



# Gold-Catalyzed Direct C(sp<sup>3</sup>)–H Acetoxylation of Saturated Hydrocarbons

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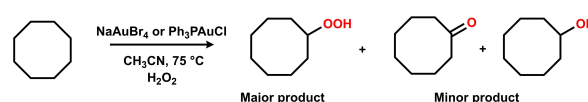
In this communication we report our studies towards the development of a gold-catalyzed direct acetoxylation of C(sp<sup>3</sup>)–H bonds. We achieve this through the use of the hyper-valent iodine reagent PhI(OAc)<sub>2</sub> in combination with a simple gold salt (HAuBr<sub>4</sub>) as the catalyst. Through a comparison of the reactivities of cyclooctane and adamantane we judge the reaction to proceed *via* hydride transfer. This is further substantiated through computational studies of the relative energies for the anions, radicals and cations derived from C–H bond cleavage of cyclooctane and adamantane relevant to the C–H cleaving step.

The activation and more broadly formulated functionalization of unreactive C–H bonds has in the past two decades become an indispensable tool. As a consequence, the once considered *inert* C–H bond has gradually been promoted to the status of a functional group.<sup>[1]</sup> In particular, the application of transition metals as catalysts has impacted this area substantially.<sup>[2]</sup> The use of gold-based catalysts has admittedly taken a niche existence and a rather narrow array of reactions has been reported that predominantly center around the modification of C(sp)<sup>2</sup>–H and C(sp<sup>2</sup>)–H bonds.<sup>[3]</sup> In contrast, the functionalization of C(sp<sup>3</sup>)–H bonds has been reported less frequently due to the comparatively lower reactivity. When these types of reactions are reported, however, it is notable that this challenging step is frequently embedded into complicated mechanistic pathways with complex reaction sequences.<sup>[4]</sup> An exception are reactions that involve intramolecular hydride shifts, facilitated by gold as catalysts, where several examples have been reported.<sup>[5]</sup>

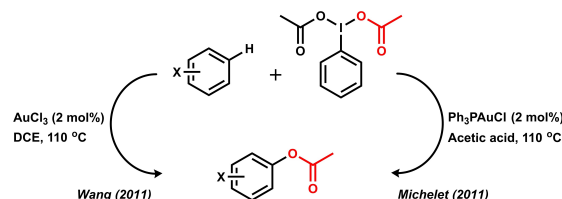
Interestingly, Periana and co-workers already reported in 2004 that gold could catalyze the oxidation of methane to methanol, which represents one of the most challenging

C(sp<sup>3</sup>)–H bond oxidation reactions.<sup>[6]</sup> Similarly, Shul'pin *et al.* reported that gold salts/complexes are capable of oxidizing C(sp<sup>3</sup>)–H bonds in simple hydrocarbons, such as cyclooctane, using either H<sub>2</sub>O<sub>2</sub> or simply aerobic conditions as the terminal oxidant (Scheme 1a).<sup>[7]</sup> These reports indicate that gold is capable of activating oxidants for the transformation of C–H into C–O bonds and demonstrate the potential for gold to serve as a catalyst for these types of transformations. In stoichiometric experiments, it was also shown that gold(III) hydroxide complexes can oxidize C(sp<sup>3</sup>)–H bonds.<sup>[8]</sup> Recently, two independent reports by the groups of Wang<sup>[9]</sup> and Michelet<sup>[10]</sup> showed that simple gold salts/complexes, when combined with PhI(OAc)<sub>2</sub>,<sup>[11]</sup> are capable of acetoxylation C(sp<sup>2</sup>)–H bonds in aromatic compounds (Scheme 1b). In addition, very similar reaction conditions were reported by Guo *et al.* for the acetoxylation of C(sp<sup>3</sup>)–H bonds of methyl sulfides.<sup>[12]</sup> Notably this reaction has been proposed to proceed *via* the initial formation of a sulfonium salt without the involvement of the gold catalyst. In the present article, we explore if the reaction conditions reported for the acetoxylation of aromatic compounds are transferable to the reaction with C(sp<sup>3</sup>)–H bonds of saturated unactivated hydrocarbons, with the aim to develop a *direct* acetoxylation reaction (Scheme 1c).

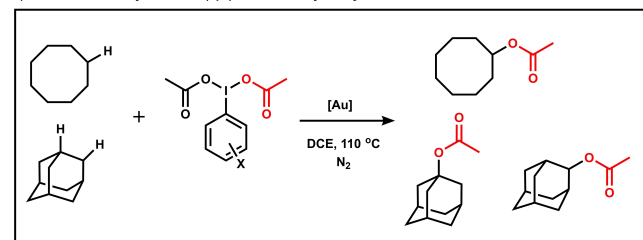
a) Shul'pin (2001)



b) Acetoxylation of arenes catalyzed by Au



c) This work: acetoxylation of C(sp<sup>3</sup>)–H bond catalyzed by Au



Scheme 1. Gold-catalyzed C–H functionalization.

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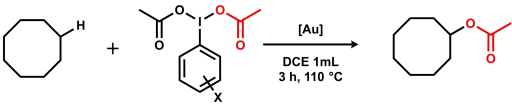
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Our exploration began with simply applying reaction conditions that mimicked those reported for the acetoxylation of aromatic compounds (Table 1) using cyclooctane as a substrate, with a reported BDE of  $95.7 \text{ kcal mol}^{-1}$ .<sup>[13]</sup> When we carried the reaction out under an atmosphere of  $\text{N}_2$  using simple  $\text{Ph}_3\text{PAuCl}$  or  $\text{AuCl}_3$  we observed an essentially stoichiometric formation of the acetoxyated product with respect to the amount of gold added (Table 1, entries 1 and 2). In contrast, when these reactions were performed under aerobic conditions a slight increase for the acetoxyated product was observed with concomitant formation of alcohol and ketone products (Table 1, entries 3 and 4). This raised the question if the alcohol and ketone products were formed with the involvement of gold, much as in the case of the report of Shul'pin *et al.*,<sup>[7a]</sup> or if there was a pathway that would not require any transition metal catalyst. We found that in the absence of gold the reaction readily produces alcohol and ketone,<sup>[14]</sup> yet does *not* lead to noticeable amounts of acetoxyated product. When oxygen was removed, this pathway leading to alcohol and ketone is suppressed (Table 1, entries 5 and 6). Furthermore, no oxygenated products were observed in the absence of gold and the oxidant under aerobic reaction conditions (Table 1, entry 7). This means that there is a  $\text{PhI}(\text{OAc})_2$ -promoted pathway towards alcohol and ketone formation, which is not affected by gold. We assign the small amount of acetoxyated product, which was also formed in the absence of oxygen, to originate from a gold-promoted process and subsequently further evaluated different gold sources (see supporting information for further details). We found that a catalytic amount of  $\text{HAuBr}_4$  resulted in an increased yield and resulted in TONs of 4.5–5. Noticeably, this was not significantly influenced by the presence or absence of air. In the presence of air, however, the background reaction, producing alcohol and ketone side products, was again observed. Throughout we have used a catalyst loading of 2 mol%. When we increased the catalyst loading to 5 mol% we

observed an increase in yield, however, the observed TON slightly decreased (Table 1, entries 9 and 10). Therefore, we have used 2 mol% for all subsequent reactions. To probe if the reaction benefitted from acid catalysis, which we introduced with the choice of gold salt made, we used the potassium congener  $\text{KAuBr}_4$  instead and observed essentially the same catalytic activity (Table 1, entry 11). A side product we occasionally observed in these transformations was acetoxyated iodobenzene (see supporting information for details), which can be ascribed to the decomposition of the oxidant. To probe if the efficiency of the process could be increased by preventing this decomposition, we tested two modifications of the oxidant, being the penta-fluoro and *p*- $\text{NO}_2$  versions (Table 1, entries 12 and 13). For the penta-fluoro substituted oxidant this resulted in no significant improvement of the TONs for the acetoxylation reaction. However, the use of the *p*- $\text{NO}_2$  substituted oxidant did increase the yield of acetoxylation slightly and provided a TON of 8.

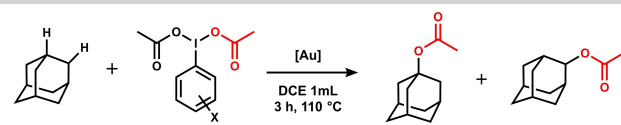
To develop a better idea of the nature of this reaction, we decided to explore the oxidation of another substrate with a comparable reported C–H BDE. We selected adamantane, which features tertiary C–H bonds with a BDE of  $96.2 \text{ kcal mol}^{-1}$ , in addition to a set of secondary ones with a BDE of  $98.4 \text{ kcal mol}^{-1}$ .<sup>[15]</sup> This choice of substrate allows us to examine how the nature of the  $\text{C}(\text{sp}^3)\text{--H}$  bond influences reactivity and also probes selectivity. When applying the reaction conditions that resulted in catalytic turnover ( $\text{HAuBr}_4$ ) we also observed acetoxylation (Table 2). This reaction showed the expected preference for the weaker tertiary C–H bond. Most notably, the TONs are higher, especially when considering the sum of acetoxyated products. Unlike in the case of cyclooctane, the amounts of alcohol and ketone formed are much lower. However, when we carried the reaction out in the absence of  $\text{HAuBr}_4$  under aerobic conditions we observed alcohol and ketone products alongside a significant amount of acetoxyated

Table 1. Acetoxylation of cyclooctane.<sup>[a]</sup>

								
Entry	Catalyst	Oxidant	Aerobic / $\text{N}_2$	-one <sup>[b,c]</sup> [%]	-ol <sup>[b,c]</sup> [%]	Yield of product <sup>[b]</sup> [%]	TON <sup>[b]</sup>	
1	$\text{Ph}_3\text{PAuCl}$	$\text{X} = \text{H}_5$	$\text{N}_2$	n/o	n/o	2	1	
2	$\text{AuCl}_3$	$\text{X} = \text{H}_5$	$\text{N}_2$	n/o	n/o	2	1	
3	$\text{Ph}_3\text{PAuCl}$	$\text{X} = \text{H}_5$	Aerobic	11	2	5	2	
4	$\text{AuCl}_3$	$\text{X} = \text{H}_5$	Aerobic	8	trace	5	2	
5	–	$\text{X} = \text{H}_5$	Aerobic	12	1	n/o	–	
6	–	$\text{X} = \text{H}_5$	$\text{N}_2$	trace	trace	n/o	–	
7	–	–	Aerobic	n/o	n/o	n/o	–	
8	$\text{HAuBr}_4$	$\text{X} = \text{H}_5$	Aerobic	8	1	8	4	
9	$\text{HAuBr}_4$	$\text{X} = \text{H}_5$	$\text{N}_2$	n/o	n/o	10	5	
10 <sup>[d]</sup>	$\text{HAuBr}_4$	$\text{X} = \text{H}_5$	$\text{N}_2$	n/o	n/o	16	3	
11	$\text{KAuBr}_4$	$\text{X} = \text{H}_5$	$\text{N}_2$	trace	trace	9	5	
12 <sup>[e]</sup>	$\text{HAuBr}_4$	$\text{X} = \text{F}_5$	$\text{N}_2$	trace	trace	10	5	
13 <sup>[e]</sup>	$\text{HAuBr}_4$	$\text{X} = p\text{-NO}_2$	$\text{N}_2$	trace	trace	16	8	

[a] Reaction conditions: substrate (2.5 mmol), oxidant (0.5 mmol), catalyst (2 mol%), DCE (1 mL),  $110^\circ\text{C}$ , 3 h. Yields lower than 1% are listed as trace. n/o = Not observed. Experiments were performed in triplicate. [b] Yields and TONs were determined by GC using mesitylene as an internal standard; [c] Yields of cyclooctanol and cyclooctanone; [d] catalyst (5 mol%); [e] Single run.

Table 2. Acetoxylation of adamantane.<sup>[a]</sup>

								
Entry	Catalyst	Oxidant	Aerobic / N <sub>2</sub>	-one <sup>[b,c]</sup> [%]	-ol <sup>[b,c]</sup> [%]	Yield of 3° acetate <sup>[b]</sup> [%]	Yield of 2° acetate <sup>[b]</sup> [%]	TON <sup>[b,d]</sup>
1	HAuBr <sub>4</sub>	X = H <sub>5</sub>	Aerobic	4	8	30	8	19
2	HAuBr <sub>4</sub>	X = H <sub>5</sub>	N <sub>2</sub>	n/o	n/o	15	4	10
3	–	X = H <sub>5</sub>	Aerobic	5	11	14	2	–
4	–	X = H <sub>5</sub>	N <sub>2</sub>	trace	trace	2	trace	–
5	–	–	Aerobic	n/o	n/o	n/o	n/o	–
6	KAuBr <sub>4</sub>	X = H <sub>5</sub>	N <sub>2</sub>	n/o	n/o	17	6	11
7	<i>p</i> -TsOH	X = H <sub>5</sub>	N <sub>2</sub>	n/o	n/o	2	trace	1
8 <sup>[e]</sup>	HAuBr <sub>4</sub>	X = F <sub>5</sub>	N <sub>2</sub>	trace	trace	16	6	11
9	HAuBr <sub>4</sub>	X = <i>p</i> -NO <sub>2</sub>	N <sub>2</sub>	trace	trace	5	1	3

[a] Reaction conditions: substrate (2.5 mmol), oxidant (0.5 mmol), catalyst (2 mol %), DCE (1 mL), 110 °C, 3 h. When yield was less than 1 %, it was indicated as trace. n/o = Not observed. Experiments were performed in triplicate. [b] Yields and TON determined by GC using mesitylene as an internal standard; [c] Yields of 1-adamantanol and 2-adamantanone; [d] Sum of TONs of acetoxylation products; [e] Single run.

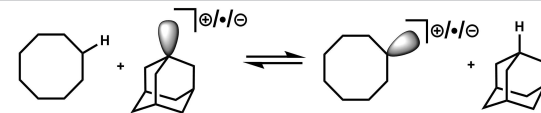
products. The acetoxylation of C(sp<sup>3</sup>)–H in benzylic acetals using PhI(OAc)<sub>2</sub> has indeed been reported.<sup>[16]</sup> Removal of oxygen almost fully prevented this. We thus attribute the formation of acetoxylation products to a gold-catalyzed process. We again precluded the involvement of acid catalysis by replacing HAuBr<sub>4</sub> with the potassium salt, which resulted in an essentially unchanged TON for the acetoxylation. We further precluded the involvement of acid by also probing the outcome of this reaction when replacing the gold salt with a catalytic amount of *p*-TsOH, which produced no meaningful amounts of oxidized adamantane.

Based on the observed trends we may ask if the nature of the C(sp<sup>3</sup>)–H oxidation step can be further narrowed down, that is, if either a proton transfer, proton coupled electron transfer (PCET) or a hydride transfer occurs in the initial functionalization step. Based on the simple stability of the corresponding carbocations, radicals and anions of adamantane and cyclooctane, the observed reactivity may be attributed through a comparison of reactivity trends. In principle, one could follow the general trends as outlined in organic chemistry text books, where the tertiary carbocation derived from the C(sp<sup>3</sup>)–H bond is more stable than the one derived from the secondary one and vice versa for the carbanion. With the reported experimental BDEs (*vide supra*) we might expect a scenario where the energetic difference is small. As we are comparing trends for two specific molecules, we decided to compute the relative stabilities using the M06-2X functional<sup>[17]</sup> in combination with the def2-TZVPPD basis set<sup>[18]</sup> and mimicked solvation effects of dichloroethane with the PCM solvation model.<sup>[19]</sup> A detailed description of the computational details can be found in the supporting information.

We find that for both the anion and the radical form, cyclooctane provides the more stable structure. In contrast, the carbocation is more favored for adamantane. This is mostly in line with our expectation, only differing in the stability of the radicals, which suggest that the BDEs are slightly more different than the reported experimental values listed above. If we recall

that the reaction conditions lead to larger TONs for adamantane than for cyclooctane, we can ascribe the higher reactivity to the ability to stabilize a carbocation/carbocation character, which would arise from hydride transfer. We further probed our computational finding by conducting competition experiments for the oxidation of cyclooctane and adamantane [See supporting information Table S9]. Under the reaction conditions listed in Tables 1 and 2 similar product ratios (1:2.4 favoring adamantane) were observed when compared with the individual experiments shown above. At first glance, this might suggest very similar reactivity of both substrates, however, the studied substrates have quite different solubility in DCE under the reaction conditions (see Figure S1). Adamantane, which we would, based on our calculations, expect to preferentially react, exhibited substantially lower solubility. Therefore, to allow for an appropriate comparison we lowered the substrate concentrations. When the solubility of adamantane was sufficient we indeed observed preferential acetoxylation of adamantane (1:3.3 favoring adamantane). This observation is in line with the calculations shown in Table 3 and corroborates our assignment of hydride transfer. This may be further substantiated by the observation of the group of de Bruin that amination of the C(sp<sup>3</sup>)–H bonds in 9,10-dihydro-9-heteroanthracenes is possible

Table 3. Computed relative stabilities.

	
Adamantane vs. Cyclooctane <sup>[a]</sup>	ΔE <sub>ZPE</sub> [kcal mol <sup>−1</sup> ]
Carbocation	6.0
Radical	−6.4
Anion	−4.0

[a] A positive value indicates that the adamantane based structure is preferred and a negative value that the cyclooctane based structure is preferred for the species with the cleaved C–H bond.

with PhINTs *via* initial hydride transfer.<sup>[20]</sup> Notably, this reaction does not require the addition of a catalyst for activation of the hypervalent iodine reagent. In the present case we therefore propose that the actual role of gold can be attributed to Lewis-acid activation of  $\text{PhI}(\text{OAc})_2$ , resulting in enhanced electrophilicity allowing for hydride transfer.

In summary, we find that the series of experiments that we report here, while TONs are humble, clearly demonstrates the capability of gold to activate oxidants for the functionalization of  $\text{C}(\text{sp}^3)\text{--H}$  bonds in simple hydrocarbons. Through comparison of the relative reactivities of cyclooctane and adamantane, we establish that a likely pathway for the functionalization of  $\text{C}(\text{sp}^3)\text{--H}$  bonds is hydride transfer. In this case the role of gold lies in the activation of the oxidant and not the  $\text{C}(\text{sp}^3)\text{--H}$  bonds. This is markedly different from the proposed mechanisms for the acetoxylation of arenes reported by Wang<sup>[9]</sup> and Michelet<sup>[10]</sup> employing very similar reaction conditions, where activation likely proceeds through electrophilic activation of the arene by gold and simple deprotonation results in the formation of a gold-bound carbanion. If we compare to the two examples of  $\text{C}(\text{sp}^3)\text{--H}$  functionalization reactions by Periana and co-workers,<sup>[6]</sup> as well as Shul'pin *et al.*,<sup>[7a]</sup> which we outlined in the introduction, there is a fundamental difference in the nature of the  $\text{C--H}$  breaking event compared to the  $\text{C}(\text{sp}^3)\text{--H}$  functionalization reported here. For example, in the oxidative transformation of methane to methanol reported by Periana and co-workers,<sup>[6]</sup> it is proposed that electrophilic activation, and thus cleavage of the  $\text{C--H}$  bond *via* deprotonation, leads to a gold-bound  $\text{CH}_3$  group as an intermediate, which subsequently leads to  $\text{C--O}$  bond formation. This is contrasted by the report of Shul'pin *et al.*<sup>[7a]</sup> which proposes that a  $\text{Au}^{\text{III}}=\text{O}$  intermediate leads to homolytic  $\text{C}(\text{sp}^3)\text{--H}$  bond cleavage resulting in a carbon-centered radical that reacts further with  $\text{O}_2$  forming a  $\text{C--O}$  bond. The results reported here, which we propose to occur *via* hydride transfer, therefore complete the full spectrum of different  $\text{C--H}$  bond breaking processes reaching from proton transfer, PCET and hydride transfer. The presented vista on  $\text{C}(\text{sp}^3)\text{--H}$  functionalization provides an alternative view of the role of gold in the functionalization of hydrocarbons and has the potential to systematically categorize this class of reactions in the field of gold catalysis.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** Acetoxylation • Gold Catalysis • Hydride Transfer • Hydrocarbon Oxidation

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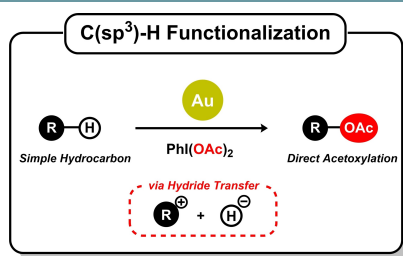
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## COMMUNICATIONS

**Gold catalysis:** A protocol for the direct acetoxylation of  $C(sp^3)-H$  bonds of saturated hydrocarbons using simple gold salts (e.g.  $HAuBr_4$ ) is reported.  $PhI(OAc)_2$  serves as the oxidant and this transformation is proposed to proceed *via* hydride transfer as the key step.



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**Gold-Catalyzed Direct  $C(sp^3)-H$  Acetoxylation of Saturated Hydrocarbons**

