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Palladium-Catalyzed Domino Carbopalladation/5-*exo*-Allylic Amination of α-Amino Allenamides: An Efficient Entry to Enantiopure Imidazolidinones

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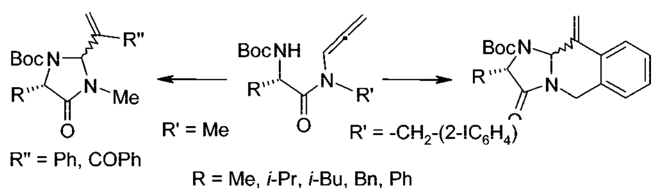
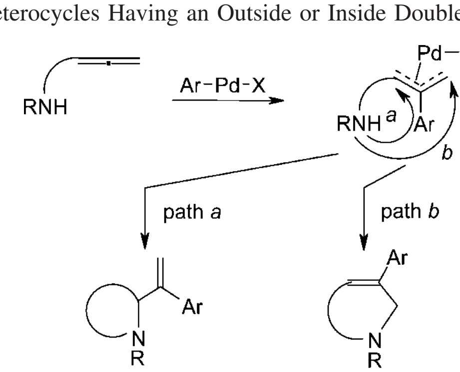
ABSTRACT



Allenamides of α-amino acids were converted into enantiopure 2-vinylimidazolidin-4-ones by a carbopalladation/*exo*-cyclization process. The products were obtained in 2.5:1−5.5:1 dr, with 94−99% ee. The palladium-catalyzed carbonylative cyclization of the same substrates afforded enone structures. Starting from properly substituted allenamides, an intramolecular carbopalladation followed by intramolecular amination gave rise to tricyclic fused-ring imidazolidinones.

Heteroannulation processes involving an allenyl functional group and transition metal catalysis have been extensively studied in the past years.[1] Among the most employed transition metals, palladium has played a relevant role when used in both 0 and II oxidation states throughout C−C, C−N, and C−O bond formations.[2,3] A variety of nitrogen-containing heterocyclic products having an outside (Scheme 1, path

Scheme 1. General Procedure for Nitrogen-Containing Heterocycles Having an Outside or Inside Double Bond



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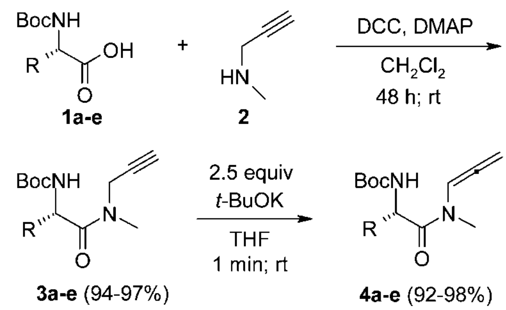
a) or inside double bond (Scheme 1, path b) were obtained by intramolecular nucleophilic attack of the nitrogen atom to a π-allylic palladium complex generated by carbopalladation of the allene starting from organic halides[4]or hypervalent iodinonium salts.[5]

Following our continuing interest in the development of new protocols toward nitrogen-containing heterocycles via intramolecular Pd-catalyzed reactions,[6] we turned our attention to the heterocyclization of substrates bearing an allene moiety and a nitrogen nucleophile. In particular, our studies were aimed at obtaining 2-vinylimidazolidin-4-ones from α-amino acid derived α-amino allenamides via a palladium-catalyzed domino carbopalladation/5-*exo*-allylic amination process. It should be noted that this type of procedure has never been reported on substrates wherein an amide group tethers the reacting function.

Because imidazolidine derivatives show interesting biological activities[7] and are used successfully as organocatalysts,[8] the discovery of new pathways for their enantiopure synthesis represents a valuable goal. Moreover, the presence of the vinylic substituent makes them important building blocks suitable for further functionalization, increasing their interest as organocatalysts.

Amino allenamides **4** were obtained in near quantitative yields by reaction of L-α-amino acids **1** and the *N*-methylpropargylamine **2**, followed by *t*-BuOK promoted isomerization of the resulting propargylamides **3** (Scheme 2). The

Scheme 2. Preparation of Allenamides **4**

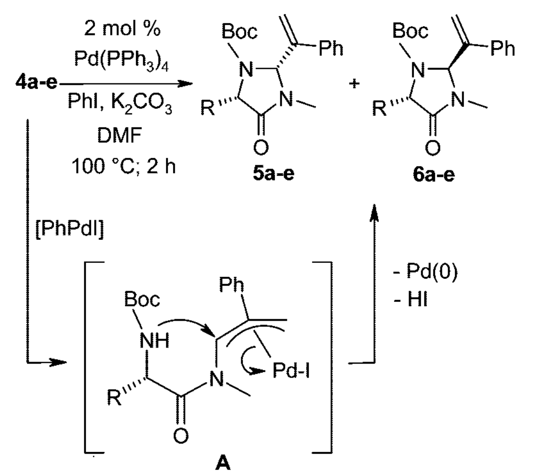


a: R = Me; **b**: R = *i*-Pr; **c**: R = *i*-Bu; **d**: R = Bn; **e**: R = Ph

exposure time of **3** to the base is crucial and must not exceed 1 min, so as to prevent the base-promoted cyclization path.[9]

The reaction conditions tested in the preliminary cyclization experiments gave straightforwardly satisfactory yields of the desired imidazole products. In fact, use of $Pd(PPh_3)_4$ (0.02 equiv), PhI (1.2 equiv), and K_2CO_3 (4 equiv) in DMF as solvent gave the products **5a−e** and **6a−e** in 2.5:1−5.5:1 diastereoisomeric ratio through an *exo*-cyclization of the π-allyl intermediate **A** (Scheme 3).

Scheme 3. Heterocyclization Reaction of Allenamides **4** by Intermolecular Carbopalladation−Intramolecular Amination



R = Me, **5a**: 65%, **6a**: 12%
R = *i*-Pr, **5b**: 55%, **6b**: 16%
R = *i*-Bu, **5c**: 54%, **6c**: 17%
R = Bn, **5d**: 50%, **6d**: 19%
R = Ph, **5e**: 52%, **6e**: 20%

Change of the catalyst (palladium acetate), the base (Et_3N, Cs_2CO_3, *t*-BuOK), or the solvent (acetonitrile, DMSO)

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resulted in less clean crude reaction mixtures with the same degree of diastereoselectivity. The heterocyclization process occurred also with PhBr as the arylating agent, although in lower yields.

The X-ray crystal structure analysis[10] of the minor product **6e** (Figure 1) revealed a *trans* relationship between the hydrogens in the stereogenic positions and indirectly proved a *cis* disposition for its diastereoisomer **5e**. Analogy of the ^{1}H NMR spectra of compounds **5e** and **6e** with those of **5a−d** and **6a−d**, respectively, allowed the assignment of their absolute configuration. The constant presence of two rotamers in the ^{1}H and ^{13}C NMR spectra of the *trans* diastereoisomers **6a−e** exclusively is the most peculiar feature allowing differentiation of the two diastereoisomers.

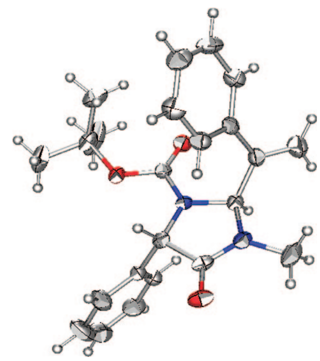


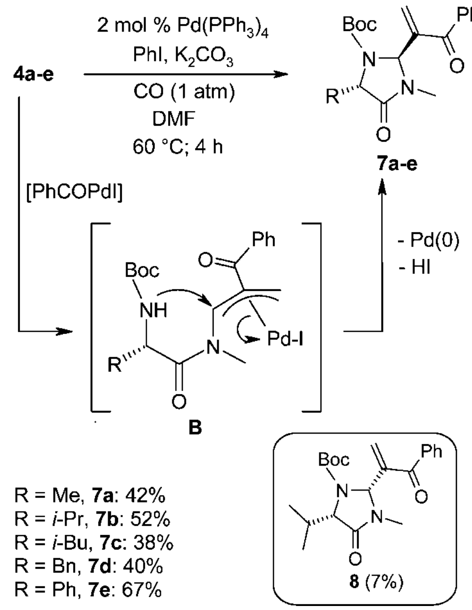
Figure 1. ORTEP drawing of compound **6e** at 30% probability level.

HPLC comparison (Chiralcel ODH column) of a sample of **5b** with that of a racemic sample obtained starting from (±)-valine proved an enantiomeric purity better than 99.0%. The same analytical procedure on compound **5e** revealed ee = 94%.

The carbopalladation/amination process was then extended to carbonylative conditions with the aim of obtaining 2-enoyl imidazolidinones. To the best of our knowledge, only one example of a Pd-catalyzed three-component carbonylation/*N*-heterocyclization of allenes with aryl iodide under CO pressure has been reported in the literature.[11]

Accordingly, running the reaction under CO at atmospheric pressure gave the enoyl imidazolidinones **7a−e**. Such a result indicated that the initially generated PhPd(II)I complex inserted carbon monoxide prior to undergoing carbopalladation, to give the new π-allyl complex **B**. Again, intramolecular allylic amination gave the final products (Scheme 4). The *trans*-configuration of **7a−e** was assigned by comparing their NMR spectra with those of compounds **6a−e** and is probably due to the bulky effect of CO group in intermediate **B**. Only the heterocyclization of the isopropyl-substituted substrate **4b** took place, giving two diastereoisomers in a

Scheme 4. Pd-Catalyzed Carbonylative Cyclization of Allenamides **4**



6:1 ratio, making possible the isolation the *cis*-product **8**. To optimize this procedure, the reaction was carried out under CO pressure (20 atm), but no improvements in diastereoisomeric ratio or time of the reaction were observed.

Finally, α-amino allenamides bearing a juxtaposed internal *o*-iodoaryl function were tested as precursors, so as to access imidazoisoquinolinones via a doubly intramolecular version of the above domino sequence. It should be noted that the intramolecular carbopalladation of allenes followed by an intramolecular amination is still a rare procedure.[12]

Thus, treatment of α-amino acids **1a−c** with amine **9** afforded the propargylamides **10a−c**, which were isomerized to allenes **11a−c** in high yields (Scheme 5). Subsequent carbopalladation/amination of the latter using Pd(PPh_3)$_4$ as

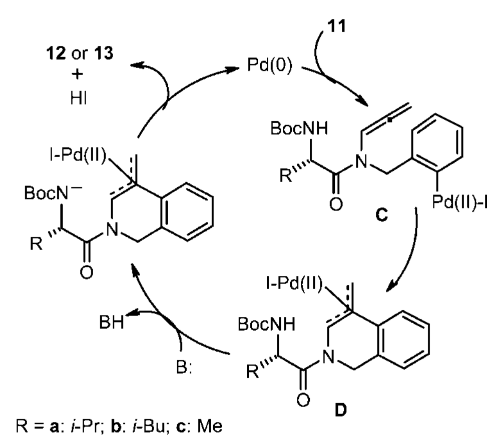
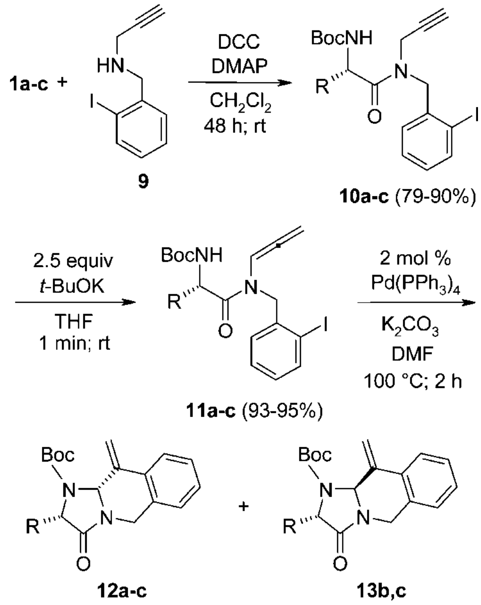


Figure 2. Catalytic cycle of intramolecular carbopalladation/intramolecular amination of allenamides **11**.

(10) Crystal data for species **6e**: orthorhombic, space group $P2_12_12_1$, a = 6.001(3) Å, b = 18.387(5) Å, c = 19.338(6) Å, V = 2134(1) Å^3, Z = 4, F(000) = 808, ρ = 1.178 g cm^{-3}, μ(Mo Kα) = 0.078 mm^{-1}. $R(F)$ and $wR(F_2)$ for $I > 2\sigma(I)$ = 0.061 and 0.105. CCDC number CCDC 717937.

Scheme 5. Heterocyclization Reaction of Allenamides **11** by Intramolecular Carbopalladation−Intramolecular Amination



R = Me, **12a**: 51%
R = *i*-Pr, **12b**: 54%; **13b**: 8%
R = *i*-Bu, **12c**: 59%; **13c**: 6%

catalyst and K_2CO_3 as base gave the expected tricyclic products **12a−c** and **13b,c** in a 6.5:1 ratio and 51−59% yields. Comparison of the ^{1}H NMR spectra of these products with those of **5a−e** allowed assignment of a *cis* configuration to the former set of major isomers and a *trans* one to the minor ones, which could be isolated only in the case of substrates arising from valine and leucine (**13b,c**).

The generation of the 1,5,10,10a-tetrahydro-2*H*-imidazo[1,2-*b*]isoquinolin-3-ones **12** and **13** can be rationalized as depicted in Figure 2. The initial generation of ArPd(II)I **C** by oxidative addition of the iodobenzene moiety to a Pd(0) species is followed by intramolecular carbopalladation of the central carbon of the allyl group to give the π-allyl complex **D**. At this point, the intramolecular nucleophilic attack of the nitrogen on the inside position of the Pd-complex generates the imidazolidinone products with concomitant expulsion of the Pd(0) species, able to restart the catalytic cycle.

In summary, we have developed a new and original approach to enantiopure imidazolidin-4-ones and imidazoisoquinolinones by means of a domino carbopalladation/allylic amination process, starting from α-amino allenamides of amino acid derivation. In all three protocols developed, the vinyl group present in the final products may allow further improvement of the known organocatalytic properties of such compounds. Moreover, the results have established the feasibility of the above heterocyclization process having an amide group in the tether, without any interference of the carbonyl oxygen. Work is now in progress to investigate the ability of the newly obtained imidazolidin-4-ones as building blocks for more complex structures and as organocatalysts in reactions involving α,β-unsaturated aldehydes.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR of new compounds. Crystal data and experimental procedures for the X-ray structure analysis of **6e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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