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Conformational Preferences and Enantiodiscrimination of Phosphino-4-(1-hydroxyalkyl)oxazoline−Metal−Olefin Complexes Resulting from an OH−Metal Hydrogen Bond

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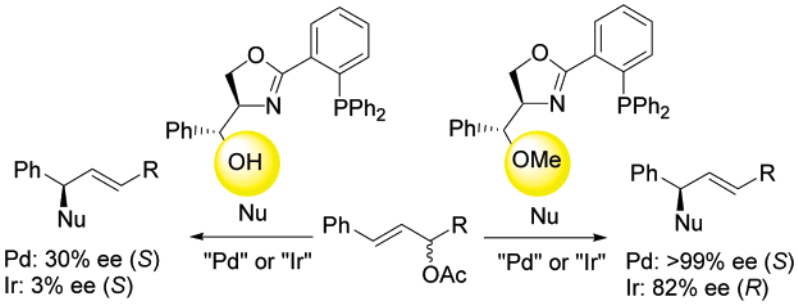

Phosphinooxazolines carrying (1-hydroxy-1-phenyl)methyl and (1-methoxy-1-phenyl)methyl substituents in the 4 position of the oxazoline ring exhibit contrasting behavior in Pd- and Ir-catalyzed allylic alkylations. Whereas catalysts with the methoxy-containing ligand generally provide products with high ee's, use of catalysts prepared from the hydroxy-containing ligand results in products with low ee's or even racemates. DFT calculations suggest the presence of a hydrogen bond with Pd(0) as the proton acceptor in the hydroxy-containing olefin−Pd(0) complexes, which induces a conformational change in the ligand, leading to different stereoselectivity.

Introduction

The steric properties of ligands employed in asymmetric metal catalysis are crucial for efficient transfer of chirality, and for control of the absolute configuration of new stereocenters. Preparation of the two enantiomers of a product usually requires access to two ligands of opposite absolute configuration. Since the ultimate source of a chiral ligand is often a naturally occurring compound existing in only one enantiomeric form, access to compounds derived from the opposite enantiomer may be limited. It would therefore be highly desirable to be able to modify the structure of the easily accessible enantiomer in such a way as to alter its enantioinducing preference.[1] Several examples of the reversal of enantioselectivity caused by modifications of catalyst structure or reaction conditions are known. These include *N*-alkylations[2] or other modifications of ligand structures;[3] change of the metal ion,[4] metal-to-ligand ratio,[5] solvent,[6] polymeric support,[7] or temperature;[8] and the use of mixtures of chiral and achiral ligands.[9] A minor struc-

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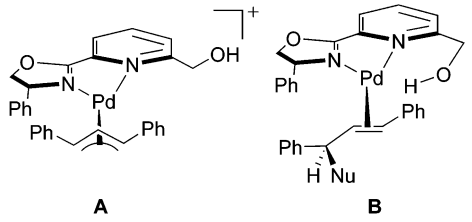

FIGURE 1. Conformations of Pd(II)−allyl (**A**) and Pd(0)−olefin (**B**) complexes with hydroxymethyl-substituted pyridinooxazolines.

tural modification of a ligand leading to a catalytic system serving as a pseudo-enantiomer was reported by Balavoine and co-workers, who found that palladium-catalyzed allylic alkylations employing bisoxazoline ligands with 4-hydroxybenzyl and 4-methoxybenzyl substituents, with the same stereochemistry, provided products with opposite absolute configuration.[10] Their explanation for this behavior was based on the assumption that the hydroxy group in the ligand was interacting via a hydrogen bond with the nucleophile.[11]

We found earlier that 2-(1-hydroxyalkyl)- and 2-(1-alkoxyalkyl)pyridinooxazolines resulted in profoundly different enantioselectivities in palladium-catalyzed allylations of dimethyl malonate.[12] This difference was found to originate in the different conformational preferences of the two types of ligands,[13] which we explained by the presence of a hydrogen bond with palladium(0) serving as the proton acceptor in the hydroxy-containing complex.[14] In the palladium(II)−allyl complexes with 2-(1-hydroxyalkyl) substituents, the hydroxy group was aligned with the pyridine ring, anti to the metal (**A**, Figure 1), whereas in the palladium(0)−olefin complex, the hydroxy group pointed toward the palladium atom with a N−C−C−O angle of −57° (**B**).[13]

For the conformational change accompanying the reduction of palladium to affect the stereochemistry of a catalytic reaction, it has to occur in the enantiodetermining step, and be essentially completed in the transition state. For this reason, metal-catalyzed allylations were considered to be suitable for our studies, because the stereochemistry of the product is usually determined during the nucleophilic attack, a step in which the oxidation state of the metal is reduced by two units. This situation was thus expected to lead to a conformational change if the hydroxy proton becomes involved in hydrogen bonding to the low-valence metal.

Hydrogen bonds between protons bound to oxygen or nitrogen and late transition metals in low-oxidation states have indeed been observed in a number of cases.[15] Experimental and computational evidence has, for example, been provided for the involvement of Pt−HN hydrogen bonds exhibiting an essentially linear three-center Pt−HN arrangement[16] in zwitterionic Pt(II) complexes with properly situated ammonium groups.[17]

We decided to explore whether the phenomenon observed in 2-(1-hydroxyalkyl)pyridinooxazolines may appear in catalytic systems with other types of ligands carrying suitably positioned hydroxyalkyl and alkoxyalkyl substituents. For this purpose we selected phosphinooxazolines (PHOX), first prepared independently by the groups of Pfaltz,[18] Helmchen,[19] and Williams[20] in 1993, which have proven to be highly versatile ligands for a range of catalytic processes.[21] A number of phosphinooxazolines carrying either hydroxy or methoxy substituents were therefore prepared and studied.

Results and Discussion

Ligand Design and Synthesis. Two types of ligands, one having a 4,5-disubstituted oxazoline ring (**1**−**4**) and one having a large substituent in the 4 position of the oxazoline ring (**5**−**8**), were considered to fulfill our requirements.

Several methods have been employed for the preparation of phosphinooxazolines.[21] The two types of ligands are known to be accessible starting from 2-halobenzonitriles and 2-halobenzoic acid chlorides, respectively, (Scheme 1).[22]

Ligand **1** was prepared, following the first of these procedures, from threoninol, which was reacted with 2-fluorobenzonitrile in the presence of cadmium acetate. Protection of the alcohol function followed by nucleophilic aromatic substitution using lithium diphenylphosphide and final deprotection gave **1** (Scheme 2).

To avoid protection/deprotection of the alcohol function, we employed a different route, starting by reaction of the appropriate amino alcohol with 2-iodobenzonitrile, for the syntheses of **2**−**4**. The phosphine function was introduced employing palladium-catalyzed coupling with diphenylphosphine, either directly to afford **3**[23] or after *O*-methylation to give **2** and **4**[24] (Scheme 3).

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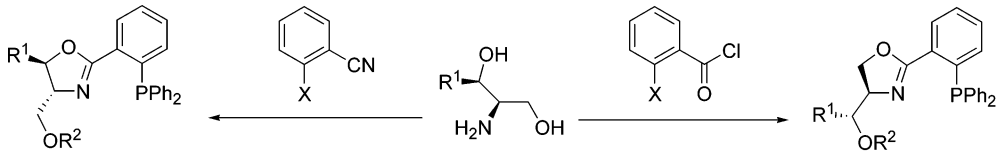
SCHEME 1



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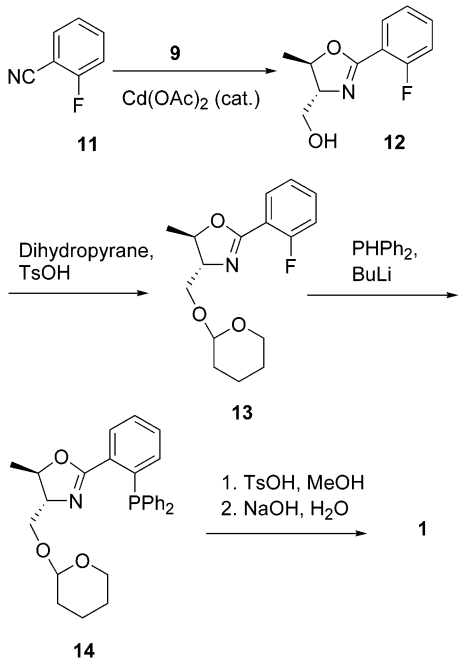
2 R^1 = Me, R^2 = Me
3 R^1 = Ph, R^2 = H
4 R^1 = Ph, R^2 = Me

9 R^1 = Me
10 R^1 = Ph

5 R^1 = Me, R^2 = H
6 R^1 = Me, R^2 = Me
7 R^1 = Ph, R^2 = H
8 R^1 = Ph, R^2 = Me

SCHEME 2



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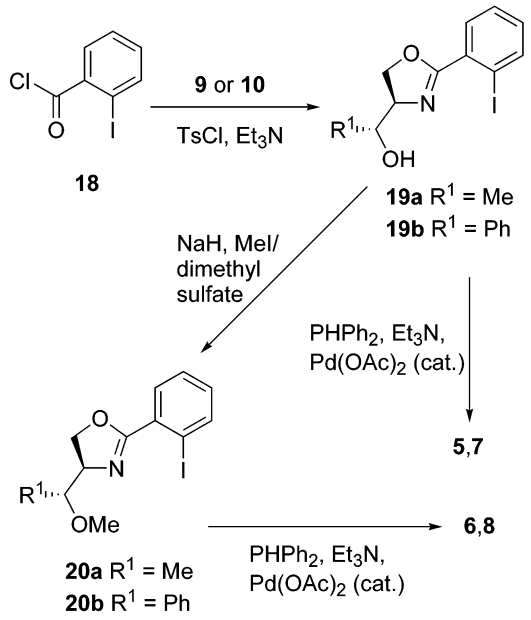

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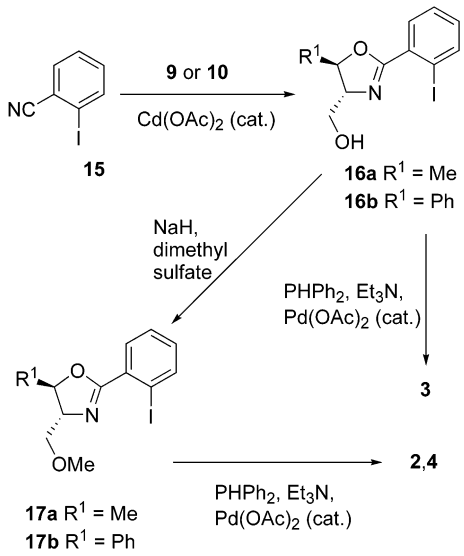

Ligands **5**−**8** were obtained from 2-iodobenzoyl chloride as shown in Scheme 4. This procedure, replacing the previously used nucleophilic substitution of the aromatic fluoride by lithium diphenylphosphide used in the preparation of *ent*-**7**[22] by palladium-catalyzed coupling of an aryl iodide with diphenylphosphine, afforded a considerably higher overall yield of **7** in fewer steps.

DFT Computations of Palladium(0)−Olefin Complexes. We decided to first study the product Pd(0)−olefin complexes of ligand **1** using the B3LYP functional[25] in Jaguar v4.0.[26] The complexes were optimized using the lacvp**/6-31G(d,p) basis set.[27,28] It was assumed that nucleophilic attack occurred at the allyl group from the side opposite to the metal at the allylic position trans to phosphorus,[29] in accordance with experimental observations.[30] Nucleophilic attack can occur either at the *endo*-π-allyl−palladium complex (**C1**), leading to olefin complex **D1**, or at the exo isomer (**C2**) leading to **D2**, with the olefin ligand having opposite absolute configuration (Figure 2). Syn−anti and anti−anti allyl complexes were

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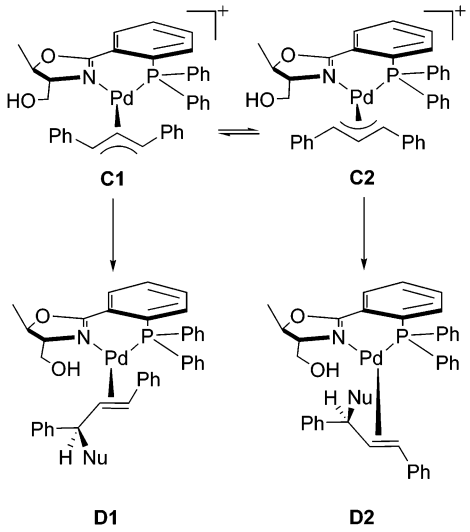

FIGURE 2. Nucleophilic attack at *endo*- and *exo*-π-allyl−palladium complexes of ligand **1**.

not considered, as such complexes have not been identified in solution or in the solid state.[31]

To simplify the computations, the substituents on the oxazoline ring, the phosphorus atom, and the olefin were replaced by hydrogen atoms. Moreover, the nucleophile was replaced by NH_2^-. The enantiodiscrimination is usually assumed to originate from the formation of the most favorable olefin complex.[32] We found an olefin complex (**D2′**) resulting from nucleophilic attack at the exo complex to be 2.6 kcal mol^{-1} lower in energy than the most stable complex attained after attack at the endo complex.[33] This is in accordance with the results by Helmchen, who has shown experimentally that the *exo*-allyl complex is more stable than the endo isomer.[34] The exo complex was also shown to lead to the major product.[30]

For both types of olefin complexes (**D1** and **D2**), the most stable conformations were found to have the hydroxy proton pointing toward palladium. For the complex arising from attack at the *exo*-allyl complex, this conformation (**D2′**) was found to be 2.1 kcal mol^{-1} lower in energy than a conformation having the hydroxy proton pointing away from palladium (**D2″**, Figure 3). Complex **D2′** was found to have an OH−Pd distance of 2.47 Å, a Pd−O distance of 3.32 Å, an O−H distance of 0.98 Å, and an O−H−Pd bond angle of 145°, all in accordance with a weak hydrogen bond.[15c] Complex **D2″**, in which the hydroxy proton is not involved in hydrogen bonding, had a slightly shorter O−H bond (0.97 Å). The closer proximity of palladium to the hydrogen atom than to the oxygen atom and the slight elongation of the O−H bond in **D2′** are arguments against donation of an oxygen lone pair to palladium as the reason for the observed conformation. Moreover, that type of interaction would rather be favored in the Pd(II) complexes.

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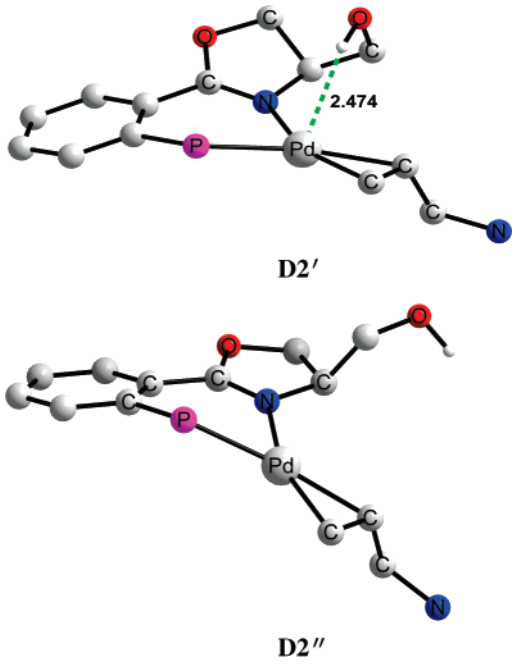


FIGURE 3. Two lowest-energy conformations of the product olefin complex **D2** arising from attack at the *exo*-π-allyl complex. **D2′** was found to be 2.6 kcal/mol lower in energy than the most stable complex from an endo attack, and 2.1 kcal/mol more stable than **D2″**. All hydrogen atoms except the hydroxy proton have been omitted for clarity.

Single-point calculations were performed using the larger lacv3p**++/6-311+G(d,p) basis set. The results confirmed complex **D2′** to be lower in energy (1.3 kcal mol^{-1}) than **D2″**. Single-point calculations were also performed on a simulation of a THF solution. Again, complex **D2′** was found to be lower in energy (0.8 kcal mol^{-1}).

To model olefin complexes of ligand **2,** the same calculations were performed, with the hydroxy group replaced by a methoxy group. Unlike the former ligand, and as expected, the most stable conformation had the methoxy group pointing away from palladium.

Palladium-Catalyzed Allylations. We next decided to study the consequences of the theoretically observed conformational preferences on the stereochemistry of the products from palladium-catalyzed allylic substitutions of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (**21**) and *rac*-3-cyclohexenyl acetate (**22**) (Scheme 5).

Substitutions of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate using [(η^3-C_3H_5)PdCl]$_2$ and ligands **1**−**8** as precatalysts were first studied in THF at 0 °C. For **1**−**6**, only minor differences in enantioselectivity were observed between reactions using hydroxy- and alkoxy-containing ligands with the same substitution pattern (Table 1), whereas **7** and **8** exhibited a somewhat larger difference (88 and 99% ee, respectively).

Even if a hydrogen bond is present in the Pd(0)−olefin complex, it might be not fully developed in the transition state, and therefore not affect the stereochemistry of the catalytic reaction to any greater extent. We reasoned that a less polar solvent should result in a less reactive allyl system, and therefore a later transition state for the

SCHEME 5

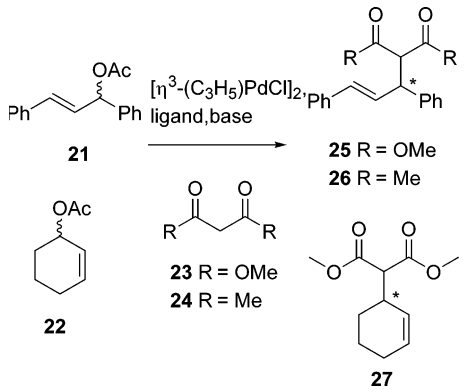


TABLE 1. Reactions of *rac*-(*E*)-1,3-diphenyl-2-propenyl Acetate with Dimethyl Malonate in THF at 0 °C for 5 h Yielding 25

entry	ligand	conversion (%)	ee (%) (abs conf)
1	**1** (OH)	99	95 (*R*)
2	**2** (OMe)	100	95 (*R*)
3	**3** (OH)	100	92 (*R*)
4	**4** (OMe)	100	88 (*R*)
5	**5** (OH)	100	97 (*S*)
6	**6** (OMe)	100	98 (*S*)
7	**7** (OH)	100	88 (*S*)
8	**8** (OMe)	100	99 (*S*)

TABLE 2. Reactions of *rac*-(*E*)-1,3-diphenyl-2-propenyl Acetate with Dimethyl Malonate in Toluene at 25 °C Yielding 25

entry	ligand	conversion (%) (time (h))	ee (%) (abs conf)
1	**1** (OH)	100 (1)	93 (*R*)
2	**2** (OMe)	100 (1)	91 (*R*)
3	**7** (OH)	100 (1)	76 (*S*)
4	**8** (OMe)	81 (18)	97 (*S*)

nucleophilic attack. To test this hypothesis, we performed the reactions using ligands **1**, **2**, **7**, and **8** in toluene at 25 °C.

A somewhat larger difference in enantioselectivity was now observed between ligands **7** and **8** (76 and 97% ee, respectively, Table 2). That this difference is not due to the nature of the substituent, the presence of a hydroxy group, seems clear from a comparison with the results using ligands **1** and **2**. The two ligands, carrying hydroxy and methoxy substituents, respectively, do not exhibit significantly different enantioselectivities. These ligands lack bulky substituents in the 4 position of the oxazoline ring, and their enantiodiscrimination is therefore not expected to be affected to any greater extent by the presence of a hydrogen bond, which leads to rotation around the carbon−carbon bond in the 4 substituent.

Use of a nucleophile less reactive than malonate is also expected to result in a later transition state for the nucleophilic attack, and therefore possibly in a more pronounced effect of a hydrogen bond leading to a different conformation of the hydroxy-containing ligand. Indeed, a considerable difference in enantioselectivity between ligands **7** and **8** was observed in toluene (35 vs >99% ee) as well as in THF (30 vs >99% ee) when acetylacetone was the nucleophile (Table 3). At the same time, ligands **1** and **2** gave products with similar enantioselectivity (80 and 84% ee, respectively, in THF).

TABLE 3. Reactions of *rac*-(*E*)-1,3-diphenyl-2-propenyl Acetate with Acetylacetone at 25 °C Yielding 26

entry	ligand	solvent	conversion (%) (time (h))	ee (%) (abs conf)
1	**1** (OH)	THF	100 (2)	80 (*R*)
2	**2** (OMe)	THF	100 (2)	84 (*R*)
3	**7** (OH)	THF	94 (15)	30 (*S*)
4	**7** (OH)	toluene	55 (15)	35 (*S*)
5	**8** (OMe)	THF	95 (2)	>99 (*S*)
6	**8** (OMe)	toluene	90 (2)	>99 (*S*)

TABLE 4. Reactions of *rac*-3-cyclohexenyl with Dimethyl Malonate in THF at 0 °C Yielding 27

entry	ligand	conversion (%) (time (h))	ee (%) (abs conf)
1	**1** (OH)	48 (15)	20 (*S*)
2	**2** (OMe)	49 (15)	5 (*S*)
3	**7** (OH)	95 (20)	59 (*R*)
4	**8** (OMe)	98 (10)	26 (*R*)

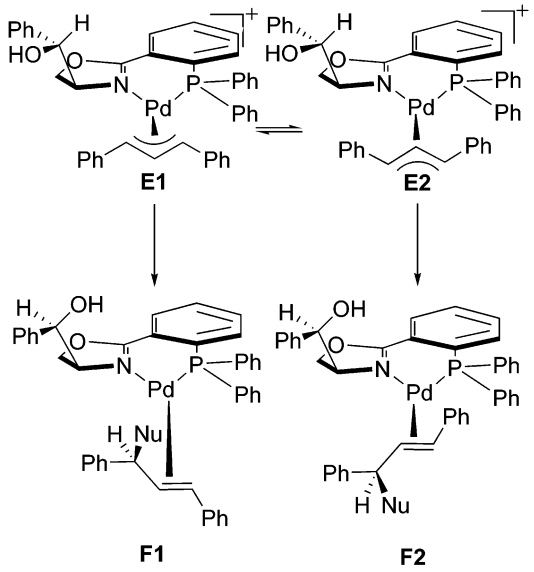
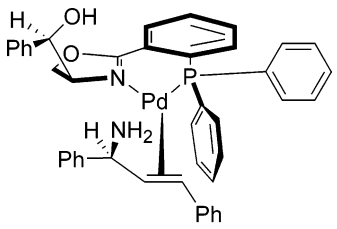


FIGURE 4. Nucleophilic attack at *endo*- and *exo*-π-allyl−palladium complexes of ligand **7**.

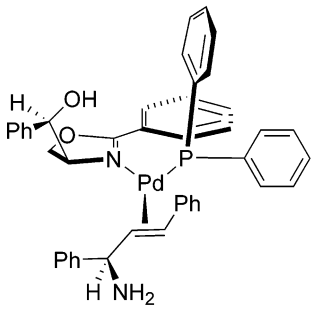
Ligands **1**, **2**, **7**, and **8** were further studied in reactions using *rac*-3-cyclohexenyl acetate as substrate. The enantioselectivities were generally lower than those observed using 1,3-diphenylpropenyl acetate, although significant differences in ee were observed between ligands **7** and **8**, as well as between **1** and **2** (Table 4). For this cyclic substrate, use of the hydroxy-containing ligands resulted in higher enantioselectivities, in contrast to reactions with 1,3-diphenylpropenyl acetate.

To rationalize the contrasting experimental results obtained using ligands **7** and **8** and the diphenyl substrate **21**, we performed calculations similar to those described for the Pd(0)−olefin complexes of ligand **1** (**D1** and **D2**) on the product olefin complexes of ligand **7** (**F1** and **F2**, Figure 4). The only simplification made was the replacement of the nucleophile by NH_2^-. The results gave valuable qualitative information on the stereoselection.[35]

In analogy to the results obtained for ligand **1**, we found the Pd(0)−olefin complex **F2** arising from attack



F1'



F2'

FIGURE 5. Conformations of Pd(0)−olefin complexes of ligand **7**. **F1′**, the most stable **F1** conformation, was found to be 1.3 kcal/mol higher in energy than **F2′**, the lowest-energy **F2** conformation.

at the *exo*-allyl complex to be lower in energy than **F1** arising from attack at the endo isomer. As **F2** represents the *S* product and **F1** the *R* product when dimethyl malonate or acetylacetone is the nucleophile, this is in agreement with the experimental results. The lowest lying conformation of **F2**, **F2′**, has a nonplanar Pd−N−C−C−C−P ring, in agreement with previous observations by Helmchen on other phosphinooxazolines.[36] The conformation of this ring determines the position of the phenyl rings, which as in analogous complexes were found to be essentially perpendicular to each other (Figure 5). The axial phenyl group has its edge and the equatorial its face toward the metal, a situation normally leading to preferential reaction of the *exo*-allyl complex. The hydroxy group in **F2′** is pointing toward Pd with a Pd−H bond length of 2.23 Å, a typical hydrogen bond distance.[15c]

Several conformational minima were found for the Pd(0)−olefin complex **F1** originating from the *endo*-allyl−palladium complex **E1**, and thus having an olefin ligand of opposite absolute configuration compared to **F2**. All conformational minima having the ligand backbone bent, and thus the phenyl groups arranged, in a way similar to **F2′** were found to be considerably higher in energy (>2.7 kcal mol^{-1}) than **F2′**. A conformational minimum, **F1′**, only 1.3 kcal mol^{-1} higher in energy than **F2′**, with an OH−Pd interaction and the ligand backbone bent in an opposite way and hence with its phenyl groups differently oriented was found, however.[37] Competition between reactions leading to **F1′** and **F2′** may be the reason why high selectivity is not achieved with ligand **7** under certain conditions.

Similar calculations were performed on the Pd(0)−olefin complexes of ligand **8**. As expected, a complex leading to the *S* product was found to be most stable. Complexes leading to the *R* product were found to have considerably higher energy (>3 kcal mol^{-1}), thus explaining the high enantioselectivities obtained using this ligand.

Iridium-Catalyzed Allylations. Phosphinooxazolines have also been found to induce high enantioselectivity in Ir-catalyzed allylations.[38] The detailed mechanism is not yet known, but it has been established that the reaction proceeds via a double inversion process.[39] The isomerization of the allyl−Ir intermediates is slower than for allyl−Pd complexes, and memory effects can be substantial.[40] Allyl carbonates generally give faster reactions than acetates, but have in some cases been shown to provide lower enantioselectivities.[41] Because of the preferred octahedral geometry of allyl−Ir(III) complexes, several complexes have to be considered. Some complexes have been isolated and characterized, but it is unclear which ones are leading to product and by which path they do so.[41]

We compared **7** and **8** as ligands in Ir-catalyzed allylations using (*E*)-cinnamyl acetate (**28**), (*E*)-cinnamyl methyl carbonate (**29**), and (*E*)-3-(4-methoxyphenyl)-2-propenyl methyl carbonate (**30**) (Table 5). The nucleophile was either prepared before the reaction using NaH or generated in situ using Cs_2CO_3. The latter method has recently been used in Rh-catalyzed allylic alkylations resulting in high enantioselectivities.[42] When comparing the results of the two ligands using the same reaction conditions, we found that ligand **8** generally gave faster reactions, higher branched:linear ratios, and considerably higher ee's. Ligand **8** afforded product **31** with an ee as high as 90% (*R*; entry 6), whereas ligand **7** generated the product with opposite absolute configuration with an ee of 6% (entry 3). Substrate **30**, having an electron-donating substituent (entries 9 and 10), gave the product **32** with higher branched:linear ratios than (and ee's similar to) **31**. Exchanging THF for toluene yielded comparable results.

Considering the ambiguities regarding the reaction mechanism, we can draw no safe conclusion about the origin of these interesting observations. Our results demonstrate, however, that the two types of ligands also in this reaction exhibit contrary behavior.

Conclusions

In summary, we have shown that palladium-catalyzed allylic alkylations of *rac*-1,3-diphenylpropenyl acetate with malonate and acetylacetone using phosphinooxazolines with (1-hydroxy-1-phenyl)methyl and (1-methoxy-

(35) Because of the large size of these systems, fully converged structures were not obtained with the standard convergence threshold, but the level of convergence of all the structures was identical and within the standard accuracy of B3LYP/LACVP**.

(36) Helmchen, G.; Kudis, S.; Sennhenn, P.; Steinhagen, H. *Pure Appl. Chem.* **1997**, *69*, 513−518.

(37) The hydroxy group is in fact interacting with the palladium from beneath because of extensive twisting of the ligand backbone. See the Supporting Information for *XYZ* coordinates.

(38) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett*. **1997**, *38*, 8025−8026.

(39) Bartels, B.; García-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, 2569−2586.

(40) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741−742.

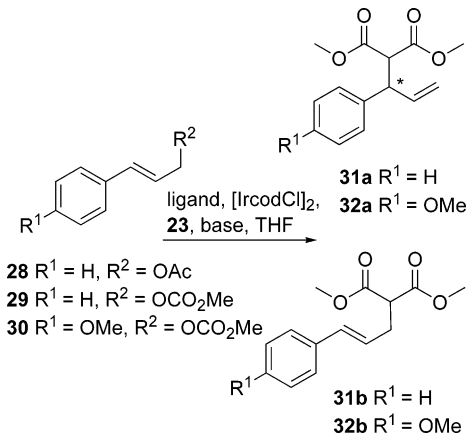
(41) García-Yebra, C.; Janssen, J. P.; Rominger, F.; Helmchen, G. *Organometallics* **2004**, *23*, 5459−5470.

(42) Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003**, *5*, 1713−1715.

TABLE 5. Reactions of 28, 29, or 30 with Dimethyl Malonate in THF at 65 °C

entry	ligand	substrate	base	product	conversion (%)	b/l	ee (%) (abs conf)
1	**7** (OH)	**28**	Cs_2CO_3	**31**	14 (5 days)	0.6	12 (*R*)
2	**8** (OMe)	**28**	Cs_2CO_3	**31**	98 (3 days)	0.6	90 (*R*)
3	**7** (OH)	**28**	NaH	**31**	67 (5 days)	0.8	3 (*S*)
4	**8** (OMe)	**28**	NaH	**31**	97 (2 days)	2.4	82 (*R*)
5	**7** (OH)	**29**	Cs_2CO_3	**31**	92 (3 days)	0.5	1 (*S*)
6	**8** (OMe)	**29**	Cs_2CO_3	**31**	98 (3 days)	4.7	68 (*R*)
7	**7** (OH)	**29**	NaH	**31**	93 (5 days)	1.4	6 (*S*)
8	**8** (OMe)	**29**	NaH	**31**	100 (2 days)	4.9	29 (*R*)
9	**7** (OH)	**30**	Cs_2CO_3	**32**	100 (20 h)	1.7	6 (*R*)
10	**8** (OMe)	**30**	Cs_2CO_3	**32**	100 (20 h)	7.5	73 (*R*)

SCHEME 6



1-phenyl)methyl substituents in the 4 position of the oxazoline ring result in different enantioselectivities. These differences are assumed to originate in the different conformations of the two types of ligands. The conformation of the methoxy-containing ligand results in an *exo*-allyl complex being the most stable, leading to products with *S* absolute configuration. For the hydroxy-containing ligand, two Pd(0)−olefin complexes, originating from *exo*- and *endo*-allyl complexes, respectively, were found to be of similar energy, which explains the low enantioselectivity observed under certain conditions.

Iridium-catalyzed allylic alkylations employing the two types of ligands also resulted in different enantioselectivities. Also here, a hydrogen bond with Ir(I) serving as the proton acceptor is assumed to be involved, but the results are more difficult to rationalize because of insufficient knowledge of the mechanism of this reaction.

Experimental Section

[(*R*,*R*)-2-(2-Fluorophenyl)-5-methyl-4,5-dihydrooxazol-4-yl]methanol (12). (*R*,*R*)-Threoninol (**9**, 2.00 g, 19.0 mmol), 2-fluorobenzonitrile (**11**, 2.32 g, 19.2 mmol), and cadmium acetate dihydrate (250 mg, 0.94 mmol) were stirred in chlorobenzene (25 mL) at reflux for 16 h. The reaction mixture was concentrated and purified by flash chromatography on silica gel (EtOAc/$CHCl_3$ continuous gradient: 0−50% $CHCl_3$). The solid obtained was crystallized from hexane/EtOAc to give **12** (1.1 g, 28%) as a white solid: mp 91 °C; $[\alpha]^{20}_D$ +76 (*c* 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.81 (1H, m), 7.43 (1H, m), 7.07−7.18 (2H, m), 4.67 (1H, m), 3.89−3.97 (2H, m), 3.66 (1H, m), 2.96 (1H, br s), 1.45 (3H, dd, J = 2.4, 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 161.3 (d, J(C,F) = 5.5 Hz), 161.1 (d, J(C,F) = 258.2 Hz), 133.0 (d, J(C,F) = 8.9 Hz), 131.0, 123.9 (d, J(C,F) = 3.8 Hz), 116.6 (d, J(C,F) = 21.9 Hz), 115.8 (d, J(C,F) = 5.5 Hz), 77.8, 75.1, 63.8, 20.6.

[(*R*,*R*)-2-(2-Diphenylphosphinophenyl)-5-methyl-4,5-dihydrooxazol-4-yl]methanol (1). To a solution of **12** (1.04 g, 4.98 mmol) and dihydropyrane (2.0 g, 23.8 mmol) in CH_2Cl_2 (15 mL) was added *p*-toluenesulfonic acid (950 mg, 5.0 mmol) in portions to prevent boiling of the solvent. The reaction was monitored by TLC. After 0.5 h, the resulting mixture was washed with 2 M NaOH. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The product was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:1) to afford (*R*,*R*)-2-(2-fluorophenyl)-5-methyl-4-(tetrahydropyran-2-yloxymethyl)-4,5-dihydrooxazole **13** (1.202 g, 82%, mixture of diastereomers) as a slightly yellow oil, which was used directly in the next step.

A solution prepared from diphenylphosphine (1.12 g, 5.75 mmol) and BuLi (2.2 mL of a 2.5 M solution, 5.5 mmol) in THF (7 mL) was added to a solution of **13** (1.202 g, 4.10 mmol) in THF (10 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 0.5 h, and then allowed to warm to −5 °C before addition of MeOH (1 mL). The solution was diluted with diethyl ether, washed with water and then brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:2) to afford (*R*,*R*)-2-(2-diphenylphosphinophenyl)-5-methyl-4-(tetrahydropyran-2-yloxymethyl)-4,5-dihydrooxazole **14** (1.18 g, 63%, mixture of diastereomers) as a colorless oil, which was used directly in the next step.

Compound **14** (1.18 g, 2.57 mmol) was dissolved in MeOH (10 mL) containing *p*-toluenesulfonic acid (488 mg, 2.57 mmol). After the reaction was completed (TLC), the solution was diluted with CH_2Cl_2, and washed with 2 M NaOH. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 2:1) to afford a yellowish foam. This foam was dissolved in boiling hexane (15 mL), and the formed solution was allowed to cool slowly. At 50 °C, diethyl ether (5 mL) was added. The resulting mixture was slowly cooled to 0 °C with the aid of an ice bath. The precipitated solid was separated, washed with hexane, and dried to afford **1** (835 mg, 87%) as a white solid: mp 115 °C; $[\alpha]^{20}_D$ +142 (*c* 1.22, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.89 (1H, ddd, J = 1.3, 3.7, 7.6 Hz), 7.42−7.24 (12H, m), 6.92 (1H, ddd, J = 0.8, 4.1, 7.6 Hz), 4.51 (1H, dq, J = 6.4, 6.4 Hz), 3.83 (1H, ddd, J = 3.5, 3.5, 6.8 Hz), 3.65 (1H, d, J = 11.4 Hz), 3.29 (1H, m), 1.62 (1H, br s), 1.33 (3H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 163.6 (d, J(C,P) = 2.9 Hz), 138.7 (d, J(C,P) = 21.8 Hz), 138.4 (d, J(C,P) = 7.3 Hz), 137.4 (d, J(C,P) = 9.7 Hz), 134.4 (d, J(C,P) = 20.9 Hz), 134.1, 133.2 (d, J(C,P) = 19.7 Hz), 131.7 (d, J(C,P) = 19.8 Hz), 130.6, 129.6 (d, J(C,P) = 2.6 Hz), 128.8, 128.63, 128.56 (d, J(C,P) = 7.5 Hz), 128.5 (d, J(C,P) = 7.4 Hz), 128.2, 77.5, 75.3, 63.9, 20.6; ^{31}P NMR ($CDCl_3$) δ −7.0. Anal. Calcd for $C_{23}H_{22}NO_2P$: C, 73.59; H, 5.91; P, 8.25. Found: C, 73.34; H, 5.90; P, 8.05.

[(*R*,*R*)-2-(2-Iodophenyl)-5-methyl-4,5-dihydrooxazol-4-yl]methanol (16a). (*R*,*R*)-Threoninol (**9**, 1.037 g, 9.88 mmol), 2-iodobenzonitrile (**15**, 2.6 g, 11.35 mmol), and cadmium

acetate dihydrate (133 mg, 0.5 mmol) were dissolved in chlorobenzene (15 mL) and stirred at reflux for 16 h. The concentrated reaction mixture was purified by flash chromatography on silica gel (eluent: EtOAc), yielding **16a** (1.236 g, 40%) as a white solid: mp 66 °C; $[\alpha]^{20}_D$ +63 (*c* 1.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.91 (1H, dd, *J* = 0.8, 8.0 Hz), 7.58 (1H, dd, *J* = 1.6, 7.7 Hz), 7.37 (1H, ddd, *J* = 1.1, 7.6, 7.6 Hz), 7.11 (1H, ddd, *J* = 1.7, 7.8, 7.8 Hz), 4.68 (1H, dq, *J* = 6.4, 6.4 Hz), 3.95 (1H, m), 3.88 (1H, dd, *J* = 4.2, 11.4 Hz), 3.65 (1H, dd, *J* = 4.7, 11.4 Hz), 2.67 (1H, br s), 1.47 (3H, d, *J* = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 165.4, 140.3, 133.6, 131.7, 130.5, 127.9, 94.7, 78.8, 75.1, 63.9, 20.6.

[(*R*,*R*)-2-(2-Iodophenyl)-5-phenyl-4,5-dihydrooxazol-4-yl]methanol (16b). Compound **16b** was prepared in the same way as **16a** starting from (*R*,*R*)-2-amino-1-phenyl-1,3-propanediol (**10**, 994 mg, 5.95 mmol), 2-iodobenzonitrile (**15**, 1.439 g, 6.28 mmol), cadmium acetate dihydrate (80 mg, 0.30 mmol), and chlorobenzene (8 mL). Flash chromatography on silica gel (eluent: EtOAc/hexane 1:1) yielded **16b** (956 mg, 40%) as a yellow oil: $[\alpha]^{20}_D$ −5.0 (*c* 1.48, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.98 (1H, m), 7.71 (1H, *J* = 1.6, 7.7 Hz), 7.46−7.32 (6H, m), 7.15 (1H, ddd, *J* = 1.7, 7.8, 8.0 Hz), 5.55 (1H, d, *J* = 7.9 Hz), 4.35 (1H, ddd, *J* = 3.9, 3.9, 7.8 Hz), 4.10 (1H, dd, *J* = 3.7, 11.6 Hz), 3.80 (1H, dd, *J* = 3.9, 11.7 Hz), 2.53 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 165.3, 140.5, 140.0, 133.2, 131.9, 130.6, 128.9, 128.5, 127.9, 125.9, 95.0, 83.3, 76.9, 63.7.

(*R*,*R*)-2-(2-Iodophenyl)-4-methoxymethyl-5-methyl-4,5-dihydrooxazole (17a). NaH (60% in oil, 187 mg, 4.67 mmol) was suspended in THF (20 mL). **16a** (1.187 g, 3.74 mmol) was added in one portion. After hydrogen evaluation stopped, dimethyl sulfate (533.2 mg, 4.23 mmol) was added dropwise. The mixture was stirred at room temperature for 30 min, whereafter diethyl ether (20 mL) and 25% aqueous ammonia solution (10 mL) were added. The organic phase was separated, washed with 2 M NaOH, water, and brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:1) to give **17a** (1.075 g, 87%) as a colorless oil: $[\alpha]^{20}_D$ +44 (*c* 1.02, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.91 (1H, m), 7.59 (1H, ddd, *J* = 1.8, 7.7, 7.7 Hz), 7.35 (1H, m), 7.09 (1H, m), 4.67 (1H, ddq, *J* = 2.0, 6.3, 6.3 Hz), 4.01 (1H, dddd, *J* = 2.2, 4.6, 7.1, 7.1 Hz), 3.69 (1H, ddd, *J* = 2.2 Hz, 4.5, 9.4 Hz), 3.39−3.47 (4H, m), 1.46 (3H, dd, *J* = 2.2, 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 164.6, 140.3, 133.9, 131.5, 130.6, 127.7, 94.5, 80.1, 74.4, 73.1, 59.3, 20.9.

(*R*,*R*)-2-(2-Iodophenyl)-4-methoxymethyl-5-phenyl-4,5-dihydrooxazole (17b). Compound **17b** was prepared in the same way as **17a** starting from NaH (60% in oil, 150 mg, 3.75 mmol), THF (15 mL), **16b** (853 mg, 2.25 mmol), and dimethyl sulfate (333.3 mg, 2.64 mmol). Flash chromatography on silica gel (eluent: EtOAc/hexane 2:1) provided **17b** (795 mg, 90%) as a colorless oil: $[\alpha]^{20}_D$ −17 (*c* 1.16, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.97 (1H, dd, *J* = 0.9, 8.0 Hz), 7.73 (1H, dd, *J* = 1.6, 7.7 Hz), 7.30−7.46 (6H, m), 7.13 (1H, ddd, *J* = 1.7, 7.8, 7.9 Hz), 5.53 (1H, d, *J* = 7.1 Hz), 4.41 (1H, ddd, *J* = 4.5, 6.9, 7.0 Hz), 3.80 (1H, dd, *J* = 4.4, 9.7 Hz), 3.66 (1H, dd, *J* = 6.7, 9.7 Hz), 3.46 (3H, s); ^{13}C NMR ($CDCl_3$) δ 164.4, 140.5, 140.4, 133.3, 131.7, 130.8, 128.7, 128.2, 127.8, 125.8, 94.7, 84.2, 75.0, 74.2, 59.3.

(*R*,*R*)-2-(2-Diphenylphosphinophenyl)-4-methoxymethyl-5-methyl-4,5-dihydrooxazole (2). Diphenylphosphine (642 mg, 3.45 mmol), **17a** (1.025 g, 3.1 mmol), and Et_3N (2.5 mL, 17.9 mmol) were dissolved in CH_3CN (20 mL). $Pd(OAc)_2$ (34.0 mg, 0.15 mmol, 5 mol %) was added, and the solution was brought to reflux for 4 h. The mixture was absorbed on silica, and purified by flash chromatography on silica gel (eluent: diethyl ether/hexane 1:3) to yield **2** (875 mg, 73%) as a slightly yellow oil: $[\alpha]^{20}_D$ +7.1 (*c* 1.46, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.89 (1H, ddd, *J* = 1.3, 3.5, 7.5 Hz), 7.37−7.25 (12H, m), 6.84 (1H, ddd, *J* = 1.0, 4.3, 7.6 Hz), 4.32 (1H, dq, *J* = 6.3, 6.3 Hz), 3.77 (1H, ddd, *J* = 4.6, 6.7, 8.2 Hz), 3.36 (1H, dd, *J* = 4.6, 9.5 Hz), 3.25 (3H, s), 2.80 (1H, dd, *J* = 8.6, 9.2 Hz), 1.20 (3H, d, *J* = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 163.8 (d, *J*(C,P) = 3.1 Hz), 138.7 (d, *J*(C,P) = 25.5 Hz), 137.84 (d, *J*(C,P) = 9.8 Hz), 137.83 (d, *J*(C,P) = 12.7 Hz), 134.4 (d, *J*(C,P) = 21.4 Hz), 133.8 (d, *J*(C,P) = 20.7 Hz), 133.3 (d, *J*(C,P) = 2.2 Hz), 131.4 (d, *J*(C,P) = 17.7 Hz), 130.4, 129.8 (d, *J*(C,P) = 2.4 Hz), 128.6, 128.39, 128.37 (d, *J*(C,P) = 7.2 Hz), 128.3 (d, *J*(C,P) = 7.6 Hz), 127.8, 79.5, 74.1, 72.5, 58.9, 20.5; ^{31}P NMR ($CDCl_3$) δ −4.3. Anal. Calcd for $C_{24}H_{24}NO_2P$: C, 74.02; H, 6.21; P, 7.95. Found: C, 73.92; H, 6.21; P, 7.79.

[(*R*,*R*)-2-(2-Diphenylphosphinophenyl)-5-phenyl-4,5-dihydrooxazol-4-yl]methanol (3).[23] Compound **3** was prepared in the same way as **2** starting from diphenylphosphine (321 mg, 1.72 mmol), **16b** (543 mg, 1.43 mmol), Et_3N (1.0 mL, 7.17 mmol), CH_3CN (10 mL), and $Pd(OAc)_2$ (16.0 mg, 0.071 mmol). Flash chromatography on silica gel (diethyl ether/hexane 2:3) provided **3** (484 mg, 78%) as a white solid: mp 48 °C; $[\alpha]^{20}_D$ +77 (*c* 1.26, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, ddd, *J* = 1.5, 3.7, 7.6 Hz), 7.44−7.26 (17H, m), 6.97 (1H, ddd, *J* = 1.3, 4.0, 7.7 Hz), 5.34 (1H, d, *J* = 7.4 Hz), 4.20 (1H, ddd, *J* = 3.1, 3.1, 7.4 Hz), 3.79 (1H, m), 3.44 (1H, m), 1.53 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 163.7 (d, *J*(C,P) = 3.0 Hz), 140.5, 139.1 (d, *J*(C,P) = 22.7 Hz), 138.5 (d, *J*(C,P) = 7.5 Hz), 137.5 (d, *J*(C,P) = 9.7 Hz), 134.5 (d, *J*(C,P) = 21.0 Hz), 134.3, 133.3 (d, *J*(C,P) = 19.7 Hz), 131.3 (d, *J*(C,P) = 19.5 Hz), 130.8, 129.8 (d, *J*(C,P) = 2.7 Hz), 128.9, 128.8, 128.7, 128.62 (d, *J*(C,P) = 7.5 Hz), 128.61 (d, *J*(C,P) = 7.4 Hz), 128.33, 128.30, 125.8, 82.3, 77.2, 63.7; ^{31}P NMR ($CDCl_3$) δ −5.9.

(*R*,*R*)-2-(2-Diphenylphosphinophenyl)-4-methoxymethyl-5-phenyl-4,5-dihydrooxazole (4).[24] Compound **4** was prepared in the same way as **2** starting from diphenylphosphine (375 mg, 2.01 mmol), **17b** (682 mg, 1.735 mmol), Et_3N (1.5 mL, 10.8 mmol), CH_3CN (10 mL), and $Pd(OAc)_2$ (19.5 mg, 0.087 mmol). Flash chromatography on silica gel (EtOAc/hexane 1:3) afforded **4** (639 mg, 82%) as a viscous colorless oil: $[\alpha]^{20}_D$ −40 (*c* 1.18, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.92 (1H, ddd, *J* = 1.0, 3.4, 7.5 Hz), 7.33−7.15 (15H, m), 7.08 (2H, dd, *J* = 1.5, 8.0 Hz), 6.80 (1H, ddd, *J* = 1.0, 4.2, 7.5 Hz), 5.10 (1H, d, *J* = 7.0 Hz), 4.10 (1H, dt, *J* = 4.6, 7.4 Hz), 3.34 (1H, dd, *J* = 4.5, 9.7 Hz), 3.18 (3H, s), 2.86 (1H, dd, *J* = 7.9, 9.6 Hz); ^{13}C NMR ($CDCl_3$) δ 163.6 (d, *J*(C,P) = 3.7 Hz), 140.6, 139.4 (d, *J*(C,P) = 26.7 Hz), 138.1 (d, *J*(C,P) = 12.4 Hz), 138.1 (d, *J*(C,P) = 10.9 Hz), 134.5 (d, *J*(C,P) = 21.4 Hz), 133.8 (d, *J*(C,P) = 20.5 Hz), 133.7 (d, *J*(C,P) = 1.5 Hz), 131.1 (d, *J*(C,P) = 17.8 Hz), 130.7, 130.2 (d, *J*(C,P) = 2.3 Hz), 128.7, 128.52 (d, *J*(C,P) = 7.0 Hz), 128.51, 128.46, 128.4 (d, *J*(C,P) = 7.4 Hz), 128.0, 127.9, 125.7, 83.7, 74.6, 74.1, 59.0; ^{31}P NMR ($CDCl_3$) δ −4.4.

(*R*,*R*)-1-[2-(2-Iodophenyl)-4,5-dihydrooxazol-4-yl]ethanol (19a). A solution of 2-iodobenzoyl chloride (**18**, 1.704 mg, 6.4 mmol) in CH_2Cl_2 (6 mL) was added dropwise at 0 °C to a solution of (*R*,*R*)-threoninol (**9**, 631 mg, 6.0 mmol), and Et_3N (3.0 mL, 21.5 mmol) in CH_2Cl_2 (14 mL), and the mixture was stirred at room temperature for 0.5 h. TsCl (1.37 mg, 7.2 mmol) was added, and the solution was brought to reflux for 16 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (eluent: EtOAc) to afford **19a** (841 mg, 44%) as a colorless oil: $[\alpha]^{20}_D$ −90 (*c* 0.77, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.96 (1H, dd, *J* = 1.0, 8.0 Hz), 7.64 (1H, dd, *J* = 1.7, 7.7 Hz), 7.40 (1H, dt, *J* = 1.1, 7.6 Hz), 7.13 (1H, dt, *J* = 1.7, 7.7 Hz), 4.51 (1H, m), 4.32−4.22 (2H, m), 3.80 (1H, m), 2.37 (1H, d, *J* = 5.6 Hz), 1.35 (3H, d, *J* = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 165.3, 140.5, 133.1, 131.8, 130.5, 127.8, 94.9, 73.1, 70.0, 69.7, 19.6.

(*R*,*R*)-[2-(2-Iodophenyl)-4,5-dihydrooxazol-4-yl]phenylmethanol (19b). A solution of 2-iodobenzoyl chloride (**18**, 847 mg, 3.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise at 0 °C to a solution of (*R*,*R*)-2-amino-1-phenyl-1,3-propanediol (**10**, 501 mg, 3.0 mmol) and Et_3N (1.5 mL, 10.8 mmol) in CH_2Cl_2 (7 mL), and the mixture was stirred at room temperature for 0.5 h. DMAP (12.2 mg, 0.1 mmol) was added followed by TsCl (686 mg, 3.6 mmol), and the solution was brought to reflux for 16 h. The reaction mixture was diluted with EtOAc, washed with 0.02 M HCl, water, 2 M NaOH, and brine, and dried over Na_2SO_4. After filtration and evaporation of the solvent, the

residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:1) followed by recrystallization from EtOAc/hexane to afford **19b** (668 mg, 59%) as a white solid: mp 104 °C; $[\alpha]^{20}_D$ −78 (*c* 2.16, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.97 (1H, d, J = 8.0 Hz), 7.63 (1H, dd, J = 1.6, 7.7 Hz), 7.46 (2H, m), 7.42−7.29 (4H, m), 7.13 (1H, dt, J = 1.6, 7.8 Hz), 4.61 (2H, m), 4.31 (1H, m), 4.21 (1H, m), 3.43 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 165.6, 140.6, 139.9, 132.8, 131.9, 130.6, 128.6, 128.3, 127.9, 127.0, 94.9, 77.2, 73.4, 69.6.

(*R*,*R*)-2-(2-Iodophenyl)-4-(1-methoxyethyl)-4,5-dihydrooxazole (20a). NaH (60% in mineral oil, 37.84 mg, 0.946 mmol, washed three times with hexane) was suspended in THF (5 mL) at 0 °C. **19a** (200 mg, 0.63 mmol) dissolved in THF (7 mL) was added, and the mixture was stirred at 0 °C for 1 h. MeI (58.9 μL, 0.946 mmol) was added dropwise, and the solution was stirred in a thawing ice bath for 16 h. The solution was diluted with diethyl ether (20 mL) and washed with H_2O (20 mL) and sat. NH_4Cl (20 mL). The combined water phases were washed with diethyl ether (3 × 20 mL), and the combined organic phases were concentrated and dried over Na_2SO_4 to afford **20a** (192.9 mg, 92%) as a yellowish oil: $[\alpha]^{20}_D$ −40 (*c* 0.71, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.93 (1H, dd, J = 0.9, 7.9 Hz), 7.63 (1H, dd, J = 1.7, 7.7 Hz), 7.37 (1H, dt, J = 1.1, 7.6 Hz), 7.11 (1H, dt, J = 1.7, 7.7 Hz), 4.60 (1H, m), 4.40 (2H, m), 3.71 (1H, dq, J = 4.8, 6.3 Hz), 3.42 (3H, s), 1.21 (3H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 165.0, 140.5, 133.6, 131.6, 130.8, 127.8, 94.5, 77.3, 69.8, 68.5, 56.8, 14.0.

(*R*,*R*)-2-(2-Iodophenyl)-4-(methoxyphenylmethyl)-4,5-dihydrooxazole (20b). Compound **20b** was prepared in the same way as **17a** starting from NaH (60% in oil, 130 mg, 3.25 mmol), THF (10 mL), **19b** (984 mg, 2.6 mmol), and dimethyl sulfate (986.4 mg, 7.82 mmol). Flash chromatography on silica gel (eluent: EtOAc/hexane 2:3) provided **20b** (914 mg, 90%) as a yellowish oil: $[\alpha]^{20}_D$ −75 (*c* 0.82, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.88 (1H, m), 7.48−7.26 (7H, m), 7.07 (1H, dt, J = 1.8, 7.7 Hz), 4.75 (1H, m), 4.42 (1H, dd, J = 2.0, 6.1 Hz), 4.25 (2H, m), 3.34 (3H, m); ^{13}C NMR ($CDCl_3$) δ 165.4, 140.1, 137.4, 133.7, 131.5, 130.7, 128.3, 128.1, 127.8, 127.6, 94.4, 84.9, 71.3, 69.0, 57.1.

(*R*,*R*)-1-[2-(2-Diphenylphosphinophenyl)-4,5-dihydrooxazol-4-yl]ethanol (5). Compound **5** was prepared in the same way as **2** starting from diphenylphosphine (156.4 mg, 0.70 mmol), **19a** (222.0 mg, 0.84 mmol), Et_3N (0.59 mL, 4.2 mmol), CH_3CN (5 mL), and $Pd(OAc)_2$ (7.86 mg, 0.035 mmol). Flash chromatography on silica gel (eluent: EtOAc/hexane 1:2) provided **5** (392 mg, 75%) as a colorless oil: $[\alpha]^{20}_D$ −110 (*c* 1.41, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.91 (1H, ddd, J = 1.1, 3.6, 7.6 Hz), 7.40 (1H, dt, J = 1.0, 7.6 Hz), 7.37−7.22 (11H, m), 6.93 (1H, m), 4.34 (1H, dd, J = 8.0, 9.5 Hz), 4.13 (1H, m), 4.05 (1H, t, J = 7.9 Hz), 3.39 (1H, m), 2.08 (1H, m), 1.11 (3H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 163.9, 138.6 (d, J(C,P) = 22.8 Hz), 138.3 (d, J(C,P) = 8.0 Hz), 137.8 (d, J(C,P) = 9.3 Hz), 134.5, 134.2 (d, J(C,P) = 20.5 Hz), 133.3 (d, J(C,P) = 19.7 Hz), 131.6 (d, J(C,P) = 20.0 Hz), 130.7, 129.6, 128.64, 128.57, 128.51 (d, J(C,P) = 6.9 Hz), 128.50 (d, J(C,P) = 6.9 Hz), 128.3, 73.3, 70.1, 69.6, 19.9; ^{31}P NMR ($CDCl_3$) δ −5.8.

(*R*,*R*)-2-(2-Diphenylphosphinophenyl)-4-(1-methoxyethyl)-4,5-dihydrooxazole (6). Compound **6** was prepared in the same way as **2** starting from diphenylphosphine (45.0 mg, 0.242 mmol), **20a** (222.0 mg, 0.201 mmol), Et_3N (0.17 mL, 1.21 mmol), CH_3CN (2 mL), and $Pd(OAc)_2$ (2.26 mg, 0.010 mmol). Flash chromatography on silica gel (eluent: EtOAc/hexane 1:9) provided **6** (48.4 mg, 62%) as a slightly yellowish oil: $[\alpha]^{20}_D$ −11 (*c* 1.10, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.91 (1H, ddd, J = 1.5, 3.6, 7.6 Hz), 7.38−7.26 (12H, m), 6.88 (1H, ddd, J = 1.2, 4.1, 7.7 Hz), 4.36 (1H, ddd, J = 4.7, 7.7, 10.0 Hz), 4.08 (2H, m), 3.41 (1H, m), 3.29 (3H, s), 0.75 (3H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 164.3 (d, J(C,P) = 2.8 Hz), 139.0 (d, J(C,P) = 25.6 Hz), 138.1 (d, J(C,P) = 12.6 Hz), 137.9 (d, J(C,P) = 9.7 Hz), 134.3 (d, J(C,P) = 21.1 Hz), 133.83 (d, J(C,P) = 20.7 Hz), 133.79, 131.5 (d, J(C,P) = 19.0 Hz), 130.5, 130.1 (d, J(C,P) = 2.7 Hz), 128.6, 128.5, 128.4 (d, J(C,P) = 6.9 Hz), 128.3 (d, J(C,P) = 7.6 Hz), 128.0, 77.2, 69.5, 67.6, 56.6, 13.3; ^{31}P NMR ($CDCl_3$) δ −4.8.

[(*R*,*R*)-2-(2-Diphenylphosphinophenyl)-4,5-dihydrooxazol-4-yl]phenylmethanol (7).[22] Compound **7** was prepared in the same way as **2** starting from diphenylphosphine (267.5 mg, 1.44 mmol), **19b** (453 mg, 1.2 mmol), Et_3N (1.0 mL, 7.2 mmol), CH_3CN (10 mL), and $Pd(OAc)_2$ (13.6 mg, 0.060 mmol). Flash chromatography on silica gel (eluent: EtOAc/hexane 1:2) afforded **7** (392 mg, 75%) as a white solid: mp 109 °C; $[\alpha]^{20}_D$ −94 (*c* 0.90, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.93 (1H, ddd, J = 1.3, 3.7, 7.6 Hz), 7.41 (1H, ddd, J = 1.1, 7.6, 7.6 Hz), 7.39−7.24 (16H, m), 6.95 (1H, ddd, J = 0.9, 3.9, 7.7 Hz), 4.47 (1H, ddd, J = 7.5, 7.5, 9.6 Hz), 4.17 (1H, m), 4.11 (1H, dd, J = 2.2, 7.5 Hz), 4.00 (1H, m), 2.88 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 164.3 (d, J(C,P) = 1.8 Hz), 140.1, 138.9 (d, J(C,P) = 23.7 Hz), 138.2 (d, J(C,P) = 8.1 Hz), 137.7 (d, J(C,P) = 10.3 Hz), 134.4, 134.2 (d, J(C,P) = 20.4 Hz), 133.4 (d, J(C,P) = 19.8 Hz), 131.4 (d, J(C,P) = 19.8 Hz), 130.9, 129.7 (d, J(C,P) = 2.8 Hz), 128.7, 128.7, 128.6, 128.5 (d, J(C,P) = 8.1 Hz), 128.5 (d, J(C,P) = 8.1 Hz), 128.3, 128.1, 127.1, 77.4, 73.5, 69.4; ^{31}P NMR ($CDCl_3$) δ −5.8.

(*R*,*R*)-2-(2-Diphenylphosphinophenyl)-4-(methoxyphenylmethyl)-4,5-dihydrooxazole (8). Compound **8** was prepared in the same way as **2** starting from diphenylphosphine (535.0 mg, 2.87 mmol), **20b** (970 mg, 2.47 mmol), Et_3N (2.0 mL, 14.4 mmol), CH_3CN (15 mL), and $Pd(OAc)_2$ (27 mg, 0.12 mmol). Flash chromatography on silica gel (eluent: diethyl ether/hexane 1:3) afforded **8** (910 mg, 82%) as a white solid: mp 48 °C; $[\alpha]^{20}_D$ +16 (*c* 0.61, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.82 (1H, ddd, J = 1.3, 3.2, 7.1 Hz), 7.43−7.22 (15H, m), 7.18 (2H, m), 6.91 (1H, m), 4.46 (1H, m), 3.90 (1H, d, J = 6.7 Hz), 3.85 (1H, t, J = 9.3 Hz), 3.75 (1H, t, J = 8.6 Hz), 3.23 (3H, s); ^{13}C NMR ($CDCl_3$) δ 165.1 (d, J(C,P) = 1.7 Hz), 138.5 (d, J(C,P) = 24.8 Hz), 137.9 (d, J(C,P) = 11.9 Hz), 137.6, 137.5 (d, J(C,P) = 9.9 Hz), 134.11 (d, J(C,P) = 21.1 Hz), 134.06 (d, J(C,P) = 21.0 Hz), 133.4 (d, J(C,P) = 1.7 Hz), 131.7 (d, J(C,P) = 18.9 Hz), 130.3, 130.1 (d, J(C,P) = 3.0 Hz), 128.59, 128.57, 128.4 (d, J(C,P) = 7.1 Hz), 128.3 (d, J(C,P) = 7.0 Hz), 128.1, 127.9, 127.8, 127.6, 85.0, 71.1, 68.4, 56.8; ^{31}P NMR ($CDCl_3$) δ −4.7. Anal. Calcd for $C_{29}H_{26}NO_2P$: C, 77.15; H, 5.80; P, 6.86. Found: C, 76.95; H, 5.92; P, 6.65.

General Procedure for the Palladium-Catalyzed Allylic Alkylations. Ligand (0.012 mmol, 2.4 mol %), [(η^3-C_3H_5)-PdCl]$_2$ (1.83 mg, 0.0050 mmol, 2.0 mol % Pd), and substrate (0.50 mmol) were dissolved in solvent (1 mL), and stirred for 1 h at room temperature. A solution/suspension of the nucleophile was prepared by adding acetylacetone/dimethyl malonate (0.70 mmol) dropwise to a suspension of NaH (60% in mineral oil, 24.0 mg, 0.60 mmol) in 5 mL of solvent. The two solutions were mixed at −78 °C, and stirred at the reported reaction temperature for the appropriate time. The samples taken were filtered through silica using EtOAc. The reaction mixture was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:6).

(*E*)-2-(1,3-Diphenylprop-2-enyl)malonic Acid Dimethyl Ester (25). Conversions and enantiomeric excesses were determined by a chiral OD-H (0.46 cm Ø × 25 cm) HPLC column (eluent: degassed 2-propanol/hexane 1:99), with a flow rate of 0.5 mL/min, UV detection at 254 nm, $t_R(R)$ = 21.3 min, $t_R(S)$ = 22.9 min. Absolute configurations were assigned by comparing the sign of the optical rotation with literature data.[19]

(*E*)-3-(1,3-Diphenylprop-2-enyl)pentane-2,4-dione (26). Conversions and enantiomeric excesses were determined by a chiral OJ (0.46 cm Ø × 25 cm) HPLC column (eluent: degassed 2-propanol/hexane 5:95), with a flow rate of 0.5 mL/min, UV detection at 254 nm, $t_R(R)$ = 37.0 min, $t_R(S)$ = 43.9 min. Absolute configurations were assigned by comparing the sign of the optical rotation with literature data.[43]

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2-(3-Cyclohexenyl)malonic Acid Dimethyl Ester 27. Conversions were determined by GC−MS. Enantiomeric excesses were determined by a chiral OD-H (0.46 cm Ø × 25 cm) HPLC column (eluent: degassed 2-propanol/hexane 0.25:99.75), with a flow rate of 0.5 mL/min, UV detection at 220 nm, t_R(R) = 30.5 min, t_R(S) = 32.0 min. Absolute configurations were assigned by comparing the sign of the optical rotation with literature data.[44]

General Procedure for the Iridium-Catalyzed Allylic Alkylations Using NaH as Base. Ligand (0.011 mmol, 4.4 mol %), $[IrcodCl]_2$ (3.36 mg, 0.0050 mmol, 4.0 mol % Ir), and substrate (0.25 mmol) were dissolved in THF (1 mL), and the solution was stirred for 15 min at room temperature. A solution of the nucleophile was prepared by adding dimethyl malonate (62.9 μL, 0.55 mmol) dropwise to a suspension of NaH (60% in mineral oil, 20.0 mg, 0.50 mmol) in THF (3 mL). The nucleophile solution was added dropwise to the catalyst solution at room temperature, and stirred at 65 °C for the appropriate time. The samples taken were filtered through silica using EtOAc. The reaction was quenched by the addition of H_2O (10 mL). The product was extracted with diethyl ether (10 mL), washed with brine (10 mL), dried over $MgSO_4$, and purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:9) to yield a mixture of branched and linear products.

General Procedure for the Iridium-Catalyzed Allylic Alkylations Using Cs_2CO_3 as Base. Ligand (0.011 mmol, 4.4 mol %), $[IrcodCl]_2$ (3.36 mg, 0.0050 mmol, 4.0 mol % Ir), substrate (0.25 mmol), and Cs_2CO_3 (162.9 mg, 0.50 mmol) were suspended in THF (2 mL), and stirred for 15 min at room temperature. Dimethyl malonate (62.9 μL, 0.55 mmol) was added dropwise at room temperature, and the mixture was stirred at 65 °C for the appropriate time. The samples taken were filtered through silica using EtOAc. The reaction was quenched by the addition of H_2O (10 mL). The product was extracted with diethyl ether (10 mL), washed with brine (10 mL), dried over $MgSO_4$, and purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:9) to yield a mixture of branched and linear products.

1-Phenyl-2-propenyl Malonic Acid Dimethyl Ester 31a and (*E*)-3-Phenyl-2-propenyl Malonic Acid Dimethyl Ester 31b. Conversions and branched:linear ratios were determined by GC−MS. Enantiomeric excesses were determined by a chiral OD-H (0.46 cm Ø × 25 cm) HPLC column (eluent: degassed 2-propanol/hexane 0.25:99.75), with a flow rate of 0.5 mL/min, UV detection at 220 nm, t_R(R) = 44.4 min, t_R(S) = 51.7 min. Absolute configurations were assigned by comparing the sign of the optical rotation with literature data.[45]

1-(4-Methoxyphenyl)-2-propenyl Malonic Acid Dimethyl Ester 32a and **(*E*)-3-(4-Methoxyphenyl)-2-propenyl Malonic Acid Dimethyl Ester 32b.** Conversions and branched:linear ratios were determined by GC−MS. Enantiomeric excesses were determined by a chiral OD-H (0.46 cm Ø × 25 cm) HPLC column (eluent: degassed 2-propanol/hexane 5:95), with a flow rate of 0.5 mL/min, UV detection at 220 nm, t_R(R) = 13.5 min, t_R(S) = 15.0 min. Absolute configurations were assigned by comparing the sign of the optical rotation with literature data.[46]

Computations. The following computational methodology was applied. First, geometry optimizations of structures were carried out using B3LYP functional[25] with the lacvp**/6-31G-(d,p) basis set.[27,28] In the second step, B3LYP energies were evaluated for the optimized geometry using the much larger triple-ζ basis, lacv3p**++/6-311+G(d,p), with additional diffuse and polarization functions. All computations were performed with the Jaguar v4.0 suite of ab initio quantum chemistry programs.[26] Solvent (THF) was represented with the following parameters: $\epsilon = 7.58$, probe radius $r_p = 2.524$ Å. Gas-phase optimized structures were used to estimate the effect of solvent on the reaction energy within the self-consistent reaction field model as implemented in the Jaguar computational package.

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Supporting Information Available: General experimental methods.^{1}H NMR spectra of compounds **1**−**8**, **12**, **16a**, **16b**, **17a**, **17b**, **19a**, **19b**, **20a** and **20b**. *XYZ* coordinates of **D2′**, **D2″**, **F1′**, and **F2′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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