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Regio- and Enantioselective Allylic Alkylation of an Unsymmetrical Substrate: A Working Model

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Abstract: The evolution of a model for understanding asymmetric allylic alkylations catalyzed by palladium with the use of ligands derived from chiral diamines and 2-diphenylphosphinobenzoic acid provides a basis for attacking the problem of regio- and enantioselective alkylations proceeding through the intermediacy of 1-monosubstituted allyl complexes. The model predicted that in the kinetic ionization of an achiral precursor the major enantiomer of the product resulting from attack at the more substituted terminus would be the mirror image of that obtained under Curtin−Hammett conditions. Experimentally, the ee was rationally varied from 66% of one enantiomer to 83% of the mirror image using the same ligand. Nonpolar solvents and the absence of counterions that coordinate to palladium favor the kinetic product. More polar solvents and counterions that coordinate well to palladium favor Curtin−Hammett conditions. For maximum regio- and enantioselectivity, the chiral racemic 3-substituted-1-alkene is the preferred substrate.

Selectivity, especially enantioselectivity, continues to be a major area of focus in organic chemistry. Transition metal catalyzed enantioselective reactions are among the most powerful in this regard.[1] In general, the enantioselectivity in metal catalyzed reactions is derived from the differentiation of enantiotopic faces of a π-system. This has been achieved with the π-systems of olefins (hydrogenation, hydroboration, epoxidation, cyclopropanation, cycloadditions), carbonyl compunds (hydride reductions, organozinc additions), and enolates (aldol reactions, alkylations, protonations). Unlike most transition metal catalyzed processes, allylic alkylations do not rely solely on a single mechanism as a source of asymmetry.[2] Although differentiation of olefin faces is one possible mechanism, the source of the enantioselectivity is complicated by the possibility that one or more other steps in the catalytic cycle may be the enantiodiscriminating step(s). Furthermore, the choice of transition metal (Pd, Ir, W, Mo, Rh)[3,4] may also have an effect on the mechanism of enantioselectivity.

The mechanism by which the catalyst imposes its chirality upon the product for metal catalyzed allylic alkylations remains obscure in most cases. Most discussions focus on the nature of the steric interactions in a static model derived from a knowledge of the structure of the π-allylmetal intermediate. In devising our family of chiral ligands, we envisioned the creation of chiral space. In this model, the sum of the interactions associated with the motions going from η^2- to η^3-metal complexes or the reverse are envisioned to dictate the chirality of the product. Unfortunately, all attempts to characterize directly the intermediates either by X-ray crystallography or NMR spectroscopy have

(1) (a) Noyori, I. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, NY, 1994. (b) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: Weinheim, Germany, 1993.

(2) (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

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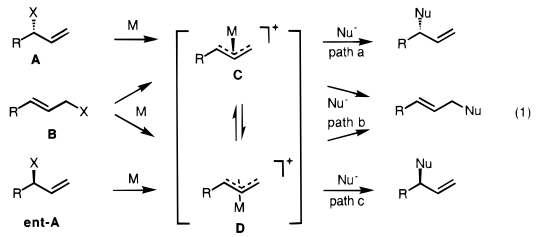
failed. Thus, we have been confronted with learning more about the nature of the process by indirect, albeit circumstantial, evidence.

1,3-Symmetrically substituted substrates are among the most studied and successful in allylic alkylations. The success of these substrates lies in the fact that from both enantiomers of the chiral racemic substrate the same symmetrical π-allyl intermediate is accessible. This transforms the problem of enantioselectivity to one of regioselectively attacking one of the enantiotopic terminal carbons of the allyl. A more challenging case is that of the unsymmetrically 1-monosubstituted π-allyl intermediate (eq 1). In this case the allyl intermediate no longer possesses a



plane of symmetry, and thus the question of enantioselectivity is much more complex. A second issue arises from the fact that the two terminal carbons of the π-allyl intermediate are no longer equivalent; one is a primary carbon while the other is secondary. Several factors will determine the regioselectivity of nucleophilic attack on a monosubstituted intermediate.[5,6] Steric factors will direct attack to the less sterically demanding primary site, while electronic factors tend to favor attack at the more electropositive secondary carbon. Which of these dominates depends on several factors, including the choice of metal, the R group in the allyl substrate, and the nucleophile. This paper describes factors inherent to chiral ligands, which are not present in achiral ones, that allow control of the regioselectivity of nucleophilic attack in palladium catalyzed allylic alkylations. Furthermore, if ideal conditions can be created, reactions that are both regio-and enantioselective may become possible. This study was also envisioned to provide additional insight into the enantiodiscriminating step.

In examining eq 1, if the metal fragment is achiral, the issues affecting the regioselectivity for the two enantiomeric intermediates **C** and **D** will be identical. When the metal is palladium, the normal bias in such a case leads to preferential formation of the achiral product via path b. On the other hand, if the metal fragment is chiral, then the intermediates **C** and **D** are diastereomeric, and the factors affecting regioselectivity for **C** may be different than those for **D**. Using the model for the ligands developed in these laboratories wherein the motions associated with going from an η^2- to η^3-complex during nucleophilic attack are responsible for the chiral recognition leads to the conclusion that the differences in these two complexes may lead one diastereomeric complex to favor attack via path a (or, alternatively, path c) and the other via path b (vide infra).

A second aspect that must be considered derives from the facts that, in the presence of chiral ligands, both the alkene−metal complexes before ionization as well as the π-allyl intermediates are diastereomeric and that the nucleophilic addition step can be considered to be the microscopic reverse of the ionization step. If ionization of **A** in the presence of a chiral complex preferentially generates **C**, then path a would be the expected "matched" route for nucleophilic attack from **C**. To the extent that ionization of ent-**A** with this same chiral complex to form **D** is unfavorable, nucleophilic attack, according to path c, would be less favorable or "mismatched" compared to path a. Furthermore, it may be argued that the complex that preferentially ionizes **A** to form **C** will preferentially ionize the regioisomeric substrate **B** to form **D** (vide infra). The fact that path b represents the microscopic reverse of that ionization then suggests that, for nucleophilic attack on **D**, path b should be favored or matched compared to path c. This scenario suggests that, to control regioselectivity of attack, it is necessary to control which of the two complexes, **C** or **D**, is attacked, i.e., chiral ligands can influence regioselectivity in ways not possible with achiral ligands. In this paper, we report a catalytic system that shows these expectations can be realized experimentally.

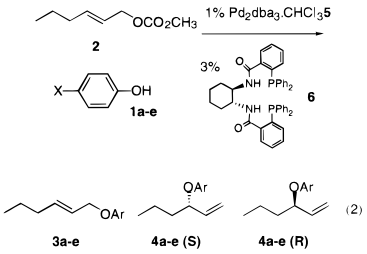
Table 1. Solvent Effects with Achiral Substrate **2** and Phenol **1a** (X = Och_3)[a]

entry	solvent	$E_tN(30)$	**3**:**4**	**4a(R)**	**4a(S)**	% ee	$t_{1/2}$ (min)
1	toluene	0.099	60:40	6.8	33.2	66 (S)	45
2	THF	0.207	48:52	12.7	39.3	51 (S)	240
3	CH_2Cl_2	0.309	42:58	32.5	25.5	12 (R)	5
4	CH_3CN	0.460	23:77	50.1	26.9	30 (R)	

[a] Reaction performed with ligand and palladium complex as outlined in eq 2.

Results

As a test case, a system which had been reported to provide poor regioselectivity with achiral ligands was chosen—the allylic alkylation of phenols, illustrated by the reaction of 4-methoxyphenol (**1a**) with methylhexenyl carbonate (**2**) (eq 2).[7] The



π-allyl generated from this substrate would bear a propyl substituent which, usually for steric reasons, generally disfavors attack at the secondary site, although for electronic reasons attack at the secondary carbon would be favored. Furthermore, this system would allow the electronic and steric effects of the nucleophile to be readily examined by simply changing the substituents on the phenol.

The first parameter we chose to examine was the solvent. These experiments clearly show that a change in solvent polarity resulted in a change in both the regio- and enantioselectivity of the allylic alkylation reaction (Table 1). Furthermore, the change in regioselectivity followed the same trend as the change in enantioselectivity. That is, the more polar solvents favored the formation of the more substituted product **4** and at the same time showed an increase in the formation of **4a(R)**. As seen

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(6) Recently, reversals in regioselectivity have been reported for 1-arylprop-2-enyl acetates using non-C_2-symmetric ligands. (a) Pretot, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (b) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *Chem. Commun.* **1997**, 561. Also see: (c) Hayashi, T.; Kishi, K.; Yamamoro, A.; Ho, Y. *Tetrahedron Lett.* **1990**, *31*, 1743. (d) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681. (e) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 8, 6297.

(7) (a) Goux, C.; Lhoste, P.; Sinou, D. *Synlett* **1992**, 725 (b) Goux, C.; Massacret, M.; Lhoste, P.; Sinou, D. *Organometallics* **1995**, *14*, 4585.

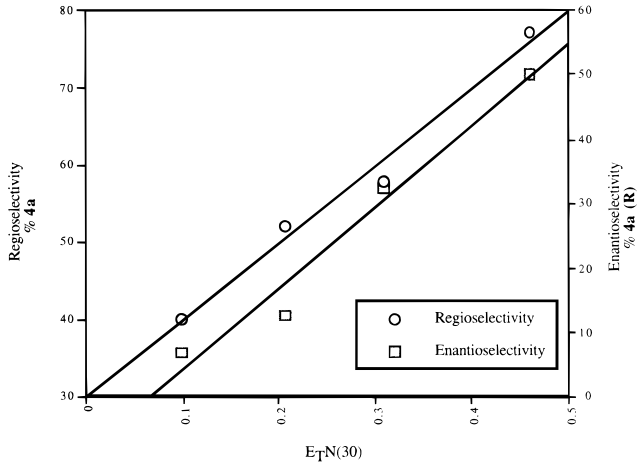
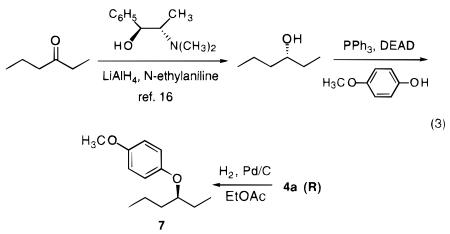


Figure 1. Effect of solvent polarity on the regio- and enantioselectivity in the palladium-catalyzed allylic alkyaltion of **2**.

from the graph (Figure 1), both of these trends correlate well with the $E_TN(30)$ solvent polarity scale.[8]

The absolute configuration of the aryl ether **4a(R)** was determined by hydrogenation of the olefin and comparison of the saturated product with an authentic sample (eq 3). The



saturated ether was prepared by a two-step protocol starting from 2-butanone. Enantioselective reduction of the ketone using *N*-methylephedrine-modified lithium aluminum hydride[9] followed by Mitsunobu reaction afforded the desired ether **7** in 37% ee (by HPLC). This is slightly higher than originally reported for the reduction of 3-hexanone to 3-hexanol, 18−20% ee based on rotation. Hydrogenation of **4a (R)** (74% ee, see Table 4, entry 10) afforded the unsaturated ether in 75% ee. The major isomer was identical to the authentic sample as determined by HPLC.

Is the change in regio- and enantioselectivity vs solvent polarity due to a change in the rate of nucleophilc attack? In analogy to an S_N2 reaction, one would expect the rate of nucleophilic attack to increase with increasing solvent polarity. However, in the case of allylic alkylation reactions, the analogy may not hold since both the nucleophile and electrophile are charged species. Polar solvents may, therefore, stabilize both reacting partners better than nonpolar solvents. The stabilization of the reactants by polar solvents may be greater than that felt in the transition state in which the charge is destroyed. This would lead to an overall decrease in the rate of nucleophilic attack as solvent polarity increases. Bosnich proposed that, in DMF, the step involving attack of the nucleophile on the π-allylpalladium intermediate was rate-determining.[10] If this is true in all solvents, we should see a correlation between the overall rates of the reaction and of the nucleophilic attack.

Table 2. Phenol Substituent Effects on Regio- and Enantioselectivity

entry	**1** (X)	σ^+	solvent	**3**:**4**	**4 (R)**	**4 (S)**	% ee
1	OCH_3 **a**	−0.28	toluene	60:40	6.8	33.2	66 (S)
2	CH_3 **b**	−0.14		63:37	9.5	27.5	47 (S)
3	H **c**	0.00		62:38	13.1	24.9	31 (S)
4	Cl **d**	0.24		55:45	20.3	24.7	10 (S)
5	CO_2CH_3 **e**	0.44		36:64	39	35	22 (R)
6	OCH_3 **a**	−0.28	CH_3CN	23:77	50.1	26.9	30 (R)
7	H **c**	0.00		40:60	42	18	40 (R)
8	CO_2CH_3 **e**	0.44		37:63	34.7	28.4	10 (R)

Therefore, we examined the rate of the reaction in the aforementioned solvents. The half-lives reported in Table 1 indicate no correlation between the half-life of the reaction and the solvent polarity. Our results mirror those of Brown who found turnover rates of 0.4, 8 and 1.2 min in CD_2Cl_2, THF and toluene, respectively.[11c] The lack of correlation between the regio- and enantioselectivity and rate does not exclude the possibility that the rate of nucleophilic attack is decreasing with solvent polarity. It does, however, suggest that the regio- and enantiodetermining step (nucleophilic attack) is not the rate-determining step in at least some of these solvents.

Although, in some (or all) solvents, phenol addition may not be rate-determining, in all cases, the nucleophile is involved in the regio- and enantiodetermining step. Therefore, changing the substituent(s) on the phenol should have an effect on the regio- and enantioselectivity. On the basis of a working hypothesis (vide infra) that the major enantiomer in the case of toluene arises from attack on the kinetically formed π-allyl intermediate and, in acetonitrile, the opposite enantiomer arises from attack on the equilibrated intermediate (e.g., corresponding to π-allyl intermediates **C** and **D** respectively of eq 1), substituent effects in the phenols, which would influence nucleophilicity, should be observed.

If this hypothesis is correct, a decrease in the rate of nucleophilic attack, while maintaining the rate of interconversion of the two diastereomeric π-allyl complexes constant, will lead to an increase in the products arising from trapping of the nonkinetically formed intermediate. In the case of eq 2, the prediction means that the amount of the S enantiomer compared to that of the R enantiomer should decrease—in other words, the ee should decrease! To probe the effect of decreasing nucleophilicity, the substituents at the para position of the phenol were varied (Table 2). In toluene as solvent, as the substituents became less electron-donating (higher Hammett σ value), the enantioselectivity deteriorated. It is reasonable to assume that a decrease in the electron-donating ability of the para substituents of phenols results in a decrease in the nucleophilicity. Thus, the decrease in enantioselectivity may arise from an increase in the rate of interconversion of the two diastereomeric complexes **C** and **D** (eq 1) relative to that of nucleophilic attack. Indeed, if the rate of nucleophilic attack is substantially decreased ($X = CO_2CH_3$) relative to that of isomerization, even in toluene, the major enantiomer is the one derived from attack on the equilibrated intermediate**.** The enantioselectivities correlate very well with the Hammett σ_p values (see Figure 2). The excellent degree of correlation is somewhat surprising if

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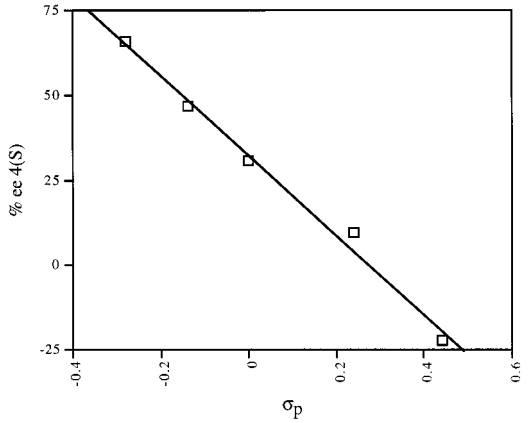
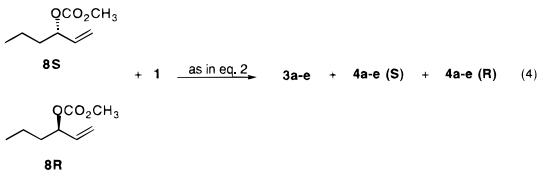


Figure 2. Phenol substituent effects on enantioselectivity of allylic alkylation of **8** in toluene.

one considers all of the steps, including deprotonation of the pronucleophile phenol, involved in the allylic alkylation which may be influenced by the substituents.

For eq 2, the major enantiomer produced when the allylic alkylation is carried out in acetonitrile is **4**(**R**). This enantiomer is presumably produced by nucleophilic attack on the equilibrated π-allyl intermediate which arises from $\pi-\sigma-\pi$ isomerization of the kinetic π-allyl intermediate. A decrease in the rate of nucleophilic attack should allow for Curtin−Hammett conditions to be approached. Thus, when acetonitrile is used as solvent for the allylic alkylation, a decrease in nucleophilicity should result in an increase in the enantiomer derived from the equilibrated π-allyl. Indeed, this is the case when the electron-donating ability of the para substituent is decreased from -OCH_3 to -H (30 and 40% ee, respectively). However, when *p*-CO_2CH_3 was used as a substituent, the trend did not hold, and the enantioselectivity decreased to 10%. Since, in this case, the phenoxide would be a good leaving group, the decrease may arise because, in acetonitrile, the reaction may become reversible.

To further examine the same effects discussed above, a study utilizing the chiral racemic substrate, 1-hexenyl 3-carbonate (**8R**/**8S**) was initiated (eq 4). In this discussion, the possibility of



ionization to the anti complex is ignored since it normally represents a higher energy transition state. To consider the expectations, eqs 1, 2, and 4 must be examined. Arbitrarily, assume that diastereomeric complex **C** is the kinetically formed complex between substrate **2** and chiral ligand **6** and, therefore, the one that should lead to attack at the primary carbon (eq 1, path b). Therfore, diastereomeric complex **D** is the one that should preferentially lead to the product of secondary attack, but only after equilibration of the two complexes. Starting from the chiral substrate **8**, 50% of the substrate directly will form diastereomer **D**, which preferentially leads to the product of secondary attack, and only the remaining 50% which forms **C** requires equilibration. Since the results with the chiral ligand **6** and substrate **2** show that **S-4a** is preferentially formed initially and **R-4a** after equilibration, the expectation becomes that the chiral racemic substrate should preferentially form the R isomer in all cases and that the ee favoring the R isomer should increase with increasing solvent polarity (i.e., increasing the relative rate of interconversion of **C** and **D**).

Table 3. Solvent Effect with Chiral Substrate

entry	solvent	**3a**:**4a**	**4a (R)**	**4a (S)**	% ee
1	Toluene	33:67	40.9	26.1	22 (R)
2	THF	33:67	40.9	26.1	22 (R)
3	CH_2Cl_2	33:67	45.6	21.4	36 (R)
4	CH_3CN	20:80	61.2	18.8	53 (R)

As can be seen in Table 3, the prediction that the major enantiomer from this reaction should have the **R** absolute configuration is validated. Furthermore, as anticipated, an increase in solvent polarity resulted in both an increase in enantio- and regioselectivity. The best results were obtained in acetonitrile which provided the secondary product in an 80:20 ratio with 53% ee. These results reinforce the hypothesis that, in polar solvents (acetonitrile), the reaction is approaching Curtin−Hammett conditions.

All of the above observations suggest that, to obtain high enantio- and regioselectivity for the formation of the secondary product **4**, the reaction should be under Curtin−Hammett conditions if possible; i.e., the rate of equilibration between π-allyl intermediates must be greater than that of nucleophilic attack. Therefore, to increase the enantio- and regioselectivity, either the rate of interconversion must increase or the rate of nucleophilic attack must decrease. While the proper choice of solvent moves in the right direction, it is not sufficient. It has been shown that anionic ligands (such as halides) can promote the $\pi-\sigma-\pi$ interconversion process via a σ-allyl intermediate **16**.[12] Åkermark reported that addition of 0.1 equiv of chloride decreased the equilibration time of *syn,anti*-π-allyl complexes to 0.5 h compared to 48 h when tetrafluoroborate was used as the counterion.[13] Recently, Togni has examined this anion effect on the allylic alkylation using ferrocenyl ligands and found that the addition of hard anions (such as fluoride) had a beneficial effect on the enantioselectivity of allylic aminations.[14] These results prompted us to examine the effect of anions on the allylic alkylation of phenols. Coordinating an anion to palladium to promote isomerization of **C** and **D** leads to the prediction that addition of a halide anion should result in a more regio- and enantioselective reaction. Furthermore based upon palladium-halide bond strengths, the order of effectiveness should be $F^- > Cl^- > Br^- > I^-$.[15]

Table 4 summarizes the series of reactions involving the effect of halide ions. As predicted, when the reaction was carried out in methylene chloride, addition of 3% fluoride or chloride (entry 2 and 3) increased the enantioselectivity to 50 and 57% ee from 36% ee when no halide was present. Furthermore, the increase in enantioselectivity was accompanied by an increase in regioselectivity. Increasing the amount of chloride present to 30% (1500 mol % relative to that of palladium) resulted in a further increase in the enantioselectivity to 65% and the regioselectivity to 80:20. Interestingly, in acetonitrile, the effect was observed to a much lesser extent. Addition of 3% tetra-*n*-

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(14) Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155.

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Table 4. Effect of Halide Ion on Enantioselectivity in the Reaction with Chiral Substrate **8** (Eq 4)

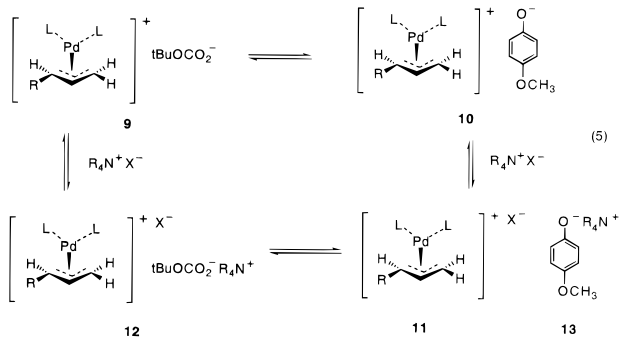
entry	solvent (concn ((M))	additive	**4a**:**3a**	% ee **(R)**
1	CH_2Cl_2 (0.5)		67:33	36
2	CH_2Cl_2 (0.5)	3% TBAT	71:29	50
3	CH_2Cl_2 (0.5)	3% Bu_4N^+ Cl^-	73:27	57
4	CH_2Cl_2 (0.5)	30% Bu_4N^+ Cl^-	80:20	65
5	CH_3CN (0.5)		80:20	53
6	CH_3CN (0.5)	3% Bu_4N^+ Cl^-	78:22	57
7	CH_2Cl_2 (0.1)	30% Me_4N^+ Cl^-	86:14	69
8	CH_2Cl_2 (0.1)	30% Et_4N^+ Cl^-	84:16	76
9	CH_2Cl_2 (0.1)	30% Bu_4N^+ Cl^-	84:16	83
10	CH_2Cl_2 (0.1)	15% Bu_4N^+ Cl^-	84:16	74
11	CH_2Cl_2 (0.1)	30% Hex_4N^+ Cl^-	84:16	86
12	CH_2Cl_2 (0.1)	30% Bu_4N^+ ClO_4^-	71:29	59
13	CH_2Cl_2 (0.1)	30% Bu_4N^+ Br^-	88:12	77
14	CH_2Cl_2 (0.1)	30% Bu_4N^+ I^-	84:16	75

butylammonium chloride increased the enantioselectivity from 53 to 57% ee. This observation is in accord with the previous hypothesis that, in acetonitrile, the relative rate of $\pi-\sigma-\pi$ isomerization is greater than that in methylene chloride. Since the rate of isomerization is already relatively fast in acetonitrile, halide has a lesser effect on the rate of isomerization.

Lowering the concentration of the reaction mixture from 0.5 to 0.1 M resulted in a significant increase in the enantioselectivity from 65 to 83% ee. The interconversion of **C** and **D** is a unimolecular process; therefore, its rate should be unaffected by concentration. On the other hand, nucleophilic attack is bimolecular, and its rate depends both on the concentration of the nucleophile and of the palladium π-allyl intermediate. Lowering the concentration of the reaction mixture should, therefore, significantly lower the rate of nucleophilic attack relative to that of interconversion of **C** and **D**.

To further probe the hypothesis that chloride was acting as an additional ligand for palladium, thereby promoting the $\pi-\sigma-\pi$ interconversion, a noncoordinating anion, perchlorate, was examined. The use of perchlorate in place of chloride dropped the enantioselectivity from 83 to 59% ee and the regioselectivity from 84:16 to 71:29. We also examined the use of other halides; moreover, our results paralleled those of Togni[14] with the enantioselectivities following the trend $Cl^- > Br^- > I^-$, in accordance with decreasing bond strength to palladium.

Although the enantioselectivity in the presence of tetrabutylammonium perchlorate (59% ee) was lower than when chloride (83% ee) was used, it was better than that obtained in its absence (36% ee). While the possibility of perchlorate behaving as a weak ligand for palladium (a promoter for the $\pi-\sigma-\pi$ isomerization) cannot be excluded, this observation may suggest that the tetraalkylammonium ion was also playing a role in the enhancement of the enantioselectivity. We have previously reported an enhancement in enantioselectivity in the allylic alkylation of malonates in the presence of tetrabutylammonium bromide.[16] For reasons already discussed, in allylic alkylations where the nucleophilic attack is the enantiodetermining step, the nucleophile's countercation may have an effect on the enantioselectivity. Let us consider the ion pairs which may be involved in the allylic alkylation of phenols with allyl carbonates (eq 5). On ionization of allyl carbonates, the first ion pair formed is that of the palladium π-allyl and the carbonate anion **9**. In the absence of tetraalkylammonium additives, **9** can undergo $\pi-\sigma-\pi$ isomerization to the diastereotopic allyl, or the carbonate can deprotonate phenol to generate the ion pair **10**. The ion

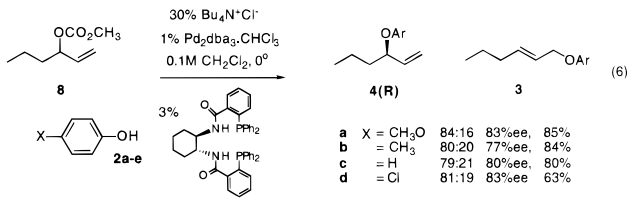


(5)

pair **10** can also undergo $\pi-\sigma-\pi$ isomerization, or it can collapse to give product. As previously discussed, it is the relative rates of these two processes that determine the enantio- and regioselectivity of the allylic alkylation. In the presence of tetraalkylammonium salts, both ion pairs **9** and **10** can undergo a metathesis reaction with the ammonium salt to eventually produce ion pair **11** and the tetraalkylammonium salt of the phenoxide **13**. When X is chloride in **11**, it has already been demonstrated to increase the rate of $\pi-\sigma-\pi$ isomerization. What is the effect of the tetraalkylammonium counterion in **13**?

To study the effect, if any, of the tetraalkylammonium cation, a series of experiments in which the R-group in the tetraalkylammonium salt was varied were conducted (see Table 4). The general trend emerged that enantioselectivity increased as the size of the R-group increased (cf. Table 4, entries 7−9). We have previously observed the same trend for allylic alkylations of malonate in the presence of tetraalkylammonium bromides.[17] We propose that the tetrabutylammonium chloride effect is the result of two complementary effects. The rate of $\pi-\sigma-\pi$ isomerization is increased in the presence of chloride, and the rate of nucleophilic attack is decreased by the formation of the tetrabutylammonium phenoxide **13**. This conclusion is in agreement with our earlier observations that higher alkyl groups slow the rate of nucleophilic attack of malonate compared to that of internal isomerization of palladium.[17]

These experiments further suggest that by approaching Curtin−Hammett conditions, good regio- and enantioselectivity should become independent of the nucleophilicity of the phenol—i.e., of the substituent on the phenol. To exemplify this point, the reactions of several phenols with chiral racemic substrate **8** were performed. As shown in eq 6, both the



(6)

regioselectivity [(81 ± 3):(20 ± 3)] and enantioselectivity (80 ± 3) were reasonably constant, suggesting that equilibration is indeed being seen.

Discussion

The working model for the class of ligands utilized herein is depicted in Figure 3. This model evolved from our initial hypothesis regarding the structural features required for creating chiral space and molecular modeling. Numerous efforts to obtain direct experimental support have failed. For example, attempts to grow crystals have been thwarted by the chemical instability

(16) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. Trost, B. M.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520.

(17) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 70.

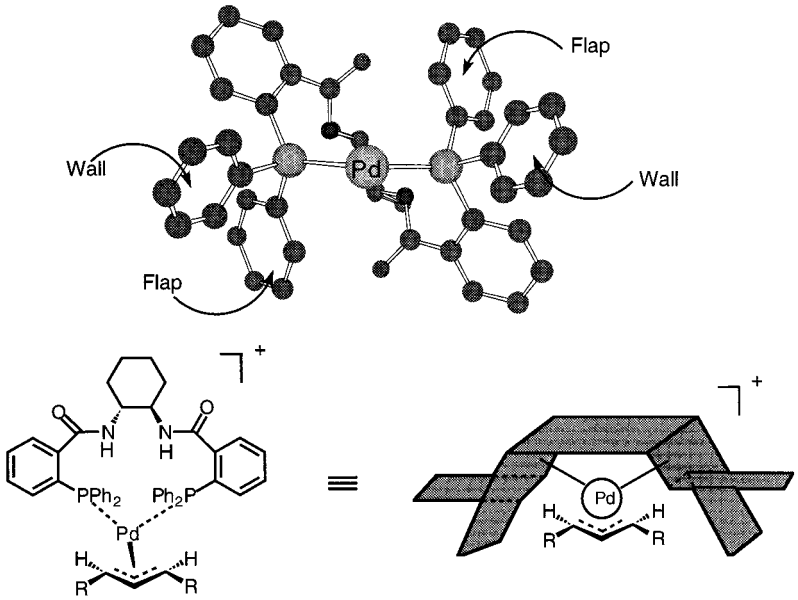


Figure 3. Model of chiral pocket and cartoon representation of complex derived from *R*,*R*-ligand **6**.

of the π-allylpalladium complexes due to the facility of loss of the elements of the alkene and HX to give simple palladium(+2) complexes which are catalytically inactive. In fact, we believe this event is the turnover-limiting event of the catalytic cycle. Studies by NMR spectroscopy have been thwarted by the complexity of the spectra due, in part, to the presence of multiple species which have precluded assignment of specific signals to specific complexes both in these laboratories as well as elsewhere.[18] Thus, understanding the nature of the asymmetric inducing event must currently rely on circumstantial evidence of studies of the type reported herein.

The cartoon model (Figure 3) derives from the ground-state structure of the ligand−palladium-π-allyl complex based on molecular modeling structures. In this model, the walls represent the chiral space created by the propeller-like array of the phenyl rings; the raised flaps represent the phenyls which lie in a plane approximately parallel to the allyl, while the lowered flaps represent phenyls which are somewhat perpendicular to the allyl.

One factor that must be addressed in developing a working model for allylic alkylation is the preferred geometry of the leaving group in the ionization reaction and the preferred trajectory of the nucleophile in the alkylation reaction. Let us consider the transition states for these processes. Based on the Hammond postulate, the structure of the transition state can be inferred from the stable structure on either side of the transition state that lies closest in energy to the transition state. The smaller the energy differences between the transition state and the intermediate, the greater the structural similarities. Since the nucleophilic attack step wherein charge on carbon is neutralized is presumably exothermic, the transition state resembles, to some extent, the π-allyl intermediate.[11] Furthermore, the transition state for ionization also should resemble the π-allyl intermediate, since this process, which creates charge on carbon, is presumably endothermic. Since these processes are, to a first approximation, the microscopic reverse of each other, the factors which influence one will do so to the other. Support for the underlying assumptions derives from the fact that, while carboxylates are good nucleophiles toward π-allylpalladium cationic complexes, any equilibrium lies heavily on the side of the allyl ester and the palladium(0) complex.

(18) We enlisted the aid of Professor A. Togni, but his group was also thwarted.

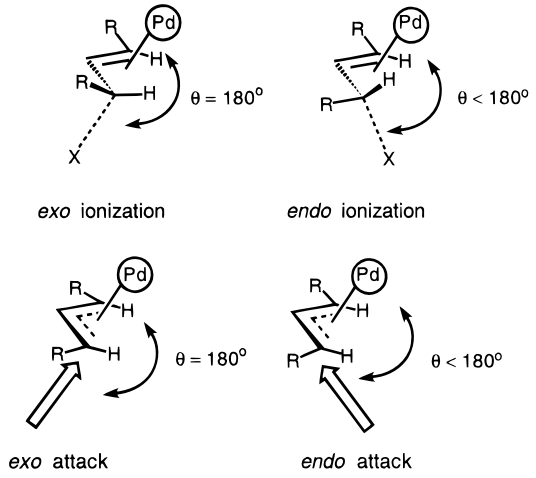


Figure 4. Transition-state trajectories for reactions with achiral catalysts.

It is important to note that the metal does not sit directly above the allyl but is situated toward the anti substituents, and the allyl cants 5−15° moving the anti substituents away from the metal.[19] This allows for better overlap with the metal d_{xy} orbital. In systems bearing *achiral* ligands, there are two possible trajectories as depicted in Figure 4. These two pathways differ in their orientation relative to the π-allyl. In one approach, the nucleophile comes in from the side of the syn substituents of the π-allyl (exo), and in the other approach from the side which bears the anti substituents of the π-allyl (endo).[20] In nucleophilic displacement reactions (S_N2), the preferred trajectory is one that places the leaving group at an angle of 180° to the approaching nucleophile. The same stereoelectronic arguments should therefore be true in the allylic alkylation reaction. If one considers palladium(0) as the nucleophile in the ionization and palladium(+2) the leaving group in the alkylation reaction, then both ionization and nucleophilic attack should occur at an angle

(19) For several X-ray structures, see: *Dictionary of Organometallic Coumpounds*; Macintyre, J. E., Ed.; Chapman and Hall: New York, NY, 1995; Vols 1−5.

(20) The terms exo and endo have been used to describe the orientation of the allyl unit in the pocket of non-C_2 symmetric ligands. For example, see: Helmchen, G.; Kudis, S.; Sennhenn, P.; Steinhagen, H. *Pure Appl. Chem.* **1997**, *68*, 513 and references 11d and e.

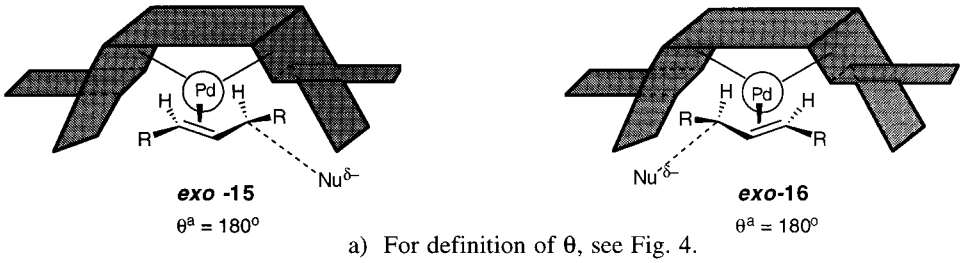
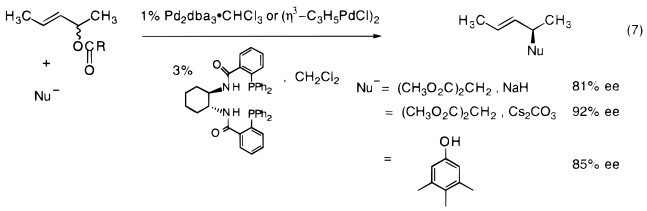


Figure 5. Transition-state trajectories for reactions with chiral catalysts.

that closely approaches 180° relative to palladium in the π-allyl. For these reasons, it is reasonable to propose the preferred trajectory for ionization and nucleophilic attack is via the exo mode.

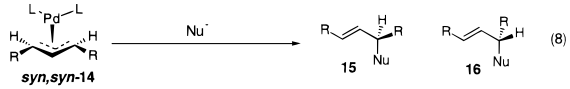
In the case of C_2-symmetric chiral ligands, there exist two transition states which satisfy this requirement as depicted in the cartoon of Figure 5, the front left quadrant proximal to the wall and the front right quadrant proximal to the flap. Attack from either rear quadrant corresponds to an endo mode and therefore can be ignored as stereoelectronically unfavorable. The question that remains is whether one exo ionization/nucleophilic attack is favored over the other?

To gain some insight into this question, the reaction of eq 7,



wherein the nucleophilic attack is the enantioselectivity-determining step, was examined. The model must be consistent with the observed depicted absolute stereochemistry of the product and the observation that the magnitude of the enantioselectivity of the product has some dependence on the structure of the nucleophile. Furthermore, it is important to note that *Z*-olefin product has never been observed. This fact suggests that either the transition state for the formation of *anti*,*syn*-π-allyl complexes is too high in energy or that the *anti*,*syn*-π-allyl is rapidly interconverting with the *syn*,*syn*-complex (by a $\pi-\sigma-\pi$ mechanism) and the relative rate for attack on the *syn*,*syn*-complex is much faster. It may also be possible that the *syn*,*anti*-complex undergoes nucleophilic attack exclusively at the allyl terminus leading to the *E*-alkene product. In any case, the anticipated higher energy for these processes involving the *anti*,*syn*-complex leads us to consider the *syn*,*syn*-intermediate as the one generating product.[21,22]

There are four possible transition states for the nucleophilic attack as depicted in Figure 5 for the desymmetrization step of eq 8. Because of the proposed preferred trajectory of nucleophilic attack, we can ignore the two endo type transition states. The first noticeable difference between the two exo transition



states is that in *exo*-**15** the nucleophile enters under a raised flap, while, in the *exo*-**16** mode, the nucleophile encounters a lowered flap. Therefore, some of the difference in the transition-state energies may come from the steric requirements for approach of the nucleophile.

That is to say, that in the *exo*-**15** transition state, the nucleophile approaches the π-allyl unit with an exo trajectory and through an open quadrant of the chiral space. It is likely that these factors are coupled with the steric interactions between the allyl unit and the cavity of the ligand. In rotating from a square planar η^3-allyl to a tetrahedral η^2-alkene, the R groups rotate away from the "walls" in the *exo*-**15** transition state but toward the "walls" in the *exo*-**16** transition state. Thus, the model "predicts" that the product derived from the *exo*-**15** transition state should be the major enantiomer as observed in the reaction of eq 8.

Extrapolating this picture to the unsymmetrical monosubstituted case of eq 1 leads to the pathway depicted in Figure 6. Considering that ionization is the microscopic reverse of nucleophilic attack, the *exo*-**15** transition state for nucleophilic attack of Figure 5 leads to the formation of diastereomeric complex **17** as the kinetically preferred one in the ionization of Figure 6. Nucleophilic attack on **17** should favor path a over path b for the same reason. On the other hand, the diastereomeric complex **18**, available by simple equilibration via a $\pi-\sigma-\pi$ sequence, should involve nucleophilic attack preferentially by path c. Examination of complexes **17** and **18** suggests that the kinetically preferred complex **17** may be less stable than **18** because the R group of **17** encounters a wall but does not do so in **18**. Molecular modeling calculations indicate that the difference between these two π-allyl complexes, **17** and **18**, is approximately 3.1 kcal/mol.[23] To the extent that the transition-state energy for attack of the nucleophile on **18** is lower than that for attack on **17**, then the overall reaction pathway may be diverted to path c over paths a and b. It is to be noted that this model predicts (1) the kinetic diastereomeric π-allyl complex **17** should favor attack at the primary carbon and (2) to the extent attack occurs on the kinetic complex at the secondary carbon, the enantiomer formed is the mirror image of that obtained by attack on the thermodynamically more stable and kinetically more reactive complex **18**. All of the results support this model. In toluene, the reaction favors primary (path a) over secondary (path b or c) attack and, to the extent the latter occurs, product formation favors enantiomer **19** (path b) over **20** (path c). Increasing polarity of the solvent stabilizes the charged intermediates and thereby should slow charge neutralization that occurs upon nucleophilic attack. By increasing the lifetime of the π-allyl intermediate, Curtin−Hammett conditions begin to

(21) In other systems,[11,20] NMR experiments have been used to determine which complex, syn,syn or syn,anti, is kinetically formed. However, all attempts to utilize this approach with our ligand have proven to be unsuccessful.

(22) In work published after submission of this manuscript, the possibility that the product derives from regioselective attack on a syn,anti complex has been discussed, see: Ramdeehul, S.; Dierkes, P.; Aquado, R.; Kamer, P. C.; van Leewen, P. W. N. M.; Osborn, J. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3118. This paper concludes, as we have for our ligands, that the steric interactions associated with the synchronous events of nucleophilic attack and rotation due to the change of hapticity are responsible for the chiral recognition.

(23) Hagelin, H., unpublished results in these laboratories.

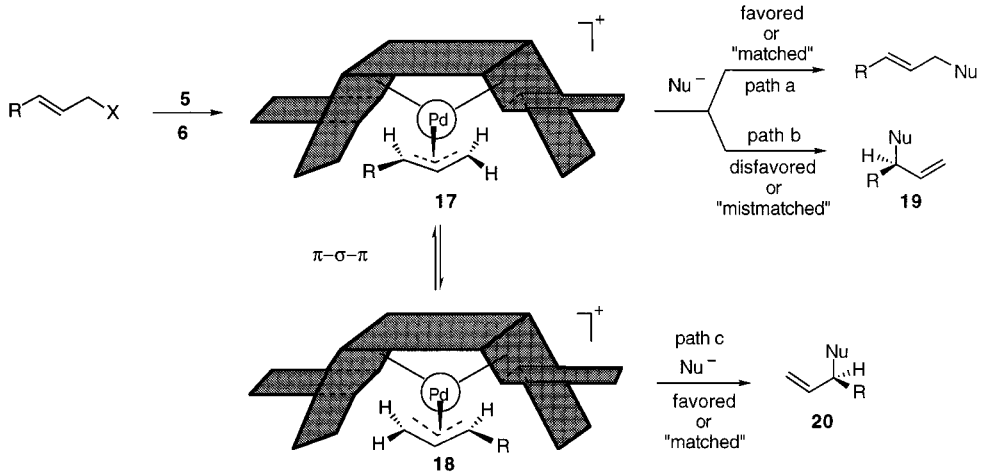


Figure 6. Predicted path for asymmetric alkylation of chiral precursor for reaction using *R,R*-ligand **6**.

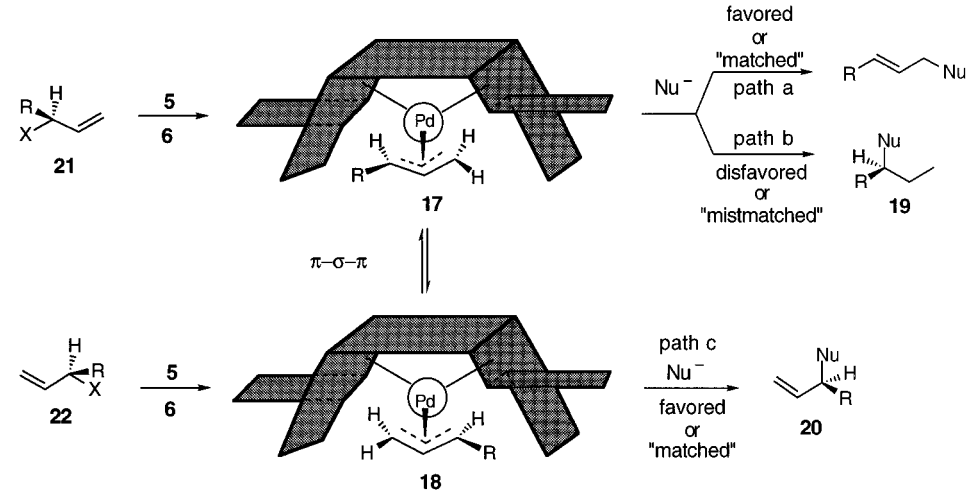


Figure 7. Predicted path for asymmetric alkylation of chiral racemic precursor for reaction using *R,R*-ligand **6**.

be approached, and path c begins to dominate. The observed linear dependencies of regioselectivity and enantioselectivity onsolvent polarity are in complete accord with these predictions. While the role of solvent may extend beyond influencing the rate of nucleophilic attack, such as affecting the rate of $\pi-\sigma-\pi$ epimerization,[24,26] insufficient data exists to discuss any such effects.

The model also makes an interesting prediction regarding the effect of the dependence of selectivities on the regioisomeric starting materials. Figure 7 depicts the pathways from the chiral racemic precursor. Again, following the precedent derived from Figure 5, enantiomer **21** should ionize to form diastereomer **17** which, as already indicated, is predisposed to react via path a (also see Figure 6) to give the achiral product. To the extent it reacts via the disfavored or mismatched path b, it will form **19**, the product of net retention. To form the chiral product via a favored or matched pathway, the kinetic diastereomer must isomerize to diastereomer **18**, which will then react via path c to give **20**. On the other hand, enantiomer **22** should ionize kinetically to form diastereomer π-allyl complex **18** directly. Thus, 50% of the starting material requires no equilibration from a less stable to a more stable and reactive diastereomer to form enantiomer **20** and only 50% of the starting material requires equilibration to follow the same path. This fact leads to the prediction that intrinsically higher regio- and enantioselectivity should be observed, starting from the racemic chiral substrate than the achiral one. Of course, if true Curtin−Hammett conditions are achieved, then it makes no difference. However, because of the inability to reach this ideal situation, the prediction should be valid. Experimentally, the prediction is verified as demonstrated by the data in Tables 1 and 3. Under our best conditions, the achiral substrate **2** with *p*-methoxyphenol at 0.1 M, in the presence of 30 mol % tetra-*n*-butylammonium chloride, gave an 80:20 ratio of **4:3** wherein **R-4** of 62% ee was the major enantiomer. Under the same conditions starting with the chiral substrate **8**, an 84:16 ratio of **4:3** (86% ee for **R-4**) was obtained. Thus, it is clear that true Curtin−Hammett conditions have been approached but not yet reached even under our best conditions. Nevertheless, the results are synthetically useful as shown by eq 6.

Conclusion

The importance of the metal catalyzed allylic alkylation has stimulated a great deal of effort to exercise control, especially regio- and enantiocontrol, in a rational way. Achieving this goal requires a detailed understanding of the factors that influence

(24) (a) Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642. (b) Faller, J. W.; Tully, M. T. *J. Am. Chem. Soc.* **1972**, *94*, 2676.

(25) (a) Sjogren, M.; Hansson, S.; Norrby, P.-O.; Åkermark, B.; Cucciolito, M. E.; Vitagliano, A. *Organometallics* **1992**, *11*, 3954. (b) Åkermark, B.; Vitagilano, A. *Organometallics* **1985**, *4*, 1275.

(26) Andersson, P. G.; Harden, A.; Tanner, D.; Norrby, P.-O. *Chem.—Eur. J.* **1995**, *1*, 12.

both regio- and enantioselectivity.[27] Regioselectivity is influenced by normally opposing steric and electronic effects.[28] Steric effects lead to attack at the less substituted terminus, whereas electronic effects lead to attack at the less electron-rich terminus which is normally the more substituted terminus. The current studies reveal a new strategy to influence regioselectivity—chiral ligands. Such ligands can exercise regiocontrol in addition to enantiocontrol in ways not possible with achiral ligands. One factor involves the effect of the chiral ligand on the preferred trajectory of approach of the nucleophile on the π-allyl intermediate by imposing a strong stereoelectronic requirement for a linear S_N2 transition state on the other regiochemistry-determining factors. A second factor influencing regioselectivity when chiral ligands are used, that does not exist with achiral ligands, is the existence of diastereomeric π-allyl complexes and their relative stability and reactivity. The intrinsic difference in reactivity of these diastereomeric complexes will also affect the regioselectivity of the process. Considering all of these factors also leads to the initially surprising conclusion that, in some cases, for maximum regio- and enantioselectivity, the chiral substrate may be preferred over the achiral one (provided that there exists a bias for forming a *syn*- vs *anti*-π-allyl complex).

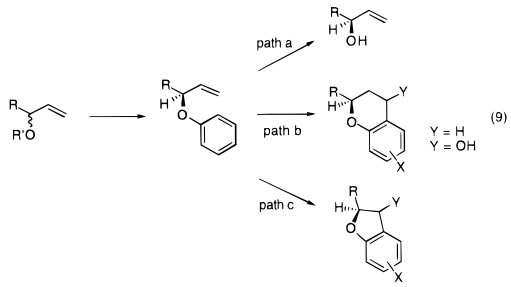
The source of the enantiocontrol by the chiral ligands remains a topic of much debate.[1,22] For our ligands, we envision the motions associated with the change in hapticity combined with the sum total of the resultant steric interactions to account for their generality and high selectivity in both ionization and nucleophilic addition steps. The current results provide support for this concept. This notion is gaining more prominence[22] and should be more carefully evaluated for related reactions.

For maximum regio- and enantioselectivity, Curtin—Hammett conditions must prevail. However, the employment of chloride ion as a promoter for facial interconversion of the palladium may be compromised because it may serve as a general base catalyst. In this role, it would speed up the rate of nucleophilic attack by the phenol and thereby counter its action in increasing the rate of facial interconversion of the palladium π-allyl intermediate. A promoter that would not function as a general base catalyst would be ideal.

The choice of nucleophile will undoubtedly also play a major role. For this study, we focused on oxygen to diminish steric demands of the nucleophile influencing the regioselectivity. As the nucleophile becomes bulkier, a point will undoubtedly be reached where its steric requirements outweigh the restrictions imposed by the ligand.

For a given nucleophile, choice of substrate, solvent, concentration, and promoter (chloride ion) can affect these relative rates to the point of making the reaction useful. To illustrate, for the synthesis of 3-(4′-methoxyphenoxy)-1-hexene, the initial reaction employing "standard" conditions based on earlier work[16] produced a 42:58 ratio of achiral (**3**) to chiral product (**4**), the latter in 12% ee. This reaction evolved into a new set of conditions that produced a 16:84 ratio where the latter had an ee of 83%. In fact, by rational modification of reaction conditions, the ee varied from 66% favoring **4**(**S**) to 83% favoring **4**(**R**) with the same chiral ligand! Thus, the model as outlined herein provides a useful working framework to understand and enhance the utility of asymmetric allylic alkylations with the chiral ligands developed in these laboratories.[29] The applicability of the concepts outlined herein to other enantioselective palladium catalyzed reactions that have been reported to have biases for attack at the more substituted terminus will be interesting to explore to see if the selectivity can be further enhanced.[6] The model may find general applications in other asymmetric reactions which rely on similar chiral environments.

The ease of cleavage of *p*-methoxyphenyl ethers to the corresponding alcohols makes this reaction a deracemization of allyl alcohols (eq 9, path a).[30] By hydroboration—oxidation



or related hydration methods followed by cyclization, chromanes, chromanols, and ultimately chromanones are available in nonracemic form (eq 9, path b).[31] Oxidative cleavage—cyclization should also provide access to the dihydrobenzofurans of high enantiopurity (eq 9, path c).

Experimental Section

All reactions that involved palladium complexes were carried out under an argon atmosphere in a degassed flask. All solvents were freshly distilled from the appropriate drying agent and were further degassed by bubbling a stream of argon through them for 15 min before use. The phenols were purchased from Aldrich and recrystallized prior to use. Allyl carbonate **2** and **8** were prepared as previously described.[7b]

General Procedure for O-Allylation. A degassed flask containing 4-methoxyphenol **1a** (25 mg, 0.20 mmol), allyl carbonate **8** (32 mg, 0.20), $Pd_2dba_3{\cdot}CHCl_3$ (2 mg, 1.9 μmol), the chiral ligand (4 mg, 5.8 μmol), and tetrabutylammonium chloride (17 mg, 0.06 mmol) is charged with CH_2Cl_2 (2 mL). The purple reaction mixture is stirred at 0° for 8 h. The resulting yellow reaction mixture is directly applied to a silica gel column. Flash chromatography eluting with 6:1 ether:petroleum ether affords an 84:16 mixture of aryl ethers **4:3** (34 mg, 85% yield, 83% ee). Compounds were characterized as 4—5:1 mixtures of **4**:**3**.

3-(4-Methoxyphenoxy)-1-hexene (4a):[7b] IR(film) 2980, 2933, 1507. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 6.88 (m, 4H), 5.86 (ddd, J = 17.3, 10.5, 6.5 Hz, 1H), 5.25 (dt, J = 17.3, 1.1 Hz, 1H), 5.20 (dt, J = 10.5, 1.1 Hz, 1H), 4.45 (dt, J = 6.5, 5.6 Hz, 1H), 3.78 (s, 3H), 1.30—1.80 (m, 4H), 0.98 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 153.7, 152.4, 138.5, 116.2, 115.6, 114.4, 79.8, 55.6, 37.7, 18.5, 13.9. Anal. Calcd for $C_{13}H_{18}O_2$ C,75.69; H, 8.80. Found C, 75.72; H, 8.59. Enantiomers were separated by HPLC using the Chiralcel OD column eluting with 99.9:0.1 heptane:2-propanol (1 mL/min). The retention times were major (**R**) 9.31 min, minor (**S**) 10.44 min, and regioisomer 18.02 min.

3-(4-Methylphenoxy)-1-hexene (4b):[7b] IR(film) 2960, 2931, 1509. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.08 (dd, J = 9.3, 0.5 Hz, 2H), 6.84 (dd, J = 9.3, 0.5 Hz, 2H) 5.87 (ddd, J = 17.3, 10.3, 6.1 Hz, 1H), 5.27 (dt, J = 17.3, 1.1 Hz, 1H), 5.21 (dt, J = 10.3, 1.1 Hz, 1H), 4.57 (dt, J = 6.5, 5.6 Hz, 1H), 2.31 (s, 3H), 1.30—1.80 (m, 4H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 156.2, 138.3, 129.7, 115.9, 114.5, 78.9, 37.7, 20.4, 18.5, 13.9. Enantiomers were separated by HPLC using the Chiralcel OD column eluting with 99.9:0.1 heptane:

(27) Compare Pergosin, P. S.; Salzman, R. *Coord. Chem. Rev.* **1996**, *155*, 35.

(28) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1984**, *106*, 6837.

(29) The results obtained herein provide impetus to reexamine the conclusions for the intermolecular reactions reported in ref 6e and will be reported in due course.

(30) Georg, G. I.; Mashava, P. M.; Akgun, E.; Milstead, M. W. *Tetrahedron Lett.* **1991**, *32*, 3151.

(31) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074.

2-propanol (0.9 mL/min). The retention times were major (**R**) 5.51 min, minor (**S**) 6.24 min, and regioisomer 11.71 min.

3-Phenoxy-1-hexene (4c):[7b] IR(film) 2960, 2933, 1494. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.27 (m, 2H), 6.95 (m, 3H), 5.88 (ddd, J = 17.4, 10.6, 6.1 Hz, 1H), 5.29 (dt, J = 17.4, 1.3 Hz, 1H), 5.22 (dt, J = 10.6, 1.3 Hz, 1H), 4.64 (q, J = 6.1, 1H), 1.30−1.80 (m, 4H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 158.4, 138.2, 129.2, 116.0, 114.7, 78.6, 37.7, 18.5, 13.9. Enantiomers were separated by HPLC using the Chiralcel OD column eluting with 99.9:0.1 heptane:2-propanol (1 mL/min). The retention times were major (**R**) 5.77 min, minor (**S**) 7.03 min, and regioisomer 19.67 min.

3-(4′-Chlorophenoxy)-1-hexene (4e):[7b] IR(film) 2960, 2932, 1490. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.22 (d, J = 9.0, Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H) 5.84 (ddd, J = 17.4, 10.4, 6.2 Hz, 1H), 5.27 (dt, J = 17.4, 1.1 Hz, 1H), 5.22 (dt, J = 10.4, 1.1 Hz, 1H), 4.57 (q, J = 6.2, 1H), 1.40−1.82 (m, 4H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 166.9, 162.3, 137.4, 131.4, 124.2, 116.7, 115.3, 78.7, 51.8, 37.6, 18.5, 13.9. Enantiomers were separated by HPLC using the Chiralcel OD column eluting with 99.9:0.1 heptane:2-propanol (0.8 mL/min). The retention times were major (**R**) 5.30 min, minor (**S**) 5.97 min, and regioisomer 7.26 min.

3-(4-(Methoxycarbonyl)phenoxy)-1-hexene (4e): IR(film) 2960, 2930, 1790, 1470. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.97 (d, J = 8.8, Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H) 5.84 (ddd, J = 17.4, 10.4, 6.4 Hz, 1H), 5.28 (dt, J = 17.4, 1.1 Hz, 1H), 5.23 (dt, J = 10.4, 1.1 Hz, 1H), 4.71 (q, J = 6.4, 1H), 3.90 (s, 3H), 1.40−1.82 (m, 4H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 157.0, 137.8, 129.1, 125.5, 117.3, 116.5, 79.2, 37.6, 18.5, 13.9. Enantiomers were separated by HPLC using the Chiralpak AD column eluting with 99:1 heptane:2-propanol (1 mL/min). The retention times were minor (**S**) 6.47 min, major (**R**) 7.27 min, and regioisomer 8.29 min.

^{1}H NMR Experiments. A degassed screw-capped NMR tube containing 4-methoxyphenol (12 mg, 0.096 mmol), Pd_2dba_3·$CHCl_3$ (0.2 mg, 0.19 μmol), and the chiral ligand (0.4 mg, 0.58 μmol) is charged with degassed CD_2Cl_2 (1 mL). A background ^{1}H NMR (500 MHz) is measured, and then allyl carbonate **2** (15 μL, 0.095 mmol) is added. Single scan spectra are acquired at 30-s intervals by arraying the preacquisition delay (pad). The conversion at each interval is determined by integrating the signal at 4.59 for the starting allyl carbonate.

3-(4-Methoxyphenoxy)-1-hexane (7a). By the Mitsunobu Reaction. To a solution of 4-methoxyphenol (307 mg, 2.45 mmol), (*R*)-3-hexanol[9] (210 mg, 2.06 mmol) and triphenylphosphine (640 mg, 1.45 mmol) in THF (20 mL) at 0° is slowly added diethyl azodicarboxylate (385 μL, 2.45 mmol), and the resulting orange-tinged solution stirred at room temperature for 6 h. The solution is diluted with ether (25 mL), washed with 2 N NaOH (2 × 20 mL) and water (25 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting solid is suspended in hexanes, filtered, and concentrated in vacuo. Flash chromatography eluting with ether affords the aryl ether (120 mg, 28%) as a colorless liquid. IR(film) 2960, 2935, 1506. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 6.85 (m, 4H), 4.07 (quint, J = 5.7 Hz, 1H), 3.79 (s, 3H), 1.35−1.70 (m, 6H), 0.98 (t, J = 7.5 Hz, 3H) 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 153.7, 152.8, 117.4, 114.6, 80.0, 55.7, 35.7, 26.5, 18.7, 14.2, 9.5. Enantiomers were separated by HPLC using the Chiralcel OD column eluting with 99.9:0.1 heptane:2-propanol (1 mL/min.). The retention times were major (**S**) 9.47 min (68.6%) and minor (**R**) 11.5 min (31.4%).

By Hydrogenation of 4a(R). A suspension of 10% Pd/C (10 mg) and **4a**(**R**) (100 mg, 0.425 mmol) in ethyl acetate (1 mL) is stirred under 1 atm of hydrogen at room temperature for 10 h. The resulting reaction mixture is filtered through a plug of Celite to afford the unsaturated aryl ether (97 mg, 97%). Enantiomers were separated by HPLC using the Chiralcel OD column eluting with 99.9:0.1 heptane:2-propanol (1 mL/min). The retention times were major (**S**) 10.06 min (86.5%) and minor (**R**) 11.73 min (13.5%).

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Supporting Information Available: Experimental details for Tables 1−4 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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