

CHEMISTRY A European Journal



Accepted Article Title: Gold(I)-Catalyzed Intramolecular C(sp3)-H Insertion by Decarbenation of Cycloheptatrienes Authors: Antonio M. Echavarren, Xiang Yin, Giuseppe Zuccarello, and Cristina García-Morales This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article. To be cited as: Chem. Eur. J. 10.1002/chem.201900919 Link to VoR: http://dx.doi.org/10.1002/chem.201900919

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Gold(I)-Catalyzed Intramolecular C(sp³)–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-centered concerted mechanism for the C(sp³)–H functionalization process.

Introduction

The direct functionalization of aliphatic C(sp³)–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(sp³)-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(sp³)-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 in envne 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 from gold(I) carbenes generated from diazo compounds^[11,12] or by different precursors.^[13,14]

We have demonstrated that 7-substituted-1,3,5-heptatrienes undergo retro-Buchner reaction in a formal decarbenation process to generate gold(I) carbenes which undergo cycloaddition, cyclopropanation, and Friedel-Crafts annulations.^[15] Our method is a safer and convenient alternative to the most common generation of metal carbenes from diazocompounds,[16] since cycloheptatriene derivatives are thermally stable molecules that can be stored indefinitely under ordinary conditions. Encouraged by our previous findings, we wondered whether gold(I) carbenes generated by retro-Buchner

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reaction would also undergo C(sp³)-H bond insertions. However, we have 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 1a).^[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 guaternary carbon center adjacent to the C(sp³)–H bond in cycloheptatriene 6 (Scheme 1b). This would result in contracting (angle) Φ in gold(I) carbene 7 to ensure close proximity of the C(sp³)-H bond to the gold(I) carbene enabling the formation of functionalized indane derivatives 8.



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

Here we describe the scope of this C(sp³)–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 effects, 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 (Table 1, entry 6). Lowering the reaction temperature to 100 °C led to indane **8a** in excellent yield (Table 1,

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entry 8). Changing the solvent to toluene, ethyl acetate or 1,4dioxane led to lower yields of **8a** (Table 1, entries 10-12).

Table 1. Synthesis of indane 8a via C(sp³)-H bond insertion.^[a]

	6	[Au] (solve	5 mol %) ent, T, h C ₆ H ₆	8a	
entry	[Au]	solvent	T (ºC)	t [h]	8a yield [%] ^[b]
1	Α	DCE	120	7/18	51/52
2	в	DCE	120	7/18	55/60
3	С	DCE	120	7/18	18/22
4	D	DCE	120	7/18	15/15
5	Е	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 ¹H 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 1,2dichloroethane) (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 provides enough steric hindrance to slow down the retro-Buchner process.



Scheme 2. Synthesis of indanes 8b-j by insertion into C(sp³)–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-alkylethersubstituted 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 TIPS and TBS protecting groups were replaced by the more labile TMS group, no C-H bond insertion was observed. Instead, only deprotected primary alcohol was recovered. Replacing the gemdimethyl moiety by spiro-fused cyclopentane ring resulted in the formation of 8q/8q' as a 1.4:1 mixture. Although the a-oxygen methylene C-H bonds are still the most reactive, functionalization of the cyclopentane C-H methylene bonds competes leading to significant amounts of 8q'.



Scheme 3. Synthesis of indanes 8k-q by insertion into $C(sp^3)$ -H bonds with an α -oxygen.

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 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 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 (*ca.* 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'**.



Scheme 4. Insertion into competing methylene and methyl C(sp³)-H bonds.

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(sp³)-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 9a1-a2 with hydroxy or acetate groups failed to give any product of C-H functionalization (Table 2, entries 1-2). However, substrate 9a3 with a TBS-protected secondary alcohol afforded tetrahydronaphthalene 10a in 30% yield by C-H insertion at the benzylic position, followed by ROH elimination (Table 2, entry 3). Methyl ether 9a4 proved to be a better substrate, leading to 10a in 71% of yield (Table 2, entry 4).

Table 2. Synthesis of dihydronaphtahlene 10a via C(sp3)-H bond insertion.

Meo H Ar Meo OMe \mathbf{G} $\mathbf{9a_1} \cdot \mathbf{a_4}$: Ar = p MeOC ₆ H ₄		A (5 mol %) DCE, 100 °C - C ₆ H ₆ , - LGH	MeO MeO C	Me 10a
entry	9	LG	t [h]	10a yield [%] ^[a]
1	9a₁	ОН	18	n.d.
2	9a2	OAc	18	n.d.
3	9a₃	OTBS	18	30
4	9a₄	OMe	2.5	71

[a] Yields determined by ¹H NMR using 3,5-dimethylpyrazol as internal standard, LG = leaving group,

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'.



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 effects (KIE).[18] Firstly, double deuterated cycloheptatriene 6k-d2 was subjected to the gold(I)-catalyzed C(sp3)-H functionalization reaction conditions (Scheme 7a). Both deuterium labels were incorporated in the final indane product 8k-d2 according to an intramolecular reaction pathway. The KIE of the C-H insertion step was determined on monodeuterated cycloheptatriene 6k-d₁ (Scheme 7b). Under identical reaction conditions, compound 6k-d₁ gave a 3.4:1:1 mixture of indanes 8ka-d1, 8kb-d1 and 8kc-d1 which corresponds to an overall KIE value of 1.7:1, which is in agreement with the concerted three-centered mechanism for metal-carbene C-H insertion reactions that usually shows KIE in the order of 1-2.5.[19]



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

Recently, we have described the generation and characterization of aryl gold(I) carbenes from their corresponding gold(I) 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 GaCl₃ at -90 °C (Scheme 8). The C-H insertion took place immediately upon activation of gold(I) carbenoid 11 with GaCl₃ at -90 °C yielding cleanly indane 8f. Gold(I) carbene 12 could not be detected by NMR because of the very fast intramolecular C-H insertion, although it was detected by ESI-MS of gold(I) carbenoid 11.

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

The insertion of gold(I) carbenes into C(sp³)-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 1,2dichloroethane 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-centered transition states TS_{I-II} or $\textbf{TS}_{\textbf{I-III}},$ 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**_{HI} (ΔG^{\ddagger} = 1.2 kcal/mol) was found to be much lower than that for TSI-III $(\Delta G^{\ddagger} = 9.4 \text{ kcal/mol})$. 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) for the red pathway or in the methylene C-H insertion, were previously isolated and confirmed by single crystal diffraction by our group.^[24]



Scheme 9. Calculated (DFT) reaction profile for the C–H insertion. L = IPr. Free energies in kcal/mol.



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

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(sp³)–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 ($\Delta G^{\dagger}_{IV-VI}$ = 10.6 kcal/mol vs $\Delta G^{\dagger}_{V-VI}$ = 11.3 kcal/mol) (Table 3, entry 1), whereas for the benzoate, nearly identical free energies were found supporting a less selective formation of mixture **8**s/**8**s' (Table 3, entry 2). As expected, the electron donating *p*-MeOC₆H₄ substituent has a stabilizing effect on **TS**_{V-VII} favoring insertion into the methylene C(sp³)–H bond (Table 3, entry 3). In contrast, the electron withdrawing *p*-NO₂C₆H₄ substituent clearly inverts the selectivity ($\Delta G^{\dagger}_{IV-VI} < \Delta G^{\ddagger}_{V-VII}$) (Table 3, 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).

Table 3. Energies for	the competitive C-H	insertions into me	thyl (blue
pathway, product VI ≈ 8') and methylene (red p	bathway, product VII	≈ 8). ^[a]

entry	R	<mark>∆G[‡]v-vii</mark> (8)	∆G‡ _{IV-VI} (8')	Cal. 8/8' ^[b]	Exp. 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 ₆ H ₄	9.8	11.0	1.6:1	1.7:1
4	<i>p</i> -NO ₂ C ₆ H ₄	11.4	10.6	1:8.7	1:5

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

Conclusions

In summary, gold(I) carbenes generated by decarbenation of 7aryl-1,3,5-heptatrienes *via* retro-Buchner reaction undergo C(sp³)–H bond insertion reactions to give access to highly functionalized indanes and dihydronapthalenes. Deuterium labelling experiments and DFT calculations support a threecenter transition state and the origin of 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 family of electrophilic metal carbenes.

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We thank the Agencia Estatal de Investigación (AEI)/FEDER, UE (CTQ2016-75960-P and FPI predoctoral fellowship to C. G.-M.), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support.

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Keywords: gold catalysis • C-H insertion • carbenes • decarbenation • indane

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