The Stille Reaction: A Density Functional Theory Analysis of the Transmetalation and the Importance of Coordination Expansion at Tin

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The transfer of an alkynyl group from $Sn(C\equiv CH)_4$ (**6**) to $PdBr(PH_3)_2(C\equiv CH)$ (**7**) was studied computationally. Nucleophilic assistance at the Sn atom during the transmetalation was modeled by using ammonia as the nucleophile. Eight distinct reaction modes have been found: they are of the cyclic or open type when only one phosphine is bound to Pd, and open when two phosphines are bound to Pd. The stabilization effect produced on the transition state by the nucleophilic assistance at Sn can be almost 10 kcal/mol. A number of stable π-complexes resulting from the substitution of either Br or PH_3 of **7** by the alkynyl group triple bond of **6** have also been found, which may correspond to the intermediates postulated in many mechanistic studies of the Stille coupling.

Introduction

The Stille reaction (eq 1) has emerged recently as a very important tool in organic synthesis.[1] Within the family of the transition metal-mediated cross-coupling reactions, it is one of the most frequently used protocols, due to the fact that stannanes are compatible with most functional groups and the reaction is run under neutral conditions.

$$R^1Sn(R^2)_3 \quad + \quad R^3\text{-}X \quad \xrightarrow{\text{Pd(0)L}_n} \quad R^1\text{-}R^3 \quad + \quad X\text{-}Sn(R^2)_3 \quad (1)$$
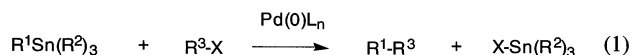
From the mechanistic standpoint, the reaction is believed to proceed via the traditional cycle of oxidative addition−transmetalation−reductive elimination.[1] In many cases, when reactive halides are used, the rate-limiting step of the reaction is the transmetalation, and in contrast to the well-studied oxidative and reductive steps, much less is known about this key step.[2] Echavarren et al. have recently been able to study the transmetalation in a system that is resistant to reductive elimination, offering therefore a qualitative description of the factors that affect this step.[3] By kinetic analysis of the coupling of alkenyl and aryl stannanes,

an intermediate has been postulated along the reaction pathway leading to the transmetalation product.[4] This intermediate, in which one molecule of ligand has become dissociated from Pd(II), has been interpreted in a number of ways: as a π-complex between tetracoordinated Pd(II) and the stannane double bond;[4] a solvento or tricoordinated complex;[5,6] or a σ-complex.[7] As a consequence of this fact, a tremendous rate acceleration is produced by ligands of reduced donicity, a fact that has been widely exploited from the synthetic standpoint.[6]

A facet of the transmetalation that has been almost completely ignored so far is the coordination/geometry changes at tin during the transmetalation. The "nontransferable" substituents at tin are often ignored in the analysis of the reaction.[8] More recently, however, Vedejs et al.[9] and Brown et al.[10] have shown that certain substituents bearing nucleophilic moieties can accelerate the transmetalation (see Chart 1), probably by some sort of intramolecular nucleophilic assistance at tin by

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(1) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.
(2) Cetinkaya, B.; Lappert, M. F.; McMeeking, J.; Palmer, D. E. *J. Chem. Soc., Dalton Trans.* **1973**, 1202. Eaborn, C.; Odell, K.; Pidcock, A. *J. Organomet. Chem.* **1975**, *96*, C38. Cardin, C. J.; Cardin, D. J.; Lappert, M. F. *J. Chem. Soc., Dalton Trans.* **1977**, 767. Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* **1978**, 357. Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Chem. Soc. Dalton Trans.* **1979**, 758. Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129.

(3) Cárdenas, D. J.; Mateo, C.; Echavarren, A. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2445. Mateo, C.; Cárdenas, D. J.; Fernández-Rivas, C.; Echavarren, A. M. *Chem. Eur. J.* **1996**, *2*, 1596. Mateo, C.; Fernández-Rivas, C.; Cárdenas, D. J.; Echavarren, A. M. *Organometallics* **1998**, *17*, 3661.
(4) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
(5) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598.
(6) Farina, V.; Roth, G. P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1995; Vol. 5, p 1. For a recent mechanistic study of a related reaction of organostannanes, see also: Ricci, A.; Angelucci, F.; Bassetti, M.; Lo Sterzo, C. *J. Am. Chem. Soc.* **2002**, *124*, 1060.
(7) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978. Casado, A.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11771. Casado, A.; Espinet, P.; Gallego, A. M.; Martinez-Ilarduya, J. *J. Chem. Soc., Chem. Commun.* **2001**, 339.
(8) For an interesting study on nucleophilically promoted Stille reaction, see: Fouquet, E.; Rodriguez, A. L. *Synlett* **1998**, 1323.
(9) Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556.
(10) Brown, J. M.; Pearson, M.; Jastrzebski, J. T. B. H.; Van Koten, G. *J. Chem. Soc., Chem. Commun.* **1992**, 1440.

Chart 1. Two Systems That Transfer R Groups in Stille Couplings at Enhanced Rates
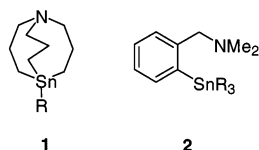
Chart 2. Possible Transitions States for Transmetalation: 3 and 4 Lead to Retention at C, 5 to Inversion
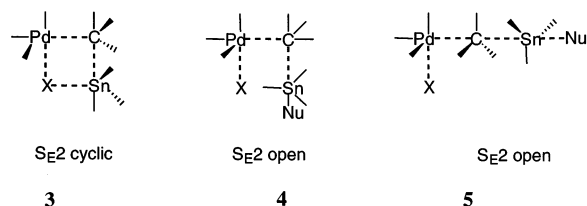
the pendant amino groups. The effect qualitatively described by Vedejs et al. is especially dramatic, because even secondary alkyl groups, which are normally resistant to transmetalation, can be coupled.

In a preliminary quantitative analysis of the importance of intramolecular nucleophilic assistance,[11] it was found that this phenomenon is solvent dependent. This is not surprising, given that other electrophilic cleavage reactions of stannanes follow different mechanisms depending on the solvent.[12] More precisely, nonpolar solvents support closed transition states, whereas polar solvents can support open ones (Chart 2, Nu = solvent or any nucleophilic species present in solution; Sn is represented as pentacoordinated for simplicity). The stereochemical consequence of this mechanistic duality is the observation that the electrophilic cleavage of tetraalkylstannanes can proceed with retention (compatible both with S_E2 cyclic and S_E2 open) or inversion (compatible only with S_E2 open) of configuration at the sp^3 carbon.[13] Results show that the effect of intramolecular nucleophilic assistance is stronger in nonpolar solvents, where the transition state is expected to be of the cyclic type.[11] This led to the proposal that in the transition state of the transmetalation tin is preferentially *hexacoordinated*, not pentacoordinated. In noncoordinating solvents, under standard conditions, one coordination site is occupied by the halide being transferred from Pd(II) to Sn(IV), the other remaining empty, which makes the reaction energetically rather unfavorable. Under this scenario, the transmetalation in nonpolar solvents should be promoted by nucleophiles. The situation is likely to be similar in polar solvents, with the solvent filling the empty coordination sites at tin. This phenomenon has a well-known counterpart in silicon chemistry: it is appreciated that hexacoordinated silicon compounds are important intermediates in a number of reactions.[14]

It was felt that a theoretical analysis of the several possible transition states for the transmetalation may

shed some light on this point and aid mechanistic interpretation.

We wish to report here such a theoretical analysis, based on ab initio calculations and aimed at evaluating and comparing the energetic consequences of the coordination geometry at Pd and Sn on the transmetalation of the Stille reaction. We devoted particular attention to the optimal geometrical requirements for the postulated inter- and intramolecular nucleophilic assistance. Worth testing, for example, was Vedejs' proposal that the nucleophile has to attack from an apical position of the tbp,[9] whereas the substituent being transferred prefers to occupy the other apical position.

As a model system for the Stille-type transmetalation, we selected the transfer of an ethynyl group from tetraethynyltin (**6**) to the bromo ethynyl Pd(II) complex **7** (eq 2). The adoption of a model where all the carbon atoms of the stannane are alkyne carbons leads to the absence of rotamers, and therefore it is expected to facilitate dramatically the search for the transition states. Although the Stille reaction is most frequently applied to the coupling between sp^2 carbon centers, examples of alkynyl moieties coupling as either the nucleophilic or electrophilic component are well known,[1] and it is hoped that the transition states computed with our model will provide good starting geometries for the calculation of the transition states of other crosscoupling substrates.
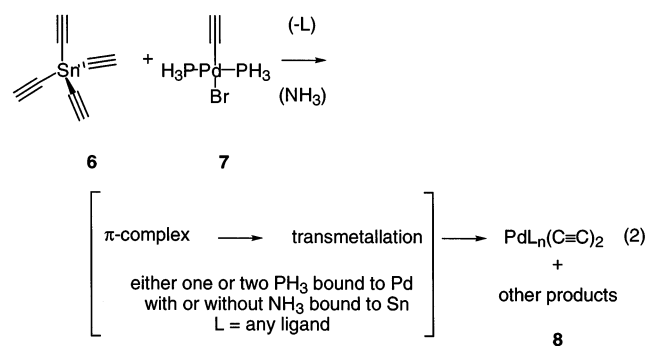
The stereochemistry assumed for the Pd reagent, the *trans* complex **7**, was based on data showing that the oxidative addition of unsaturated halides to Pd(0) produces square-planar complexes of the *trans* configuration, presumably through equilibration of a kinetically labile *cis* isomer.[1] The product of the transmetalation, on the other hand, has been usually represented as a Pd(II) complex with two *trans* carbon substituents,[1] isomerizing to a *cis* species prior to reductive elimination, although this view has been challenged.[7] We judged, however, that choosing **7** rather than the corresponding *cis* isomer was not critical in exploring the potential energy surface of the transmetalation and that any alteration could eventually be done along with other refinements of the model. The transition structures of the transmetalation were searched among those whose composition included either one or two phosphine ligands bound to Pd. The transmetalation modes in which two phosphines remain bound to Pd throughout the transmetalation process (associative mechanism) are the most obvious reaction pathways to investigate, and most substitution processes at Pd follow this associative process. The transmetalation in which only

(11) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73.

(12) Rahm, A.; Grimeau, J.; Pereyre, M. *J. Organomet. Chem.* **1985**, *286*, 305, and references therein.

(13) Abraham, M. H. In *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1973; Vol. 12, p 211.

(14) Holmes, R. H. *Chem. Rev.* **1990**, *90*, 17. Chuit, C.; Corriu, J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371.

one phosphine ligand is present (L-dissociative mechanism) was suggested mainly by the experimental observation that the transmetalation is inhibited by "excess" ligand present in solution. In an attempt to clarify the mechanistic details of the transfer of an alkynyl moiety from Sn to Pd, we investigated in some detail possible π-complexes arising from the substitution of a ligand present on Pd by an alkynyl group bound to Sn. Such species have been postulated as intermediates in the trasmetalation involving alkenyl groups. The postulated (vide supra) effects of donor atoms at Sn during the transmetalation were modeled by allowing the participation of a molecule of ammonia in the Sn coordination sphere. This was considered a useful model, because in both **1** and **2** the accelerating effect is due to an amine moiety. In the present investigation, the actual structures of species resulting from the transmetalation (**8**) were not predefined but are those resulting as the first minimum energy species following the transition state, and no attempt was made to investigate their transformation into the final and more obvious product of a transmetalation.

Computational Details

All calculations were carried out using the Gaussian 98 program package.[15] In particular, for all optimizations the density functional theory (DFT) approach was followed, using Becke's three-parameter hybrid method with LYP correlation (B3LYP)[16] and the basis set LanL2DZ (using Hay and Wadt's ECP with the corresponding DZ basis set for Pd, Sn, Br, P,[17] and Dunning−Huzinaga's DZ basis set for C, H, and N[18]). The B3LYP/LanL2DZ combination has proved to be quite reliable in energy and geometry computations in systems containing transition metals.[19] Transition states (TSs) were searched without symmetry constraints following the method of Schlegel (as implemented in the "TS" option of Gaussian Input) starting with approximate geometries of transition states found by empirical exploration of the potential energy surface along hypothetical reaction coordinates. For a better accuracy, we have repeated all optimizations with an improved basis set, using as starting points the minima and TSs obtained at the LanL2DZ level. The modified basis set contained polarization d functions on the Sn, Br, and P atoms (with exponents 0.18, 0.364, and 0.434, respectively).[20] In some cases intrinsic reaction coordinate (IRC) calculations were carried out to confirm correlation of transition states with products. For all optimized transition states, a normal-mode analysis was

(15) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, J. M.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Foz, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzelez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.6; Gaussian Inc.: Pittsburgh, PA, 1998. For a practical guide, see: Foresman, J. B.; Frisch, A. *Exploring Chemistry with Electronic Structure Methods*; Gaussian Inc.: Pittsburgh, 1996.
(16) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
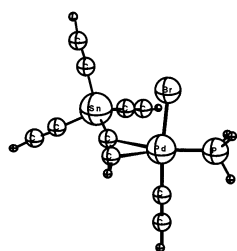(17) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270.
(18) Dunning, T. H.; Hay, P. G. In *Modern Theoretical Chemistry*; Schaefer, H. F., III, Ed.; Plenum: New York, 1976, Vol. 3, p 1.
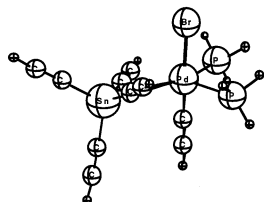(19) Niu, S.; Hall, M. B. *Chem. Rev.* **2000**, *100*, 353. Dedieu, A. *Chem. Rev.* **2000**, *100*, 543.
(20) Check, C. E.; Faust, T. O.; Bailey, J. M.; Wright, B. J.; Gilbert, T. M.; Sunderlin, L. S. *J. Phys. Chem. A* **2001**, *105*, 8111.

Table 1. Electronic Energies (ΔDFT), Electronic Plus Zero-Point Energies (ΔE), and Electronic Energies Plus Thermal Free Energy (ΔG) of Formation of All Species Referred to Phosphine, Ammonia, and Reagents 6 and 7 (kcal/mol); Calculations Performed at LanL2DZ Level or with the Improved Basis Set (LanL2DZ + d) Containing Polarization d Functions for P, Sn, and Br Atoms

	LanL2DZ			LanL2DZ + d		
compound	ΔDFT	ΔE	ΔG	ΔDFT	ΔE	ΔG
9-Pd-Sn	12.9	11.3	13.1	13.2	11.8	13.8
10-Pd-Sn*	13.9	12.8	24.0	14.6	13.8	25.1
11-Pd*	30.8	28.6	18.2	28.0	26.1	16.0
12-PdP-Sn.1	18.2	18.5	31.2	17.7	18.1	31.0
13-PdP-Sn.2	18.3	18.2	31.6	20.0	20.1	33.6
14-PdP-Sn*	18.4	18.5	31.8	17.9	18.1	31.6
15-SnN	−12.1	−9.1	0.9	−11.4	−8.5	1.4
16-Pd-axSnN	−1.0	0.5	12.2	0.3	1.8	13.7
17-Pd-eqSnN.1	−3.3	−1.4	10.9	−2.1	−0.2	12.1
18-Pd-eqSnN.2	−4.9	−3.1	9.1	−3.2	−1.4	10.8
19-PdP-SnN.1	−2.4	1.4	25.1	−1.4	2.2	26.1
20-PdP-SnN.2	1.6	5.0	28.1	2.4	5.7	29.1
21-PdSn.cy*	31.6	29.4	32.3	30.0	28.0	31.2
22-PdSn.op*	27.9	25.6	27.4	27.8	25.7	27.7
23-PdPSn*	22.0	22.1	36.0	21.2	21.3	35.4
24-PdSnN.cy*	18.0	19.1	31.8	19.0	20.1	32.9
25-PdSnN.op*	10.5	11.7	23.5	10.6	11.9	24.0
26-PdSnN.tbp1*	5.0	6.7	20.1	6.0	7.8	21.3
27-PdSnN.tbp2*	3.7	5.2	18.0	5.0	6.5	19.5
28-PdSnN.oct1*	14.7	15.6	27.6	14.5	15.4	27.9
29-PdSnN.oct2*	7.2	8.4	20.5	8.2	9.5	21.7
30-PdPSnN*	1.3	4.9	29.3	1.4	4.9	29.5
31-Prod.1	28.9	26.7	27.6	26.5	24.5	25.9
32-Prod.2	18.2	18.2	18.2	21.1	19.2	19.9
33-Prod.3	1.7	3.4	15.1	3.5	5.2	17.2
34-Prod.4	1.7	3.0	14.0	5.0	6.4	17.5
35-Prod.5a	*	*	*			
36-Prod.5b+5a	11.6	11.8	11.2	6.4	6.2	5.9
37-Prod.5c+5a	−6.1	−2.5	7.0	−9.2	−6.2	3.5

performed in order to confirm that only one imaginary frequency was present and that it was associated with the transition state of the reaction coordinate under investigation.

Results

The electronic energies, the electronic energies corrected for the zero-point energy, and the electronic energies corrected for the thermal free energy of all intermediates (T = 298 K), transition structures, and products calculated in this study are gathered in the Supporting Information. Table 1 contains, for an easier evaluation of the reaction profiles, the readily derived values of electronic energy differences (ΔDFT), the same plus ZPE correction (ΔE), and the differences of free energies (ΔG) for all species, taking as references the isolated tetraethynyltin **6** plus the diphosphine complex **7** and free ammonia; as an example, the energy of formation of **9** was calculated by adding the energies of **9** and the free phosphine and subtracting the energies of complexes **6** and **7**. The structures of all species computed in this study are displayed in Charts 3−9. In particular, Charts 3−5 show those species (mainly π-complexes) that might precede the actual transmetalation on the reaction coordinate. Charts 6−8 contain the structures of the transition states leading to transmetalated products; Chart 9 shows a number of products or intermediates found by exploring the reaction coordinate beyond the transition structure; as mentioned in the Introduction, no attempt was made to track the development of the first minimum energy
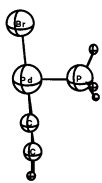
Chart 3. Reagents, Intermediates Preceding the Transmetalation (species resulting from phosphine and bromine displacement without nucleophilically assisted Sn), and Transition Structures Leading to Their Formation from Reagents (in parentheses, free energies of formation as defined in Table 1)
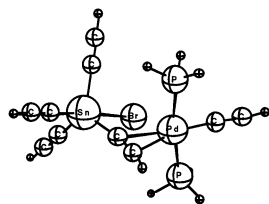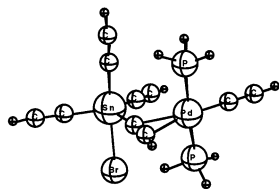

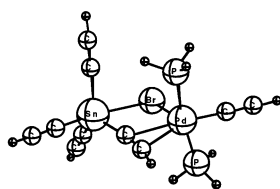**9 Pd-Sn** (13.8)   **10 Pd-Sn*** (25.1)

11 Pd* (16.0)   **12 PdP-Sn.1** (31.0)

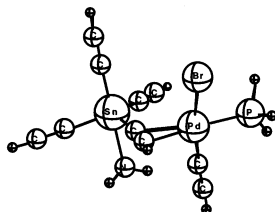**13 PdP-Sn.2** (33.6)   **14 PdP-Sn*** (31.6)

Chart 4. Reagents and Transmetalation Intermediates (phosphine displacement) with Nucleophilically Assisted Sn (in parentheses, free energies of formation as defined in Table 1)
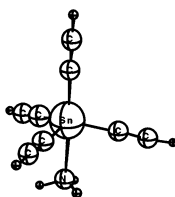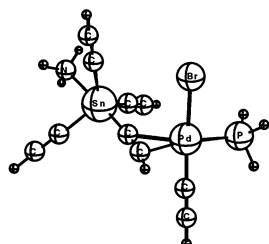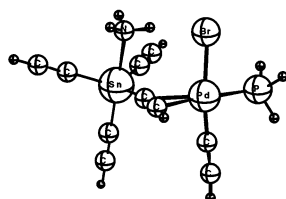

15 SnN (1.4)   **16 Pd-axSnN** (13.7)
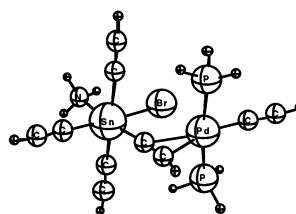
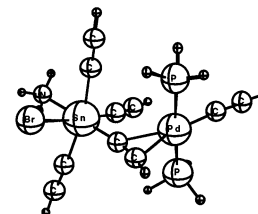**17 Pd-eqSnN.1** (12.1)   **18 Pd-eqSnN.3** (10.8)

species found after each transition state to the final transmetalation product.

Chart 5. Transmetalation Intermediates (bromine displacement) with Nucleophilically Assisted Sn (in parentheses, free energies of formation as defined in Table 1)
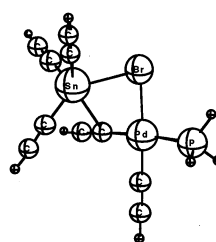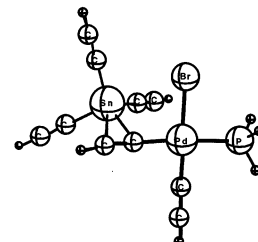

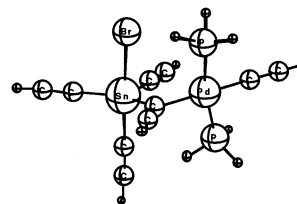**19 PdP-SnN.1** (26.1)   **20 PdP-SnN.2** (29.1)

Chart 6. Transmetalation Transition States (after phosphine or bromine displacement) without Nucleophilically Assisted Sn (in parentheses, free energies of formation as defined in Table 1)

**21 PdSn.cy*** (31.2)   **22 PdSn.op*** (27.7)

23 PdPSn* (35.4)

As a general feature, the free energies of formation (ΔG) may differ from the corresponding 0 K energies (ΔDFT and ΔE) by up to 12 kcal/mol; in particular, ΔG is higher than ΔE (or ΔDFT) for all species involving an association reaction, such as the formation of binuclear complexes (without phosphine expulsion) or the addition of ammonia. Conversely, ΔG is lower than ΔE for species resulting from a dissociation, such as a phosphine loss, but the two quantities are comparable in the case of binuclear complex formation with phosphine exclusion. These differences are clearly related to entropy factors. The following discussion will focus mainly on ΔG values.

On the pathways leading to transition states, a number of π-complexes were found, originating from the substitution of one phosphine or the bromide atom of the complex **7** by the alkyne moiety of **6**. As mentioned in the Introduction, these complexes were investigated systematically for different reasons: they are possible intermediates preceding the actual transfer of the alkynyl group from Sn to Pd and might have an important role in bringing reagents together in the specific case of an alkyne transmetalation; also, π-complexes have been postulated in the transmetalation of

Chart 7. Transition States (after phosphine displacement) with Nucleophilically Assisted Sn (in parentheses, free energies of formation as defined in Table 1)
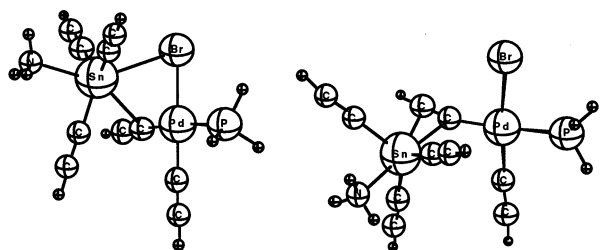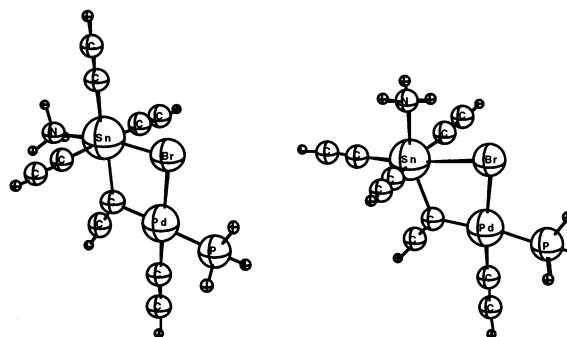

24 PdSnN.cy* (32.9)   **25 PdSnN.op*** (24.0)
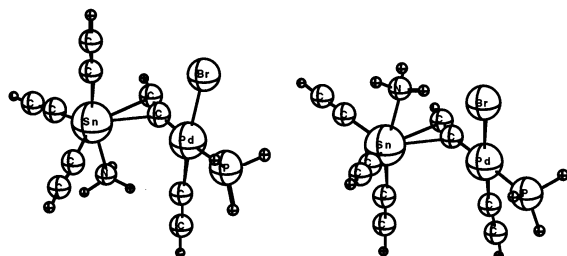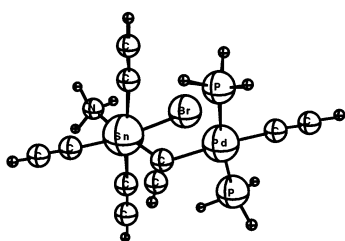

26 PdSnN.tbp1* (21.3)   **27 PdSnN.tbp2*** (19.5)

28 PdSnN.oct1* (27.9)   **29 PdSnN.oct2*** (21.7)

Chart 8. Transmetalation Transition State (after bromide displacement) with Nucleophilically Assisted Sn (in parentheses, free energies of formation as defined in Table 1)


30 PdPSnN* (29.5)

alkenes, and data on related alkynes might provide useful insights.

In the formation of the monophosphine complex **9** (**Pd-Sn**, $\Delta G = 13.8$ kcal/mol, $\Delta E = 11.8$) the interaction of an ethynyl group in **6** with the coordination site of **7**

Chart 9. Products of Transmetalation or Minimum Energy Species Following the Transmetalation Step (in parentheses, free energies of formation as defined in Table 1)
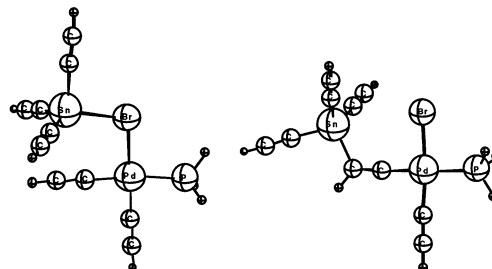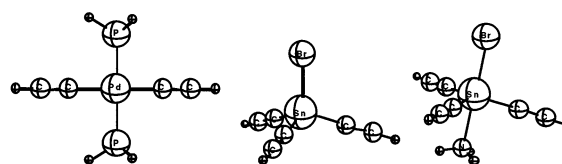

31 Prod.1 (25.9)   **32 Prod.2** (19.9)
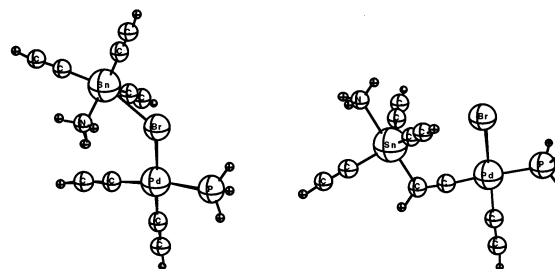
33 Prod. 3 (17.2)   **34 Prod.4** (17.5)

35 Prod.5a   **36 Prod.5b** (5.9)   **37 prod.5c** (3.5)

freed by a phosphine does not fully compensate for the enthalpic loss of a Pd−phosphine bond. Two possibilities were considered for the formation of complex **9**: one is the associative displacement of the phosphine of **7** by the alkynyl group of **6** via the transition structure **10** (**Pd-Sn***, $\Delta G = 25.1$, $\Delta E = 13.8$ kcal/mol); the other a L-dissociative mode via the tricoordinate species **11** (**Pd***, $\Delta G = 16.0$ kcal/mol, $\Delta E = 26.1$ kcal/mol). Although both the associative and dissociative paths are clearly possible, the free energy for the associative process is quite high due to an unfavorable entropic contribution, and the dissociative mode via **11** seems much more favorable.

In the π-complex containing two phosphines, **12** (**PdP-Sn.1**, $\Delta G = 31.0$ kcal/mol), formed by displacement at Pd(II) of the Br atom by an ethynyl group of **6**, Br is strongly interacting with Sn, which is at the center of a trigonal bipyramid with Br in the apical position. For the ligand exchange converting **7** and **6** into **12**, the transition state **14** (**PdP-Sn***, $\Delta G = 31.6$) was found, which is quite close to **12** in free energy and in geometry. The formation of the π-complex **12** is energetically much less favorable than that of **9**. As expected, the triple bond coordinating to Pd(II) in species **9** and **12** is quasi-perpendicular to the plane of the Pd coordination sphere. Finally, in complex **12** Br is not strongly interacting with Pd, although the two atoms might seem close to each other; in fact rotamer **13** (**PdP-Sn.2**, ΔG

= 33.6 kcal/mol), in which Pd and Br are much farther from each other, is almost isoenergetic with **12**.

To evaluate the effect of ammonia bound to Sn on the transition states leading to transmetalation, it was necessary to evaluate the effect of ammonia on the starting material **6** and all the possible intermediates preceding the actual transmetalation step. We have thus calculated the energy and geometry of a number of ammonia-containing π-complexes analogous to **11** and **12**. First we have considered that tetraethynyltin and ammonia can themselves combine to form the tbp adduct **15** (**SnN**, $\Delta G = 1.4$ kcal/mol), in which ammonia occupies one of the two apical positions. Each of the two different ethynyl groups (apical and equatorial) of the pentacoordinate Sn complex **15** can bind to the tricoordinate Pd species **11** to generate several π-complexes, i.e., **16**−**18**. Complex **16** (**Pd-axSnN**, $\Delta G = 13.7$ kcal/mol), for instance, can be seen as resulting from the coordination of the apical alkynyl group of **15** via the free coordination site of **11**. Complexes **17** (**Pd-eqSnN.1**, $\Delta G = 12.1$ kcal/mol) and **18** (**Pd-eqSnN.2**, $\Delta G = 10.8$ kcal/mol) are two rotamers of the π-complex resulting from interaction of **11** with one of the equatorial ethynyl groups of **15**. In general, it seems that coordination of **11** with equatorial alkynes in **15** is significantly more favorable than the interaction with the apical alkyne, probably for steric reasons. Complex **19** (**PdP-SnN.1**, $\Delta G = 26.1$) and its rotamer **20** (**PdP-SnN.2**, $\Delta G = 29.1$ kcal/mol) can be seen as derived from displacement of bromine in **7** by any of the alkynyl groups of **15**; these structures were deemed representative of other conceivable stereoisomers and rotamers, and no further related structure was considered. In general, for all ammonia-containing complexes **15**−**20** there is a cooperative effect between the formation of the π-bond and the Sn−N bond; this is most apparent with **19**, whose formation from NH$_3$, **6**, and **7** ($\Delta G = 26.1$ kcal/mol) is lower by 6.3 kcal/mol than it would be expected combining the free energy of reaction of NH$_3$ and **7** (to give the σ-complex **15**, $\Delta G = 1.4$ kcal/mol) with the free energy of reaction of **6** and **7** (to give the π-complex **12**, $\Delta G = 31.0$ kcal/mol).

The coordination compounds described above were used as starting points for exploring the potential energy surface, searching for transition states of the actual transmetalation reaction. Considering first the case of transition states where ammonia is absent, we were able to find two transition structures (**21** and **22**) related to **9** and one (**23**) related to **12**. Transition structures **21** (**PdSn.cy***, $\Delta G = 31.2$ kcal/mol) and **22** (**PdSn.op***, $\Delta G = 27.7$ kcal/mol), related to **9**, can be described respectively as "cyclic" and "open". In both structures, the Pd center binds both the bromine atom and the alkyne carbon undergoing the transmetalation in a square-planar environment. In **21**, the four atoms involved in the bond-breaking and bond-forming process are not on the same plane, but form a quite puckered four-membered ring. In contrast, the open transition state **22** is characterized by the absence of a Sn−Br bond and by a Sn atom binding the transferring ethynyl group in a quasi-π mode. Perhaps surprisingly, the open transition state **22** is more stable by 3.5 kcal/mol than the cyclic one **21**. Exploration of the reaction coordinate from **21** toward products led to the minimum energy

species **31** (**Prod.1**, $\Delta G = 25.9$ kcal/mol), where the transmetalation has taken place, but the Br atom of the tin product is still coordinated to the fourth site of the Pd sphere, through what is clearly a weak interaction, given the highly energetic **31**. We have not investigated the exchange between the bromostannane and the phosphine, which is a trivial step and should be highly favored energetically. A search for products starting from **22** led instead to an unusual carbene-like complex, **32** (**Prod.2**, $\Delta G = 19.9$ kcal/mol), a structure that has never been postulated nor observed experimentally. The Pd−C bond of the transferred alkynyl group is indeed shorter than a normal single bond (1.91 Å), suggesting partial carbene character. The possible pathway leading from **32** to final and more obvious transmetalation products, such as **35** and **36**, was not investigated.

The transition structure **23** (**PdPSn***, $\Delta G = 35.4$ kcal/mol) is the only one that we have calculated for the transmetalation in which two phosphine moieties are bound to Pd and Sn is not nucleophilically assisted; we consider this structure as representative of other isomers and rotamers that one can conceive. As a distinctive feature, this kind of structure has a lower electronic energy than transition states **21** and **22**, but a higher free energy. Displacement of tightly bound bromide by the alkynyl moiety, to give the transmetalation substrate **19**, is extremely unfavorable energetically, but after this step the transmetalation appears to occur very smoothly, with a very low activation barrier, probably due to the cationic and therefore highly electrophilic nature of the Pd(II) center. As compared to **21** and **22**, the extent of formation of the Pd−C bond is lower in transition state **23**; the alkynyl group being transferred is in the equatorial plane of the tbp centered on Sn, while the Br atom is not interacting at all with Pd (open transition state).

We were able to find six different modes of transmetalation involving ammonia as a Sn ligand and only one phosphine bound to Pd. These are represented by structures **24**−**29** and are related to complexes **16**−**18**. On the basis of the coordination at tin, these transition states can be divided into three types: trigonal bipyramid in which the alkynyl group being transferred is apical (**24** and **25**); trigonal bipyramid in which the alkynyl group being transferred is equatorial (**26** and **27**); and finally octahedral (**28** and **29**). The transition structure **30** is the only one that was considered in the case of two phosphines bound to Pd (transition structure related to complex **20**).

Trigonal bipyramid transition structures **24** (**Pd-SnN.cy***, $\Delta G = 32.9$ kcal/mol) and **25** (**PdSnN.op***, $\Delta G = 24.0$ kcal/mol), which represent the transfer of the apical alkynyl group of complex **12**, rank highest in energy. Because of the relationship between the alkynyl group being transferred and the remaining three (almost equivalent) spectator carbon ligands, these transition structures can be related to the closed transition state **21** and the cyclic transition state **22**, respectively, from which they differ for the presence of ammonia bound to Sn. As compared with **21** and **22**, the presence of ammonia in **24** and **25** makes the distribution of the three spectator ethynyl ligands around the Sn atom flatter, while the four-membered ring formed by the atoms involved in the closed transmetalation structure

24 is more puckered than in the related structure **21**. The open transition structure **25** is more stable that the cyclic structure **24**, which parallels the situation observed with the corresponding transition states **21** and **22**, where ammonia is absent. The products of transmetalation occurring through **24** and **25** were found to be **33** (**Prod.3**, $\Delta G = 17.2$ kcal/mol) and **34** (**Prod.4**, $\Delta G = 17.5$ kcal/mol), which are readily recognized as ammonia-containing analogues of **31** and **32**; interestingly, the difference in energy between **33** and **34** is much lower than the energy difference between the respective products lacking ammonia.

The two trigonal bipyramidal transition structures in which the alkynyl group being transferred is equatorial are **26** (**PdSnN.tbp1***, $\Delta G = 21.3$ kcal/mol) and **27** (**PdSnN.tbp2***, $\Delta G = 19.5$ kcal/mol) and are of the open type; in fact the Sn atom is not bound to Br but interacts with the π-electron system of the alkynyl group being transferred. The Pd coordination sphere has a quasi-planar structure whose plane is almost parallel to the axis of the trigonal bipyramid centered on Sn. The two structures **26** and **27** are rotamers, and the difference in energy is the same as observed for the related ground state structures **17** and **19**, to which they are probably related; TS structures **27** is the one endowed with the lowest free energy among all the ones found in this study.

Transition structures **28** (**PdSnN.oct1***, $\Delta G = 27.9$ kcal/mol) and **29** (**PdSnN.oct2***, $\Delta G = 21.7$ kcal/mol) are two stereoisomers featuring a cyclic transition state in which the geometry around Sn is a slightly distorted octahedron; the difference is the relative position of NH_3 and the alkynyl group being transferred, which are *cis* and *trans*, respectively. The Pd, Sn, Br, and C atom of the transferring alkynyl group form a rather flat trapezoid, the Br atom forming an elongated bond both with Pd and with Sn. As a further common feature, unlike all other transition structures mentioned above, the Pd−C bond is formed to a much lesser extent and the two structures do not receive any stabilization from the π-interaction of the Sn atom with the alkynyl group being transferred. However, isomerism deeply affects the relative energy of the two structures. The formation of **29** is apparently much more favorable than **28**, both enthalpically (5.9 kcal/mol) and in free energy (6.2 kcal/mol), thus indicating a clear preference for transferring the ligand that is *trans* rather than *cis* to the donor ligand bound to Sn.

The transition structure **30** (**PdPSn***, $\Delta G = 29.5$ kcal/mol), the only one considered for the trasmetalation in which two phosphines are present on Pd and NH_3 is bound to Sn, is of the open type because the Br atom has already been totally tranferred to Sn upon formation of the parent complex **20**; the structure around Sn is obviously octahedral. This structure does not compare favorably, in terms of free energy, with most of the transition structures where the Pd has only one phosphine in the coordination sphere (**24**−**29**). It is worth noting that exploration of the reaction coordinate from **30** led to the Pd complex **35**, in which the two carbon substituents are *trans*.

Discussion

On the basis of the above results, we can trace and compare six different pathways for the transmetalation of eq 2 (Figure 1). They are of three basic types: (A) via a π-complex in which the alkynyl group of **6** being tranferred has displaced a phosphine moiety of **7** and an open transition state with one phosphine moiety bound to Pd; (B) via a π-complex as in A and a cyclic transition state with one phosphine moiety bound to Pd; (C) via a π-complex in which the alkynyl group of **6** being transferred has displaced the bromide atom of **7** and a transition state with two phosphine moieties bound to Pd. For each type there are two modes: (N) nucleophilically assisted at Sn and (U) nucleophilically unassisted. Because of their high energy, two possible reaction pathways of type AN and BN, involving transition structures **24** and **25**, will not be considered in the following discussion.

Among the three reaction pathways with nucleophilic unassisted Sn, the one of type AU, through the open transition state **22**, is the most favored one. It should be noted, however, that such species receives substantial stabilization by the π-interaction of the Sn atom with the unsaturation of the group being transferred. Such an interaction, which is clearly an important factor in the transfer of an alkyne, might be progressively less important in providing the intermediate with stability when the group being transferred is a vinyl, a phenyl, or an alkyl; in addition, the role of any donor solvent would most likely be to coordinate the highly electrophilic tin atom, making **22** an unlikely transition state under typical experimental conditions. Less favored is the reaction path of type BU through the closed transition state **21**, which may however be less disfavored over the open one when the group being transferred is not capable of π-interaction with the stannane. The reaction pathway of type CU through the transition structure **23**, where two phosphines are bound to Pd, is the most disfavored among all those calculated. Transition state **23** is likely to involve a substantially higher charge separation than **21** and **22**, as deduced from their dipole moments, which are 7.11, 2.25, and 2.01 D, respectively; for this reason, **23** might be relevant only in solvents of high dielectric constant. Also, transition structures such as **23** might be favorable in cases of substrates where the bond between Pd and the halogen or pseudohalogen (e.g., triflate) is especially weak; studies have shown that, at least with aryl and vinyl triflates, where the triflate forms a much weaker bond to Pd than Br, such a pathway occurs, and it is characterized by inhibition of coupling by added halide and no inhibition by added ligand.[6] The dielectric constant of the solvent, the type of stannane, and the halogen (or pseudo-halogen) involved in the transmetalation must be expected to affect the relative profiles of the three reaction types. More calculations are required to quantify the role of these variables in each separate case.

Perhaps the most striking result obtained in this study is the uniform drop in activation barrier of the transmetalation when a nucleophile such as ammonia is added to the coordination sphere of Sn. Such a drop is quite significant (8.2 and 9.5 kcal/mol, respectively) for the transmetalation paths of type A and B and less dramatic (4.9 kcal/mol) for the transmetalation of type C (Figure 1, compare AU with AN, BU with BN, and CU with CN). Here again, it should be noticed that the most stable transition state **27** is stabilized by the
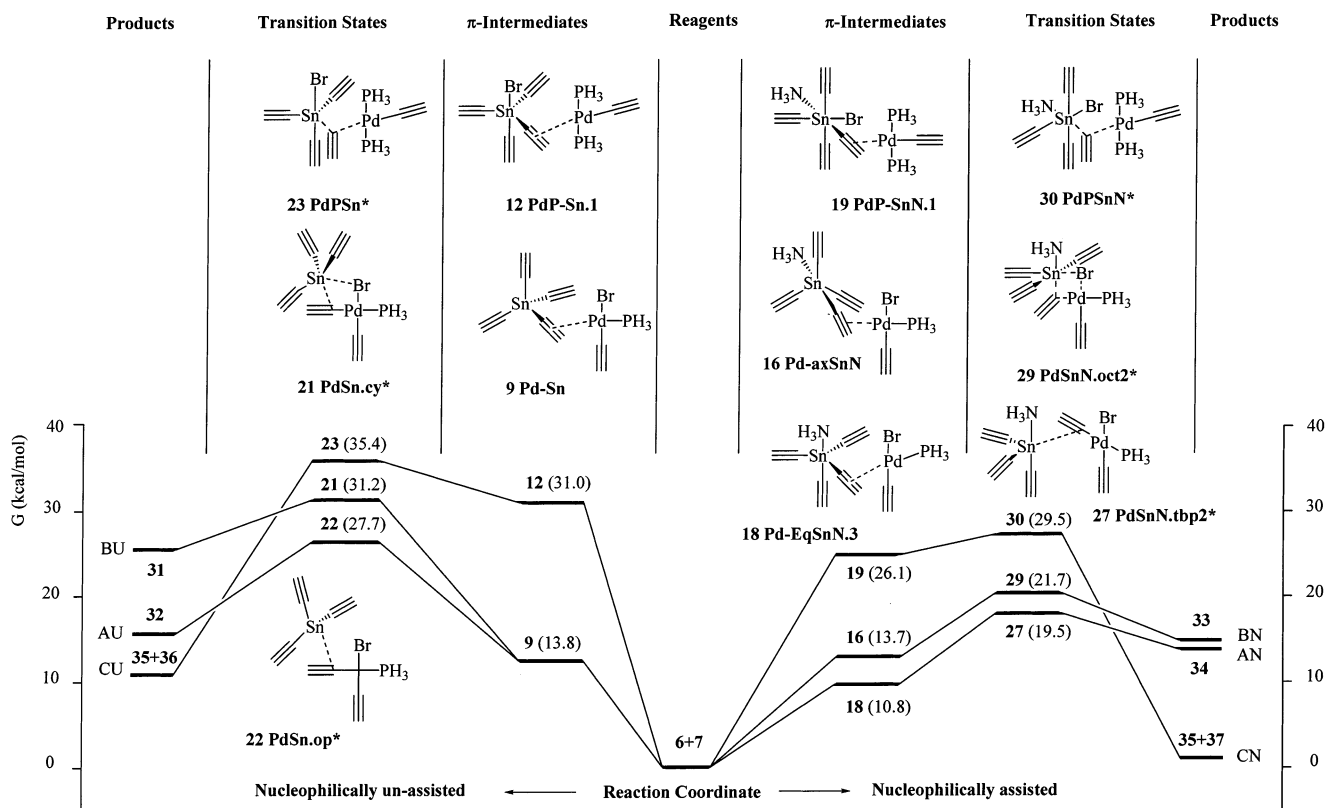
Figure 1. Pathways of the transmetalation of eq 2. (A) Phosphine displacement, open transition state. (B) Phosphine displacement, cyclic transition state. (C) Bromine displacement (only of open type). (N) Nucleophilically assisted. (U) Nucleophilically unassisted. The numbers in bold in the energy diagram indicate structures, and numbers in parentheses are the corresponding energies. Structures are also schematically drawn in the panel (see also Charts **3**−**9**).

π-interaction of Sn with the alkynyl group involved in the transmetalation, so that the open assisted reaction pathway should be expected to be less favored in systems where such a π-interaction is less important or impossible.

There seems to be a strong preference for the nucleophile to be *trans* to the transferring alkynyl group in the closed reaction pathway BN. Indeed, transition state **29** is about 7 kcal/mol more stable than its isomeric structure **28**, where the nucleophile is in the *cis* position; also, the Sn−C bond that is breaking is much shorter in **29** than in **28**, indicating an earlier transition state, consistent with a faster transmetalation. This is in agreement with the proposal by Vedejs regarding the operative mechanism with stannatranes such as **1**, although this preference would involve an octahedral rather than a trigonal bipyramid structure around the Sn atom in the transition state.

Conclusion

This work constitutes the first computational study of the Stille transmetalation step (eq 2). The possible coordination geometries at Pd and Sn during the transmetalation were systematically considered. Ten transition structures were located, and six basic reaction pathways have been traced. Our calculations strongly support the formation of a π-complex between the unsaturated stannane and the Pd center, which can occur with loss of a phosphine moiety or, less favorably,

of the bromine atom. This is qualitatively consistent with kinetic studies postulating π-complexes as intermediates in the transmetalation of vinyltins.[4] The calculations suggest that Pd tends to adopt a tetracoordinated planar structure, and energy minima with pentacoordinated Pd species have not been found. Transition states and intermediates analogous to the ones proposed by Espinet, in which the σ-C−Sn bond associatively displaces one of the phosphines at Pd, without the intermediacy of a π-complex,[7] were not found in this study. In addition, our data provide strong theoretical backing for the hypothesis that coordination expansion at tin plays a major role in facilitating transmetalation. These results have strong practical implications: carefully tuned nucleophilic catalysis is likely to provide a strong synthetic advantage in the coupling of organotin reagents under Pd catalysis. The creative design of such systems, already precedented,[8−10] is likely to continue to provide new solutions to this type of cross-coupling chemistry. Further studies should extend to alkenyl, alkyl, and aryl stannanes, and it is hoped that the geometries found in this study may constitute a good starting point for transition state search in those systems as well.