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Gold-Catalyzed Synthesis of 1,3-Diaminopyrazoles from 1-Alkynyltriazenes and Imines

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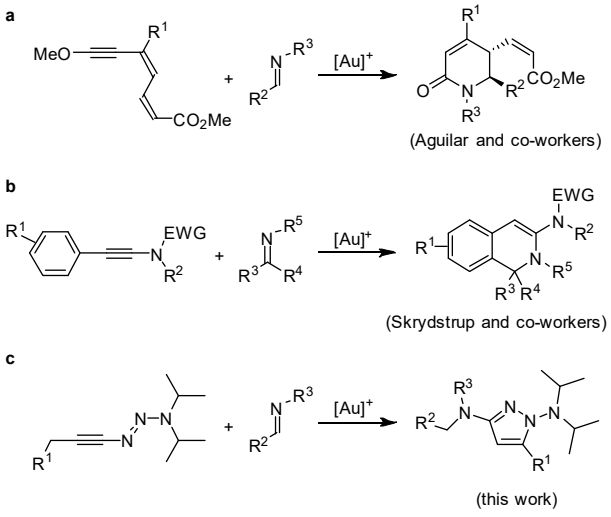
A new procedure for the synthesis of highly substituted 1,3-diaminopyrazoles is described. As substrates, we have employed 1-alkynyltriazenes and imines. The formation of pyrazoles was achieved by two-fold C-N coupling reactions in the presence of (JohnPhos)AuCl and $AgNTf_2$ as catalyst precursors. The regioselectivity of the reaction was inferred from a crystallographic analysis of one reaction product.

Keywords: catalysis • heterocycles • gold • imine • triazene

Introduction

Gold(I) complexes are able to activate alkynes towards the attack of carbon and heteronucleophiles.[1,2] This feature is the basis for numerous Au-catalyzed processes, which allow converting alkynes into more complex products.[1–10] So far, there are few examples of intermolecular reactions between alkynes and imines.[11–15] Aguilar and co-workers have reported that 5,6-dihydropyridin-2-ones can be obtained by reaction of push-pull 1,3-dien-5-ynes with aldimines (Scheme 1a).[12] The reactions proceed with good diastereo- and regioselectivity. However, the substrate scope with respect to the alkyne was found to be limited. More recently, Skrydstrup and co-workers were able to show that 1,2-dihydroisoquinolines are accessible by Au-catalyzed coupling of imines with ynamides (Scheme 1b).[13]



Scheme 1. Au-catalyzed intermolecular reactions between alkynes and imines.

We have recently described a simple method for the preparation of 1-alkynyltriazenes.[16] This procedure relies on the coupling of alkynyl Grignard reagents with lithium amides and nitrous oxide. Subsequently, we found that 1-alkynyltriazenes have a reactivity profile similar to ynamides.[17] Inspired by the work of Skrydstrup[13] and others,[18–20] we have started to explore the reactivity of 1-alkynyltriazenes in gold-catalyzed reactions. During the course of these investigations, we observed that 1-alkynyltriazenes can be coupled with imines to give 1,3-diaminopyrazoles (Scheme 1c). Details about these findings are reported below.

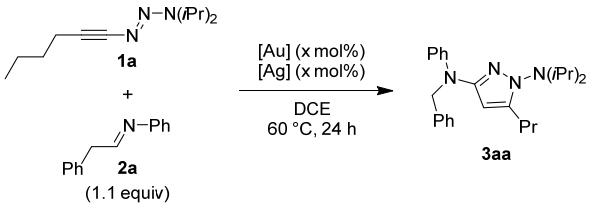
Results and Discussion

While studying the reactivity of 1-alkynyltriazenes in gold-catalyzed reactions, we observed that 1,3-diaminopyrazoles are formed in reactions with imines (Scheme 1c). Pyrazoles in general, and aminopyrazoles in particular, have received considerable interest in the context of medicinal chemistry.[21,22] We were therefore interested to explore the scope and the limitations of this new Au-catalyzed reaction.

First, we screened different gold complexes for their ability to catalyze the coupling reaction. As test substrates, we used 1-hexynyl-3,3-diisopropyltriazene (**1a**) and N-benzylideneaniline (**2a**) (Table 1). The reactions were performed in dichloroethane at 60 °C using 10 mol% of a Au complex with or without a silver salt as additive. The catalyst performance was evaluated by determining the yield of the product **3aa** after 24 h using ^{1}H NMR spectroscopy and trimethoxybenzene as the internal standard.

Out of the five gold complexes tested, the best results were obtained for (JohnPhos)AuCl in combination with $AgNTf_2$ as activating agent (Table 1, entry 6).[23] The triflamide counterion was found to be of importance, since $AgBF_4$ gave inferior results (entry 7).[24] Neither the Au complex alone, nor the silver salt alone, were able to catalyze the reaction (entries 8 and 9). Reducing the catalyst concentration to 5 or 2.5 mol% resulted in significantly lower yields, even when the reaction time was prolonged to 48 h (entries 10 and 11).

Table 1. Screening of different catalysts.

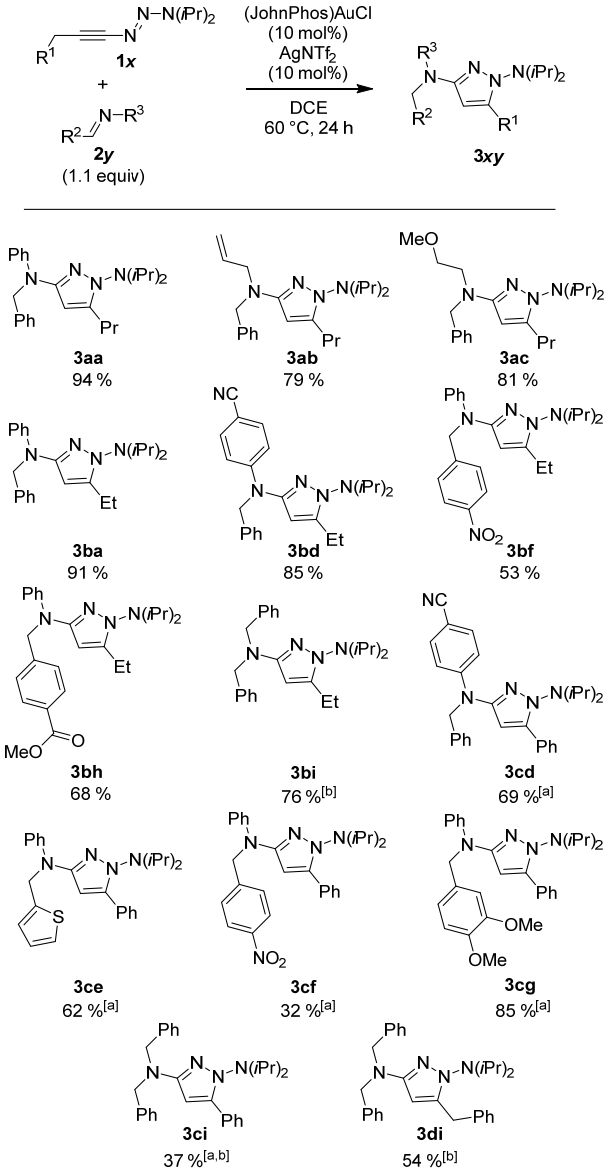


Entry	Au Complex	x (mol%)	AgX	Yield[a]
1	(IPr)AuNTf$_2$	10	/	32
2	(PPh$_3$)AuNTf$_2$	10	/	22
3	(SPhos)AuNTf$_2$	10	/	65
4	(CyJohnPhos)AuCl	10	AgNTf$_2$	20
5	(dppp)Au$_2$Cl$_2$	10	AgNTf$_2$	29
6	(JohnPhos)AuCl	10	AgNTf$_2$	99
7	(JohnPhos)AuCl	10	AgBF$_4$	54
8	(JohnPhos)AuCl	10	/	0
9	/	0	AgNTf$_2$	0
10	(JohnPhos)AuCl	5	AgNTf$_2$	66[b]
11	(JohnPhos)AuCl	2.5	AgNTf$_2$	34[b]

[a] The yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] The reaction was analyzed after 48 h.

Using the optimized reaction conditions, we have examined the scope of the reaction (Scheme 2). By variation of the triazene, we were able to introduce different alkyl groups as well as a phenyl group in 5-position of the heterocyclic products. The imine could be varied substantially, including substrates with functional groups such as nitro, cyano, ester and ether functions. For most reactions, the yields of the products were good, even though the heterocycles **3cf** and **3ci** were only isolated with yields of 32 and 37%, respectively. It is worth noting that the purity of the imine starting material was found to be of importance. Reactions with imines containing traces of aldehydes and/or imines gave significantly reduced yields.

The formation of the pyrazoles **3*xy*** was corroborated by NMR spectroscopy and high resolution mass spectrometry. However, these techniques were not sufficient to unambiguously determine the regioselectivity of the reaction. We thus performed a single crystal X-ray analysis of **3ba**. The result confirmed that coupling had occurred between the N-atom of the imine and the Cα-atom of the former alkynyltzriazene (Figure 1).



Scheme 2. Scope of the reaction between 1-alkynyltriazenes and imines. [a] The reaction was performed at 40 °C. [b] The reaction time was prolonged to 48 h.

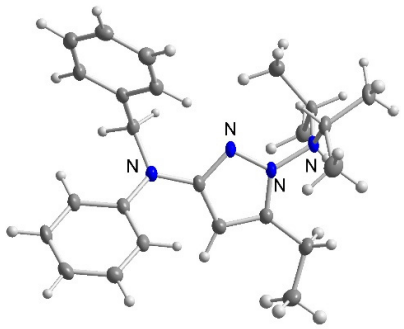
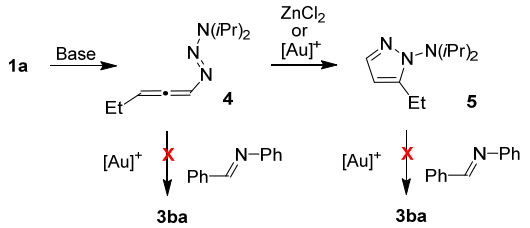


Figure 1. Molecular structure of **3ba** in the crystal. The thermal ellipsoids are at the 50% probability level.

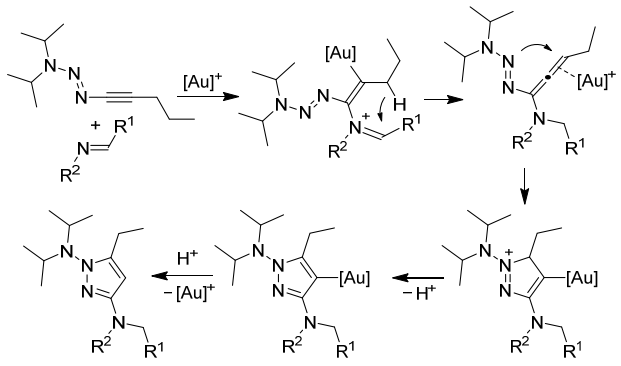
1-Alkynyltriazenes with a methylene group adjacent to the triple bond can undergo a base-induced isomerization into 1-allenytriazenes.[25] In

the presence of $ZnCl_2$, the latter can further rearrange into N-aminopyrazoles. In order to evaluate if these isomers participate directly in the Au-catalyzed coupling with imines, we have synthesized the 1-allenyltriazene **4** and the aminopyrazole **5** (Scheme 3). These compounds were then subjected to the coupling conditions. Both reactions failed to give the coupling product **3ba**, indicating that neither **4** nor **5** are intermediates in the catalytic conversion of **1a** into **3ba**. Interestingly, we observed that the combination of (JohnPhos)AuCl and $Ag(NTf_2)$ was also able to promote a clean isomerization of the allenyltriazene **4** into the aminopyrazole **5**. Catalytic amounts of a gold complex can thus be used as a viable alternative to $ZnCl_2$ for this type of rearrangement ($ZnCl_2$ cannot be used in catalytic amounts[25]).



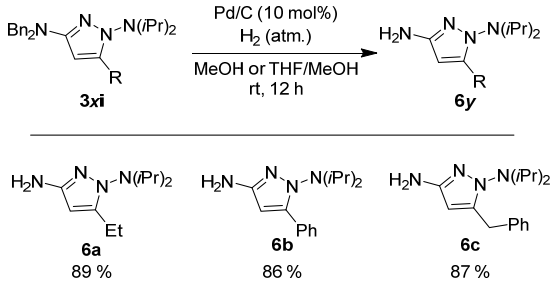
Scheme 3. Base-induced isomerization of **1a** gives the allenyltriazene **4**, which can be converted into the N-aminopyrazole **5**. Under catalytic conditions, neither **4** nor **5** react with the imine to give **3ba**.

The control experiments outlined in Scheme 3 suggest that the Au-catalyzed reaction starts with a coupling between the triazene and the imine. We would like to propose the following mechanism: the Au-activated alkyne undergoes first a coupling with the imine, followed by a 1,5-hydride shift (Scheme 4). The resulting allenyltriazenes is poised for an intramolecular C-N coupling involving the central N-atom of the triazene group. A proton shift and demetalation would then give the product.



Scheme 4. Proposed mechanism for the Au-catalyzed reaction between 1-alkynyltriazenes and imines.

Hydrogenation of **3*xi*** gave the pyrazoles **6a–c** in good yields (Scheme 5). The primary amine group could be used to for further functionalization of the heterocycles. The group of Wong, for example, has shown that aminopyrazoles can be converted into biologically active pyrazolo-pyrimidines by reaction with formamide in the presence of PBr_3.[26] Other transformations of aminopyrazoles include sulfonylation[27] and acylation[28] reactions, which were also carried out in the context of medicinal chemistry studies.



Scheme 5. Hydrogenation of **3*xi*** gives the 1,3-diaminopyrazoles **6a–c**.

Conclusions

We have developed a new method for the synthesis of 1,3-diaminopyrazole derivatives. The method is based on the coupling of 1-alkynyltriazenes and imines in the presence of a gold catalyst. The direct synthesis of highly substituted 1,3-diaminopyrazoles via gold(I) catalysis is unprecedented, and it complements existing methods for the preparation of these heterocyclic compounds. From a more general point of view, our results are further evidence for the synthetic utility of 1-alkynyltriazenes. So far, we have stressed that 1-alkynyltriazenes are activated alkynes with a reactivity profile similar to ynamides.[17,29] The present results show that the triazene function can participate directly in chemical transformations via C-N coupling reactions. The reactivity of 1-alkynyltriazenes in other transition metal-catalyzed reactions is currently explored in our laboratory.

Experimental Section

Materials and methods:

All reactions were carried out under an atmosphere of dry dinitrogen using Schlenk and glovebox techniques. All reagents and catalysts were obtained from commercial suppliers. Details about the analytical instruments are given in the Supporting Information. The triazenes **1a–d** and **4** were prepared according to published procedures.[16,17,25] The imines were obtained by condensation reactions from the corresponding amines and aldehydes as described in the literature.[13,30,31]

Syntheses of the diaminopyrazoles **3*xy***:

(JohnPhos)AuCl (13.2 mg, 10 mol%) and $AgNTf_2$ (9.7 mg, 10 mol%) were added to a solution of the 1-alkynyltriazene (250 μmol) and the imine (1.1 equiv., 275 μmol) in DCE (10 mL). Unless mentioned otherwise, the reaction was stirred for 24 h at 60 °C. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on deactivated silica (NEt_3) with a gradient of pentane to pentane/diethyl ether (2%) as eluent. The analytical data of the products are given in the Supporting Information.

Hydrogenation of the diaminopyrazoles **3*xi***:

Pd/C (10 mol%) was added to a solution of **3*xi*** (50–80 μmol) in MeOH (2 ml), and the suspension was stirred for 12 h at room temperature under an atmosphere of H_2. The suspension was filtered, and the

solvent was removed under vacuum to afford the products **6a**–**c**. The analytical data of the products are given in the Supporting Information.

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

Acknowledgements

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Author Contribution Statement

LNJ and KS conceived the study, LNJ performed the experiments and analyzed the data, RS and FFT performed the crystallographic analyses, LNJ and KS co-wrote the article.

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