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Regioselective Synthesis of Functionalized Pyrroles *via* Gold(I)-Catalyzed [3+2] Cycloaddition of Stabilized Vinyl Diazo Derivatives and Nitriles

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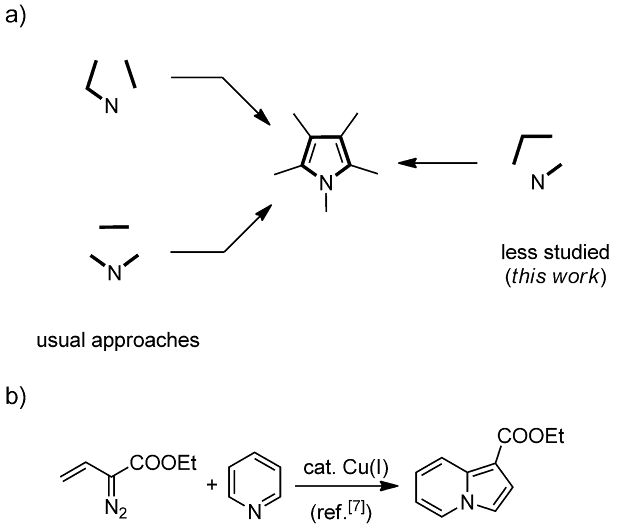
Abstract: The reaction of nitriles with alkenyldiazo compounds in the presence of gold catalysts provides functionalized pyrrole derivatives in moderate to high yields. This formal [3+2] cyclization reaction takes place with complete regioselectivity. The observed regiochemical outcome suggests the attack of the nitrile to the terminal position of the alkenylgold carbenoid (vinylogous reactivity). A broad range of nitriles (including those bearing functional groups) is compatible with this cyclization reaction.

Keywords: [3+2] cyclization; diazo compounds; gold catalysis; nitriles; pyrroles

Owing to their presence in several naturally occurring compounds of biological importance and in many pharmaceuticals, pyrroles represent one of the most relevant classes of heterocycles.[1] For this reason, numerous synthetic methodologies to access such compounds have been described in the last decades including classical condensation reactions as well as most recently cyclization reactions based on the use of transition metal promoters.[1,2] Despite these advances, the development of new regioselective approaches to the preparation of functionalized pyrrole derivatives from easily available starting reagents still remains an area of intense interest. Many of the methods for preparing functionalized pyrroles, among them the classical Hantzsch or Knorr synthesis, rely on the use of [3+2] cyclocondensation reactions between appropriate substrates (Scheme 1a). Surprisingly, the reaction of simple nitriles toward C_3 synthons in [3+2] cyclization reactions has been little explored.[3–5] However, nitriles are especially attractive as partners for formal [3+2] cycloaddtions because of the great number of nitriles that are commercially available and, consequently, the development of such approaches would be very interesting from a synthetic point of view.

On the other hand, the significance of vinyldiazo compounds as C_3 synthons in metal-catalyzed synthesis of nitrogen heterocyclic compounds is well established.[6] In this regard, our group recently reported the copper(I)-catalyzed regioselective [3+2] cyclization of pyridines toward vinyldiazoacetates leading to functionalized indolizine derivatives (Scheme 1b).[7] DFT calculations on this process support a reaction pathway involving initial formation of a copper vinyl carbenoid, which then would evolve *via* Michael-type addition of the pyridine nitrogen. Subsequent cyclization followed by aromatization would afford the final products.



Scheme 1. a) [3+2] Cyclization approaches to the pyrrole ring; b) copper(I)-catalyzed [3+2] cyclization of pyridines and vinyldiazo compounds.

On the basis of these results, we hypothesized that a related mechanistic scenario involving nitriles instead of pyridines might provide a direct entry to the pyrrole nucleus. Herein, we report the realization of this goal; specifically, we describe the gold(I)-catalyzed [3+2] cyclization of nitriles toward alkenyldiazo compounds leading to a convenient method for the preparation of functionalized pyrrole derivatives. Nitriles have previously been used as inert solvents in reactions involving vinyl carbenoid intermediates,[8] only a few gold-catalyzed reactions have ever been reported to activate nitriles.[9]

For our exploratory studies we selected readily available ethyl 2-diazobut-3-enoate (**1a**) as substrate and a series of transition metal catalysts (5 mol%) in acetonitrile (**2a**) as solvent at room temperature (see the Supporting Information for full details). Unfortunately, copper complexes, which proved to be competent catalysts in our previous research, did not afford the expected pyrrole.[10] On the other hand, despite the fact that rhodium and silver complexes have been widely used in the development of catalytic applications of alkenyldiazo compounds, no desired product was formed when the reaction was run in the presence of $Rh_2(OAc)_4$ or $AgNTf_2$. Next, we turned our attention to the use of gold catalysts. It should be noted that gold complexes have emerged in the last years as promising catalysts for the catalytic decomposition of diazo compounds.[11,12] In this regard, we were pleased to find that stirring overnight a mixture of diazo compound **1a** and $IPr(CH_3CN)AuSbF_6$ (5 mol%) in acetonitrile at room temperature afforded pyrrole derivative **3a** in 80% after chromatographic purification (see Table 1). Interestingly, a comparable yield was observed when the reaction was conducted in dichloromethane, thus enabling not only the use of non-volatile nitrile counterparts but also of a smaller excess of the nitrile. It should be noted that this formal [3+2] heterocyclization reaction takes place with total regioselectivity. The regioisomer formed suggests the attack of the nitrogen of the nitrile to the C-4 (vinylogous position) of the vinyldiazo compound.[13]

Next, we explored the scope of this gold-catalyzed [3+2] cyclization reaction (Table 1). First, the reaction of diazo compound **1a** with an array of synthetically valuable nitriles was examined. Thus, good yields were achieved with nitriles bearing alkyl groups of different nature (primary, secondary, tertiary or cyclic) affording the corresponding pyrroles **3a**–**e**. Apparently, the degree of steric hindrance near the reactive nitrile group was found not to have a dramatic impact on the efficiency of the reaction. Reactions with aromatic nitriles also proceeded smoothly to afford 2-arylpyrroles **3f**–**3k**, and those with both electron-rich and electron-deficient aryl groups gave the expected products in good yields. Extension of the reaction to nitriles having a fused aryl or a heteroaryl substituent proceeed successfully affording 2-(1-naphthyl)- and 2-(2-furyl)pyrroles **3l** and **3m** in 56% and 61%, respectively. Notably, a range of functionality in the nitrile component was compatible with this protocol. Thus, an ester function is well tolerated affording the pyrrole derivative **3n** in moderate yield. α,β-Unsaturated nitriles were also found to be suitable reagents in this gold-catalyzed [3+2] cyclization reaction affording efficiently the synthetically relevant 2-vinylpyrrole derivatives **3o** and **3p**.[14] Interestingly, despite the fact that a range of alkenes and alkynes was found to react with alkenyl diazo compounds in the presence of gold catalysts,[12b] the reaction of diazo compound **1a** with nitriles bearing an alkene or alkyne function in a remote position takes place with complete chemoselectivity affording in good yields the pyrroles **3q** and **3r** resulting from the exclusive participation of the nitrile function.

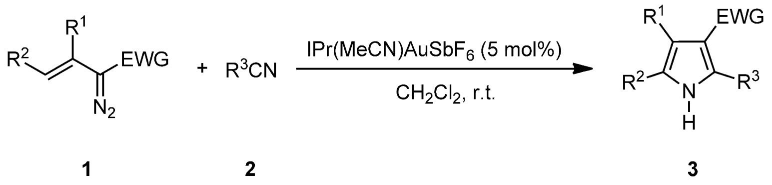
We next investigated the scope of the diazo component and found that this catalytic [3+2] cyclization is not limited to diazo compounds bearing an alkoxycarbonyl group. For example, it can be also applied to diazo derivatives with other stabilizing groups, like phosphonate [diazo compound **1b**; $R^1=R^2=H$, $EWG=PO(OEt)_2$] and sulfonyl (diazo compound **1c**; $R^1=R^2=H$, $EWG=SO_2Me$) furnishing pyrrole derivatives **3s** and **3t**, respectively, in moderate yields. In relation to the substitution on the vinyl moiety of the diazo component we observed that alkyl groups at the Cα atom of the substrates are tolerated. Thus, diazoacetate **1d** ($R^1=Me$, $R^2=H$, $EWG=COOEt$) reacts with benzonitrile under the standard reaction conditions affording the expected 2,3,4-trisubstituted pyrrole **3u** in moderate yield (63%).[15] Conversely, β-substituted diazoacetate **1e** ($R^1=H$, $R^2=Et$, $EWG=COOEt$) afforded the corresponding 2,3,5-trisubstituted pyrrole derivative **3v** in a diminished yield, thus indicating a deleterious effect of substitution at the Cβ position on the reaction.

This gold-catalyzed [3+2] cyclization has been further extended to the synthesis of some deuterated pyrrole derivatives. Thus, the reaction of diazo compound **1a** (R^1, $R^2=H$, $EWG=COOEt$) with deuterated acetonitrile afforded in good yield **3a-D$_3$**. On the other hand, diazo compound **1a-D** ($R^1=D$, $R^2=H$, $EWG=COOEt$) was transformed into pyrroles **3a-D** and **3f-D** by treatment with acetonitrile and benzonitrile, respectively.

On the basis of previous reports by us and others,[12] a mechanistic proposal to rationalize the obtained results is depicted in Scheme 2.

Thus, the initial reaction of the alkenyl diazo compound with the gold complex would afford a gold alkenyl carbenoid intermediate **I** which can be better described as an allyl gold cation **I′**.[16,17] Next, regioselective nucleophilic attack of the nitrile to the C-3

Table 1. Scope of the Au-catalyzed [3+2] cyclization reaction of alkenyldiazo compounds **1** and nitriles **2**.[a]



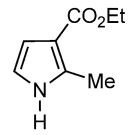
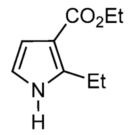
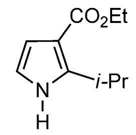
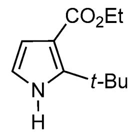
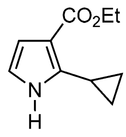
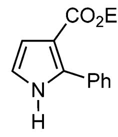
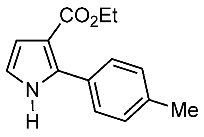
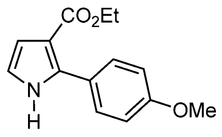
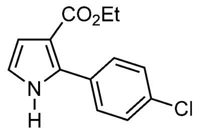
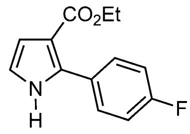
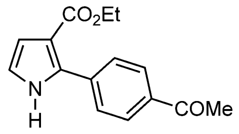
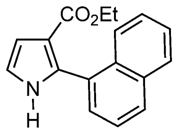
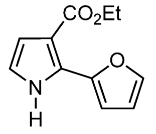
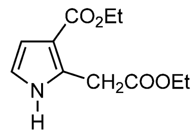
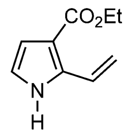
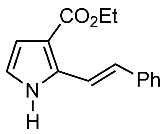
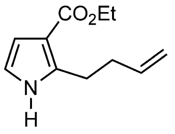
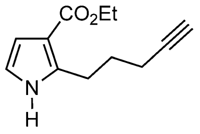
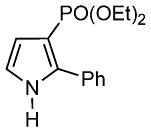
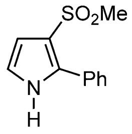
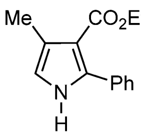
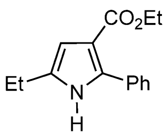
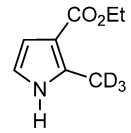
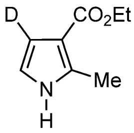
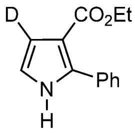
 **3a** (80%)[b]	 **3b** (72%)[b]	 **3c** (77%)	 **3d** (58%)
 **3e** (64%)	 **3f** (88%)[c]	 **3g** (68%)	 **3h** (73%)
 **3i** (69%)	 **3j** (62%)	 **3k** (66%)	 **3l** (56%)
 **3m** (61%)	 **3n** (52%)	 **3o** (71%)	 **3p** (74%)
 **3q** (86%)	 **3r** (72%)	 **3s** (62%)	 **3t** (49%)
 **3u** (63%)[d]	 **3v** (30%)		

Table 1. (continued)

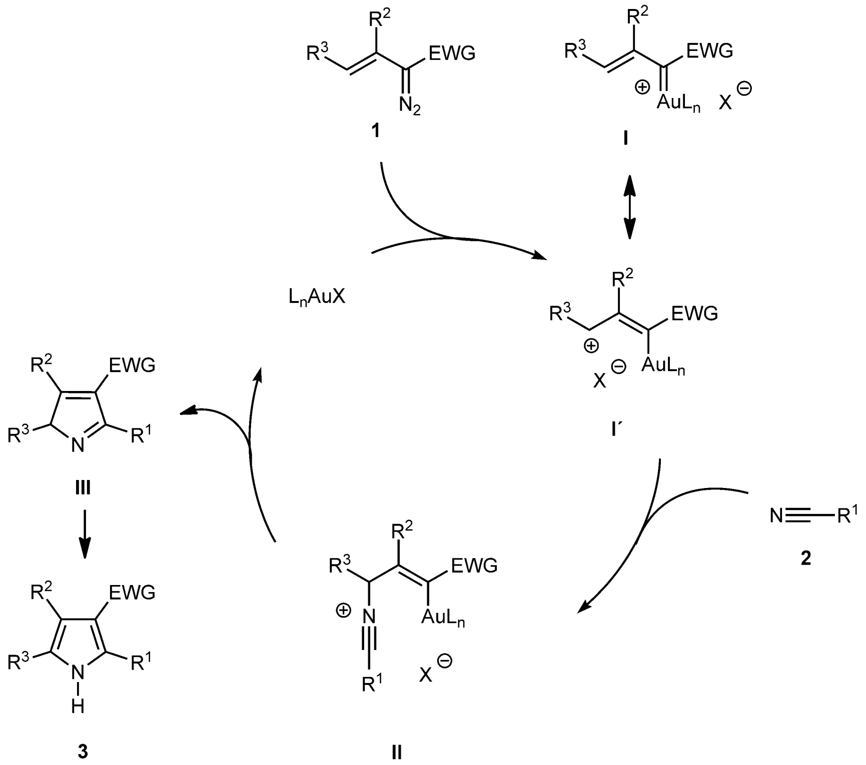
		
3a-D$_3$ (73%)[b]	**3a-D** (76%)[b]	**3f-D** (66%)[c]

[a] *Reaction conditions:* **1** (0.5 mmol), **2** (5.0 mmol), IPrAu(MeCN)SbF$_6$ (5 mol%), CH$_2$Cl$_2$ (0.1 M), room temperature, 14–24 h. Isolated yields after column chromatography are given.

[b] The nitrile was used as solvent.

[c] Reaction run at 70 °C in 1,2-dichloroethane.

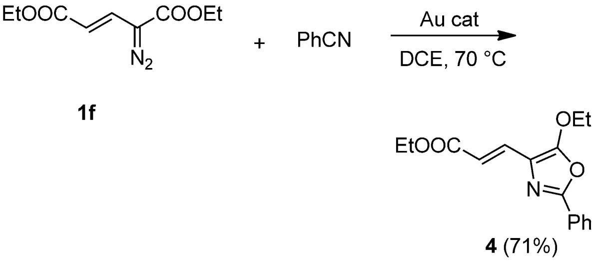
[d] Small amounts (<5%) of a tetrasubstituted pyrrole were also obtained (see ref.[15]).



Scheme 2. Proposed mechanism for the Au(I)-catalyzed synthesis of pyrrole derivatives **3** from diazo compounds **1** and nitriles **2**.

allyl cation would form the intermediate **II**,[9b] which by cyclization would afford intermediate **III**. Final tautomerism would lead to the pyrrole derivatives. In contrast to the well documented protodeauration of the gold-carbon bond in alkenyl gold complexes,[18] the transformation of intermediate **II** into **III** represents a less common case of attack of an alkenyl gold intermediate to an electrophilic carbon center.[19,20]

According to our mechanistic hypothesis and taking into account that it is currently accepted that the nature and, hence, the reactivity of alkenyl gold carbenoids depend largely on the substituents, we envision that an electron-withdrawing group at the vinyl moiety of the diazo component may help to destabilize the allyl gold cation resonance form **I′** and favour a carbenic pathway (participation of resonance form **I**). To test this hypothesis, we subjected vinyl diazo compound **1f** and benzonitrile to the standard reaction conditions (Scheme 3). According to our expectations this reaction did not lead to the corresponding pyrrole derivative; instead, the oxazole derivative **4** was obtained in good yield (71%) after chromatographic purification. This result would be consistent with a higher carbene character of the corresponding intermediate[21,22] and demonstrated that, in agreement with previous studies,[17] the reactivity of vinyl gold carbenoids generated from diazo compounds can



Scheme 3. Au-catalyzed reaction of diazo compound **1f** and benzonitrile: synthesis of oxazole derivative **4**.

be modified by the adequate selection of the substituents on the vinyl moiety.

In summary, we have developed a general and efficient approach to the pyrrole nucleus from easily available diazo compounds and nitriles. This process represents one of the few cases of the involvement of nitriles in gold-catalyzed reactions as well as a new application of diazo compounds in gold catalysis. Moreover, the reported method represents an unusual example of transition metal-catalyzed [3+2] cyclization approach to pyrroles involving nitriles as reaction partners. A broad range of nitriles (including those bearing functional groups) is compatible with this cyclization reaction. In agreement with previous reports, the regioselectivity pattern of the process (vinylogous attack) can be explained in terms of the formation of a gold-vinyl carbenoid with a high electrophilic character at the terminal position. Further applications of this new gold-catalyzed heterocyclization are currently being studied in our group.

Experimental Section

Representative Procedure for the Synthesis of Pyrrole 3a

To a solution of **1a** (70 mg, 0.5 mmol) in acetonitrile (5 mL) was added IPrAu(MeCN)SbF$_6$ (21.6 mg, 0.025 mmol, 5 mol%). The mixture was stirred 14 h at room temperature (disappearance of **1a** checked by TLC). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO$_2$, 3:1 hexanes/ethyl acetate) to afford **3a** as a yellow oil; yield: 61 mg (80%).

Acknowledgements

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[10] Only products resulting from the decomposition of the starting diazo compound were observed.

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[14] C-vinylpyrroles have been extensively used in organic synthesis as convenient building blocks for the construction of complex pyrrole systems. For a review on this topic, see: B. A. Trofimov, L. N. Soberina, A. P. Demenev, A. I. Mikhaleva, *Chem. Rev.* **2004**, *104*, 2481.

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[16] The preference for the 1,3-dipole resonance form related to **I′** in alkenyl gold intermediates bearing an electron-withdrawing group at the carbene center has been recently reported: G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 12598.

[17] The actual nature (gold-stabilized carbenes *vs.* allyl gold carbocations) of alkenylgold carbenoids has, until recently, been a matter of discussion. For some interesting contributions on this topic, see: a) A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232; b) G. Seidel, R. Mynott, A. Fürstner, *Angew. Chem.* **2009**, *121*, 2548; *Angew. Chem. Int. Ed.* **2009**, *48*, 2510; c) A. S. K. Hashmi, *Angew. Chem.* **2008**, *120*, 6856; *Angew. Chem. Int. Ed.* **2008**, *47*, 6754; d) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard III, F. D. Toste, *Nat. Chem.* **2009**, *1*, 482; e) R. B. Dateer, K. Pati, R.-S. Liu, *Chem. Commun.* **2012**, *48*, 7200; f) V. López-Carrillo, N. Huguet, A. Mosquera, A. M. Echavarren, *Chem. Eur. J.* **2011**, *17*, 10972. For recent reviews on the generation of dipolar species related to intermediate **I**, see: g) D. Garayalde, C. Nevado, *ACS Catal.* **2012**, *2*, 1462; h) F. López, J. L. Mascareñas, *Beilstein J. Org. Chem.* **2011**, *7*, 1075. For similar results on the higher homologues of such carbenoids, see: i) M. M. Hansmann, F. Rominger, A. S. K. Hashmi, *Chem. Sci.* **2013**, *4*, 1552; j) M. M. Hansmann, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem.* **2013**, *125*, 2653; *Angew. Chem. Int. Ed.* **2013**, *52*, 2593.

[18] For recent studies on the isolation and protodeauration of vinyl gold intermediates, see: a) A. S. K. Hashmi, A. M. Schuster, F. Rominger, *Angew. Chem.* **2009**, *121*, 8396; *Angew. Chem. Int. Ed.* **2009**, *48*, 8247; b) C. M. Krauter, A. S. K. Hashmi, M. Pernpointner, *ChemCatChem* **2010**, *2*, 1226; c) A. S. K. Hashmi, *Gold Bull.* **2009**, *42*, 275.

[19] For related cyclization reactions involving alkenyl gold intermediates and carbenium-type electrophiles, see: a) E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 5578; *Angew. Chem. Int. Ed.* **2006**, *45*, 5452; b) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804; c) A. S. K. Hashmi, T. Häffner, W. Yang, S. Pankajakshan, S. Schäfer, L. Schultes, F. Rominger, W. Frey, *Chem. Eur. J.* **2012**, *18*, 10480; d) A. S. K. Hashmi, S. Pankajakshan, M. Rudolf, E. Enns, T. Bander, F. Rominger, W. Frey, *Adv. Synth. Catal.* **2009**, *351*, 2855; e) A. S. K. Hashmi, M. Bührle, R. Salathé, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 2059. See also ref.[12]

[20] It should be mentioned that, although the cationic mechanism depicted in Scheme 2 accounts well for the

results, we cannot rule out an alternative pathway proceeding *via* Lewis acid activation of the nitrile, followed by attack of the diazocompound to the corresponding nitrilium ion and subsequent cyclization with loss of nitrogen. Some common Lewis acids [$Cu(OTf)_2$, $Zn(OTf)_2$, BF_3OEt_2, $AlCl_3$, $TiCl_4$, $SnCl_4$] were tested to gain insight into the mechanism of the reaction. No desired pyrrole derivative was detected in these reactions (see the Supporting Information for details).

[21] The formation of oxazoles in the reaction of α-oxo gold carbene intermediates with nitriles has been recently reported: W. He, C. Li, L. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 8482.

[22] The geometries of oxazole **4** and the isomeric pyrrole (diethyl 5-phenyl-1*H*-pyrrole-2,4-dicarboxylate) were fully optimized at the B3LYP/6–31G* level of theory. From these calculations, oxazole **4** is predicted to be 28.4 kcal mol^{-1} less stable than the pyrrole isomer. Consequently, the oxazole **4** seems to be the kinetically favoured product.

8 Regioselective Synthesis of Functionalized Pyrroles *via* Gold(I)-Catalyzed [3+2] Cycloaddition of Stabilized Vinyl Diazo Derivatives and Nitriles

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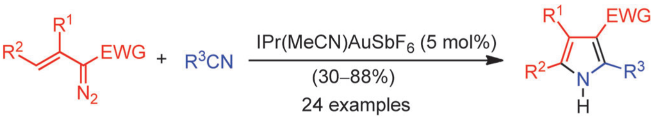

- **C–C and C–N bonds formed**
- **total regioselectivity**
- **broad scope and high functional group tolerance**

IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene