JOC Note

Cyclization Reactions Involving Palladium-Catalyzed Carbene Insertion into Aryl Halides

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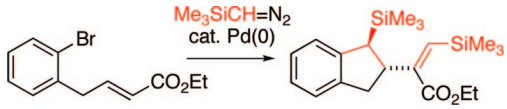


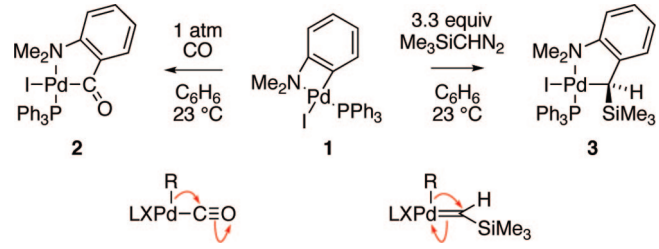
Palladium is shown to catalyze the insertion of trimethylsilylmethylene into aryl halides, leading to benzylpalladium intermediates that cyclize to give indenylsilanes through carbopalladation of pendant alkenes or allenes. Allylsilanes generated through these processes are susceptible to protodesilylation in situ.

There is growing interest in palladium-catalyzed reactions that insert carbene fragments derived from diazo compounds.[1] Diazo compounds like trimethylsilyldiazomethane (TMSD) are convenient precursors to metal carbenes.[2] Using TMSD, Sole and co-workers showed that trimethylsilylmethylene inserts readily into palladium−carbon bonds in analogy to insertion of CO (Scheme 1).[3]

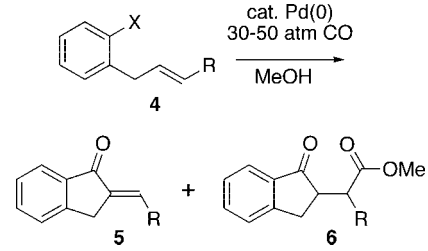
The insertion of trimethylsilylmethylene into a palladium−carbon bond can be envisioned to occur through migration of the arene to the empty orbital of the carbene. Insertion of trimethylsilylmethylene is particularly exciting because it introduces the new carbon atom as a stereogenic center, whereas CO insertion does not. A particular advantage of inserting trimethylsilylmethylenes into arene−palladium bonds is that it generates a benzyltrimethylsilyl functional group, which can be nucleophilically activated by catalytic fluoride.[4]

Negishi and co-workers have shown that palladium can catalyze the carbonylative Heck cyclization of 2-iodoarenes to produce indane ring systems.[5] In these reactions, the indanone ring is generated through CO insertion followed by insertion of a pendant olefin. The resulting intermediate can then efficiently proceed to product through either β-hydride elimination (**5**) or a second CO insertion (**6**), depending on the conditions (Scheme 2). Indanes are present in the drug Aricept[6] and a wide range of natural products[7] and bioactive compounds.[8]

SCHEME 1. Insertion of Carbenes versus Insertion of CO



SCHEME 2. Single and Double Insertion of CO



We sought to explore a version of the Negishi carbonylative cyclization reaction in which trimethylsilylmethylene takes the place of CO (Scheme 3). Little is known about the ability of carbene insertion to compete with other important processes like olefin insertion (carbopalladation) or β-hydride elimination.[9] To increase the utility of TMSD in palladium-catalyzed reactions we set out to study the competition between carbene insertion and other processes like carbopalladation and β-hydride elimination in the context of a palladium-catalyzed indane formation reaction.

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(4) (a) Bennetau, B.; Dunogues, J. *Tetrahedron Lett.* **1983**, *24*, 4217–4218. (b) Zhang, W.-X.; Ding, C.-H.; Luo, Z.-B.; Hou, X.-L.; Dai, L.-X. *Tetrahedron Lett.* **2006**, *47*, 8391–8393. (c) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901–6905.

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(9) For interesting recent examples, see: Peng, C.; Cheng, J. J.; Wang, J. B. *J. Am. Chem. Soc.* **2007**, *129*, 8708–8709. (b) Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566–1567.

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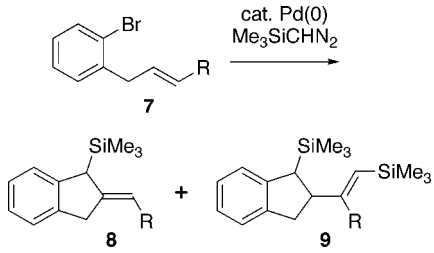
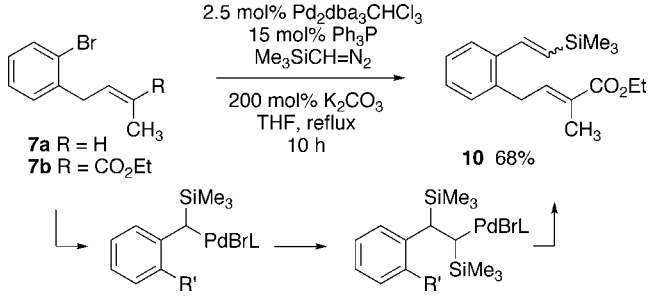
SCHEME 3. Single and Double Insertion of Trimethylsilylmethylene



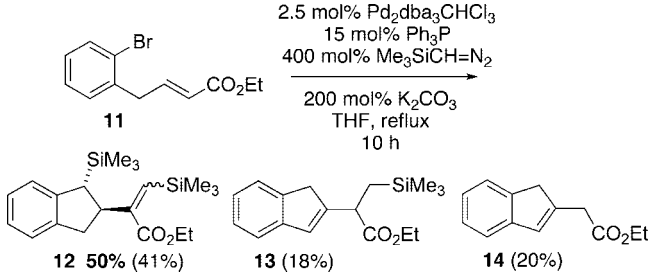
Initially, we examined the reaction of 2-allylbromobenzene with 4 equiv TMSD in the presence of a palladium catalyst, but low mass balance was observed, along with low yields of insertion products, which proved difficult to separate. When an extra methyl group was incorporated into the substrate, aryl halide **7a** afforded small amounts of the desired indanes as part of an inseparable mixture. When the reaction was carried out on α,β-unsaturated ester **7b**, the primary product was the styrylsilane **10**, as a 1:1 mixture of *E* and *Z* isomers, arising from two sequential carbene insertions and loss of Me_3Si-Br (Scheme 4). Clearly, the desired carbopalladation of the trisubstituted olefin is significantly slower than a second carbene insertion. Indeed, when a large excess of TMSD was added, styrylsilane **10** was formed in 68% yield. The choice of base is crucial for this reaction because soluble bases like triethylamine isomerize the α,β-unsaturated ester to a β,γ-unsaturated ester.

SCHEME 4. Double Insertion without Carbopalladation



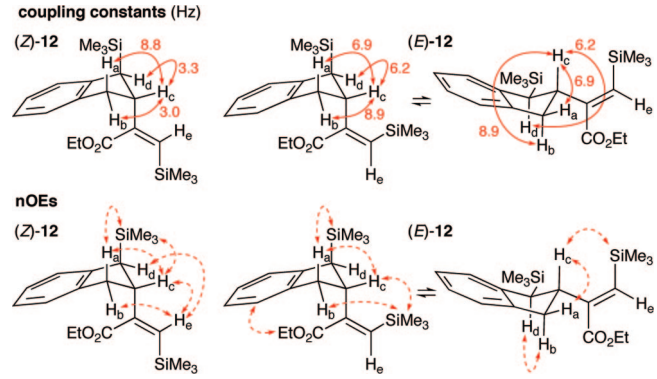
When the reaction was carried out on α,β-unsaturated ester **11**,[10] the carbopalladative cyclization was more facile and three indane products were isolated: indane **12** (1:1 mixture of isomers) and indenes **13** and **14** (Scheme 5).

SCHEME 5. Formation of Indanes and Indenes



The two isomers of indane **12** were separated by HPLC, and we then set out to assign the relative configuration of each isomer with respect to the indane substituents and the configuration of the double bond. The double bond configuration of (*Z*)-**12** was established through an nOE between the olefinic proton H_e and the ring protons H_b, H_c, and H_d (Scheme 6). The coupling constants observed for (*Z*)-**12** were consistent only with the *anti*-isomer in a diaxial conformation and were within 1 Hz of the calculated coupling constants (MM2).

SCHEME 6. Diagnostic ^{1}H NMR Data for Isomers of 12



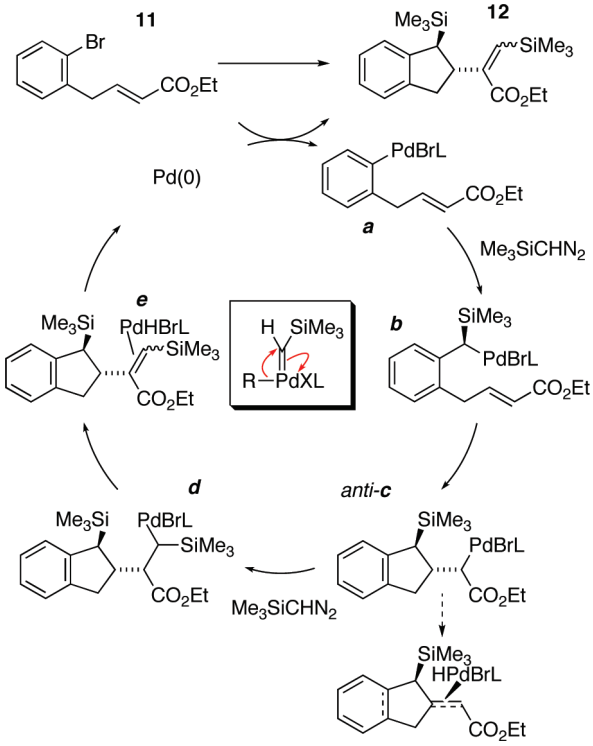
The double bond configuration of (*E*)-**12** was readily assigned on the basis of a strong nOE between the allylic proton H_c and the vinylic trimethylsilyl and the absence of an nOE between the allylic proton H_c and the olefinic proton H_e. The ^{1}H NMR data for (*E*)-**12** were not consistent with a rigid conformation, making it more difficult to establish the relative configuration of the substituents on the five-membered ring. For example, the benzylic protons H_a and H_b of (*E*)-**12** exhibited overlapping signals, even at 800 MHz. In contrast, the same protons were well-resolved for the *anti*-diaxial isomer (*Z*)-**12** at 500 MHz. Both the benzylic trimethylsilyl group and H_d exhibited cross-ring nOEs to the H_a/H_b system. It is not possible for H_d to exhibit a cross-ring nOE to the H_a/H_b system unless it spends time in an axial conformation; in fact, the coupling constants seem to have values midway between those predicted for the diaxial and diequatorial isomers of (*E*)-**12**. All evidence points to an *anti*-relationship between the ring substituents in the (*E*)-**12** isomer where steric congestion leads to conformers that equilibrate on the ^{1}H NMR time scale.

The formation of indane **12** is accounted for by the mechanism depicted in Scheme 7. Arylpalladium bromide, ***a***, can undergo carbene insertion to generate benzylpalladium intermediate, ***b***. Intramolecular carbopalladation leads to indane, ***c***. Indane, ***c***, has two choices: β-hydride elimination or carbene insertion. Apparently, β-hydride elimination is slow because it would place both the HPdBrL moiety and the benzylic trimethylsilyl group on the α-face of the indane—too close for comfort. Instead, intermediate ***c*** inserts another trimethylsilylmethylene to generate intermediate ***d***, which undergoes β-hydride elimination. Dissociation of the HPdBrL from the vinylsilane generates the indane product **12**.

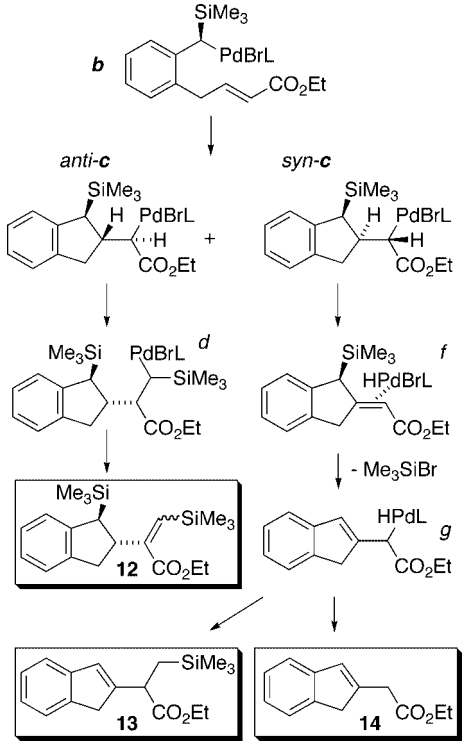
Why is the *syn*-isomer of indane **12** not observed? Carbopalladation of intermediate ***b*** is clearly the focal point for this question, but we could not find a rationale for stereoselective cyclization. Instead, we began to speculate that the carbopalladative cyclization of intermediate ***b*** generates both *anti*- and *syn*-isomers (Scheme 8). *Anti*-**c** has a significant steric barrier toward β-hydride elimination, but *syn*-**c** does not. β-Hydride elimination of *syn*-**c** would place the HPdBrL moiety on the face of the allylsilane that is opposite the trimethylsilyl group. In this orientation, the allylsilane of intermediate ***f*** is stereoelectronically predisposed to transmetallate onto the Pd(II),

(10) Huang, Q.; Larock, R. *Org. Lett.* **2002**, *4*, 1291–1294.

SCHEME 7. Proposed Catalytic Cycle



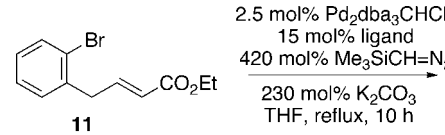
SCHEME 8. Different Fates of *anti*- and *syn*-Indane Intermediates



generating allyl-hydridopalladium intermediate ***g***. Allylsilanes are known to react readily with Pd(II) at room temperature or below.[11] For example, allyltrimethylsilane reacts with $PdCl_2$ at room temperature to produce the μ-bridged dimer $[C_3H_5PdCl]_2$ in high yield.[12] The hydridopalladium intermediate ***g*** can reductively eliminate to form indene **14** or undergo insertion of another trimethylsilylmethylene and then reductively eliminate to form **13**. Based on the ratio of indane **12** to indenes **13** and **14**, the cyclization of intermediate ***b*** generates a 1:1 mixture of *anti*- and *syn*-disubstituted indanes. Sterics and stereoelectronics then conspire to force them down different reaction pathways.

We sought to improve the yield of the indene products **13** and **14** relative to indane **12** by changing the ligands. To achieve this we needed to control the diastereoselection in the carbopalladative cyclization of intermediate ***b***. Ligands offer one element of control in diastereoselective Heck cyclizations.[13] Recall that when triphenylphosphine was used as the ligand, the protodesilylated product **13** was isolated in only 20% yield (Scheme 9). Bulkier ligands gave more of the indene **14** and less of the indane **12**. Surprisingly, bulky ligands led to negligible amounts of indene **13**. With tris-(*o*-anisyl)phosphine, the yield of indene **14** was improved to 49%, and the yield of indane **12** was diminished to 4%; thus, the stereoselection could be forced to over 11:1 in favor of *syn*-**c** over *anti*-**c**. Unfortunately, the overall mass balance was lower than the reaction in the presence of triphenylphosphine.

SCHEME 9. Bulky Ligands Favor Indene 11



ligand	yield **14**	ratio **14** / **12**
Ph_3P	**20%**	1 : 2
o-Tol_3P	**36%**	3 : 1
(*c*-Hex)$_2$biphP	**38%**	5 : 1
(*o*-MeOPh)$_3$P	**49%**	11 : 1

Isolation of achiral indene **14**, without the benzylic trimethylsilyl group, is a disappointment. In theory, halting halodesilylation of intermediate ***f*** (Scheme 8) would allow us to isolate an allylsilane like **8**. Silver salts have been shown to prevent the Pd-catalyzed protodesilylation of vinylsilanes during Heck reactions.[14] However, when silver triflate was added to the reaction of **11**, no turnover was observed and starting material remained unreacted. The halide may indeed be important for oxidative addition,[15] but the full role of halide in our reaction remains to be fully defined.

Carbopalladation of allenes generates η^3-allylpalladium intermediates, which are well-behaved in the presence of diazo compounds. However, Pd(0) is well-known to catalyze the addition of secondary amines to phenylallene in the presence of ammonium halide catalysts in refluxing THF, nearly identical to the conditions we used for carbenylative cyclizations.[16] Undaunted, we subjected the allene **15** to the carbenylative cyclization conditions using 1.1 equiv of TMSD and 2 equivs of piperidine (Scheme 10). Cyclized indene **17** was isolated in

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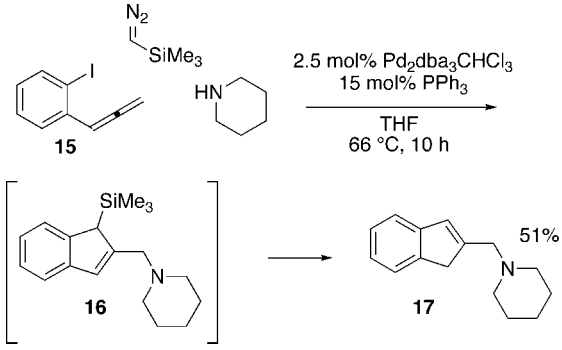
51% yield, presumably formed by way of the sensitive indenylsilane **16**.

The mechanism for protodesilylation of indenylsilane **16** is unclear but may be due to simple acid-catalyzed protodesilylation. Indenyltrimethylsilane is 10^8 more reactive toward nucleophilic protodesilylation than benzyltrimethylsilane.[17] Indeed, when an authentic sample of indenyltrimethylsilane was stirred with 1 equiv of piperidinium iodide at 66 °C, it underwent quantitative protodesilylation in a few hours. Ironically, indenylsilanes are more reactive toward η^3-allylpalladium intermediates than other allylsilanes,[18] however, dimeric indene products were not observed.

SCHEME 10. Allenes Generate Allylamines through Insertion



In conclusion, we have shown that TMSD can serve as a carbene equivalent in carbenylative cyclization reactions leading to indenes. Two types of aryl halide substrates were examined: aryl halides with pendant alkenes and aryl halides with pendant allenes. Both types of substrates generate benzylpalladium intermediates through carbene insertion, and these benzylpalladium intermediates undergo intramolecular carbopalladation to produce indenes. However, the fate of these indenyl intermediates is different. Substrates with pendant alkenes regenerate the palladium(0) catalyst through β-hydride elimination, whereas substrates with pendant allenes regenerate palladium(0) through attack of a nucleophile on an η_3-allylpalladium intermediate. Protodesilylation reactions can be facile under the conditions of the reaction. Thus, the TMSD can serve as either a trimethylsilylmethylene equivalent or a methine equivalent.

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(18) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595–2598.

Experimental Section

Representative Procedure. A round-bottomed flask fitted with a reflux condenser was charged with $Pd_2dba_3 \cdot CHCl_3$ (0.0069 mmol, 7.1 mg), (o-MeOPh)$_3$P (0.041 mmol), K_2CO_3 (0.55 mmol, 76 mg), and arene **7b** (0.27 mmol, 72 mg) under argon. The contents were dissolved in 3.0 mL of THF, and the mixture was stirred for several minutes until a colorless yellow solution was obtained. The reaction vessel was heated to 66 °C and a solution of TMSD (1.1 mmol in 1 mL THF) was then added via syringe pump over 10 h. The reaction was allowed to cool to 23 °C, and the mixture was filtered through a plug of silica gel to remove the palladium salts. The filtrate was concentrated in vacuo to afford a yellow residue that was purified by HPLC (silica 5 μ, 250 mm × 22 mm, step gradient 1–15% EtOAc/Hex) to give indene **14** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (d, J = 7.4 Hz, 1 H), 7.31 (d, J = 7.7, 1 H), 7.23 (dd, J = 7.7, 7.5, 1 H), 7.15 (dd, J = 7.5, 7.4, 1 H), 6.70 (s, 1 H), 4.17 (q, J = 7.1, 2 H), 3.52 (s, 2 H), 3.46 (s, 2 H), 1.28 (t, J = 7.1, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2 C, 145.0 C, 143.7 C, 141.4 C, 130.2 CH, 126.5 CH, 124.6 CH, 123.7 CH, 120.8 CH, 61.1 CH_2, 41.5 CH_2, 37.4 CH_3, 14.4 CH_3. IR (thin film) 3054, 1986, 1725 cm^{-1}; HRMS (ESI) m/z calcd for for $C_{13}H_{14}O_2Na$ $[M + Na]^+$, 225.0892; found, 225.0893.

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Supporting Information Available: Procedures and characterization data for **7a**, **7b**, **10**−**14**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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