ≤3% (by GC) of the isomeric methyl *(E)*-cinnamate over several hours at 0 °C. Finally, cyclopropanation of methyl *(Z)*-cinnamate with either palladium(II) acetate or complex **7e** led to the cis-cyclopropane, with a small amount of trans-cyclopropane (≤3%, by capillary GC) being formed, thus showing that cyclopropanation is highly stereospecific, although the product was again racemic.

As palladium(II) complexes are known to isomerize certain cyclopropanes under extreme conditions[23j] we thought it might be possible that, in fact, there was discrimination in the formation of the cyclopropane, but then the products were racemized by interaction with either the palladium catalyst or the presumed palladium-carbenoid intermediate. To test this hypothesis we prepared enantiomerically enriched (80% ee) ethyl *trans*-2-phenyl cyclopropanecarboxylate by the Evans method[13a] and treated it with 5 mol % palladium(II) diacetate (Figure 6). No racemization or decomposition was detected after 20 h at room temperature. Also, treatment of this cyclopropane with diazomethane in the presence of complex **15b** produced no decomposition or racemization. The final determination was made by cyclopropanating methyl *(E)*-cinnamate with complex **15b** and diazomethane in the presence of the enantiomerically enriched cyclopropane. Racemic methyl *trans*-2-phenyl cyclopropanecarboxylate was isolated, in addition to ethyl *trans*-2-phenyl cyclopropanecarboxylate, still in 80% ee. Clearly racemization of an initially formed cyclopropane was not the problem.

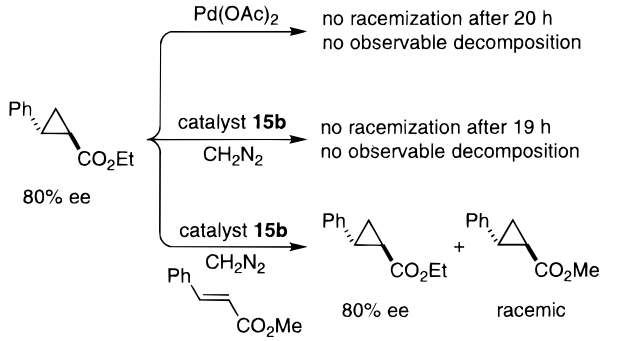


Figure 6. Control experiments ruling out the racemization of an initially scalemic cyclopropane. Enantiomeric excesses were determined by chiral phase (β-cyclodextrin) GC.

Discussion

Summary of Results. The most important, and perplexing, portion of this study was the complete lack of asymmetric induction in the cyclopropanation process regardless of the type of chiral palladium complex (**2**, **7**, **15**) used. Further investigation demonstrated that the bis(oxazoline) ligands were indeed having an effect on the catalytic activity of the palladium, as demonstrated by the differences in efficiency (**7e** ≈ **7f** > **7b** ≈ **7h** > **7d** > **7a** ≈ **7g**), although the reason for these differences is unclear. There was little variation in catalyst efficiencies over a 50-fold concentration window and the catalytically active species appeared to remain constant throughout the reaction. Spectroscopic analysis showed that **7e** is partially decomplexed to ligand **6e** cleanly and quickly upon treatment with diazomethane, while **7g** forms both free ligand **6g** and an as yet unidentified oxazoline-type species. Control experiments demonstrated that cyclopropanation occurred with retention of olefin configuration and that racemization of the product cyclopropane was not occurring.

Enantioselectivity. It is clear that whatever the exact mechanism of cyclopropanation is in these systems, no discrimination of the olefin faces was taking place. Since it is now well established that bis(oxazolines) and related ligands offer excellent asymmetric environments for a number of transformations, we feel that partial, or complete, ligand dissociation is occurring during the course of this cyclopropanation reaction. If this were not the case then at least some degree of enantioselection should have been observed. As the products were racemic in all cases we must conclude that the reaction is taking place in the ligand sphere of some palladium complex which is no longer chelated to its bis(oxazoline) ligand.

Two other explanations may be considered for the lack of enantioselectivity, though neither is well supported by the data presented. First, a trace impurity in the

(28) Harris, T. D.; Neuschwander, B.; Boekelheide, V. *J. Org. Chem.* **1978**, *43*, 727

(29) Doyle, M. P.; Wang, L. C.; Loh, K.-L. *Tetrahedron Lett.* **1984**, *25*, 4087.

palladium complexes could be the "true" catalyst. However this seems unlikely due to the differences in efficiency among the catalysts **7**, and the similar reactivity of the catalysts **15**, which were derived from completely different palladium sources.

Second, it could be that an active catalyst must first be formed from a bis(oxazoline) precatalyst. The reduction of palladium(II) salts to palladium(0) in the presence of diazomethane has been previously noted.[30] In the course of these studies we have found that palladium(0) sources which lack phosphine ligands, specifically $(dba)_2Pd$, are excellent catalysts for cyclopropanation. Complications tend to arise when phosphine ligands are used in the presence of diazomethane,[16a] and, presumably for this reason, tetrakis(triphenylphosphine)palladium(0) is a rather poor catalyst for this reaction. While we have observed the precipitation of palladium-black in the reactions with palladium(II) diacetate and bis(benzonitrile)palladium(II) dichloride, similar deposition has not been observed with the bis(oxazoline)palladium catalysts. In addition, complex **7e** was recovered from the reaction mixture in good yield with only minor amounts of contaminants. If catalysis were due to palladium(0) or other irreversibly formed decomposition product), then only 5−10% of the starting palladium(II) could have been reduced (as ca. 93% of the catalyst was recovered). Therefore, upon treatment of the reaction mixture with additional olefin and diazomethane ("two-salvo" experiments), there should be a sufficient amount of complex **7e** in solution to generate "new" palladium(0), in addition to the palladium(0) already present in solution. As the efficiency for this experiment (Figure 4) was less than in the corresponding control experiment at 0.05 M initial substrate, we can conclude that formation of trace palladium(0) (or other trace catalytic species) from the initial complex **7** is probably not relevant in this system unless it can be cycled back to **7** after a short time (to allow recovery).

Catalyst Efficiency. The evaluation of the differentially substituted complexes **7** was highly instructive, showing that the ligands were having an effect on the reactivity of the palladium catalysts. Figure 1 clearly shows that the sterically hindered complexes, i.e. **7e**, cyclopropanate olefins much more rapidly than the less hindered complexes, i.e. **7g**. In addition, catalysts which affect cyclopropanation more efficiently also decomposed diazomethane more readily. An explanation for this hierarchy was not obvious. We had originally considered two primary explanations, based on aggregation and an inactive adduct, though subsequent experiments seemed to rule out both of these possibilities.

Concentration Studies. As the observed range of reactivities was, on first analysis, contrasteric, we hypothesized that aggregation might be playing a role in the catalyst reactivities. If one considers a system where the monomer is catalytically active, while an aggregate (size not specified) is inactive or slow reacting, then if the monomer concentration in solution is high, reactivity should be high. As complex **7e** is more hindered around palladium than **7d**, it could be that **7d** exists in a more aggregated state in solution than **7e** and hence is less reactive. The slight concentration effect observed (Figure 2), opposite to that predicted by this explanation, coupled with the results for the 4-ethyl-substituted complex **7f,** seriously challenged the involvement of aggregation in this system.

Spectroscopic Results. Although McCrindle and coworkers[21] have isolated and characterized several chloromethyl palladium(II) and platinum(II) complexes arising from methylene insertion, no such species were observed by NMR spectroscopy in this system. The results were, nonetheless, very interesting. In both **7e** and **7g**, addition of diazomethane quickly produced free ligand. In addition, complex **7g** also produced two sets of new oxazoline-type signals. This dissociation could be due to the steric or mechanistic requirements of the decomposition of diazomethane, which presumably occurs via a palladium−carbenoid reacting with excess diazomethane. Bis(oxazoline) ligand **6e** was formed by partial decomplexation of **7e** upon treatment of the latter with diazomethane. Catalyst **7g**, however, formed a more complex mixture which we believe to include a monodentate bis(oxazoline)palladium complex. Such a monodentate bis(oxazoline) would no longer be C_2-symmetric and therefore could account for both sets of unassigned signals in the ^{13}C NMR spectrum, in addition to the similarity of the ^1H NMR spectrum to that of a palladium-complexed oxazoline. Interestingly, a portion of the ligand apparently reassociates with the palladium after time, as demonstrated by the addition of diazomethane to complex **7e** or **7g** and reanalysis after 48 h.

Steric Rationale. Partial ligand dissociation is also suggested by the higher efficiency of the hindered complexes. The dissociation observed in the NMR experiments could be due to either the hindrance around palladium being too great for cyclopropanation to occur in the ligand sphere, or that the mechanism of cyclopropanation (or diazomethane decomposition) *requires* loss of one or more donors from palladium. This rationale fits with most of the data; however, to bring complexes **7a** and **7g** into the manifold, two factors must be considered. The first is that increasing the bulk at the 4-position of the oxazoline changes the mechanism of cyclopropanation, and the second is a proposed electronic interaction of the π-basic benzyl group.

It is possible that complexes **7d** and **7g** react from a nondissociated state, due to the mild steric requirement of the 4-unsubstituted bis(oxazoline) ligands. The different reactivities could perhaps be explained by the increased bulk in general of complex **7g** which may affect the approach of either diazomethane or the olefin during the cyclopropanation. A corollary to this hypothesis is that the sterically demanding complexes react through a partially or completely dissociated form. This analysis would concur with the results obtained, except in the case of the benzyl-substituted complex **7a**. On the basis of this rationale, one would expect complex **7a** to be roughly as efficient as **7b**, though experimentally it is much slower. This may be related to the electronic as well as steric differences between benzyl and other 4-substituents investigated.

Electronic Rationale. Doyle has proposed the interaction of nonbonded electrons with an electrophilic rhodium carbenoid derived from $Rh_2(MEPY)_4$.[8d] Specifically, this interaction, between the carbenoid carbon and the ester carbonyl groups, is proposed to explain stabilization of the favored carbene rotamers and therefore rationalize their observed selectivities in the intermolecular cyclopropanation of styrene with diazoacetates. It is possible that the same type of interaction could occur

(30) Tomilov, Y. V.; Bordakov, V. G.; Dolgii, I. E.; Nefodov, O. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, 582, in ref 16a.

in **7a**, with the phenyl ring acting as a π-donor to the electron deficient carbenoid center. This interaction would stabilize the palladium−carbenoid, making it less reactive, which could be the cause of the low efficiency of complex **7a**.

As mentioned above, ligand dissociation could simply result from steric congestion, or it could be an integral part of the mechanism of cyclopropanation. If one considers the mechanism to involve a palladium−carbenoid, then it is very likely that one donor, either an oxazoline nitrogen or chloride, must dissociate during the reaction. Formation of the carbenoid initially provides a five-coordinate 18-electron species. If olefin coordination precedes cyclopropanation, as is suggested in the literature, then one ligand *must* dissociate to form a 16-electron carbenoid, to allow for such olefin coordination. Though Doyle's experiments show that a precoordinated olefin is unreactive toward diazoacetate, that study does not rule out olefin complexation to an activated palladium−carbenoid or related species. As most mechanistic rationales of cyclopropane formation involve an intermediate metallocyclobutane, it seems likely that the olefin must enter the ligand sphere of a coordinatively unsaturated palladium for efficient metallocyclobutane formation.

Control Experiments. From the results of several control experiments we have shown that (1) no olefin complexation to either complex **7e**, **7g**, or palladium(II) diacetate was detected; (2) the cyclopropanation of methyl *(Z)*-cinnamate was highly stereospecific, as had been previously reported;[31] and (3) the cyclopropanes were not racemized during the reaction.

The stereospecificity provides important information about the interaction of the olefin with the metal−carbenoid and suggests that bonding is established to both olefinic carbons simultaneously or at least faster than bond rotation. It should be noted that forming two carbon−carbon bonds is not required, as metallocyclobutane formation would also result in retention of olefin configuration. This would be consistent with two of the three proposals currently in the literature concerning the interaction of metal carbenoids with the olefins (Figure 7).[32] Either concerted metallocyclobutane formation, path a, reminiscent of olefin metathesis, or the concerted dipolar pathway b would be consistent with this fact. Path c is unlikely to be in operation due to the many reports in the literature which suggest that palladium cyclopropanation occurs with little charge buildup in the transition state.[8b,c,16] The metallocyclobutane route is strongly supported as a mechanism open to group 10 metals from work by Casey[33] and Jennings[34] on platina(IV)cyclobutanes in olefin metathesis and cyclopropanation and a recent report from Hoffman and co-workers on a pallada(II)cyclobutane.[35] In several cases, treatment

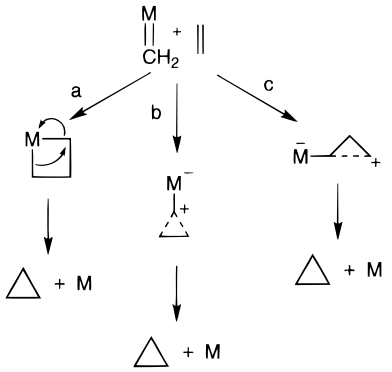


Figure 7. Three limiting mechanisms for metal−carbenoid cyclopropanation.[33]

of the metallocyclobutane with a soft ligand (carbon monoxide, a phosphine, or DMSO, for example) resulted in the stereospecific extrusion of the corresponding cyclopropane. We feel that this secondary interaction of an initially uncoordinated donor with the palladium center is an important part of the catalytic cycle. In addition, it is likely that there must be an open site on the palladium to effect formation of the metallocyclobutane.

Mechanistic Rationale. Although the results presented are indeed perplexing, we feel that a unified picture of the mechanism of this reaction can be formulated. We propose that during the course of the reaction, either partial or complete ligand dissociation/reassociation takes place, such that the reaction proceeds through one of two palladium carbenoids, **18** (Figure 8) or **19** (Figure 9) depending on the steric environment around palladium (unhindered, Figure 8, **7a**, **7d**, **7g**, and hindered, Figure 9, **7b**, **7c**, **7e**, **7f**, **7h**). Both cases will be considered independently.

Unhindered Complexes. The first stage of this proposal involves attack of diazomethane on the starting complex **16** to provide, nominally, the trigonal bipyramidal carbenoid **17** (Figure 8). We propose that such a carbenoid rapidly loses one donor group to reform a square planar 16-electron complex. Due to the relatively high affinity of chloride, the monodentate 16-electron complex **18** is formed by loss of one of the oxazoline nitrogen electron pairs. This species is then free to interact with the olefin and undergo cyclopropanation, or decompose diazomethane, reforming the initial complex **16**.

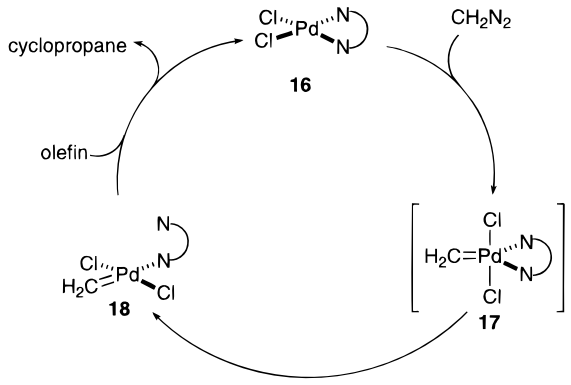


Figure 8. Proposed catalytic cycle of cyclopropanation with "unhindered" bis(oxazoline)palladium complexes.

Compared to the parent complex **7d**, the 5,5-disubstituted complex **7g** was less efficient in catalyzing cyclo-

(31) Nakamura, A.; Koyama, T.; Otsuka, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 593. Additionally, these authors briefly mention attempting asymmetric cyclopropanation of styrene with ethyl diazoacetate and various palladium catalysts. No details are provided, though none of the catalysts provided enantiomerically enriched cyclopropanes.

(32) Al-Essa, R. J.; Puddephatt, R. J.; Thompson, P. J.; Tipper, C. F. H. *J. Am. Chem. Soc.* **1980**, *102*, 7546.

(33) (a) Casey, C. P.; Scheck, D. M.; Shusterman, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 4233. For related work on tungsten carbene cyclopropanation see: (b) Casey, C. P.; Shusterman, A. J. *Organometallics* **1985**, *4*, 736. and references therein. For reviews on metallocyclobutanes see: (c) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241. (d) Puddephatt, R. J. *Coord. Chem. Rev.* **1980**, *33*, 149.

(34) (a) Reference 34d. (b) Hanks, T. W.; Jennings, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 5023.

(35) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A.; Menzer, S.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 100.

propanation. This behavior can be understood on steric grounds both in the lower propensity of the square planar complex **16** to bind an additional ligand as well as in the increased steric hindrance in the square planar complex **18**. The buttressing effect of the 5,5-dimethyl groups in **7g** resist the dissociation of an oxazoline in the trigonal bipyramidal complex **17** thus discouraging formation of the reactive species **18**. It is important to note that the reactivity of **7g** did not change significantly in the second salvo experiment showing that, after initial stages of reaction, the original bidentate bis(oxazoline) complex is probably reformed. Indeed it may be necessary to reassociate the oxazoline ligand to promote reductive elimination, as has been observed in some metallocyclobutane systems.

Hindered Complexes. As in the foregoing scenario, attack of diazomethane on the complex **16** initially provides the trigonal bipyramidal palladium-carbenoid (Figure 9). However, due to the extreme hindrance of complexes **7b**,**c**,**e**,**f**,**h**, the trigonal bipyramidal intermediate analogous to **17** is proposed to break down very quickly (or perhaps **17** is a transition state on the way) to the square-planar carbenoid complex **18**. As there are still significant steric interactions of the oxazoline 4-substituents and the palladium moiety, the bis(oxazoline) ligand is completely lost providing the "free" palladium−carbenoid **19**. Reaction of this "free" metal−carbenoid with the olefin is then extremely fast and unselective. In this case, ligand reassociation must again take place during reductive elimination for the reasons discussed above. This may be either reassociation of a decomplexed bis(oxazoline) or transfer of a ligand from another molecule of starting complex. The NMR data also falls in line with this explanation, as no "intermediate", i.e. monodentate, complex was observed with **7e**, only free ligand and starting complex. The divergent reactivity of the benzyl complex **7a** can still be explained by the stabilization (saturation) of the intermediate **18** through a phenyl π-complexation.

The unfortunate fact that stands out in this analysis is the lack of enantioselectivity in the aryl−oxazoline **15** cases. One would expect, on the basis of the rationales presented above, that such a complex would provide some enantioselectivity, due to the inability of the ligand to completely dissociate. Preliminary results suggest that these compounds can be recovered from the reaction media unchanged, though in modest yield.[36] However, it is known that simple aryl palladium halides are not stable, unless protected by bulky ligand or stabilized by the formation of a palladacycle (as in the starting complexes **15**).[23j] If ligand dissociation were taking place in this series as well, similar to the hindered six-membered chelates **7**, then the resulting aryl palladium halide may not be stable with respect to formation of palladium(0) and the aryl halide **14**. Although none of this compound was observed in these initial recovery experiments, we feel that we cannot rule out adventitious palladium(0) catalysis in the aryl systems at this time. Further studies on the kinetics and reactivity of such aryl-oxazoline based catalysts are necessary to judge what modifications, if any, could be made to afford an enantioselective cyclopropanation catalyst.

(36) In a preliminary experiment, ethyl cinnamate, diazomethane (3.5 equiv), and **15b** (25 mol %) were combined and after separation of the cyclopropane product, the catalyst could be recovered in two fractions: 42% mass recovery of pure (>90% by NMR) **15b** and 29% mass recovery of impure **15b**.

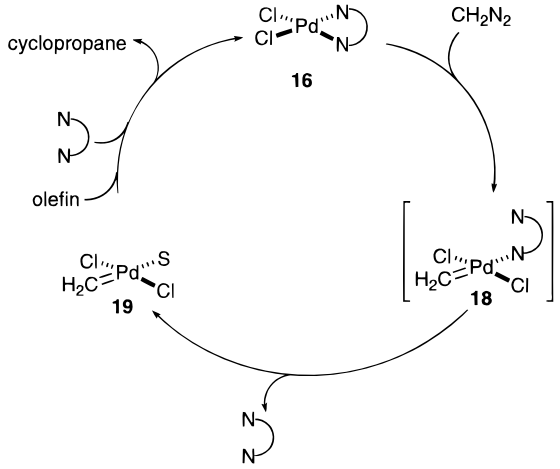


Figure 9. Proposed catalytic cycle of cyclopropanation with "hindered" bis(oxazoline)palladium complexes.

Conclusion

We have demonstrated that although no asymmetric induction is observed in the bis(oxazoline)palladium(II)-catalyzed cyclopropanation of olefins, the ligands are having a dramatic and fascinating effect on the reactivity of the palladium center. Several generations of palladium complexes were synthesized and their reactivities characterized, though none proved to be an effective asymmetric catalyst. We feel that the cyclopropanation is taking place via an uncoordinated palladium−carbenoid in which the chiral bis(oxazoline) ligand is completely removed from the reactive palladium center. In addition, bis(oxazoline) complexes lacking substituents at the 4-position may proceed through a different, partially coordinated carbenoid. This aspect, mechanistically and synthetically, is currently under further investigation.

Experimental Section

General. Short-path (bulb-to-bulb) distillations were performed on a Kugelrohr apparatus; boiling points (bp) correspond to uncorrected air bath temperatures (ABT), mp are uncorrected. Analytical GC employed either a 50 m HP-1 (methylsilicone, Hewlett-Packard), a 50 m HP-5 (5% phenylmethylsilicone, Hewlett-Packard), or a 30 m β-cyclodextrin (J&W Scientific) capillary column. Analytical TLC was performed on Merck silica gel plates with indicator (QF-254). Visualization was realized with UV light, iodine, phosphomolybdic acid, potassium permanganate, and/or ninhydrin. Column chromatography was performed according to Still,[37] using EM Science 230−400 mesh silica gel. All reactions were performed in oven (140 °C) and/or flame-dried glassware under an atmosphere of dry nitrogen, except for reactions involving water or diazomethane which were performed open to the air. All reactions using diazomethane were performed in glassware without ground glass joint (Clear-Seal). Diazomethane was transferred via flame-polished volumetric pipettes. Solvents for chromatography and extraction were technical grade and distilled from the indicated drying agents: hexane, pentane, and CH_2Cl_2 ($CaCl_2$); *tert*-butyl methyl ether (TBME) ($CaSO_4$/$FeSO_4$); ethyl acetate (K_2CO_3). Reaction solvents were distilled from the indicated drying agents: CH_2Cl_2 (P_2O_5), THF, Et_2O (Na, benzophenone), benzene (CaH_2), toluene (Na), MeOH (Mg). *n*-Butyllithium was titrated using the method of Gil-

(37) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2928.

man.[38] Removal of solvent was by rotary evaporation, unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300, 400, or 500 MHz ^{1}H (75.5, 100, 125 MHz ^{13}C) with residual chloroform (7.26 ppm for ^{1}H, 77.0 ppm for ^{13}C) as the internal reference unless otherwise noted. ^{19}F NMR spectra were recorded at 376 MHz using trifluromethylbenzene as a reference (−63.73 ppm). Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broadened). Coupling constants, J, are reported in hertz. Mass spectrometry was performed by the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Infrared spectra (IR) are reported in cm^{-1} with indicated intensities: s (strong, 67−100%), m (medium, 34−66%), w (weak, 0−33%). Optical rotations are reported as follows: $[\alpha]^{24}_D$ (c = g/100 mL, solvent). Elemental analyses were performed by the University of Illinois Microanalytical Service laboratory.

Materials. Diethylmalonyl dichloride and thionyl chloride were distilled before use. Mesyl chloride and triethylamine were distilled from CaH_2, and methanesulfonic acid was distilled from P_2O_5. Hemimellitic acid and common amino acids were obtained from commercial sources and used without further purification. Compounds **8a**, **8b**, **8c**, **6a**, **6b**, **6c**, and (*S*)-2-amino-3-methyl-3-phenyl-1-butanol were prepared as previously described.[3bb]

(*S*)-*N*,*N*′-Bis[1-(hydroxymethyl)-2-phenylethyl]ethanediamide (4a). Diethyl oxalate (1.30 mL, 0.96 mmol) and (*S*)-phenylalanol (**3a**) (302 mg, 2.00 mmol, 2.10 equiv) were heated to reflux in toluene (15 mL) for 3 h. During this time fine white crystals precipitated out of solution. The mixture was cooled to rt, and hexane (20 mL) was added. The product was collected by filtration, washed with hexane (40 mL), and dried (100 °C at 0.2 mmHg) to afford 0.331 g (97%) of the bisamide **4a** as white crystals. An analytical sample was obtained by recrystallization from methanol: mp 217−217.5 °C (MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) 8.35 (d, J = 9.1, 2 H), 7.25−7.12 (m, 10 H), 4.88 (t, J = 5.5, 2 H), 3.91 (m, 2 H), 3.36 (m, 4 H), 2.83 (m, 2 H), 2.69 (m, 2 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 159.46, 138.86, 128.97, 128.15, 126.00, 62.28, 53.02, 36.09; IR (KBr) 3296 (s), 1656 (s); MS (EI, 70 eV) 356 (M$^+$, 2), 223 (100); TLC R_f 0.26 (CH_2Cl_2/CH_3OH, 10/1). Anal. Calcd for $C_{20}H_{24}N_2O_4$ (356.43): C, 67.40; H, 6.79; N, 7.86. Found: C, 67.42; H, 6.85; N, 7.94.

(*S*)-*N*,*N*′-Bis[1-(hydroxymethyl)-2-methylpropyl)]-ethanediamide (4b). A mixture of (*S*)-valinol (**3b**) (13.28 g, 128.7 mmol, 3.00 equiv) and oxamide (3.78 g, 42.9 mmol) was heated to 170 °C for 4 h. Gas evolution was monitored by a mineral oil bubbler and ceased after 2.5 h. The bubbler was removed, and the reaction mixture was allowed to cool to rt. The orange residue was recrystallized twice from CH_2Cl_2/hexane containing EtOH (1 mL) to afford 7.64 g (68%) of the bisamide **4b** as a white solid. Concentration of the mother liquors and a second recrystallization afforded an additional 2.06 g (18%, 86% combined yield) of **4b**: mp 200−201 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, DMSO-d_6) 8.15 (d, J = 9.3, 2 H), 4.67 (t, J = 5.3, 2 H), 3.46 (m, 6 H), 1.83 (m, 2 H), 0.86 (d, J = 6.8, 6 H), 0.79 (d, J = 6.8, 6 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 159.90, 60.99, 56.78, 28.55, 19.58, 18.75; IR (KBr) 3291 (s), 1651 (s); MS (EI, 10 eV) 260 (M$^+$, 8), 229 (100); TLC R_f 0.34 (CH_2Cl_2/CH_3OH, 10/1). Anal. Calcd for $C_{12}H_{24}N_2O_4$ (260.34): C, 55.36; H, 9.29; N, 10.76. Found: C, 55.41; H, 9.40; N, 10.89.

(*S*)-*N*,*N*′-Bis[1-(chloromethyl)-2-phenylethyl]ethanediamide (5a). Thionyl chloride (1.5 mL, 12.1 mmol, 2.9 equiv) was added quickly to a suspension of **4a** (1.482 g, 4.16 mmol) in toluene (30 mL) at 60 °C. The reaction mixture was maintained at 60−70 °C for 1 h and then heated to 90 °C for 4 h. The mixture was cooled to rt, poured into a cold (0 °C) solution of 20% aqueous KOH (100 mL), and extracted with CH_2Cl_2 (3 × 150 mL). The organic extracts were washed with brine (1 × 150 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated. Recrystallization of the resulting off-white solid from toluene/hexane afforded 1.41 g (86%) of **5a** as a white powder: mp 197.5−198.5 °C (toluene/hexane); ^{1}H NMR (300 MHz) 7.66 (d, J = 8.8, 2 H), 7.37−7.20 (m, 10 H), 4.41 (m, 2 H), 3.63 (dd, J = 4.2, 11.4, 2 H), 3.52 (dd, J = 3.7, 11.4, 2 H), 2.98 (d, J = 7.3, 4 H); ^{13}C NMR (75.5 MHz) 158.80, 136.08, 129.21, 128.83, 127.11, 51.42, 45.61, 37.25; MS (EI, 70 eV) 301 (100); TLC R_f 0.90 (CH_2Cl_2/CH_3OH, 10/1). Anal. Calcd for $C_{20}H_{22}Cl_2N_2O_2$ (393.32): C, 61.08; H, 5.64; Cl, 18.03; N, 7.12. Found: C, 61.23; H, 5.66; Cl, 18.01; N, 7.14.

(*S*)-*N*,*N*′-Bis[1-(chloromethyl)-2-methylpropyl]ethanediamide (5b). Thionyl chloride (0.435 mL, 5.02 mmol, 2.2 equiv) was added quickly to a suspension of **4b** (591 mg, 2.27 mmol) in toluene (15 mL) at 65 °C. The reaction mixture was maintained at 60−70 °C for 30 min and then heated to 90 °C for 90 min. The mixture was cooled to rt, poured into a cold (0 °C) solution of 20% aqueous KOH (40 mL), and was extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were washed with a 20% aqueous solution of KOH (1 × 60 mL) and saturated aqueous $NaHCO_3$ (1 × 60 mL) and then were combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated. Recrystallization of the resulting off-white solid from toluene/hexane afforded 641 mg (95%) of **5b** as a white powder: mp 165−166 °C (toluene/hexane); ^{1}H NMR (300 MHz) 7.58 (br d, J = 9.1, 2 H), 3.91 (m, 2 H), 3.68 (m, 4 H), 2.04 (m, 2 H), 0.99 (d, J = 6.73, 6 H), 0.95 (d, J = 6.8, 6 H); ^{13}C NMR (75.5 MHz) 159.33, 55.93, 45.62, 29.22, 19.19, 18.54; MS (EI, 70 eV) 298 (MH$^+$, 5), 69 (100); TLC R_f 0.44 (CH_2Cl_2). Anal. Calcd for $C_{12}H_{22}Cl_2N_2O_2$ (297.23): C, 48.49; H, 7.46; Cl, 23.86; N, 9.42. Found: C, 48.50; H, 7.45; Cl, 23.54; N, 9.39.

(*S*)-4,4′-Bis(phenylmethyl)-4,4′,5,5′-tetrahydro-2,2′-bioxazole (1a). Potassium hydroxide (0.460 g, 8.20 mmol, 2.5 equiv) and **5a** (1.276 g, 3.24 mmol) were heated to reflux in methanol (40 mL) for 3 h. Potassium chloride gradually precipitated as the reaction proceeded. The reaction mixture was cooled to rt, poured into H_2O (50 mL), and extracted with CH_2Cl_2 (3 × 60 mL) and TBME (1 × 60 mL). The organic extracts were washed with brine (1 × 75 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to afford 0.910 g (88%) of bis(oxazoline) **1a**: mp 131−132 °C (hexane/EtOAc); $[\alpha]^{24}_D$ = −82° (c = 1.23, CH_2Cl_2); ^{1}H NMR (300 MHz) 7.27 (m, 10 H), 4.61 (m, 2 H), 4.37 (t, J = 8.9, 2 H), 4.17 (t, J = 8.2, 2 H), 3.28 (dd, J = 5.0, 13.9), 2.71 (dd, J = 9.3, 13.9, 2 H); ^{13}C NMR (75. MHz) 155.07, 137.09, 129.08, 128.66, 126.71, 72.70, 68.20, 41.09; IR (KBr) 1628 (s); TLC R_f 0.15 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.39): C, 74.98; H, 6.29; N, 8.74. Found: C, 74.90; H, 6.38; N, 8.73.

(*S*)-4,4′-Bis(1-methylethyl)-4,4′,5,5′-tetrahydro-2,2′-bioxazole (1b). Potassium hydroxide (0.340 g, 6.06 mmol, 2.3 equiv) and **5b** (0.797 g, 2.68 mmol) were heated to reflux in methanol (40 mL) for 1 h. Potassium chloride gradually precipitated as the reaction proceeded. The reaction mixture was cooled to rt, poured into H_2O (50 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were washed with brine (1 × 100 mL) and then combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc, 1/1) and recrystallization (pentane) to afford 0.535 g (89%) of **1b** as fine white needles: mp 54.5−55 °C (pentane); $[\alpha]^{24}_D$ = −190 (c = 0.70, $CHCl_3$); ^{1}H NMR (300 MHz) 4.38 (m, 2 H), 4.06 (m, 4 H), 1.80 (m, 2 H), 0.97 (d, J = 6.7, 6 H), 0.87 (d, J = 6.8, 6 H); ^{13}C NMR (75.5 MHz) 154.40, 73.02, 70.95, 32.32, 18.86, 18.15; IR (KBr) 1628 (s); MS (EI, 70 eV) 224 (M$^+$, 3), 181 (100); TLC R_f 0.18 (CH_2Cl_2). Anal. Calcd for $C_{12}H_{20}N_2O_2$ (224.30): C, 64.26; H, 8.99; N, 12.49. Found: C, 64.46; H, 9.06; N, 12.47.

(*S*)-4,4′-Bis(phenylmethyl)-4,4′,5,5′-tetrahydro-2,2′-bioxazolepalladium(II) Dichloride (2a). Representative Procedure I. Bis(benzonitrile)palladium(II) dichloride (0.320 g, 0.83 mmol, 1.00 equiv) and **1a** (0.267 g, 0.83 mmol) were dissolved in CH_2Cl_2. The reaction mixture was stirred for 90 min at rt. Hexane (40 mL) was added, the reaction mixture was cooled to 0 °C, and the product was collected by filtration to afford 0.333 g (81%) of the palladium complex **2a** as a yellow-orange powder: $[\alpha]^{24}_D$ = +250° (c = 1.14, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$/CD_2Cl_2, 1/1) 7.45−7.28 (m, 10 H),

(38) (a) Gilman, H.; Cartledge, F. K.; Sim, S.-Y. *J. Organomet. Chem.* **1963**, *1*, 8. (b) Whitesides, G. M.; Casey, C. P.; Kriege, J. F. *J. Am. Chem. Soc.* **1971**, *93*, 1379.

4.82−4.75 (m, 6 H), 3.64 (m, 2 H), 3.03 (m, 2 H); ^{13}C NMR (125.8 MHz, $CDCl_3/CD_2Cl_2$, 1/1) 159.70, 134.44, 129.55, 128.85, 127.38, ~77*, 64.00, 39.23; IR (CH_2Cl_2) 1651 (m). Anal. Calcd for $C_{20}H_{20}Cl_2N_2O_2Pd$ (497.70): C, 48.27; H, 4.05; Cl, 14.25; N, 5.63; Pd, 21.38. Found: C, 48.40; H, 4.04; Cl, 14.36; N, 5.57; Pd, 21.20.

***N,N′*-Bis(2-hydroxyethyl)-2,2-diethyl-1,3-propanediamide (8d). Representative Procedure II.** Diethylmalonyl dichloride (1.68 mL, 9.78 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a cold (0 °C) solution of ethanolamine (**3d**) (1.25 g, 20.5 mmol, 2.1 equiv) in CH_2Cl_2 (30 mL) over 30 min. A white precipitate formed immediatly, and the mixture became difficult to stir. After complete addition of diethylmalonyl dichloride, triethylamine (3.40 mL, 24.2 mmol, 2.5 equiv) was added quickly and the mixture allowed to warm to rt and stir for 12 h. The heterogeneous mixture was poured into H_2O (200 mL) and extracted with $CHCl_3$ (15 × 30 mL). The organic extracts were combined, dried ($MgSO_4$), and filtered, and the filtrate was concentrated to give a crude solid which was purified by silica gel chromatography (CH_2Cl_2/MeOH, 9/1) and recrystallization from EtOAc/hexane to provide 2.07 g (86%) of the bisamide **8d** as small white crystals: mp 113−114.5 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 3.60 (t, J = 5.9, 4 H), 3.35 (t, J = 5.9, 4 H), 1.88 (q, J = 7.6, 4 H), 0.80 (t, J = 7.6, 6 H); ^{13}C NMR (100 MHz) 175.52, 61.48, 59.67, 42.92, 29.63, 9.84; IR (KBr) 3323 (s), 3252 (m), 1632 (s); MS (CI, methane, 130 eV) 247 (MH^+, 100); TLC R_f 0.26 ($CHCl_3$/MeOH, 9/1). Anal. Calcd for $C_{11}H_{22}N_2O_4$ (246.30): C, 53.64; H, 9.01; N, 11.37. Found: C, 53.91; H, 9.00; N, 11.46.

2,2′-(1-Ethylpropylidene)bis(4,5-dihydrooxazole) (6d). Representative Procedure III. Bisamide **8d** (1.14 g, 4.61 mmol) was suspended in toluene (20 mL) at 65 °C. Thionyl chloride (1.34 mL, 18.4 mmol, 4.0 equiv) was added quickly, and the resulting mixture was stirred at 65−70 °C for 5 h. The mixture was cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and was extracted with $CHCl_3$ (10 × 20 mL). The organic extracts were combined, dried (Na_2SO_4), and filtered, and the filtrate was concentrated to provide a yellow oil. The crude amide was heated to reflux in 5% methanolic NaOH solution (10 mL) for 2 h, during which time NaCl precipitated from the reaction mixture. The mixture was cooled to rt and concentrated, the residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and filtered, and the filtrate was concentrated to give an oil which was purified by bulb-to bulb distillation to afford 0.863 g (89%) of the bis(oxaozline) **6d** as a white waxy solid. An analytical sample was obtained by sublimation (65 °C at 0.3 mmHg): mp 66−67 °C; ^{1}H NMR (400 MHz) 4.42 (t, J = 9.3, 4 H), 3.83 (t, J = 9.3, 4 H), 1.55 (q, J = 7.4, 4 H), 0.78 (t, J = 7.4, 6 H); ^{13}C NMR (100 MHz) 168.17, 67.31, 54.11, 46.63, 25.50, 8.27; IR ($CHCl_3$) 1656 (s); MS (CI, methane, 130 eV) 211 (MH^+, 100); TLC R_f 0.08 (CH_2Cl_2/acetone, 4/1). Anal. Calcd for $C_{11}H_{18}N_2O_2$ (210.28): C, 62.83; H, 8.63; N, 13.32. Found: C, 62.78; H, 8.70; N, 13.30.

2,2′-(1-Ethylpropylidene)bis(4,5-dihydro-5,5-dimethyloxazole) (6g). Representative Procedure IV. The bisamide **8g** (0.923 g, 3.1 mmol) and methanesulfonic acid (1.20 mL, 18.5 mmol, 6.1 equiv) were heated to reflux in CH_2Cl_2 (35 mL) for 12 h in a Soxhlet extractor with calcium hydride in the thimble. The reaction mixture was cooled to rt and then poured into H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated to give a colorless oil which was distilled (bulb-to-bulb) to give 0.748 g (92%) of the bis(oxazoline) **6g** as a white solid: bp 80 °C (ABT), 0.4 mmHg; ^{1}H NMR (400 MHz) 3.57 (s, 4 H), 1.94 (q, J = 7.6, 4 H), 1.34 (s, 12 H), 0.80 (t, J = 7.6, 6 H); ^{13}C NMR (100 MHz) 166.97, 83.50, 66.35, 46.20, 27.33, 23.94, 7.94; IR ($CHCl_3$) 1649 (s); MS (CI, methane, 130 eV) 267 (MH^+, 100); TLC R_f 0.17 (pentane/Et_2O, 1/1). Anal. Calcd for $C_{15}H_{26}N_2O_2$ (266.38): C, 67.63; H, 9.84; N, 10.52. Found: C, 67.53; H, 10.17; N, 10.48.

***(S)*-2,2′-(1-Ethylpropylidene)bis[4,5-dihydro-4-(phenylmethyl)oxazole]palladium(II) Dichloride (7a). Representative Procedure V.** Ligand **6a** (0.667 g, 1.82 mmol) and $(PhCN)_2PdCl_2$ (0.711 g, 1.85 mmol, 1.0 equiv) were combined in CH_2Cl_2 (30 mL) and stirred at rt for 14 h. The deep red solution was filtered through Celite and concentrated to afford a dark paste which was triturated with pentane (3 × 30 mL). The residue was recrystallized from CH_3NO_2/Et_2O to provide 0.687 g (69%) of the palladium complex **7a** as orange needles: mp 246 °C dec (CH_3NO_2/Et_2O); $[\alpha]^{24}_D$ = +68.0° (c = 0.97, $CHCl_3$); ^{1}H (400 MHz) 7.40−7.20 (m, 10 H), 5.04 (m, 2 H), 4.45 (dd, J = 2.5, 9.0, 2 H), 4.11 (t, J = 8.8, 2 H), 3.91 (dd, J = 2.7, 12.7, 2 H), 2.33 (dd, J = 11.2, 12.7, 2 H), 2.00 (q, J = 7.6, 4 H), 0.85 (t, J = 7.6, 6 H); ^{13}C NMR (100 MHz) 168.79, 135.95, 129.57, 128.66, 127.00, 71.66, 67.13, 51.36, 39.86, 31.55, 9.74; IR ($CHCl_3$) 1652 (s). Anal. Calcd for $C_{25}H_{30}Cl_2N_2O_2Pd$ (567.85): C, 52.88; H, 5.33; N, 4.93; Cl, 12.49; Pd, 18.74. Found: C, 52.78; H, 5.35; N, 5.07; Cl, 12.36; Pd, 18.44.

***N*-[1-(Ethoxycarbonyl)-1-ethylpropyl]benzophenone Imine (9).** A solution of KHMDS (7.51 g, 37.6 mmol, 1.1 equiv) in THF (40 mL) was added via cannula to the benzophenone imine of glycine ethyl ester[20] (9.17 g, 34.3 mmol) in THF (150 mL) at −73 °C to give a bright yellow solution which was allowed to stir for 1 h. Iodoethane (3.30 mL, 41.2 mmol, 1.2 equiv) was added quickly, and the solution was allowed to warm to rt and stir for 3 h. The now heterogeneous mixture was again cooled to −74 °C, and a second portion of KHMDS (7.47 g, 37.5 mmol, 1.1 equiv) in THF (45 mL) was added via cannula. The deep orange mixture was stirred at −73 °C for 50 min, and a second portion of iodoethane (3.30 mL, 41.2 mmol, 1.2 equiv) was added quickly. The reaction mixture was allowed to warm to rt and stir overnight (10 h), poured into H_2O (100 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and filtered, and the filtrate concentrated to give 11.00 g (100%) of the dialkylated imine **9** as a yellow oil which was used in the next step without purification: ^{1}H NMR (300 MHz) 7.58−7.11 (m, 10H), 3.75 (m, 2 H), 1.93 (q, J = 7.4, 4 H), 1.12 (t, J = 7.2, 3 H), 0.91 (t, J = 7.4, 6 H).

Ethyl 2-Amino-2-ethylbutanoate (10).[39] Hydrochloric acid (1 M, 51 mL, 1.5 equiv) was added dropwise over 45 min to a solution of the crude imine **9** (11.00 g, 34.0 mmol) in Et_2O (100 mL) at 0 °C, and the two-phase mixture was allowed to stir at rt overnight (14 h). The aqueous layer was removed and washed with CH_2Cl_2 (2 × 25 mL). The combined organic layers were extracted with 2 M hydrochloric acid (2 × 20 mL) and the aqueous layers were combined and concentrated to give a solid mass which was dissolved in a saturated aqueous solution of $NaHCO_3$ (100 mL) and stirred for 30 min. The resulting suspension was extracted with CH_2Cl_2 (5 × 35 mL), the organic phases were combined, dried (Na_2SO_4), and filtered, and the filtrate was concentrated to give a yellow oil which was purified by bulb-to-bulb distillation to provide 4.99 g (92%) of the amino ester **10** as a clear, colorless oil: bp 85 °C (ABT), 15 mmHg; ^{1}H NMR (400 MHz) 4.18 (q, J = 7.4, 2 H), 1.80−1.55 (m, 4 H), 1.25 (t, J = 7.4, 3 H), 0.84 (t, J = 7.6, 6 H).

2-Amino-2-ethylbutanol (3f).[40] A solution of amino ester **10** (4.81 g, 30.2 mmol) in Et_2O (75 mL) was added to a solution of lithium aluminum hydride (5.80 g, 152.8 mmol, 5.0 equiv) in Et_2O (150 mL) at such a rate as to maintain reflux (1.5 h). The reaction mixture was then stirred at rt overnight (14 h), cooled to 0 °C, and quenched by cautious addition of H_2O (7 mL) followed by 15% aqueous NaOH solution (7 mL) and finally H_2O (21 mL). Eventually (2 h), the gray salts turned white, the reaction mixture was filtered, and the salts were washed with Et_2O. The Et_2O fractions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by bulb-to-bulb distillation to provide 3.28 g (93%) of the amino alcohol **3f** as a clear, colorless oil: bp 130 °C (ABT), 20 mmHg; ^{1}H NMR (400 MHz) 3.29 (s, 2 H), 2.00 (br, 3 H), 1.34 (m, 4 H), 0.82 (t, J = 7.6, 6 H).

***(S)*-2-[(Trifluroacetyl)amino]-3-methylbutanoic Acid Methyl Ester (11).** Trifluoroacetic anhydride (4.30 mL, 26.2

(39) Rosenmund, K. W. *Chem. Ber.* **1909**, *42*, 4470.
(40) Collins, R. F. *Chem. Ind.* **1957**, 704.

mmol, 1.0 equiv) was added dropwise to a solution of valine methyl ester (3.44 g, 26.2 mmol) and triethylamine (4.00 mL, 28.6 mmol, 1.1 equiv) in CH_2Cl_2 (50 mL) at −74 °C over 5 min. After complete addition the reaction mixture was stirred at −74 °C for 1 h, quenched with saturated aqueous $NaHCO_3$ solution (20 mL), and allowed to warm to rt. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate afforded a slightly yellow oil which was distilled to provide 8.83 g (98%) of the trifluoroacetamide **11** as a clear, colorless oil: bp 90 °C (ABT), 5 mmHg; $[\alpha]^{24}_D = +33.4°$ ($c = 0.72$, CH_2Cl_2); ^{1}H NMR (400 MHz) 6.83 (br, 1 H), 4.58 (dd, J = 4.6, 8.5, 1 H), 3.79 (s, 3H), 2.26 (m, 1 H), 0.97 (d, J = 6.8, 3 H), 0.94 (d, J = 6.8, 3 H); ^{13}C NMR (100 MHz) 170.93, 156.95, 115.74, 57.43, 52.70, 31.40, 18.67, 17.57; ^{19}F NMR (376 MHz) −73.78 (s); IR (neat) 3326 (s); 1736 (s), 1725 (s), 1712 (s); MS (CI, methane, 130 eV) 228 (MH^+, 10), 168 (100); TLC R_f 0.73 (CH_2Cl_2/acetone, 1/1). Anal. Calcd for $C_8H_{12}F_3NO_3$ (227.16): C, 42.30; H, 5.32; N, 6.17. Found: C, 41.98; H, 5.50; N, 6.24.

(*S*)-2,2,2-Trifluoro-*N*-[2-hydroxy-2-methyl-1-(methylethyl)propyl]acetamide (12). A solution of trifluoroacetamide **11** (8.09 g, 35.6 mmol) in THF (40 mL) was added dropwise to methylmagnesium bromide (3 M in Et_2O, 60 mL, 180 mmol, 5.1 equiv) in 60 mL of THF over 1 h. The reaction mixture was heated to reflux for 6 h and then was cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution (50 mL), and extracted with TBME (4 × 50 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate gave a yellow oil which was distilled (bulb-to-bulb) to provide 7.53 g (93%) of the alcohol **12** as a clear, colorless oil: bp 85 °C (ABT), 0.4 mmHg; $[\alpha]^{24}_D = -12.9°$ ($c = 1.32$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 6.75 (br, 1 H), 3.75 (dd, J = 2.7, 10.3, 1 H), 2.21 (m, 1 H), 1.77 (s, 1 H), 1.34 (s, 3 H), 1.19 (s, 3 H), 0.94 (d, J = 6.8, 3 H), 0.92 (d, J = 6.8, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.79 (q, J = 36.2), 116.20 (q, J = 288), 72.83, 60.65, 29.38, 28.35, 27.27, 21.97, 16.56; ^{19}F NMR (376 MHz, $CDCl_3$) −76.61 (s); IR (neat) 1720 (s), 1712 (s); MS (CI, methane, 70 eV) 210 (M-OH, 100); TLC R_f 0.60 (CH_2Cl_2/*i*PrOH, 9/1). Anal. Calcd for $C_9H_{16}F_3NO_2$ (217.20): C, 47.57; H, 7.10; N, 6.16. Found: C, 47.70; H, 7.16; N, 6.45.

(*S*)-2-Amino-1,1,3-trimethylbutanol (3h). The trifluoroacetamide **12** (6.00 g, 26.1 mmol) was heated to reflux in 5% methanolic NaOH soltuion (45 mL) for 5 h. The reaction mixture was cooled to rt and concentrated. The residue was dissolved in CH_2Cl_2 (30 mL) and partitioned with H_2O (50 mL), and the aqueous phase was extracted with CH_2Cl_2 (6 × 30 mL). The combined organic extracts were washed with brine (50 mL), and the aqueous phase was back-extracted with CH_2Cl_2 (2 × 30 mL). The organic phases were combined, dried (Na_2SO_4), filtered, and concentrated. The resulting oil was distilled (bulb-to-bulb) to provide 3.07 g (90%) of the amino alcohol **3h** as a clear, colorless oil: bp 73 °C (ABT), 15 mmHg; $[\alpha]^{24}_D = -14.3°$ ($c = 3.18$, CH_2Cl_2); ^{1}H NMR (400 MHz) 2.38 (d, J = 2.7, 1 H), 1.90 (m, 1 H), 1.17 (s, 3 H), 1.09 (s, 3 H), 0.94 (d, J = 6.8, 3 H), 0.85 (d, J = 6.8, 3 H); ^{13}C NMR (100 MHz) 71.75, 64.02, 28.38, 28.31, 24.44, 23.07, 16.37; IR (neat); 3400 (m), 3338 (m), 1469 (m); MS (CI, methane, 130 eV) 132 (MH^+, 23), 114 (100); TLC R_f 0.06 (CH_2Cl_2/*i*PrOH, 9/1). Anal. Calcd for $C_7H_{17}NO$ (131.22): C, 64.07; H, 13.06; N, 10.67. Found: C, 63.84; H, 13.15; N, 10.60.

2-Bromo-1,3-benzenedicarbonyl Dichloride. Thionyl chloride (5 mL, 8.16 mmol, 3.1 equiv) and 2-bromo-1,3-benzenedicarboxylic acid (0.650 g, 2.65 mmol) were heated to reflux for 1 h. The excess thionyl chloride was distilled off, and the residue was recrystallized from hexane to provide 0.648 g (87%) of the acid chloride as a white solid: mp 78−79 °C (hexanes); ^{1}H NMR (400 MHz) 8.01 (d, J = 8.1, 2 H), 7.62 (t, J = 8.1, 1 H); ^{13}C NMR (100 MHz) 165.93, 138.85, 134.05, 127.87, 117.27; IR ($CDCl_3$) 1786 (s); MS (CI, isobutane, 130 eV) 285 (M + H, 5)), 283 (MH^+, ^{81}Br, ^{35}Cl and ^{79}Br, ^{37}Cl, 11), 281 (MH^+, ^{79}Br, ^{35}Cl, 7), 247 (100). Anal. Calcd for $C_8H_3BrCl_2O_2$ (281.92): C, 34.08; H, 1.07; Cl, 25.15; Br, 28.34. Found: C, 34.22; H, 1.08; Cl, 25.13; Br, 28.32.

2-Iodo-1,3-benzenedicarbonyl Dichloride. Thionyl chloride (3 mL, 4.98 mmol, 5.1 equiv) and 2-iodo-1,3-benzenedicarboxylic acid (0.284 g, 0.971 mmol) were heated to reflux for 45 min. The excess thionyl chloride was removed by distillation, and the residue was recrystallized from dry hexane to provide 0.247 g (77%) of the acid chloride as a white solid: mp 70−71 °C (hexanes); ^{1}H NMR (400 MHz) 7.90 (d, J = 7.8, 2 H), 7.64 (t, J = 7.8, 1 H); ^{13}C NMR 167.68, 143.23, 132.95, 128.74, 89.16; IR ($CDCl_3$) 1782 (s); MS (CI, isobutane, 130 eV) 330 (MH^+, 6), 293 (100). Anal. Calcd for $C_8H_3Cl_2IO_2$ (328.92): C, 29.21; H, 0.92; Cl, 21.56; I, 38.58. Found: C, 29.34; H, 0.96; Cl, 21.49; I, 38.45.

(*S*)-Bis[2-hydroxy-1-(phenylmethyl)ethyl]-2-bromo-1,3-benzenediamide (13a). Following representative procedure II: 2-bromo-1,3-benzenedicarbonyl dichloride (0.200 g, 0.711 mmol), L-phenylalaninol (**3a**) (0.215 g, 1.42 mmol, 2.0 equiv), and triethylamine (0.396 mL, 2.84 mmol, 4.0 equiv) provided, following silica gel chromatography (10/1 $CHCl_3$/MeOH), 0.317 g (87%) of the bisamide **13a** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD drops) 7.34−7.19 (m, 15 H), 4.34 (m, 2 H), 3.71 (dd, J = 4.2, 11.5, 2 H), 3.62 (dd, J = 4.9, 11.5), 3.02 (dd, J = 7.3, 13.9, 2 H), 2.91 (dd, J = 7.8, 13.9, 2 H); TLC R_f 0.3 ($CHCl_3$/methanol, 10/1).

(*S*)-2,2′-(2-Bromo-1,3-phenylene)bis[4,5-dihydro-4-(phenylmethyl)oxazole] (14a). Representative Procedure VI. Methanesulfonyl chloride (0.1 mL, 1.29 mmol, 2.1 equiv) was added to a solution of **13a** (0.313 g, 0.61 mmol) and triethylamine (0.256 mL, 1.84 mmol, 3.0 equiv) in CH_2Cl_2 (2 mL). The solution was stirred at rt for 14.5 h, diluted with $CHCl_3$ (20 mL) washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was dissolved in 5% methanolic KOH solution (10 mL) and stirred at rt for 23 h. The reaction mixture was diluted with H_2O (5 mL) and brine (15 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were dried (K_2CO_3), filtered, and concentrated. The residue was purified by silica gel chromatography ($CHCl_3$/acetone 10/1) to afford 0.185 g (64%) of the bis(oxazoline) **14a** as a clear, colorless oil: ^{1}H NMR (400 MHz) 7.62 (d, J = 7.1, 2 H), 7.61−7.22 (m, 11 H), 4.64 (m, 2 H), 4.40 (t, J = 8.9, 2 H), 3.22 (dd, J = 5.4, 13.7, 2 H), 2.84 (dd, J = 8.1, 13.7, 2 H); ^{13}C NMR (100 MHz) 163.50, 137.60, 132.64, 131.96, 129.36, 128.53, 126.93, 126.55, 121.38, 72.12, 68.09, 41.47; IR ($CHCl_3$) 1659 (s); MS (CI, isobutane, 130 eV) 477 (MH^+, ^{81}Br, 23), 475 (MH^+, ^{79}Br, 24), 397 (100); TLC R_f 0.25 ($CHCl_3$/acetone, 10/1). Anal. Calcd for $C_{26}H_{23}BrN_2O_2$ (475.39): C, 65.69; H, 4.88; Br, 16.81; N, 5.89; Found: C, 65.88; H, 4.90; Br, 17.00; N, 5.94.

(*S*)-2,2′-(1,3-Phenylene)bis[4,5-dihydro-4-(phenylmethyl)oxazole]-2-palladium(II) Bromide (15a). Representative Procedure VII. Tris(dibenzylideneacetone)dipalladium dihydrate[26] (0.104 g, 0.11 mmol, 0.51 equiv) and **14a** were dissolved in benzene (7 mL). The deep purple solution was degassed (3 × freeze-pump-thaw cycles) and heated to reflux until the purple color had faded to light green (30 min). The reaction mixture was concentrated, and the crude product was purified by silica gel chromatography (CH_2Cl_2) to provide 0.092 g (74%) of the palladium complex **15a** as a yellow solid. An analytical sample was obtained by recrystallization from TBME/CH_2Cl_2: mp 280 °C dec (TBME/CH_2Cl_2); $[\alpha]^{24}_D$ +234.6° (c= 1.2, $CHCl_3$); ^{1}H NMR (400 MHz) 7.39 (d, J = 7.08, 4 H), 7.31−7.13 (m, 8 H), 4.71−4.64 (m, 6 H), 3.72 (d, J = 11.5, 14.3, 2 H), 3.02 (dd, J = 7.8, 13.6, 2 H); ^{13}C NMR (100 MHz) 174.65, 168.50, 136.32, 129.80, 129.40, 128.57, 127.12, 126.76, 124.11, 74.88, 63.65, 40.24; IR ($CHCl_3$) 1616 (m); MS (FAB) 397 (M − PdBr, 18); TLC R_f 0.47 (hexane/EtOAc, 3/1). Anal. Calcd for $C_{26}H_{23}BrN_2O_2Pd$ (581.79): C, 53.68; H, 3.98; Br, 13.73; N, 4.82; Pd, 18.29. Found: C, 53.66; H, 3.98; Br, 13.75; N, 4.87; Pd, 18.17.

Representative Procedure for the Cyclopropanation of Electron-Deficient Olefins. The cyclopropanation of ethyl *(E)*-cinnamate catalyzed by **7c** will serve as the representative procedure for palladium-catalyzed cyclopropanations. The same basic procedure was used for all cyclopropanations reported herein. However, all cyclopropanations for the mechanistic studies (concentration effects, substituent effects,

NMR experiments, etc.) were performed in CH_2Cl_2 with standardized diazomethane (0.25 M in CH_2Cl_2).[19]

Preparative Experiment: A solution of **7c** (0.004 g, 8.0 μmol, 0,01 equiv) and ethyl *(E)*-cinnamate (120 μL, 0.71 mmol) in CH_2Cl_2/Et_2O (2/1, 4 mL) was cooled to 0 °C. To this solution CH_2N_2 (0.20 M in Et_2O, 10 mL, 2.0 mmol, 2.8 equiv) was added dropwise over a 20 min period. The reaction mixture was allowed to warm to rt and then filtered through a pad of Celite and concentrated. Purification of the residue by silica gel chromatography (hexane/EtOAc, 40/1) and bulb-to-bulb distillation afforded 0.125 g (93%) of the cyclopropane as a clear oil that solidified upon standing: bp 110−115 °C (ABT), 0.5 mmHg; ^{1}H NMR (300 MHz) 7.35−7.05 (m, 5 H), 4.19 (q, J = 7.1, 2H), 2.52 (m, 1 H), 1.91 (m, 1 H), 1.60 (m, 1 H), 1.34 (m, 1 H), 1.30 (t, J = 7.1, 3 H).

"Kinetic" experiment for 0.25 M initial olefin concentration: A solution of **7c** (0.0025 g, 5.0 μmol, 0.01 equiv) and ethyl *(E)*-cinnamate (85 μL, 0.5 mmol) in CH_2Cl_2 (4 mL) was cooled to 0 °C. To this solution, CH_2N_2 (0.25 M in CH_2Cl_2, 2 mL, 0.5 mmol, 1 equiv) was dropwise over 5 min. The solution stirred for 5 min, and then a small aliquot was removed, passed through a short plug of silica gel, and assayed for conversion by GC. After withdrawing the aliquot, another 1 equiv of CH_2N_2 was added as described above. This was repeated for a total of 4 equiv of CH_2N_2. All reaction profiles presented are the average of at least two independent experiments. For reactions in which initial olefin concentration varied, the same scale (0.5 mmol) olefin and titer of diazomethane (0.25M) was used.

"Two-Salvo" experiment: A cyclopropanation was performed exactly as above ("Kinetic" Experiment for 0.25 M initial olefin concentration) and following the final addition of CH_2N_2 the yellow mixture was allowed to stir at 0 °C for 1h to dissipate the excess CH_2N_2. At this point, the mixture was assayed by GC, additional ethyl *(E)*-cinnamate (85 μL, 0.5 mmol) was added, followed again by the serial addition of CH_2N_2.

Representative Procedure for Diazomethane Generation. The method of Black and co-workers[19] was followed, except that CH_2Cl_2 was substituted for Et_2O. No problems arose because of this change, and, in fact, diazomethane titers appeared to rise using the chlorinated versus ethereal solvent. A representative example of generation is provided below.

A Diazald distillation apparatus was fitted with a 250 mL round-bottomed distillation pot and a 500 mL round-bottomed flask as a receiver. The reaction vessel was heated with a water bath to 65−70 °C, and the receiver was cooled to ca. −40 °C (controlled *i*PrOH/CO_2). KOH (20.3 g, 361 mmol, 2.0 equiv) was dissolved in 2-methoxyethanol/H_2O 2/1 and heated to 60−65 °C. Diazald (40.5 g, 181 mmol) in CH_2Cl_2 (250 mL) was added slowly over a period of roughly 2.5 h. Soon after the addition commenced, CH_2Cl_2 and diazomethane started to collect in the receiver. After the final addition, another portion of CH_2Cl_2 (15 mL) was added and allowed to distill over. This was repeated until the distillate was colorless (usually only once). The diazomethane solution was then titrated by adding 1 mL to a known excess of benzoic acid and titrating the residual acid with 0.5 M NaOH. Typical titers ranged from 0.4−0.6 M (corresponding to roughly 60−70% yield), more concentrated solutions usually resulting from faster addition of Diazald. The diazomethane solution was poured into a Nalgene screw-cap bottle and stored at −20 °C for weeks without incident. The titer remained essentially constant over 1−2 days, dropping slowly over a period of 6−8 weeks. For cyclopropanation, the diazomethane solution was titrated, and then an appropriate amount diluted to 0.25 M and used within 24 h.

Acknowledgment. We are grateful to the Pharmacia and Upjohn Co. for support of this research. R.A S. and J.P.E. thank the University of Illinois for Graduate Fellowships, and A.-M.F. thanks the NSERC (Canada) for a postdoctoral fellowship.

Supporting Information Available: Complete ^{1}H and ^{13}C NMR assignments, IR and MS data for all characterized compounds; experimental procedures and characterization data for **2b**, **8e**−**h**, **6e**,**f**,**h**, **7b**−**h**, **13b**,**c**, **14b**,**c**, **15b**,**c**, and crystal data for **15c** (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be obtained from the ACS; see any current masthead page for ordering information.

JO970044Z