Nitrogen Heterocycles

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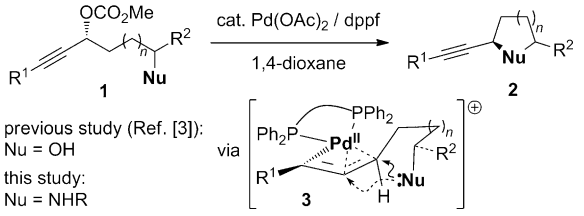
Ligand Bite Angle-Dependent Palladium-Catalyzed Cyclization of Propargylic Carbonates to 2-Alkynyl Azacycles or Cyclic Dienamides**

David S. B. Daniels, Alison S. Jones, Amber L. Thompson, Robert S. Paton, and Edward A. Anderson**

Abstract: *The regioselectivity of the palladium-catalyzed cyclization of propargylic carbonates with sulfonamide nucleophiles is critically dependent on the bite angle of the bidentate phosphine ligand. Ligands with small bite angles favor attack on the central carbon atom of an allenylpalladium intermediate to afford cyclic dienamide products, whereas the use of those with large bite angles leads to alkynyl azacycles, with high stereoselectivity. A computational analysis of the reaction pathway is also presented.*

Stereoselective heterocycle synthesis is of fundamental importance in pharmaceutical and natural product research.[1,2] We recently reported a palladium-catalyzed asymmetric approach to 2-alkynyl oxacycles from propargylic carbonates equipped with internal alcohol nucleophiles (**1**→ **2**, Nu = OH; Scheme 1).[3] Key to this reaction is the high



Scheme 1. Cyclization of propargylic carbonates to alkynyl heterocycles.

fidelity of stereochemical transfer from the carbonate to the oxacycle, and the high regioselectivity of attack by the oxygen nucleophile on the distal carbon atom of the intermediate allenylpalladium complex **3**, as opposed to the central carbon atom as is usually observed in such systems.[4] We were interested in the dependence of these selectivities on the nature of the nucleophile and elected to explore nitrogen nucleophiles, which might not only offer further insight into the reaction, but also a stereoselective entry to alkynyl azacycles, which are important synthetic targets.[5] We report herein the results of these studies, including our finding that the regioselectivity of the cyclization can be tuned through the choice of ligand to give either alkynyl azacycles or cyclic dienamides, and computational studies that correlate this reactivity dichotomy with the structures of the allenylpalladium intermediates.

Investigations began with sulfonamide carbonate **4a**, which cyclized to pyrrolidine **5a** with excellent stereoselectivity under the conditions we had optimized for oxygen nucleophiles (Table 1, entry 1).[3,6,7] However, in contrast to our previous study, a significant amount of cyclic enamide **6a** was formed through competitive attack by the sulfonamide on the central carbon atom of the intermediate allenylpalladium species **3** (see mechanistic discussion below).[8,9]

The ratio of these products was insensitive to variation of the temperature or solvent (Table 1, entries 2–5), but highly dependent on the nature of the bidentate phosphine ligand (Table 1, entries 5–10). A dramatic switch in selectivity was observed between dppe (**5a**/**6a** 19:81; Table 1, entry 6) and DPEphos (**5a**/**6a** 89:11; entry 10),[10] with a modest increase in stereoselectivity observed for the latter in 1,4-dioxane (97% *ee*; entry 11). The role of additives, which had beneficial effects on regioselectivity in our related oxacycle study, was next examined.[3] The use of boric acid or $B(OMe)_3$ entirely prevented the formation of **6a**, but required higher temperatures for full conversion and led to decreased stereoselectivity (Table 1, entries 12 and 13); lowering of the temperature improved matters, but the reaction under these conditions was capricious on larger scales (Table 1, entry 14). The nature of the nitrogen protecting group proved important: whereas other sulfonamides (compounds **4b–d**) were viable substrates, albeit with slightly reduced selectivity, amide **4e** and the free amine **4f** did not cyclize (Table 1, entries 15–19). The conclusion of this optimization was that catalyst systems that favored the formation of either the pyrrolidine (DPEphos) or the dienamide (dppe) had been identified, and although dienamide formation could be prevented through the addition of boronate additives, the loss of enantioselectivity was viewed as too high a price to pay. Subsequent reactions were therefore conducted in dioxane at 100 °C (conditions that ensured rapid conversion) in the absence of additives.

We prepared a range of mono- and disubstituted sulfonamide carbonates to examine the reaction scope and selectivity with each of these ligands. Beginning with DPEphos

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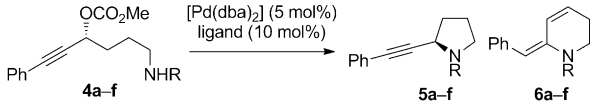
Table 1: Optimization of the azacyclization of carbonates **4a–f**.[a]



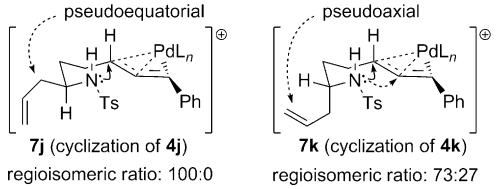
4a: R = Ts **4d**: R = $PMPSO_2$
4b: R = Ms **4e**: R = Ac
4c: R = Ns **4f**: R = H

Entry	Substrate	Solvent	*T* [°C]	Ligand	Additive (0.5 equiv)	**5**/**6**[b]	Yield [%][c]	*ee* [%][d]
1	**4a**	1,4-dioxane	100	dppf	–	71:29	63	96
2	**4a**	*n*-butanol	100	dppf	–	71:29	n.d.[e]	94
3	**4a**	DME	85	dppf	–	70:30	n.d.	95
4	**4a**	toluene	100	dppf	–	71:29	n.d.	95
5	**4a**	toluene	60	dppf	-	71:29	48	95
6[f]	**4a**	**toluene**	**60**	**dppe**	**–**	**19:81**	**60**	**95**
7	**4a**	toluene	60	dppp	–	32:68	n.d.	95
8	**4a**	toluene	60	dppb	–	48:52	n.d.	96
9[f]	**4a**	toluene	60	dpppe	–	69:31	n.d.	95
10[g]	**4a**	toluene	60	DPEphos	–	89:11	78	94
11	**4a**	**1,4-dioxane**	**60**	**DPEphos**	**–**	**89:11**	**77**	**97**
12	**4a**	1,4-dioxane	80	DPEphos	$B(OH)_3$	100:0	86	90
13	**4a**	1,4-dioxane	80	DPEphos	$B(OMe)_3$	100:0	83	92
14[f]	**4a**	1,4-dioxane	60	DPEphos	$B(OMe)_3$	100:0	62[h]	97
15	**4b**	toluene	100	DPEphos	–	87:13	72	n.d.[e]
16	**4c**	toluene	100	DPEphos	–	74:26	55	n.d.
17	**4d**	toluene	100	DPEphos	–	86:14	73	n.d.
18	**4e**	toluene	100	DPEphos	–	–	n.r.[i]	–
19	**4f**	toluene	100	DPEphos	–	–	n.r.	–

[a] Reactions were conducted with **4** (97% *ee*; 25 μmol), $[Pd(dba)_2]$ (5 mol%), and the ligand (10 mol%) at a concentration of 0.1 M for 15 min, unless stated otherwise. [b] The product ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Yield of the major product after isolation. [d] The *ee* value was determined by HPLC on a chiral stationary phase (see the Supporting Information for details). [e] n.d. = not determined. [f] The reaction was conducted for 30 min. [g] The reaction was conducted for 45 min. [h] The reaction proceeded to 70% conversion. [i] n.r. = no reaction. dba = dibenzylideneacetone; Ts = *p*-toluenesulfonyl; Ms = methanesulfonyl; 4-Ns = *p*-nitrobenzenesulfonyl; PMP = *p*-methoxyphenyl; DME = 1,2-dimethoxyethane; dppf = 1,1′-bis(diphenylphosphanyl)ferrocene; dppe, dppp, dppb, dpppe = 1,*n*-bis(diphenylphosphanyl)alkane ligand (ethane, *n* = 2; propane, *n* = 3; butane, *n* = 4; pentane, *n* = 5); DPEphos = (oxybis(2,1-phenylene))bis(diphenylphosphane).

(Table 2, entries 1–7), we found that the alkyl alkyne **4g** cyclized equally efficiently as the aryl alkyne **4a** to deliver pyrrolidine **5g** in excellent yield and regioselectivity (81%, 97% *ee*; Table 2, entry 1).[11] The cyclization could be applied to the synthesis of alkynyl piperidines, with **5h** produced in good yield and excellent enantioselectivity (Table 2, entry 2); however, the formation of azepane **5i** was less successful, and to our surprise was accompanied by the formation of significant amounts of the corresponding eight-membered cyclic dienamide (entry 3).[12] The cyclization of enantiomerically pure disubstituted sulfonamide carbonates **4j–m** proceeded in good yield and diastereoselectivity in all cases (Table 2, entries 4–7), thus enabling efficient access to both *cis*- and *trans*-disubstituted alkynyl pyrrolidines and piperidines. The regioselectivity of the reactions was consistently high,[7] with that of the cyclization of **4j** (Table 2, entry 4) to the *trans*-disubstituted pyrrolidine **5j** being particularly notable (single regioisomer, d.r. > 99:1). The exceptional efficiency of this cyclization (as opposed to that of **4k**; Table 2, entry 5) can be rationalized by the possible conformations of the allenylpalladium(II) intermediates **7j** and **7k** (Scheme 2). In the case of **7j** (arising from **4j**), a pseudoequatorial disposition of the allyl side chain reinforces the stereoelectronic requirement for *anti*-S_N2' reductive elimination. The contrasting cyclization of **4k** necessitates an axial orientation of the allyl substituent in **7k**, which evidently results in lower regioselectivity. An equivalent trend is seen for piperidines **5l** and **5m**, albeit with less disparity between the two diastereomers, probably owing to a less "tight" transition state with reduced conformational influence by the allyl substituent.

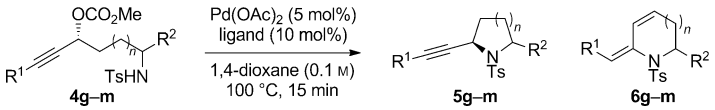
Having established a stereoselective cyclization to alkynyl azacycles with DPEphos as the ligand, attention turned to the complementary regioselective cyclization with dppe. This investigation again began with carbonate **4g** (Table 2, entry 8), which now cyclized to enamide **6g** with good regioselectivity (16:84) and excellent stereoselectivity for the formation of a single alkene isomer (> 95:5). We were particularly pleased to reverse the regioselectivity of the cyclization of **4h**, for which the dppe system conferred excellent regioselectivity for the formation of seven-membered enamide **6h** (Table 2, entry 9), in spite of a presumed thermodynamic preference

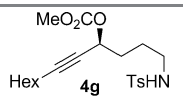
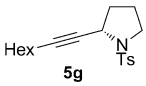
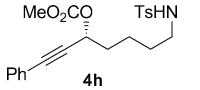
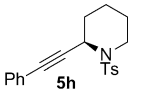
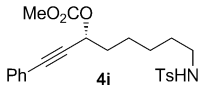
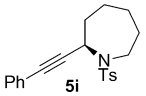
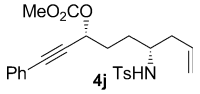
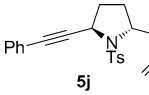
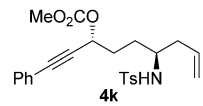
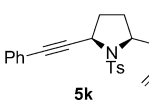
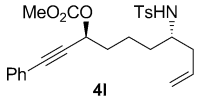
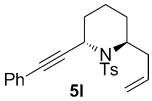
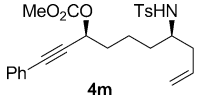
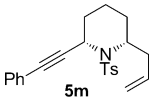
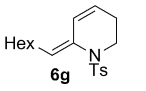
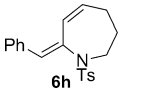
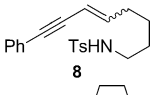
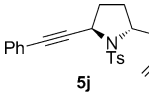
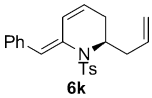
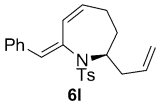
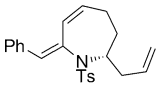


Scheme 2. Proposed conformations of allenylpalladium complexes **7j** and **7k** in the cyclization of **4j** and **4k** to pyrrolidines **5j** and **5k**, respectively.

for piperidine synthesis. This success could not be maintained for the formation of the eight-membered dienamide (Table 2, entry 10); instead, only the elimination product **8** was formed. This result underlines the complete disfavoring of cyclization at the distal allene carbon atom with the ligand dppe. The reactions of the disubstituted sulfonamide carbonates **4j–m** (Table 2, entries 11–14) afforded interesting results. In this case, the powerful kinetic propensity for cyclization to a five-membered ring overrode the influence of the ligand, and for the configurationally matched substrate **4j** resulted in the formation of pyrrolidine **5j** as the major product. However,

Table 2: Cyclization of sulfonamide carbonates **4** to alkynyl azacycles **5** and cyclic dienamides **6**.[a]



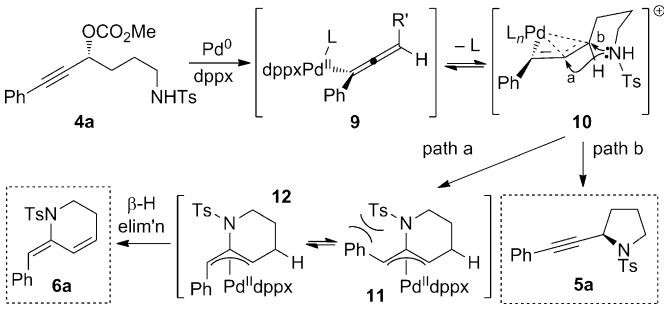
Entry	Substrate	Major product	Yield [%][b]	*ee* [%]/d.r. of **5**[c]	*E*/*Z* ratio of **6**[d]	**5**/**6**[d]
1[e]	 **4g**	 **5g**	81[f]	97	90:10	90:10
2	 **4h**	 **5h**	61	98	85:15	80:20
3	 **4i**	 **5i**	26	n.d.	66:33[g]	75:25
4	 **4j**	 **5j**	76	>99:1	–	100:0
5	 **4k**	 **5k**	86	95:5	>95:5	73:27
6	 **4l**	 **5l**	68	96:4	80:20	77:23
7	 **4m**	 **5m**	60	97:3	75:25	85:15
8[e]	**4g**	 **6g**	61[f]	n.d.	>95:5	16:84
9	**4h**	 **6h**	67	n.d.	>95:5	18:82
10	**4i**	 **8**	78	–	1:1[h]	–
11	**4j**	 **5j**	71	>95:5	>95:5	65:35
12	**4k**	 **6k**	83	92:8	>95:5	40:60
13	**4l**	 **6l**	64	>90:10	95:5	18:82
14	**4m**	 **6m**	13[i]	>90:10	88:12	17:83

[a] Reactions in entries 1–7 were performed with DPEphos as the ligand; reactions in entries 8–14 were performed with dppe as the ligand. [b] Combined yield of isolated **5** and **6**, unless stated otherwise. [c] The *ee* values in entries 1 and 2 were determined by HPLC on a chiral stationary phase. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [e] The reaction was performed with [Pd(dba)$_2$] and the ligand. [f] Yield of the major product after isolation. [g] The major alkene isomer is assumed to have the *E* configuration by analogy to other enamide products. [h] The *E*/*Z* ratio of **8** is shown. [i] Remaining material was unreacted **4m**.

for substrates **4l** and **4m**, the reduced driving force for six-membered-ring formation now restored high regioselectivity for the formation of azepane enamides **6l** and **6m**, although the latter reaction only proceeded with partial conversion, even with extended reaction times.

The contrasting outcomes of these reactions can be explained by a mechanism that begins with *anti*-S_N2' oxidative addition[13] by the bidentate-phosphine-complexed palladium(0) catalyst to give an η^1-allenylpalladium species **9** (Scheme 3). Through ligand dissociation, the metal is able to bind to the remote double bond of the allene to form a nonlinear cationic η^3-allenylpalladium species **10**.[14] Attack on the central allene carbon atom of **10** (path a) leads to a π-allylpalladium intermediate **11**, which can equilibrate with **12** through a π–σ–π interconversion pathway. β-Hydride elimination from intermediate **12**, which is probably favored as a result of lower 1,3-allylic strain, leads to the (*E*)-enamide **6a**. With DPEphos, path b is favored—namely, attack at the terminal (distal) carbon atom of the allenyl palladium system to give pyrrolidine **5a** through *anti*-S_N2' reductive elimination.[15]

To rationalize this dramatic switch in regioselectivity according to the choice of ligand,[16] we modeled the structures of the cationic η^3 complexes by carrying out quantum-chemical calculations. First, the structure of the parent complex $[Pd(PH_3)_2]$ bound to the allenyl cation (i.e. $[(HC{=}C{=}CH_2)Pd(PH_3)_2]^+$ (**13**); Figure 1), was optimized at the wB97XD/def2-TZVPP level of theory.[17] Overlap of the allenyl π_2 nonbonding molecular orbital (MO) with the PdL_2 $2b_1$ MO (which is predominantly formed from the metal d_{xy} orbital) leads to a bonding orbital 1a″ and an antibonding orbital 2a″ (the LUMO of the complex). As the bonding MO 1a″ features greater electron density on the terminal carbon atoms of the allene than on the central carbon atom, the greater



Scheme 3. Proposed mechanisms for the formation of alkynyl azacycles and dienamides.

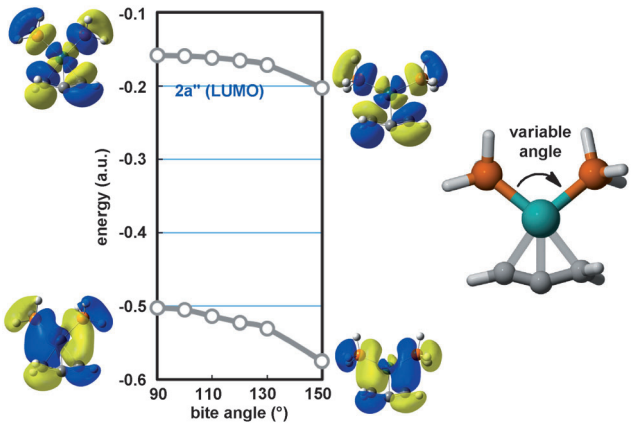


Figure 2. Calculated variation in the LUMO energy with the ligand bite angle for $[(HC{=}C{=}CH_2)Pd(PH_3)_2]^+$ (**13**).

the degree of metal–allene bonding, the more negative charge will be located on these carbon atoms, and the higher in energy the antibonding orbital (2a″) will be. Both factors disfavor nucleophilic attack at the terminal positions of the allenylpalladium complex, and attack at the central carbon atom becomes more favorable.

To investigate the effect of the ligand bite angle[18] on the electronic structure of complex **13**, we systematically varied the angle between the two phosphine ligands in 10° increments. As this angle increases, metal–allenyl bonding lessens, and there is a progressive drop in LUMO energy (Figure 2). This effect is caused by a lowering in energy of the PdL_2 $2b_1$ MO, as mixing between d_{xz} and P 3s orbitals decreases as the bite angle increases;[12] larger bite angles thus lead to heightened reactivity at the terminal carbon atoms, at which the LUMO coefficient is non-zero. The changes in the computed charges at the carbon atoms are negligible, thus suggesting that the variation in regioselectivity is not due to electrostatic interactions with the nucleophile, but rather to increasing orbital control of the reaction.

The structures of the complexes of the 1-phenyl-3-methylallenyl cation with the various bidentate-phosphine-complexed palladium species employed in this study (i.e. $[(PhC{=}C{=}CHMe)Pd(dppx)]^+$) were then optimized; computed structures of the dppe and DPEphos complexes are shown in Figure 3a. Correlation of the calculated allene bending angles with the ligand bite angles[18] (Figure 3b) and the experimentally observed pyrrolidine/enamide ratio (Figure 3c) shows a clear trend between structure and reactivity.[15] As the ligand bite angle increases and allenyl–palladium

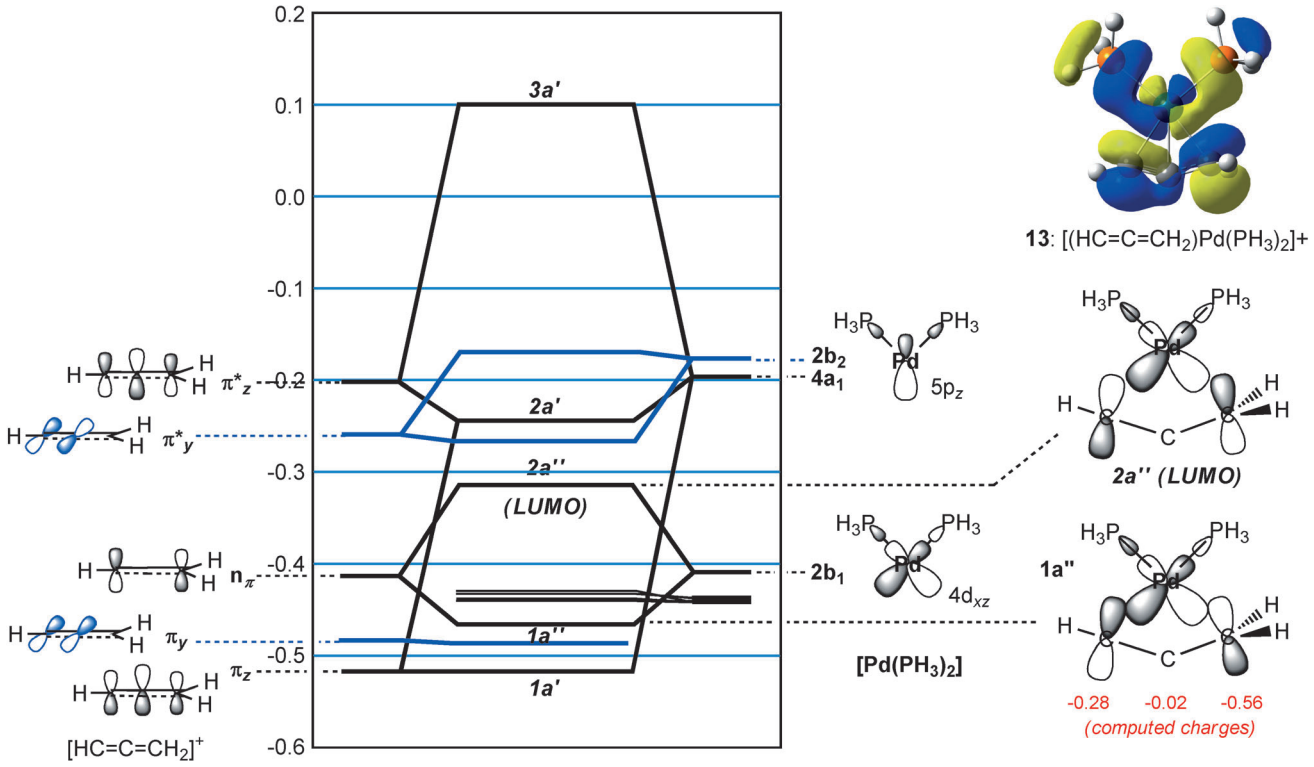


Figure 1. Molecular-orbital diagram of $[(HC{=}C{=}CH_2)Pd(PH_3)_2]^+$ (**13**) and its fragments (EH//wB97XD/def2-TZVPP).

bonding weakens, there is an elongation of the Pd–C bonds to the terminal carbon atoms (Figure 3a) and a flattening of the allenyl group; its structure begins to resemble that of the allenyl cation, thus favoring terminal attack.[19] With the charges on the atoms again varying little between these structures, correlation with the MO calculations on **13** strongly suggests a lower-energy LUMO for DPEphos than for dppe. Therefore, attack on the terminal carbon atom to give the alkynyl azacycle product is favored.

In conclusion, we have developed a catalyst-dependent regioselective cyclization of propargylic carbonates equipped with sulfonamide nucleophiles. Alkynyl pyrrolidines and piperidines are accessed through the use of bidentate phosphine ligands with large bite angles, and piperidine/azepane enamides using ligands with small bite angles. This method offers an expedient entry to both ring systems and important insight into the structure and mechanism of the reactions of allenylpalladium complexes.

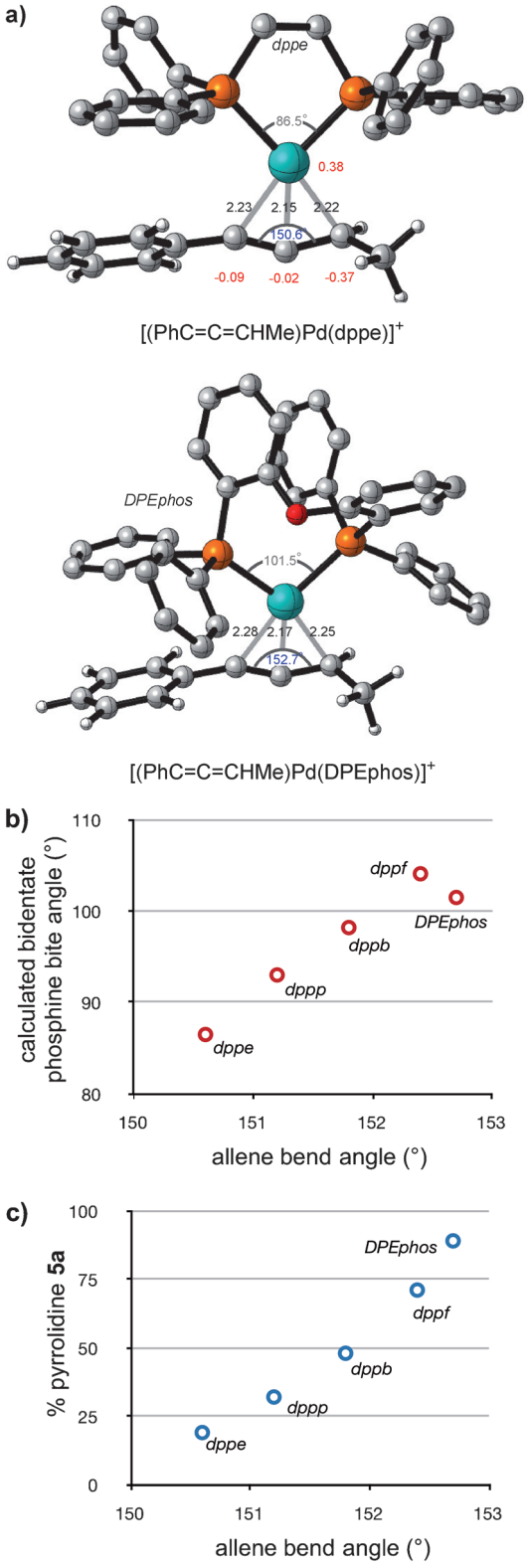


Figure 3. a) Optimized structures (wB97XD/6-31G(d)) of the dppe and DPEphos complexes [(PhC=C=CHMe)Pd(dppx)]$^+$. b,c) Relationship of the calculated allene bend angle to the calculated bidentate-phosphine bite angle (b) and the observed regioselectivity (c).

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0.007(10), −0.002(12), and 0.00(1) for **5a**, **5j**, and **5k**, respectively. CCDC 965014, 965015, and 965016 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[10] Owing to issues with the purification of the products to remove dba (see also Table 2, entry 8), $Pd(OAc)_2$ was used for subsequent reactions; no differences in reactivity or selectivity were observed between these Pd sources.

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