Gold-Catalyzed C–H Oxidative Polyacyloxylation Reaction of Hindered Arenes

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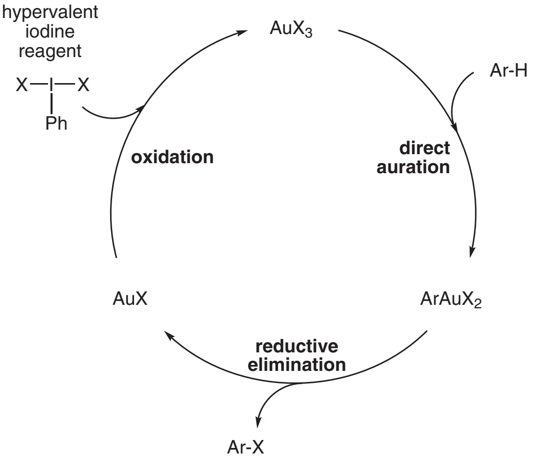
Abstract: The synthesis of polyacyloxylated aromatic derivatives was achieved in moderate yields using a gold-catalyzed C–H activation strategy and di(acetoxy)iodobenzene as an oxidant.

Key words: homogeneous catalysis, arenes, esters, oxidation, gold

The use of hypervalent iodine reagents has constantly increased over the years and has found widespread applications in organic chemistry.[1] These oxidants have become extremely popular because of their ready availability, their low toxicity, and the level of selectivity they allow, particularly in association with transition metal catalysts. The development of synthetic strategies for the direct oxidative conversion of aromatic C–H bonds into carbon–heteroatom or carbon–carbon bonds represents a critical challenge in organic chemistry and an increasing number of transition-metal-catalyzed methodologies in combination with mild oxidizing agents have been developed to address this problem.[2] Although a large variety of transition-metal catalysts and oxidants have been investigated, the palladium/hypervalent iodine reagent couple plays a central role in C–H oxidative functionalization due to its high activity and selectively in ligand-directed transformations.[3] However, its reactivity is strongly diminished by steric hindrance on the substrate[4] especially in the absence of pre-coordination by a directing group.[5] As a consequence, the search for new, highly active catalytic systems allowing oxidative C–H functionalization of aromatic rings is of foremost importance. Gold catalysis recently emerged as a new and very exciting area of research mainly due to its unique Lewis acid carbophilic reactivity.[6] The electrophilicity of gold complexes has also been demonstrated in the Csp^2-H activation of arenes. As early as the 1930s, initial contributions from Isbell and Kharasch postulated auration of nonactivated aromatic rings in the presence of Au(III) salts.[7] This type of reactivity was later investigated by Braunstein et al.[8] Subsequent reductive elimination from the aryl-Au(III) complex liberates a functionalized arene compound and a Au(I) species. In the presence of an external oxidant, regeneration of the Au(III) active intermediate occurs, allowing the development of catalytic versions of such transformations (Scheme 1).[9]

Examples of such reactions using hypervalent iodine reagents as oxidants have been described recently in the literature. In 2007, the group of He reported direct amidation of hindered arenes in the presence of $AuCl_3$ catalyst at room temperature using iminoiodanes as oxidant (Scheme 2, equation 1).[10] In 2008, Tse and co-workers reported the homo- and hetero-coupling of arenes in the presence of $HAuCl_4$ as the catalyst using diacetoxyiodobenzene **1** (DAIB) as the oxidant (Scheme 2, equation 2).[11] In 2009, the groups of Waser[12] and Nevado[13] independently described the alkynylation of electron-rich arenes and heteroarenes catalyzed by gold complexes using hypervalent iodine reagents (Scheme 2, equation 3). Finally, in 2011, we[14] and the group of Wang[15] independently reported the acyloxylation of non-activated arenes in the presence of **1** and a gold catalyst, [$(PPh_3)AuCl$] and $AuCl_3$, respectively (Scheme 2, equation 4). Selective carbon–oxygen bond formation starting from arenes is indeed particularly challenging and interesting as phenols and derivatives are both building blocks that are frequently found in organic synthesis and structural scaffolds in biology, material sciences and pharmaceutics.[16] In line with our research program initiated on gold-catalyzed carbon–oxygen bond-forming reactions,[17] we decided to investigate the gold-catalyzed polyacyloxylation of aromatic ring systems using hypervalent iodine reagents as oxidizing agents.



Scheme 1 General postulated mechanism of Au-catalyzed arene oxidative C–H functionalization

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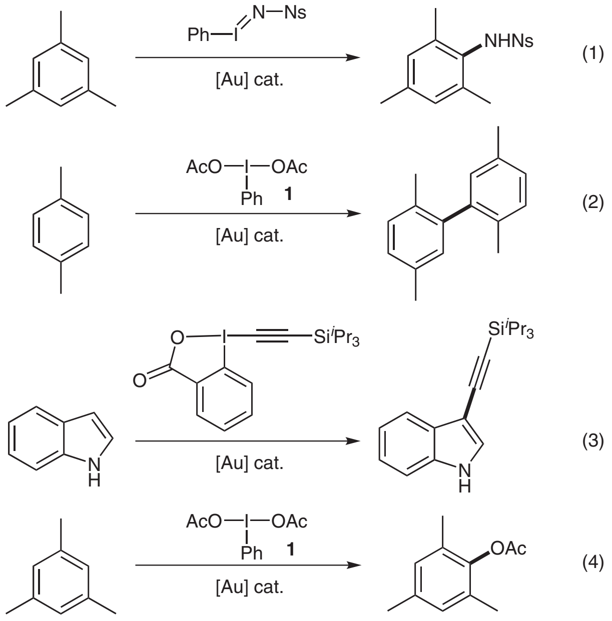
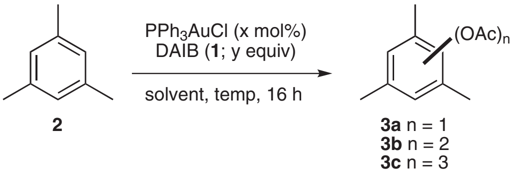


Scheme 2 Gold-catalyzed hypervalent iodine reagent-based C–H functionalization of arenes

Noticeably, in the course of our studies concerning the Au-catalyzed acyloxylation of aromatic systems,[14] we observed the formation of diacyloxylated arenes resulting from the activation of two C–H bonds, as significant side-products. We therefore anticipated that variations of the reaction conditions would allow the preferential formation of polyacyloxylated products. In this paper, we describe the di- and triacyloxylation of hindered nonactivated aromatic rings.

At the beginning of our investigation, we evaluated the degree of acyloxylation of mesitylene **2** under different sets of conditions in the presence of DAIB **1** as the oxidant and [(PPh$_3$)AuCl] as a stable, easy to handle gold catalyst precursor. As presented in Table 1, the diacetoxymesitylene (**3b**) was obtained as a major product in the presence of [(PPh$_3$)AuCl] (3 mol%) and DAIB **1** (3 equiv) in acetic acid (AcOH) (compared Table 1, entry 4 to entries 1 and 2). Lower catalyst loadings (entries 1 and 2) led predominantly to the monoacetoxylated product **3a**, whereas higher catalyst loading did not significantly improve the level of C–H oxidative addition of acid (entry 5). A slightly higher level of activation was observed in 1,2-dichloroethane (DCE), only 2 mol% [(PPh$_3$)AuCl] and 3 equivalents of DAIB **1** were necessary to obtain a better yield of **3b** (entry 3). Lowering the temperature of the reaction had a strong detrimental effect on the oxidation in DCE (entries 6 and 7). Increasing the oxidant to substrate ratio to 5 in acetic acid and DCE did not significantly improve the yield or the product distribution (entry 8 versus 3 and entry 9 versus 2). The best yield of diacetoxylated **3b** was obtained in DCE using 8 mol% gold catalyst and 5 equivalents of **1** (entry 12). Finally, a higher yield of the triacetoxylated product **3c** was obtained in the presence of 4 mol% gold catalyst and 5 equivalents of **1** (entry 10). Total yields of acyloxylation products **3a**–**c** (40–67%) remained moderate in all cases, and a complex mixture of biaryl isomers resulting from the direct heterocoupling reaction between **3a** and **3b** and iodobenzene represents the major by-products of this transformation.[18]

Table 1 Optimization of the Au-Catalyzed C–H Polyacetoxylation Reaction of Mesitylene[a]



Entry	[(PPh$_3$)AuCl] (mol%)	Oxidant **1** (equiv)	Solvent	Yield (%)[b] **3a**	**3b**	**3c**
1[c]	1	3	AcOH	38	3	0
2	2	3	AcOH	45	11	0
3	2	3	DCE	7	24	8
4	3	3	AcOH	12	29	9
5	5	3	AcOH	10	30	11
6[d,e]	2	3	DCE	34	1	0
7[f]	2	3	DCE	15	23	4
8	2	5	DCE	11	29	8
9	2	5	AcOH	44	10	1
10	4	5	DCE	1	26	23
11	4	5	AcOH	9	22	9
12	8	5	DCE	3	36	28

[a] Reaction conditions: mesitylene **2** (0.2 mmol, 0.5 M), DAIB **1** (y equiv), 110 °C unless otherwise stated. Conversions >98% unless otherwise specified.
[b] Yields of the monoacetoxylated, diacetoxylated and triacetoxylated products **3a**, **3b** and **3c** determined by GC.
[c] 95% conversion.
[d] 87% conversion.
[e] Reaction run at 80 °C.
[f] Reaction run at 100 °C.

To get a better understanding of origins of the discrepancy between the reactivities when the solvent was changed from acetic acid to DCE, a kinetic analysis of the polyacetoxylation of **2** in the presence of [(PPh$_3$)AuCl] (4 mol%) as the catalyst and **1** (3 equiv) was undertaken in both solvents (Figure 1 and Figure 2). The reaction was markedly faster in DCE; starting mesitylene **2** was completely consumed within two hours, whereas full conversion was only reached after six hours in AcOH. The final product ratio observed in DCE for **3a**/**3b**/**3c** was 1:3:1. It should also be noticed that the formation of diacetoxylated adduct **3b** did not evolve in acetic acid whereas its ratio significantly increased in 1,2-dichloroethane. As a consequence, one may envisage the polyacetoxylation reaction in 1,2-dichloroethane versus in acetic acid, starting from **3b** (see Table 2).

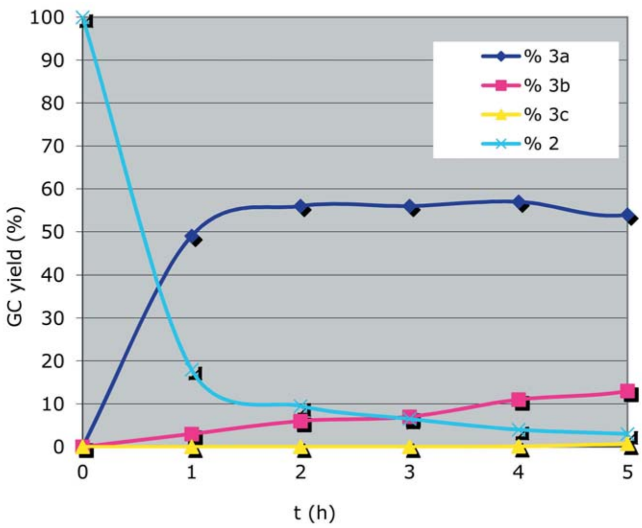


Figure 1 Plot of mesitylene **2** consumption and concomitant formation of acetyloxylated products **3a**, **3b** and **3c** in acetic acid

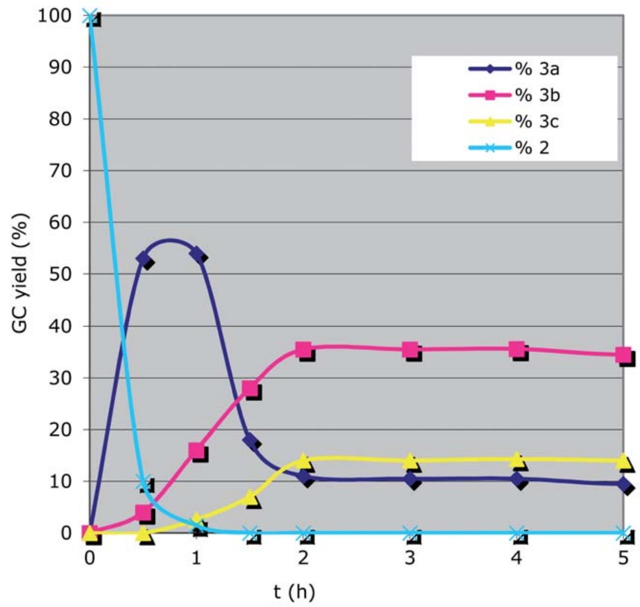
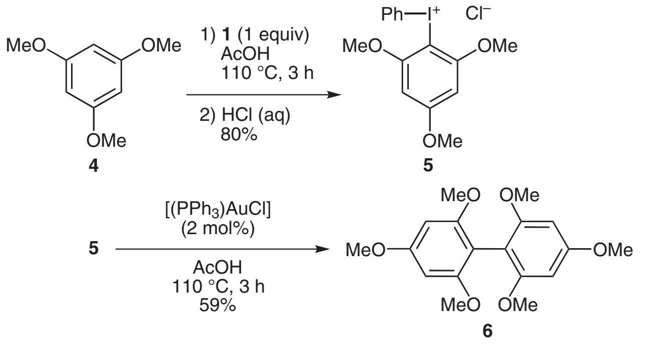


Figure 2 Plot of mesitylene **2** consumption and concomitant formation of acetyloxylated products **3a**, **3b** and **3c** in 1,2-dichloroethane

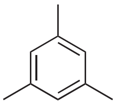
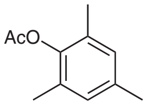
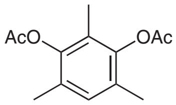
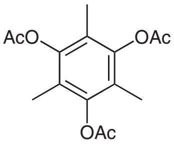
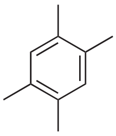
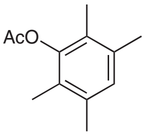
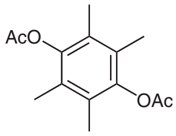
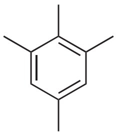
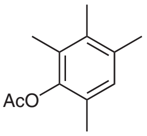
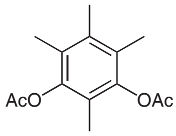
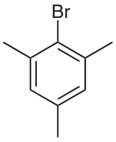
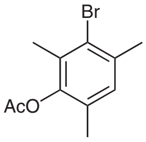
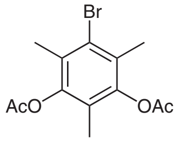
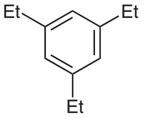
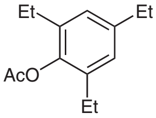
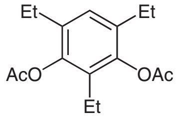
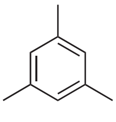
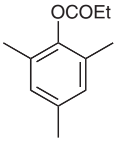
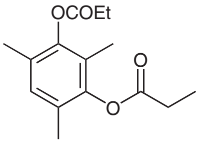
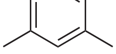
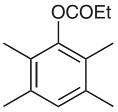
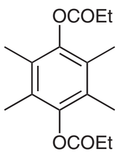
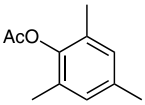
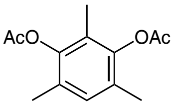
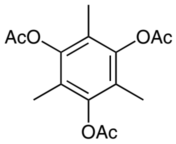
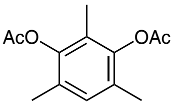
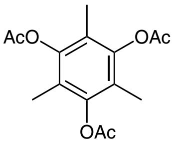
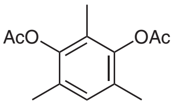
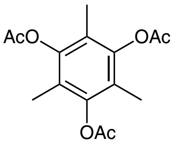
Moreover, the observed decrease in acetoxylation yields for arenes possessing electron-donating groups in acetic acid can be explained by the reactivity found in the case of 1,3,5-trimethoxybenzene **4** (Scheme 3). The reaction of **4** with **1** (1 equiv) in the presence of [$(PPh_3)AuCl$][19] (2 mol%) did not lead to any acetoxylated derivative, but instead afforded a diaryliodonium salt **5**.[20] This salt was isolated in 80% yield under the same reaction conditions in the absence of gold catalyst. Addition of the gold catalyst to this intermediate **5** then furnished only the direct arene coupling product **6**. These latter experiments seem to exclude the involvement of diaryl iodonium salt intermediates in gold-catalyzed direct acyloxylation reactions.



Scheme 3 Diaryliodonium **5** formation and reactivity in the presence of the gold(I) precatalyst

Considering the observed kinetics and polyacetoxylated product ratio, we selected the catalytic conditions of [$(PPh_3)AuCl$] (2 mol%) and DAIB (3 equiv) in DCE at 110 °C for a screening of the C–H oxidation reaction of a variety of substituted arenes (Table 2). In the case of mesitylene **2**, diacetoxymesitylene (**3b**) was obtained in 31% isolated yield as the major product, whereas the mono- and tri-acetoxylated product **3a** and **3c** were isolated in 8 and 12% yield, respectively (entry 1). Tetramethyl-substituted benzenes **7** and **9** were diacetoxylated in 46 and 29% yields, respectively (entries 2 and 3), whereas 2-bromomesitylene **11** was diacetoxylated in 43% yield (entry 4). The reaction seems to be strongly hampered by an additional increase of the steric bulk of the arene substituents. When treated with DAIB (3 equiv), 1,3,5-triethylbenzene **13** was converted in 65% yield into the monoacetoxylated product **14a**, whereas the diacetoxylated product **14b** is only observed in a marginal 10% yield (entry 5). In this case, the use of three equivalents of oxidant in 1,2-dichloroethane allows the formation of the monoacetoxylated product **14a** in a significantly higher yield compared to that described in our initial contribution in the presence of 1.3 equivalents of DAIB in acetic acid (65 versus 46% yield).[14] These gold-catalyzed C–H oxidative reactions can also be conducted in carboxylic acid solvents, leading to the corresponding polyacyloxylated products. When mesitylene **2** and 1,2,4,5-tetramethylbenzene **7** were treated with DAIB (3 equiv) in propionic acid, the diacyloxylated products **15b** and **16b** were formed in 39 and 41% yields, respectively (entries 6 and 7). As a test experiment, the monoacetoxylated product **3a** was treated in the presence of two equivalents of DAIB (entry 8); under these conditions the di- and tri-acetoxylated products **3b** and **3c** were formed in 65 and 20% yield, respectively. Finally, the diacetoxylated product **3b** was treated with either 1.3 or 2 equivalents of **1** in the presence of 2 mol% [$(PPh_3)AuCl$] (entries 9 and 10); in these cases the triacetoxylated product **3c** was isolated in 40 and 49% yield, respectively.

Table 2 Arene Polyacyloxylation Reaction[a]

Entry	Substrate	Product			Yield (%)[b]
1	**2** 	**3a** 	**3b** 	**3c** 	**3a**, 8 **3b**, 31 **3c**, 12
2	**7** 	**8a** 	**8b** 		**8a**, trace **8b**, 46
3	**9** 	**10a** 	**10b** 		**10a**, trace **10b**, 29
4	**11** 	**12a** 	**12b** 		**12a**, trace **12b**, 43
5	**13** 	**14a** 	**14b** 		**14a**, 65 **14b**, (10)[c]
6[d]	**2** 	**15a** 	**15b** 		**15a**, trace **15b**, 39
7[d]	**7** 	**16a** 	**16b** 		**16a**, trace **16b**, 41
8[e]	**3a** 	**3b** 	**3c** 		**3b**, 65 **3c**, 20
9[f]	**3b** 	**3c** 			**3c**, 40
10[g]	**3b** 	**3c** 			**3c**, 49

[a] Reaction conditions: arene (0.5 M, 0.5 mmol), DAIB **1** (3 equiv), 110 °C, DCE, 16 h.
[b] Isolated yields after column chromatography.
[c] Estimated yield by GC analysis.
[d] Reaction run in propionic acid.
[e] DAIB **1** (2 equiv) used.
[f] DAIB **1** (1.3 equiv), 110 °C, 16 h, 58% conversion.
[g] DAIB **1** (2 equiv), 110 °C, 16 h, 58% conversion.

In conclusion, we have described a gold(I)-catalyzed methodology that affords direct polyacyloxylation of non-activated hindered arenes. The reaction proceeds in the presence of a gold(I) precatalyst [(PPh$_3$)AuCl] using di(acetoxy)iodobenzene as a source of acetoxy or acyloxy moieties. Although yields remain moderate, the present methodology allows direct carbon–oxygen bond formation with challenging, unactivated and sterically encumbered arene substrates.

All starting materials were purchased from commercial sources and used without further purification. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded with a Bruker AV 300 instrument. Signals are expressed in ppm (δ) and internally referenced to residual protic solvent signals. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities. Mass spectrometry analyses (direct introduction by either chemical ionization with ammonia or electrospray ionization) were performed at the Ecole Nationale Supérieure de Chimie de Paris, Chimie ParisTech. Column chromatography was performed with GEDURAN Si 60 silica gel (40–63 μm). Petroleum ether (PE) refers to the fraction boiling in the 40–65 °C range. Structure and purity of the isolated products **3a**,[21] **6**,[22] **8a**,[23] **10a**,[14] **12a**,[14] **14a**,[14] **15a**,[14] **16a**[14] and **16b**[14] were confirmed by comparison of their spectral data with those reported in the literature.

Mesitylene Polyacetoxylation in DCE; Typical Procedure

1,3,5-Trimethylbenzene (**2**; 60 mg, 0.5 mmol) was added to a solution of di(acetoxy)iodobenzene (DAIB, **1**; 483 mg, 1.5 mmol) and [(PPh$_3$)AuCl] (4.9 mg, 0.01 mmol) in DCE (1 mL) under an air atmosphere in a pressure tube. The tube was sealed and the reaction was heated to 110 °C for 16 h. The volatiles were removed under reduced pressure and the crude residue was purified by flash column chromatography (PE–EtOAc, 98:2→70:30).

Mesitylene Polyacetoxylation in AcOH; Typical Procedure

1,3,5-Trimethylbenzene (**2**; 60 mg, 0.5 mmol) was added to a solution of di(acetoxy)iodobenzene (DAIB, **1**; 483 mg, 1.5 mmol) and [(PPh$_3$)AuCl] (4.9 mg, 0.01 mmol) in glacial AcOH (1 mL) under an air atmosphere in a pressure tube. The tube was sealed and the reaction was heated to 110 °C for 16 h. After cooling to r.t., the mixture was diluted with (*i*-Pr)$_2$O (15 mL) and treated with sat. aq NaHCO$_3$ (15 mL). The organic layer was collected, dried with MgSO$_4$, the solvents were removed under reduced pressure, and the crude residue was purified by flash column chromatography (PE–EtOAc, 98:2→70:30).

1,3-Diacetoxy-2,4,6-trimethylbenzene (3b)

Yield: 11 mg (31%); white solid.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.94 (s, 1 H), 2.33 (s, 6 H), 2.11 (s, 6 H), 1.95 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 168.8, 146.4, 129.7, 127.7, 123.0, 20.4, 16.1, 10.3.

MS (CI, NH$_3$): *m/z* (%) = 254 (100) [M + NH$_4$]$^+$.

1,3,5-Triacetoxy-2,4,6-trimethylbenzene (3c)

Yield: 21 mg (12%); white solid.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.33 (s, 9 H), 1.93 (s, 9 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 168.4, 146.3, 121.4, 20.4, 10.4.

MS (CI, NH$_3$): *m/z* (%) = 312 (100) [M + NH$_4$]$^+$.

1,4-Diacetoxy-2,3,5,6-tetramethylbenzene (8b)

Yield: 124 mg (46%);white solid.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.35 (s, 6 H), 2.05 (s, 12 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 169.2, 145.6, 127.0, 20.5, 13.1.

MS (CI, NH$_3$): *m/z* (%) = 268 (100) [M + NH$_4$]$^+$.

1,3-Diacetoxy-2,4,5,6-tetramethylbenzene (10b)

Yield: 37 mg (29%); white solid.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.34 (s, 6 H), 2.20 (s, 3 H), 2.06 (s, 6 H), 1.93 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 169.0, 146.0, 134.5, 126.4, 119.9, 20.5, 16.1, 13.3, 10.4.

MS (CI, NH$_3$): *m/z* (%) = 268 (100) [M + NH$_4$]$^+$.

1,3-Diacetoxy-5-bromo-2,4,6-trimethylbenzene (12b)

Yield: 43 mg (43%); white solid.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.35 (s, 6 H), 2.23 (s, 6 H), 1.91 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 167.4, 145.1, 127.8, 121.5, 19.3, 16.3, 9.5.

MS (CI, NH$_3$): *m/z* (%) = 334 (100) [M + NH$_4$]$^+$.

1,3-Bis(propionyloxy)-2,4,6-trimethylbenzene (15b)

Yield: 21 mg (39%); yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.93 (s, 1 H), 2.62 (q, *J* = 7.6 Hz, 4 H), 2.09 (s, 6 H), 1.92 (s, 3 H), 1.31 (t, *J* = 7.6 Hz, 6 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 172.1, 146.4, 129.6, 127.5, 123.0, 27.4, 16.1, 9.4.

MS (CI, NH$_3$): *m/z* (%) = 282 (100) [M + NH$_4$]$^+$.

Synthesis of 2,4,6-Trimethoxyphenyl Phenyl Iodonium Chloride (5)

1,3,5-Trimethoxybenzene (**4**; 168 mg, 1 mmol) was added to a solution of di(acetoxy)iodobenzene (DAIB, **1**; 322 mg, 1 mmol) in glacial AcOH (1 mL) under an air atmosphere. The reaction mixture was heated to 110 °C for 1 h. After cooling to r.t., the mixture was diluted with EtOAc (15 mL) and treated with sat. aq NaHCO$_3$ (15 mL). The aqueous layer was acidified with 1 M HCl and extracted with EtOAc (3 × 30 mL). The organic layer was collected, dried with MgSO$_4$, and the solvents were removed under reduced pressure to give **5**.

Yield: 320 mg (80%); white powder.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.99–7.95 (m, 2 H), 7.44–7.38 (m, 1 H), 7.29–7.25 (m, 2 H), 6.14 (s, 2 H), 3.85 (s, 3 H), 3.84 (s, 6 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 166.2, 160.4, 133.3, 131.1, 130.6, 119.7, 91.4, 90.1, 56.7, 55.8.

MS (ESI): *m/z* (%) = 371 (100) [$C_{15}H_{16}O_3I$]$^+$.

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