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Gold Catalysis |Hot Paper|

Gold(I)-Catalyzed Intramolecular C(sp^3)–H Insertion by Decarbenation of Cycloheptatrienes

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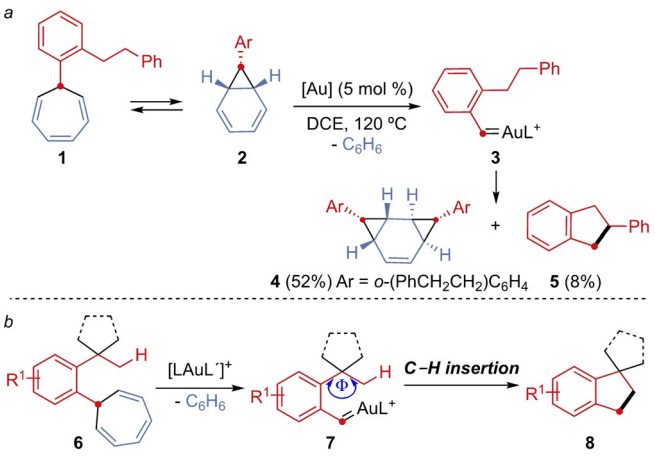
Abstract: A novel synthesis of indanes and dihydronaphtalenes based on the intramolecular insertion into C(sp^3)–H bonds of gold(I) carbenes generated by retro-Buchner reaction (decarbenation) has been developed. Deuterium-labeling and kinetic isotope effect experiments, DFT calculations, and generation of the proposed carbene intermediate from a well-characterized gold(I) carbenoid support the involvement of a three-center concerted mechanism for the C(sp^3)–H functionalization process.

Introduction

The direct functionalization of aliphatic C(sp^3)–H bonds by metal carbene insertion is a powerful strategy for the straightforward access of complex structures in an atom economical fashion.[1,2] Despite the low reactivity of C(sp^3)–H bonds, metal-catalyzed bond-insertion reactions have been described using Cu, Rh, and Ru carbenes prepared in situ from diazo compounds.[3] In contrast, the Au-mediated versions are scarce.[3a,4] The group of Pérez reported the first C(sp^3)–H insertion of gold(I) carbenes derived from ethyl diazoacetate to functionalize linear alkanes.[5,6] Later, the groups of Toste[7a] and Malacria[7b] demonstrated that gold(I) carbenes generated by enyne cyclizations undergo C–H insertions intramolecularly. The groups of Zhang,[8] Hashmi[9] and Malacria[10] also found that gold(I) vinylidene intermediates or α-oxo gold(I) vinylidenes undergo C–H insertion reactions to access complex hydrocarbon skeletons and functionalized cyclopentanones. Other C–H functionalizations have been reported using gold(I) carbenes generated from diazo compounds[11,12] or by different precursors.[13,14]

We have demonstrated that 7-substituted-1,3,5-cycloheptatrienes undergo retro-Buchner reaction in a formal decarbenation process to generate gold(I) carbenes, which undergo cyclopropanation, cycloaddition, and Friedel–Crafts annulations.[15] Our method is a safer and convenient alternative to the most common generation of metal carbenes from diazo-compounds,[16] since cycloheptatriene derivatives are thermally stable molecules that can be stored under ordinary conditions. Encouraged by our previous findings, we wondered whether gold(I) carbenes generated by retro-Buchner reaction would also undergo C(sp^3)–H bond insertions. However, it was previously observed that cycloheptatriene **1** reacts in presence of a gold(I) catalyst at 120 °C in 1,2-dichloroethane via decarbenation through norcaradiene **2** losing benzene to generate gold(I) carbene **3**, which reacts to give biscyclopropane **4** as the major product by the intermolecular cyclopropanation of **2** (Scheme 1 a).[15a] In addition, small amounts of indane **5** (8%) were obtained by intramolecular C–H insertion at the benzylic position. We postulated that the intramolecular C–H insertion could become the major pathway exploiting the Thorpe–Ingold effect, placing the C–H bond closer to the reactive gold(I) carbene carbon atom. To do so, we envisioned to introduce a quaternary carbon center adjacent to the C(sp^3)–H



Scheme 1. Precedents and substrate design for C(sp^3)–H bond insertion. C_6H_6 = benzene.

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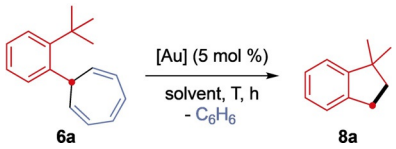
bond in cycloheptatriene **6** (Scheme 1 b). This would result in contracting (angle) Φ in gold(I) carbene **7** to ensure close proximity of the C(sp^3)–H bond to the gold(I) carbene enabling the formation of functionalized indane derivatives **8**.

Herein, we describe the scope of this C(sp^3)–H bond functionalization for the synthesis of a wide diversity of indanes and provide support of the mechanism by deuterium-labeling experiments, determination of the kinetic isotope effect, DFT calculations, as well as by generation of the proposed carbene intermediate under stoichiometric conditions from a well-characterized gold(I) carbenoid.

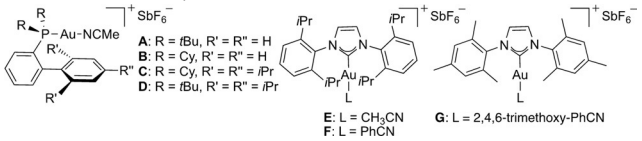
Results and Discussion

We first studied the reaction of 7-(2-(*tert*-butyl)phenyl)cyclohepta-1,3,5-triene (**6a**) to give indane **8a** with different Au^I complexes **A**–**G** at 120 °C in 1,2-dichloroethane (Table 1, entries 1–7). Among the screened catalysts, complex **F** proved to be the most suitable for this transformation (entry 6). Lowering the reaction temperature to 100 °C led to indane **8a** in excellent yield (entry 8). Changing the solvent to toluene, ethyl acetate or 1,4-dioxane led to lower yields of **8a** (entries 10–12).

Table 1. Synthesis of indane **8a** through C(sp^3)–H bond insertion.[a]

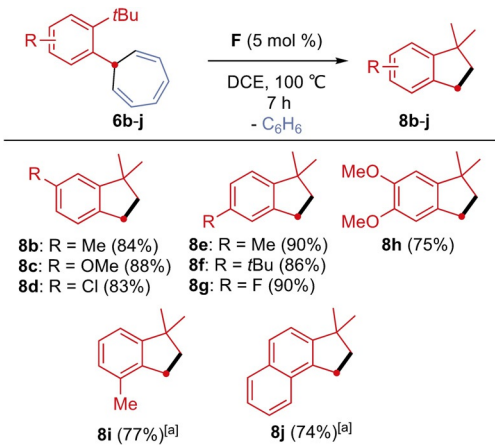


Entry	[Au]	Solvent	T [°C]	t [h]	**8a** yield [%][b]
1	A	DCE	120	7/18	51/52
2	B	DCE	120	7/18	55/60
3	C	DCE	120	7/18	18/22
4	D	DCE	120	7/18	15/15
5	E	DCE	120	7	80
6	F	DCE	120	7	86
7	G	DCE	120	7	trace
8	F	DCE	100	7	93 (85)[c]
9	F	DCE	80	7	72
10	F	toluene	100	7	44
11	F	EtOAc	100	7	50
12	F	1,4-dioxane	100	7	30



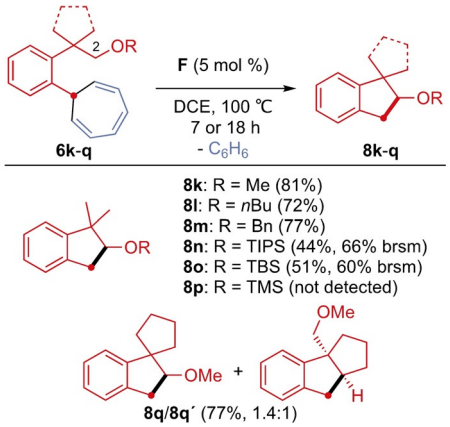
[a] **6a** = 0.2 mmol scale. 0.025 M. [b] Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yields in parentheses. DCE = 1,2-dichloroethane.

Both *para*- and *meta*-substituted cycloheptatrienes afforded the corresponding indane products (**8b**–**g**) in excellent yields under the optimized reaction conditions (100 °C, 7 h in 1,2-dichloroethane) (Scheme 2). Indane **8h** was isolated in slightly lower yield due to the competing cyclopropanation of a second molecule of starting material by the gold(I) carbene.[15a] The formation of indanes **8i** and **8j** required higher temperatures (120 °C) and longer reaction times (12 h). In these cases, the *ortho*-substituent or the benzo-fused ring provide enough steric hindrance to slow down the retro-Buchner process.



Scheme 2. Synthesis of indanes **8b–j** by insertion into C(sp^3)–H bonds. [a] Reactions at 120 °C for 12 h.

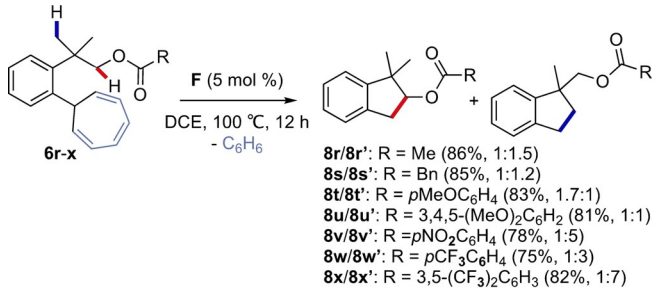
Activated C–H bonds alpha to an oxygen atom also participated in the retro-Buchner/C–H insertion reaction to yield 2-alkylether-substituted indanes (**8k**–**q**) (Scheme 3). The insertion reaction in compound **6m** takes place with complete site selectivity at the C-2 position rather than at the benzylic methylene. This result confirms the preferential formation of 5-membered over larger sized rings in metal-catalyzed intramolecular C–H insertion reactions.[17] 2-Silylether-substituted indanes **8n**–**o** were only obtained in moderate yields presumably due to the concomitant cleavage of the silicon protecting group. Indeed, when bulky triisopropylsilyl (TIPS) and *tert*-butyldimethylsilyl (TBS) protecting groups were replaced by the more labile trimethylsilyl (TMS) group, no C–H bond insertion was observed. Instead, only deprotected primary alcohol was recovered. Replacing the *gem*-dimethyl moiety by spiro-fused cyclopentane ring resulted in the formation of **8q**/**8q′** as a 1.4:1 mixture. Although the α-oxygen methylene C–H bonds are still



Scheme 3. Synthesis of indanes **8k–q** by insertion into C(sp^3)–H bonds with an α-oxygen. brms = based on the recovered starting material.

the most reactive, functionalization of the cyclopentane C–H methylene bonds competes leading to significant amounts of **8q′**.

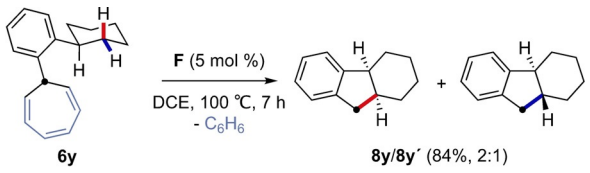
The fine tuning between electronic, steric and conformational factors for the preferred site and regioselectivity of C–H bond insertion reactions becomes more evident in the reactions of substrates **6r–x** (Scheme 4). The methyl C–H and the



Scheme 4. Insertion into competing methylene and methyl C(sp^3)–H bonds.

methylene C–H bonds compete in the reaction with the gold(I) carbene leading to indanes **8r–x** and **8r′–x′** in excellent 75–86% overall yields. In the case of R = Me or benzyl (Bn), although **8r′–s′** were obtained as the major products, considering statistical factors, insertion into methylene C–H bonds is 2.7–2:1 faster than that at the methyl C–H bonds. In the reaction of **6t–u** bearing esters with electron-donating groups, the preference for methylene C–H bond functionalization is even more pronounced (about 3–5 times faster). On the other hand, esters with electron-withdrawing groups slow down the C–H bond insertion at the methylene, leading to the preferred formation of **8v′–x′**.

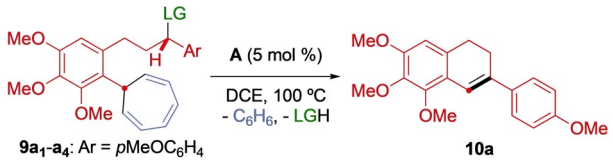
o-Cyclohexylphenyl cycloheptatriene **6y** undergoes insertion preferentially into the axial C–H bond to form *cis*-fused **8y** rather than *trans*-fused **8y′** (Scheme 5).



Scheme 5. Insertion into competing axial and equatorial C(sp^3)–H bonds.

To expand the scope of the C–H insertion of gold(I) carbenes, we attempted the synthesis of 6-membered rings. Thus, we studied the reaction of substrates of type **9** bearing a benzylic C–H bond in which further activation was provided by an α-OR group (Table 2). Substrates **9a$_1$–a$_2$** with hydroxy or acetate groups failed to give any product of C–H functionalization (entries 1–2). However, substrate **9a$_3$** with a TBS-protected secondary alcohol afforded dihydronaphthalene **10a** in 30% yield by C–H insertion at the benzylic position, followed by ROH elimination (entry 3). Methyl ether **9a$_4$** proved to be a better substrate, leading to **10a** in 71% of yield (entry 4).

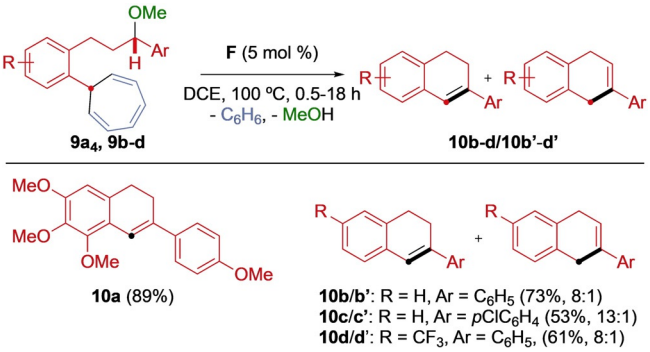
Table 2. Synthesis of dihydronaphtahlene **10a** through C(sp^3)–H bond insertion.



Entry	9	LG	*t* [h]	10a yield [%][a]
1	9a$_1$	OH	18	n.d.
2	9a$_2$	OAc	18	n.d.
3	9a$_3$	OTBS	18	30
4	9a$_4$	OMe	2.5	71

[a] Yields determined by ^{1}H NMR using 3,5-dimethylpyrazol as internal standard. LG = leaving group. TBS = *tert*-butyldimethylsilyl. n.d. = not detected.

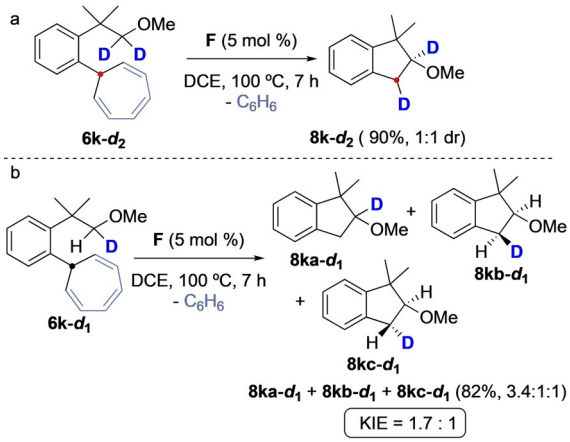
Further optimization of the reaction conditions revealed that gold complex **F** was the best catalyst allowing the isolation of dihydronaphtalene **10a** in 89% yield as a single double bond isomer (Scheme 6). Products **10b–d** were obtained in good yields (53–73%) together with small amounts of their double bond isomers **10b′–d′**.



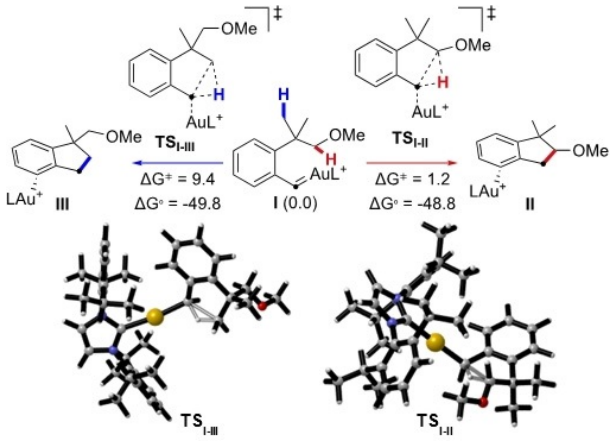
Scheme 6. Gold(I)-catalyzed synthesis of dihydronaphtalenes by C–H insertion reaction and elimination of methanol.

To shed light into the mechanism of the gold(I)-catalyzed retro-Buchner/C–H insertion reaction, we performed deuterium labelling experiments and measured the kinetic isotope effect (KIE).[18] Firstly, double deuterated cycloheptatriene **6k-*d*$_2$** was subjected to the gold(I)-catalyzed C(sp^3)–H functionalization reaction conditions (Scheme 7a). Both deuterium labels were incorporated into the final indane product **8k-*d*$_2$** according to an intramolecular reaction pathway. The KIE of the C–H insertion step was determined on monodeuterated cycloheptatriene **6k-*d*$_1$** (Scheme 7b). Under identical reaction conditions, compound **6k-*d*$_1$** gave a 3.4:1:1 mixture of indanes **8ka-*d*$_1$**, **8kb-*d*$_1$** and **8kc-*d*$_1$**, which corresponds to an overall KIE value of 1.7:1. This value is in agreement with a concerted three-center mechanism for a metal–carbene C–H insertion reaction, which usually shows KIE values in the order of 1–2.5.[19]

Recently, we have described the generation and characterization of aryl gold(I) carbenes from their corresponding gold(I)

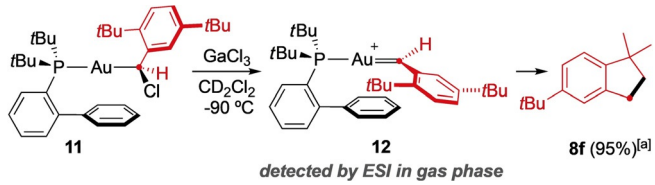


Scheme 7. a) Deuterium labelling and b) KIE experiments on the C–H insertion of **6k**.



Scheme 9. Calculated (DFT) reaction profile for the C–H insertion. L = *i*Pr. Free energies in kcal mol^{-1}.

carbenoids.[20] These reactive carbenes were found to be the genuine intermediates in the cyclopropanation of olefins by gold(I)-catalyzed retro-Buchner/cyclopropanation reaction. Hence, we synthesized gold(I) carbenoid complex **11** bearing a di-*tert*-butylphenyl group,[21] which was subjected to chloride abstraction with $GaCl_3$ at −90 °C (Scheme 8). The C–H insertion



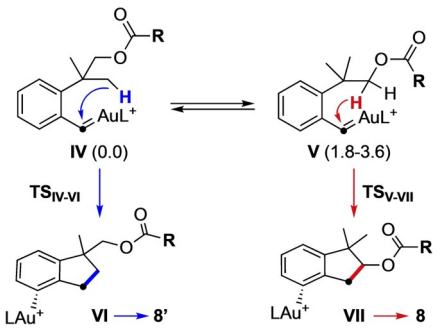
Scheme 8. Activation of gold(I) carbenoid **11** and formation of indane **8f**. [a] ^{1}H NMR yield calculated with diphenylmethane as internal standard.

took place immediately upon activation of gold(I) carbenoid **11** with $GaCl_3$ at −90 °C yielding cleanly indane **8f**. Gold(I) carbene **12** could not be detected by NMR spectroscopy because of the very fast intramolecular C–H insertion, although it was detected by ESI-MS of gold(I) carbenoid **11**.

The insertion of gold(I) carbenes into C(sp^3)–H bonds was further investigated theoretically by DFT calculations at M06, 6-31G(d) (C, H, N, O) and SDD (Au) level of theory, representing 1,2-dichloroethane solvent with PCM and starting from optimized gold(I) carbenes.[15c] First, we studied the selective formation of indane **8k** from **6k** (see Scheme 3). After the retro-Buchner reaction, highly reactive gold(I) carbene **I** could insert intramolecularly into the C–H bonds adjacent to oxygen (Scheme 9, red pathway) and/or C–H bonds of the methyl groups (Scheme 9, blue pathway) through three-center transition states $TS_{I–II}$ or $TS_{I–III}$, respectively.[22,23] Due to the donation of electron density from OMe to the electron-deficient carbon center in the transition state, the calculated free energy of activation to reach $TS_{I–II}$ ($\Delta G^{\ddagger} = 1.2$ kcal mol^{-1}) was found to be much lower than that for $TS_{I–III}$ ($\Delta G^{\ddagger} = 9.4$ kcal mol^{-1}). These results are consistent with the experimental selective formation of indane **8k** from **6k** by carbene C–H insertion. In addition, structures similar to intermediate **II** with gold(I) bound to the aromatic ring in a η^1-fashion, which was found to be the minimum (−48.8 kcal mol^{-1}) for the red pathway or in the methylene C–H insertion, were previously isolated and confirmed by single crystal X-ray diffraction by our group.[24]

Next, we studied the C–H insertion reaction with substrates **6r–t** and **6v** containing electron withdrawing ester substituents, which experimentally delivered the corresponding indanes as a mixture of **8r–t**, **8v** by carbene insertion into the methylene C(sp^3)–H adjacent to the ester group, and products **8r′–t′**, **8v′** by carbene insertion into the C–H of the methyl groups (see Scheme 4). Gold(I) carbenes **IV** and **V** are rotamers which can easily interconvert into each other and, respectively form (η^1-indane)gold(I) intermediate **VI** through $TS_{IV–VI}$ (blue pathway) leading to products **8′** or **VII** via $TS_{V–VII}$ (red pathway) to give products **8** (Scheme 10).

The nature of substituent R has a direct effect on the relative rates of the C–H insertion. For the acetate (R = Me), insertion into methyl C–H bond is slightly favored ($\Delta G^{\ddagger}_{IV–VI} = 10.6$ kcal mol^{-1} versus $\Delta G^{\ddagger}_{V–VII} = 11.3$ kcal mol^{-1}) (Table 3, entry 1), whereas for the benzoate, nearly identical free energies were found supporting a less selective formation of mixture **8s/8s′** (entry 2). As expected, the electron donating *p*-MeOC$_6$H$_4$ substituent has a stabilizing effect on $TS_{V–VII}$ favoring insertion into



Scheme 10. Calculated reaction profiles for the competitive C–H insertions into methyl (blue pathway, leading to product **8′**) and methylene (red pathway, leading to products **8**).

Table 3. Energies for the competitive C–H insertions into methyl (blue pathway, product **VI**→**8′**) and methylene (red pathway, product **VII**→**8**).[a]

Entry	R	$\Delta G^{\neq}_{\text{V–VII}}$ (**8**)	$\Delta G^{\neq}_{\text{IV–VI}}$ (**8′**)	Calcd **8**/**8′**[b]	Exptl **8**/**8′**[c]
1	Me	11.3	10.6	1:7.8	1:1.5
2	Ph	10.4	10.6	1:2.3	1:1.2
3	*p*-$MeOC_6H_4$	9.8	11.0	1.6:1	1.7:1
4	*p*-$NO_2C_6H_4$	11.4	10.6	1:8.7	1:5

[a] Free energy barriers in kcal mol^{-1}. [b] Product ratio calculated at 100 °C. [c] Product ratio obtained experimentally at 100 °C.

the methylene C(sp^3)–H bond (entry 3). In contrast, the electron withdrawing *p*-$NO_2C_6H_4$ substituent clearly inverts the selectivity ($\Delta G^{\neq}_{\text{IV–VI}} < \Delta G^{\neq}_{\text{V–VII}}$) (entry 4). These theoretical values are in qualitative agreement with the experimentally observed ratios of the formation of products **8** and **8′** (Table 3, columns 5 and 6).

Conclusion

Gold(I) carbenes generated by decarbenation of 7-aryl-1,3,5-cycloheptatrienes by retro-Buchner reaction undergo C(sp^3)–H bond insertion reactions to give access to highly functionalized indanes and dihydronapthalenes. Deuterium-labelling experiments and DFT calculations support a three-center transition state, as well as the origin of the insertion selectivity. In accordance with previous reports, electron-donating substituents adjacent to the C–H bond facilitate the insertion reaction. The C–H bond insertion has also been observed in a reaction of a gold(I) carbene generated from a well-characterized gold(I) carbenoid, which further supports the conclusion that the species involved in gold(I)-catalyzed retro-Buchner reactions belong to the family of electrophilic-metal carbenes.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbenes · C–H insertion · decarbenation · gold catalysis · indanes

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