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Reactivity of Diazo Compounds

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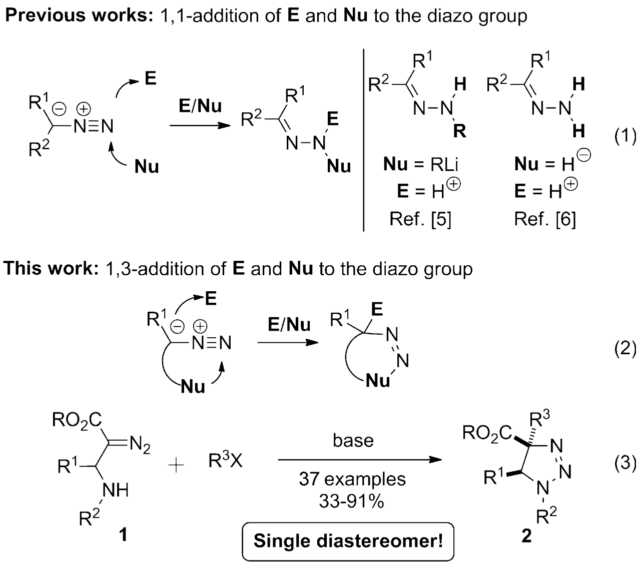
A New Reactivity Mode for the Diazo Group: Diastereoselective 1,3-Aminoalkylation Reaction of β-Amino-α-Diazoesters To Give Triazolines**

*Alexey Kuznetsov, Anton V. Gulevich, Donald J. Wink, and Vladimir Gevorgyan**

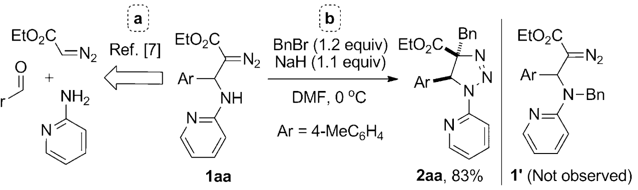
Abstract: *A novel mode of reactivity for the diazo group, the 1,3-addition of a nucleophile and an electrophile to the diazo group, has been realized in the intramolecular aminoalkylation of β-amino-α-diazoesters to form tetrasubstituted 1,2,3-triazolines. The reaction exhibited a broad scope, good functional group tolerance, and excellent diastereoselectivity. In addition, a new Au-catalyzed intramolecular transannulation reaction of the obtained propargyl triazolines to give pyrroles has been discovered.*

Diazo compounds are important building blocks that have been extensively studied over the years.[1,2] They are widely used in organic chemistry due to the high energy and diverse reactivity of the diazo group. Primarily, diazo compounds are utilized in denitrogenative generation of metal carbene species.[3] On the other hand, reactions with preservation of the diazo group are also known. Thus, [3+2] cycloaddition reactions of diazo compounds are commonly used for the synthesis of N-heterocycles.[4] There are also scattered reports on the reaction of nucleophiles and electrophiles with the diazo group in a 1,1-fashion in which both, nucleophile and electrophile, are added to the terminal nitrogen atom of the diazo group. Reactions of this type are limited to the addition of nucleophiles (RLi or hydride ion), followed by protonation, to produce hydrazones [Scheme 1, Eq. (1)].[5,6] Herein we disclose a novel reactivity mode of diazo compounds: a 1,3-addition of a nucleophile and an electrophile at the nitrogen and carbon atom of the diazo group [Eq. (2)], respectively. This reactivity mode was applied in the highly diastereoselective aminoalkylation reaction of the β-amino-α-diazoesters **1** with alkyl halides furnishing 1,2,3-triazolines **2** [Eq. (3)].

Recently, we have developed a method for the synthesis of β-pyridylamino-α-diazoesters through a three-component coupling reaction of 2-aminoazines, aldehydes, and diazo compounds [Scheme 2, reaction (a)].[7] Upon investigation of the synthetic utility of the obtained products, we found an unexpected reactivity of the diazo group. Thus, an alkylation reaction of *N*-pyridyl diazo compound **1aa** with benzyl bromide in the presence of NaH produced 1,2,3-triazoline **2a**, the product of C-alkylation of the diazo group, instead of the expected N-alkylation product **1′** [Scheme 2, reaction (b)].[8] This reaction proceeds exclusively in a *trans* manner with respect to the aryl substituent at the β-position of the diazoester.[9]



Scheme 1. Reaction of diazo compounds with nucleophiles and electrophiles: 1,1- and 1,3-addition.



Scheme 2. Diastereoselective aminoalkylation of β-pyridylamino-α-diazoester **1aa**.

Not only is the observed aminoalkylation reaction conceptually interesting, because it represents the first example of an intramolecular 1,3-addition of a nucleophile and an electrophile to the diazo group, but it also holds synthetic promise as a modular approach toward valuable 1,2,3-triazoline molecules.[10] Accordingly, we turned our attention to the investigation of the scope of this new transformation (Table 1). Gratifyingly, we found that this aminoalkylation

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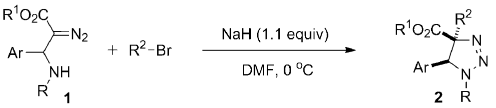
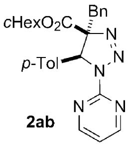
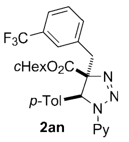
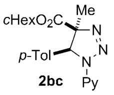
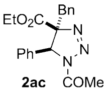
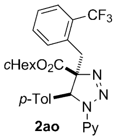
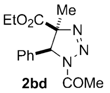
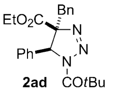
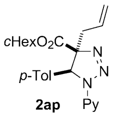
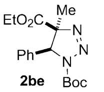
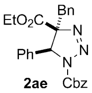
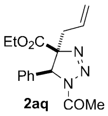
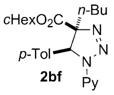
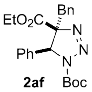
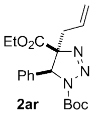
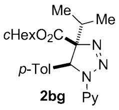
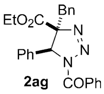
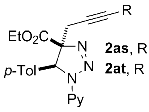
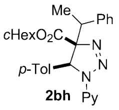
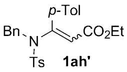
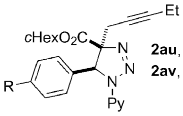
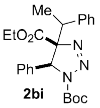
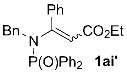
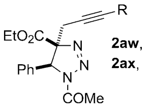
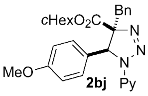
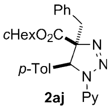
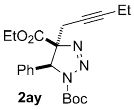
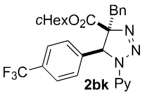
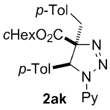
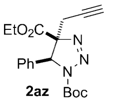
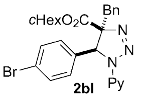
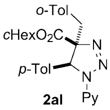
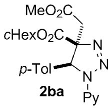
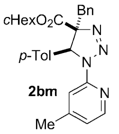
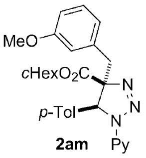
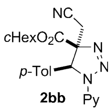
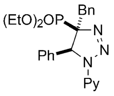
Table 1: The scope of the aminoalkylation reaction of β-amino-α-diazoesters **1**.[a]



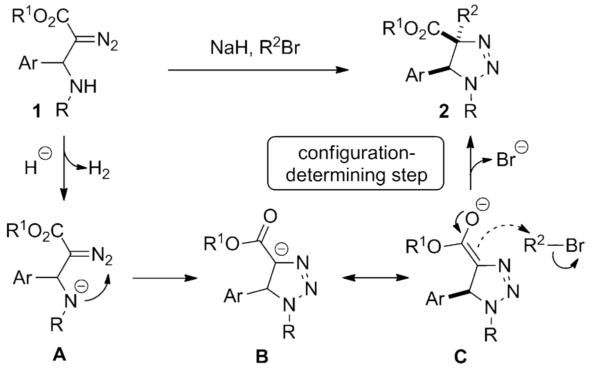
Entry	Product	Yield [%]	Entry	Product	Yield [%]	Entry	Product	Yield [%]
1	 **2ab**	71	13	 **2an**	86	28	 **2bc**	71[e]
2	 **2ac**	81	14	 **2ao**	69	29	 **2bd**	79[e]
3	 **2ad**	49	15	 **2ap**	78	30	 **2be**	56[e]
4	 **2ae**	58	16	 **2aq**	71	31	 **2bf**	47 66[f]
5	 **2af**	85	17	 **2ar**	75	32	 **2bg**	49[g]
6	 **2ag**	36[b]	18 19	 **2as**, R = Et **2at**, R = Ph	69 59	33	 **2bh**	67
7	 **1ah'**	65	20 21	 **2au**, R = Br **2av**, R = CF_3	64 58	34	 **2bi**	59
8	 **1ai'**	61[c]	22 23	 **2aw**, R = Et **2ax**, R = Ph	62 76	35	 **2bj**	70
9	 **2aj**	87 64[d]	24	 **2ay**	70	36	 **2bk**	67
10	 **2ak**	83	25	 **2az**	59	37	 **2bl**	54
11	 **2al**	91	26	 **2ba**	41	38	 **2bm**	62
12	 **2am**	89	27	 **2bb**	45	39		–[h]

[a] Yields of isolated products, d.r. > 99:1 in all cases unless otherwise noted. [b] d.r. 97:3. [c] Yield determined by NMR spectroscopy. [d] BnOTf was used. [e] MeI was used. [f] *n*BuI was used. [g] *i*PrI was used. [h] Trace of product, the starting diazo compound was recovered. Py = 2-pyridyl, *p*-Tol = 4-$CH_3C_6H_4$, *o*-Tol = 2-$CH_3C_6H_4$, Cbz = carboxybenzyl, Boc = *tert*-butoxycarbonyl.

reaction is quite general with respect to the substituent at the N_β atom of the diazoester **1**.

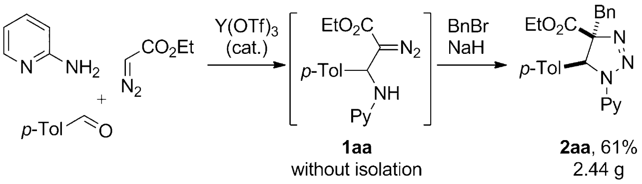
Thus, upon reaction of **1** with benzyl bromide, triazolines bearing pyrimidyl (**2ab**), acetyl (**2ac**), pivaloyl (**2ad**), carboxybenzyl (**2ae**), and *tert*-butoxycarbonyl (**2af**) groups at the N atom were formed in high yields and diastereoselectivities (Table 1, entries 1–5). In the case of β-*N*-benzoyl diazoester, the product **2ag** was formed in a low yield and diastereoselectivity (entry 6), whereas β-*N*-tosyl amino and β-*N*-diphenylphosphonyl diazoesters produced the corresponding enamines **1ah′** and **1ai′** as major products (entries 7 and 8). Next, we examined the scope of alkylating agents in this transformation. It was found that benzyl triflate is also a competitive reaction partner; however the product **2aj** was obtained in a slightly lower yield than in the case of reaction with benzyl bromide (Table 1, entry 9). Benzyl bromides having electron-donating (entries 10–12) or electron-withdrawing groups (entries 13 and 14), as well as allyl bromide (entries 15–17), also underwent the aminoalkylation reaction with different diazo compounds producing the desired products in high yields. This reaction also works with internal (entries 18–24) and terminal (entry 25) propargyl bromides as well as with methyl bromoacetate (entry 26) and bromoacetonitrile (entry 27) as the alkylating agent. Notably, simple aliphatic alkylating agents, such as methyl iodide (entries 28–30), *n*-butyl iodide, and *n*-butyl bromide (entry 31), efficiently participated in the aminoalkylation reaction. Notably, secondary alkyl halides (entries 31–33) produced the corresponding triazolines in good yields. The reaction showed good tolerance with respect to the electronic properties of the aryl substituent and *N*-pyridyl group of β-amino-α-diazoesters (entries 35–38, 20 and 21). However, it was found that this aminoalkylation reaction was not efficient with the diazomethylenephosphonate derivative (entry 39).

The proposed mechanism for the aminoalkylation reaction of β-amino-α-diazoesters implies initial deprotonation of the amino group of **1** with sodium hydride to produce anion **A**, which undergoes cyclization to form enolate **B**/**C** (Scheme 3). The subsequent nucleophilic attack of the enolate at the electrophile approaches from the less sterically hindered side and leads to the formation of the corresponding 1,2,3-triazoline **2** in a highly diastereoselective fashion.



Scheme 3. The proposed mechanism for the aminoalkylation reaction of β-amino-α-diazoesters.

Noteworthy, the β-amino-α-diazoesters **1** are easily available through the previously reported methods proceeding by a base-[11] or acid-mediated[12] addition of diazoacetates to imines. Furthermore, β-pyridylamino-α-diazoesters can be obtained through a three-component coupling reaction previously developed in our group (Scheme 1).[7] Accordingly, the newly discovered aminoalkylation reaction provides a direct access to triazolines starting from commercially available aldehydes, amines, diazo compounds, and alkyl halides. To this end, we demonstrated the feasibility of this approach by an efficient gram-scale synthesis of 1,2,3-triazoline **2aa** through a formal four-component coupling reaction of 2-aminopyridine, an aldehyde, a diazo compound, and benzyl bromide (Scheme 4).



Scheme 4. Four-component synthesis of triazoline **2aa** from 2-aminopyridine, aldehyde, ethyl diazoacetate and benzyl bromide. *p*-Tol = 4-$CH_3C_6H_4$, Py = 2-pyridyl.

In continuation of our studies on the synthesis of heterocycles through transition-metal-catalyzed cycloisomerization reactions of alkynes[13] and transannulation reactions of triazoles,[14] a potential heterocyclization reaction of propargyl triazolines **2as**–**av** was investigated [Scheme 5, Eq. (1)]. We screened different transition-metal catalysts and found that under the Au-catalyzed conditions, propargyl triazolines **2as**–**av** undergo a denitrogenative cycloisomerization reaction with formation of tetrasubstituted pyrroles **5** [Scheme 5, Eq. (1)]. It is believed that triazoline **2** produces enamine **E** through a metal-catalyzed denitrogenative rearrangement of the open triazoline form **D**.[15] A subsequent aminoauration of the triple bond of **E** results in the formation of a vinyl–gold intermediate **F**,[16] which gives pyrrole **3** upon protodemetalation and aromatization.[17] The proposed mechanism was supported by the observation of trace amounts of intermediate **E** in the reaction mixtures. Moreover, by treatment of triazoline **2aw** with $AgBF_4$, we were able to isolate enamine **4** in good yield. Under the standard Au-catalyzed reaction conditions, **4** was efficiently transformed into pyrrole **3c** [Scheme 5, Eq. (2)].

The reaction works with *N*-pyridyl and *N*-acyl triazolines possessing ethyl- and phenyl-substituted propargyl moieties and produced pyrroles **3a**–**d** in good yields. The substrates possessing Br and CF_3 substituents at the aryl ring also produced the corresponding pyrroles **3e**,**f** in moderate yields. This cycloisomerization process represents the first example of a denitrogenative transannulation reaction of 1,2,3-triazolines with alkynes, which is complementary to the denitrogenative transannulation of 1,2,3-triazoles.[14,18]

In conclusion, we have developed a highly diastereoselective intramolecular aminoalkylation reaction of β-amino-

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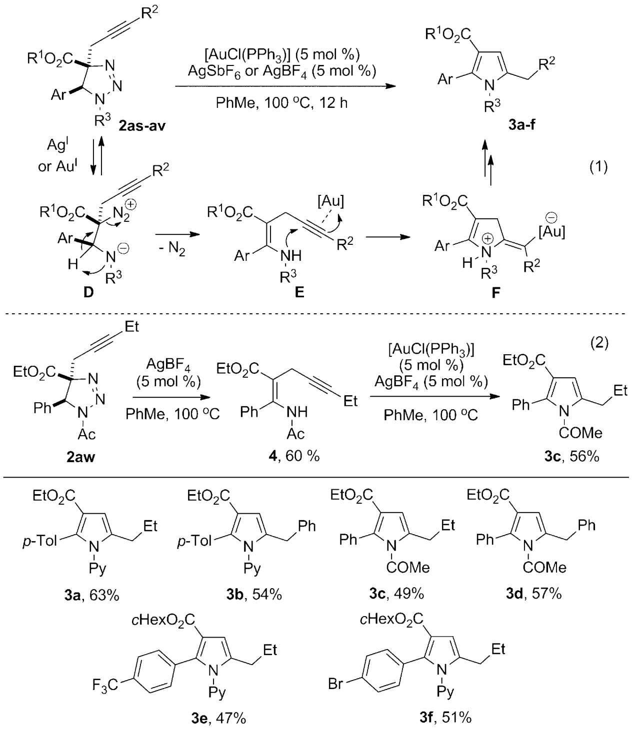

Scheme 5. The Au-catalyzed cycloisomerization of triazolines into pyrroles.

α-diazoesters leading to the tetrasubstituted 1,2,3-triazolines. The reaction features a novel 1,3-addition of a nucleophile and an electrophile to the diazo group of a diazo compound. It proceeds with a variety of C-electrophiles and demonstrates a broad scope with respect to the substituent at the amino and aryl groups of β-amino-α-diazoesters as well as good functional group tolerance. We also discovered the first gold-catalyzed intramolecular denitrogenative transannulation reaction of propargyl triazolines to give pyrroles.

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Keywords: aminoalkylation · diastereoselectivity · diazo compounds · heterocycles · triazolines

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[1] For general reviews on the reactivity of diazo compounds, see: a) X. Zhao, Y. Zhang, J. Wang, *Chem. Commun.* **2012**, *48*, 10162; b) Y. Zhang, J. Wang, *Eur. J. Org. Chem.* **2011**, 1015; c) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417; d) D. J. Timmons, M. P. Doyle, *J. Organomet. Chem.* **2001**, *617–618*, 98.

[2] For reviews on the application of diazo compounds, see: a) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**; b) H. W. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857–1869.

[3] For a recent review on carbene chemistry, see: a) *Contemporary Carbene Chemistry* (Eds.: R. A. Moss, M. P. Doyle), Wiley, Hoboken, **2013**.

[4] For reviews on cycloaddition reactions of diazo compounds, see: a) G. Maas in *The Chemistry of Heterocyclic Compounds*, *Vol. 59* (Eds.: A. Padwa, W. Pearson), Wiley, New York, **2002**, pp. 539–621; b) H. Suga, K. Itoh in *Methods and Applications of Cycloaddition Reactions in Organic Syntheses* (Ed.: N. Nishiwaki), Wiley, Hoboken, **2014**, pp. 175–204.

[5] For selected examples of the reactions of diazo compounds with organometallic reagents, see: a) E. Yasui, M. Wada, N. Takamura, *Tetrahedron Lett.* **2006**, *47*, 743–746; b) E. Yasui, M. Wada, N. Takamura, *Tetrahedron* **2009**, *65*, 461–468; For reactions of diazo compounds with potassium malonate, see: c) M. Regitz, A. Liedhegener, D. Stadler, *Justus Liebigs Ann. Chem.* **1968**, *713*, 101–112.

[6] For the reduction of diazo compounds using hydride reagents, see: E. Yasui, M. Wada, N. Takamura, *Chem. Pharm. Bull.* **2007**, *55*, 1652–1654.

[7] A. V. Gulevich, V. Helan, D. J. Wink, V. Gevorgyan, *Org. Lett.* **2013**, *15*, 956–959.

[8] The stereoselectivity was determined by GC-MS and NMR spectroscopy of the crude reaction mixtures.

[9] X-ray analysis of the product **2ay** confirmed the *trans*-orientation of the Ar group and the alkyl residue (see the Supporting Information for details). CCDC 995385 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] For examples of biologically active 1,2,3-triazolines, see: a) P. K. Kadaba, T. Dixit, *Curr. Med. Chem.* **2003**, *10*, 2109–2121; b) Y. Dürüst, H. Karakuş, M. Kaiser, D. Tasdemir, *Eur. J. Med. Chem.* **2012**, *48*, 296–304; For the use of 1,2,3-triazolines as synthetic intermediates, see: c) P. D. Pohlhaus, R. K. Bowman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 2294–2295; d) S. Zeghada, G. Bentabed-Ababsa, A. Derdour, S. Abdelmounim, L. R. Domingo, J. A. Sáez, T. Roisnel, E. Nassar, F. Mongin, *Org. Biomol. Chem.* **2011**, *9*, 4295–4305; e) D. Margetić, R. N. Warrener, D. N. Butler, C.-M. Jin, *Tetrahedron* **2012**, *68*, 3306–3318; f) B. Baskar, K. Wittstein, M. G. Sankar, V. Khedkar, M. Schürmann, K. Kumar, *Org. Lett.* **2012**, *14*, 5924–5927; g) K. Hayashi, H. Tanimoto, H. Zhang, T. Morimoto, Y. Nishiyama, K. Kakiuchi, *Org. Lett.* **2012**, *14*, 5728–5731; h) D. de Loera, A. Stopin, M. A. Garcia-Garibay, *J. Am. Chem. Soc.* **2013**, *135*, 6626–6632; For the use of 1,2,3-triazolines in total synthesis, see: i) B. Gebhardt, C. M. König, C. Schleth, M. Dauber, U. Koert, *Chem. Eur. J.* **2010**, *16*, 5934–5941.

[11] For the base-mediated addition of diazo compounds to imines, see: a) N. Jiang, Z. Qu, J. Wang, *Org. Lett.* **2001**, *3*, 2989–2992; b) N. Jiang, J. Wang, *Tetrahedron Lett.* **2002**, *43*, 1285–1287; c) Y. Zhao, N. Jiang, J. Wang, *Tetrahedron Lett.* **2003**, *44*, 8339–8342; d) Y. Zhao, Z. Ma, X. Zhang, Y. Zou, X. Jin, J. Wang, *Angew. Chem.* **2004**, *116*, 6103–6106; *Angew. Chem. Int. Ed.* **2004**, *43*, 5977–5980; e) S. Chen, Y. Zhao, J. Wang, *Synthesis* **2006**, 1705–1710; f) C. G. Goodman, D. T. Do, J. S. Johnson, *Org. Lett.* **2013**, *15*, 2446–2449; For a review, see: g) Y. Zhang, J. Wang, *Chem. Commun.* **2009**, 5350–5361.

[12] For the acid-mediated addition of diazo compounds to imines, see: a) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2005**, *127*, 9360–9361; b) T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 10054–10055; c) K. Maruoka, T. Hashimoto, *Synthesis* **2008**, 3703–3706; d) T. Hashimoto, H. Kimura, H. Nakatsu, K. Maruoka, *J. Org. Chem.* **2011**, *76*, 6030–6037; e) T. Hashimoto, H. Kimura, Y. Kawamata, K. Maruoka, *Nat. Chem.* **2011**, *3*, 642–646; f) H. Zhang, X. Wen, L. Gan, Y. Peng, *Org. Lett.* **2012**, *14*, 2126–2129; g) M. L. Kantam, V. Balasubrahmanyam, K. B. S. Kumar, G. T. Venkanna, F. Figueras, *Adv. Synth. Catal.* **2007**, *349*, 1887–1890.

[13] For recent examples of cycloisomerization reactions, see: a) R. Kazem Shiroodi, A. S. Dudnik, V. Gevorgyan, *J. Am. Chem. Soc.* **2012**, *134*, 6928–6931; b) Z. Li, D. Chernyak, V. Gevorgyan, *Org. Lett.* **2012**, *14*, 6056–6059; c) A. S. Dudnik, Y. Xia, Y. Li, V.

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Gevorgyan, *J. Am. Chem. Soc.* **2010**, *132*, 7645 – 7655; For reviews, see: d) R. Kazem Shiroodi, V. Gevorgyan, *Chem. Soc. Rev.* **2013**, *42*, 4991 – 5001; e) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, *113*, 3084 – 3213.

[14] For reviews on transannulation reactions, see: a) B. Chattopadhyay, V. Gevorgyan, *Angew. Chem.* **2012**, *124*, 886 – 896; *Angew. Chem. Int. Ed.* **2012**, *51*, 862 – 872; b) A. V. Gulevich, V. Gevorgyan, *Angew. Chem.* **2013**, *125*, 1411 – 1413; *Angew. Chem. Int. Ed.* **2013**, *52*, 1371 – 1373.

[15] The thermal test reaction of triazoline **2as** under transition-metal-free conditions did not produce any product.

[16] For the cycloisomerization of propargyl enamines into pyrroles, see: a) J. Barluenga, M. Tomás, V. Kouznetsov, A. Suárez-Sobrino, E. Rubio, *J. Org. Chem.* **1996**, *61*, 2185 – 2190; b) R. S. Robinson, M. C. Dovey, D. Gravestock, *Tetrahedron Lett.* **2004**, *45*, 6787 – 6789.

[17] For selected cycloisomerization reactions proceeding via vinyl–gold intermediates, see: a) A. S. K. Hashmi, A. M. Schuster, F. Rominger, *Angew. Chem.* **2009**, *121*, 8396 – 8398; *Angew. Chem. Int. Ed.* **2009**, *48*, 8247 – 8249; b) A. S. K. Hashmi, A. M. Schuster, S. Gaillard, L. Cavallo, A. Poater, S. P. Nolan, *Organometallics* **2011**, *30*, 6328 – 6337; c) A. S. K. Hashmi, *Gold Bull.* **2009**, *42*, 275 – 279.

[18] For the synthesis of pyrroles through denitrogenative transannulation reactions of triazoles with alkynes, see: a) T. Miura, M. Yamauchi, M. Murakami, *Chem. Commun.* **2009**, 1470 – 1471; b) B. Chattopadhyay, V. Gevorgyan, *Org. Lett.* **2011**, *13*, 3746 – 3749; c) Y. Shi, V. Gevorgyan, *Org. Lett.* **2013**, *15*, 5394 – 5396.

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