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Gold-Catalyzed Direct Amination of Arenes with Azodicarboxylates

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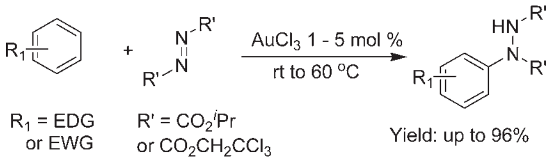
ABSTRACT



Gold(III) chloride catalyzed direct amination of arenes with azodicarboxylates was developed. The new catalytic system was active to a broad range of substrates, and the reaction was carried out under mild conditions. It represents the first catalytic system for the direct amination of electron-deficient arenes with azodicarboxylates to the best of our knowledge. This reaction provides an important approach for the synthesis of heterocyclic compounds in pharmaceutical and chemical industries.

Aryl hydrazides are highly valuable synthetic intermediates for the preparation of heterocycles such as indoles, pyrazoles, *etc*.[1] In addition, they could also be deprotected into aromatic amines and aryl hydrazines, which are well utilized in the pharmaceutical industry and other industries.[2] Traditionally, aryl hydrazides could be obtained by the reaction of aryllithium or aryl magnesium bromide reagents with azodicarboxylates.[3] Y. Leblanc et al. recently described the catalytic amination of electron-rich arenes with bis(2,2,2-trichloroethyl)azodicarboxylate.[4] In Leblanc's systems, Lewis acids or Brønsted acids were used as catalysts based on pioneering works in the 1960s.[5] Later, diethyl azodicarboxylate (DEAD) was also proven to be a suitable reagent for catalytic amination of electron-rich arenes with strong Lewis acid Sc(OTf)$_2$.[6] Great improvements were obtained in these procedures compared to the stoichiometric reactions. However, only electron-rich arenes are active in Leblanc's[4] and follower's methods.[6,7] T. H. Kim and J. N. Kim et al. modified Leblanc's method, and the resulting method could be applied to the amination of a broader range of arene substrates including arenes with certain electron-withdrawing groups.[8] However the modified method used stoichiometric super acid (TfOH) and a large amount trifluoroacetic acid (as solvent) that limited its application. In view of these facts, it is still highly desirable to develop efficient ways for the direct amination of a broad range of arenes, especially for electron-deficient arenes. In the pursuit of more efficient catalytic systems, we found that gold(III) chloride showed an extremely high efficiency in the amination of arenes with azodicarboxylates. Not only electron-rich arenes but also electron-deficient ones could be aminated under mild conditions.

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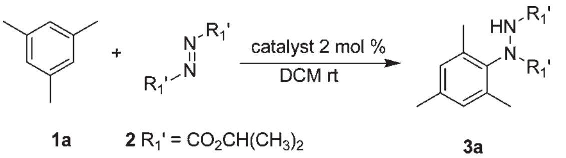
To the best of our knowledge, it is the first example of the catalytic direct amination of electron-deficient arenes with azodicarboxylates.[9]

In previous amination research, most of the efforts have focused on the activation of azodicarboxylates with Lewis acids or Brønsted acids.[4] In order to enhance the reaction activity, we conceived a dual activation proposal with gold(III) chloride as a catalyst. Gold(III) chloride is well-known for the activation of a $C_{Ar}-H$ bond. Aryl gold(III) complexes could be generated at room temperature under anhydrous conditions.[10,11] On the other hand, it is also known that gold(III) chloride (or the aryl gold(III) complex) could activate the azodicarboxylates. Therefore, the catalytic activity of gold(III) chloride in the direct amination of arenes with azodicarboxylates was investigated.

Table 1. Amination of Mesitylene with Diisopropyl Azodicarboxylate in Dichloromethane (DCM)[a]

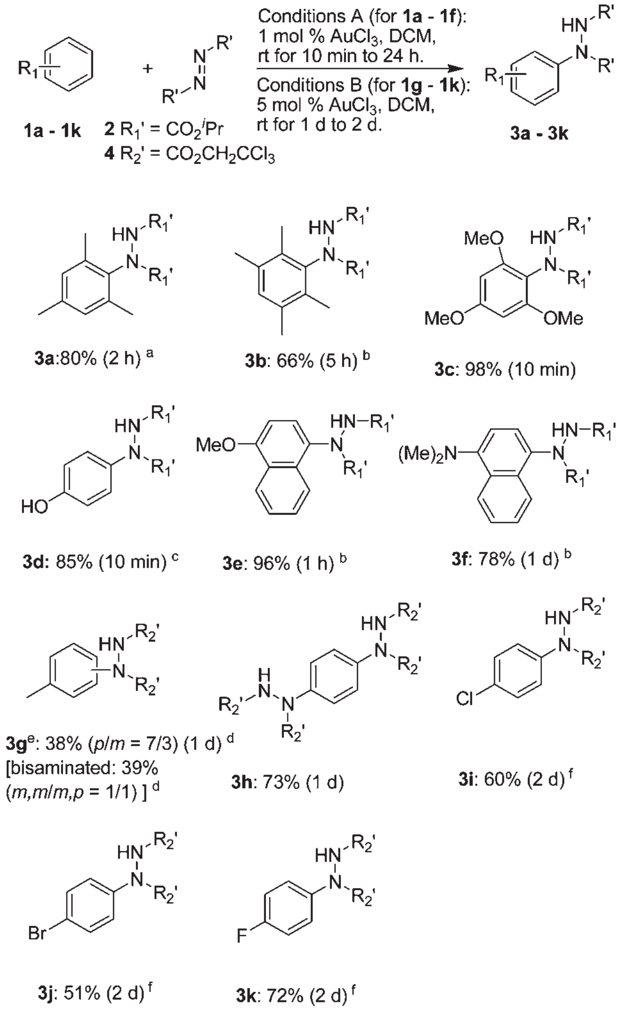


entry	catalyst	time (h)	yield (%)[b]
1	$AuCl_3$	2	57 (34)[c]
2	$Cu(OTf)_2$	24	26
3	AgOTf	24	10
4	$Sc(OTf)_2$	24	6
5	$AuCl_3$ 1 mol %	2	80 (16)[c]
6	HCl in dioxane 20 mol %	24	trace

[a] Conditions: mestylene (2 mmol, 2 equiv), **2** (1 mmol), catalyst (2 mol %), DCM (1 mL), all except **2** are added in the glovebox before the mixture was moved out. Rt for 2 to 24 h. [b] Isolated yield. [c] Isolated yield of bisaminated product.

Initially, gold(III) chloride together with other typical Lewis acids and Brønsted acid catalysts were tested in a model reaction of mesitylene and diisopropyl azodicarboxylate (Table 1). With 2 mol % gold(III) chloride as the catalyst, the reaction was completed within 2 h affording an aminated product in 57% yield (34% for a bisaminated product, based on azodicarboxylate). When 2 mol % $Cu(OTf)_2$, AgOTf, and $Sc(OTf)_2$ were used as catalysts, the yields of desired product were as low as 26%, 10%, and 6%, respectively even after the reaction times were prolonged to 24 h (Table 1, entries 2−4). Only a trace amount of product was observed in the reaction with HCl (in dioxane, 20 mol %) as the catalyst. This result excluded the possibility that the reaction was catalyzed by in situ generated HCl from gold(III) chloride metalation of arenes (Table 1, entry 6). These amination results indicated the superb catalytic activity of gold(III) chloride. The yield of the monosubstituted product was further improved to 80% when the loading of gold(III) chloride was decreased to 1 mol % (Table 1, entry 5).

Scheme 1. Amination of Various Arenes with Azodicarboxylates



[a] Isolated yield of bisaminated product is 16%. [b] 2 mol % catalyst was used. [c] 1 equiv phenol was used. [d] The yields of mono- and bisaminated mixtures could be improved to 43% and 42%, respectively by performing the reaction in 1,2-dichloroethane (DCE) (0.7 mL) at 80 °C for 1 d. [e] Both mono- and bisaminated products are unseparated mixtures of isomers. [f] DCE was the solvent, and the reaction temperature was 60 °C.

Encouraged by these promising results, we investigated the substrate scope of arenes. The amination products of phenol and 1,3,5-trimethoxylbenzene could be achieved in excellent yields within 10 min in the presence of 1 mol % gold catalyst (Scheme 1, **3a** and **3d**). For the reaction of durene, the yield of amination product (**3b**) was moderate (66%) even after a longer reaction time (5 h) and double the amount of catalyst (2 mol %). This low yield probably is due to the bulkiness of durene. Naphthalenes with different functional groups were also suitable substrates for the amination reactions (**3e**, **3f**). To our disappointment, the reactions gave low yields with inactive arenes toluene and benzene as substrates.

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To further expand the scope of the methodology, different commercially available azodicarboxylates were tested in the amination of inactive arenes. Gratifyingly, with bis(2,2,2-trichloroethyl)azodicarboxylate **4** and 5 mol % $AuCl_3$, the inactive arenes including halo benzenes could be converted to hydrazides in moderate to good yields.[12] For benzene, a 1,4-bisaminated product (**3h**) was obtained as a single regioisomer. The reaction of toluene with **4** was very complex giving a mixture of monoaminated products (p/m = 7/3) and bisaminated products ($m,m/m,p$ = 1/1). The amination of halo benzenes afforded para-directed products (**3i**, **3j**, **3k**). Herein, for monosubstituted benzene substrates, only para-aminated products (**3d**, **3e**, **3f**, **3i**, **3j**, **3k**) were obtained, indicating excellent regioselectivity with gold(III) chloride as catalyst.

A series of control experiments were conducted to gain insight into the mechanism. Since AuCl and $HAuCl_4$ could be generated as a byproduct in the process of $AuCl_3$ metalation of arenes, control reactions of fluorobenzene and azodicarboxylate with 5 mol % AuCl or $HAuCl_4$ were performed. Under the same conditions, the yields of the desired product with the AuCl catalyst (8%) and $HAuCl_4$ catalyst (21%) were much lower than that with $AuCl_3$ (72%). The results suggested the amination reaction was mainly catalyzed by $AuCl_3$. In order to probe the interaction of the $AuCl_3$ catalyst and azodicarboxylates, reactions of azodicarboxylates and stoichometric amounts of $AuCl_3$ were performed. In the absence of arene, the NMR (^1H and ^{13}C) shifts of azodicarboxylates remained unchanged upon addition of $AuCl_3$. However, an obvious ^1H shift was observed when azodicarboxylate was added to the system in the presence of both gold(III) chloride and arenes.[11] This evidence suggested auration may indeed occur and it was aryl gold(III) complexes, not $AuCl_3$, which activated the azodicarboxylate. To identify any kinetic isotope effects, a competition experiment between bromobenzene and its deuterated derivative was also performed. The amination reaction did not exhibit a kinetic isotope effect ($k_H/k_D = 1.0$), which indicated that the C−H bond cleavage of arene was not involved in the rate-determining step in the overall catalytic processes.[13]

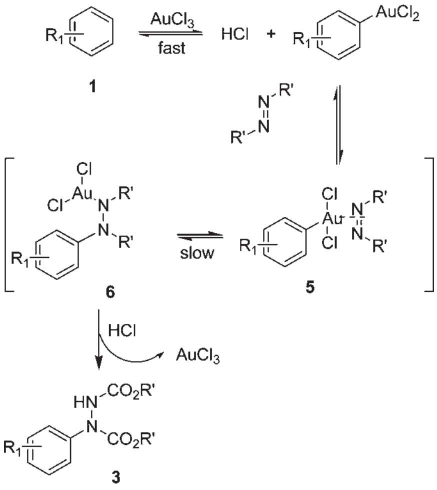

Figure 1. Proposed reaction pathway of the $AuCl_3$-catalyzed amination of arenes.

Based on the above mechanistic clues and data, a proposed major pathway of the $AuCl_3$-catalyzed amination of arenes via C−H bond activation is shown in Figure 1. In the first step, aryl gold(III) complexes were generated quickly and then coordinated with azodicarboxylate affording complex **5**. A reduction coupling reaction occurred slowly in complex **5** resulting in the formation of intermediate **6**, which could be protonated quickly to form aryl hydrazide and regenerate the $AuCl_3$ catalyst.

In summary, we have developed a new catalytic system for the direct amination of arenes with azodicarboxylates by using $AuCl_3$ as a catalyst. The reactions are highly efficient so that electron-poor arenes could also be catalytically aminated. The present work is expected to be a useful method for the synthesis of heterocyclic compounds with biological activity in the pharmaceutical industry.

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Supporting Information Available. Experimental procedures and NMR of products. This material is available free of charge via Internet at http://pubs.acs.org.

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[11] For original study on $AuCl_3$ metalation of arenes, see: (a) Kharasch, M. S.; Isbell, H. S. *J. Am. Chem. Soc.* **1931**, *53*, 3053. (b) de Graaf, P. W. J.; Boersma, J.; van der Kerk, G. J. M. *J. Organomet. Chem.* **1976**, *105*, 399. (c) Fuchita, Y.; Utsunomiya, Y.; Yasutake, M. *J. Chem. Soc., Dalton Trans.* **2001**, 2330.

[12] No product was detected in the reactions with 5 mol% $Cu(OTf)_2$ catalyst or without catalyst.

[13] This result is consistent with the reported fact in ref 10. The metalation reaction between $AuCl_3$ and arene happened very quickly to generate aryl gold(III) complexes. For KIE experiments, see the Supporting Information.