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Combined Experimental and Theoretical Study of the Mechanism and Enantioselectivity of Palladium-Catalyzed Intermolecular Heck Coupling

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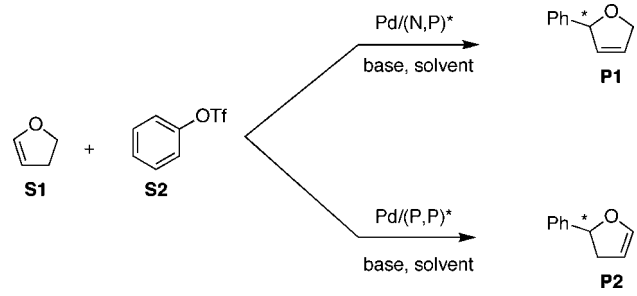
Abstract: The asymmetric Heck reaction using P,N-ligands has been studied by a combination of theoretical and experimental methods. The reaction follows Halpern-style selectivity; that is, the major isomer is produced from the least favored form of the pre-insertion intermediate. The initially formed Ph-Pd(P,N) species prefers a geometry with the phenyl *trans* to N. However, the alternative form, with Ph *trans* to P, is much less stable but much more reactive. In the preferred transition state, the phenyl moiety is *trans* to P, but significant electron density has been transferred to the alkene carbon *trans* to N. The steric interactions in this transition state fully account for the enantioselectivity observed with the ligands studied. The calculations also predict relative reactivity and nonlinear mixing effects for the investigated ligands; these predictions are fully validated by experimental testing. Finally, the low conversion observed with some catalysts was found to be caused by inactivation due to weak binding of the ligand to Pd(0). Adding monodentate PPh_3 alleviated the precipitation problem without deteriorating the enantioselectivity and led to one of the most effective catalytic systems to date.

Introduction

The Heck reaction was discovered[1] more than 25 years ago and still stands out as one of the most versatile methods for creating new carbon−carbon bonds. Its applicability to highly functionalized substrates confers upon the reaction a very wide substrate scope, and it has been used in a number of syntheses of complex natural products.[2] More recent development of the Heck reaction has focused on the possibility of controlling its enantioselectivity. A number of reports[3] have addressed the application of chiral bidentate phosphine ligands such as BINAP and chiral N,P-donor ligands to the asymmetric Heck coupling of alkyl and aryl triflates with various olefins in both intra- and intermolecular fashion. Since the first report by Hayashi et al.,[4] the Heck coupling of 2,3-dihydrofuran (**S1**) and phenyl triflate (**S2**) has been frequently used as a standard reaction to study the asymmetric intermolecular Heck reaction (Scheme 1). In this system, N,P-donor ligands yield 2-phenyl-2,5-dihydrofuran (**P1**) as the major product, whereas bidentate phosphine ligands mostly give the rearranged species 2-phenyl-2,3-dihydrofuran (**P2**).

Scheme 1. Heck Reaction of 2,3-Dihydrofuran and Phenyl Triflate



We recently reported[5] the enantioselective Heck reaction catalyzed by Pd complexes of a new class of chiral thiazole phosphine ligands that we originally developed for the iridium-catalyzed hydrogenation of non-functionalized olefins.[6] These ligands induced a high degree of enantioselectivity in the Heck

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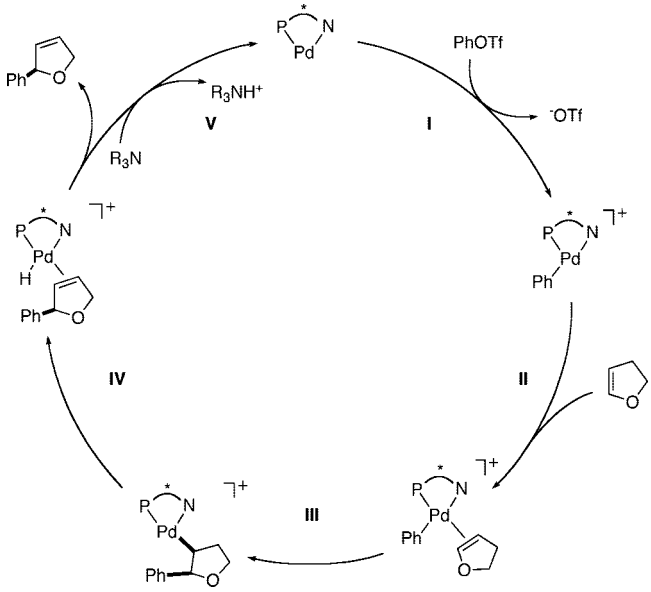
10.1021/ja802991y CCC: $40.75

Scheme 2. Mechanism of Intermolecular Heck Reaction between 2,3-Dihydrofuran and Phenyl Triflate



coupling between alkyl and aryl triflates and 2,3-dihydrofuran under microwave (MW) heating.

Although admirable results have been obtained in the well-studied palladium-catalyzed Heck coupling, most studies of its mechanism have focused on achiral systems. The generally accepted mechanism of the Heck reaction with 2,3-dihydrofuran and phenyl triflate has been given in a number of publications and is shown in Scheme 2.[7] The catalytic cycle starts with the oxidative addition of phenyl triflate to the Pd(0)−(N,P*) complex formed *in situ* to give a Pd(II) complex (step I, Scheme 2). Two types of Pd(II) complexes can be formed because the phenyl group can be positioned *trans* to either the phosphorus or the nitrogen in the N,P-ligand. The coordination of 2,3-dihydrofuran to the Pd(II) complex may occur from two different faces, resulting in four possible isomeric Pd(II)−π-alkene complexes (step II). Subsequent alkene insertion into the Pd−Ph bond (step III) gives an alkyl−Pd(II) complex that undergoes β-hydride elimination to form a hydridopalladium olefin complex (step IV); the alkene dissociates from these species to give the chiral product. The active Pd(0) complex is finally regenerated by reductive deprotonation with the aid of base (step V).[8]

Considering the large number of reports that have dealt with the development of the asymmetric Heck reaction, there are comparatively few reports that discuss the factors governing the enantiodetermining step of the reaction. So far, all attempts to rationalize the enantioselectivity have been based on ligand structure−enantioselectivity relationships. In one of the few reports that aimed to understand the origin of the reaction's enantioselectivity, Uemura et al. isolated the chiral (N,P)−Pd(II) intermediate formed after oxidative addition of *p*-carbomethoxyphenyl triflate and, using NMR spectroscopy, showed that the aryl moiety is *trans* to the nitrogen.[7b] On the basis of this finding, they proposed a selectivity model for the reaction. In another paper, Guiry et al. evaluated sterically hindered 2-dialkyl-3-hydrofurans,[9] which led to a better understanding of the steric repulsions in the reaction. However, neither of these studies offered a complete understanding of the transition state in the enantiodetermining step.

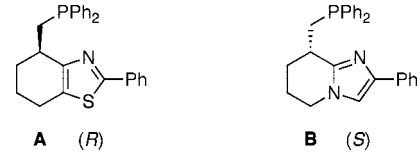


Figure 1. Thiazole (**A**) and imidazole (**B**) ligands used in this study.

We now give a full account of the mechanism and a rationalization of the enantioselectivity for the asymmetric Heck coupling using palladium catalysts with chelating N,P-ligands. We have performed a hybrid density functional study (B3LYP) that covers a large range of possible intermediates and transition states in the reaction. We have also carried out an experimental study to gain support for the conclusions drawn from the theoretical calculations.

Results and Discussion

The asymmetric Heck reaction between 2,3-dihydrofuran (**S1**) and phenyl triflate (**S2**) has become the standard test system and was therefore chosen as the model reaction for our study of mechanism and enantioselectivity (Scheme 1). In our earlier report, a catalyst containing the thiazole-based N,P-donor ligand **A** was found to be excellent in the Heck coupling of **S1** and **S2**, so this ligand was chosen for the study (Figure 1). As a comparison, we also wanted the study to include a ligand having a similar structure but different electronic properties. Previously, we reported the use of chiral imidazole phosphine ligands in the Ir-catalyzed asymmetric hydrogenation of olefins.[10] These ligands are based on the same design as **A** and give similar results in the hydrogenation of unfunctionalized olefins, which confirms the structural similarity of the two ligand types. We reasoned that the imidazole phosphine **B** could also be employed in the asymmetric Heck reaction of **S1** and **S2**. Initial studies of the Heck reaction with the imidazole ligand **B** resulted in high enantioselectivity (93% enantiomeric excess (ee)), but the reaction was much slower than with the thiazole ligand **A**. Because **A** and **B** are pseudoenantiomers,[11] Heck reactions using them as ligands demonstrated enantiodescrimination in opposite directions.

Computational Study. Initially, we evaluated the relevant parts of the catalytic cycle using thiazole ligand **A**. The free energy profile is shown in Figure 2. We have concentrated on steps in which bonds to the hydrofuran moiety are either formed or broken (colored in Figure 2). These include the migratory insertion and the β-hydride elimination. For completeness, we have also included intermediates (but not transition states) in

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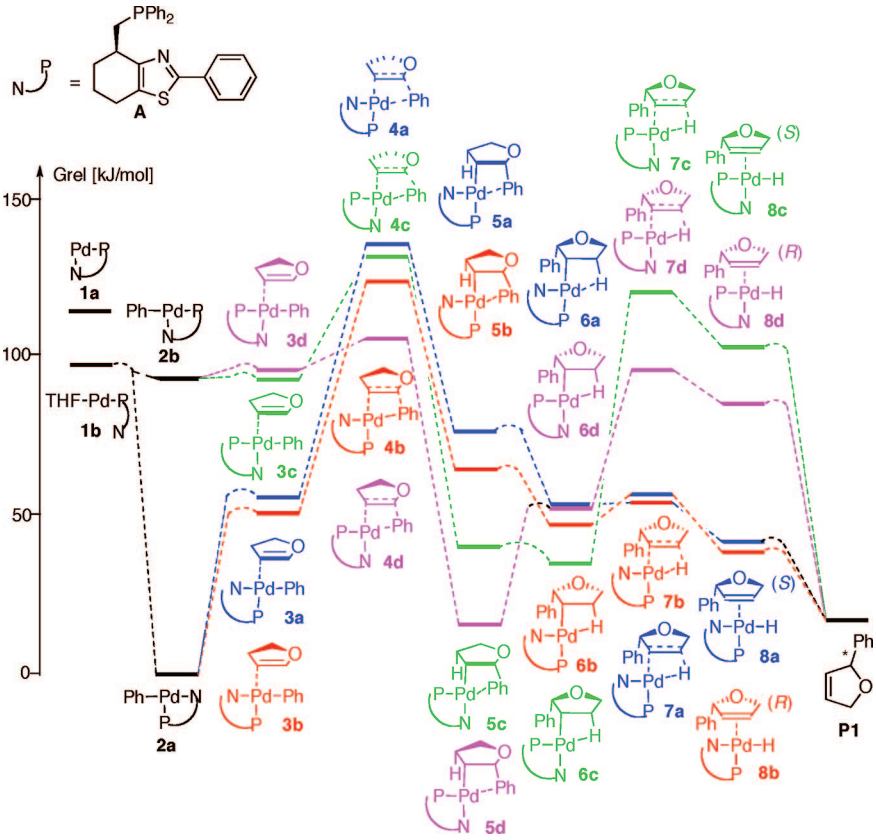

Figure 2. Free energy profile for the asymmetric Heck reaction between 2,3-dihydrofuran and phenyl triflate with the thiazole ligand **A**. Palladium complexes **2**−**8** are cationic.

the remainder of the catalytic cycle (black in Figure 2). The normalized Gibbs free energy values for all calculated intermediates and transition states are shown in Table 1. All the steps are explained and discussed in detail below.

Step I. Oxidative Addition of Phenyl Triflate. In the initial Pd(0) complex **1**, it is beneficial to have an explicit solvent (THF) molecule coordinated to Pd, even though this means breaking the Pd−N bond to leave the ligand coordinating in a monodentate fashion, as **1b** is favored over **1a** by 17 kJ/mol (Table 1). We have previously investigated the oxidative addition in detail,[12] and, as it is not expected to influence the enantioselectivity of the reaction, the transition state (TS) for this step has not been modeled here. There is a huge energy difference of 93 kJ/mol (Table 1) between the two possible oxidative addition products **2a** and **2b**, which have the phenyl group *cis* and *trans* to phosphorus, respectively. This energy difference can be ascribed to the large trans influences of both the phosphine and phenyl ligands, which makes these ligands prefer to be *cis* to each other.

The large trans influence of the phenyl group (Ph) is also obvious from the elongation of the Pd−P and Pd−N bonds when they are positioned *trans* to Ph (Table 2). Though the Pd−C bond is more or less the same length in complexes **2a** and **2b**, the Pd−P bond length is increased by 0.17 Å when going from **2a** to **2b**, whereas the Pd−N bond length is increased by 0.10 Å when going from **2b** to **2a**. Even though both the Pd−N and Pd−P bonds lengthen when positioned *trans* to the phenyl group, the Pd−P bond is elongated to a larger extent, indicating a higher degree of destabilization in this case. This is in accordance with the Pd−P bond having a larger trans influence than the Pd−N bond.

Step II. 2,3-Dihydrofuran Coordination. The next step is the formation of a π complex between Pd and the alkene. Because 2,3-dihydrofuran (DHF) is not a regular alkene, but an enol ether, it coordinates to Pd almost exclusively through C4, due to the excess of electron density on this atom. The phosphine and phenyl moieties still prefer to be *cis* to each other; however, the energy difference between *cis*/*trans* isomers of complex **3** is smaller than for **2**, because the π-coordinated alkene also exerts a trans influence. Again, this is reflected in the relevant bond lengths (Table 2). Complexes **3a** and **3b**, which have Ph and N positioned *trans* to each other, show an elongation of the Pd−N bonds due to the trans influence of Ph, as well as an elongation of the coordination between Pd and the alkene caused by the trans influence of P. The complexes **3c** and **3d**, with Ph and P *trans* to each other, have only one elongated bond, the Pd−P bond. Thus, in the case of complex **3**, we have either two weakly destabilized bonds or one significantly destabilized bond. The energies (Table 1) tell us that the first situation is favored by around 40 kJ/mol.

Step III. Migratory Insertion. In the next step, the Ph group is transferred from Pd to the alkene, with concomitant breaking of the alkene π bond and formation of two new σ bonds. This means that, from a complex having a strongly destabilizing C−Pd bond *trans* to P, **3c** and **3d**, we now get a complex with an almost empty site *trans* to P (no full bond between the phenyl group and Pd is present), which is very energetically favorable. Therefore, the π complex of highest energy (**3d**) is converted into the most stable σ complex (**5d**). The stabilizing effect of

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Table 1. Gibbs Free Energies in Solution for the Compounds Shown in Figure 2

complex	G_{sol}[a] (kJ/mol)	ΔG_{sol}[b] (kJ/mol)
1a	114	17
1b	97	0
2a	0	0
2b	93	93
3a	56	5
3b	51	0
3c	93	42
3d	95	44
4a	135	30
4b	123	18
4c	132	27
4d	105	0
5a	79	63
5b	60	44
5c	40	25
5d	16	0
6a	53	31
6b	46	14
6c	32	0
6d	51	19
7a	55	0
7b	56	1
7c	120	65
7d	96	41
8a	41	1
8b	40	0
8c	103	63
8d	85	45
P1	18	

[a] Gibbs free energies relative to the complex of lowest energy, **2a**. [b] Gibbs free energy for each complex relative to the most stable complex of that type (same numbers, **a**−**d**).

Table 2. Bond Lengths (Å) between Pd and Its Four Coordinating Atoms for **2a,b** and **3a**−**d**

complex	Pd−P	Pd−N	Pd−C(Ph)	Pd−C(DHF)
2a	2.27	2.20	2.00	
2b	2.44	2.10	1.98	
3a	2.33	2.32	2.02	2.42
3b	2.35	2.28	2.03	2.41
3c	2.49	2.22	2.03	2.27
3d	2.45	2.23	2.07	2.23

removing the phenyl group from the position *trans* to P can already be identified in the insertion TS, which means that the π complex of highest energy has the lowest TS. This is an example of a Halpern-type selectivity, in which the least favored intermediate leads to the most favored product, as first demonstrated for the Rh-catalyzed hydrogenation of enamides.[13]

Step IV. β-Hydride Elimination. It is clear from the reaction paths in Figure 2 that, once the reaction has reached the σ complex **5**, with coordination between the phenyl group and Pd, it can never revert, as all possible forward processes have lower activation barriers than the reverse reactions. The forward reactions will proceed by a 120° rotation about the Pd−C σ bond, forming the agostic intermediates **6**. From here, β-hydride elimination via TS **7** leads to hydride complexes **8**. We have not investigated the various possibilities for further reaction of **8**, because experimental results show that it is deprotonated by the external base before any potential isomerizations. This gives the 2-phenyl-3,4-dihydrofuran product (**P1**) and re-forms the Pd(0)−ligand complex needed to close the catalytic cycle.

The same trans influence considerations apply to the β-hydride elimination step (IV) as for the carbopalladation step (III), except that here the situation is reversed. The transformation starts out with a very stable σ complex with an almost empty site *trans* to P (only a weak agostic interaction is present). Transferring the hydride to this empty site gives a product complex (**7d**) that is high in energy due to the *trans* relationship of the Pd−H and the Pd−P bonds, which both exert strong trans influences. Again, this uphill transformation is already reflected in the β-hydride elimination TS (**7**), which is of highest energy for the two reaction paths (**7c** and **7d**) in which H ends up *trans* to P.

Enantiodetermining Step: Migratory Insertion (Step III). It appears from the reaction profile that, in all cases, the insertion TS (**4**) is higher in energy than the β-hydride elimination TS (**7**). The insertion step is therefore expected to be irreversible, which means that only this step, in which the stereochemistry is set, will influence the enantioselectivity of the reaction. Because the subsequent steps have lower energy barriers, the reaction will follow the path that goes through the insertion TS of lowest energy, and the enantioselectivity of the reaction is therefore governed by the relative energies of the four possible insertion TSs. In this case, series **d** (purple graph in Figure 2) describes the reaction path with the insertion TS of lowest energy. This reaction path leads to the formation of the *R* product, which is indeed observed experimentally. Furthermore, the high enantioselectivity of the reaction (88% ee) is reflected in the large energy difference of 27 kJ/mol (Table 1) between TS **4d** and the lowest energy TS for the *S* product, **4c**.

We have discussed the electronic effects that are the basis for the energy difference between the *cis*/*trans* isomeric complexes. However, electronic effects cannot account for the fact that the insertion TS giving the *R* enantiomer is preferred over the TS giving the *S* enantiomer, because the considerations concerning the trans effect are just as valid for both competing reaction paths (series **c** and **d**, Figure 2). Whereas electronic effects account for the relative energy of the different *cis*/*trans* isomers, the relative energy of the diastereomers is determined by steric effects. Figure 3 shows the diastereomeric pair of insertion TSs that have P *trans* to the phenyl group (**4c** and **4d**), both as ball-and-stick and as space-filling models. In both **4c** and **4d**, the phenyl group on the thiazole ring is twisted out of conjugation due to steric strain in the molecule. However, there is significantly less steric strain in TS **4d**, which leads to the *R* product, than in TS **4c**, which gives the *S* product. This is most evident in the space-filling TS models, which show several unfavorable van der Waals interactions between the two interacting phenyl groups in TS **4c**, and none in TS **4d**. These steric effects are expected to account for the energy difference of 27 kJ/mol (Table 1) between the two TSs. The steric crowding connected with the formation of a *S* stereocenter and the unfavorable electronic features of having *trans* P and C moieties make TS **4a** the most energetically disfavored of all the insertion TSs (Figure 2, Table 1).

Comparison with Imidazole Ligand B. In studying the effect of imidazole ligand **B** on the Heck reaction, we evaluated only the selectivity-determining insertion TS and the intermediates preceding it on the reaction path. The free energy profile for these steps is shown in Figure 4, and the corresponding Gibbs free energies are presented in Table 3. The overall reaction paths with the two ligands **A** and **B** are very similar. A minor difference, however, is that the coordination of an explicit solvent molecule to the Pd(0) complex and consequent monodentate coordination of the ligand are not energetically favorable for the imidazole ligand (**9**, Figure 4), in contrast to the thiazole

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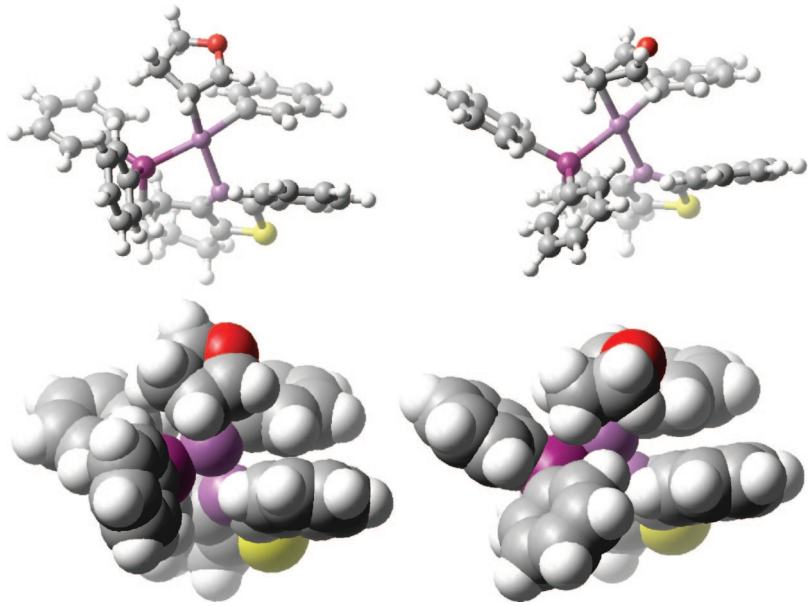


Figure 3. Transition states **4c** (left) and **4d** (right) (migratory insertion).

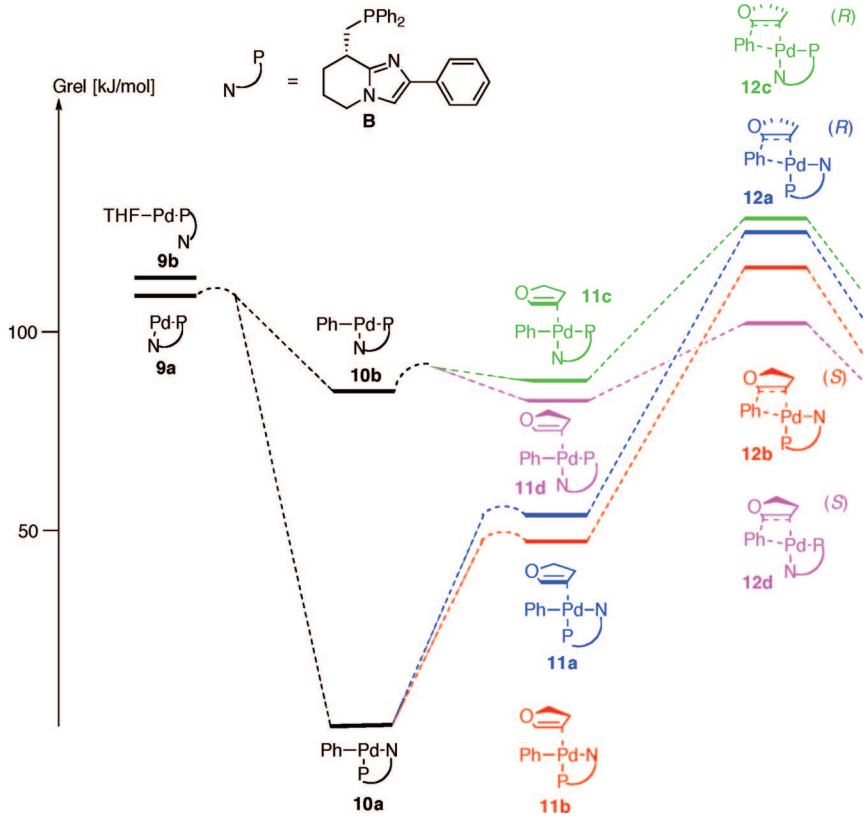


Figure 4. Free energy profile for the asymmetric Heck reaction between 2,3-dihydrofuran and phenyl triflate, catalyzed by a Pd complex with the imidazole ligand **B**. Palladium complexes **10**−**12** are cationic.

case (**1**, Figure 2). The oxidative addition product **10** shows the same large preference (88 kJ/mol, Table 3) for a *trans* relationship between the Ph and N as did **2**. This preference is retained, though attenuated, in the π complex **11**. As before, the energetically favored insertion TS is the one having P *trans* to the phenyl group that is being transferred from Pd to the double bond and leading to the *S* product.

To summarize, the two ligands show very similar behavior. Of the steps calculated here, the resting state in each case is the $[L-Pd-Ph]^+$ cation with the phenyl group *trans* to N, but the most preferred reaction path in each case requires the resting state to first undergo a configurational switch to place the phenyl group *trans* to P. The overall barrier from the resting state to the selectivity-determining carbopalladation TS is also similar in both cases: 105 kJ/mol using ligand **A** and 103 kJ/mol using ligand **B**. However, we were also interested to see whether direct competition between the two pseudoisomeric ligands for a limited amount of Pd would produce a nonlinear effect; that is,

Table 3. Gibbs Free Energies in Solution for the Compounds Shown in Figure 4

complex	G_{sol}[a] (kJ/mol)	ΔG_{sol}[b] (kJ/mol)
9a	115	0
9b	124	9
10a	0	0
10b	88	88
11a	55	6
11b	49	0
11c	89	40
11d	84	35
12a	126	23
12b	118	15
12c	130	27
12d	103	0

[a] Gibbs free energies relative to the complex of lowest energy, **10a**. [b] Gibbs free energy for each complex relative to the most stable complex of that type (same numbers, **a**−**d**).

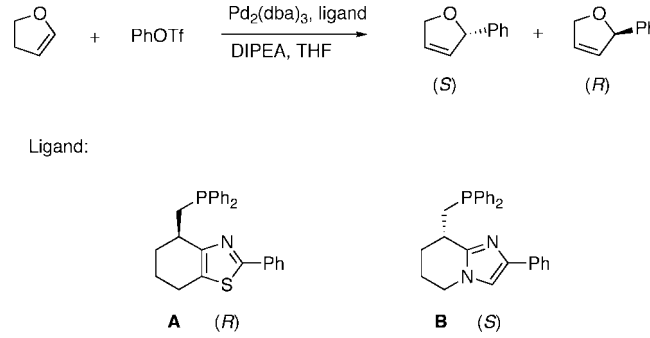
whether the concentration ratio of ligands **A** and **B** affects the enantiomeric ratio (er) of the chiral product **P1** linearly. To connect the two studies, we compared the two initial Pd−L, complexes **1a** and **9a** with ligands **A** and **B**, respectively, and found that coordination of Pd to ligand **B** is favored by 9 kJ/mol. At the Pd(II) stage, the difference is even larger: ligand **B** is always preferred over ligand **A**, with energy differences ranging from 11 to 23 kJ/mol for corresponding points up to and including the carbopalladation steps (**4** and **12**, respectively). Thus, in a mixed system, where **A** and **B** compete for Pd, we predict that the reaction selectivity will be dominated by ligand **B**.

Experimental Study. The theoretical study indicated that Pd complexes of both ligands should catalyze the Heck reaction with similar magnitudes of asymmetric induction, and that these Heck reactions should proceed at similar rates for both ligands. We also found that imidazole **B** binds more strongly to palladium and therefore would be expected to dominate the reaction in a mixed system if the ligands were competing for Pd; that is, there should be a strong nonlinear effect upon mixing the pseudoenantiomers. In order to confirm these predictions, we performed a simple experimental study utilizing ligands **A** and **B** in the Heck reaction. The Heck coupling of 2,3-dihydrofuran **S1** and phenyl triflate **S2** using $Pd_2(dba)_3$ as catalyst precursor was studied using the Hünig's base and microwave heating. Opposite enantiomers of thiazole ligand **A** and imidazole ligand **B** were synthesized for the study.

Surprisingly, the two ligands showed quite different behavior in the experiments. A Heck reaction run in the presence of the thiazole ligand **A** (**A**:Pd = 2:1) went to completion within 4 h and was highly enantioselective (Table 4, entry 1). The corresponding reaction using the imidazole ligand **B** proceeded to only 36% conversion, but with even higher enantioselectivity (Table 4, entry 2). However, when thiazole **A** was used in equal amounts with palladium under otherwise identical reaction conditions, the reaction went to only 22% conversion (Table 4, entry 3). The Heck reactions with imidazole ligand **B** gave nearly identical results, regardless of the ligand-to-palladium ratio (Table 4, entries 2 and 4). Precipitation of palladium black was observed in these reactions, and we therefore conclude that the reactions that give low conversion do so because of catalyst inactivation early in the reaction. It seems that only ligand **A** is able to keep Pd(0) from precipitating, and only when used in 2 equiv relative to Pd.

In order to confirm the predicted nonlinear effects, the Heck reaction reaction was run with both **A** and **B** in the reaction

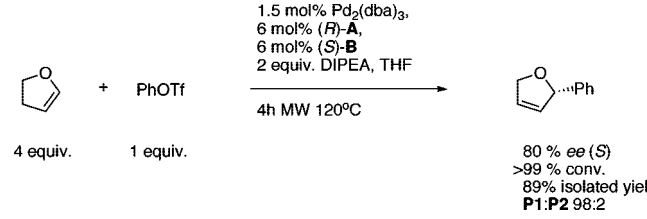
Table 4. Heck Reaction of 2,3-Dihydrofuran and Phenyl Triflate Utilizing Ligands **A** and **B**[a]



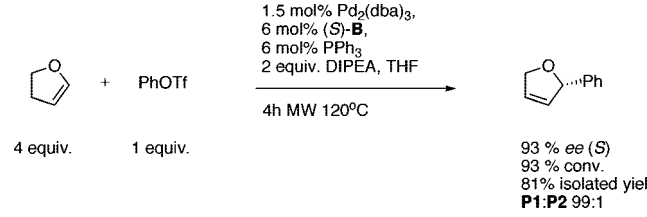
entry	[Pd] (mol %)	ligand **A** (mol %)	ligand **B** (mol %)	conv[b] (%)	**P1**:**P2**[c]	**P1** ee[d] (%)
1	3	6		>99 (82)	92:8	88 (*R*)
2	3		6	36	92:8	94 (*S*)
3	3	3.2		22	99:1	87 (*R*)
4	3		3.2	44	90:10	93 (*S*)

[a] Reaction conditions: 2,3-dihydrofuran (2.0 mmol), PhOTf (0.5 mmol), DIPEA (1.0 mmol), $Pd_2(dba)_3$ (1.5 mol %), ligand **A** or **B** (mol %, see table), THF (3 mL), MW 120 °C, 4 h. [b] Determined by GC with *n*-tridecane as internal standard. Isolated yield in parentheses. [c] Determined by chiral GC/MS. [d] Determined by chiral GC/MS. The conversions and ee values are presented as the mean values of two reactions.

Scheme 3. Competitive Study with Ligands **A** and **B** in the Heck Reaction



Scheme 4. Heck Reaction with Imidazole **B** as Ligand and PPh_3 as Additive



mixture (Scheme 3). Because different enantiomers of the ligands **A** and **B** were used and these result in different enantiomers of the product, it was possible to see which of the ligands was forming the active chiral catalyst. In a perfectly linear system, the er of the product should equal the ratio of the two pseudoenantiomeric ligands, but from the computational study, we expect ligand **B** to dominate in the present system. Indeed, the competitive reaction with ligands **A** and **B** gave the same sense of enantiodiscrimination to give (*S*) product and an ee value almost as high as that obtained in reactions run with ligand **B** alone (80%, cf. 93% for **B** alone). This result confirms that the imidazole ligand **B** is forming the active chiral catalyst by binding more strongly to the Pd than does the thiazole ligand **A**. To our surprise, the reaction went to completion, which is not the case when imidazole is the only ligand. One reason for this could be that the free thiazole is stabilizing the "naked"

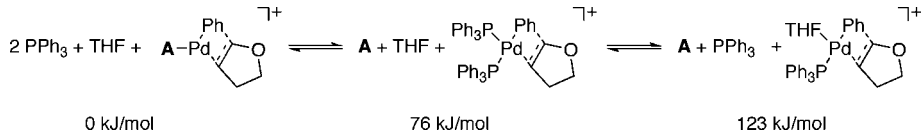


Figure 5. Isodesmic comparison of transition states with and without chiral ligand.

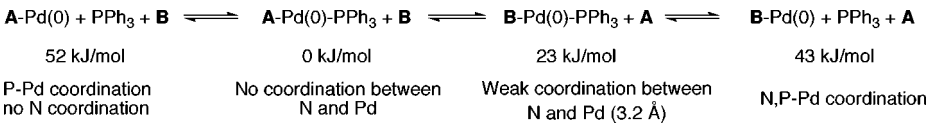


Figure 6. Isodesmic comparison of the Pd(0) complexes that can form when both chiral ligands, **A** and **B**, and PPh_3 are present in the reaction mixture.

Pd(0) complex. To evaluate this possibility, we tested the reaction with imidazole ligand **B** and PPh_3 as an additive (Scheme 4). Most gratifyingly, this led to high conversion (93%) and the same ee (93%) as imidazole **B** gives in the absence of PPh_3.

Though the addition of a nonchiral ligand could have led to a deterioration of the enantioselectivity by opening a parallel, nonselective path, this appears not to be the case. We verified this computationally by calculating the two pathways for Heck reaction without any chiral moiety possible in this system: a pathway with two PPh_3 ligands, or a pathway with one PPh_3 and one THF solvent molecule coordinated to Pd. The results are shown as an isodesmic comparison of the relevant transition states in Figure 5. Clearly, the reaction is completely dominated even by the relatively weak ligand **A**. The same comparison with ligand **B** would produce energy differences that were larger by 13 kJ/mol (i.e., 89 and 136 kJ/mol).

Finally, the beneficial effect of PPh_3 is shown in Figure 6. Pd(0) strongly prefers to be ligated by two phosphines rather than by the P and N termini of **A** and **B**. Coordination by two phosphines leads to complexes that resist precipitation due to their high stability. Importantly, the stabilization occurs only for the high-energy Pd(0) state. The Pd(II) complexes are too crowded to allow facile coordination of the relatively bulky PPh_3 ligand; thus, we see no detrimental effect of PPh_3 on reaction rates.

An achiral ligand can successfully stabilize a highly selective and active catalyst that suffers from metal precipitation, as long as this achiral ligand does not produce an active catalyst. This concept could have wide-ranging implications for homogeneous catalysis. Many reactions catalyzed by noble metals are plagued by problems of precipitation. Though adding ligand that binds well to the low-valent state might inhibit the reaction slightly, it can also confer a definite advantage by inhibiting metal precipitation, thus yielding a much more effective catalytic system overall. Naturally, this concept requires the stabilizing ligands to be incompetent in the selectivity-determining step of the catalytic cycle. The use of PPh_3 in the Heck reaction fulfills this requirement beautifully, and we envision that the same principle could be applied to many other metal-catalyzed processes.

Conclusions

Using DFT calculations, we have elucidated the source of the high enantioselectivity conferred in the Heck reaction by the current class of P,N-ligands. The reactions follow a Halpern-style selectivity. It is important to note that, in cases like this, structural outcomes cannot be rationalized on the basis of observable complexes, because the major enantiomeric product is formed from the least populated intermediate. The nonlinear effects, which were predicted on the basis of the relative binding strengths of two ligands, were verified experimentally. Though some experiments were inefficient due to catalyst precipitation—an effect that cannot easily be addressed computationally—catalyst deactivation could be avoided without deterioration of the high stereoselectivity by addition of an achiral ligand. The effect of the achiral ligand was rationalized by additional computational studies. The role of the achiral ligand as a stabilizing but nonparticipating agent could be extremely useful in other metal-catalyzed processes, the turnover of which is limited by catalyst inactivation due to precipitation.

Experimental Section

Computational Details. All calculations were performed using Jaguar, version 6.0, release 12.[14] We employed the B3LYP hybrid functional[15–17] with the LACVP**basis set,[18] which uses an effective core potential for Pd and the 6-31G** basis set for the other atoms.

All complexes were optimized in the gas phase, and single-point solvation energies were then determined using parameters suitable for THF (dielectric constant, epsout = 7.43; probe radius, radprb = 2.5241416). Vibrational analysis using the analytic Hessian was performed for the gas-phase geometries, and the final free energies (G_{sol}) were obtained by adding the thermodynamic contributions (at 393.15 K) to the solution-phase potential energies. The Cartesian coordinates for all optimized geometries are available in the Supporting Information.

Experimental Details. THF was freshly distilled from sodium benzophenone ketyl under N_2 prior to use. 2,3-Dihydrofuran, phenyl triflate, $Pd_2(dba)_3$, and tridecane were purchased from Sigma-Aldrich and used as received. Diisopropylethylamine (DIPEA) was distilled from ninhydrin and then from potassium hydroxide. Ligands **A**[6b] and ligand **B**[10] were synthesized according to reported procedures. Flash chromatography was performed using silica gel 60 Å (37−70 μm). Analytical thin-layer chromatography was carried out utilizing 0.25 mm precoated plates, silica gel 60 UV_{254}, and spots were visualized under UV light. NMR samples were dissolved in $CDCl_3$ and analyzed at room temperature; ^1H (500 MHz) and ^{13}C (126 MHz) NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts for protons were referenced to the shift of the residual $CHCl_3$ (δ 7.26). Carbon spectra were referenced to the shift of the ^{13}C signal of $CDCl_3$ (δ 77.0). Conversions and ee values were determined by chiral GC-MS (B-DM) using the following method: 80 °C, 0.3 °C/min 90 °C, 5 °C/min 125 °C, 14.5 psi, 1.5 mL/min. The retention times (t_R, min)

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are as follow: phenyltriflate, 6.6; tridecane, 32.0; (*S*)-**P1**, 32.6; (*R*)-**P1**, 35.3; (*S*)-**P2**, 27.3; (*R*)-**P2**, 29.5. Tridecane was used as an internal standard for determining conversion of the reaction. Microwave heating was carried out using an automatic single-mode synthesizer from Biotage, which produces a radiation frequency of 2.45 GHz.

Representative Procedure for MW-Assisted Asymmetric Intermolecular Heck Reaction of 2,3-Dihydrofuran and Phenyl Triflate (Table 4, Entry 1). Ligand **A** (12.4 mg, 0.03 mmol) and $Pd_2(dba)_3$ (6.8 mg, 0.0075 mmol) were weighed into a MW vial, and dry THF (3 mL) was added. The vial was sealed and then evacuated and backfilled with N_2 (three times). The mixture was gently heated to reflux and then allowed to cool to room temperature. Phenyl triflate (81 μL, 0.5 mmol, 1 equiv), 2,3-dihydrofuran (151 μL, 2.0 mmol, 4 equiv), DIPEA (174 μL, 1 mmol, 2 equiv), and tridecane (30 μL, 0.125 mmol, 0.25 equiv) were added. A small sample was removed for conversion determination before the mixture was MW-heated at 120 °C for 4 h. After cooling, the mixture was diluted with Et_2O and filtered through silica. The filtrate was analyzed by chiral GC-MS (B-DM). The conversion of the reaction was >99% with 87% ee (*S*). The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography on silica gel using CH_2Cl_2:pentane (1:1) as the eluent to afford a clear oil as the pure product (0.060 g, 82% yield). The ^{1}H NMR spectrum of the pure product corresponded to the reported data.[19]

Competitive Asymmetric Heck Reaction Utilizing Ligands A and B (Scheme 3). Ligands **A** (12.4 mg, 0.03 mmol) and **B** (11.9 mg, 0.03 mmol) were weighed into separate vials, and dry THF (1.5 mL) was added to each vial. The two solutions were mixed together and then added to a MW vial containing $Pd_2(dba)_3$ (6.8 mg, 0.0075 mmol). The vial was sealed and then evacuated and backfilled with N_2 (three times) before the mixture was heated gently. After the mixture cooled, phenyl triflate (81 μL, 0.5 mmol, 1 equiv), 2,3-dihydrofuran (151 μL, 2.0 mmol, 4 equiv), DIPEA (174 μL, 1 mmol, 2 equiv), and tridecane (30 μL, 0.125 mmol, 0.25 equiv) were added. A small sample was removed for conversion determination before the mixture was MW-heated at 120 °C for 4 h. After cooling, the mixture was diluted with Et_2O and filtered through silica. The filtrate was analyzed by chiral GC-MS (B-DM) (>99% conversion, 80% ee (*S*), **P1**:**P2** (98:2)). The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography on silica gel using CH_2Cl_2:pentane (1:1) as the eluent to afford a clear oil as the pure product (0.065 g, 89% yield). The ^{1}H NMR spectrum of the pure compound corresponded to the reported data.[19]

Asymmetric Heck Reaction with Ligand B and Additive PPh_3 (Scheme 4). Ligand **B** (11.9 mg, 0.03 mmol) and $Pd_2(dba)_3$ (6.8 mg, 0.0075 mmol) were weighed into a MW vial, and dry THF (2 mL) was added. The vial was sealed and then evacuated and backfilled with N_2 (three times). The mixture was gently heated and then allowed to cool to room temperature. A solution of triphenylphosphine (7.9 mg, 0.03 mmol) in dry THF (1 mL) was added, and the mixture was stirred for 10 min at room temperature. Phenyl triflate (81 μL, 0.5 mmol, 1 equiv), 2,3-dihydrofuran (151 μL, 2.0 mmol, 4 equiv), DIPEA (174 μL, 1 mmol, 2 equiv), and tridecane (30 μL, 0.125 mmol, 0.25 equiv) were added. A small sample was taken for conversion determination before the mixture was MW-heated at 120 °C for 4 h. After cooling, the mixture was diluted with Et_2O and filtered through silica. The filtrate was analyzed by chiral GC-MS (B-DM) (93% conversion, 93% ee (*S*), **P1**:**P2** (99:1)). The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography on silica gel using CH_2Cl_2:pentane (1:1) as the eluent to afford a clear oil as the pure product (0.059 g, 81% yield). The ^{1}H NMR spectrum of the pure compound corresponded to the reported data.[19]

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Supporting Information Available: Cartesian coordinates for all optimized geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

JA802991Y

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