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Gold-Catalyzed Oxidative Acyloxylation of Arenes[§]

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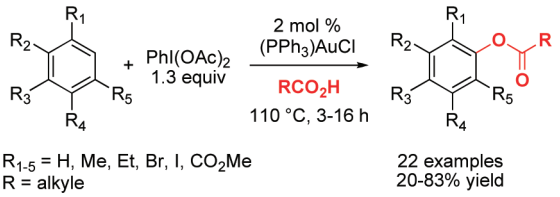
ABSTRACT



A variety of nonactivated hindered aromatic rings are acyloxylated (22 examples, up to 83% yield) in the presence of PPh_3AuCl as the catalyst and di(acetoxy)iodobenzene as the oxidant. The reaction proceeds at 110 °C in an acid media and allows the formation of both hindered acetoxy and acyloxy derivatives. This methodology nicely complements the Pd-catalyzed arene acyloxylation reaction, which is not operating on hindered substrates and allows the Au-catalyzed unprecedented acyloxylation reaction of arenes, implying various carboxylic acids.

Homogeneous gold catalysis has emerged in the past few years as a very exciting area of research due to its unique Lewis acid carbophilic properties.[1] More recently, the electrophilicity of gold has been exploited in Csp^2-H activation of arenes. Since the initial works of Kharasch and Isbell,[2] and later on Braustein,[3] it is well established that auration of nonactivated aromatic rings occurs under mild conditions in the presence of Au(III) complexes. Subsequent reductive elimination liberates the functionalized aryl compound and a Au(I) species. This transformation can be made catalytically by the regeneration of the Au(III) species in the presence of an external oxidant. After a long period of underutilization of this concept, in the past decade, a number of synthetic functionalizations of aromatic substrates including C–C,[4] C–N[5] and C–X[6] bond forming reactions have been described (Scheme 1).[7] In line with our research program initiated on gold-catalyzed carbon–oxygen bond-forming reactions,[8] we decided to investigate

[§] Dedicated to Dr. C. Bruneau on the occasion of his 60th birthday.

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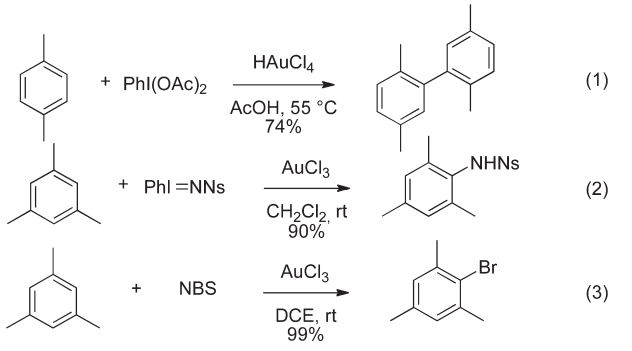
the gold-catalyzed acyloxylation of aromatic systems. Selective oxidation of nonactivated aromatic rings[9] indeed represents a highly interesting and challenging organic transformation as aryl esters[10,11] and phenols[12] are extremely frequent synthetic building molecules found in pharmaceuticals, polymers or natural products.

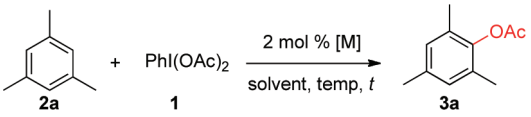
Scheme 1. Selected Examples of Au(I)/Au(III)-catalyzed C−H Functionalization of Arenes



Considering the recent work from Nevado,[4e,13] Tse[4b,d] and co-workers on gold-catalyzed C−C coupling reactions, we selected DAIB[14,15] (di(acetoxy)iodobenzene) as a suitable oxidant for gold(I) complexes, the main issue being to drive the reaction toward acyloxylation versus C−C bond formation. We therefore wish to report our preliminary investigations allowing the acetoxylation and acyloxylation reactions of nonactivated hindered arenes.[16]

At the outset of our studies, the model substrate mesitylene **2a** was reacted with 1.3 equiv of DAIB **1** in the presence of 2 mol % of a variety of gold salts (Table 1). We initially used $(PPh_3)AuCl$, as a stable, easy to handle gold precursor. Whereas the reactivity in acetonitrile and dichloroethane was particularly disappointing (Table 1, entries 1 and 2), we were pleased to find that the use of acetic acid led to the desired product **3a**, despite in a low yield (Table 1, entry 3). Increasing the temperature to 110 °C afforded **3a** in moderate 51% yield (table 1, entry 4). The use of an excess of DAIB **1** (Table 1, entry 5) did not give better results, whereas prolonged reaction time afforded the arylacetate **3a** in 62% isolated yield (Table 1, entry 6). The importance of the gold catalyst was checked and the reaction does not proceed in the absence of $(PPh_3)AuCl$ (Table 1, entry 7).

Table 1. Gold- versus Transition Metal-catalyzed Acetoxylation of Mesitylene in the Presence of DAIB[a]



entry	catalyst	solvent	temp (°C)	t (h)	yield (%)[b]
1	$(PPh_3)AuCl$	CH_3CN	60	1	<5
2	$(PPh_3)AuCl$	CH_2ClCH_2Cl	100	16	<5
3	$(PPh_3)AuCl$	CH_3CO_2H	80	2.5	10
4	$(PPh_3)AuCl$	CH_3CO_2H	110	2.5	51
5[c]	$(PPh_3)AuCl$	CH_3CO_2H	110	2.5	40
6	$(PPh_3)AuCl$	CH_3CO_2H	110	12	62[d]
7		CH_3CO_2H	110	2.5	trace
8	AuCl	CH_3CO_2H	110	2.5	29
9	$(PPh_3)AuNTf_2$	CH_3CO_2H	110	2.5	42
10	$AuCl_3$	CH_3CO_2H	110	2.5	49
11	$HAuCl_4$	CH_3CO_2H	110	2.5	29
12	Au_2O_3	CH_3CO_2H	110	2.5	21
13	Ag(OAc)	CH_3CO_2H	110	2.5	trace
14	$PtCl_2$	CH_3CO_2H	110	2.5	trace
15	$Pd(OAc)_2$	CH_3CO_2H	110	2.5	6

[a] Conditions: 0.5 mmol of mesitylene **2a** and 1.3 equiv of di(acetoxy)-iodobenzene **1** in 1 mL of solvent. n.d. not determined. [b] Yields have been determined by GC analysis using *n*-octadecane as internal standard. [c] Reaction perfomed with 2 equivalents of di(acetoxy)iodobenzene **1**. [d] Isolated yield.

We then evaluated the efficiency of the gold precursor catalyst in the acetoxylation reaction and checked the conversion and yield after 2.5 h (Table 1, entries 8−12). The use of polymeric gold(I) chloride and cationic PPh_3AuNTf_2[17] gave lower yields of the desired product (Table 1, entries 8−9). Interestingly,[16] gold trichloride (Table 1, entry 10) had a similar activity to $(PPh_3)AuCl$ but its hygroscopicity and hazardous manipulation drove us to prefer $(PPh_3)AuCl$. Other gold(III) salts such as $HAuCl_4$ or Au_2O_3[8f] were tested in the reaction process, but both led to low yields (Table 1, entries 11−12). We finally compared the activity of $(PPh_3)AuCl$ with other metallic salts such as silver, platinum and palladium catalysts (Table 1, entries 13−15), none of them leading to a significant amount of **3a**. The case of the use of $Pd(OAc)_2$ is particularly remarkable as palladium catalysts represent a milestone in selective

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(12) Rappoport, Z. *The Chemistry of Phenols*; Wiley-Interscience-VCH: Weinheim, 2003.
(13) 3-Acetoxylation of 1-benzylindole was a side reaction (12% yield) in the Au-catalyzed ethynylation of arenes, see 4e.
(14) For the first use of DAIB in Pd-catalyzed acetoxylation of benzene, see: Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal., A: Chem.* **1996**, *108*, 35.
(15) For selected recent reviews regarding the chemistry of hypervalent iodine reagents, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (b) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052. (c) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517.
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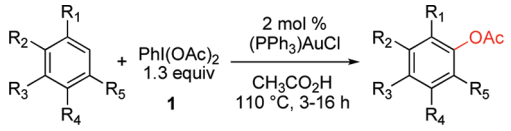
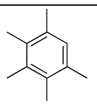
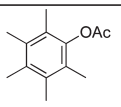
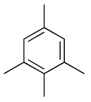
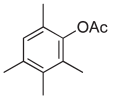
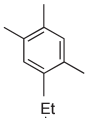
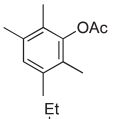
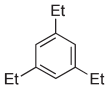
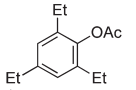
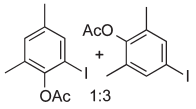
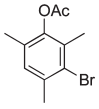
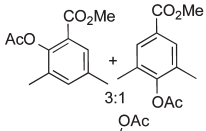
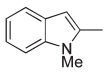
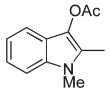
(18) (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

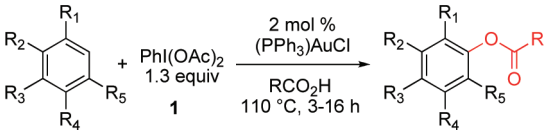
Table 2. Substrate Scope of the Gold-catalyzed Acetoxylation of Arenes in the Presence of DAIB[a]

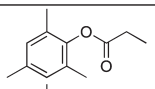
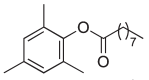
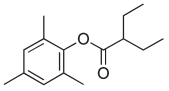
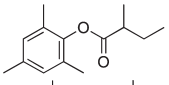
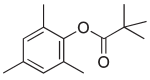
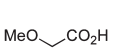
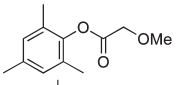
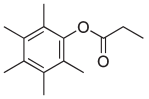
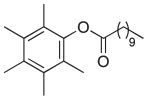
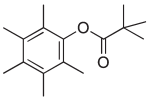
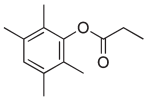
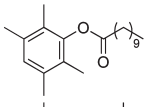


entry	substrate		aryl ester product		yield (%)[a]
1		**2b**		**3b**	83
2		**2c**		**3c**	65
3		**2d**		**3d**	63
4		**2e**		**3e**	46
5		**2f**		**3f** **3f'**	55
6		**2g**		**3g**	62
7		**2h**		**3h** **3h'**	50[b]
8		**2i**		**3i**	20

[a] Reaction conditions: 0.5 mmol of arene and 1.3 equiv of di(acetoxy)-iodobenzene **1** in 1 mL of acetic acid. [b] Isolated yields. [c] Ratio and structures determined by 2D NMR experiments.

Table 3. Acid Scope of the Gold-catalyzed Acyloxylation of Arenes in the Presence of DAIB[a]



entry	ArH	acid	aryl ester product		yield (%)[b]
1	**2a**			**4**	80
2	**2a**			**5**	76
3	**2a**			**6**	62
4	**2a**			**7**	64
5	**2a**			**8**	75
6	**2a**			**9**	32
7	**2b**			**10**	59
8	**2b**			**11**	61
9	**2b**			**12**	68
10	**2d**			**13**	42[c]
11	**2d**			**14**	48[c]
12	**2d**			**15**	49
13	**2g**			**16**	55

[a] Reaction conditions: 0.5 mmol of arene **2a**–**g** and 1.3 equiv of di(acetoxy)iodobenzene **1** in 1 mL of carboxylic acid. [b] Isolated yields after column chromatography. [c] the corresponding diacyloxy derivative was also isolated (**17** 40% entry 10, **18** 12% entry 11).

C–H activation by transition metals[18] and were subsequently investigated in depth in the acetoxylation of aromatic rings.[19] This lack of reactivity may be accounted for by the steric hindrance of the mesitylene, which has been previously observed by Crabtree and co-workers.[14,20] Using the optimized system consisting of 2 mol % of $(PPh_3)AuCl$ and 1.3 equiv of **1** at 110 °C in acetic acid, the arene scope of the reaction was explored. We selected aryl derivatives that do not present two adjacent nonsubstituted carbons to avoid the competitive formation of biphenyl derivatives

(19) For selected key contributions regarding the Pd-catalyzed acetoxylation of aromatic rings, see: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (c) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285. (d) Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584. (e) Mutule, I.; Suna, E.; Olofsson, K.; Pelcman, B. *J. Org. Chem.* **2009**, *74*, 7195. (f) Powers, D. C.; Xiao, D. Y.; Geibel, M. A. L.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14530. (g) Liu, Q.; Li, G.; Yi, H.; Wu, P.; Liu, J.; Lei, A. *Chem.—Eur. J.* **2011**, *17*, 2353. (h) Sun, C.-L.; Liu, J.; Wang; Zhou, X.; Li, B.-J.; Shi, Z.-J *Synlett* **2011**, 844.

(20) For a more general discussion, see: Kaliany, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149.

(21) For the reactions of anisole, 1,3-dimethoxybenzene, 1,4-dimethylbenzene and 1-acetyl-4-methylbenzene, see Supporting Information for other examples.

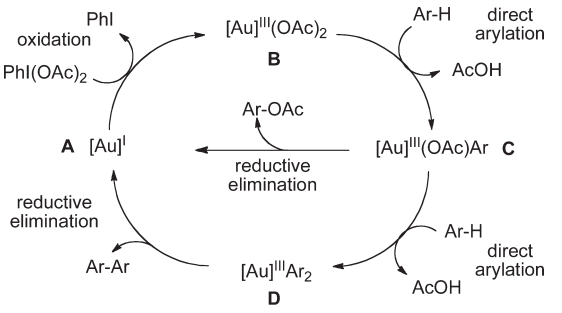
through direct oxidative coupling of the aromatic rings.[4b,d,21] The results are summarized in Table 2. Yields are good for a variety of methyl-substituted benzenes (Table 2, entries 1−4). Halogen-containing arenes are also acetoxylated in moderate to good yields (Table 2, entries 5−6). In the case of 1-iodo-3,5-dimethylbenzene, the reaction led to a mixture of regioisomers **3f** and **3f′** in a 1:3 ratio (Table 2, entry 5). The presence of an electron-withdrawing group on the aromatic ring was not deleterious to the acetylation reaction but also gave a mixture of nonseparable regioisomers **3h** and **3h′** in 50% yield (Table 2, entry 7). The reaction of the electron-rich nitrogen heterocycle 1,2-dimethylindole **2i** was also tried but gave the acetylated derivative **3i** in low yield (Table 2, entry 8), which is in full agreement with Nevado's group's results.[4e]

We further challenged this methodology by investigating the unprecedented acyloxylation reaction of arenes in the presence of the same catalytic system. Considering that the formation of bis(acyloxy)iodoarenes could be achieved by ligand metathesis between DAIB and carboxylic acids,[22] we postulated that the replacement of acetic acid by other acids would result in the direct incorporation of the latter in the product. The acyloxylation reactions were therefore carried out in a carboxylic acid as solvent, and rewardingly proceeded efficiently for a variety of carboxylic acids (Table 3).

Mesitylene **2a** was engaged in acyloxylation reactions in the presence of several carboxylic acids (Table 3, entries 1−6) and led to the corresponding esters **4**−**8** in good yields (62−80%) except in the case of 2-methoxyethanoic acid, which was unstable under the reaction conditions. Noteworthy that the steric hindrance of the carboxylic acid moiety does not seem to hamper the reaction. The esters **10**−**12** derived from propanoic, undecanoic and pivalic acids (Table 3, entries 7−9) and 1,2,3,4,5-pentamethylbenzene were obtained in 59−68% isolated yields. Interestingly, the reaction of 1,2,4,5-tetramethylbenzene **2d** gave rise to the desired esters **13**−**15** accompanied with variable amount of the corresponding diesters **17**−**18**, depending on the steric hindrance of the carboxylic acid (Table 3, entries 10−12). The reaction conditions were compatible with the bromoaromatic ring (Table 3, entry 13), and 3-bromo-2,4,6-trimethylphenyl propionate **16** was obtained in 55% isolated yield.

The mechanism of this transformation based on a Au(I) precatalyst **A** may involve an initial oxidation upon reaction with **1** to give an Au(III) intermediate **B** (Scheme 2).[7] The second step involves the arylation of the gold center to give complex **C** and the liberation of one equivalent of acetic acid. In the case of hindered arenes, reductive elimination occurs from complex **C** leading to the formation of the acyloxylated arene product and the regeneration of Au(I) complex **A**. In the case of nonhindered arene substrates (Scheme 1, eq 1),[4b,d] the arylation of a second arene molecule leads to the formation of the diarylated complex **D**. Reductive elimination then occurs to liberate the biphenyl product and regenerates precatalyst **A**.

Scheme 2. Proposed Mechanism



In conclusion, we have developed a gold-catalyzed oxidative acyloxylation reaction of nonactivated hindered arenes associating $(PPh_3)AuCl$ as a simple and easy to handle precursor and DAIB as oxidant. We could demonstrate that this association allows the formation of hindered acetyl-functionalized aromatic rings and more remarkably acyloxyderivatives in moderate to good isolated yields. This methodology opens new perspectives in the selective oxidation of nonactivated aromatic rings for the synthesis of aryl esters and phenols. Further studies will be dedicated to improve the efficiency of this gold catalytic system.

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Supporting Information Available. Experimental procedures and characterization data of acyloxylated products **3a**−**i** and **4**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) Stang, P. J.; Boehshar, M.; Wingert, H.; Kitamura, T. *J. Am. Chem. Soc.* **1988**, *110*, 3272.