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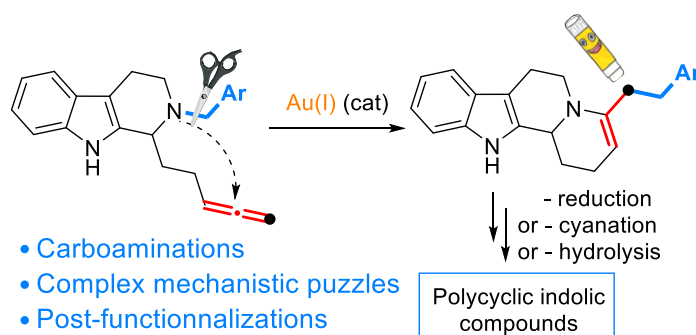
Gold-Catalyzed Carboamination of Allenes by Tertiary Amines Proceeding with Benzylic Group Migration

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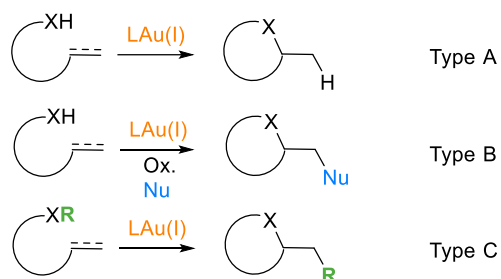
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Abstract. Tertiary amines bearing a benzyl-type group (CH_2Ar) undergo Au(I)-catalyzed intramolecular addition to allenes. A formal 1,3-transfer of the CH_2Ar group takes place during the cyclization. As demonstrated by both experimental and DFT studies, these unprecedented intramolecular carboaminations involve two consecutive [3,3] rearrangements *via* a dearomatized intermediate. Because of the poor stability of the enamine products, protocols were developed to convert them *in situ* to more stable polycyclic chiral compounds.

After almost two decades of intense research, homogeneous gold catalysis has established itself as an inescapable field in organic synthesis.^{[1],[2]} The π -acidic properties Au(I) complexes enable a vast range of catalytic reactions, leading to a huge structural diversity. Among the popular reactivity of these complexes, hydrofunctionalizations of unsaturated substrates hold a salient position. The diversity of nucleophiles combined with various unsaturated electrophilic partners lead to an efficient access to a number of important heterocycles.^[3] In most cases, the reactions evolve through a general similar pathway combining 1) activation of the unsaturation, 2) addition of the nucleophile and 3) protodeauration reaction. This strategy was very efficiently applied to hydrofunctionalization^[4] of alkynes,^[5] allenes^[6] or alkenes (Scheme 1, type A).^[7] In some reactions though (mainly from alkenes), it is possible to oxidize the intermediate gold species and promote an additional functionalization by a nucleophile resulting most of the time into a formal double heterofunctionalization (Scheme 1, type B).^{[1h, 8],[9]} However, reactions performed with functionalized nucleophiles (no X-H bond), for which the protodeauration step cannot take place, may lead to both cyclization and a transfer of the functional group *via* intriguing mechanisms (Scheme 1, type C). In these reactions, no external oxidant is needed

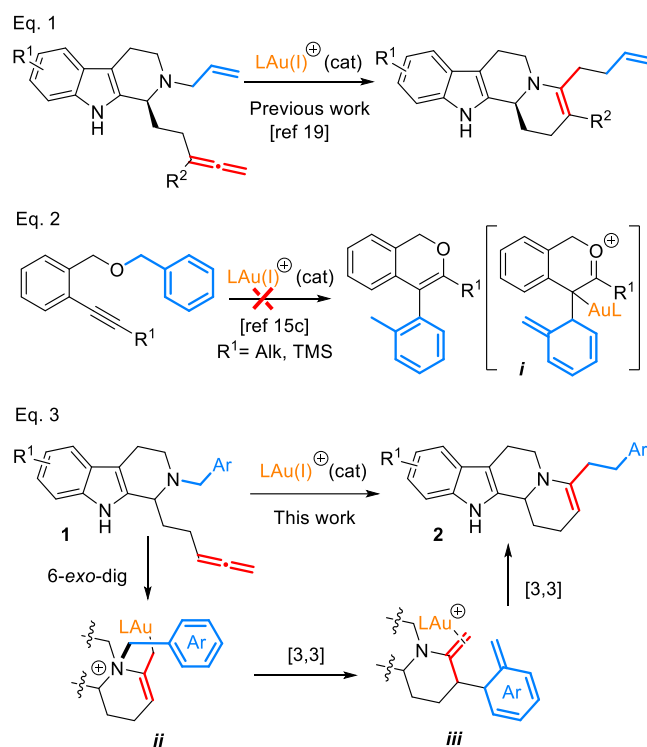
since no redox cycle operates. A number of chemical functions have been shown to efficiently transfer during the cyclizations of *O*-, *N*- or *S*- centered nucleophiles to mostly alkynes electrophiles, such as alkyl,^[10] silyl,^[11] sulfonyl,^[12] arylidene,^[13] propargyl^[14] or allyl groups.^[10a, 15] All these reactions raise questions regarding the associative or dissociative nature of the mechanism, which appears to be strongly depends on the heteroatom and the migratory group.



Scheme 1. General heterocyclization processes with Au(I) catalysts

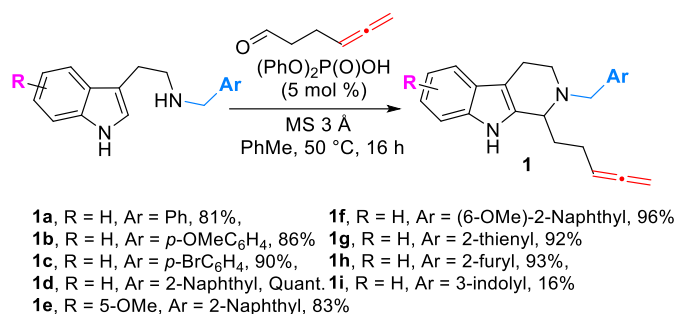
Over the last years, we have developed a number of Au(I)-catalyzed strategies to the functionalization of indoles.^{[16],[17]} Recently, we pioneered a new type of intramolecular cyclizations from *N*-allyltetrahydro- β -carbolines that undergo gold-catalyzed carboamination of their allene moiety,^[18] resulting in cyclization products with the concomitant 1,3-migration of the allyl group (Scheme 2, eq. 1).^[19] Seeking to question the possibility to do related cyclizations with more challenging migrating groups, we hypothesized that benzylic groups should lead to structurally resembling compounds, with the migration of the whole CH_2Ar group. To our knowledge, cyclizations occurring with transfer of a benzyl group have been reported using platinum catalysis in the course of the synthesis of benzofurans,^[20] but there is only a single example of a cyclization occurring with a transfer of a *p*-MeOBn upon gold catalysis, reported only in a review.^{[21],[22]} In addition, precedents from Hashmi evidenced the difficulty to transfer benzyl groups in related reactions,^[15c] likely because of the energetically demanding dearomatization in intermediate *i* (Eq. 2).^[23] It is however not to exclude that some aryls groups may be able to participate to such reactions, and we anticipated that tetrahydro- β -carbolines **1** could lead to indolo[2,3-*a*]quinolizidines **2** *via* the ammonium salt *ii* and the dearomatized intermediate *iii*, that would further undergo an additional [3,3] sigmatropic rearrangement (Scheme 2, eq. 3).

In this paper, we show that a range of CH_2Ar groups can be efficiently transferred and lead to valuable molecules. The whole process was also applied to different scaffolds. A DFT study assessed the mechanistic hypothesis.^[24]



Scheme 2. Au(I)-catalyzed carboamination of allenes

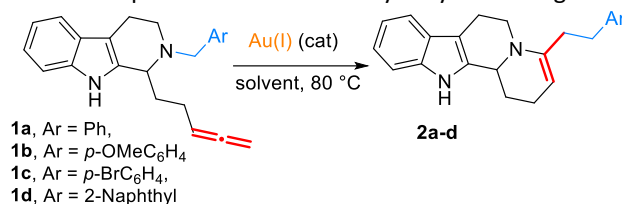
We first prepared in good yields a series of tetrahydro- β -carbolines **1** by using the Pictet-Spengler reaction^[25] between a series of tryptamines protected by a range of benzylic groups and hexa-4,5-dienal.



Scheme 3. Synthesis of tetrahydro- β -carbolines **1**

A suitable catalytic system was sought using tetrahydro- β -carbolines **1** as substrates (Table 1). We first engaged **1a** in the reaction with the JohnPhosAuSbF₆.MeCN catalyst^[26] **3a** in toluene (Table 1, entry 1), but no conversion was observed. The effect of an electron donating group and a halogen were checked using compounds **1b** and **1c** but, again, no reaction took place (Entries 2-3). Those results confirmed that benzylic groups embedding a phenyl ring do not undergo the dearomatization step included in the mechanistic hypothesis. On the other hand, when the naphthylmethyl-protected tetrahydro- β -carboline **1d** was used, a high NMR conversion of **1d** in **2d** was monitored, in particular when the solvent was switched to DCE (entries 4-7). Both the Gagosz catalyst **3b**^[27] and the IPrAuBF₄ complex **3c** showed lower activity (entries 8-9). Further studies revealed that the reaction necessitates shorter reaction time (4 h, entry 10) but that a lower catalyst loading results in a significant decrease in the catalytic activity despite prolonged reaction times (entry 11).

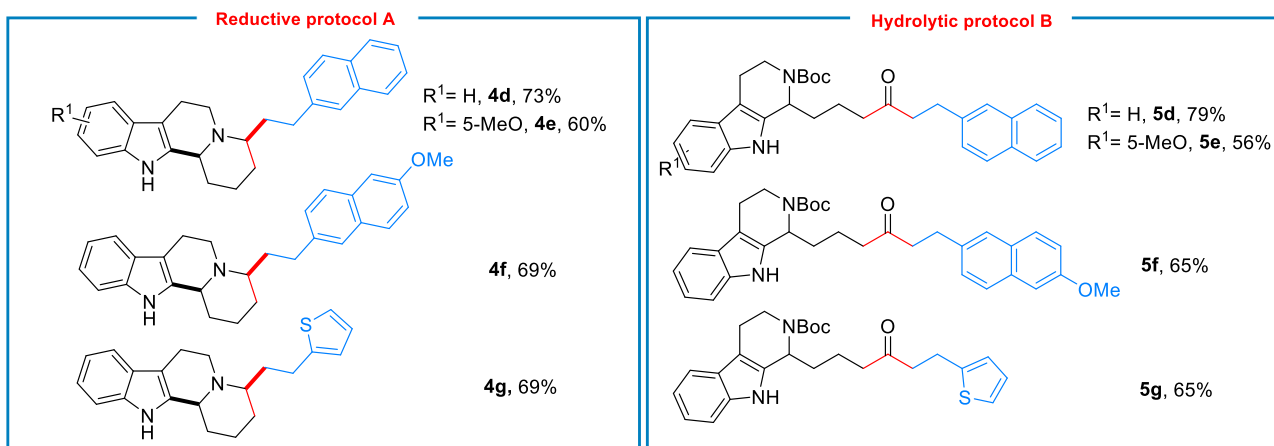
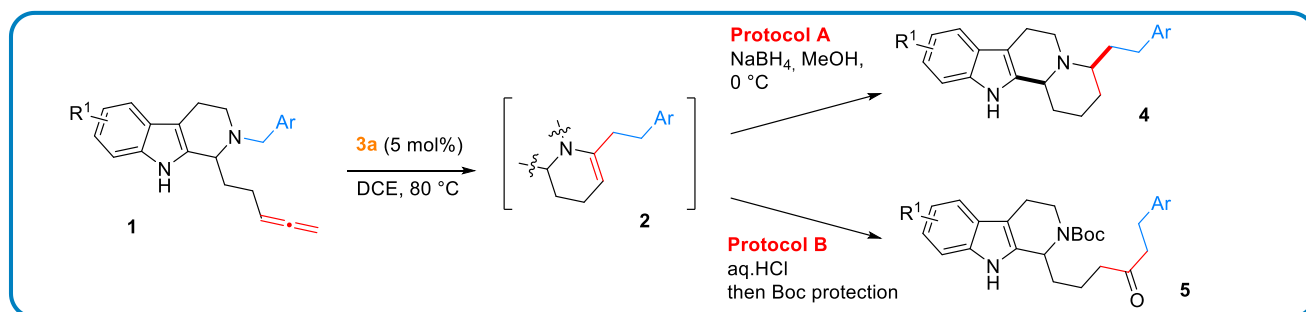
Table 1. Optimization of the catalytic system using **1a-d**



Entry	1	cat (mol %)	solvent	conv (%) ^a
1	1a	3a (5)	PhMe	2a , 0
2	1b	3a (5)	PhMe	2b , 0
3	1c	3a (5)	PhMe	2c , 0
4	1d	3a (5)	PhMe	2d , 50
5	1d	3a (5)	DCE	2d , 100
6	1d	3a (5)	THF	2d , 65
7	1d	3a (5)	DMF	2d , 35
8	1d	3b (5)	DCE	2d , 35
9	1d	3c (5)	DCE	2d , 0
10	1d	3a (5)	DCE	2d , 100 ^b
11	1d	3a (2.5)	DCE	2d , 60 ^c



a) Measured by ¹H NMR. Reactions were performed for 16 h. b) Reaction performed over 4 h. c) Reaction performed over 24 h.



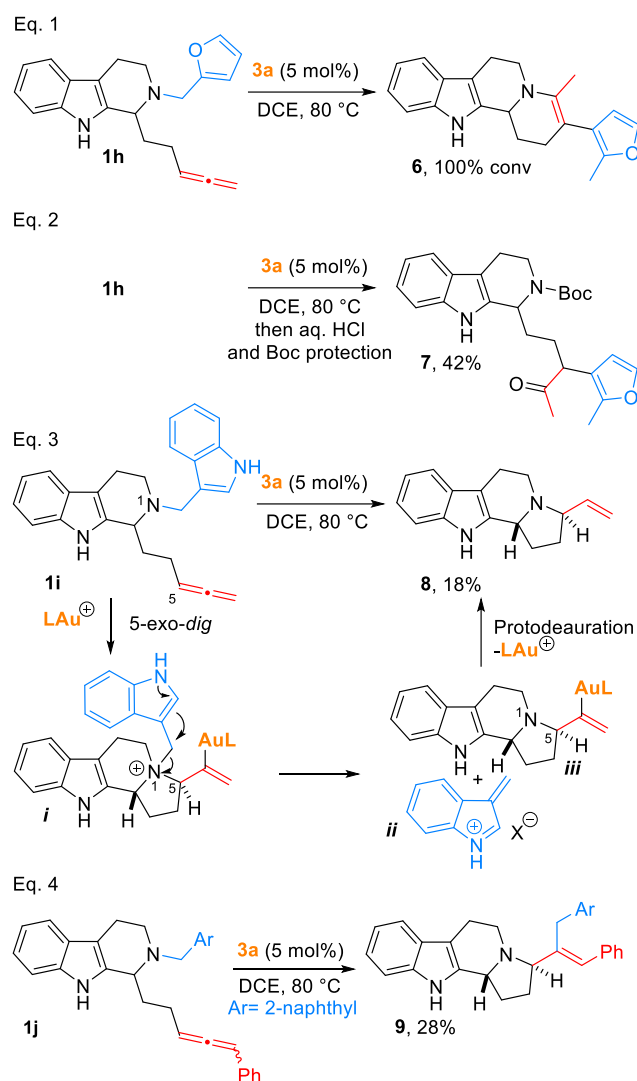
Scheme 4. Scope of the Reaction

As we observed in our previous studies,^[19] the enamine nature of product **2d** complicates its purification and isolation because of its high reactivity. For this reason, we established two different protocols to directly convert compounds **2d** into a stable product (Scheme 4). In a first approach, we directly reduced the enamine resulting from the carboamination to the corresponding amine by addition of NaBH₄ and MeOH after completion of the Au(I)-catalyzed reaction. This resulted in the formation of compound **4d** as a single diastereoisomer in 73% yield (See the Supporting Information for optimization of the reduction). NOESY studies revealed that compound **4d** is *cis*-configured.

In a second valorization strategy of the unstable enamine product **3d**, we added aqueous HCl to promote its hydrolysis and protected *in situ* the resulting amine with a Boc group to lead to the stable ketone **5d** in 79% yield.^[28] At the end, the product obtained results from a formal carbonylation of the allene, though the mechanism evolves through a carboamination. This constitutes an interesting approach, since direct carbonylation of allenes systems is, to our knowledge, not reported in the literature, in sharp contrast with hydration^[29] and carboalkoxylation^[30] with gold, or other transition metals.^{[31],[32]}

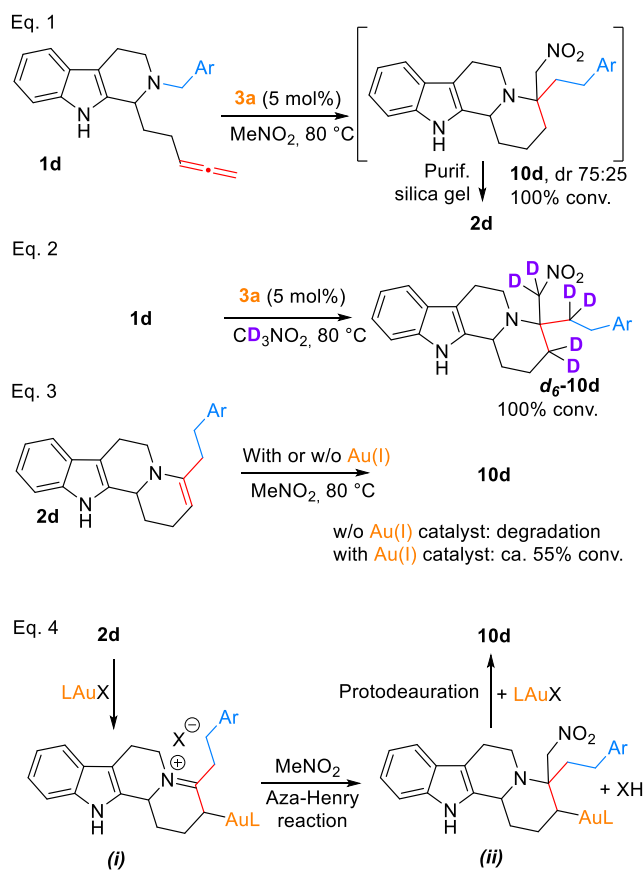
We next engaged other tetrahydro- β -carbolines **1** in the gold-catalyzed carboamination and applied for each substrate both the reductive and the hydrolytic protocols. The reaction tolerated the presence of a methoxy group at position 5 of the indole ring, resulting in the isolation of both **4e** and **5e**, in 60% and 56% yield, respectively. We also confirmed that the 7-methoxynaphthylmethyl group allows the carboamination process to **4f** in 69% yield. When the acidic workup was applied, product **5f** was obtained in 65% yield. Finally, the 2-thienylmethyl moiety also participated in the reaction, leading to **4g** and **5g** in good yields.

Interestingly, the analogous compound **1h** bearing a furylmethyl group undergoes the cyclization but delivered very selectively compound **6** instead of the expected compound **2h** (Scheme 5, eq. 1), likely stemming from a direct rearomatization (see intermediate *iii*, Scheme 2) and not a [3,3] rearrangement. This compound is however poorly stable on silica gel but could be fully characterized as a mixture with the catalyst (See the Supporting Information). When the hydrolysis workup B was applied to the crude mixture, compound **7** was obtained in 42% yield after Boc protection (eq. 2). Interestingly, the tetrahydro- β -carboline **1i** also evolved through an original pathway, leading to compound **8** as the main identifiable product of the reaction, that we previously obtained using palladium catalysis^[33] (eq. 3). Most likely, this products arises from the 5-*exo*-trig cyclization of the amine to the allene^[34] leading to intermediate *i*, followed by the cleavage of the nitrogen-indolylmethyl bond, forming an azafulvenium ion *ii* and protodeauration of intermediate *iii* by mean of the azafulvene ion. Finally, tetrahydro- β -carboline **1j** featuring a 1,3-disubstituted allene (see the Supporting Information for its synthesis) also led to unique reactivity (eq. 4).^[35] Upon exposure of **1j** to Au(I)-catalyzed conditions compound **9** was obtained in 28% yield as a single diastereomer, along with other non-identified compounds. NOESY experiments confirmed the *trans* configuration between both stereogenic centers and the *E* configuration for the olefin. This product again results from a 5-*exo*-trig cyclization with the delivery of the benzylic moiety at the central carbon atom of the initial 1,2-propadienic system.



Scheme 5. Au(I)-catalyzed cyclizations with furyl and indolyl substituents and 1,3-disubstituted allene

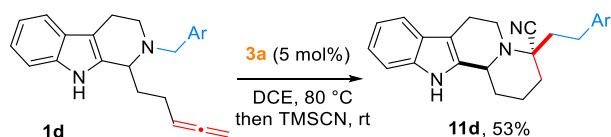
During the optimization process, an interesting observation arose from cyclization experiments performed from **1d** in nitromethane with catalyst **3a** (Scheme 6, eq. 1). This reaction furnished the nitro compound **10d** with full conversion as a couple of diastereomers (dr 75/25). This compound likely results from the nucleophilic addition of nitromethane to the intermediate enamine **2d**. It is however not stable on silica gel and undergoes elimination leading to the final product **2d**. Because of its intrinsic instability, compound **10d** could be characterized only as the crude product without removal of the catalyst (see the Supporting Information) and its structure was also confirmed by HRMS. Interestingly, when the reaction was performed in deuterated nitromethane, the ^1H NMR spectra of the product fitted that of **10d**, with however the disappearance of the two protons adjacent to the nitro group and of two additional CH_2 (eq. 2).



Scheme 6. Using MeNO₂ as solvent

In order to confirm that **10d** is indeed formed from enamine **2d** and if the Au(I) catalyst plays a role in its formation, a batch of enamine **2d** (as pure as possible despite its instability, see the Supporting Information) was then stirred at 80 °C in deuterated nitromethane in the presence or absence of the gold catalyst (eq. 3). In the absence of the catalyst, despite the full conversion of **2d**, the reaction showed only traces of **10d** and led mostly to degradation. On the contrary, in the presence of catalyst **3a**, the formation of **10d** was confirmed, even if the reaction was not complete (ca 55% conv.), confirming the role of the Au(I) catalyst in this step. Nitro-Mannich reactions have already been catalyzed by Lewis acids,^[36] but to our knowledge, this behavior is not common for enamines in Au(I) catalysis and has never been documented. Our hypothesis is that enamine **2d** coordinates the Au(I) complex to generate iminium (*i*), that is trapped by the nitromethane in the course of the Aza-Henry reaction leading to (*ii*). Finally, protodeauration generates the final product **10d** (eq. 4). The cyclization performed in deuterated nitromethane corroborates well this hypothesis.

Since these results in nitromethane showed that a C-centered nucleophile could act as a trapping agent, we next attempted to trap the enamine product **2d** with trimethylsilylcyanide. The addition of TMSCN after the Au(I)-catalyzed cyclization of **1d** gratifyingly led to the formation of the cyanide **11d**, isolated with 53% yield as a single diastereomer (Scheme 7). NOESY NMR analysis showed that the cyanide was delivered on the same side of the enamine than when NaBH₄ was used. In contrast with compound **10d**, **11d** showed great stability both on silica gel and upon storage.



Scheme 7. Extension of the reactivity to the cyanation of intermediate product 2d. Ar= 2-naphthyl

In order to secure the initial mechanistic hypothesis, we first verified experimentally that the reaction operates solely *via* an intramolecular mechanism by using cross experiments (see the Supporting Information).

The model cyclization of tetrahydro- β -carbolines **1a** (Ar = Ph) and **1d** (Ar= 2-naphthyl) were studied by DFT computations with the JohnPhos ligand on the gold atom and compared with those reported earlier with a vinyl group^[19] (see the Supporting Information for details). All energies are Gibbs free energies in kcal/mol at 353 K including a solvent correction for dichloromethane. The computed mechanistic options are shown in Figure 1. Starting from the allene gold(I) complex **A**, a 6-*exo*-dig cyclization leads to the allylgold species **B**. A suprafacial [3,3]-sigmatropic shift of the CH₂R group provides the *exo*-enamine gold complex **C**. A second [3,3]-sigmatropic shift transforms the latter into the *endo*-enamine gold complex **D**. Alternatively, electrophilic cleavage of the Csp³-Au bond of **B** by the CH₂R group leads to **D** directly, but this could be only modeled with R = vinyl. From **C**, one can imagine a proton elimination that would lead to the allylgold species **E**. Protodemetalation finally gives **F**, which is actually the isolated product when R = vinyl. On the other hand, a simple dissociation of the active species LAu⁺ from **D** delivers **H** (=compounds **2**), which is experimentally obtained when R = 2-naphthyl (**H_d**=**2d**). Another scenario to get **2** would be the dissociation of LAu⁺ from **C** to give **G**, followed by a [3,3]-sigmatropic shift (Cope rearrangement).

The formation of **B** through **TS_{AB}**, appears kinetically and thermodynamically much more favorable with R = vinyl. The second step requires 25.2 kcal/mol of free energy of activation to reach **TS_{BC}** with R = vinyl, 22.1 kcal/mol with R = Ph and 18.1 kcal/mol with R = 2-naphthyl.^[37] There is a strong difference in the exergonicity of this step, which is very strong with R = vinyl (-31.4 kcal/mol), weak with R = Ph (-2.7 kcal/mol) and average with R = 2-naphthyl (-12.5). This can be explained by the loss of aromaticity in the latter two cases compared to the former. This loss is complete with R = Ph, hence a weak exergonicity, and partial with R = 2-naphthyl, meaning an average exergonicity.

With R = vinyl, the third step seems inaccessible, as reaching **TS_{CD}** would necessitate 38.0 kcal/mol. Reaching **D** from **B** through **TS_{BD}** is in fact even more difficult since a barrier of 39.5 kcal/mol would have to be overcome. Complex **C** could then give **G** and finally **H** through **TS_{GH}**, but this last step demands as much as 31.2 kcal/mol of free energy of activation. The last scenario in this case is the protodemetalation via **E** to give **F**, which is indeed the product observed experimentally with R = vinyl.^[19]

The R = 2-naphthyl showcases an interesting and subtle balance that rationalizes the different outcome compared to R = vinyl. On one hand, the loss of aromaticity is only partial, so it does not hamper the formation of **C**. On the other hand, the recovery of aromaticity facilitates the final Cope transposition that was impossible with R = vinyl.

The case of R = 2-furyl is also interesting and provides valuable confirmation of the existence of dearomatized intermediates **C** since this compound necessarily stems from the **A-B-C-E-F** pathway, similarly to the case of R = vinyl. The reaction from **1i** leading to **8** also testifies that the 5-*exo*-trig initial addition of the amine to the allene is thermodynamically favored over the 6-*exo*-dig addition, but is in most cases unproductive and reversible. This was the case in our previous studies with allyl groups, where the 5-*exo*-trig addition ($\Delta G_{353} = 1.6$ kcal/mol, **Ik** -19.4 kcal/mol) was calculated to be favored over the 6-*exo*-dig addition ($\Delta G_{353} = 7.3$ kcal/mol, -22.2 kcal/mol).^[19] On the contrary, with R = indolyl, intermediate **li** is probably formed easily but evolves to compound **8** because of the electron-density of the indolyl moiety (see Scheme 5, eq. 3). Conversely, the formation of **9** would result from the same pathway, through the formation of intermediate **Ij** (R= 2-naphthyl, see the Supporting Information for exact structure) and a direct transfer of the benzylic group from the nitrogen atom to the vinylgold(I), highlighting another possibility in this mechanistic puzzle.

In conclusion, we have reported a new type of carboamination reaction of allenes with tertiary amines, leading to unstable enamine products that were converted to stable polycyclic scaffolds *via* a reductive treatment or an acidic hydrolysis protocol. This set of results is a proof of concept that allenes can undergo carboaminations of amines with the transfer of a benzylic group, with interesting mechanistic pathways ongoing and original elementary steps, such as the dearomatization/cope rearrangement sequence. These steps could be assessed by DFT calculations and experimentally verified by the reaction of a number of starting material that probed the mechanistic pathways.

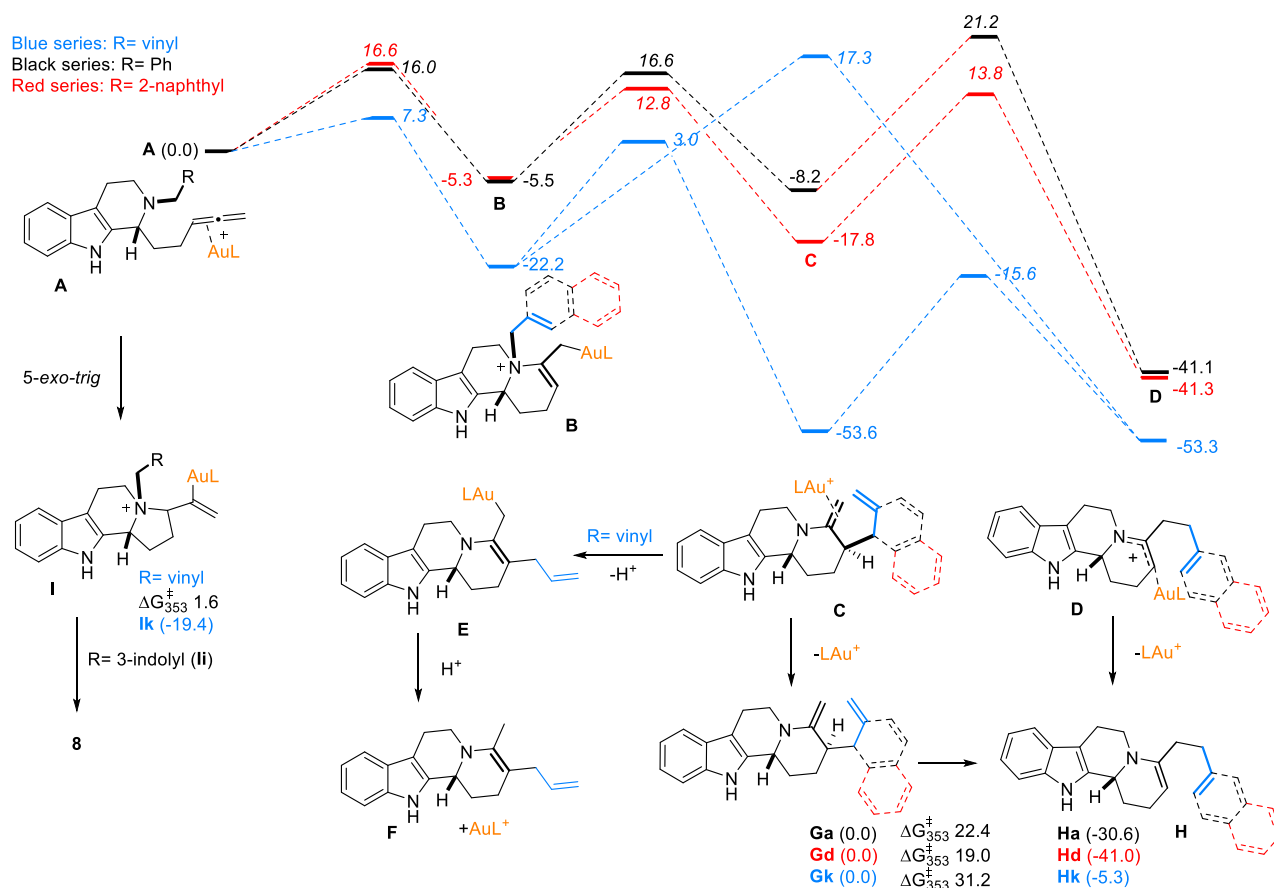


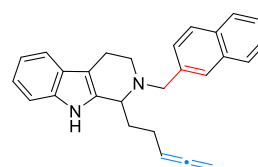
Figure 1. Free Energy Profile ($\Delta G_{353}^{\ddagger}$, kcal/mol) Relative to Complex A (free energies of the transition states are in italics)

Experimental Section

Details of the experimental procedures, spectroscopical data, NMR spectra and computational data.

General procedure 1 for the synthesis of tetrahydro- β -carbolines **1:** A mixture of *N*-Benzyl tryptamine (1 equiv.), (PhO)₂PO₂H (0.1 equiv.) and 3 Å molecular sieves (70 mg for 0.15 mmol of starting material, powdered) in toluene was stirred for 5 min at room temperature under an argon atmosphere. Subsequently, aldehyde (2 equiv.) was added, and the mixture was stirred at 50 °C for the 16 h under an argon atmosphere. After the reaction was completed, the reaction mixture was filtered over celite path. The filtrate

was concentrated under *vacuum* and purified by flash chromatography to give the desired product **1**.



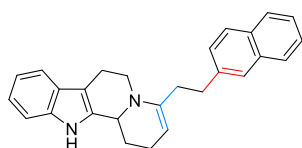
2-(naphthalen-2-ylmethyl)-1-(penta-3,4-dien-1-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole **1d**: Prepared according to the general procedure 1 from

2-(1*H*-indol-3-yl)-*N*-(naphthalen-2-ylmethyl)ethan-1-amine (415 mg, 1.38 mmol), hexa-4,5-dienal (271 mg, 2.76 mmol), (PhO)₂PO₂H (34 mg, 0.138 mmol) and 3 Å molecular sieves (660 mg) in toluene (19 mL). **1d** was obtained after column chromatography on silica gel (eluent: Petroleum ether/EtOAc, 90/10) as an oil (428 mg, 1.13 mmol, 82 %).

IR (neat) ν_{\max} = 3406, 3053, 2935, 2843, 1953, 1685, 1465, 1446, 857, 821, 741 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ = 7.88-7.77 (m, 3H, H_{ar}), 7.73 (s, 1H, H15), 7.68 (brs, 1H, H9), 7.61 (dd, J = 8.5, 0.5 Hz, 1H, H_{ar}), 7.57-7.52 (m, 1H, H_{ar}), 7.51-7.43 (m, 2H, H_{ar}), 7.36-7.30 (m, 1H, H_{ar}), 7.22-7.09 (m, 2H, H_{ar}), 5.08 (quint., J = 6.6 Hz, 1H, H12), 4.61 (td, J = 3.3, 6.7 Hz, 2H, H13), 3.93 (s, 2H, H14), 3.81-3.73 (m, 1H, H1), 3.35-3.22 (m, 1H, H3a), 3.06-2.90 (m, 2H, H3b and H4a), 2.65-2.54 (m, 1H, H4b), 2.28-2.09 (m, 2H, H11), 2.03-1.79 (m, 2H, H10). ^{13}C NMR (75 MHz, CDCl_3) δ = 208.7 (C_{q} , C_{ar}), 137.5 (C_{q} , C_{ar}), 136.0 (C_{q} , C_{ar}), 135.3 (C_{q} , C_{ar}), 133.5 (C_{q} , C_{ar}), 133.0 (C_{q} , C_{ar}), 128.0 (CH, C_{ar}), 127.8 (CH, 2 C_{ar}), 127.5 (CH, 2 C_{ar}), 127.5 (C_{q} , C_{ar}), 126.1 (CH, C_{ar}), 125.7 (CH, C_{ar}), 121.6 (CH, C_{ar}), 119.5 (CH, C_{ar}), 118.2 (CH, C_{ar}), 110.8 (CH, C_{ar}), 108.1 (C_{q} , C_{ar}), 90.1 (CH, C12), 75.4 (CH_2 , C13), 57.7 (CH_2 , C14), 55.9 (CH, C1), 44.6 (CH_2 , C3), 33.9 (CH_2 , C10), 24.7 (CH_2 , C11), 17.9 (CH_2 , C4). HRMS (ESI) m/z : calc for $\text{C}_{27}\text{H}_{27}\text{N}_2$ [$\text{M}+\text{H}$] $^+$ 379.2174, found 379.2174.

General procedure 2 for cyclization: The corresponding tetrahydro- β -carboline **1** (1 equiv.) and **3a** (5 mol%) were placed in a Schlenk tube and flushed with cycles of *vacuum*/argon (3 times). The DCE was added and the reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was filtered over celite and concentrated under *vacuum* to give the desired product **2**.

Application to the synthesis of 4-(2-(naphthalen-2-yl)ethyl)-



1,2,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine **2d**. Prepared according to the general procedure 2 from **1d** (20 mg,

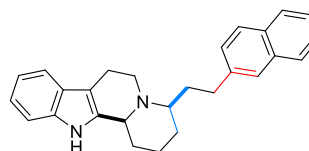
0.053 mmol) and catalyst **3a** (2.0 mg, 2.6 μmol), **2d** was obtained as a crude yellow solid (22 mg, 100 % NMR yield) that was not further purified. NMR data were obtained after a fast purification on silica gel (eluent: PhMe/MTBE gradient): ^1H NMR (500 MHz, CDCl_3) δ = 7.83-7.74 (m, 3H, $3H_{\text{ar}}$), 7.65 (s, 1H, H15), 7.50 (d, J = 7.6 Hz, 1H, H_{ar}), 7.46-7.39 (m, 2H, H_{ar}), 7.37 (d, J = 8.2 Hz, 1H, H21), 7.34-7.29 (m, 1H, H_{ar}), 7.15 (t, J = 7.7 Hz, 1H, H_{ar}), 7.10 (t, J = 7.1 Hz, 1H, H_{ar}), 4.63 (s, 1H, H12), 4.29 (d, J = 8.9 Hz, 1H, H1), 3.44-3.38 (m, 1H, H3a), 3.34-3.37 (m, 1H, H3b), 3.08-2.92 (m, 2H, H14), 2.88-2.76 (m, 2H, H3), 2.71-2.62 (m, 1H, H13a), 2.50-2.42 (m, 1H, H13b), 2.14-2.02 (m, 2H, H10a and H11a), 2.02-1.89 (m, 2H, H10b and H11b). ^{13}C NMR (75 MHz, CDCl_3) δ = 144.6 (C_{q} , C_{ar}), 139.9 (C_{q} , C_{ar}), 136.2 (C_{q} , C_{ar}), 135.3 (C_{q} , C_{ar}), 133.8 (C_{q} , C_{ar}), 133.6 (C_{q} , C_{ar}), 132.1 (C_{q} , C_{ar}), 127.9 (CH, C_{ar}), 127.7 (CH, C_{ar}), 127.6 (CH, C_{ar}), 127.6 (CH, C_{ar}), 126.5 (CH, C_{ar}), 126.0 (CH, C_{ar}), 125.2 (CH, C_{ar}), 121.6 (CH, C_{ar}), 119.5 (CH, C_{ar}), 118.2 (CH, C_{ar}), 111.0 (CH, C_{ar}), 109.3 (C_{q} , C_{ar}), C 102.3 (CH, C12), 54.4 (CH, C1), 44.4 (CH_2 , C3), 36.1 (CH_2 , C13), 35.1 (CH_2 , C14), 26.0 (CH_2 , C10), 22.3 (CH_2 , C11), 22.1 (CH_2 , C4). HRMS (ESI) m/z : calc for $\text{C}_{27}\text{H}_{27}\text{N}_2$ [$\text{M}+\text{H}$] $^+$ 379.2174, found 379.2174.

General procedure 3 for cyclisation and *in situ* reduction: The corresponding carboline **1** (1 equiv.) and **3a** (5 mol%) were placed in a Schlenk tube and flushed with cycles of *vacuum*/argon (3 times). The DCE was added and

the reaction mixture was stirred at 80 °C for 4 h. After completion, MeOH was added and the reaction cooled to 0 °C. Then NaBH_4 (1.1 equiv.) was added and the reaction mixture stirred at 0 °C for 1 h. After completion, the reaction mixture was concentrated under *vacuum*. The crude mixture was purified by flash chromatography to give the desired product **4**.

4-(2-(naphthalen-2-yl)ethyl)-1,2,3,4,6,7,12,12b-

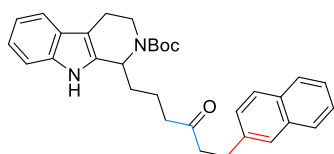
octahydroindolo[2,3-a]quinolizine (**4d**):



Prepared according to the general procedure 3 from **1d** (138 mg, 0.36 mmol) and catalyst **3a** (2.0 mg, 18

μmol), in DCE (3.6 mL), NaBH_4 (15.0 mg, 0.40 mmol) and MeOH (3.6 mL), **4d** was obtained after column chromatography on silica gel (eluent: Petroleum ether/EtOAc, 60/40) as an oil (100 mg, 0.26 mmol, 73 %). IR (neat) ν_{\max} = 3409, 3198, 2932, 1599, 1453, 1264, 816, 732, 700 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ = 7.85-7.78 (m, 3H, 3 H_{ar}), 7.71 (br s, 1H, H9), 7.68 (s, 1H, H15), 7.51 (d, J = 7.6 Hz, 1H, H_{ar}), 7.48-7.43 (m, 2H, 2 H_{ar}), 7.40 (dd, J = 0.9 and 8.2 Hz, 1H, H_{ar}), 7.31 (d, J = 7.9 Hz, 1H, H_{ar}), 7.15 (t, J = 7.6 Hz, 1H, H_{ar}), 7.11 (t, J = 7.3 Hz, 1H, H_{ar}), 3.58-5.51 (m, 1H, H3a), 3.49 (d, J = 11.0 Hz, 1H, H1), 3.02-2.93 (m, 2H, H4a and H14a), 2.93-2.84 (m, 1H, H14b), 2.84-2.77 (m, 1H, H4b), 2.59-2.51 (m, 1H, H22), 2.51-2.41 (m, 1H, H3b), 2.15-1.92 (m, 4H, H10a, H11a and H13), 1.85-1.78 (m, 1H, H12a), 1.75-1.53 (m, 3H, H10b, H11b and H12b). ^{13}C NMR (125 MHz, CDCl_3) δ = 140.3 (C_{q} , C_{ar}), 136.1 (C_{q} , C_{ar}), 135.8 (C_{q} , C_{ar}), 133.7 (C_{q} , C_{ar}), 132.0 (C_{q} , C_{ar}), 128.0 (CH, C_{ar}), 127.7 (CH, C_{ar}), 127.6 (C_{q} , C_{ar}), 127.5 (CH, C_{ar}), 127.4 (CH, C_{ar}), 126.2 (CH, C_{ar}), 126.1 (CH, C_{ar}), 125.2 (CH, C_{ar}), 121.3 (CH, C_{ar}), 119.3 (CH, C_{ar}), 118.1 (CH, C_{ar}), 110.9 (CH, C_{ar}), 108.3 (C_{q} , C_{ar}), 58.1 (CH, C22), 52.7 (CH, C1), 49.4 (CH_2 , C3), 33.6 (CH_2 , C14), 30.2 (CH_2 , C10), 28.4 (CH_2 , C13), 28.2 (CH_2 , C11), 21.1 (CH_2 , C4), 19.8 (CH_2 , C12). HRMS (ESI) m/z : calc for $\text{C}_{27}\text{H}_{29}\text{N}_2$ [$\text{M}+\text{H}$] $^+$ 381.2331, found 381.2340.

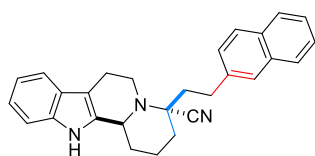
General procedure 4 for cyclisation and *in situ* hydrolysis and protection: The corresponding carboline **1** (1 equiv.) and **3a** (5 mol%) were placed in a Schlenk tube and flushed with cycles of *vacuum*/argon (3 times). The DCE was added and the reaction mixture was stirred at 80 °C for 4 h. After completion, the reaction cooled to 0 °C and HCl_{aq} 1.0 M (2.0 equiv.) was added dropwise. After 1 h Et_3N (10 equiv.) was added and the reaction mixture stirred at 0 °C for 5 min. Then Boc_2O (1.5 equiv.) was added and the reaction mixture was allowed to warm up to room temperature and was further stirred for 3 h. After completion, the layers were separated, the aqueous phase was extracted with EtOAc (2x). The combined organics phases were dried over MgSO_4 and concentrated under *vacuum*. The crude mixture was purified by flash chromatography to give the desired product **5**. The NMR spectra of these compounds present the characteristic signals of rotamers.



tert-butyl 1-(6-(naphthalen-2-yl)-4-oxohexyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (**5d**):

Prepared according to the general procedure 4 from **1d** (107 mg, 0.28 mmol) and catalyst **3a** (10.9 mg, 14 μ mol), in DCE (2.8 mL), HCl_{aq.} 1.0 M (560 μ L, 0.56 mmol), Et₃N (393 μ L, 2.82 mmol) and Boc₂O (92 mg, 0.42 mmol) **5d** was obtained after column chromatography on silica gel (eluent: Petroleum ether/EtOAc, 80/20) as an oil (110 mg, 0.26 mmol, 79 %). IR (neat) ν_{max} = 3320, 2972, 2934, 1684, 1663, 1414, 1159, 1031, 733, 701 cm^{-1} . ¹H NMR (500 MHz, CDCl₃) δ = 8.36 and 8.06 (m, 1H), 7.82-7.78 (m, 1H), 7.78-7.73 (m, 2H), 7.61 (s, 1H), 7.49-7.41 (m, 3H), 7.31 (d, J = 7.8 Hz, 2H), 7.16 (t, J = 7.0 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 5.39-5.03 (m, 1H), 4.55-4.21 (m, 1H), 3.19-2.97 (m, 3H), 2.93 - 2.71 (m, 3H), 2.69-2.61 (m, 1H), 2.56-2.37 (m, 2H), 1.85-1.67 (m, 4H), 1.50 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ = 210.4 (C_q), 154.4 (C_q), 138.6 (C_q), 136.1 (C_q), 134.7 (C_q), 133.7 (C_q), 132.2 (C_q), 128.2 (CH), 127.8 (C_q), 127.7 (CH), 127.6 (CH), 127.2 (CH), 127.0 (C_q), 126.6 (CH), 126.2 (CH), 125.5 (CH), 121.8 (CH), 119.5 (CH), 118.1 (CH), 111.7 (CH), 111.1 (CH), 80.1 (C_q), 51.3 and 50.3 (CH), 44.2 (CH₂), 42.7 and 42.5 (CH₂), 38.9 and 37.7 (CH₂), 34.6 and 34.1 (CH₂), 30.1 (CH₂), 28.6 (CH₃), 21.6 and 21.3 (CH₂), 20.3 (CH₂). HRMS (ESI) m/z : calc for C₃₂H₃₇N₂O₃ [M+H]⁺ 497.2804, found 497.2813.

Gold-catalyzed carboamination and in situ cyanation: The



carboline **1d** (50 mg, 0.13 mmol) and **3a** (5.1 mg, 6.6 μ mol) were placed in a Schlenk tube and flushed with cycles of vacuum/argon (3 times).

DCE (1.3 mL) was added and the reaction mixture was stirred at 80 °C for 4 h. After completion, the reaction cooled to 0 °C. Then TMSCN (33.2 μ L, 0.27 mmol) was added and the reaction mixture stirred at 0 °C for 4 h. After completion, the reaction mixture was concentrated under vacuum. The crude mixture was purified by flash chromatography on silica gel (eluent: Petroleum ether/EtOAc, 70/30) to give **10d** as an oil (28.3 mg, 0.07 mmol, 53 %).

IR (neat) ν_{max} = 3416, 2924, 2845, 2318, 1454, 1265, 819, 734 cm^{-1} . ¹H NMR (500 MHz, CDCl₃) δ = 7.87-7.80 (m, 3H), 7.77 (brs 1H), 7.67 (s, 1H), 7.53-7.44 (m, 3H), 7.38-7.33 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 3.86 (d, J = 11.5 Hz, 1H), 3.51 (dd, J = 5.1, 11.6 Hz, 1H), 3.06-2.90 (m, 3H), 2.85-2.79 (m, 1H), 2.62 (dt, J = 3.8, 11.7 Hz, 1H), 2.45 (ddd, J = 5.2, 12.1, 14.0 Hz, 1H), 2.32 (ddd, J = 5.1, 12.0, 14.2 Hz, 1H), 2.16 (d, J = 12.3 Hz, 1H), 2.10 (d, J = 12.1 Hz, 1H), 2.02-1.87 (m, 3H), 1.61 (dq, J = 4.8, 12.2 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 138.4 (C_q), 136.3 (C_q), 134.6 (C_q), 133.8 (C_q), 132.8 (C_q), 128.5 (CH), 127.8 (CH), 127.6 (CH), 127.2 (C_q), 127.1 (CH), 126.5 (CH), 126.3 (CH), 125.6 (CH), 121.8 (CH), 119.8 (CH), 119.0 (C_q), 118.3 (CH), 111.0 (CH), 108.4

(C_q), 61.2 (C_q), 56.8 (CH), 45.5 (CH₂), 40.2 (CH₂), 34.6 (CH₂), 30.0 (CH₂), 29.4 (CH₂), 22.1 (CH₂), 21.3 (CH₂). HRMS (ESI) m/z : calc for C₂₈H₂₈N₃ [M+H]⁺ 406.2283, found 406.2285.

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