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ARTICLE TYPE

Palladium-catalyzed carbocyclization/cross-coupling reactions of two different allenic moieties: Synthesis of 3-(buta-1,3-dienyl) carbazoles and mechanistic insights

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A palladium-catalyzed chemo-, regio- and stereoselective carbocyclization/cross-coupling sequence of two different α -allenols to afford 3-(*E*-buta-1,3-dienyl) carbazoles is reported.

Allenes are versatile synthetic intermediates in organic synthesis.^{1,2,3} However, the reported work involving the use of two different allenes, was limited to oxycyclization/cross-coupling reactions;⁴ being missed the carbocyclization/cross-coupling sequence. We report herein a controlled carbocyclization/cross-coupling domino reaction of indole-tethered allenols and α -allenic esters for the direct preparation of the chemically and biologically relevant carbazole nucleus.

The structure of starting materials for the carbocycle formation, arene-tethered allenols **1**,⁵ suggests at least two possibilities for reactivity, namely, C-cyclization *versus* O-cyclization.⁶ Disappointingly, upon treating the benzene-tethered allenol **1a** with α -allenic acetate **2a** at room temperature with 5 mol% PdCl₂ in DMF, it was found that the 2,5-dihydrofuran **3a** arising from a heterocyclization/cross-coupling process was formed in 59% yield (Scheme 1).⁷ In an attempt to improve the carbocyclization efficiency under similar reactions conditions, we screened a different aromatic allenol system such as indole-tethered allenol **1b** on reacting with α -allenic acetate **2a**. Interestingly, not the 2,5-dihydrofuran **3b** but the benzo-annulation adduct,⁸ carbazole **4a**, was exclusively obtained (Scheme 1), resulting in failure the carbocyclization/cross-coupling sequence because the cross coupling step was missed.

Scheme 1 Divergent cyclization reactions of allenols **1a** and **1b** under palladium catalysis. PMP = 4-MeOC₆H₄.

Attempts of the domino reaction using Pd(OAc)₂ and [Pd(PPh₃)₄] also failed. The use of additives, such as K₂CO₃, FeCl₃, and PPh₃ did not show any appreciable difference. Apparently, allenol derivatives **1b** and **2a** have inadequate

reactivity for the joint participation in the coupling process. Fortunately, an interesting and useful temperature effect next emerged from the observation that the simple heating at 80°C resulted in the formation of the desired carbocyclization/cross-coupling adduct **5a** in a reasonable 71% yield (Scheme 2). The overall transformation can be roughly explained invoking a 6-*endo*-trig allene carbocyclization followed by cross-coupling and final dehydration. Thus, it is possible to suppress the formation of the cycloisomerization/dehydration adduct by performing the reaction at higher temperature, yielding carbazole **5a** as the exclusive product.⁹ A general trend can be deduced on the basis of these results: carbazole **4a** is the kinetic control product while carbazole **5a** is the thermodynamic control product. We applied this protocol to the generation of different carbazoles **5b–i** by the successfully use of variously substituted allenic esters **2b–i** (Scheme 2). We also decided to undertake a study of the potential use of more diverse allenols **1** in this novel reaction. The palladium-catalyzed carbocyclization/cross-coupling sequence of hindered phenyl-substituted indole-tethered allenol **1c** failed. By contrast, non-substituted allenol **1d** efficiently reacted to afford the corresponding 3-(buta-1,3-dienyl) carbazole **5k** (Scheme 2). Importantly, all products were obtained as single isomers, that is, with complete *E* selectivity with regard to the newly established C=C double bond, as determined by qualitative homonuclear NOE difference spectra.

Scheme 2 Synthesis of 3-(buta-1,3-dienyl) carbazoles **5** through carbocyclization/cross coupling reactions of allenol derivatives **1** and **2** under palladium catalysis at 80 °C.

A possible pathway for the palladium-catalyzed generation of functionalized carbazoles **5** is outlined in Scheme 3. Initial Pd(II)-coordination to the 1,2-diene moiety leads to the allenepalladium

complex **1b,d-PdCl₂**. Species **1b,d-PdCl₂** suffers an intramolecular chemo- and regioselective 6-*endo*-trig carbocyclization reaction to produce the palladadihydrocarbazole **6**. Loss of HCl with concurrent dehydration under the reaction conditions produces aryl palladium intermediate **8**. The coupling of intermediate palladacarbazole **8** with **2** leading to species **13** takes place regioselectively at the central allene carbon atom of **2**. Finally, a *trans*- β -deacetoxyallenylation generates, in a highly stereoselective manner, 3-(buta-1,3-dienyl) carbazoles **5** as single *E*-isomers with concomitant regeneration of the Pd(II) species. Worthy of note, the carbopalladation of carbazolyl palladium intermediate **8** to form the corresponding π -allylic palladium intermediate is totally chemoselective towards the allenic acetate **2** since homodimerization from the coupling with other molecule of free allenol **1b** did not occur.

Scheme 3 Mechanistic explanation for the palladium-catalyzed preparation of 3-(buta-1,3-dienyl) carbazoles **5**.

To gain more insight into the reaction mechanisms of the above palladium-catalyzed cyclization reactions, a computational (DFT) study was carried out.¹⁰ First, we computed the experimentally observed preference of allenol **1b** towards the carbocyclization reaction in the presence of PdCl₂ (Scheme 1). As readily seen in Figure 1, it can be concluded that the initially formed allenepalladium complex **1b-Pd** is completely transformed into dihydrocarbazole **6** via the saddle point **TS1**. This extraordinary regioselectivity takes place under both kinetic and thermodynamic control, in view of the higher activation energy required for the formation of dihydrofuran **6'** ($\Delta\Delta G^\ddagger_{298} = 5.2$ kcal/mol), as well as the considerably lower reaction energy computed for cycloadduct **6** ($\Delta\Delta G_{R,298} = 16.6$ kcal/mol). Subsequent loss of HCl (which produces intermediate **7**) and H₂O leads to aromatic carbazole **8**, a palladium(II) complex able to react with the second allenic moiety.

Palladacarbazole **8** is then transformed into the final carbazole **4a** via protonolysis of the carbon-palladium bond mediated by HCl. Our calculations (Figure 2) suggest that this step starts from complex **10**, where the HCl is weakly bonded to the transition metal, which easily evolves to complex **12** through the saddle point **TS2** (activation barrier of only 2.7 kcal/mol) in an exergonic process ($\Delta G_{R,298} = -17.6$ kcal/mol). Subsequent decooordination of PdCl₂ will form the observed carbazole **4a**. Interestingly, complex **8** can also coordinate a new allene ligand

(model allene **9** in the calculations) to produce the allenepalladium complex **11**. This species evolves to complex **13** via the transition state **TS3**, a saddle point associated with the new carbon-carbon bond formation. From the data in Figure 2, this step is kinetically disfavored respect to the above-mentioned C-Pd protonolysis ($\Delta\Delta G^\ddagger_{298} = 9.7$ kcal/mol) but thermodynamically favored ($\Delta\Delta G_{R,298} = 5.4$ kcal/mol). This finding strongly supports our hypothesis that carbazole **4a**, derived from complex **12**, is the kinetically-controlled product whereas carbazoles **5**, derived from complex **13**, are thermodynamically favored.

Figure 1 Computed reaction profile of allenepalladium complex **1b-Pd**.¹¹

The process leading to carbazoles **5** ends with the easy rotation about the C-C bond in complex **13**, which can produce two different complexes, **14-trans** and **14-cis**. These species possess the adequate geometry to undergo the final deacetoxyallenylation reaction via the corresponding saddle points **TS4-trans** and **TS4-cis**, respectively. Strikingly, the *trans*-deacetoxyallenylation reaction (via **TS4-trans**) is kinetically ($\Delta\Delta G^\ddagger_{298} = 2.2$ kcal/mol) and thermodynamically favored over the analogous *cis*-process (via **TS4-cis**). This justifies the complete stereoselectivity of the transformation which exclusively produces 3-(buta-1,3-dienyl) carbazoles **5** as single *E*-isomers. This step, albeit exergonic occurs with the highest activation barrier ($\Delta G^\ddagger_{298} = 19.7$ kcal/mol) computed for the entire reaction profile, and therefore constitutes the bottle-neck of the transformation. Furthermore, this finding explains why a high temperature is experimentally required to produce carbazoles **5** (easily formed by decooordination of CIPd(OAc) in complex **15**). Finally, the PdCl₂ catalyst is regenerated by protonolysis of the released CIPd(OAc) complex with HCl (computed activation barrier of 8.2 kcal/mol) forming AcOH as reaction product as well.

We have also computed the corresponding **11** to **13** reaction for the unprotected α -hydroxyallene (denoted as **11bis** to **13bis**). Not surprisingly, the more nucleophilic free OH of the allene can coordinate the metal center thus stabilizing the initial complex **11bis**. This is translated into a higher activation barrier via **TS3bis** compared to the reaction involving **TS3** via the OAc-complex **11**, where the OAc cannot coordinate the metal and acts as a mere spectator in this C-C bond formation process (Figure 3). Moreover, the OAc is essential in the final step of the process because it helps to release the initial catalyst through the formation of the CIPd(OAc) complex. Obviously, the

corresponding complex formed with the OH (with only one possibility of coordination) would be thermodynamically less

stable thus leading to a more difficult release of the initial Pd catalyst.

Figure 2 Computed reaction profile of complex **8** to produce complexes **12** and **15**.¹¹

Figure 3 Computed reaction profile of α -hydroxyallene **11bis** to produce carbazole **13bis**.¹¹

In conclusion, a combined experimental and computational study of a palladium-catalyzed synthetic route to 3-(*E*-buta-1,3-dienyl) carbazoles from two different α -allenols has been accomplished.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of new compounds, and copies of NMR spectra. See DOI: 10.1039/b000000x/

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Graphical Abstract

An efficient palladium-catalyzed synthetic route to 3-(*E*-buta-1,3-dienyl) carbazoles from two different allene-ols has been reported. The reaction was found to proceed with complete control of product chemo-, regio- and stereoselectivity through a carbocyclization/cross-coupling sequence. The mechanism of this process has additionally been investigated by a computational study showing that carbazoles are the kinetically-controlled product whereas buta-1,3-dienylcarbazoles are thermodynamically favored.

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