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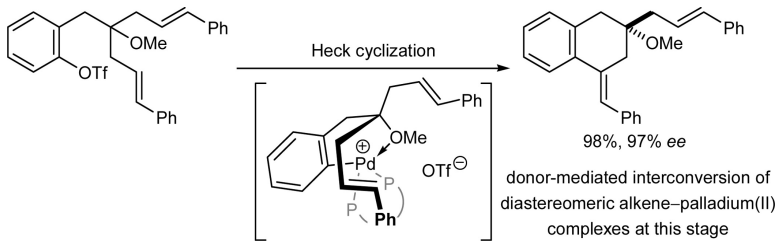
J. Am. Chem. Soc., **2007**, 129 (44), 13455-13463• DOI: 10.1021/ja072571y • Publication Date (Web): 13 October 2007



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Oxygen Donor-Mediated Equilibration of Diastereomeric Alkene−Palladium(II) Intermediates in Enantioselective Desymmetrizing Heck Cyclizations

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Abstract: This investigation examines the origin of enantioselection in the desymmetrization of an acyclic prochiral Heck cyclization precursor. High asymmetric induction (97−98% ee) is attributed to a temporary interaction of a Lewis basic oxygen donor with weakly Lewis acidic palladium(II). A series of control experiments combined with quantum-chemical model calculations provided sound evidence for a mechanism involving oxygen donor-mediated, rapid equilibration of diastereomeric alkene−palladium(II) complexes prior to the selectivity-determining ring-closing event, a Curtin-Hammett scenario. Our study also highlights the importance of the cationic pathway (triflate counter anions versus halido ligand) and alkene stereochemistry (*E* versus *Z*) in asymmetric Heck reactions.

1. Introduction

The enantioselective desymmetrization of prochiral (achiral)[1] as well as *meso*[2] compounds is certainly an elegant technique in stereoselective synthesis.[3] Breaking of the symmetry plane in these precursors is effected by differentiation of heterotopic functional groups upon reaction with a chiral, nonracemic reagent or catalyst. An attractive feature of this approach originates from the fact that even processes not capable of forming a stereogenic, tetravalent carbon might be performed in an asymmetric sense. In principle, the Mizoroki−Heck reaction[4] is such a transformation unless β-hydride elimination, which usually reestablishes the alkene fragment, is steered away from the site of C−C bond formation. In order to selectively realize alternative β'-hydride elimination, the β-carbon atom generated in the migratory insertion step must not have any accessible hydrogens attached to it. This is the case when a quaternary carbon center is formed and for cyclic and, therefore, rigid skeletons, in which a synperiplanar arrangement of the C_β−H bond and the C_α−Pd^{II} bond is conformationally inaccessible. The realization that asymmetrically substituted carbons are thereby directly accessible[5] largely re-evaluated the synthetic importance of the enantioselective intramolecular[6] Heck reaction,[7] making it a pivotal C−C bond-forming process in complex molecule synthesis.[8] Conversely, indirect formation of a stereogenic carbon is achieved in a desymmetrizing Heck reaction, in which the site of C−C bond formation is not coinciding with the prochiral center.

The desymmetrizing or so-called group-selective Heck reaction was developed by Shibasaki almost two decades ago.[9] The diastereocontrolled cyclization of prochiral **1** (Figure 1) using a chirally modified palladium catalyst afforded a *cis*-bicyclo-[4.4.0]decane system with high enantiomeric excess (92% ee). In this ring closure, the stereochemistry of the vicinal stereogenic carbon atoms is set at the former prochiral center as well as at the site of C−C bond formation since β'-hydride elimination is clearly favored for conformational reasons. Later, Feringa accomplished the desymmetrization of structurally related **2** (Figure 1) using a monodentate ligand in excellent enantiomeric excess (96% ee);[10] epimerization of the intermediate C_α−Pd^{II} bond through a palladium enolate enabled conventional β-hydride elimination. In recent years, Lautens[11] and Bräse[12] reported

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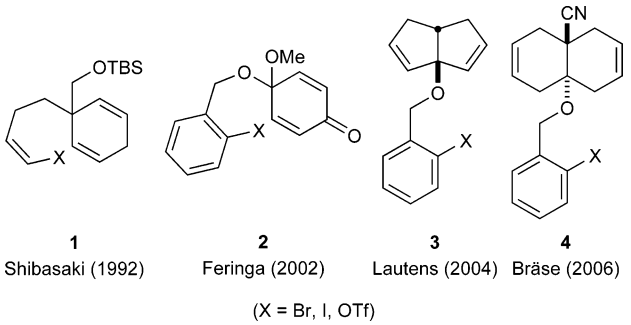
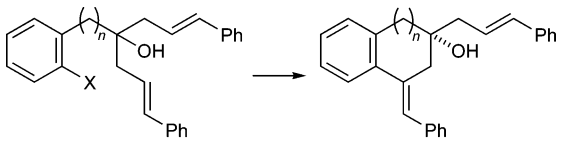
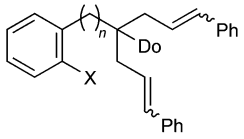


Figure 1. Structural motifs of desymmetrizing Heck cyclizations.

Scheme 1. A Novel Structural Motif for Desymmetrization[a]





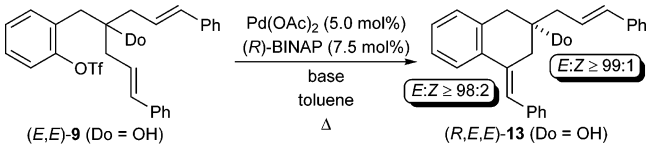
precursor	Do	X	*n*
(*E*,*E*)-**7**	OH	Br	1
(*E*,*E*)-**8**	OH	OTf	0
(*E*,*E*)-**9**	OH	OTf	1
(*Z*,*Z*)-**9**	OH	OTf	1
(*E*,*E*)-**10**	$OSiEt_3$	OTf	1
(*E*,*E*)-**11**	OMe	OTf	1
(*Z*,*Z*)-**11**	OMe	OTf	1
(*E*,*E*)-**12**	H	OTf	1

[a] For the detailed description of all cyclization precursor syntheses, see Supporting Information. Do = donor.

the desymmetrization of precursors having either a *cis*-bicyclo[3.3.0]octane (**3**, Figure 1) or a *trans*-bicyclo[4.4.0]decane (**4**, Figure 1) core. Heck annulation yielded the tricyclic structures in 99% ee and 84% ee, respectively; structural reasoning again rationalized high diastereoselectivity and regioselective β'-hydride elimination.

All these examples corroborated the impression that, in order to allow for efficient differentiation of the enantiotopic unsaturated branches, these must be incorporated into a cyclic and, therefore, rigid framework. Nevertheless, we envisioned the desymmetrizing Heck cyclization of open-chain precursors having the general structure **5** (Scheme 1). Their ring closure would produce benzannulated carbocycles **6** only with stereogenic information remote from the actual C−C bond-forming site.[13] Our investigation commenced with cyclization experiments of a series of several oxygen-containing precursors (*E*,*E*)-**7**−(*E*,*E*)-**10** as well as deoxygenated (*E*,*E*)-**12** (Scheme 1).[14] Within this survey, we found that the level of enantioinduction was markedly dependent on (a) the presence of the hydroxy group, (b) its position relative to the leaving group X ($n = 1$ superior to $n = 0$), and (c) the leaving group in X (OTf superior to Br) itself.[14] These cooperative factors, Lewis basic oxygen atom in ideal proximity to palladium(II) and cationic pathway of the Heck reaction, indicated an unusual neighboring-group

Table 1. Desymmetrization of Cyclization Precursors (*E*,*E*)-**9**−(*E*,*E*)-**12**[a]



(*E*,*E*)-**9** (Do = OH)
(*E*,*E*)-**10** (Do = $OSiEt_3$)
(*E*,*E*)-**11** (Do = OMe)
(*E*,*E*)-**12** (Do = H)

(*R*,*E*,*E*)-**13** (Do = OH)
(*R*,*E*,*E*)-**14** (Do = $OSiEt_3$)
(*R*,*E*,*E*)-**15** (Do = OMe)
(*S**,*E*,*E*)-**16** (Do = H)

entry	precursor	donor	base	*T* [°C]	*t* [h]	product[b]	ee [%][c]	yield [%][d]
1	(*E*,*E*)-**9**	OH	K_2CO_3	80	15	(*R*,*E*,*E*)-**13**	88	74
2	(*E*,*E*)-**9**	OH	K_2CO_3	60	36	(*R*,*E*,*E*)-**13**	94	82
3	(*E*,*E*)-**9**	OH	TMP	80	15	(*R*,*E*,*E*)-**13**	88	36
4	(*E*,*E*)-**10**	$OSiEt_3$	K_2CO_3	80	15	(*R*,*E*,*E*)-**14**	2	55
5	(*E*,*E*)-**11**	OMe	K_2CO_3	80	15	(*R*,*E*,*E*)-**15**	89	87
6	(*E*,*E*)-**11**	OMe	K_2CO_3	50	15	(*R*,*E*,*E*)-**15**	92	45
7	(*E*,*E*)-**11**	OMe	K_2CO_3	35	90	(*R*,*E*,*E*)-**15**	96	31
8	(*E*,*E*)-**11**	OMe	TMP	80	15	(*R*,*E*,*E*)-**15**	93	83
9	(*E*,*E*)-**11**	OMe	TMP	50	15	(*R*,*E*,*E*)-**15**	97	84
10	(*E*,*E*)-**11**	OMe	TMP	50	36	(*R*,*E*,*E*)-**15**	97	98
11	(*E*,*E*)-**11**	OMe	TMP	35	90	(*R*,*E*,*E*)-**15**	98	40
12	(*E*,*E*)-**12**	H	K_2CO_3	80	15	(*S**,*E*,*E*)-**16**	18	71
13	(*E*,*E*)-**12**	H	TMP	80	15	(*S**,*E*,*E*)-**16**	8	86

[a] All reactions were conducted with a substrate concentration of 0.1 M in toluene with 4.0 equiv of the respective base. [b] The absolute configuration was determined for (*R*,*E*,*E*)-**15** (Sections 5 and 6 in Supporting Information); the absolute configurations of (*R*,*E*,*E*)-**13** and (*R*,*E*,*E*)-**14** were assigned by chemical correlation with (*R*,*E*,*E*)-**15**. [c] See Supporting Information for details. [d] Yield of analytically pure product isolated after flash column chromatography on silica gel. TMP = 2,2,6,6-tetramethylpiperidine.

effect[15] in a catalyst-controlled Heck cyclization. In this contribution, we now disclose a full account of our investigations—including further improved substrate (*E*,*E*)-**11**—directed at understanding the subtle factors controlling enantioselection. Supported by quantum-chemical calculations, an unprecedented enantioselectivity-discriminating mechanism emerges.

2. Results and Discussion

2.1. Desymmetrizing Heck Cyclizations of *E*,*E*-Configured Precursors. When subjecting prochiral diene (*E*,*E*)-**9** to conventional Heck conditions in toluene at 80 °C, we were pleased to find exclusive formation of a single diastereomer (*R*,*E*,*E*)-**13** in good enantiomeric excess (Table 1, entry 1). The enantiomeric excess improved significantly at 60 °C (Table 1, entry 2), but at even lower temperatures, transtriflation from $C(sp^2)$−OTf to $C(sp^3)$−OH became a competing side reaction. Various organic and inorganic bases were also tested but had little effect on enantioselection (e.g., Table 1, entry 3).[14a] It is interesting to note that both K_2CO_3 and Cs_2CO_3 in toluene were effective, whereas no conversion was observed when polar DMF was used. At that time, we believed that any increase of the level of enantioselection might only be possible if the reaction temperature were further decreased. We hoped to achieve exactly that by protecting the hydroxy group and thereby preventing triflyl migration in (*E*,*E*)-**9**. Hence, silyl-protected (*E*,*E*)-**10** was cyclized under the initial reaction conditions. To our surprise, this Heck reaction was sluggish, and (*R*,*E*,*E*)-**14**

(13) A 3,6-dimethoxy-functionalized substrate **5** ($n = 1$) was of particular interest to us as its cyclization would provide a catalytic asymmetric access to the AB-ring synthon of anthracycline antibiotics: Oestreich, M.; Sempere-Culler, F.; Machotta, A. B. *Synlett* **2006**, 2965−2968.

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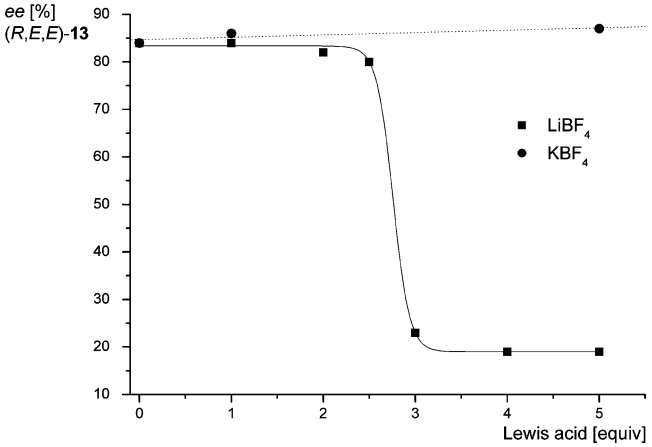

Figure 2. Desymmetrizing Heck cyclization of (*E*,*E*)-**9** in the presence of variable amounts of Lewis acid. Reaction conditions: (*E*,*E*)-**9**, $Pd(OAc)_2$, (*R*)-BINAP, $LiBF_4$ or KBF_4, Et_3N, THF, 60 °C.

was isolated in poor yield and with completely eroded enantiomeric excess (Table 1, entry 4)!

This pronounced effect indicated that a suitably located oxygen donor in the cyclization precursor might be decisive for enantiocontrol. Aware of the precedent of a hydroxy-directed Heck reaction,[16−18] we suspected that the hydroxy group in (*E*,*E*)-**9** might interact with the palladium(II) center during the catalytic cycle. Steric demand as well as attenuated Lewis basicity of the oxygen donor in (*E*,*E*)-**10** might account for our experimental finding.

This hypothesis was then substantiated by an extensive survey of the enantioselective desymmetrization of the corresponding methyl ether (*E*,*E*)-**11** (Table 1, entries 5−11). Cyclization of (*E*,*E*)-**11** under the initial reaction conditions cleanly provided (*R*,*E*,*E*)-**15** with an enantiomeric excess (Table 1, entry 5), which compared well with the data obtained from the cyclization of (*E*,*E*)-**9** (Table 1, entry 1). As anticipated, the decomposition-free ring closure of (*E*,*E*)-**11** was now possible at remarkably low temperatures; enantiomeric excesses of 92% ee at 50 °C and 96% ee at 35 °C were high, yet chemical yields were moderate (Table 1, entries 6−7). Importantly, substantially higher yields and again improved enantioselectivities were obtained by exchanging K_2CO_3 for TMP (Table 1, entries 8−11), a base that had been less efficient in the cyclization of (*E*,*E*)-**9** (Table 1, entry 3). Under optimized reaction conditions, (*E*,*E*)-**11** was cyclized in 98% yield and 97% ee (Table 1, entry 10).

With strong evidence for a pivotal role of oxygen in the Heck reaction, we performed the Heck cyclization of deoxygenated (*E*,*E*)-**12** under conditions identical to those for (*E*,*E*)-**9** and (*E*,*E*)-**11**. In agreement with our proposal, less reactive cyclization precursor (*E*,*E*)-**12** gave tetralin (*S**,*E*,*E*)-**16** in almost racemic form (Table 1, entries 12 and 13).

2.1.1. Control Experiment I. Influence of Excess Lewis Acidic Cations. We reasoned that the proposed coordination of the oxygen donor, −OH or −OMe, to weakly Lewis acidic palladium(II) might be severely disturbed by addition of external Lewis acidic cations. To test for this, we chose $LiBF_4$ as the source of the Lewis acid since large quantities are soluble in THF; therefore, Heck cyclizations (*E*,*E*)-**9** → (*R*,*E*,*E*)-**13** were conducted in homogeneous THF solution using Et_3N as the base (reference reaction: 84% ee and 70% yield at 60 °C). In a series of experiments with variable equivalents of $LiBF_4$ (based on cyclization precursor (*E*,*E*)-**9**), a distinct effect on the level of enantioselection was found (Figure 2). The enantiomeric excess (∼80% ee) remained nearly unchanged in the presence of 1.0−2.5 equiv of $LiBF_4$; at higher concentrations of Lewis acidic lithium cations (3.0−5.0 equiv), the enantiomeric excess (∼20% ee) collapsed. Conversely, KBF_4 (1.0−5.0 equiv) had no effect whatsoever on the stereochemical outcome of this transformation (∼85% ee). These results imply that, at high lithium(I) concentrations, the Lewis basic sites at oxygen are not available for palladium(II) coordination. Less Lewis-acidic potassium(I) is not capable of coordinatively saturating the oxygen donor.

2.1.2. Control Experiment II. Influence of the Counteranion. Cationic versus Neutral Pathway. In a vast oversimplification, there are two mechanistic scenarios commonly presumed to govern Heck reactions.[19] These, termed *cationic* and *neutral* pathways, refer to the formal charge at palladium(II) after oxidative addition/alkene coordination prior to migratory insertion and are dependent on the counteranions present. The nature of the counteranion determines the reaction pathway:[19] weakly or noncoordinating anions such as the triflate anion will dissociate, thereby creating a vacant coordination site at palladium(II) (*cationic* pathway). On the other hand, strongly coordinating anions such as halides will remain coordinated at palladium(II) throughout the catalytic cycle (*neutral* pathway). As verified in several asymmetric Heck reactions using bidentate ligands, this has strong implications on the enantioselectivity-controlling alkene capture/migratory insertion process.[7,20] The latter is believed not to proceed through a pentacoordinate alkene−palladium(II) complex.[21]

The desymmetrizing Heck cyclization of aryl triflate (*E*,*E*)-**9** (and (*E*,*E*)-**11**) should proceed by the cationic pathway. Consequently, oxidative addition followed by dissociation provides a vacant Lewis acidic site at palladium(II) capable of coordinating a proximal Lewis basic oxygen donor. Starting from the corresponding aryl bromide (*E*,*E*)-**7**, a neutral pathway should be followed. On the basis of these considerations, we predicted poor enantiocontrol for the cyclization of (*E*,*E*)-**7**, yet the first experiment in this survey seemed to show the opposite (Table 2, entry 1). A closer look revealed, though, that (*R*,*E*,*E*)-**13** was formed with 86% ee at 5% yield which, in turn, corresponded to a single turnover using 5.0 mol % $Pd(OAc)_2$. At higher temperature, conversion was raised and enantiomeric excesses decreased to almost zero (Table 2, entries 2 and 3). From these experiments, we concluded that stereoinduction is dependent on bromide concentration, which gradually increases with conversion.

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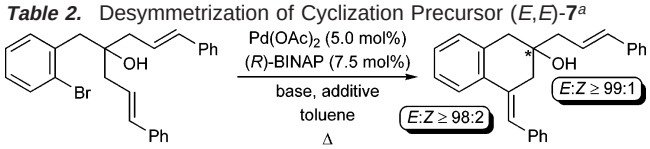
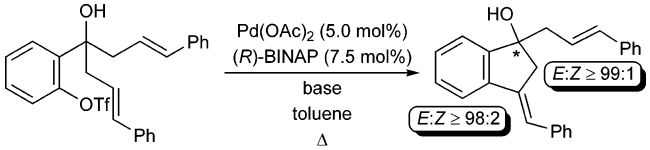
Table 2. Desymmetrization of Cyclization Precursor (*E*,*E*)-**7**[a]



entry	precursor	base, additive	*T* [°C]	*t* [h]	product	ee [%][b]	yield [%][c]
1	(*E*,*E*)-**7**	K_2CO_3	80	15	(*R*,*E*,*E*)-**13**	86	5
2	(*E*,*E*)-**7**	K_2CO_3	100	15	(*R*,*E*,*E*)-**13**	44	13
3	(*E*,*E*)-**7**	K_2CO_3	100	20	(*R*,*E*,*E*)-**13**	4	68
4	(*E*,*E*)-**7**	K_2CO_3, Ag_2CO_3 (1.4 equiv)	80	20	(*S*,*E*,*E*)-**13**	12	13
5	(*E*,*E*)-**7**	Ag_2CO_3 (2.0 equiv)	100	20	(*S*,*E*,*E*)-**13**	1	58

[a] All reactions were conducted with a substrate concentration of 0.1 M in toluene with 4.0 equiv of the respective base. [b] See Supporting Information for details. [c] Yield of analytically pure product isolated after flash column chromatography on silica gel.

Table 3. Desymmetrization of Cyclization Precursor (*E*,*E*)-**8**[a]



entry	precursor	base	*T* [°C]	*t* [h]	product	ee [%][b]	yield [%][c]
1	(*E*,*E*)-**8**	K_2CO_3	80	15	(*R**,*E*,*E*)-**17**	46	35
2	(*E*,*E*)-**8**	K_2CO_3	50	15	(*R**,*E*,*E*)-**17**	46	30
3	(*E*,*E*)-**8**	TMP	80	15	(*R**,*E*,*E*)-**17**	48	88
4	(*E*,*E*)-**8**	TMP	50	15	(*R**,*E*,*E*)-**17**	53	48

[a] All reactions were conducted with a substrate concentration of 0.1 M in toluene with 4.0 equiv of the respective base. [b] See Supporting Information for details. [c] Yield of analytically pure product isolated after flash column chromatography on silica gel.

The cyclizations of (*E*,*E*)-**7** in the presence of halide scavengers, which provide an entry into the cationic pathway, are still in need of an explanation. The net result from a screening of silver salts and different bases is that yields and enantioselectivities were poor but (*S*,*E*,*E*)-**13** is generated with inverted absolute configuration (Table 2, entries 4 and 5). Similar observations have been reported by Overman in the past.[20]

2.1.3. Control Experiment III. Variation of the Position of the Oxygen Donor Relative to the Palladium(II) Center. An intramolecular interaction of the oxygen donor with the intermediate palladium(II) center would certainly require their ideal vicinity. Such a situation appeared to be the case for (*E*,*E*)-**9**, but would it be the same for (*E*,*E*)-**8**, in which the position of the hydroxy group relative to the C(sp^2)−OTf bond is changed? Selected data for the enantioselective ring closure (*E*,*E*)-**8** → (*R**,*E*,*E*)-**17** are summarized in Table 3 (entries 1−4). The moderate enantioselectivities clearly demonstrate that coordinative Pd−O interaction by a virtually planar five-membered chelate is not favored. Chemical yields with TMP as the base were substantially higher than with K_2CO_3, but the observed enantioselectivities were invariably ∼50% ee.

2.2. Discussion of Quantum-Chemical Model Calculations. We used quantum-chemical calculations at the B3LYP/LACV3P**++//B3LYP/LACVP** level of theory of a simplified model system in the gas phase to obtain information on the elementary steps at the palladium center in these Heck cyclizations.[22] For this, we introduced several simplifications: (1) The terminal phenyl substituents in the substrate were omitted. (2) BINAP was simplified to a (*Z*,*Z*)-bis-1,4-(dimethylphosphino)buta-1,3-diene. (3) Instead of triflate, mesylate was modeled as leaving group. Of course, we are fully aware that this approach will not enable the reproduction of detailed steric effects and exact enantioselectivities. Our goal was primarily to acquire information about the coordination numbers at palladium in catalyst intermediates, the nature of the rate-determining step, and the nature of the stereoselectivity-determining step.

The picture for the computed elementary steps at the palladium center is straightforward, and the qualitative conclusions might be considered as reasonable also for the full, experimental system. In the overall uncharged combination of the 14 valence electron palladium(0) complex and the model substrate, we arbitrarily normalized their computed free energies to zero.

BINAP−palladium(0) must be considered as the catalyst resting state. It is unclear whether (κ^2P-BINAP)Pd (**M1**) or η^2-alkene complex (**M2**) of (κ^2P-BINAP)Pd is the most stable species since the free energy differences are smaller than the computational accuracy of our model calculations (Figure 3). At small equilibrium concentrations, the (κ^2P-BINAP)Pd fragment coordinates the aryl π-system of the substrate in an η^2 mode. In **M3**, the coordination of palladium to an unsubstituted arene position is favored over the "active" substitution mode in complex **M4**.

The barrier for the activation of the C−O bond of the aryl triflate via transition state **M5** is higher than expected from the experimental observations. The mesylate model, however, is a poorer leaving group than the triflate, and the missing solvation in the calculations further explains the high computed barrier. Nevertheless, the oxidative addition step is clearly the rate-determining and rate-limiting step in the overall catalytic cycle. The initial product of the oxidative addition is the ion pair **M6**$^+$**·OTf**$^-$. The cationic d^8-ML_3 palladium(II) is coordinated in a T-shape environment by two phosphorus atoms and the aryl ligand. The sulfonate is hydrogen-bridged to the hydroxy group of the former substrate.

The sulfonate counteranion is known to be easily replaced in the coordination sphere of palladium(II). In Figure 4, we omitted the sulfonate anion, and the energy of the cationic palladium(II) cation **M6**$^+$ was arbitrarily normalized to zero. Thus, absolute energy comparisons between Figure 3 on the one side, and Figures 4 and 5 on the other side are not viable. The palladium atom in complex **M6**$^+$ is highly unsaturated. Therefore, the coordination of the hydroxy group to the isomer **M7**$^+$ is highly exergonic. It is not surprising that the alkenes

(22) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200−1211. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. (d) *Jaguar 6.5*; Schrödinger, Inc.: Portland, OR, U.S.A., 2006. (e) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650−654. (f) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299−310. (g) Schaftenaar, G.; Noordik, J. H. *J. Comput.-Aided Mol. Design* **2000**, *14*, 123−134. (h) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265−3269. (i) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; v. R. Schleyer, P. *J. Comput. Chem.* **1983**, *4*, 294−301. (j) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100. (k) Perdew, J. P.; Zunger, A. *Phys. Rev. B* **1981**, *23*, 5048−5079. (l) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822−8824.

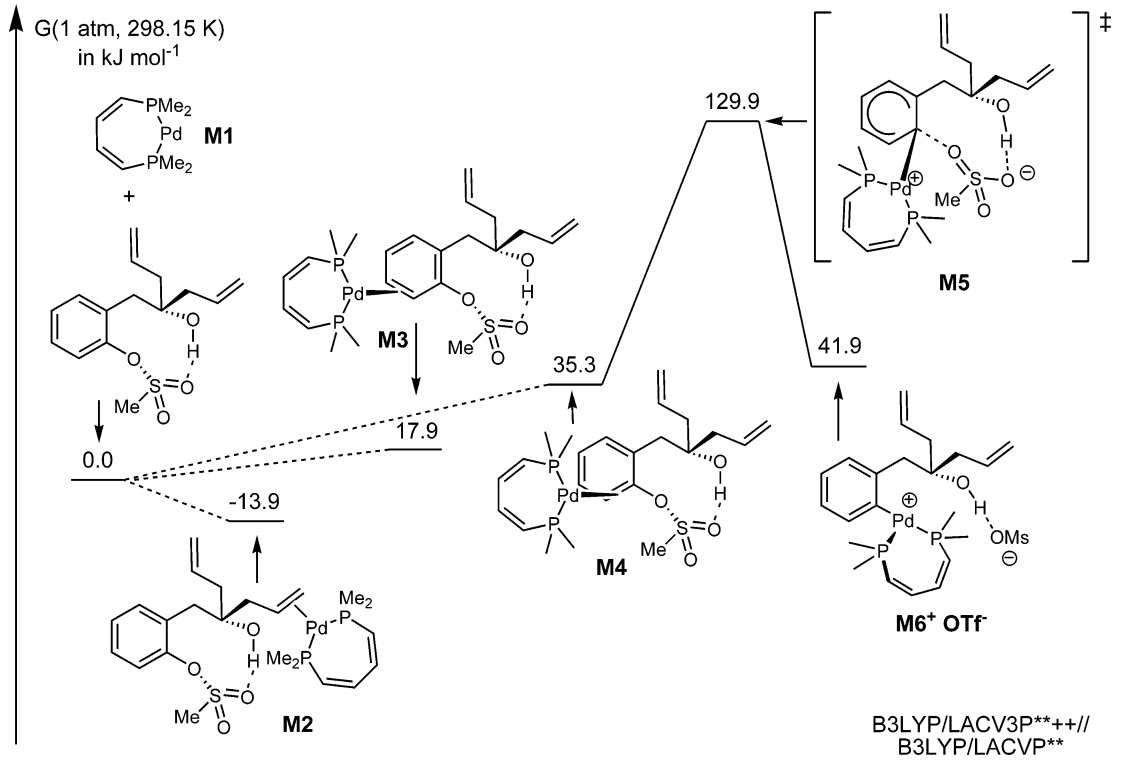


Figure 3. Computed catalyst resting state and rate-determining oxidative addition step.

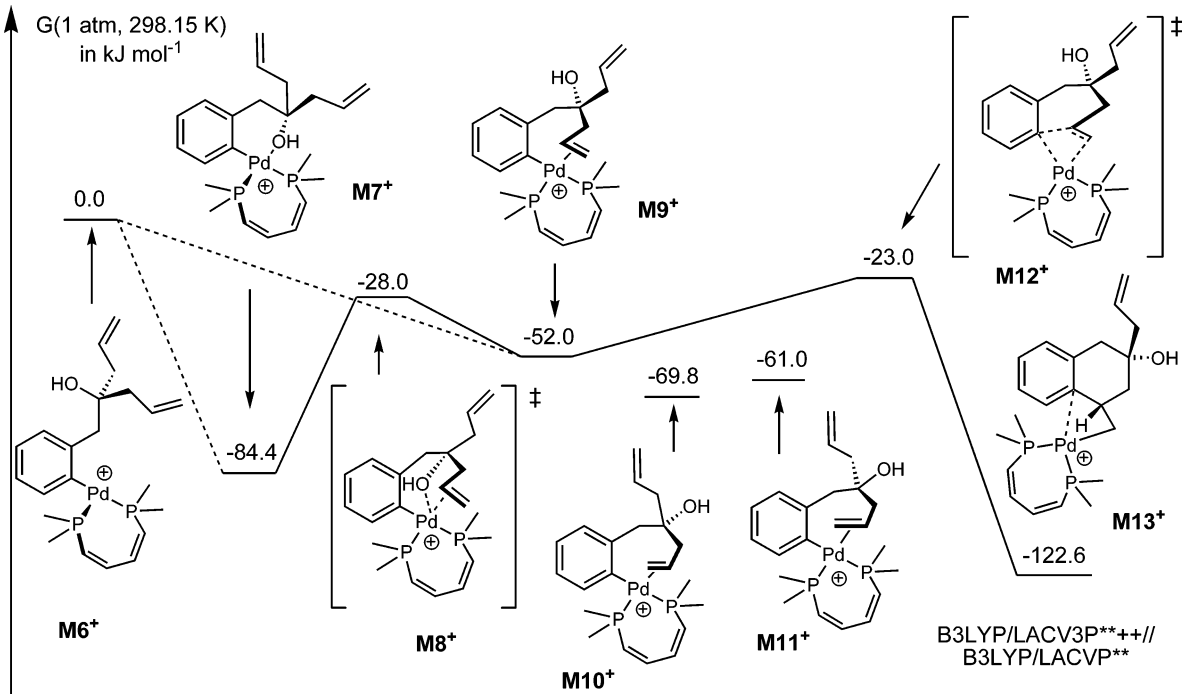


Figure 4. Saturation of the "hot" 14-valence electron palladium(II) cation, rapid ligand exchange, and irreversible stereoselectivity-determining alkene insertion.

bind less tightly to the metal in complexes **M9**$^+$, **M10**$^+$, and **M11**$^+$. The simultaneous coordination of both the hydroxy group and one of the two alkenes at palladium in **M8**$^+$, however, is only a ligand-exchange transition state between two 16-valence electron species. Eighteen-valence electron palladium(II) species are rarely local minima;[23] 16-valence electrons at palladium are usually equivalent to electronic saturation.[24]

The somewhat lower barrier for this alcohol ligand- versus alkene ligand-exchange rearrangement makes the latter faster than the insertion of a coordinated alkene into the C(sp^2)−Pd bond. The hydroxy group might be considered as an intramolecular mediator that facilitates ligand-exchange rearrangements,

(23) Izatt, R. M.; Watt, G. D.; Eatough, D.; Christensen, J. J. *J. Chem. Soc. A.* **1967**, *8*, 1304−1308.

(24) (a) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364−3366. (b) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366−374. (c) Vicente, J.; Arcas, A. *Coord. Chem. Rev.* **2005**, *249*, 1135−1154. (d) Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201−2203. (e) Trzeciak, A. M.; Ziolkowski, J. J. *Coord. Chem. Rev.* **2005**, *249*, 2308−2322.

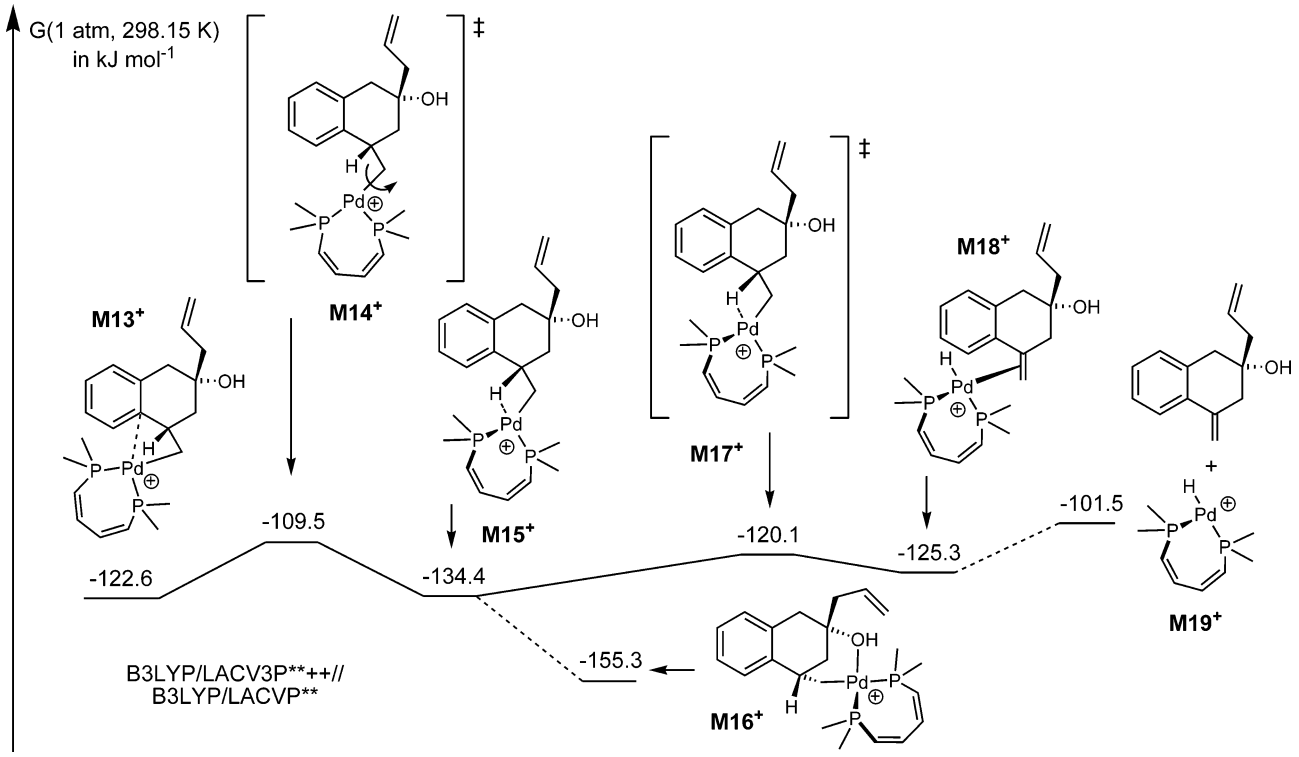


Figure 5. Rearrangement into an agostic complex and β-hydride elimination.

thereby enabling the rapid equilibration toward the alkene complex with the most facile migratory insertion. Such an insertion is highly exergonic and thus irreversible. Despite the formation of a C−C bond in **M12**$^+$, the palladium in **M13**$^+$ remains coordinated at the aryl ipso carbon.

The interaction of palladium with the aromatic π system in **M13**$^+$ is weak, and the rearrangement via the transition state **M14**$^+$ to a β-agostic complex **M15**$^+$ is facile and essentially isoenergetic (Figure 5). The coordination of the hydroxy group at the palladium cation in **M16**$^+$ is again exergonic but too weak to prevent the eventual β-hydride elimination via transition state **M17**$^+$. Deprotonation of either the cationic palladium(II)−alkene hydride complex **M18**$^+$ or a cationic palladium(II) hydride **M19**$^+$ closes the catalytic cycle by reformation of the palladium(0) catalyst resting state.

2.3. Mechanistic Proposal: A Curtin-Hammett-Type Scenario.[25] At the first glance, the Lewis basic oxygen donor appears to be an enantioselectivity-directing "anchor" group. Based on the quantum-chemical model calculations, however, the coordination of the oxygen to the palladium(II) alkene cation intermediate is only temporary. The oxygen ligand enhances the rate for the equilibration of the diastereotopic alkene coordination modes to the (*R*)-BINAP palladium aryl fragment. The ring closure is facile and fast, and an efficient and even faster equilibration is mandatory to translate the free enthalpy barrier difference of the alkene insertion processes into a high enantiomeric excess (Figure 6).

Without hydroxy or methoxy groups, either one of the alkene fragments coordinates to the initially formed 14-valence electron palladium species. This ligand−metal bond formation is instantaneous after an almost barrierless rotation around a single bond. Thus, the coordination of the alkene is fast, and almost randomly, either one of the two diastereotopic alkene fragments coordinates.

An associative alkene-to-alkene ligand exchange is sterically essentially impossible in the real, nonsimplified complex, while the insertion of the coordinated alkene into the C(sp^2)−Pd bond is fast. However, the coordination and dissociation of alkenes in the wrong orientation such as in the oxygen-free analogues of **M10**$^+$ and **M11**$^+$, which would eventually lead to a seven-membered ring product, have to be considered as an unproductive equilibrium. Without intramolecular mediation of the alkene ligand exchange by oxygen ligand atoms, the coordination of the alkene fragment decides upon the diastereoselectivity of the insertion elementary step, and thus it also decides upon the enantioselectivity of the overall reaction.[26]

2.4. Diastereospecificity of the Desymmetrizing Intramolecular Heck Reaction. Cyclization of *Z,Z*-Configured Precursors. As part of our study, we also investigated the influence of the double bond geometry on the stereochemical course of the intramolecular Heck reaction of **9** and **11**. Of course, we were primarily interested in enantiomeric excesses and absolute configurations of cyclization products **13** and **15**, respectively, when using *Z,Z*-configured substrates (*Z,Z*)-**9** and (*Z,Z*)-**11**. Aside from absolute stereocontrol, the diastereospecificity (that is, *E* as well as *Z* configuration in **9**/**11** is retained in **13**/**15**) was of interest.

Surprisingly, cyclization precursors (*Z,Z*)-**9** and (*Z,Z*)-**11** were both significantly less reactive than their diastereomers (*E,E*)-**9**

(25) (a) Curtin, D. *Rec. Chem. Prog.* **1954**, *15*, 111−128. (b) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134. (c) Zefirov, N. S. *Russ. J. Org. Chem.* **1997**, *33*, 138−139. (d) http://www.iupac.org/goldbook/C01480.pdf.

(26) We also wondered whether hydrogen bonding of the hydroxy group to the triflate might facilitate the activation of the substrate's Ar−OTf bond by enhancing the triflate's leaving group capability. However, the reactions of the methoxy derivative and the deoxygenized substrate operate at comparable rates.

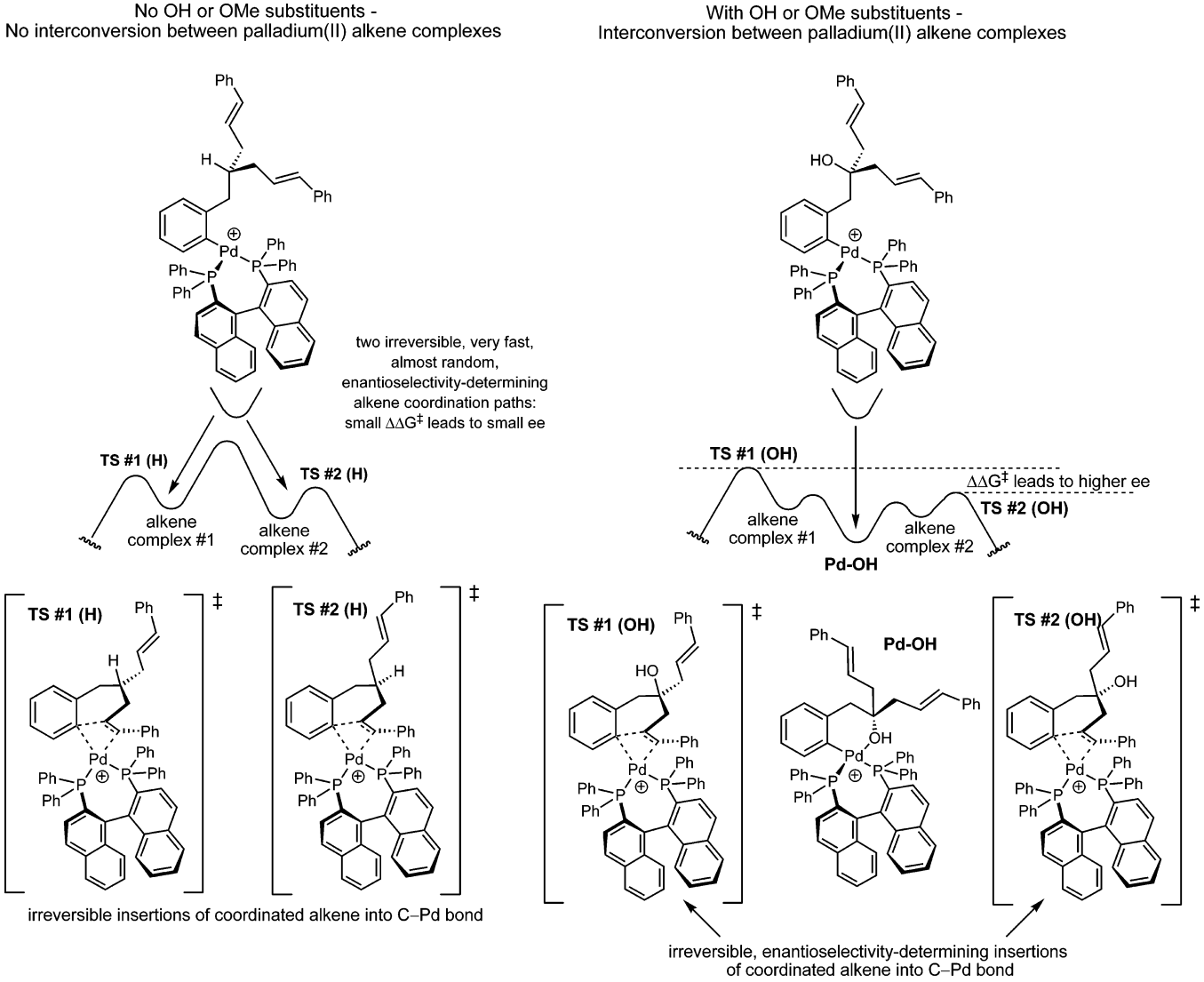


Figure 6. (Left) Random coordination of alkene to palladium(II) and low enantioselectivities for substrates without Lewis basic oxygen. (Right) Curtin-Hammett-type scenario, oxygen donor-mediated equilibration and high enantioselectivities for substrates with Lewis basic oxygen.

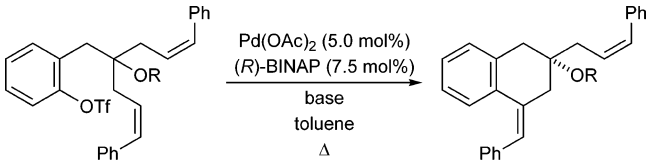
and (*E*,*E*)-**11** (Table 4). A reaction temperature of 100 °C finally facilitated the cyclization of (*Z*,*Z*)-**9** and (*Z*,*Z*)-**11**. In the presence of K_2CO_3 as the base, completely isomerized (*R*,*E*,*E*)-**13** (63% ee) and (*R*,*E*,*E*)-**15** (80% ee) were isolated in high yields (Table 4, entries 1 and 2). Careful analysis and purification of the crude product allowed for the reisolation of minor amounts of (*E*,*E*)-**9**, which is a sound indication of predominant pre-Heck[27] rather than post-Heck double bond isomerization by the palladium hydride species.

When using TMP as the base, we were pleased to find that no palladium hydride-mediated *E*,*Z* isomerization to the thermodynamically favored *E*-alkenes occurred. (*Z*,*Z*)-**9** and (*Z*,*Z*)-**11** cyclized in moderate to good yields and with poor enantiomeric excesses (Table 4, entries 3 and 4). Absolute configuration of (*R*,*Z*,*Z*)-**13** and (*R*,*Z*,*Z*)-**15** was assigned by chemical correlation, iodine-catalyzed isomerization, with (*R*,*E*,*E*)-**13** and (*R*,*E*,*E*)-**15**, respectively.

This base-dependent difference of the diastereochemical outcome might be rationalized by the physical state of the bases.

(27) Sonesson, C.; Larhed, M.; Nyqvist, C.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 4756−4763.

Table 4. Desymmetrization of Cyclization Precursor (*Z*,*Z*)-**9** and (*Z*,*Z*)-**11**[a]

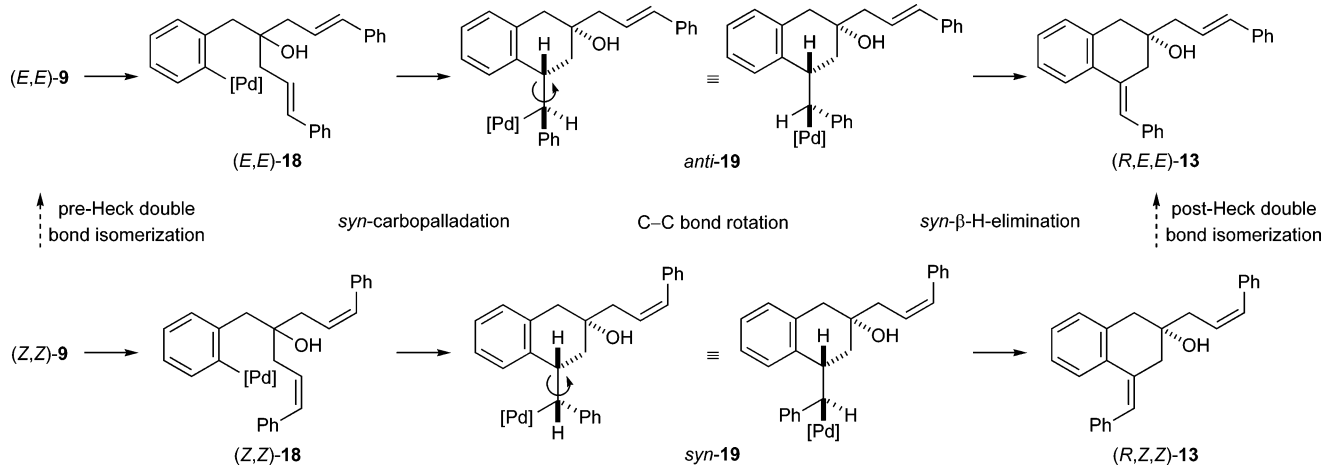


(*Z*,*Z*)-**9** (R = H)
(*Z*,*Z*)-**11** (R = Me)
(*R*,*Z*,*Z*)-**13** (R = H)
(*R*,*Z*,*Z*)-**15** (R = Me)

entry	precursor	base	*T* [°C]	*t* [h]	product	ee [%][b]	yield [%][c]
1	(*Z*,*Z*)-**9**	K_2CO_3	100	20	(*R*,*Z*,*Z*)-**13**	-	*d*
2	(*Z*,*Z*)-**11**	K_2CO_3	100	20	(*R*,*Z*,*Z*)-**15**	-	*e*
3	(*Z*,*Z*)-**9**	TMP	100	20	(*R*,*Z*,*Z*)-**13**	33	61[f]
4	(*Z*,*Z*)-**11**	TMP	80	20	(*R*,*Z*,*Z*)-**15**	38	80

[a] All reactions were conducted with a substrate concentration of 0.1 M in toluene with 4.0 equiv of the respective base. [b] See Supporting Information for details. [c] Yield of analytically pure product isolated after flash column chromatography on silica gel. [d] The desired product was not detected; instead, (*R*,*E*,*E*)-**13** (58%, 63% ee) and (*E*,*E*)-**9** (15%) were isolated. [e] The desired product was not detected; instead, (*R*,*E*,*E*)-**15** (86%, 80% ee) was isolated. [f] Isolated along with the 2(2*E*)-isomer (*R*,*Z*,*E*)-**13** (6%) and the 4*E*-isomer (*R*,*E*,*Z*)-**13** (3%).

Scheme 2. Diastereospecific Desymmetrizing Heck Cyclizations



Reductive elimination of palladium hydrides might be fast under homogeneous conditions (TMP as the base) while being hampered under heterogeneous conditions (K_2CO_3 as the base) which, in turn, opens the undesired *syn*-hydropalladation reaction channel.

The pair of diastereospecific Heck reactions ((*E*,*E*)-**9** → (*R*,*E*,*E*)-**13** and (*Z*,*Z*)-**9** → (*R*,*Z*,*Z*)-**13**) is outlined in Scheme 2. It is a particularly nice example of stereospecific *syn*-carbopalladation (**18** → **19**) as well as *syn*-β-hydride elimination (**19** → **13**). The poor catalytic turnover in the *Z*,*Z* series might originate from an energetically unfavorable β-hydride elimination of *syn*-**19**, forming a *cis*-stilbene unit (*syn*-**19** → (*R*,*Z*,*Z*)-**13**); conversely, β-hydride elimination of *anti*-**19** will liberate a thermodynamically more stable *trans*-stilbene unit (*anti*-**19** → (*R*,*E*,*E*)-**13**).

3. Conclusion

A directing effect of an oxygen donor was first seen by Heck[16] and, later, further verified by Cacchi and Ortar[17] as well as Kang[18] in regioselective Heck arylations. Controlling regio- or diastereoselectivity in intermolecular Heck reactions by a covalently bound heteroatom donor has generally been an emerging area in recent years.[15,28] Several amine- and pyridine-based systems were introduced by Hallberg,[29] Carretero,[30] and Itami and Yoshida.[31]

The present study demonstrates for the first time the unique influence of a weak donor on enantioselection in an asymmetric Heck reaction. We initially assumed that a similar directing effect governs asymmetric induction in the desymmetrizing Heck ring closure of the acyclic prochiral cyclization precursor (*E*,*E*)-**9**,[14a] but in contrast to the above-mentioned processes, combined experimental and quantum-chemical examinations revealed a refined, unprecedented mechanistic picture. A series of control experiments substantiates temporary coordination of a Lewis basic oxygen to weakly Lewis acidic palladium(II) as the pivotal enantioselectivity-controlling structural element,[32] which mediates or, more precisely, facilitates equilibration of diastereomeric alkene−palladium(II) complexes prior to the irreversible, stereochemistry-determining migratory insertion. In principle, this situation resembles an intramolecular Curtin-Hammett scenario as the ratio of the diastereomeric alkene−palladium(II) complexes is not reflected in the level of enantioselection. In the absence of the Lewis basic oxygen, the energetic barrier for interconversion of the diastereomeric alkene−palladium(II) complexes is substantially higher than the activation energy for alkene insertion into the C(sp^2)−Pd bond. Consequently, the ratio of the initially formed diastereomeric alkene−palladium(II) complexes is reflected in the level of enantioselection.

This conceptually interesting neighboring-group effect also underscores the fundamental influence of weak donors in palladium-catalyzed asymmetric C−C bond-forming reactions. With a vacant coordination site at palladium(II) (cationic pathway) and the oxygen donor in ideal proximity to it, high chemical yield (98%) and excellent enantiomeric excess (97% ee) were obtained under unusually mild reaction conditions (50 °C).

The findings disclosed herein as well as a recent seminal contribution by Curran[33] clearly corroborate that exploration of the stereochemistry-determining step in asymmetric Heck processes is worthwhile, providing insight beyond conventional mechanistic reasoning.

We also studied the influence of the double bond configuration in the cyclization precursor on the level of enantioselectivity. High enantiomeric excess was only seen for *E*,*E* diastereomers ((*E*,*E*)-**11** → (*R*,*E*,*E*)-**15**, 83%, 93% ee, TMP as base); the corresponding *Z*,*Z*-configured substrates were less reactive and selective ((*Z*,*Z*)-**11** → (*R*,*Z*,*Z*)-**15**, 80%, 38% ee, TMP as base). While under those conditions diastereospecific,

(28) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.
(29) (a) Andersson, C.-M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757−5761. (b) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217−8225. (c) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2003**, *125*, 3430−3431.
(30) (a) Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129−7130. (b) Díaz Buezo, N.; de la Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890−3900.
(31) (a) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2001**, *123*, 11577−11585. (b) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2004**, *126*, 11778−11779. (c) Itami, K.; Yoshida, J.-i. *Synlett* **2006**, 157−180.
(32) Overman presented evidence for a unique directing effect of an alkene unit in a diastereoselective Heck cyclization. We had also considered such an interaction in our system (*E*,*E*)-**9**, but unselective ring closure of (*E*,*E*)-**12** dispelled this idea (Table 1): (a) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785−3788. (b) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859−4862.
(33) Lapierre, A. J. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2007**, *129*, 494−495.
(34) Sempere-Culler, F. Diploma Thesis, Albert-Ludwigs-Universität, Freiburg, Germany, 2004.

it is interesting to note that, using solid K_2CO_3 as the base, complete *E*,*Z* isomerization occurred ((*Z*,*Z*)-**11** → (*R*,*E*,*E*)-**15**, 86%, 80% ee). Pre-Heck double bond scrambling is likely.[27]

Acknowledgment. The research was (in part) supported by the International Research Training Group Freiburg-Basel (GRK 1038) (predoctoral fellowship to A.B.M., 2005−2006) and the Fonds der Chemischen Industrie. M.O. is indebted to the Deutsche Forschungsgemeinschaft for an Emmy Noether fellowship (2001−2006). B.F.S. thanks the Verband der Chemischen Industrie, the Ludwigs-Maximilians-Universität München as well as the Freie Universität Berlin, the Dr. Otto Röhm-Gedächtnisstiftung, and the Deutsche Forschungsgemeinschaft (Str 861/2-1) for financial support. We thank Dipl.-Chem. Fernando Sempere-Culler[13,14a,34] for significant contributions in the early phase of the project, Ilona Hauser for the large-scale preparation of 3-bromo-1-trimethylsilyl-1-propyne, Gerd Fehrenbach for performing the HPLC analyses, and Dr. Manfred Keller for a X-ray crystal structure analysis (all Albert-Ludwigs-Universität Freiburg).

Supporting Information Available: Starting material syntheses, characterization data as well as ^1H and ^{13}C NMR spectra for all new compounds, and determination of absolute configuration including molecular structure (X-ray); Cartesian coordinates and energy data of computed model complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

JA072571Y