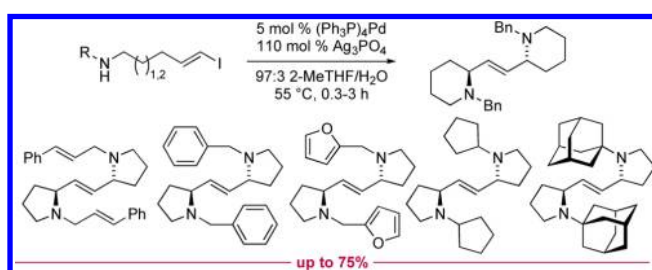


Pd-Catalyzed Bis-cyclization/Dimerization
Reactions of ω -Aminovinyl HalidesAvinash Khanna, Ilandari Dewage Udara Anulal Premachandra, Paul D. Sung, and
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ABSTRACT

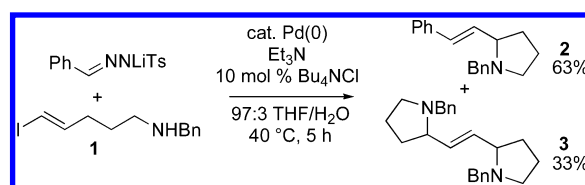


Palladium is shown to catalyze the dimerization and cyclization of vinyl halides to generate pyrrolidine and piperidine dimers connected by a trans-ethylene bridge. The reaction tolerates a variety of *N*-alkyl substituents, including adamantyl. This remarkable dimerization reaction generates the skeleton of the alkaloid hyalbidone in a single step. A crossover experiment with a vinyl halide and a vinyl bromide is consistent with a Michael-type addition to a vinylpalladium cation to generate a Pd(0) alkylidene intermediate.

We recently reported an intramolecular carbenylative amination reaction that employed *N*-tosylhydrazones as carbene precursors to generate 2-substituted pyrrolidines **2**.¹ During optimization of the carbenylative amination, we noted that dimerization of the vinyl halide was competing with the desired carbenylation reaction to form bis-pyrrolidine **3** (Scheme 1). When the *N*-tosylhydrazone was omitted from the reaction, the bis-pyrrolidine dimer **3** was formed in 67% yield. Intrigued by this unprecedented dimerization, we set out to explore the scope and potential applications of the reaction.

First we sought to identify which components of the heavily optimized carbenylative insertion were necessary for the dimerization reaction and to improve the yield of the dimer (Table 1). Among the catalyst precursors that we examined (Ph₃P)₄Pd proved to be more efficient than Pd₂dba₃·CHCl₃ or Pd(II) precatalysts (entries 1–5). Reducing the amount of lithium *tert*-butoxide to just 1.1 equiv was beneficial (entries 1, 6, and 7), but surprisingly, lithium hydroxide was less efficient than lithium *tert*-butoxide, even though water is a cosolvent. Other metal alkoxides were less efficient (entries 7, 10, and 11).

Scheme 1. Dimerization as a Competing Side Reaction in Carbenylative Amination



Substitution of lithium *tert*-butoxide with silver salts as bases led to a dramatic acceleration of the reaction rate, reducing the half-life to < 1 h (entries 12–15). The triethylamine additive proved to be dispensable (entries 18 and 20). Ultimately, the best yields with silver phosphate were obtained at 55 °C (entries 18 and 20).

Other experiments not shown in Table 1 revealed that the added water was essential for good yields and that other solvents were less efficient. Surprisingly, doubling the amount of Pd catalyst to 10 mol % reduced the yield of dimer **3**.

The optimized dimerization reaction generates only the trans alkene. The configuration of the double bond in **3**

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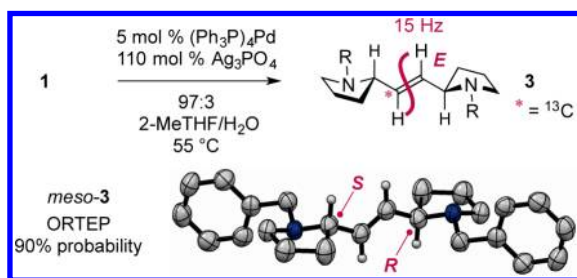
Table 1. Optimization of the Bis-cyclization/Dimerization of Vinyl Iodide **1** to Generate Dimer **3**

entry	Pd source (mol %)	phosphine (mol %)	base (equiv)	equiv Et ₃ N	temp	time	yield
1	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	Ph ₃ P (15%)	<i>t</i> -BuOLi (2.2)	2	23 °C	24 h	61%
2	(Ph ₃ P) ₄ Pd (5.0%)	-	<i>t</i> -BuOLi (2.2)	2	23 °C	24 h	65%
3	(Ph ₃ P) ₂ PdCl ₂ (5.0%)	-	<i>t</i> -BuOLi (2.2)	2	23 °C	24 h	47%
4	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	dppe (5%)	<i>t</i> -BuOLi (2.2)	2	23 °C	24 h	50%
5	Pd(OAc) ₂ (5.0%)	Ph ₃ P (10%)	<i>t</i> -BuOLi (2.2)	2	23 °C	24 h	18%
6	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	Ph ₃ P (15%)	<i>t</i> -BuOLi (4.4)	2	23 °C	24 h	33%
7	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	Ph ₃ P (15%)	<i>t</i> -BuOLi (1.1)	2	23 °C	24 h	67%
8	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	Ph ₃ P (15%)	-	2	23 °C	24 h	10%
9	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	Ph ₃ P (15%)	LiOH (1.1)	2	23 °C	24 h	48%
10	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	Ph ₃ P (15%)	<i>t</i> -BuONa (1.1)	2	23 °C	24 h	<20%
11	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	Ph ₃ P (15%)	<i>t</i> -BuOK (1.1)	2	23 °C	24 h	55%
12	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	Ph ₃ P (15%)	Ag ₂ CO ₃ (1.1)	2	23 °C	3 h	51%
13	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	Ph ₃ P (15%)	Ag ₃ PO ₄ (1.1)	2	23 °C	3 h	61%
14	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	Ph ₃ P (15%)	Ag ₃ PO ₄ (0.37)	2	23 °C	3 h	65%
15	Pd ₂ dba ₃ ·CHCl ₃ (2.5%)	Ph ₃ P (15%)	Ag ₃ PO ₄ (0.11)	2	23 °C	3 h	49%
16	(Ph ₃ P) ₄ Pd (5.0%)	-	Ag ₃ PO ₄ (1.1)	2	23 °C	3 h	71%
17	(Ph ₃ P) ₄ Pd (5.0%)	-	Ag ₃ PO ₄ (0.37)	2	23 °C	3 h	50%
18	(Ph ₃ P) ₄ Pd (5.0%)	-	Ag ₃ PO ₄ (1.1)	2	55 °C	1 h	72%
19	(Ph ₃ P) ₄ Pd (5.0%)	-	Ag ₃ PO ₄ (1.1)	2	80 °C	0.16 h	65%
20	(Ph ₃ P) ₄ Pd (5.0%)	-	Ag ₃ PO ₄ (1.1)	0	55 °C	1 h	75%

^aTemperature dependence studies were carried out in 2-methyl-tetrahydrofuran.

was established rigorously as *E* by the 15 Hz coupling constants in the ¹³C satellites for the olefinic protons (Scheme 2). With alkoxide bases, dimer (*E*)-**3** was present as a mixture of two different stereoisomers in an ~95:5 ratio, differing in configuration at the stereogenic centers. With silver phosphate a single stereoisomer was obtained. The stereochemistry of the dimer **3** was rigorously established as *meso* by a crystal structure (Scheme 2). Of note, *meso* dimers of this kind cannot be efficiently made through olefin metathesis.

Scheme 2. NMR and X-ray Crystallography Establish the Configuration of the Double Bond and the Relative Configuration

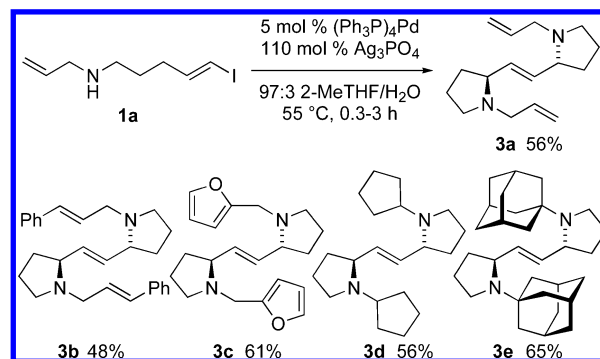


With optimized conditions for stereoselective formation of the dimer **3** we next assessed the tolerance of the reaction to variations of the *N*-alkyl substituent (Scheme 3). The reaction was chemoselective, tolerating terminal olefins and styryl groups to give **3a** and **3b** in 56% and 48% yield, respectively. The reaction tolerated electron-rich furans to give dimer **3c** in good yield. Surprisingly, cyclopentyl and even 1-adamantyl substituents were well tolerated on the

amino group. However, the *N*-adamantyl substrate required a slightly longer reaction time (3 h) to generate **3e**.

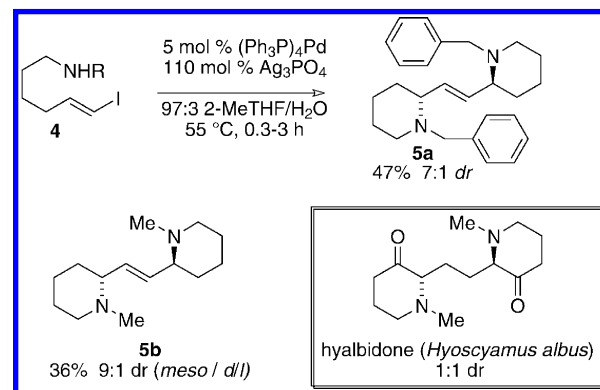
The bis-piperidines are formed less efficiently than bis-pyrrolidines under the optimized reaction conditions (Scheme 4). However the dimerization of **4** directly generates the skeleton of the bis-piperidine alkaloid hyalbidone in a single step. The natural product hyalbidone was isolated as a mixture of *meso* and *d/l* isomers from the roots of *H. albus*.² It is not clear whether the mixture of stereoisomers occurs in Nature or was the result of epimerization during isolation.

Scheme 3. The Bis-cyclization/Dimerization Reaction Tolerates a Variety of *N*-Alkyl Groups



The dimeric products accessed by our reaction bear a remarkable resemblance to the dimeric products noted by Balme et al. in the Pd-catalyzed reactions of terminal ω -sulfonylalkyne **6** (Scheme 5). The products observed by Balme³ were rationalized to arise from carbopalladation of a terminal alkyne by a hydridopalladium species leading to Pd(0) alkylidene intermediate **7**.⁴

Scheme 4. One-Step Synthesis of the Hyalbidone Skeleton



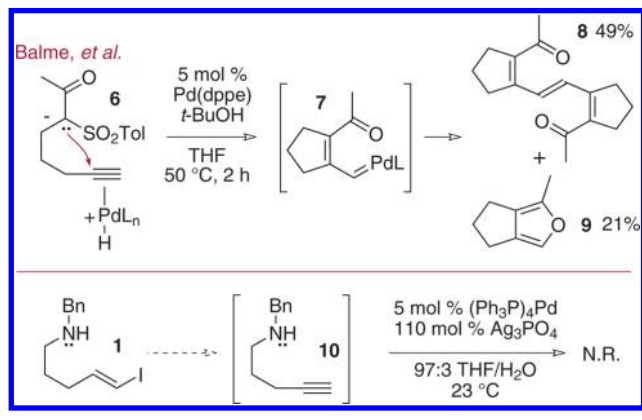
(2) (a) Sauerwein, M.; Ishimaru, K.; Shimomura, K. *Phytochemistry* **1991**, *30*, 2977–2978. (b) Sauerwein, M.; Shimomura, K.; Wink, M. *Bioforum* **1994**, *17*, 462–463.

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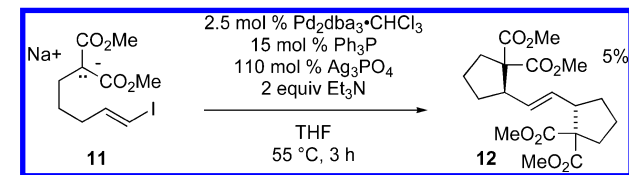
We do not observe alkyne intermediates in our dimerization reactions. To test whether our reaction was occurring through a *syn* elimination to form a terminal alkyne intermediate, we synthesized the terminal alkyne **10** and subjected it to the bis-cyclization/dimerization reaction conditions. No dimer was formed, and the alkyne starting material **10** was recovered. Thus, the bis-cyclization/dimerization reaction reported in this work is complementary to, yet distinct from, the desulfonylative dimerization of alkynes reported by Balme.

Scheme 5. The Balme Dimerization of Terminal Alkynes Is Distinct from Reactions of Vinyl Halides



The Balme system exploited a C-centered nucleophile to forge the cyclodimer **8**. To test the potential for C-nucleophiles in our cyclodimerization, substrate **11** was synthesized and subjected to the optimized conditions from Scheme 3. None of the desired dimer was formed even when water was omitted to prevent hydrolysis of the malonate ester. Using slightly modified conditions, the hindered bis-cyclopentane **12** was formed in a modest 5% yield, representing a single turnover (Scheme 6).

Scheme 6. Bis-cyclization/Dimerization with a Carbon Nucleophile



The beneficial effect of silver is consistent with the involvement of a vinylpalladium(II) cation (Scheme 7). Inspired by the palladium carbenes proposed for the Balme reaction, we hypothesized that the ω -amino group on intermediate **a** might be poised to add to the vinylpalladium cation in a process resembling a Michael addition.⁵

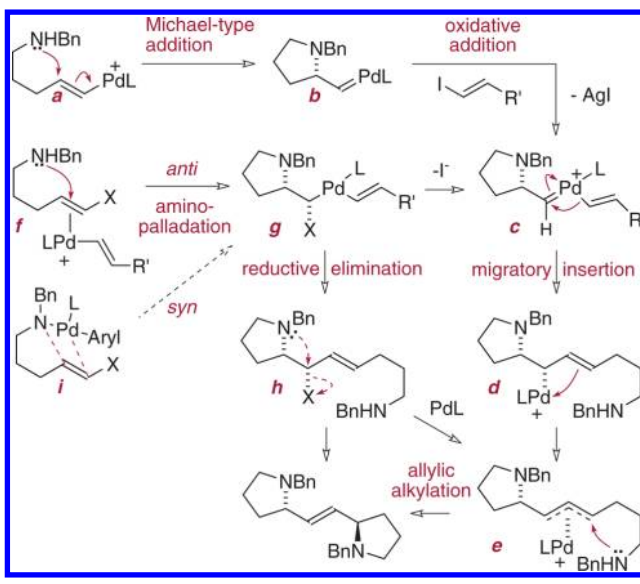
(5) Tsuji et al. have speculated that Michael-type addition of an enolate to an allenylpalladium species might produce a palladium carbene. Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196–2198.

The resulting Pd(0) carbene **b** could then undergo oxidative addition, much like Pd(0) complexes with *N*-heterocyclic carbene ligands, to generate vinylpalladium carbene **c**. Migratory insertion would generate an η^1 -allylpalladium intermediate **d** which could undergo an allylic alkylation through the η^3 -allylpalladium intermediate **e**.

Alternatively, the first C–N bond might arise through an intramolecular aminopalladation reaction of **f** or **i** to generate α -iodopalladium carbenoid intermediate **g**. α -Elimination of the halide would produce the same palladium carbene intermediate **c** that was invoked for the Michael-type addition mechanism. Palladium carbenoid **g** is also set up for reductive elimination to generate an allyl iodide **h** that could undergo substitution through an S_N2' reaction or a Pd-catalyzed allylic alkylation.

The starting materials in this bis-cyclization reaction bear a striking resemblance to *N*-Boc and *N*-aryl substrates used in the Wolfe reaction and related processes.⁶ However, both Balme⁷ and Wolfe⁸ have independently noted the failure *N*-alkylamines (and specifically *N*-benzylpent-4-en-1-amine) to engage in intramolecular *syn* aminopalladation reactions, presumably due to the difficulty in forming the amidopalladium intermediate **i** (X = H). Given the lack of precedence for Wolfe reactions of *N*-alkylamines, we are reluctant to invoke *syn* aminopalladation. Complexes such as **f** would be well-suited for an *anti* aminopalladation, analogous to a Wacker reaction, leading to the palladium carbenoid **g**.⁹ Given the potential for vicinal amino groups to promote substitution with double inversion,¹⁰ the stereospecificity of the aminopalladation cannot be used to rationalize formation of the *meso* bis-pyrrolidine **3** from either diastereomer of intermediate **g**.

Scheme 7. A Variety of Mechanistic Pathways Leading to Dimer

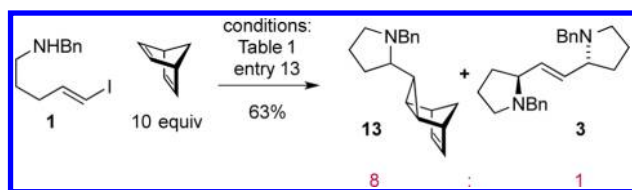


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When vinyl iodide **1** was subjected to the dimerization reaction in the presence of norbornadiene an 8:1 mixture of cyclopropane **13** and dimer **3** was obtained. The formation of cyclopropanes is consistent with Pd(0) alkylidene intermediates. We recently showed that vinyl iodide **1** and related compounds **1a–1e** could cyclopropanate norbornadiene (Scheme 8), consistent with palladium-alkylidene intermediate **b** in Scheme 7.^{11,3} Unfortunately, cyclopropanation of norbornenes is also consistent with a double carbopalladation sequence proposed by Catellani et al. or a carbopalladation/aminopalladation/reductive elimination sequence.^{12,13} When styrene was added to the reaction mixture, no cyclopropanation was observed. Thus, it is unclear whether formation of cyclopropanes from vinyl iodide **1** and norbornadiene is evidence for a Pd(0) alkylidene intermediate or merely symptomatic of the unique reactivity of norbornenes.

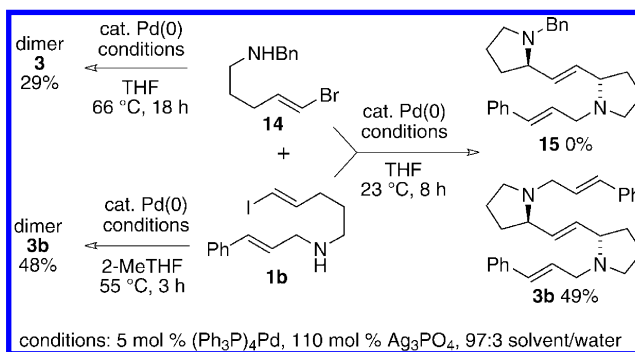
Scheme 8. A Cyclopropanation Experiment



In order to gather mechanistic insight we set up a crossover experiment, taking advantage of the sluggish oxidative addition of vinyl bromides relative to vinyl iodides (Scheme 9). Vinyl bromide **14** gives little reaction at 55 °C over 3 h, conditions under which vinyl iodide **1b** generates dimer **3b** in 48% yield. The vinyl bromide can be coaxed to form dimer **3** in 29% yield at higher temperature and with an extended reaction time. When 50 mol % of vinyl iodide **1b** and 50 mol % of vinyl bromide **14** were subjected to the reaction, the only dimer that formed was the bis-cinnamylamine dimer **3b**, isolated in 49% yield. None of the bis-benzylamine dimer **3** and none of the mixed dimer **15** were observed during the reaction or after workup. Some of the vinyl bromide (35%) starting material was recovered, whereas the vinyl iodide was completely consumed.

Based on the result of this crossover experiment, the aminopalladation pathway in Scheme 7 is untenable because the intermediate cationic Pd(II)·olefin complex **f** would

Scheme 9. A Crossover Experiment



be expected to undergo intramolecular aminopalladation at comparable rates regardless of whether the halide substituent X was bromide or iodide. The intermediate **g** (X = Br) would either generate mixed dimer **15** or, if unreactive, reduce the catalytic turnover and yield; neither of these results was observed. In contrast, the exclusive formation of dimer **3b** is consistent with the Michael-type addition/oxidative addition pathway in which both of the vinyl halides that are incorporated into the dimer participate through successive oxidative additions. The ability to access Pd(0) alkylidene intermediates such as **b** in Scheme 7 from vinyl halides would offer immense potential for construction of complex molecules.¹⁴

In conclusion we have described the first example of a bis-cyclization/dimerization reaction of vinyl iodides that generates *meso* bis-pyrrolidines and bis-piperidines. The reaction tolerates a range of *N*-alkyl substituents and was used to synthesize the skeleton of the alkaloid hyalbidone in a single step. A crossover experiment is consistent with a novel Michael-type addition of an amine to a vinylpalladium cation giving rise to a Pd(0) alkylidene intermediate.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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