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Palladium-Catalyzed Catellani Aminocyclopropanation Reactions with Vinyl Halides

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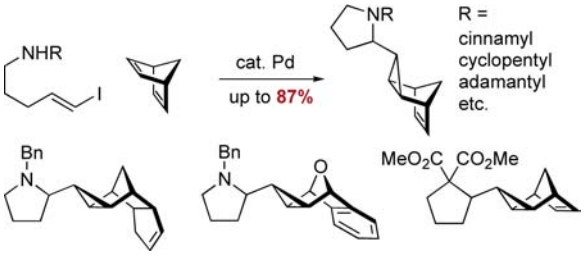
ABSTRACT



Palladium is shown to catalyze an intramolecular aminocyclopropanation of norbornenes with aliphatic vinyl halides in good yields. The reaction tolerates a variety of amine substituents and gives good results with a variety of carbocyclic and oxabicyclic [2.2.1] alkene acceptors. Notably, stabilized enolate nucleophiles were also employed in cyclopropanation reactions.

Norbornenes are gaining increasing attention for their participation in metal-catalyzed reactions, for example as traceless participants in C−H activation reactions[1] and as ligands for asymmetric catalysis.[2] Norbornenes are also exceptional substrates for cyclopropanation. Palladium(0) can catalyze the cyclopropanation of norbornenes using traditional carbene precursors such as α-diazo esters[3] and various carbenoid precursors.[4]

Vinyl halides have received scant attention as reagents for cyclopropanation. In the 1980s Catellani and co-workers reported that tandem Heck reactions of vinyl bromides with norbornene generate three types of cyclopropane products (Scheme 1). In the presence of potassium acetate, 1-bromo-1-octene reacts via β-hydride elimination to generate vinylcyclopropane **1**.[5] β-Styryl bromide generates intermediates that can be trapped with hydride donors or secondary amines such as benzylcyclopropane **2** and cyclopropylcarbinylamine **3**.[6] It was proposed that all three products arise from a tandem reaction involving intermolecular carbopalladation of norbornene to give vinylnorbornane **4**,

[†] A.K. and I.D.U.A.P. contributed equally to this work.

(1) (a) Catellani, M.; Motti, N.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512–1522. (b) Martins, A.; Mariampillai, B.; Lautens, M. *Top. Curr. Chem.* **2010**, *292*, 1–33. (c) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78–79. (d) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563–14572. (e) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824–889. (f) Elena Motti, E.; Della Ca', N.; Xu, D.; Armani, S.; Aresta, B. M.; Catellani, M. *Tetrahedron* **2013**, *69*, 4421–4428.

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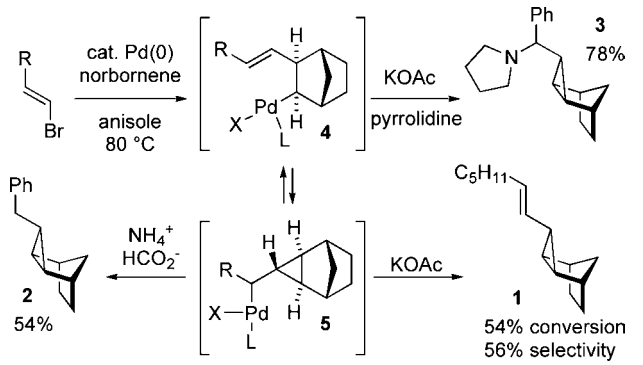
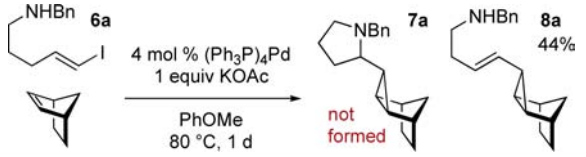
followed by intramolecular carbopalladation to give cyclopropylcarbinylpalladium intermediate **5**.[7]

Scheme 1. Common Reactive Intermediates in Catellani Cyclopropanations Can Generate Three Different Products



Other than styryl bromide, no other vinyl halides have been shown to generate cyclopropylcarbinylamines, presumably due to facile β-hydride elimination that leads to formation of vinylcyclopropanes analogous to **1**. We set out to explore this distinctive aminocyclopropanation reaction using vinyl halides other than styryl bromides.

Scheme 2. Aminocyclopropanation Reactions

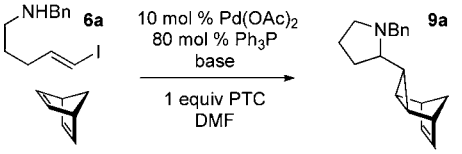


In order to favor this unique aminocyclopropanation reaction, we turned to a vinyl iodide substrate **6a** with a pendant secondary amine. Under the conditions reported for styryl bromide, none of the cyclopropylcarbinylamine **7a** was observed and we isolated only (*E*)-vinylcyclopropane **8a**, resulting from β-hydride elimination (Scheme 2).

In order to promote the formation of pyrrolidine **7a**, we changed both the alkene acceptor and the reaction conditions. We substituted norbornadiene for norbornene since it has been reported to provide higher yields in palladium-catalyzed cyclopropanation reactions with diazo compounds.[3a] We also changed the reaction conditions to those reported by Torii for reductive trapping of a putative cyclopropylcarbinylpalladium intermediate using formic acid as a hydride source.[8] In a footnote, Torii and co-workers reported the isolation of a cyclopropane in 84% yield by reacting a vinyl iodide, norbornene, Ph_3P, $Pd(OAc)_2$, and Et_3N in DMF. Therefore, we set out to optimize the aminocyclopropanation of norbornadiene under the Torii conditions (Table 1).

(8) (a) Torii, S.; Okumoto, H.; Ozaki, H.; Nakayasu, S.; Tadokoro, T.; Kotani, T. *Tetrahedron Lett.* **1992**, *33*, 3499–3502. The cyclopropanation reaction was mentioned in ref 8a without a full description of the reaction conditions. (b) Torii, S.; Okumoto, H.; Ozaki, H.; Nakayusu, S.; Kotani, T. *Tetrahedron Lett.* **1990**, *31*, 5319–5322.

Table 1. Optimization of the Aminocyclopropanation of Norbornadiene



entry	equiv Ph_3P	equiv amine	equiv nbd	PTC	temp	vessel	yield
1	0.4	2 Et_3N	2		80 °C		39%
2	0.8	2 Et_2NH	5		80 °C		52%
3	0.8	2 Et_2NH	10		80 °C		64%
4	0.8	2 Et_2NH	10	Bu_4NCl	66 °C		73%
5	0.8	2 Et_2NH	10	Bu_4NCl	80 °C		79%
6	0.8	2 Et_2NH	10	Bu_4NCl	100 °C		57%
7	0.4	2 Et_2NH	10	Bu_4NCl	80 °C		56%
8	0.8	–	10	Bu_4NCl	80 °C		21%
9	0.8	2 Bu_3N	10	Bu_4NCl	80 °C		36%
10	0.8	2 Et_3N	10	Bu_4NCl	80 °C		56%
11	0.8	2 Et_2NH	10		80 °C	sealed	66%
12	0.8	2 Et_2NH	10	Bu_4NCl	80 °C	sealed	81%
13	0.8	3 Et_2NH	10	Bu_4NCl	80 °C	sealed	82%
14	0.8	1 Et_2NH	10	Bu_4NCl	80 °C	sealed	70%
15	0.8	2 *n*-$PrNH_2$	10	Bu_4NCl	80 °C	sealed	72%

The reaction is complete in less than 1 h with a large excess of norbornadiene and additional phosphine (Table 1, entries 1–3). The yields slightly improved in the presence of the phase transfer catalyst tetra-*n*-butylammonium chloride (entry 2 and 4), and the optimal temperature was 80 °C (entries 4–6). Unfortunately, the reaction was less efficient when the amount of triphenylphosphine was reduced (entries 5 and 7). The optimal stoichiometry was found to be 2 equiv of diethylamine, and secondary amine additives were superior to tertiary or primary amines (entries 8–15). To better accommodate the volatile reaction components, the reaction was carried out in sealed tubes, ultimately providing yields over 80% (entries 12 and 13). The optimized conditions (entry 12) favor the participation of an amine nucleophile in the cyclopropanation reaction as opposed to β-hydride elimination.

The relative stereochemistry of the amine product **9a** was established by the presence of a positive steady state NOE from one of the protons on the norbornene bridge C7 to one of the cyclopropane protons and an absence of NOEs between the proton at C8 and the protons at C2 and C3 (Figure 1).

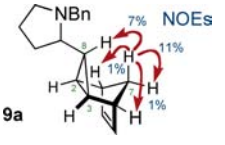
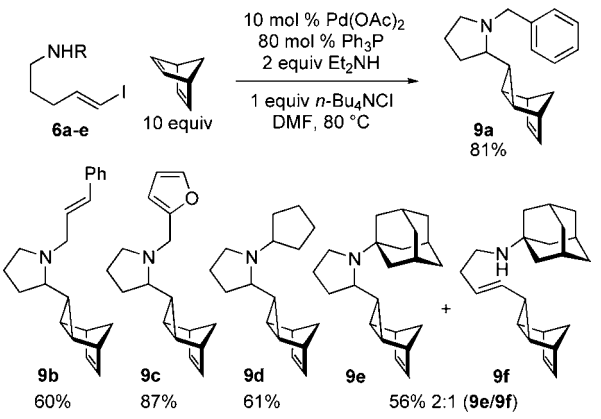


Figure 1. Establishing the relative stereochemistry.

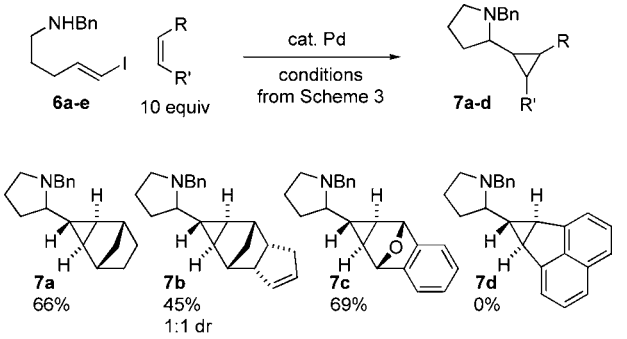
With optimized conditions in hand, we next explored the tolerance of the amine nitrogen substituent to varying degrees of steric hindrance (Scheme 3). The reaction conditions led to chemoselective cyclopropanation of the nobornadiene acceptor without a competing reaction of a pendant cinnamyl group in **9b**. The reaction furnished cyclopropanes in yields up to 87%. As expected, the bulky *N*-cyclopentylamine **9d** was formed in lower yield. The exceedingly hindered adamantyl group of adamantylamine **6e** led to a slower reaction and an inseparable 2:1 mixture of pyrrolidine **9e** and vinylcyclopropane **9f** in 56% yield. The *N*-benzyl vinyl bromide corresponding to **6a** also provided the cyclopropylcarbinylamine **9a** in 53% yield.

Scheme 3. Intramolecular Aminocyclopropanation with Variations in the Amine Substituent



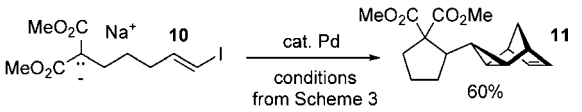
We next set out to explore variations in the alkene acceptor. Norbornene and dicyclopentadiene were slightly less efficient than norbornadiene (Scheme 4). The adduct of dicyclopentadiene **7b** was obtained as an inseparable 1:1 mixture of diastereomers. An oxabicyclic [2.2.1] substrate generated the aminocyclopropane **7c** in 69% yield.[9] The cyclic alkene acenaphthylene, which has been shown to resist β-hydride elimination, generated none of the cyclopropane **7d**.[10]

Scheme 4. Scope of Alkene Acceptor



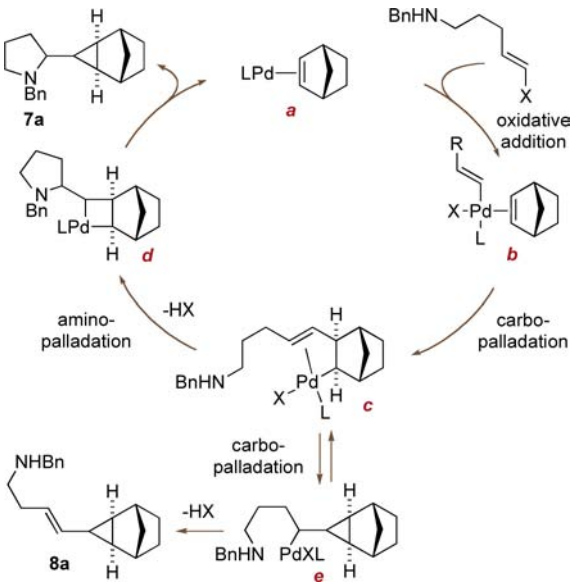
We set out to test carbon nucleophiles in the Catellani cyclopropanation. The malonate anion **10**, generated with sodium hydride, produces the corresponding cyclopropane adduct **11** in 60% yield under the optimized conditions (Scheme 5).

Scheme 5. Carbon Nucleophiles Generate Carbocyclic Rings in Conjunction with Cyclopropanation



The mechanism of these unique cyclizations and cyclopropanations is still unclear. In their seminal report Catellani and co-workers proposed the intermediacy of cyclopropylcarbinylpalladium intermediate **5** (Scheme 1) in the aminocyclopropanation reaction.[6] The first step involves an oxidative addition to form vinylpalladium halide ***b*** (Scheme 6), followed by intermolecular carbopalladation across the norbornene double bond to give *exo*-norbornylpalladium intermediate ***c***. The *exo* palladium atom is unable to undergo *syn* β-hydride elimination but is poised to carbopalladate across the *exo* vinyl group to produce cyclopropylcarbinylpalladium intermediate ***e***. Carbon−nitrogen bond formation could occur via a reductive elimination[6] or ionization of XPd^- to give a cyclopropylcarbinyl cation, both of which would generate the aminocyclopropane product. Reductive elimination seems less likely as a mechanism for C−N bond formation given the challenges that have been documented[11] with

Scheme 6. Mechanistic Models for Intramolecular Aminocyclopropanation



(9) The substrate is known to undergo cyclopropanation reactions with high *exo* selectivity: Tenaglia, A.; Marc, S. *J. Org. Chem.* **2006**, *71*, 3569–3575.

(10) Dyker, G. *J. Org. Chem.* **1993**, *58*, 234–238.

Buchwald–Hartwig aminations. However, the olefin and palladium groups in norbornylpalladium intermediate ***c*** are poised for an aminopalladation to give palladacyclobutane ***d***. Palladacyclobutanes have previously been invoked in the mechanisms for palladium catalyzed cyclopropanation.[4g,12] In previous studies of aminopalladations, *N*-alkylamines have been shown to aminopalladate *anti*[13] whereas *N*-aryl and *N*-sulfonylamines have been shown to aminopalladate *syn*.[14] Moreover, the participation of malonate anions is consistent with the well-accepted *anti*-carbopalladation mechanism.[15]

In summary, we show for the first time that the Catellani reaction can be applied to aliphatic vinyl halides—not just styryl bromide—and can even engage stabilized enolates as well as amine nucleophiles. The reaction is selective for norbornenes over other alkenes, even acenaphthylene, which, like norbornenes, should generate palladium intermediates that resist β-hydride elimination. Ultimately, the mechanism of the reaction is unclear, but given the participation of both alkylamines and stabilized enolates as nucleophiles, we favor a mechanism involving palladacyclobutanes such as ***d*** in Scheme 6.

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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.

The authors declare no competing financial interest.

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