Synthetic Methods

DOI: 10.1002/anie.201409970

Intramolecular C–H Activation through Gold(I)-Catalyzed Reaction of Iodoalkynes**

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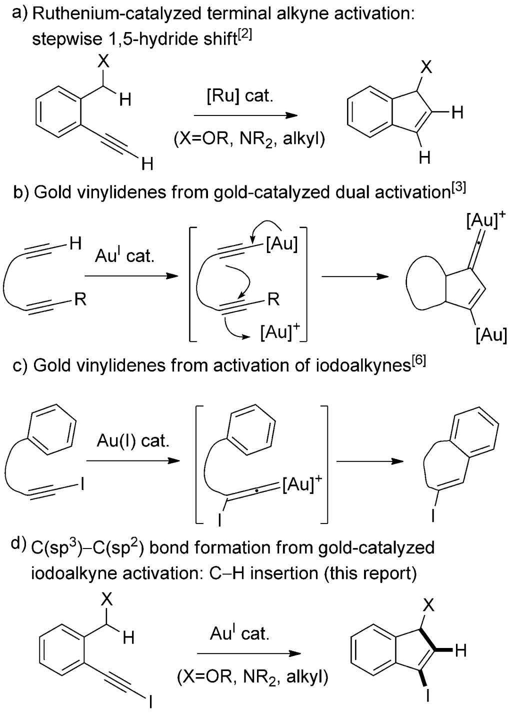
Abstract: *The cycloisomerization reaction of 1-(iodoethynyl)-2-(1-methoxyalkyl)arenes and related 2-alkyl-substituted derivatives gives the corresponding 3-iodo-1-substituted-1H-indene under the catalytic influence of IPrAuNTf$_2$ [IPr = 1,3-bis(2,6-diisopropyl)phenylimidazol-2-ylidene; NTf$_2$ = bis(trifluoromethanesulfonyl)imidate]. The reaction takes place in 1,2-dichloroethane at 80 °C, and the addition of ttbp (2,4,6-tri-tert-butylpyrimidine) is beneficial to accomplish this new transformation in high yield. The overall reaction implies initial assembly of an intermediate gold vinylidene upon alkyne activation by gold(I) and a 1,2-iodine-shift. Deuterium labeling and crossover experiments, the magnitude of the recorded kinetic primary isotopic effect, and the results obtained from the reaction of selected stereochemical probes strongly provide support for concerted insertion of the benzylic C–H bond into gold vinylidene as the step responsible for the formation of the new carbon–carbon bond.*

The search for new ways to access key reactive intermediates is key to advancing synthetic methodology. A number of processes relying on catalytic generation of metal vinylidenes are known.[1] C(sp^3)–C(sp^2) catalytic coupling reactions involving intermediate ruthenium vinylidenes have been presented.[2] Gold(I) catalysis has also been shown to be successful in a scenario in which dual gold catalysis plays a prevalent role.[3] Iodoalkynes are an interesting class of acetylenes endowed with remarkable structural features[4] and reactivity,[5] and have been proposed as precursors for gold vinylidenes.[6] Herein, the merging of iodoalkynes with gold(I)-catalysis to achieve C(sp^3)–H bond activation, through prior generation of iodovinylidenes, is documented (Scheme 1).



Scheme 1. Basis for the proposed C(sp^3)–H bond activation triggered by iodovinylidene generation from gold-catalyzed iodoalkyne isomerization.

The reactivity of 2-(iodoethynyl)benzyloxy derivatives towards gold(I) catalysts was explored to determine the feasibility of product formation, arising from a gold iodovinylidene[7] intermediate, through C–H insertion chemistry rather than involving the oxygen atom in addition processes. It is worth noting that these are demanding substrates, as the related non-iodine-substituted alkynes take part in gold(I)-catalyzed carboalkoxylation reactions.[8] Data are collected in Table 1 for gold-catalyzed reactions of **1a**, thus illustrating an initial screening in the search for efficient catalysts and reaction conditions to accomplish the desired C–H activation process.

Previously, the N-heterocyclic gold complex IPrAuNTf$_2$ was found to be an efficient and robust catalyst in the hydroarylation reaction of iodoalkynes, reactions aimed at the elaboration of heterocycles through 1,2-iodine shifts.[6b,c] The reactivity of IPrAuNTf$_2$ was tested in the target cycloisomerization of **1a** into **2a**. At room temperature, **2a** was not observed. Heating **1a** with IPrAuNTf$_2$ (5 mol %) at 80 °C in 1,2-dichloroethane (DCE) gave rise to the full disappearance of the iodoalkyne, but **2a** could not be isolated from the crude reaction mixture (entry 1). At this point two different actions were undertaken. Both the reactivity of gold catalysts, based on alternative ligands, and the effect of additives were explored. While the first approach did not led to satisfactory results (entries 2–4), the second was successful.[9] Gratifyingly, addition of the hindered ttbp base (ttbp = 2,4,6-tri-*tert*-

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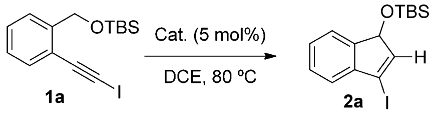
[**] Financial support by the Spanish MINECO (Grant CTQ2013-41511-P) is acknowledged. P.M.-P. thanks the Spanish Government for a FPU predoctoral fellowship. We thank Dr. Fernando Rodríguez (Univ. of La Rioja) for the X-Ray analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201409970.

Table 1: Cycloisomerization of **1a** into **2a**: Influence of the experimental conditions.



Entry[a]	Catalyst	Additive (equiv)	*t* [h]	Conv. [%][b]	Yield [%][b]
1	IPrAuNTf$_2$	–	1	100	[c]
2	JohnPhosAuNTf$_2$	–	24	10	0
3	(RO)$_3$PAuNTf$_2$	–	24	8	0
4	Ph$_3$PAuNTf$_2$	–	24	14	0
5	IPrAuNTf$_2$	ttbp (1)	9	100	62
6	IPrAuNTf$_2$	ttbp (0.5)	3.5	100	56
7	IPrAuNTf$_2$	ttbp (0.25)	2.5	100	60
8	IPrAuNTf$_2$	ttbp (0.1)	1	100	61
9	IPrAuNTf$_2$	ttbp (0.1)	9[d]	100	48
10	IPrAuNTf$_2$	ttbp (0.1)	24[e]	52	6

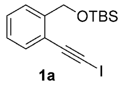
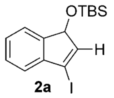
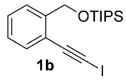
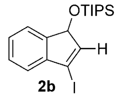
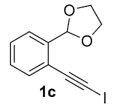
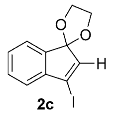
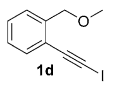
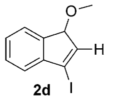
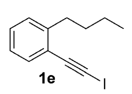
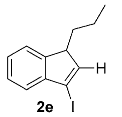
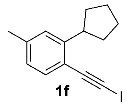
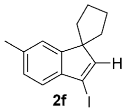
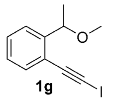
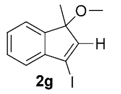
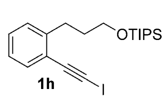
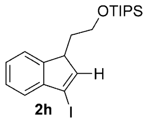
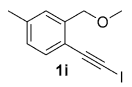
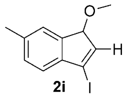
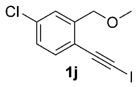
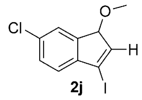
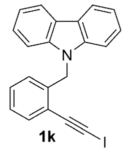
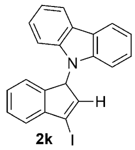
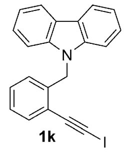
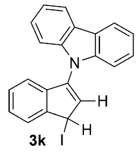
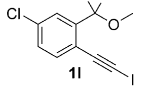
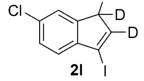
[a] Reaction conditions: 0.1 mmol of **1a**, 5 mol% of the catalyst, 0.1 M in DCE. [b] Yield and conversion estimated from ^{1}H NMR analysis of the crude reaction mixture upon addition of 1,3,5-trimethoxybencene, as internal standard. [c] Final product decomposes under the reaction conditions. [d] Reaction temperature 50 °C. [e] Reaction temperature 20 °C. DCE = 1,2-dichloroethane, IPr = 1,3-bis(2,6-diisopropyl)phenylimidazol-2-ylidene; NTf$_2$ = bis(trifluoromethanesulfonyl)imidate, TBS = *tert*-butyldimethylsilyl.

butylpyrimidine) allowed the identification of **2a** in the crude reaction mixtures (entries 5–10).[10] Further adjustment of the amount of added ttbp and the reaction time furnished an initial set of reaction conditions for the conversion of **1a** into **2a** (entry 8).[11] Decreasing the reaction temperature to 50 °C required a significantly extended reaction time for the complete consumption of **1a** and thus resulted in a lower yield (entry 9). The reaction conditions outlined in entry 8 of Table 1 were then used to obtain and isolate several products from different iodoalkynes **1**.

Interestingly, the targeted reaction is associated with the distinct reactivity of the iodine-substituted derivatives, and also provides support for the hypothesis that the iodoalkyne–iodovinylidene isomerization step takes place smoothly. The synthesized indene derivatives **2** are shown in Table 2, which also details the specific reaction conditions used for the synthesis of each of the assembled carbocyclic frames.[12] The cycloisomerization of **1** into **2** was conducted on a 0.2 mmol scale of the parent compound. The outcome for the reaction with and without addition of ttbp are reported (see methods B and A, respectively), thus highlighting the beneficial effect of this additive in accessing **2**, for all the given examples. The model compound **1a** gives rise to the desired cyclization in moderate yield, while the more sterically demanding **1b** affords the corresponding product in a significantly higher yield.[13] The acetal **1c** and the alkyl ether **1d** also react under these reaction conditions.[14]

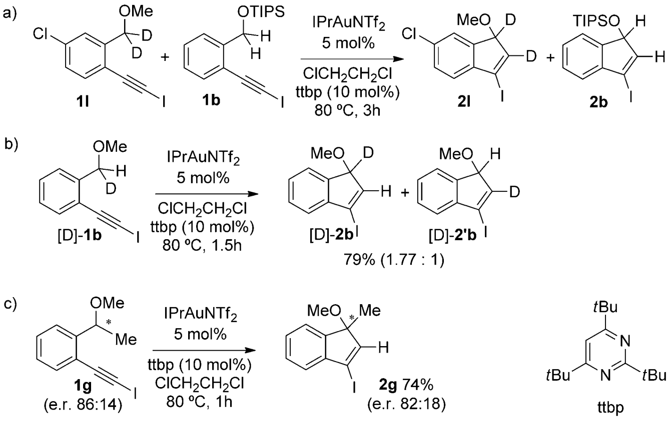
Moreover, the activation of the benzylic C–H bond in a simple linear alkyl chain gives the indene **2e** in high yield (Table 2, entry 5). Tertiary benzylic positions and substrates showing additional remote functionality, including a carbazole ring at the benzylic position, also undergo this reaction

Table 2: Indene derivatives through C–H bond activation.

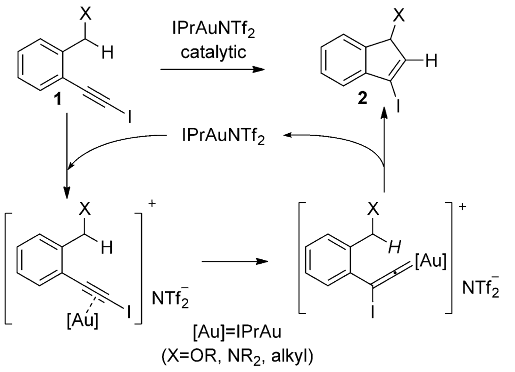
Entry	1	Method[a]	*t*	2	Yield [%][b]
1	 **1a**	A B	10 min 1 h	 **2a**	22 57
2	 **1b**	A B	15 min 1 h	 **2b**	26 91
3	 **1c**	A B	1 h 1 h	 **2c**	79 91
4	 **1d**	A B	10 min 1.5 h	 **2d**	45 87
5	 **1e**	A B	15 min 1 h	 **2e**	90 97
6	 **1f**	A B	1.5 h 2.25 h	 **2f**	89 93
7	 **1g**	A[c] B	– 1.5 h	 **2g**	– 84
8	 **1h**	A[d] B[d]	4 h 18 h	 **2h**	28 84
9	 **1i**	A[c] B	– 40 min	 **2i**	– 78
10	 **1j**	A B	35 min 1 h	 **2j**	89 96
11	 **1k**	A B	24 h 1.5 h	 **2k**	32 78
12	 **1k**	A B	24 h 1.5 h	 **3k**	41[e] 91[e]
13	 **1l**	B[d]	4 h	 **2l**	72

[a] Method A: 0.2 mmol of **1**, IPrAuNTf$_2$ (5 mol%), 0.1 M in DCE, 80 °C. Method B: The same as for Method A, but adding ttbp (10 mol%). [b] Yield of isolated **2**. [c] The product decomposes under the reaction conditions. [d] Additional 5 mol% of IPrAuNTf$_2$ added. [e] **2k** isomerizes into **3k** using Et$_3$N treated silica gel for the isolation.

(entries 6–12). The reaction of **1l**, the dideuterated-benzyl analogue of **1j**, gives **2l** in reasonable yield, thus retaining the deuterium, which becomes equally split between the benzylic and vinylic positions. Notably, a more sluggish reaction for **1l**, in comparison to that of **1j**, was observed and required a longer reaction time and higher catalyst loading (entries 10 and 13).



Scheme 2. Mechanistic insights: further experimental data. TIPS = triisopropylsilyl.



Scheme 3. Proposed direct C–H insertion reaction into gold iodovinylidenes catalytically generated from iodoalkynes.

The mechanism for this new reaction was analyzed by using a crossover reaction, evaluating the magnitude of the primary kinetic isotopic effect (PKIE) from an intramolecular competition experiment[15] and testing the robustness of the stereochemistry. Relevant information is depicted in Scheme 2. As depicted in Scheme 2a, H/D scrambling was not observed when mixture of **1b** and the doubly deuterium labeled compound **1l** was reacted with IPrAuNTf$_2$. Inspection of the crude reaction mixture by NMR spectroscopy was conclusive in this regard.[12] This result suggests an intramolecular character of the hydrogen-transfer process. In the same way, the catalytic activation of [D]-**1b** (Scheme 2b) provides a value of 1.77 for k_H/k_D, which was easily estimated upon recording NMR data for the mixture of compounds obtained.[12] Furthermore, the reaction of the enantioenriched chiral probe **1g** provides key information to assess the timing of the C–H bond-cleavage and the C–C bond-making events. Interestingly, the stereochemistry remained unaltered.[16] Overall, these data do not support alternative gold-catalyzed C–C bond-forming events involving a stepwise hydride-transfer process to give the intermediate gold vinylidene.[17] At the same time, the absence of H/D scrambling processes, the recorded PKIE value, which is in line with those reported for C–H insertion reactions involving metal carbenes,[18] or ruthenium(II) and platinum(II) vinylidenes[2a] generated from terminal alkynes, as well as the retention of stereochemistry for the enantioenriched probes are in keeping with the mechanistic proposal outlined in Scheme 3. The proposed generation of an iodovinylidene intermediate leading to product formation in one step is in accordance with collected data. The proposed mechanism differs from those documented for indene-formation processes involving metal vinylidenes generated upon activation of terminal alkynes using platinum[2a,19] or ruthenium.[2a,b]

In short, a new catalytic transformation of iodoalkynes is presented. The resulting iodine-substituted indenes are versatile building blocks, which are not easy to assemble using other approaches such as carbocycle iodination. From a mechanistic persepctive, this study reveals a distinct reaction path for C–H insertion reactions involving metal vinylidenes, through use of an appropriate gold catalyst and switching from hydrogen to iodine as the substituent in the parent alkyne precursor. It also impacts ongoing efforts to access gold vinylidene, a growing and promising research area, by contributing to efforts in search of alternative precursors.

Experimental Section

Method B (Table 2): The substrate **1** (1 equiv, 0.2 mmol) is dissolved in 1,2-dichloroethane (2 mL) under argon atmosphere. Then, 2,4,6-tri-*tert*-butyl pyrimidine (0.1 equiv, 0.02 mmol) and IPrAuNTf$_2$ (0.05 equiv 0.01 mmol) are added consecutively. The mixture is stirred and heated to 80 °C until total depletion (TLC) of **1** is observed. The reaction cooled to room temperature, was concentrated under vacuum, and the residue was purified by flash chromatography (specific conditions for each substrate are given in the Supporting Information)

Received: October 10, 2014
Revised: November 28, 2014
Published online: January 21, 2015

Keywords: alkynes · C–C coupling · cyclization · gold · reaction mechanisms

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[9] For details on reaction conditions see the Supporting Information.

[10] Other bases with different features were tested (see page 3 in the Supporting Information). Only weak bases such as 2,6-dichloropyridine or norbornene resulted in full conversion, although less efficiently than ttbp to generate **2a**. Less hindered or more basic ones did not result in full conversion. It is likely that the role of the base implies a subtle balance between the catalyst reactivity and the decomposition of the product. Overall, the use of the base results in a robust and reproducible reaction and higher yields. Interestingly, in some cases it was possible to monitor by the formation and fast decomposition of the product (by TLC) in the absence of the base.

[11] Different metal catalysts were tested under this experimental protocol, with AuCl and $PtCl_2$ among them. For both the consumption of **1a** occurred after reacting for 1 h and 4 h, respectively. The formation of **2a** was evident by NMR analysis of the crude reaction mixtures but, in both cases additional products were present.

[12] For the synthesis and characterization of **1** and **2**, including copies of the spectra, and mechanistic details, see the Supporting Information.

[13] **1a** nicely isomerizes to **2a** in high yield, however, competitive formation of minor amounts of an alternative cyclization product, likely from oxygen getting involved as nucleophile, was noticed in the crude reaction mixture. These two products turned out to be difficult to separate and **2a** was isolated in moderate yield. For the catalytic conversion of **1b** into **2b**, no evidence of alternative by-product was found by NMR analysis of the corresponding crude reaction mixture.

[14] 1-(bromoethynyl)-2-(methoxymethyl)benzene, an analogue of **1d**, was tested under the same reaction conditions. No cyclization was observed and the starting material was recovered essentially unaltered. The cyclization of 1-(iodoethynyl)-2-(1-methoxyethyl)cyclohex-1-ene resulted in a sluggish reaction where no cycloisomerization was observed.

[15] The magnitude of the internal intramolecular isotope effect might be slightly slower than the intermolecular isotope effect. See: K. B. Wiberg, L. H. Slaugh, *J. Am. Chem. Soc.* **1958**, *80*, 3033 – 3039.

[16] A stepwise transformation involving strong ion pairing could not be safely disregarded on this basis. However, the counteranion effect was tested without noticeable deviation of the behavior as shown in Scheme 2c. Thus, when **1g** (e.r. 86:14) was treated with 5 mol% of IPrAuCl/$AgSbF_6$ and ttbp (10 mol%) in DCE at 80 °C, for 0.5 h, **2g** was isolated in 53% yield (e.r. 81:19). This result might provide additional evidence for the concerted insertion step.

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[18] This value is in good agreement with those recorded and computed for insertion reactions of $C(sp^3)$–H bonds into metal carbenes. See for instance: a) P. Wang, J. Adams, *J. Am. Chem. Soc.* **1994**, *116*, 3296 – 3305; b) H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063 – 3070; c) E. Nakamura, N. Yoshikai, M. Yamanaka, *J. Am. Chem. Soc.* **2002**, *124*, 7181 – 7192.

[19] Theoretical calculations predicted platinum vinylidene being generated in the rate-limiting step for this tertiary C–H benzylic insertion reaction. See: G. B. Bajracharya, N. K. Pahadi, I. D. Gridnev, Y. Yamamoto, *J. Org. Chem.* **2006**, *71*, 6204 – 6210.