Sequential Base-Promoted Annulation/Palladium-Catalyzed Domino 1,5-Enyne Arylation and Vinylation of *α*-Propargylaminohydrazones

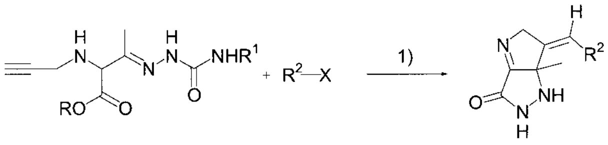
Elisabetta Rossi,* Antonio Arcadi,* Giorgio Abbiati, Orazio A. Attanasi, and Lucia De Crescentini

1,2-Diazabuta-1,3-dienes represent versatile building blocks in organic synthesis because they offer easy access to a wide variety of heterocyclic compounds by 1,4-conjugate addition and subsequent cyclization reactions.[1] Moreover, Michael reaction adducts of the 1,2-diazabuta-1,3-diene system may act as nitrogen ligands[2] for transition metal catalysts, which leads to unusual reaction pathways.[3] In common with other Michael additions, 1,2-diazabuta-1,3-dienes undergo divergent copper-promoted annulation reactions to form functionalized imidazolines/imidazoles under regiocontrol, whereas the base-promoted cyclization provides both 1-substituted and 1-unsubstituted 4-aminocarbonyl-1*H*-pyrazol-5(2*H*)-ones.[4]

A variety of metal-catalyzed reactions of enynes, which involve a broad range of early and late transition metals, are of interest in the synthesis of functionalized carbo/heterocycles.[5] The classes of reaction that involve the metal-catalyzed functionalization of enynes include cycloisomerization,[6] reductive cyclization,[7] bismetallative cyclization,[8] carbonylative cyclizations,[9] and dimerization/cyclization.[10] One-pot domino reactions of enynes provide a valuable procedure for easy access to five- and six-membered heterocycles containing a 1,3-diene structure, which can lead to bicyclic compounds through in situ Diels–Alder reactions.[11] Domino reactions are emerging as powerful strategies in modern synthetic organic chemistry, and the discovery of new reaction sequences able to produce functional compounds constitutes a challenge both from the academic and industrial points of view.[12]

The *α*-propargylaminohydrazone adducts **1a–c** (Scheme 1, Table 1), which contain a 1,4-diazo-1,6-azenyne system, turned out to be useful substrates for further metal-catalyzed processes. In this context, we investigated the palladium-catalyzed arylation and vinylation reactions of *α*-propargylaminohydrazones. Here we report a new, efficient synthetic methodology for the preparation of (*Z*)-6-arylidene/vinylidene-6a-methyl-1,5,6a-tetrahydro-2*H*-pyrrolo[3,2-*c*]pyrazol-3-ones (for example, **3a–h**) through remarkable sequential base-promoted annulation/palladium-catalyzed, domino 1,5-enyne arylation and vinylation reactions.

The treatment of **1a–c** with anhydrous piperidine in the presence of aryl iodide/triflate derivatives **2a–h** and Pd(OAc)$_2$/DPPF (Ac = acetyl; DPPF = 1,1′-bis(diphenylphosphanyl)ferrocene) catalytic system gave **3a–h** in good yields (Scheme 1, Table 1). The structure of compounds **3** was confirmed by one- (^{1}H, ^{13}C) and two-dimensional (COSY, HETCOR, NOESY) NMR spectral analysis, and by mass spectroscopy. NOESY experiments clearly demonstrate that the geometry of the exocyclic double bond is *Z* for all compounds **3a–h**. Moreover, ^{1}H and ^{13}C NMR signals arising from the vinyl substituted pyrazolones **3e–h** are split because of the presence of multiple isomers.



1a-c **2a-h** **3a-h**

Scheme 1. Reagents and conditions: 1) Pd(OAc)$_2$, DPPF, piperidine, RT, 24 h. Spectroscopic data of new compounds can be found in the Supporting Information.

The absence of nuclear Overhauser enhancement (NOE) interactions between the olefinic protons on the exocyclic double bond and on the cyclohexene ring in **3e** was explained by the results of a conformational search[13] at the AM1[14] semiempirical level to evaluate the conformational energies of **3e**. The results show that the conformers with lower steric energies have spatial arrangements which are in agreement with the observed NOE interactions. Moreover, the analysis of all the observed minima show that there is only one local minimum, with a spatial arrangement compatible with a NOE interaction between the two olefinic protons (<3 Å apart), however the steric energy of this minimum is about 10 kJ mol^{-1} higher than that of the global minimum structure.

A reasonable rationale for the production of **3** is depicted in Scheme 2. The reaction involves the formation of the 1-aminocarbonyl-1*H*-pyrazol-5(2*H*)-ones **4** derivatives obtained by the piperidine-promoted annulation reaction of **1a–c**, according to our previous findings.[4b] Solvolytic cleavage at N-1 of **4** gives **5**; ureas **6** were isolated as reaction side products. Compounds **3a–h** are formed through the palladium-catalyzed domino arylation or vinylation/carbocyclization of **5**. Thus, the regioselective *syn* addition of the σ-vinyl/aryl palladium complex on the triple bond of **7** affords the σ-vinyl palladium intermediate **8**, which forms intermediate **9** by a carbocyclopalladation step. Finally, the elimination of HPdX from **9** produces the *Z* pyrazolone derivatives **3** stereospecifically and regenerates the active catalyst. The stereochemical outcome of the reaction is in agreement with the sequence illustrated in Scheme 2 and with the results

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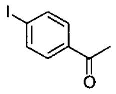
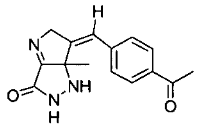
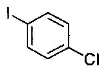
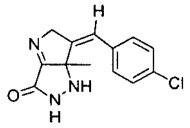
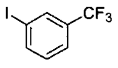
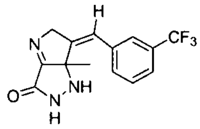
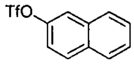
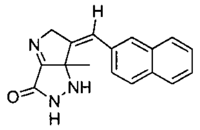
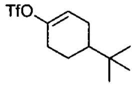
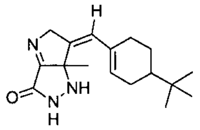
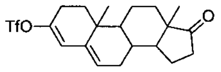
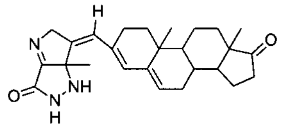
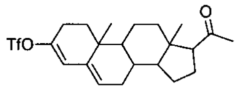
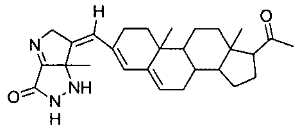
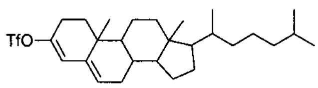
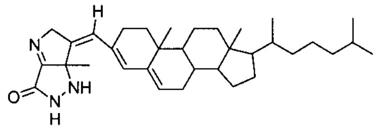
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

Table 1. Compounds **1**–**3**.

1	R	R^1	**2**	Structure	**3**	Structure	Yield[a] [%]
a	Me	H	**a**		**a**		67
b	Et	H	**b**		**b**		68
c	Me	Ph	**c**		**c**		67
			d		**d**		64
			e		**e**		62
			f		**f**		66
			g		**g**		64
			h		**h**		65

[a] Yields refer to single runs and isolated products.

obtained in the bimetallic palladium-catalyzed cyclization of enynes.[8]

Although the Pd^{II}-catalyzed intramolecular cyclization of enynes has been utilized for the preparation of five-membered ring systems,[6a, 15] to our knowledge, the sequential palladium-catalyzed reaction reported here is the first example of a domino, palladium-catalyzed, intermolecular arylation/vinylation combined with an intramolecular[16] carbopalladation process of a 1,5-enyne derivative, which leads to fused heterocycles through a regioselective 5-*endo-dig* annulation reaction, followed by β-hydride elimination with cleavage of the N–H bond. Only a few examples of σ-aryl/vinyl palladium complexes involved in cascade[17] carbopalladation and domino palladium-catalyzed intermolecular arylation/vinylation-intramolecular[14] carbopalladation processes of 1,6- or 1,7-enynes have been reported.

In conclusion, we have developed a new efficient Pd-catalyzed ene-type carbocyclization and current efforts are now focused on these and related substrates, to access the synthetic potential of this procedure.

Experimental Section

The appropriate halides or triflates **2a**–**h** (1 mmol), $Pd(OAc)_2$ (11.22 mg, 0.05 mmol), and DPPF (27.72 mg, 0.05 mmol) were added to a nitrogen-flushed solution of **1a**–**c** (1 mmol) in dry piperidine (6 mL). The reaction mixture was stirred at room temperature for 24 h, poured into HCl (0.1 M, 100 mL) and extracted twice with ethyl acetate. The organic layer was dried over Na_2SO_4, evaporated to dryness, and the crude product was purified by flash chromatography on silica gel. Elution with petroleum ether/ethyl acetate afforded pure **3a**–**h**.

3a: M.p. 139.7–141.9 °C ; IR (KBr): $\tilde{\nu} = 3360, 3186, 1718, 1682, 1560\,cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 1.98$ (s, 3H, CH_3), 2.58 (s, 3H, CH_3CO), 2.93 (br s, 1H, D_2O-exchange, NH), 4.05 (dd, $^2J(H,H) = 15$ Hz, $^4J(H,H) = 2$ Hz, 1H, CH_2), 4.35 (dd, $^2J(H,H) = 15$ Hz, $^4J(H,H) = 2$ Hz, 1H, CH_2), 6.70 (t, $^4J(H,H) = 2$ Hz, 1H, =CH), 7.32 (d, $^3J(H,H) = 7.8$ Hz, 2H, aromatic), 7.88 (d, $^3J(H,H) = 7.8$ Hz, 2H, aromatic), 8.82 (br s, 1H, D_2O-exchange, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): $\delta = 13.9$ (CH_3), 26.9 (CH_3CO), 54.9 (CH_2), 78.2 (C_{sp3}), 126.2 ($C_{sp2}H$, 2C; aromatic), 129.3 ($C_{sp2}H$, 2C; aromatic), 134.6 (=$C_{sp2}H$), 137.0 (C_{sp2}), 137.2, (C_{sp2}), 138.0, (C_{sp2}), 164.1 (C=N), 178.1 (C=O), 197.8 (C=O); MS (70 eV): *m/z* (%): 269 (100) [M^+]; Elemental analysis calcd (%) for $C_{17}H_{15}N_3O$: C 73.62, H 5.45, N 15.15; found: C 73.79, H 5.57, N 14.85.

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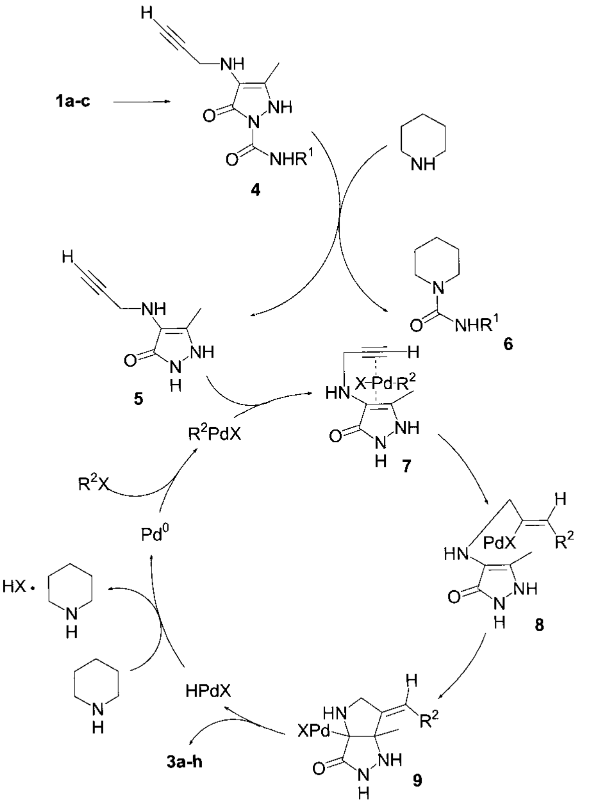

Scheme 2. A plausible catalytic cycle for the formation of **3**.

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The First Isolable 4-Silatriafulvene[**]

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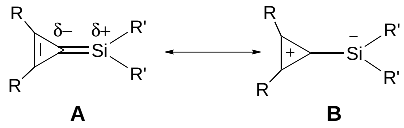
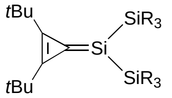
Among various silicon–carbon doubly bonded compounds (silaethenes),[1] 4-silatriafulvenes have attracted much attention because of their unique electronic properties;[2,3] the intrinsic polarity of the Si=C bond in 4-silatriafulvene (**A**) is expected to be reduced by the significant contribution of resonance structure **B** (Scheme 1).

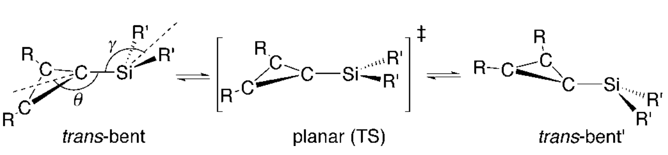


Scheme 1.

We recently generated the first 4-silatriafulvene derivative, 1,2-di-*tert*-butyl-4,4-bis(trimethylsilyl)-4-silatriafulvene (**1a**),[2] as a reactive intermediate and demonstrated that **1a** is much less reactive toward *tert*-butyl alcohol than is usual for silaethenes and isomerizes to the corresponding silacyclobutadiene at high temperatures. Theoretical calculations for 4-silatriafulvene derivatives have predicted the fluxional nature of the 4-silatriafulvene skeletons, which are not planar around the Si=C bond but *trans*-bent, with large bend angles and an energy difference of only 1.0 kcal mol^{-1} between the *trans*-bent and planar structures at the MP2/6-311++G**+ZPE level (Scheme 2).[3d]



1a, $SiR_3 = SiMe_3$
1b, $SiR_3 = SiMe_2tBu$



Scheme 2. Skeletal inversion of silatriafulvene.

Although Schumann et al. have reported the isolation of stable 4-germa-, 4-stanna-, and 4-plumbatriafulvenes,[4] no stable 4-silatriafluvene has been synthesized to date.[5] By use of bulky *tert*-butyldimethylsilyl groups instead of trimethylsilyl groups in **1a**, we synthesized the first stable 4-silatria-

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