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Carbenylative Amination and Alkylation of Vinyl Iodides via Palladium Alkylidene Intermediates

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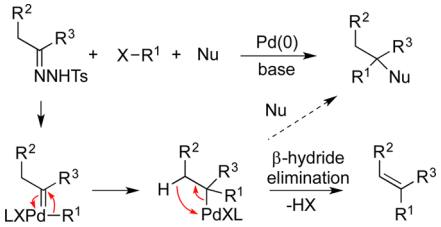
Supporting Information

ABSTRACT: Most palladium-catalyzed reactions involving insertion of alkylidenes with α-hydrogens undergo β-hydride elimination from alkylpalladium(II) intermediates to form alkenes. Vinyl iodides were shown to generate η^3-allylpalladium intermediates that resist β-hydride elimination, preserving the sp^3 center adjacent to the carbene moiety. Acyclic stereocontrol (*syn*/*anti*) for carbenylative amination and alkylation reactions was low, suggesting a lack of control in the migratory insertion step. Highly hindered carbene precursors inexplicably led to formation of *Z*-alkenes with high levels of stereocontrol.

Palladium-catalyzed carbenylative insertion processes are gaining increasing attention, as they are analogous to widely used carbonylative insertion processes. Three-component carbenylative cross-coupling reactions offer a powerful method for joining molecular fragments through one-carbon units, similar to three-component carbonylative cross-coupling reactions. In initial applications, diazo compounds served as the major carbene precursors, but more recently, *N*-tosylhydrazone anions have been used to expand the scope of carbene precursors to include benzylidene and alkylidene derivatives.[1] When there are hydrogens adjacent to the carbene center, carbene insertion is usually followed by β-hydride elimination, which out-competes nucleophilic trapping and erases any stereochemical information created in the carbene insertion step (Scheme 1).

Scheme 1. β-Hydride Elimination Out-Competes Nucleophilic Trapping



Most palladium-catalyzed carbene insertion processes involve RPdX complexes derived from oxidative addition of aryl (pseudo)halides[2] and benzylic and allylic halides.[3] In other processes, RPdX complexes arise from addition of nucleophiles to Pd(II).[4] Regardless of how the migratable group ends up on the Pd(II) intermediate, migration to the alkylidene ligand ultimately results in substituted olefins due to the rapidity of β-hydride eliminations. Two-component reactions of Pd(0) alkylidenes with carbon monoxide or isonitriles lead to ketenes or ketenimines, respectively, without β-hydride elimination.[5,6]

In rare instances, three-component carbenylative insertions have been observed to out-compete β-hydride elimination using η^1-to η^3-allyl or oxa-allyl transitions,[7−9] but the generality of this approach has not previously been demonstrated. Palladium catalysts have been used to unite vinyl iodides with nucleophiles and carbene precursors incapable of β-hydride elimination: trimethylsilyl, carboxyalkyl, aryl, and vinyl (Figure 1).[9,10] In this work, we demonstrate that simple alkylidene groups can efficiently engage in three-component carbenylative cross-coupling reactions of vinyl iodides without β-hydride elimination. Furthermore, we demonstrate the utility of *N*-trisylhydrazones as alkylidene precursors that react faster than the corresponding *N*-tosylhydrazones.

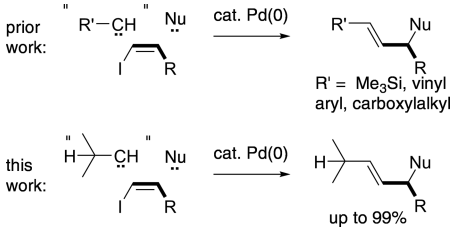


Figure 1. Carbenylative amination and alkylation with alkylidene carbenes without β-hydride elimination.

We initiated the investigation of carbenylative insertion reactions of ω-aminovinyl iodide **1** and isobutyraldehyde *N*-tosylhydrazone **2a** using conditions similar to those used in our previous work on carbenylative amination of benzaldehyde tosylhydrazones (Scheme 2).[10b] The only product isolated from the reaction was the known dimer **4** (31%),[10b,11] and a large amount of unreacted vinyl iodide **1** (68%) was recovered. We speculated that the low solubility of the lithiated *N*-

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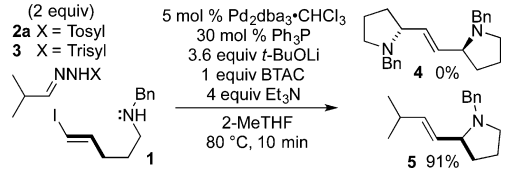
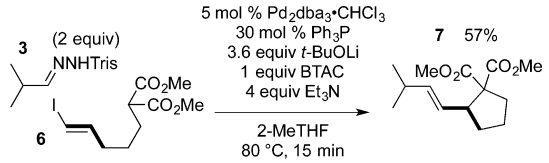
tosylhydrazone was responsible for its failure to engage in the reaction. When the corresponding *N*-trisylhydrazone **3** was employed as the alkylidene precursor, the lithiated *N*-trisylhydrazone exhibited better solubility in the reaction and afforded the desired pyrrolidine **5** in 15% yield. From there, the conditions were optimized to afford pyrrolidine **5** in 91% yield, and there was no evidence of dimer **4** or products resulting from elimination of the alkylidene α proton.

Scheme 2. Intramolecular Carbenylative Amination with an Alkylidene Precursor



Alkenylcyclopentanes are found in a variety of natural products, such as brefeldin C, doproston B, isopulo'upone, and amaminol A. To test the potential for carbon nucleophiles in the intramolecular carbenylative insertion reaction, substrate **6** was synthesized and subjected to the optimized reaction conditions (Scheme 3). The lithium enolate of malonate **6** produces the

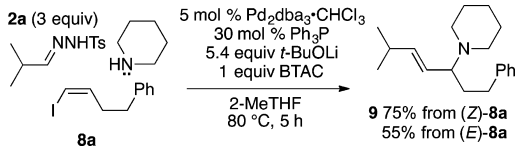
Scheme 3. Intramolecular Carbenylative Alkylation with an Alkylidene Precursor



corresponding alkenylcyclopentane **7** in 57% yield. The low yield is probably attributable to the sensitivity of the substrate. Srivastava and co-workers have previously shown related ε-iodovinylmalonates to be highly sensitive to alkoxides.[12] When malonate **6** was exposed to potassium carbonate, lithium *tert*-butoxide, or potassium *tert*-butoxide at 80 °C for 1 h, increasing levels of decomposition (17%, 52%, and 100%, respectively) were observed.

A three-component version of the reaction was tested using piperidine as the external nucleophile and *Z*-vinyl iodide **8a** (Scheme 4). Under the conditions optimized for intramolecular

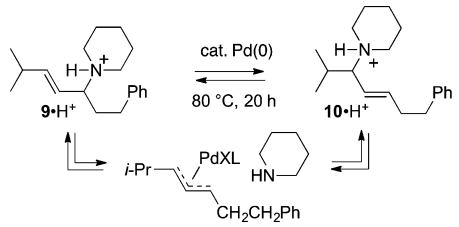
Scheme 4. Intermolecular Carbenylative Amination with Alkylidene Precursors



trapping with vinyl iodide **1**, none of the desired allylamine **9** was observed. Under these conditions, trisylhydrazone **3** was too reactive as a carbene source. When *N*-tosylhydrazone **2a** was used along with 4 equiv of piperidine, the desired allylamine **9** was obtained in 44% yield. The triethylamine additive can be omitted from the reaction conditions. Under the optimized conditions, 5 equiv of piperidine was used and the amount of *N*-tosylhydrazone and lithium *tert*-butoxide was increased, leading to a 75% isolated yield of the carbenylative amination product **9**. When the *E* isomer of vinyl iodide **8a** was employed in the reaction, the product was obtained in lower yield (55%). Previously, it had been shown that *Z*-vinyl iodides and *E*-vinyl iodides give comparable yields in intramolecular carbenylative aminations.[10b]

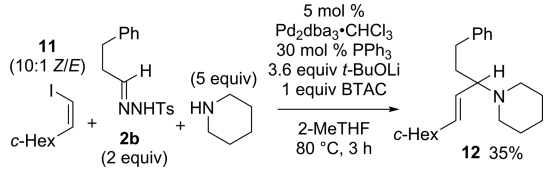
The reaction is believed to involve intermolecular attack of piperidine on an η^3-allylpalladium intermediate on the least hindered side of the allyl fragment.[13] When fewer equivalents of lithium *tert*-butoxide were used, allylamine **9** (55%) was accompanied by the allylic regioisomer **10** (25%). The poor regioselectivity is probably attributable to the faster palladium-catalyzed equilibration of the protonated forms of allylic amines **9** and **10** (Scheme 5).[14] To test this hypothesis, we exposed product **9** to the less basic conditions, without the vinyl iodide starting material, for 20 h and found it to produce an 80:20 mixture of allylamines **9** and **10**.

Scheme 5. Allylamines Slowly Isomerize under the Conditions of the Reaction



In theory, regioisomer **9** should be highly favored under kinetic conditions regardless of how one accesses the η^3-allylpalladium intermediate. When the vinyl iodide, rather than the *N*-tosylhydrazone, is substituted with a secondary alkyl group, the amine still prefers to attack at the least hindered side of the allylic system. Reaction of vinyl iodide **11** with *N*-tosylhydrazone **2b** generated allylamine **12** (Scheme 6), analogous to the preferred formation of regiosomer **9** over **10**. The net transformation is a carbenylative cross-coupling, similar to a carbonylative cross-coupling reaction with carbon monoxide.

Scheme 6. Carbenylative Cross-Coupling with a Hindered Vinyl Iodide



With optimized conditions for the intermolecular carbenylative cross-coupling reaction in hand, we next set out to explore variations in the alkylidene precursor **2a**–**d**, the vinyl iodide, **8a** and **8b**, and the nucleophile (Scheme 7). The sulfonylhydrazone anions compete with other nucleophiles in the reaction by attacking the η^3-allylpalladium intermediate,[15] and formation of *N*-allylated hydrazone **23** accounts for 20–30% of the mass balance based on NMR of the crude reaction mixtures. In the absence of a nucleophile, a mixture of diene products, resulting from β-hydride elimination, was observed along with adduct **23** (22%). Diethyl malonate afforded comparable yields and resulted in a 13:1 regioisomeric mixture of allylic alkylation

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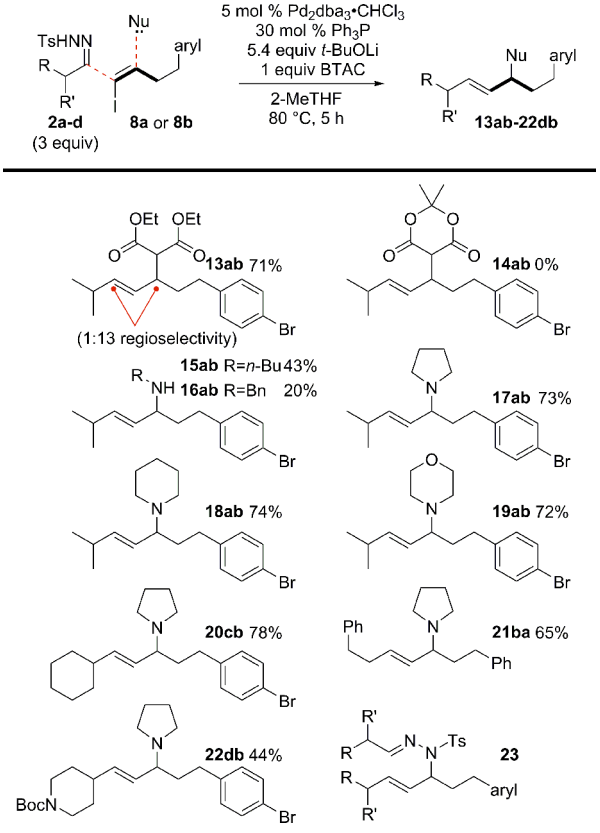
Scheme 7. Scope of Intermolecular Carbenylative Alkylation and Amination with Alkylidene Precursors



products (**13ab**). Not surprisingly, when Meldrum's acid was utilized as the nucleophile, none of the desired adduct **14ab** was obtained, probably due to the weaker nucleophilicity of the conjugate base ($pK_a' = 4.97$). Butylamine and benzylamine gave modest yields of the desired coupling products **15ab** and **16ab**, respectively. The cyclic secondary amines, pyrrolidine, piperidine, and morpholine, gave good yields (**17ab**–**19ab**). The superiority of cyclic amines in three-component carbenylative amination reactions was demonstrated in previous studies.[9,10a] The carbenylative amination and alkylation reactions proceed with high chemoselectivity; oxidative addition across the Ar–Br bond was not observed. We next explored the tolerance of different alkyltosylhydrazones, and the coupling reactions furnished yields up to 78% (**20cb**, **21ba**, and **22db**).

Valdés and co-workers have previously shown that palladium-catalyzed reactions of *N*-tosylhydrazones derived from α-chiral ketones proceed with preservation of stereochemistry.[1b] Since carbenylative amination reactions create new stereogenic centers it is possible to assess the potential for acyclic stereocontrol. The Felkin–Anh model reliably predicts the acyclic stereocontrol in nucleophilic additions to carbonyls with α-chiral centers (Figure 2a). Chiral centers might also affect 1,2-migration reactions in alkylpalladium carbene complexes, but that behavior has never been studied. There have been surprisingly few studies of

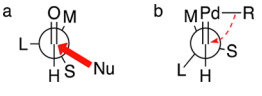
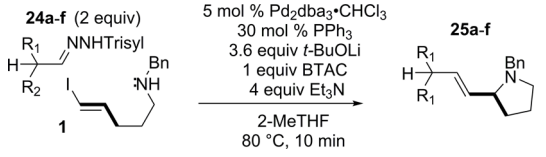


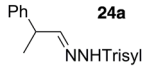
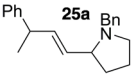
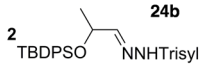
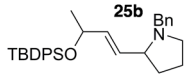
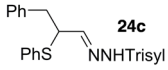
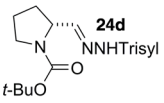
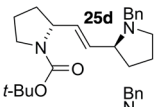
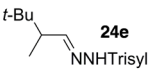
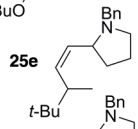
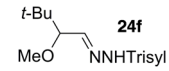
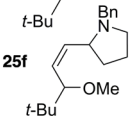
Figure 2. Acyclic stereocontrol: (a) nucleophilic addition to carbonyls, (b) 1,2-migration to palladium carbenes.

asymmetric 1,2-migrations to discrete acyclic carbocations, which are structurally analogous to late metal carbenes; none involve an adjacent stereogenic center.[16]

The effect of adjacent stereogenic centers in migratory carbene insertions was evaluated by utilizing chiral alkyl *N*-trisylhydrazones **24a–f** in intramolecular carbenylative aminations (Table 1). Unfortunately, the products were obtained as nearly

Table 1. Stereoselectivity in Carbenylative Amination

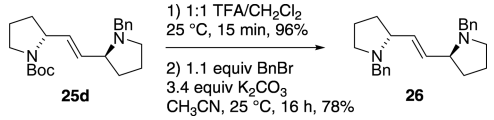


entry	starting material	product	yield (%)	dr
1			72	55:45
2			77	58:42
3		—	0	—
4			75	65:35 *anti*:*syn*
5			72	56:44
6			99	50:50

equal mixtures of *syn* and *anti* diastereomers. *N*-Trisylhydrazones **24a** and **24b** afforded pyrrolidines **25a** and **25b**, respectively, in good yields, but thioether **24c** gave none of the desired product, and 85% of the vinyl iodide was recovered. *N*-Boc-pyrrolidine **24d** gave a slight preference for the one diastereomer of **25d**.

The stereochemistry of the major diastereomer of **25d** was assigned as *anti* by converting the inseparable mixture to the corresponding bis-*N*-benzyl-bis-pyrrolidines; the major diastereomer was shown to be identical to the known *meso* (*anti*) isomer **26** (Scheme 8).[11] To our surprise, when sterically encumbered

Scheme 8. Assignment of Relative Stereochemistry by Conversion to Known Bis-pyrrolidine



N-trisylhydrazones **24e** and **24f** were employed the products were obtained as the *Z* alkenes ($J \leq 7.9$ Hz) with none of the expected *E* alkene products (Table 1, entries 5 and 6). To test the effect of steric encumbrance on alkene geometry, the hindered *N*-tosylhydrazone **27** was tested and shown to give only the *E* product **28** (Scheme 9). Thus, sterics alone is not sufficient to explain formation of *Z* products **25e** and **25f**.

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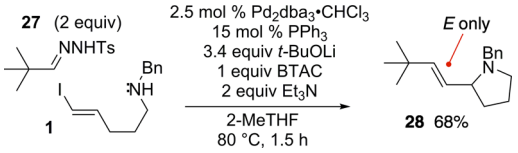
Scheme 9. Sterically Encumbered *N*-Tosylhydrazone 27 Shown To Give Only the *E* Product 28



Adjacent stereogenic centers seem to exert much less influence in migration to palladium carbenes than they do in the corresponding nucleophilic addition to carbonyls. This may be due to the elevated temperatures used for the palladium reactions and/or the difference in preferred angles for 1,2-migration processes versus carbonyl additions.

In conclusion, unstabilized alkylidene groups are shown to participate in palladium-catalyzed carbenylative amination and carbenylative alkylation reactions, without β-hydride elimination, with high efficiency for both intramolecular and intermolecular processes. Good yields are obtained under conditions that minimize a number of competing processes such as palladium-catalyzed ionization of allylic amines, competing addition of metalated hydrazones to η^3-allylpalladium complexes, and base-promoted decomposition of vinyl iodides with pendant malonate groups. *N*-Trisylhydrazones are shown to give superior results relative to *N*-tosylhydrazones when faster rates of participation are needed from the alkylidene precursor. When there is a stereogenic center adjacent to the metal carbene carbon, the resulting products are obtained with low levels of *syn*/*anti* stereocontrol but high levels of *E* or *Z* selectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02820.

Experimental details, characterization of new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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