ARTICLES

Recent Developments and New Perspectives in the Heck Reaction

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More than two decades ago, Mizoroki[1] and Heck[2] independently discovered the palladium-catalyzed arylation and vinylation of olefins. This methodology, known worldwide as the Heck reaction (Scheme 1),[3] is attractive from a synthetic point of view because high chemoselectivity and mild reaction conditions are associated with low toxicity and cost of the reagents.[4] During the past few years, the experience obtained in several palladium-based reactions helped in understanding the rules which govern the coordination−insertion of unsaturated systems on palladium(II) complexes. In fact, this process has a central role in determining the reaction rate, stereoselectivity, and regioselectivity of intra- and intermolecular Heck reactions, hydrosilylations, oligomerizations of olefins, and olefin−CO copolymerizations.[5]

The purpose of this account is to review and critically evaluate the results on the Heck reaction recently obtained by several research groups. These results can be explained on the basis of a common mechanistic hypothesis for the coordination−insertion process of unsaturated systems on palladium(II) complexes (Scheme 2, step b).
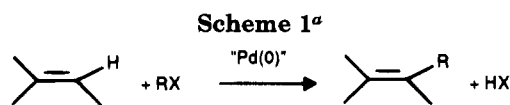
Heck Reaction Mechanism

Oxidative Addition (Scheme 2, Step a). Except for the case of aryl iodides, the presence of ligands is necessary in order to effect oxidative addition of RX to the palladium(0) complex at a reasonable temperature (Scheme 2, step a).[6] The catalytically active species is a 14-electron complex, $L_2Pd(0)$,[7] and effective ligands in the Heck reaction are monodentate[3] and bidentate phosphines[8] and 1,10-phenanthroline derivatives.[9]

Coordination−Insertion (Scheme 2, Step b). The geometry of the complex is a central point, and

Scheme 1[a]

[a] R = aryl, vinyl; X = I, Br, COCl, OTf, etc.

Scheme 2. The Heck Reaction: General Mechanism

several theoretical studies aimed at the identification of the reactive species in the coordination−insertion of unsaturated systems on Pd(II) and Pt(II) complexes have appeared in the literature. The orbital studies on the insertion of ethylene into a Pt−H bond carried out by Thorn and Hoffmann[10] gave two important pieces of information: (1) The insertion process requires a coplanar assembly of the metal, ethylene, and the hydride. Therefore, the insertion process is stereoselective and occurs in a *syn* manner. This is in agreement with experimental observations by Heck.[11] (2) The energy barrier for the generation of the
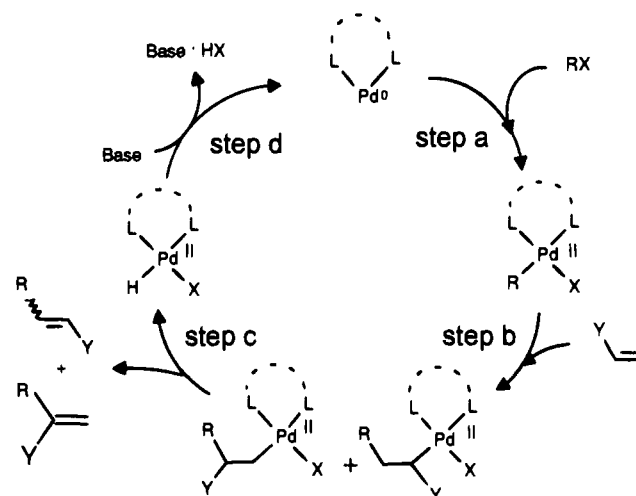
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(1) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971,** *44,* 581.

(2) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972,** *37,* 2320.

(3) (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985. (b) Heck, R. F. *Org. React. (N.Y.)* **1982,** *27,* 345.

(4) Cabri, W. *Chim. Ind. (Milan)* **1993,** *75,* 314 and references therein.

(5) Colman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, CA, 1987.

(6) Other leaving groups have been described in the literature, but their applications are limited. Sulfinates: (a) Garves, K. *J. Org. Chem.* **1970,** *35,* 3273. Sulfonyl chlorides: (b) Kasahara, A.; Izumi, T.; Azami, H.; Yamamoto, S. *Chem. Ind. (London)* **1988,** 51. Iodonium salts: (c) Moriarty, R. M.; Epa, W. R.; Awasthi, A. K. *J. Am. Chem. Soc.* **1991,** *113,* 6315. Diazonium salts: (d) Kikukawa, K.; Naritomi, M.; He, G.-H.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1985,** *50,* 299 and references therein.

Scheme 3. The Coordination–Insertion Process
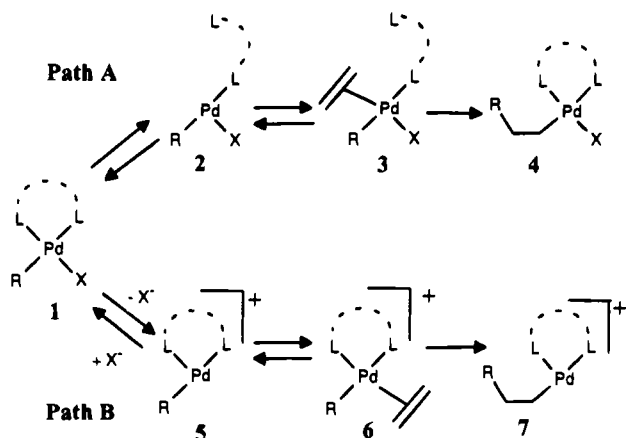
reactive configuration in a tetracoordinated complex is low with respect to a pentacoordinated one. Therefore, pentacoordinated species are possibly not involved in the coordination process. These results are also supported by experimental work on the chemistry of in-plane coordinated double bonds[12] and by kinetic studies.[13]

Results of catalytic as well as stoichiometric studies on the coordination–insertion process of an olefin on a palladium(II) complex in the Heck reaction[14] and in olefin–CO copolymerization[15] support a mechanism based on two reaction pathways (Scheme 3): path A involves coordination of the olefin *via* dissociation of one neutral ligand; path B involves coordination of the olefin *via* dissociation of the anionic ligand. Two coordination sites of the square planar complexes **3** and **6** are occupied by the olefin and the fragment R that has to migrate onto the π-system. Therefore, the control exerted by the catalyst depends on the remaining two ligands, which are one neutral and one anionic in the neutral complex **3** (path A) or both neutral in the cationic complex **6** (path B).

Historically, the Heck reaction was the functionalization of olefins by aryl iodides, aryl bromides, aroyl chlorides, or the corresponding vinyl halides, carried out without ligands in the case of aryl iodides or in the presence of monodentate phosphines [i.e., PPh₃ or P(o-Tol)₃] with the other compounds.[3] Under these reaction conditions a square planar palladium(II) oxidative addition complex with a weak Pd–PR₃ bond (or Pd–solvent bond when phosphine ligands are not present) and a strong Pd–I(Br,Cl) bond[16] is generated. Therefore, the coordination of the unsaturated system takes place *via* dissociation of one of the neutral ligands, and a neutral palladium(II) complex is formed (Scheme 3, path A).[13] In this context, the Heck observation, "Chelating diphosphines...in general do not produce useful catalysts",[17] was valid because only aryl halides were used. In fact, with bidentate ligands a decrease of the reaction rates or sometimes a complete suppression of the reaction is observed.[14,15] The approach of the olefin is hampered by the competitive coordination of the ligand, the equilibrium **1** ⇌ **2** being shifted to the left.[14b]

The introduction of triflates as leaving groups gave a completely different scenario owing to the lability of the Pd–OTf bond[18] present in the oxidative addition complex **1**. In 1991 we[14c] and Ozawa–Hayashi[14d] independently proposed the formation of cationic palladium(II) complexes in the coordination–insertion process of the Heck reaction. In fact, combining triflate as leaving group and bidentate phosphorous or nitrogen ligands, the coordination of the unsaturated system takes place *via* dissociation of the counterion (Scheme 3, path B), affording the cationic palladium(II) complex **6**. The complex **6** can give high asymmetric induction when the diphosphine is chiral while complex **3** cannot.[14d] Furthermore, the reactivity of complexes **2** and **5** depends on the charge density of the unsaturated system.[14c] Competitive experiments showed that the neutral complex **2** reacts faster with electron poor olefins (good π-acceptors and poor σ-donors). In contrast, the cationic complex **5** reacts faster with electron rich olefins (poor π-acceptors and good σ-donors).[9a]

The Heck reaction is a flexible methodology. In fact, it is easy to switch from one mechanism to the other.[14b] Complex **3** can be generated using halides as leaving group or by simple addition of halide anions to the reaction of aryl and vinyl triflates. The labile Pd–OSO₂R bond is substituted with the strong Pd–I(Br,Cl) bond.[19] On the other hand, complex **6** can be generated using triflate as leaving group or by addition of sequestrating agents of halide anions, such as AgY[20] or TlY[21] salts (Y = nitrate, carbonate, phosphate, acetate, triflate, etc.), to the reaction of aryl and vinyl halides. The strong Pd–I(Br,Cl) is substituted with a labile Pd–Y bond.

β-Hydride Elimination–Dissociation (Scheme 2, Step c). The β-hydride elimination is stereoselec-

(7) (a) Negishi, E.-i.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1336. Amatore and Jutand showed that L₂PdX⁻ (X = Cl or Br) can be involved in the oxidative addition of aryl halides to zerovalent palladium complexes carried out in the presence of halide anions. See: (b) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.

(8) (a) Chen, Q.-Y.; Yang, Z.-Y. *Tetrahedron Lett.* **1986**, *27*, 1171. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1990**, *55*, 3654.

(9) (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1993**, *58*, 7421. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *Synlett* **1992**, 871.

(10) Thorn, D. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 2079.

(11) Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707.

(12) (a) Rakowsky, M. H.; Woolcock, J. C.; Rettig, M. F.; Wing, R. M. *Organometallics* **1988**, *7*, 2149. (b) Miki, K.; Kai, Y.; Kasai, Y.; Kurosawa, H. *J. Am. Chem. Soc.* **1983**, *105*, 2482.

(13) Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505.

(14) Catalytic studies: (a) See ref 9a. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481. (c) Cabri, W.; Candiani, I.; DeBernardinis, S.; Francalanci, F.; Penco, S.; Santi, R. *J. Org. Chem.* **1991**, *56*, 5796. (d) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. Stoichiometric studies: (e) Yamamoto, A.; Kawataka, F.; Kayaki, Y.; Shimizu, I. 7th IUPAC Symposium on Organo-Metallic Chemistry directed towards Organic Synthesis, Kobe, September 1993, Abstr. No. 137A.

(15) (a) Dekker, G. P. C. M.; Elsevier, C. J.; Vrieze, K.; van Leeuwen, P. W. N. M.; Roobeek, C. F. *J. Organomet. Chem.* **1992**, *430*, 357. (b) Markies, B. A.; Rietveld, M. H. P.; Boersma, J.; Spek, A. L.; van Koten, G. *J. Organomet. Chem.* **1992**, *424*, C12. (c) Ozawa, F.; Hayashi, T.; Koide, H.; Yamamoto, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1469. (d) Brumbaugh, J. S.; Whittle, R. R.; Parvez, M.; Sen, A. *Organometallics* **1990**, *9*, 1735.

(16) Henry, P. M. *Palladium Catalyzed Oxidation of Hydrocarbons*; D. Riedel: Dordrecht: Holland, 1980; pp 11–15.

(17) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146.

(18) The lability of the Pd–OTf and Pt–OTf bonds is well documented. See: (a) Dekker, G. P. C. M.; Elsevier, C. J.; Vrieze, K.; van Leeuwen, P. W. N. M. *Organometallics* **1992**, *11*, 1598. (b) Stang, P. J.; Kowalsky, M. H.; Schiavelli, M. D.; Longford, D. *J. Am. Chem. Soc.* **1989**, *111*, 3347.
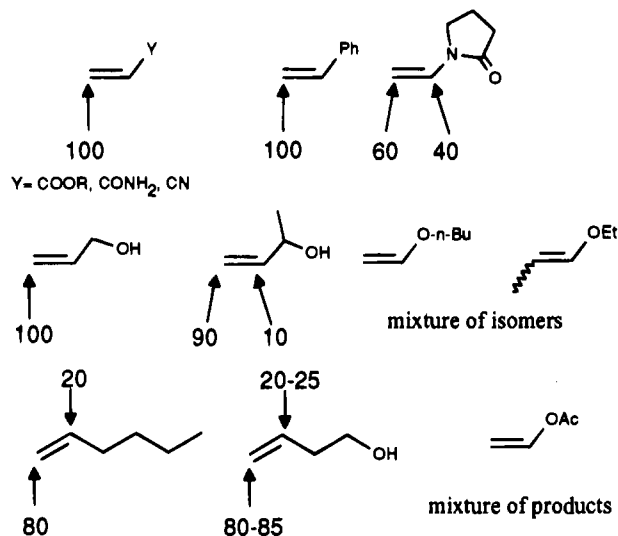
(19) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

(20) Leading references: (a) Larock, R. C.; Gong, W. H.; Baker, E. *Tetrahedron Lett.* **1989**, *30*, 2603. (b) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (c) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896.

(21) Leading references: (a) Reference 14b. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *Tetrahedron Lett.* **1991**, *32*, 1753. (c) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687.

Scheme 4

dissociation   dissociation
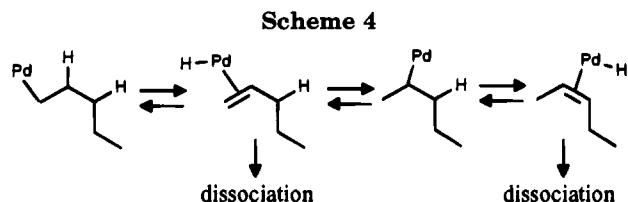
**Scheme 5. Heck Reaction Regioselectivity.
Coordination−Insertion Process *via* Path A**

100   100   60   40

Y = COOR, CONH$_2$, CN

100   90   10   mixture of isomers

20   20-25

80   80-85   mixture of products

tive and occurs in a *syn* manner;[11] its efficiency is related to the dissociation of the olefin from the palladium(II)−hydride complex. The β-hydride elimination is a reversible process, and a slower dissociation of the olefin can determine the formation of several products because of the isomerization of the double bond (Scheme 4). This disadvantage can be eliminated, in reactions between cyclic olefins and aryl halides, by adding Ag(I)[20a,b] or Tl(I) salts.[21c]

Recycling of the L$_2$Pd(0) (Scheme 2, Step d).
The presence of a base is necessary in order to transform the L$_2$Pd(H)X into the starting L$_2$Pd(0) complex and close the catalytic cycle. Typical bases are trialkylamines (Et$_3$N, ^{i}Pr$_2$NEt, etc.) or inorganic salts (AcONa, K$_2$CO$_3$, etc.); however, good results were sometimes obtained with either Proton Sponge or Tl(I) or Ag(I) salts.

Regioselectivity

Aryl Derivatives.   Intermolecular Heck Reaction. The regioselectivities of the arylation of several classes of olefins usually reported in books and reviews[3,5,17,22] are described in Scheme 5. All these results have been obtained using procedures that favor the coordination−insertion process *via* dissociation of the ligand (Scheme 3, path A). Our results on the intermolecular arylation of olefins modified substantially this scheme allowing the extension of the synthetic usefulness of the Heck reaction (cf. Schemes 5 and 6). The protocol, centered on the use of aryl

**Scheme 6. Heck Reaction Regioselectivity.
Coordination−Insertion Process *via* Path B**

100   60   40   100   100

Y = COOR, CONH$_2$, CN

100   5   95   100   100

80-85   90

20-25   10   5   95
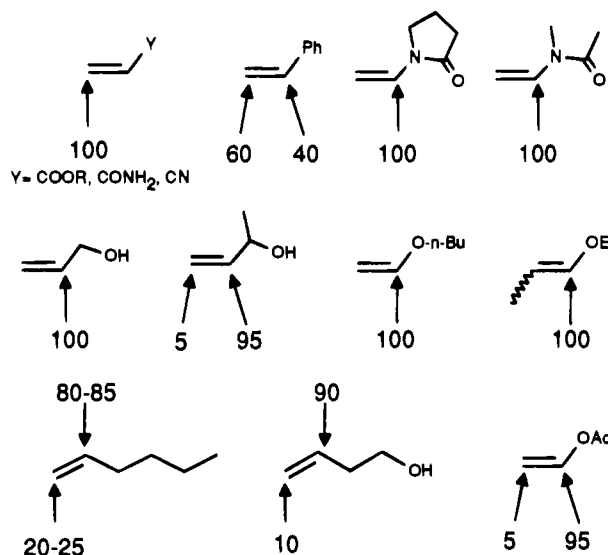
triflates[8b,9,14b,c,23a] or aryl halides/(Tl(I)[14b,21b] and the generation *in situ* of the palladium(0) catalyst from Pd(OAc)$_2$ and bidentate phosphorous ligands (i.e., DPPP, DPPF),[24] allows the coordination−insertion process to follow path B. Preferential formation of the branched products in the arylation of heterosubstituted olefins (enol ethers, enol amides, and vinyl acetate), allyl alcohols, and homoallyl alcohols was observed independently of the substituents on the aryl triflate, the reaction temperature, and the solvent (Scheme 6). Similar results were obtained in the reaction between aryl triflates and enol ethers or enol amides carried out in the presence of bidentate nitrogen ligands (i.e., 1,10-phenanthroline derivatives).[9] The best selectivities and yields were obtained using neocuproine[24] as palladium ligand.

The selected examples of Table 1 show that the regioselectivity is related only to the coordination−insertion pathway. Steric factors always favor the migration of the R group in complexes **3** and **6** to the less substituted carbon with formation of the linear products. However, when the reaction proceeds *via* dissociation of the counterion (path B), electronic factors predominate. In fact, the coordination of the π-system in a cationic complex **6** determines an increase of the polarization, and selective migration of the aryl moiety (formally as anion) onto the carbon with the lower charge density is observed.

The flat nature of 1,10-phenanthroline derivatives allows the Heck reaction to be carried out at lower temperature than that required in the case of the corresponding bidentate phosphorous ligands because of a decreased steric hindrance above and below the coordination plane (Table 1). Unfortunately, with bidentate nitrogen ligands the substitutions on the aryl triflate affect the reaction course. In fact, low regioselectivities and conversions were observed with electron-withdrawing and electron-donating groups,

(22) (a) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, p 799. For the arylation of heteroatom-substituted olefins, see: (b) Davis, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433.

(23) (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558. For a review on synthetic transformations of aryl and vinyl triflates, see: (b) Ritter, K. *Synthesis* **1993**, 735.

(24) DPPP = 1,3-bis(diphenylphosphino)propane; DPPF = 1,1'-bis-(diphenylphosphino)ferrocene; neocuproine − 2,9-dimethyl-1,10-phenanthroline; (R)-BINAP = (R)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; Proton Sponge = 1,8-bis(dimethylamino)naphthalene; PMP = 1,2,2,6,6-pentamethylpiperidine.

Table 1. Palladium-Catalyzed Reaction between Aryl Derivatives 8a–c and Butyl Vinyl Ether 9 in DMF[9a,14b]
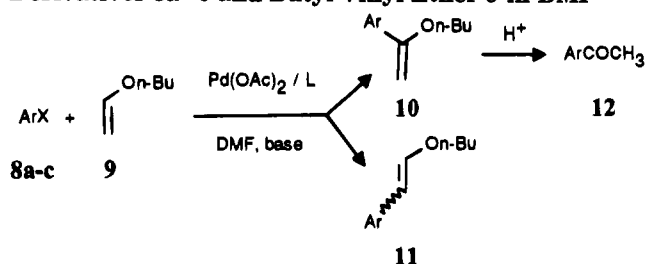
ArX[a]	ligand	base	conditns	10/11	12, % yield	path
8a	DPPP	Et₃N	100 °C, 18 h	67/33	63	A
8a	DPPP	TlOAc	80 °C, 1 h	>99/1	92	B
8b	DPPP	Et₃N	100 °C, 18 h	61/39	54	A
8b	DPPP	TlOAc	80 °C, 0.7 h	>99/1	97	B
8c	PPh₃	Et₃N	100 °C, 1.5 h	63/37	55	A
8c	DPPP	Et₃N	60 °C, 0.5 h	>99/1	97	B
8c	neocuproine	Et₃N	40 °C, 2.5 h	>99/1	95	B

a 8a, 1-naphthyl iodide; 8b, 1-naphthyl bromide; 8c, 1-naphthyl triflate.

Table 2. Palladium-Catalyzed Arylation of β-Amino[25] and β-Phosphorus[26] Functionalized Vinyl Ethers 17
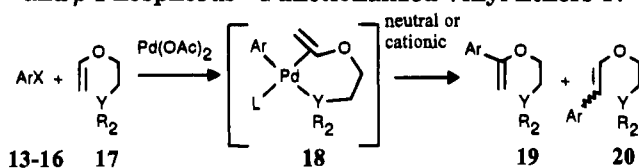
ArX[a]	(CH₃)₂N	ligand	conditns	19/20	20, % yield
13	(CH₃)₂N		80 °C, 16 h	3/97	82
14	(CH₃)₂N	PPh₃	80 °C, 16 h	4/96	52
15	Ph₂P		80 °C, 0.5 h	<1/99	75
16	Ph₂P		80 °C, 0.75 h	<1/99	81

a 13, PhI; 14, PhBr; 15, 3-CNC₆H₄OTf; 16, 4-NO₂C₆H₄OTf.

respectively.[9a] Therefore, unless the substrate is unstable at high temperature the use of DPPP or DPPF as ligands is preferred.

Recently, Hallberg[25] and Badone[26] reported the arylation of modified enol ethers, containing nitrogen and phosphorous derivatives, respectively (Table 2). The formation of the corresponding linear products was observed because both substrates behave as bidentate ligands, **18**. The arylation of these β-amino and β-phosphorus functionalized vinyl ethers carried out in the absence of ligands or in the presence of monodentate phosphines gave results that are complementary to the results described by us using butyl vinyl ether **9** (cf. Tables 1 and 2). However, preferential formation of the branched products **19** was observed when the reaction between aryl triflates and **17** (R = (CH₃)₂N) was carried out in the presence of DPPP. In this case, the coordination–insertion process follows path B and the olefin behaves as a monodentate ligand with formation of complex **6**.[25c]

(25) (a) Larhed, M.; Andersson, C. M.; Hallberg, A. *Acta Chem. Scand.* **1993**, *47*, 212. (b) Andersson, C.-M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757. (c) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285.

(26) Badone, D.; Guzzi, U. *Tetrahedron Lett.* **1993**, *34*, 3603.

Stereoselectivity

Over the years several chiral ligands for asymmetric catalysis have been synthesized and studied.[27] However, the best enantiomeric purities in the Heck reaction have been obtained using a bidentate phosphine ligand, chiral BINAP.[24]

Intermolecular Asymmetric Heck Reaction. Generally, the Heck reaction has been used to incorporate aryl, vinyl, or benzyl moieties on sp² carbons (Scheme 1). However, several examples of allylic cross-coupling with cyclic alkenes have been reported.[3] It is worth noting that with cyclic olefins the hydrogen present on the functionalized carbon cannot be involved in the β-hydride elimination process, being anti with respect to the carbon–palladium(II) bond; therefore, the R group is incorporated on an sp³ carbon.

In this context, Hayashi and Ozawa have reported significant results on the stereoselective intermolecular Heck reactions using aryl triflates and the catalyst generated *in situ* from Pd(OAc)₂ and (R)-BINAP.[14d,28] The selected examples reported in Table 3 were carried out under analogous conditions (benzene, 30–60 °C). When the mechanism follows path B, the chiral ligand is strongly attached to the metal with both phosphorus atoms throughout the coordination–insertion process, determining an effective transfer of the chiral information from the catalyst to the substrate. The breakthrough was the combination of (R)-BINAP as ligand (other chiral ligands gave bad results) and triflate as leaving group (entries 1 and 2). However, the stereoselectivity was dependent on the added base; in fact, with simple trialkylamines the enantiomeric purity of the major product ranged between 63% and 93%. In contrast, with Proton Sponge[24] the enantiomeric purity ranged between 87% and >96% irrespective of the aryl substitution (entries 2 vs 3 and 4 vs 5). As previously observed, if the dissociation of the olefin from the palladium(II)–H species is not sufficiently fast, the migration of the double bond cannot be avoided (Scheme 4). In this case, Ozawa and Hayashi proposed that a kinetic resolution process, *via* selective isomerization of the minor enantiomer, allowed an increase in the stereoselectivity of the reaction with a concomitant decrease in the yield. In fact, using Proton Sponge as added base, the ee increased, but low **25/26** ratios were obtained (entries 3 and 5).

The steric influence of (R)-BINAP determines the high enantioselectivity of the reaction. Unfortunately, only electron-rich systems like 2,3-dihydrofuran and N-substituted 2-pyrrolines are sufficiently reactive.[29] As pointed out above, electronic factors affect the coordination process and cationic complexes like **5** react faster with electron rich olefins.[9a,14c]

The palladium-catalyzed asymmetric alkenylation carried out using [Pd{(R)-BINAP}₂] as precatalyst did not suffer from the drawbacks of the corresponding

(27) Kagan, H. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: London, 1985; Vol. 5, Chapter 1.

(28) Hayashi, T.; Kubo, A.; Ozawa, F. *Pure Appl. Chem.* **1992**, *64*, 421 and references therein.

(29) The arylation of 4H-1,3-dioxin by phenyl triflate under Ozawa–Hayashi conditions failed. However, the use of DMF as solvent and slightly higher temperature allowed isolation of 4-phenyldioxin in 37% yield with an estimated enantiomeric excess of 35%. See: Sakamoto, T.; Kr⁻ `, Y.; Yamanaka, H. *Tetrahedron Lett.* **1992**, *33*, 6845.

Table 3. Intermolecular Asymmetric Heck Reaction[28,30]
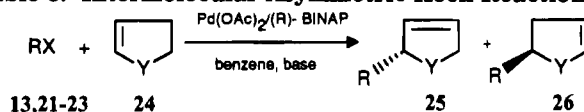
entry	Rx[a]	Y	base	25/26	25	26	path
					\% ee (\% yield)		
1	**13**	O	Et$_3$N	92/8	(23)	(2)	A
2	**21**	O	^{i}Pr$_2$NEt	89/11	93 (71)	67 (7)	B
3	**21**	O	Proton Sponge	71/29	>96 (46)	17 (24)	B
4	**22**	N(COOMe)	Et$_3$N	86/14	66 (74)	11 (12)	B
5	**22**	N(COOMe)	Proton Sponge	56/44	83/19	4 (15)	B
6	**23**	O	Proton Sponge	0/100		87 (58)	B
7	**23**	N(COOMe)	Proton Sponge	0/100		96 (45)	B

a **21**, PhOTf; **22**, 4-ClC$_6$H$_4$OTf; **23**, 1-cyclohexenyl triflate.

Table 4. Intramolecular Asymmetric Heck Reaction for the Stereoselective Synthesis of *cis*-Decalin Derivatives[32a]
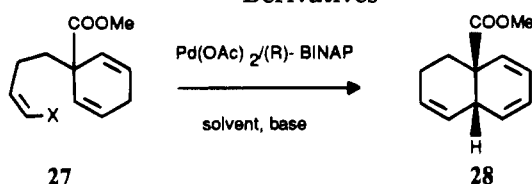
entry	X	base	conditns	28, \% ee (\% yield)	path
1	I	Et$_3$N	NMP	0.4	A
2	I	AgCO$_3$	NMP, 60 °C, 210 h	58 (65)	B
3	I	Ag$_3$PO$_4$	NMP, 60 °C, 188 h	69 (48)	B
4	OTf	K$_2$CO$_3$	toluene, 60 °C, 55 h	91 (54)	B

arylation.[30] In fact, compound **26** was the only reaction product (entries 6 and 7). Using this methodology, the stereoselective alkenylation of *cis*-2-cycloalkene-1,4-diols has been recently reported by Prasit.[31] The corresponding arylation failed.

Intramolecular Asymmetric Heck Reaction. Highly stereoselective palladium-catalyzed cyclizations have been reported by Shibasaki[32] and Overman.[33] It is worth noting that the best results in terms of stereoselectivity, reaction rate, and yield have been obtained using BINAP as ligand and the halide/Ag(I) system or triflate as leaving group.

Among the several examples reported by Shibasaki for the stereoselective synthesis of *cis*-decalins,[32a] hydrindans,[32a] and indolizidines,[32b] it is possible to appreciate the increase in enantiomeric purity moving from path A to path B in the *cis*-decalin series (Table 4). The addition of Ag(I) salts as sequestrating halide agents to the reaction of the vinyl iodide derivative allowed isolation of the cyclized product in good yields and enantiomeric purities (entries 1–3). However, as in the case of the intermolecular stereoselective Heck reaction, the best results have been obtained using the

(30) Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505.

(31) Prasit, P.; Chua, P.; Roy, P. 7th IUPAC Symposium on Organo-Metallic Chemistry directed towards Organic Synthesis, Kobe, September 1993, Abstr. No. S 18.

(32) (a) Shibasaki, M.; Sato, Y.; Kagechika, K. *Yuki Gosei Kagaku Kyokaishi* **1992**, *50*, 826 and references therein. (b) Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4965. (c) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477.

(33) (a) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. This methodology was used for the stereoselective synthesis of (−)-physostigmine; see: (b) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949.

Scheme 7
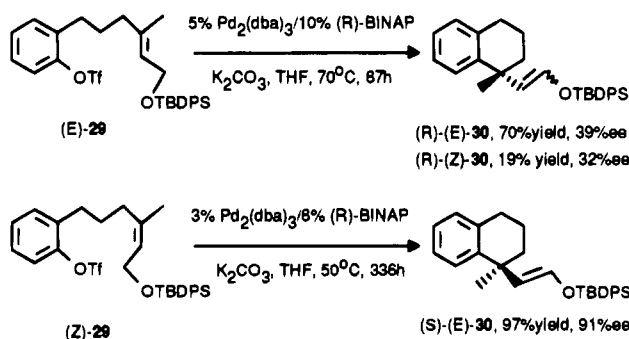
Scheme 8
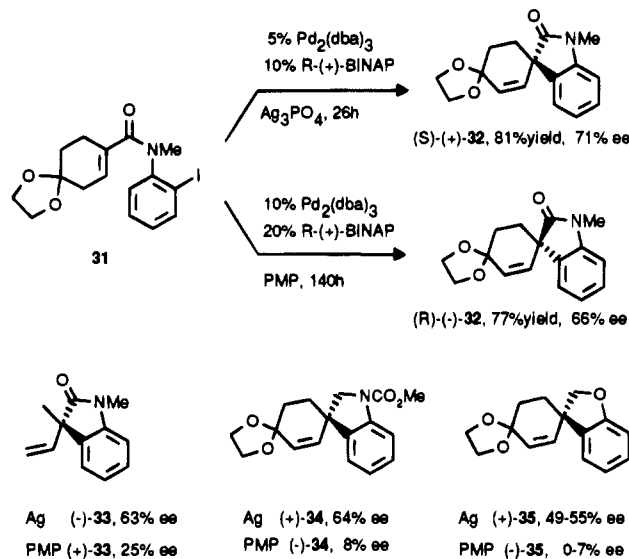
corresponding triflate derivative (entry 4). Another important result was the synthesis of tetralin derivatives having a benzylic quaternary carbon center *via* asymmetric intramolecular Heck reaction using triflate as leaving group.[32c] In this case the enantioselectivity of the reaction was related to the geometry of the olefin present in the starting material (Scheme 7).
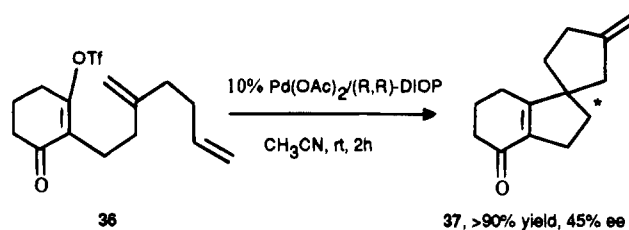
Overman reported the stereoselective synthesis of quaternary carbon *via* asymmetric intramolecular Heck reaction (Scheme 8).[33] The enantiomeric purity of the reactions carried out at 80 °C in *N,N*-dimethylacetamide with (*R*)-BINAP and the aryl iodide/Ag(I) system ranged between 49% and 71%. However, when

PMP[24] was used as base in the absence of the Ag(I) salt, long reaction times but still good stereoselectivities of the opposite enantiomers were obtained. These results seem to be in contrast with the mechanism of the coordination—insertion process described in Scheme 3. In fact, in the absence of Ag(I) the reaction follows path A and the transfer of the chiral information should be difficult. However, when the double bond is not in a cyclic ring (**33**), the ee drops to 25%, and with more flexible substrates the products (**34 and 35** were almost racemic. Therefore, even though (*R*)-BINAP was coordinated only by one of the phosphorus atoms, with rigid substrates like **31** an effective transfer of the chiral information was observed *via* path A.

Polycyclizations. The palladium-catalyzed polyene cyclization is an attractive synthetic methodology,[34] however, there is only one example of the corresponding stereoselective version using chiral ligands (Scheme 9). Overman reported in 1989 that the cyclization of a trienyl triflate **36** carried out in the presence of (*R,R*)- or (*S,S*)-DIOP afforded the target product **37** with an enantiomeric excess of

Scheme 9

45%.[35] Possible applications of this approach, *via* path B, to polycyclic compounds are unexplored.

Concluding Remarks

From a mechanistic point of view, the coordination—insertion process described in Scheme 3 explains the effects that several factors (leaving groups, neutral ligands, additives, and olefin substituents) have on the reaction course. This mechanistic model is a useful tool for a better understanding of the scope and limitations of the Heck reaction.

Taking into consideration the high level of regio- and stereoselectivity control obtained during the last five years and the flexibility of the methodology, the Heck reaction offers excellent opportunities in the synthesis of polyfunctional compounds.

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(34) (a) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813. Very interesting results have been reported by Grigg on palladium-catalyzed tandem-cyclization-anion capture processes. See, for example: (b) Burns, B.; Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron* **1992**, *48*, 7297.

(35) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.