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Gold-Catalyzed Halogenation of Aromatics by *N*-Halosuccinimides**

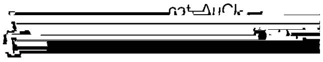
*F[illegible] M[illegible], J[illegible] M[illegible], D[illegible]u, F[illegible] L[illegible], [illegible], J[illegible]**

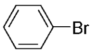
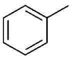
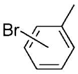
Halogenation of aromatic compounds is one of the fundamental reactions in organic chemistry.[1] *N*-Bromo- , *N*-iodo- , and *N*-chlorosuccinimide (NBS, NIS, and NCS, respectively) are highly useful halogenating reagents in laboratories in terms of their ease of handling, as well as the generation of relatively inert succinimide as the by-product. Various halogenation systems usingh NXS (X = Br, I, or Cl) have been developed,[2–4] but halogenating unactivated aromatics proceeds only in the presence of strong Lewis acids or protonic acids.[3] Moreover, reaction conditions are in general very harsh, such as high catalyst loadings,[3f,i] high reaction temperatures,[3e] or considerably acidic solutions.[3c] Some of these reported catalytic systems proceed under relatively milder reaction conditions. For example, Tanemura et al. reported a method for the halogenation of aromatic rings using NXS in the presence of NH_4NO_3 or $FeCl_3$ in MeCN.[3g] The reaction works with unactivated aromatics, but the catalyst loading is high (10–100 % mol). Yamamoto et al. reported halogenation with $ZrCl_4$ as the catalyst, and although the catalyst loading is low (5 mol %) the substrate scope is limited to electron-rich aromatic rings.[2q] Moreover, benzylic halogenation occurs when halogenating alkyl-substituted benzene derivatives, which is also a general side reaction in many other halogenation systems. In view of these facts, we still consider it highly desirable to develop milder and more efficient halogenation methods.

The previous studies have focused on the activation of NXS through complexation or protonation of the carbonyl oxygen atom of NXS by acids to enhance the reactivity of the halogenation process (Scheme 1 a). We envisaged that a dual activation of both the aromatic ring and NXS might greatly enhance the reactivity (Scheme 1 b). For this purpose, the formation of a C_{Ar}–M bond through direct metallation of a C_{Ar}–H bond is required. In principle, the cleavage of a C_{Ar}–H bond to form C_{Ar}–M bond proceeds through oxidative addition or electrophilic substitution mechanisms by metal complexes having either low or high oxidation states, respectively.[5]

Gold-catalyzed transformations have been hot topics in organic chemistry in recent years.[6] It has been documented that gold(III) can electrophilically metallate C_{Ar}–H bonds to

Table 2: AuCl$_3$-catalyzed bromination of aromatic rings by NBS.[a]



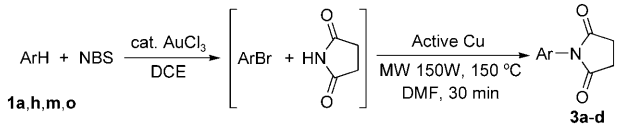
Entry	ArH		AuCl$_3$ (mol %)	*T* [°C]	*t* [h]	ArBr		Yield [%][b]
1		**1a**	1	80	11		**2a**	> 99
2		**1b**	1	[illegible]	40		**2b, 2b'**	>

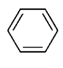
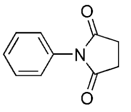
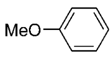
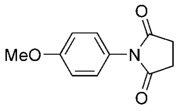
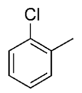
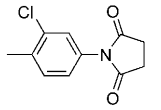
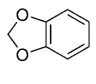
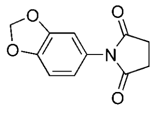
First, we compared the efficiency of typical acid catalysts developed for halogenation reaction using NBS. Therefore, the bromination of benzene with NBS was carried out in DCE at 80 °C for 24 hours (Table 1). To our delight, 1 mol % of AuCl$_3$ gave nearly a quantitative yield of bromobenzene (Table 1, entry 1), whereas FeCl$_3$ and FeBr$_3$, widely used as Lewis acid catalyst in this type of reaction, only afforded the product in 27 % and 25 % yield, respectively, at a 20 mol % catalyst loading, (Table 1, entries 2 and 3). BF$_3$·OEt$_2$, another strong Lewis acid known for its ability to activate NXS, gave only a 7 % yield with the same catalyst loading. NH$_4$NO$_3$ and ZrCl$_4$, which have been efficient catalysts in the systems reported by Tanemura et al.[3g] and Yamamoto and coworkers,[2q] were not efficient in that a less than 5 % yield of desired product was observed (Table 1, entries 5 and 6). Pd(OAc)$_2$, which has been used in direct aromatic C−H bond activation,[9] gave no product (Table 1, entry 7). Since reactions between gold(III) trichloride and aryl compounds generates HCl, as indicated in previous literature,[7a] the possibility exists that in situ generated HCl may catalyze the reaction. However, when 20 mol % of HCl was used as the catalyst under identical conditions, no product was observed (Table 1, entry 9), thereby ruling out the possible HCl catalysis. Finally, the strong acid catalyst H$_2$SO$_4$ (20 mol %) could catalyze the reaction but with low efficiency (Table 1, entry 10). These bromination results clearly demonstrate the superb catalytic activity of AuCl$_3$ as compared with other Lewis acid or protonic acid catalysts.

Next, the scope of this AuCl$_3$-catalyzed bromination was examined with a variety of aromatic substrates (Table 2). The results demonstrated wide substrate scope, including some unactivated aromatic substrates. Most substrates were treated with one equivalent of NBS and 0.01 to 1 mol % of AuCl$_3$, affording the corresponding aryl bromides in high yields. Clean conversion was observed in all cases: GC/MS analysis indicates that only monobromination products are formed. Additionally, benzylic bromination did not occur when the alkyl-substituted benzene derivatives were subjected to the reaction (Table 2, entries 2–6 and 13). Bromination of electron-rich aromatics, such as anisole (**1h**) and 1,4-dimethoxybenzene (**1i**), requires only 0.01 mol % catalyst. A control experiment indicated that no reaction took place in the absence of the $AuCl_3$ catalyst in these cases. Notably, aromatic rings bearing moderately strong electron-withdrawing substituents can also be brominated, although a higher catalyst loading and longer reaction time are required in such cases (Table 2, entries 11–14). However, for aromatics with strong electron-withdrawing substituents, such as a nitro group, the bromination did not occur with 5 mol % of $AuCl_3$ at 80°C (Table 2, entry 16).

In addition to the low catalyst loading, this halogenation process only uses one equivalent of NBS and the reaction proceeds with high yields. The halogenation is clean with succinimide as the only by-product. These advantages allow the possibility of combining this $AuCl_3$-catalyzed halogenation with other transition metal catalyzed transformations such as C–N and C–C bond-forming reactions. First, we conceived that the in situ produced succinimide could be utilized as a nitrogen source in the sequential C–N bond formation. Upon the completion of the halogenation reaction, active copper[10] was added to the solution and the reaction mixture was set to microwave irradiation for 30 minutes at 150°C.[11] To our delight, the corresponding aryl amides were obtained in good yields (Table 3). Therefore, this two-step transformation constitutes an indirect strategy for converting an aromatic C–H bond into a C–N bond.

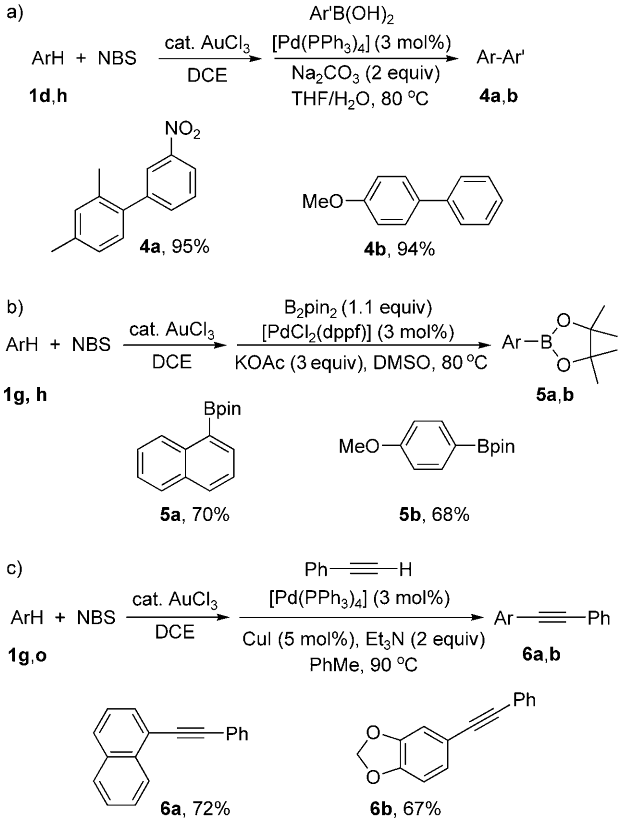
Table 3: Converting arenes into aniline derivatives.[a]



Entry	ArH		Product		Yield [%][b]
1		**1a**		**3a**	83
2		**1h**		**3b**	78
3		**1m**		**3c**	57
4		**1o**		**3d**	65

[a] First step: arene (1 mmol), NBS (1 mmol), see Table 2 for the reaction conditions. Second step: Active Cu (5 mmol), DMF 1 mL; MW 150W, temp 150°C, time 30 min. [b] Yield of isolated product.

Next, we examined the combination of halogenation with palladium-catalyzed transformations, namely the Suzuki–Miyaura cross-coupling, Miyaura borylation, and Sonogashira coupling reactions (Scheme 2 a,b,c respectively). All three types of palladium-catalyzed coupling reactions turned out to be compatible with the $AuCl_3$-catalyzed halogenation conditions. In a typical procedure, the arene was first converted into the corresponding aryl bromide under the conditions shown in Table 2. Upon completion of bromination, the solvent was removed and the crude product was directly subjected to the palladium-catalyzed coupling reaction without additional purification. The two-step reaction afforded satisfactory yields in all cases.



Scheme 2. Sequential transformation: bromination and a) Suzuki–Miyaura cross-coupling, b) Miyaura borylation, and c) Sonogashira coupling.

The extraordinarily high efficiency of the $AuCl_3$ catalysis in aromatic halogenations raises intriguing questions concerning its reaction mechanism. We hypothesized a dual activation mode with the generation of arylgold(III) species as the key intermediate as shown in Scheme 1 b. This hypothesis is based on the following: 1) It has been documented in the literature that simple aromatic groups readily react with $AuCl_3$ to form arylgold(III) species at room temperature.[7] Moreover, arylgold species have been recently proposed as intermediates in gold-catalyzed transformations;[8a–d] 2) Gold catalysts are soft Lewis acids and therefore only weakly bond to a hard Lewis base such as the carbonyl oxygen atom. However, as shown by the results summarized in Table 1, AuCl is far more reactive as compared with other strong Lewis acids such as FeCl , FeBr$_3$, and AlCl$_3$ in the bromination reaction with NBS, which implies different activation modes are operative in these reactions. For thenormal Lewis acid or protonic acid catalysis, the activation of NBS is realized through coordination of carbonyl oxygen atom. Therefore, in the case of AuCl$_3$, a dual activation of both the aromatic substrate and NBS seems likely.

To gain insights into the mechanism, a kinetic isotopic effect (KIE) was measured through intermolecular compet$_6$itive bromination of benzene and [D

$_3$, FeBr$_3$, ZrCl$_4$, and AuCl$_3$

$_3$·OEt$_2$, FeBr$_3$

[8] a) Z. Li, D. A. Capretto, R. O. Rahaman, C. He, *J. A . C .* . **2007**, *129*, 12058; b) Z. Shi, C. He, *J. O . C .* **2004**, *69*, 3669; c) Z. Shi, C. He, *J. A . C .* . **2004**, *126*, 5964; d) Z. Shi, C. He, *J. A . C .* . **2004**, *126*, 13596; e) M. T. Reetz, K. Sommer, *E . J. O . C .* **2003**, 3485; f) G. Dyker, E. Muth, A. S. K. Hashmi, L. Ding, *A v. t . C* . **2003**, *345*, 1247; g) A. S. K. Hashmi, L. Schwarz, J. H. Choi, T. M. Frost, *A . C .* **2000**, *112*, 2382; *A . C . I t. E .* **2000**, *39*, 2285; h) Y. Luo, C. J. Li, *C , C u .* **2004**, 1930; i) X. Sun, W. Sun, R. Fan, J. Wu, *A v. t . C* . **2007**, *349*, 2151.

[9] For example, see: C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, **2000**, *287*, 1992.

[10] P. H. Gore, G. K. Hughes, *J. C .* **1959**, 1615.

[11] L. D. S. Yadav, B. S. Yadav, V. K. Rai, *t* **2006**, 1868.

[12] H. Zollinger, *A v. . O . C .* **1964**, *2*, 163.

[13] The KIE data for aromatic auration is not available. For KIE studies on electrophilic aromatic metallation, see: a) J. A. Tunge, L. N. Foresee, *O t* **2005**, *24*, 6440; b) W. Lau, J. K. Kochi, *J. A . C .* . **1986**, *108*, 6720.

[14] For details, see the Supporting Information.