



## Palladium-catalyzed olefin migration and 7-*endo-trig* cyclization of dehydroalanines

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### ARTICLE INFO

#### Article history:

Received 22 December 2017

Accepted 20 January 2018

Available online 31 January 2018

#### Keywords:

Ugi reaction

Dehydroalanines

Palladium catalysis

1,4- and 1,5-olefin migration

$\beta$ -Amino elimination

### ABSTRACT

1,4- or 1,5-migration of a double bond of dehydroalanines under palladium catalysis is reported. The process occurred with several highly-substituted dehydroalanines under mild typical Heck reaction conditions. Although this was one of the first reports of a palladium-catalyzed 1,5-olefin migration, the outcome of the reaction was susceptible to the starting material. Mechanistically, the process involved a five- (1,4-migration) or six-membered ring (1,5-migration) organopalladium intermediate, which cleaved a C–N bond in an  $\beta$ -amino elimination process.

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Undoubtedly, palladium-mediated carbon–carbon bond-forming reactions are essential tools in the armory of the synthetic organic chemist.<sup>1</sup> Indeed, complex transformations, which in the past were not accessible by traditional methodologies, are now possible with palladium chemistry.<sup>2</sup> Within this field, the Heck–Mizoroki cross-coupling reaction has been a great contribution to organic synthesis.<sup>3</sup> Several heterocyclic compounds of biological significance<sup>4</sup> or complex natural products<sup>5</sup> have been assembled using a Heck reaction.<sup>6</sup> Thus, because of its versatility, this methodology has also been applied in certain intramolecular reactions to construct carbocycles and heterocycles of various sizes.<sup>7</sup> Palladium catalysis has also been applied in particular types of rearrangement processes. For example, ring expansion of spirocyclopropanes,<sup>8</sup> synthesis of 4-arylnicotinates through a domino reaction,<sup>9</sup> and 1,4-hydrogen shift,<sup>10</sup> have been mediated by palladium catalysis. Interestingly, during the palladium catalyzed synthesis of 7-, 8-, and 9-membered rings under typical Heck conditions, Gibson detected the formation of the rearranged by-product **2**, derived from the *ortho* iodo precursor **1** (after 120 h!), but no further details of this observation were disclosed (Scheme 1).<sup>11</sup> More recently, Xu and co-workers observed the Pd(OAc)<sub>2</sub> catalyzed formation of the styrene derivatives **4** from enamine **3**. In this study, the 1,4-alkene migration was highly dependent

both on the nature of the ligand and the base used in the reaction.<sup>12</sup>

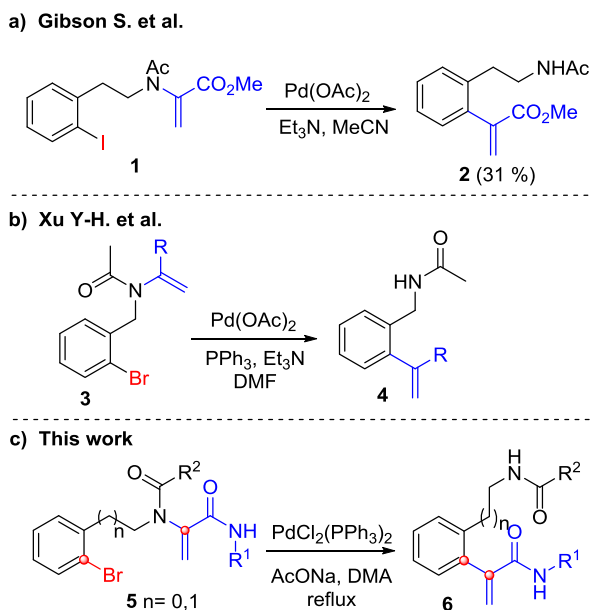
In our ongoing efforts to develop useful synthetic protocols based on Pd-catalyzed domino processes applied to Ugi 4-CR-derived (four-component reaction) dehydroalanines, we recently observed that palladium-mediated 1,4- and 1,5-double bond migrations are possible in this system. Given the paucity of information associated with this rearrangement, we decided to explore its scope, and the preliminary results are disclosed herein (Scheme 1).

Our endeavour commenced with the study of the dehydroalanine **5a** (Scheme 2) which was easily prepared from *o*-bromobenzyl amine, acetic acid, *tert*-butyl isocyanide and benzoyloxy acetaldehyde in two steps (Ugi 4-CR/elimination) in 65% yield under previously reported conditions.<sup>13</sup> Surprisingly, when **5a** was submitted to the action of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (10 mol%) and 2 equivalents of AcONa in refluxing dimethylacetamide (DMA), a mixture of the pyrroloisoindolone **13a** and the corresponding rearranged acrylamide **6a** was achieved in good yield (61%) after 6 h (entry 1, Table 1). In principle, both products could have been produced through a Pd-catalyzed tandem process, consisting initially of a 5-*exo* Heck-type cyclization to generate intermediate palladium species **12**, which may then react by two different processes. It may undergo the interesting formation of an sp<sup>3</sup>–sp<sup>3</sup> bond generating a second 5-membered ring to afford **13a**, or undergo a  $\beta$ -amino elimination process by C–N bond fragmentation with concomitant double bond regeneration to produce the rearranged

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Scheme 1. Palladium-catalyzed rearrangements of alkenes.

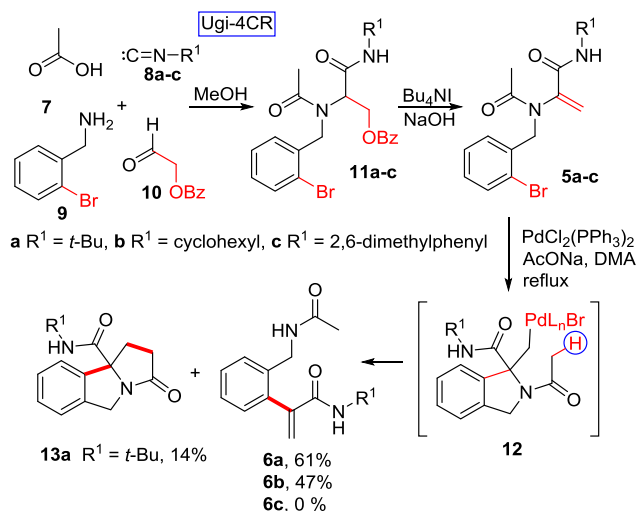
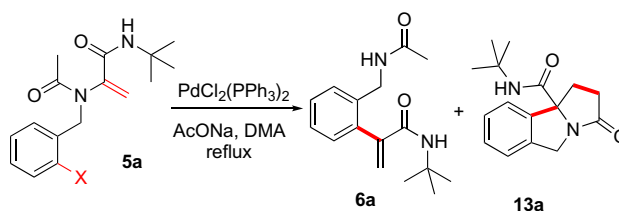
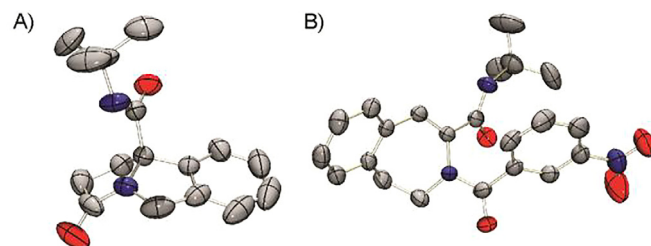
Scheme 2. Pd-Catalyzed sp<sup>3</sup>-sp<sup>3</sup> C-C bond formation and olefin 1,4-migration.

Table 1

Influence of the equivalents of catalyst, base and halide used in the transformation.



Entry	X	Time (h)	Catalyst	Base	<b>6a</b> (%)	<b>13a</b> (%)
1	Br	6	10%	2.0 eq	61	14
2	Br	12	10%	1.5 eq	33	–
3	Br	12	10%	1.0 eq	30	–
4	Br	12	5%	2.0 eq	27 <sup>a</sup>	–
5	Cl	48	10%	2.0 eq	25 <sup>b</sup>	–

<sup>a</sup> 25% of starting material recovered.<sup>b</sup> 38% of starting material recovered.Fig. 1. X-ray structure of: (A) tricycle **13a** (CCDC number 1532303); (B) benzoazepine **14a** (CCDC 1532294). Hydrogen atoms were removed for clarity.

acrylamide **6a** (The lack of an alpha hydrogen in **12a** prevents the typical  $\beta$ -hydride elimination of a Heck process).<sup>14</sup>

The structure **13a** was unambiguously established by single crystal X-ray analysis (Fig. 1). It is worth noting that even though the yield of the tricycle **13a** was low (14%), the outcome is relevant because it represents a novel example of a Pd-catalyzed formation of an sp<sup>3</sup>-sp<sup>3</sup> single bond, featuring a C–H functionalization. In an attempt to increase the yield of the tricyclic compound, the reaction temperature was maintained at reflux for three days, although no significant differences were detected (51% for **6a** and 10% for **13a**). On the assumption that the acrylamide **6a** might be an intermediate in the formation of the pyrroloisindolone **13a**, it was subjected to the above conditions for 5 days. However, no transformation of **6a** into **13a** was detected, thus indicating that the generation of the two compounds follows independent pathways from intermediate **12**.

When equivalents of the base were reduced, the rearrangement product **6a** was isolated in lower yields and longer reaction times (entry 2–3, Table 1). Interestingly, the tricyclic derivative **13a** was not observed under these conditions. When the load of the palladium catalyst was reduced, **6a** was obtained in only 27% yield along with recovered starting material (25%, entry 4). Similar result was found when chloride derivative was submitted to the same conditions (entry 5); 25% yield of **6a** and 38% of the starting material was recovered after 48 h.

Surprisingly, when the *tert*-butyl group was replaced by cyclohexyl in the amide moiety of **5b**, the main product isolated was the corresponding rearranged acrylamide **6b** (47% yield), and the benzofused heterocycle **13b** was not detected (Scheme 2). Further modification of the substituent in the amide with a 2,6-dimethylphenyl group (**5c**) resulted in decomposition of the starting material and no major product was isolated. The limited information regarding such rearrangements led us to examine the scope of

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