Synthesis of Indenes by the Tandem Gold(I)-Catalyzed Claisen Rearrangement/Hydroarylation Reaction of Propargyl Vinyl Ethers

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Abstract. The tandem gold(I)-catalyzed propargyl Claisen rearrangement/hydroarylation reaction of suitable propargyl vinyl ethers, followed by in situ reduction of the resulting carbonyl group, provides functionalized indenes in good to excellent yields. The reaction occurs at room temperature in dichloromethane in the presence of 3 mol % [IPrAuCl]/$AgBF_4$ as the best catalytic system. With phosphine ligands no cyclization of the allene intermediate instead occurs. A variety of substituents and functional groups present on the substrate are tolerated. The effect of the aryl ring substituents and the results of a DFT computational study suggest that the final hydroarylation is the rate determining step of this cascade process. Further in situ chain elongation, prior final work up of the tandem process, can be carried out by Wittig olefination of the aldehyde functionality, thus incrementing the diversity of the products obtained.

Introduction

The development of efficient methods for the synthesis of indenes (benzocyclopentadienes)[1] continues to attract interest among the organic chemists' community as these compounds show a variety of biological activities, including antitumor, anticonvulsant, antiallergic, anti-hypercholesterolemic, fungicidal, herbicidal, and antimicrobial activities.[2] The indene framework is also found in natural products (Figure 1),[3] and it finds application in material science,[4] and in the preparation of ligands for metal complexes, e.g. ligands for tailored metallocene complexes used to catalyze olefin polymerization.[5]

Metal-catalysis has been widely exploited to build this important carbocycle through a variety of processes,[1a, 1k-w] including those based on the [1,2]- or [1,3]-rearrangement and carbocyclization of propargylic esters and carbonates.[6] Given the high efficiency of Au(I) in activating triple bonds,[7] gold-catalysis has been exploited, too, for the synthesis of indenes by such an approach,[8a-b],[9] while other methods based on gold(I)-catalysis include the carbocyclization of 1-alkynyl-2-(methoxymethyl)benzene derivatives,[8c-e], the carbocyclization of 1,5- and 1,6-enynes embodying an aryl ring,[8f-j] the C_{sp3}-H bond activation in diarylacetylene derivatives,[8k] the formal (3+2) cycloaddition between allenes and aryl gold(I)-carbenes,[8l] tandem transformations of 1,5-diynes embodying an aryl ring via a gold-vinylidene intermediate,[8m-o] and a few other multicomponent processes.[8p-r]

We have recently reported that suitably substituted propargyl vinyl ethers **1** undergo a propargyl Claisen rearrangement[10] followed by a Nazarov cyclization when subjected to gold(I)-catalysis, which efficiently provided functionalized cyclopentadienes **2** fused with various *N*-hetero- and

carbocycles.[11] [Schema 1, (a)] In this process, the gold-catalyzed [3,3]-rearrangement generates a gold-allene complex which, once formed, immediately undergoes the 4π-electrocyclization plausibly via the corresponding pentadienyl cation to form the final product.[12] While in the rearrangement of propargylic esters the final products are cyclopentenones o cyclopentadienyl alkanoates,[9] the tandem propargyl Claisen rearrangement/Nazarov reaction provides cyclopentadienes bearing, on one side chain, an aldehyde group which could be subjected to further in situ elaboration for chain elongations. Given the importance of indenes, and in continuation of our study on gold-catalyzed rearrangement processes involving propargyl alcohol derivatives,[13] we decided to evaluate whether the same approach could be used for the construction of such important ring systems by exploiting the rearrangement of 3-aryl-substituted propargyl vinyl ethers **3** [Scheme 1, (b)]. Gold-catalyzed cascade processes which form indenes, involving the [3,3]-rearrangement of propargylic ester derivatives followed by cyclization of the gold-allene complex intermediate,[8a-b] as well as the direct Au(I)-catalyzed hydroarylation of allenes,[8b] have been reported. However, the achievement of our synthetic objective was not so obvious as the final cyclization involves the disruption of the aromaticity of the phenyl ring, with the consequence that the optimal conditions (gold ligand, temperature, counterion) for the initial Claisen rearrangement could be unsuitable for the subsequent step of the cascade process and vice versa. In this paper we report on an experimental and computational study of the tandem gold(I)-catalyzed Claisen rearrangement/hydroarylation cyclization of 3-aryl-substituted propargyl vinyl ethers and show that it efficiently provides polyfunctionalized indenes. Moreover, we demonstrate that further in situ elaboration of the aldehyde functionality is possible by Wittig olefination, thus enlarging the variety of products which can be obtained by this methodology.

Results and Discussion

The synthesis of the substrates (Scheme 2) for the gold-catalyzed reaction was carried out by treatment of the corresponding propargylic alcohols **5** with ethyl vinyl ether in the presence of $Hg(OAc)_2$.[14], [15] While this methodology is suitable for small scale preparations, e.g. in the evaluation of the scope of the gold-catalyzed tandem process, we looked for an alternative approach to vinyl ethers **6** when these were needed in larger amount, in order to avoid the use of the mercury salt.[16] Out of the many approaches we experimented, the best is depicted in Scheme 3. As shown, converting **5a** into the corresponding acetate and then treating with $InCl_3$ in nitromethane at 50 °C in the presence of 2-bromo-1-ethanol, provided bromide **7a** in 78% yield over the two steps.[17] The next elimination step was carried out by treatment of **7a** with a strong base (*t*-BuOK in toluene) which provided model compound **6a** in 91%.[18]

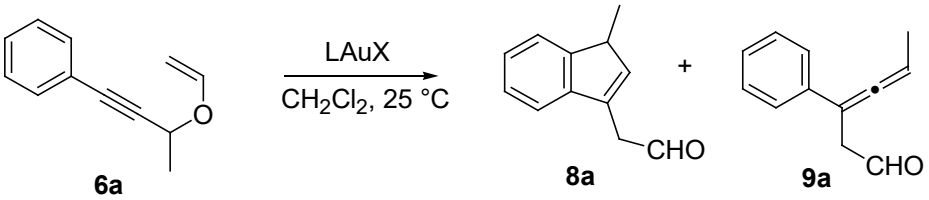
We used this substrate to find the best reaction conditions for the gold(I)-catalyzed process and the results of the screening of various gold(I)-catalysts and gold(I)-precatalyst/silver salt combinations are reported in Table 1. The reactions were carried out by adding a solution of the substrate in DCM to a solution of the catalyst (3 mol %) generated by mixing the gold and silver salts in the same solvent at 25 °C. The $[Ph_3PAu]^+BF_4^-$ and $[Ph_3PAu]^+TfO^-$ catalysts (entries 1 and 2) have been shown to catalyze the Claisen rearrangement of propargyl vinyl ethers.[10a] With 3 mol % of these catalysts in CH_2Cl_2 substrate **6a** was quickly (less than 30 min) and quantitatively converted into allene **9a**.[19] However, we did not observe even traces of indene **8a** in the crude reaction mixtures by prolonging the reaction times. Gold salts with Ph_3P and electron-rich phosphine ligands were all competent catalysts in the tandem Claisen rearrangement/Nazarov cyclization of enynyl vinyl ethers,[11] but as

it is evident from entries 1-2 and 4-5, they seem unable to promote the final hydroarylation step with substrate **6a**. Instead, with the NHC (NHC = N-heterocylic carbene) ligand IPr and various anions (entries 6-10) we always observed the formation of indene **8a**. The [IPrAuCl]/$AgBF_4$ catalytic system was the best in the gold(I)-catalyzed formation of indene from propargylic acetates,[8b] and the same occurred with our substrate (entry 8).[20] With 3 mol % of this catalyst we observed (by ^1H NMR) the immediate (less than 5 min) conversion of the substrate into allene **9a**, half of which already cyclized to indene **8a** (**8a**/**9a** ratio = 1:1 after 5 min). After 15 min, the ratio was 3.2:1 and in 25 minutes the reaction was complete. With 1 mol % of the catalyst the reaction was complete in 3 h. Commercial $[IPrAu(CH_3CN)]^+BF_4^-$ (entry 9) catalyzed the reaction, too, ruling out any role of the silver salt in the hydroarylation step. On the other hand, $AgBF_4$ alone (entry 16) was able to catalyze the Claisen rearrangement, but not the cyclization, and similarly in the presence of the IPrAuCl salt alone (entry 15) only the [3,3]-rearrangement occurred.

We tested other NHC gold complexes (entries 11-14) and quite surprisingly, among these, only the SIPr ligand was effective, although the reaction was slightly slower than with IPr ligand (the **8a**/**9a** ratio was 1:1 after 15 min).[21] With ICy, ItBu, and IMes ligands only allene **9a** was formed. Interestingly, in the Au(I)-catalyzed tandem [3,3]-rearrangement-hydroarylation of propargylic acetates to form indenes, other NHC ligands were able (although not as efficiently as IPr) to promote the hydroarylation step.[8b]

Having found the best reaction conditions, these were used to evaluate the scope with 3-aryl-substituted propargyl vinyl ethers bearing various groups (R^3) on the aromatic ring and substituents (R^1, R^2) on the carbynolic position (Scheme 4). To avoid both partial degradation of aldehydes **8** and double migration to the exocyclic position during chromatography on silica gel (which generates α,β-unsaturated aldehydes), the reaction products were reduced in situ to the corresponding alcohols **10** by $NaBH_4$ after dilution of the dichloromethane solution with MeOH (method A).[22] As an alternative, upon completion of the reaction, the crude aldehydes were isolated after an aqueous work-up, dissolved in MeOH and then reduced (method B). By using the former procedure (method A), simple indene **10a** was obtained in 80% yield after chromatography. Electron-donor groups on the aromatic ring made the reaction faster and, with the exception of the *o*-methyl substituted substrate **6c**, which reacted in 1.5 h, alcohols **10b**-**10f** were all obtained in 15 min. *m*-Methyl- and *m*-methoxy-substituted substrates (**6d** and **6f**, respectively) of course provided a mixture of isomers deriving from ring closure at the *ortho* and *para* position. However, in the case of the *m*-methoxy-substituted compound, attack to the *para* position prevailed (86:14 ratio in the crude reaction mixture) and pure isomer **10f** could be isolated by chromatography in good yield.[23a] With aromatic rings bearing amino- and alkoxy-substituted methyl groups (**6g** and **6h**, respectively), the reaction proceeded smoothly, too, providing alcohols **10g** and **10h** in good yield (62 and 75% yield, respectively). In the case of **6h**, the reaction was carried out with the commercial $[IPrAuCH_3CN]BF_4$ and, as for the model compound **6a**, it was just slightly slower than with the [IPrAuCl]/$AgBF_4$ catalytic system. The latter, as well as the preformed catalyst, were used to carried out the reaction with the propargyl vinyl ether bearing a dioxolane moiety in *para* position (**6i**). The reaction was slow (2 h for a complete conversion of the allene intermediate) and in both case we observed an almost complete trans-acetalization during the gold(I)-catalyzed step. Thus compound **10i** could be obtained in 63% yield after chromatography.[24]

Table 1. Optimization of the reaction conditions[a]



entry	catalyst[b]	time (min)	**6a** (%)[c]	**8a** (%)[c]	**9a** (%)[c]
1	$[Ph_3PAuCl]/AgBF_4$	30	-	-	100
2	$[Ph_3PAuCl]/AgOTf$	30	-	-	100
3	$[(p\text{-}CF_3C_6H_4)_3PAuCl]/AgOTf$	30	-[d]	-	-
4	$^tBu_3PAuNTf_2$[e]	30	-	-	100
5	$[Cy_3PAuCl]/AgOTf$	30	-	-	100
6	$[IPrAuCl]/AgSbF_6$	30	-	100[f]	-
7	[IPrAuCl]/AgOTf	40	-	100[f]	-
8	$[IPrAuCl]/AgBF_4$	25	-	100	-
9	$IPrAu(CH_3CN)BF_4$[e]	60	-	100	-
10	$IPrAuNTf_2$[e]	120	-	50	50
11	$[SIPrAuCl]/AgBF_4$	55	-	100	-
12	$[ICyAuCl]/AgBF_4$	55	-	-	100
13	$[ItBuAuCl]/AgBF_4$	55	-	-	100
14	$[IMesAuCl]/AgBF_4$	55	78[g]	-	22
15	IPrAuCl	55	-	-	100
16	$AgBF_4$	60	-	-	100

[a]*Conditions*: Reactions carried out on 0.2-0.3 mmol of **6a** in CH_2Cl_2 (0.05 M) at 25 °C under N_2 atmosphere. [b]Prepared by mixing the silver salt (3 mol %) and the gold chloride (3 mol %) in CH_2Cl_2 before addition of the substrate unless otherwise noted. IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene), IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene), ItBu = 1,3-di-t-butylimidazol-2-ylidene, ICy = 1,3-bis(cyclohexyl)imidazol-2-ylidene. [c]Relative amount determined by ^1H NMR of the crude reaction mixture. [d]Complete degradation of the starting material. [e]Commercially available. [f]Some degradation of the starting material occurred. [g]Devinylation of **6a** to alcohol **5a** occurred.

As expected on the basis of the above results, which suggest that the hydroarylation could be the rate determining step of the process (see later), the hydroarylation of the allene intermediate was in fact very slow with electron-withdrawing groups on the aromatic ring (**6j**-**6l**). In two cases (**6k**, bearing a *m*-F group, and **6l**, bearing a *p*-CO_2Me group) either the long reaction times or the heating led to an almost equimolar mixture of isomers as a consequence of the shift of the double bond to the position 1 in the five-membered ring. Such an isomerization could be observed, to a very minor extent and regardless the presence or absence of a silver salt in the reaction mixture, also for other substrates for which, however, the adoption of method B allowed us to overcome the problem.[25] As in the case of the *m*-OMe-substituted substrate, also with *m*-F-substituted propargyl vinyl ether **6k** the ring closure occurred predominantly (85% by ^1H NMR analysis of the crude reaction mixture) at the *para* position.[23b]

Finally, a few substrates with different substitution at the carbynolic position were evaluated and in all cases the reaction provided the target compounds (**10m-p**) in good to excellent yield. Benzyl-substituted indene **10n**, however, which was obtained isomerically almost pure (95%) from **6n** after

3 h in the presence of 6 mol % of the catalyst, underwent a slight double bond isomerization during the chromatography on silica gel and it was eventually obtained as a 9:1 mixture of isomers. With the *gem*-dimethyl substituted substrate **6o**, because of the double substitution at the propargylic moiety, the reaction was slower (3.5 h) than with the model substrate **6a** but provided the target compound **10o** in an excellent 93% yield. Similarly, the reaction of **6p** was slow (16 h) and it was carried out in the presence of 6 mol % of the catalyst, but it nevertheless provided compound **10p** in 92% yield.

The only substrates which seem unsuitable for this gold(I)-catalyzed cascade process are those bearing an aryl ring at the carbynolic position (Scheme 5). Simple phenyl substituted propargyl vinyl ether **6q**, under various conditions, always quantitatively provided the corresponding allene **9q**. We thought the lack of reactivity could be due to the stabilization by the phenyl ring of the positively charged gold(I)-complex intermediate [Scheme 1, (b)] making it less reactive, but the result obtained with dichloro-substituted substrate **6r** (Scheme 5) instead suggests that it is either the greater stability of the aryl- substituted allene intermediates or the steric hindrance in the ring closure step by the aryl ring the possible reason.

A plausible mechanism for the tandem Claisen/hydroarylation reaction and the energies calculated relative to complex **II** are reported in Scheme 6.[26] Upon coordination of the triple bond to the cationic gold(I) complex, a very fast [3,3]-rearrangement of **II** occurs and conversion of the substrate into allene **V** is immediate. This is experimentally observed for all types of substrates suggesting that the Claisen rearrangement is not the rate determining step of the process. The calculated transition state energies for the rearrangement steps (**TS1** and **TS2**) are in fact low with both IPr and Ph_3P ligands (<10-12 kcal/mol), whereas the ring closure of allene-gold(I) complex **IV**, which is in equilibrium with the free allene **V**, presents a higher barrier (17.9 and 17.8 kcal/mol) and thus is the rate determining step. When the cyclization is slow or does not take place, allene **V** can be isolated. The cyclization step takes place according to a classic electrophilic aromatic substitution to form **VI** and during this step a partial positive charge develops on the aromatic ring (**TS3**), which explains the effect of the substituents we observed when assessing the scope of the reaction. After proton elimination from C7a (to restore aromaticity) and protodeauration of **VII**, indene **VIII** is eventually formed. We carried out an experiment with deuterated [D]-**6a** (Scheme 7) and found out that all deuterium was incorporated in the product at position C1, meaning that, contrarily to what observed in the tandem Claisen/Nazarov reaction [Scheme 1, (a)] we have recently studied, no [1,2]-H shift from position 1 to position 2 occurs.[11] Another important difference with the tandem Claisen/Nazarov process is that we were never able to observe (and isolate) the allene intermediates in that case, as the cyclization was a fast step, especially with carbocyclic substrates.[11]. Two important points in the present cascade process are the role of the BF_4^- counterion and the effect IPr gold(I)-ligand, which together form the best combination. Tetrafluoroborate is a weakly coordinating anion[27] and this could favor coordination of LAu^+ cationic complex to allene **V** to re-generate allene-gold complex **IV** (e.g. compare entries 9 and 10, as well as 7 and 8 in Table 1). Since the calculated energies (Scheme 6) are almost the same for both IPr and Ph_3P ligands, explaining the efficiency of the NHC gold ligand compared to the phosphine ligands, with which we never observe ring closure of the allene **V** intermediates, is more difficult. It has been suggested that, in the rearrangement of a model propargyl acetate to form the corresponding allene, the latter is the resting state with a NHC ligand (IMe) and that allene coordination to gold is favored with the IMe ligand compared to a phosphine.[9d] We calculated the energies associated to the dissociation equilibrium

of complex **IV** (Scheme 8) and found that the phosphine ligand is able to stabilize more efficiently the LAu^+ species, as the uphill energy is only +3.9 kcal/mol compared with +7.3 kcal/mol for the NHC carbene. Thus the equilibrium is more shifted to the left with the latter ligand with which the formation of allene-gold(I) complex intermediate **IV** from allene **V** is more favored. The reason why, a part from SIPr, the other NHC catalysts are unable to promote cyclization, is instead unclear at the moment.

Finally, to demonstrate that aldehyde intermediates **8** can be directly employed just after their formation for further chain elongation without prior work-up of the gold-catalyzed step, we studied the Wittig reaction of **8o** and **8p** with selected phosphorus ylides (Scheme 9). The reactions were carried out by transferring by syringe the dichloromethane solution containing the crude aldehyde to a THF solution of the preformed ylide at 0 °C and leaving under stirring until complete consumption of **8**. With simple $Ph_3P{=}CH_2$ the reaction led to the terminal olefin **11** in 70% yield after chromatography. No isomerization of the double bonds was observed. Similarly, the reaction occurred quantitatively with a substituted ylide prepared from *n*-hexylphosphonium iodide, which provided *cis* olefins **12** in 80% yield. Finally, after rearrangement and cyclization of **6p**, the crude aldehyde **8p** was reacted with ylide **13**, prepared from the corresponding commercial phosphonium bromide, which furnished compound **14** in 71% yield.

Conclusions

In conclusion, the tandem gold(I)-catalyzed propargyl Claisen rearrangement/hydroarylation reaction of aryl-substituted propargyl vinyl ethers is an efficient way to obtain functionalized indenes. The reaction occurs at room temperature in dichloromethane in the presence of [IPrAuCl]/$AgBF_4$ as the best catalytic system for both the propargyl Claisen rearrangement and the subsequent allene cyclization (the hydroarylation step). Instead, with phosphine ligands no cyclization of the allene intermediate occurs, which is probably due to the higher stabilization of the free cationic gold(I) in the equilibrium involving coordination/decoordination of the allene intermediate to gold(I) as suggested by DFT computations. Various groups and substituents on the aryl ring and at the carbynolic position of the propargyl vinyl ether are tolerated. The effect of the substituents on the aryl ring suggests that the final hydroarylation is the rate determining step of this cascade process with a calculated free activation energy of about 18 kcal/mol for both the NHC and phosphine ligand. Further functionalization can be achieved in situ prior final work of the tandem process by a chain elongation carried out by Wittig reaction on the aldehyde functionality, thus incrementing the diversity of the products obtained.

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15) Propargylic alcohols **5** were either commercially available or prepared by Sonogashira coupling of substituted bromo- and iodobenzenes with the requisite alkynol (see Experimental Section).
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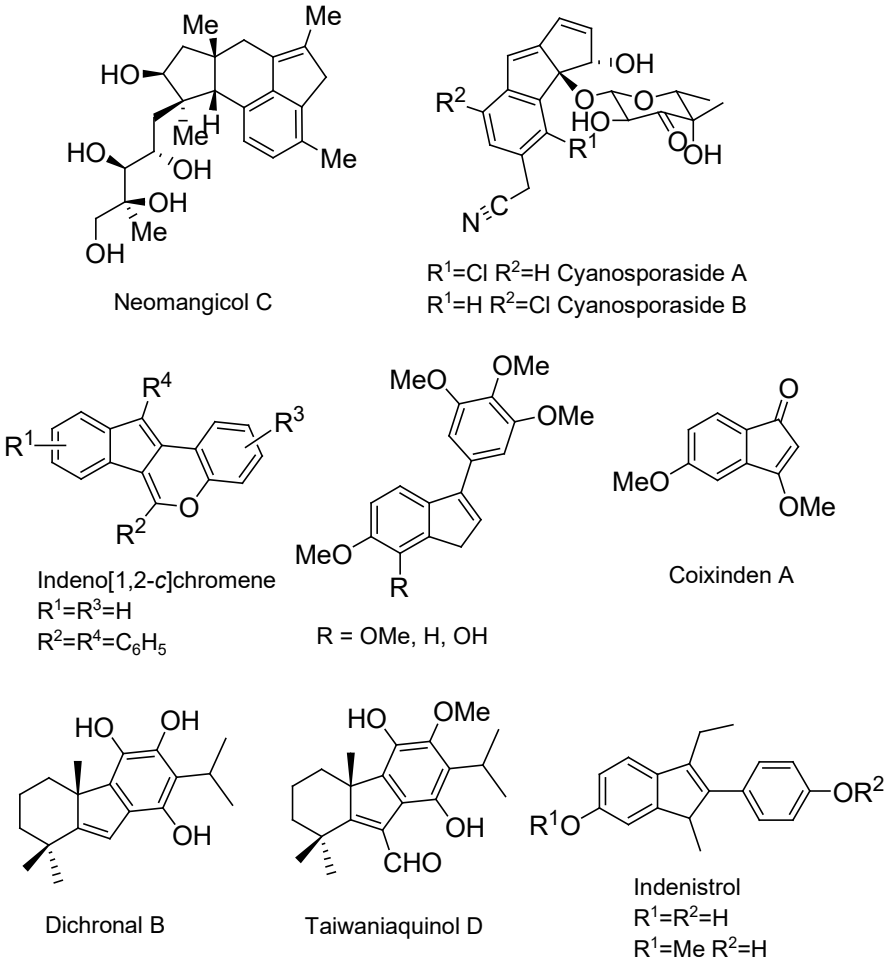
19) Allene **9a** undergoes degradation during chromatography and it was characterized as crude reaction mixture. Diagnostic ^{1}H NMR signals are the doublet at 1.81 ppm of the methyl group which couples with allene proton resonating at 5.62 ppm as a quartet of triplet (due to a long range coupling with the CH_2 group). The proton of the carbonyl group is a triplet at 9.74 ppm. See Experimental Section and also Supporting Information for NMR spectra.
20) For reviews on NHC ligands for gold(I) catalysis, see: (a) Gatineau, D.; Goddard, J.-P.; Mouriès-Mansuy, V.; Fensterbank, L. *Isr. J. Chem.* **2013**, *53*, 892 – 900. (b) Marion, N.; Nolan, S. P. *Chem. Soc. Rev*. **2008**, *37*, 1776–1782.
21) IPr is a weaker ligand than the corresponding saturated SIPr and therefore could leave the metal center more electron poor than its saturated congener. Consequently, its metal complexes could be more reactive in activating unsaturations toward nucleophilic attacks. Fantasia, S.; Petersen, J. L.; Jacobsen, H.; Cavallo, L.; Nolan, S. P. *Organometallics* **2007**, *26*, 5880-5889.
22) For this reason aldehyde **8a** was characterized as crude reaction mixture. Diagnostic ^{1}H NMR signals are the quartet at 3.53 ppm for the proton at C1 which couples with the methyl at the same position and which resonates as a doublet at 1.33 ppm. 2-H is a singlet at 6.40 ppm and the CHO proton is found a 9.79 ppm as a triplet. See Experimental Section and also Supporting Information for NMR spectra.
23) (a) The structure of isomer **10f** was assigned on the basis of the chemical shift and coupling constants of aromatic protons. The two protons *ortho* to the methoxy group (at positions 4 and 6) are shielded and resonate below 7.00 ppm. The 4-H is a doublet at 6.87 ppm with a very small ^4J with the proton at position 6 (0.6 Hz) and the latter is a doublet of doublet at 6.77 ppm with a larger vicinal coupling constant (8 Hz) with 7-H which resonates as a doublet at 7.29 ppm. (b) The ratio between the 5-F and 7-F isomers was 85:15 in the crude reaction mixture. The structure of major isomer **10k** was assigned (for both double bond isomers) on the basis of the chemical shift and coupling constants of aromatic protons. The two protons *ortho* to the F atom at C4 and C6 resonates as dd ($^3J_{HF}$ = 8.8 Hz and $^4J_{HH}$ = 2.4 Hz) and ddd ($^4J_{HH}$ = 2.4 Hz, $^3J_{HH}$ = 8.4 Hz, $^3J_{HF}$ = 8.7 Hz,), respectively. The proton at C7 resonates instead as a dd ($^4J_{HF}$ = 5.2 Hz and $^3J_{HH}$ = 8.4 Hz).
24) The structure of compound **10i** was assigned by analysis of ^{1}H, ^{13}C and bidimensional NMR spectra (gCOSY and gHSQC) (see Supporting Information). Diagnostic ^{1}H NMR signals (in $CDCl_3$) are the triplet at 5.19 ppm for the proton of the dioxolane moiety which couples with the side chain CH_2 group at C3, which in turn is a doublet at 2.90 ppm The benzylic protons at C6 is a doublet at 4.73 ppm for the coupling with the proton of the hydroxyl group.
25) In some cases we observed a slow isomerization in $CDCl_3$ (for example when recording ^{13}C NMR spectra overnight) and in such cases we used CD_3OD as the solvent for the characterization.

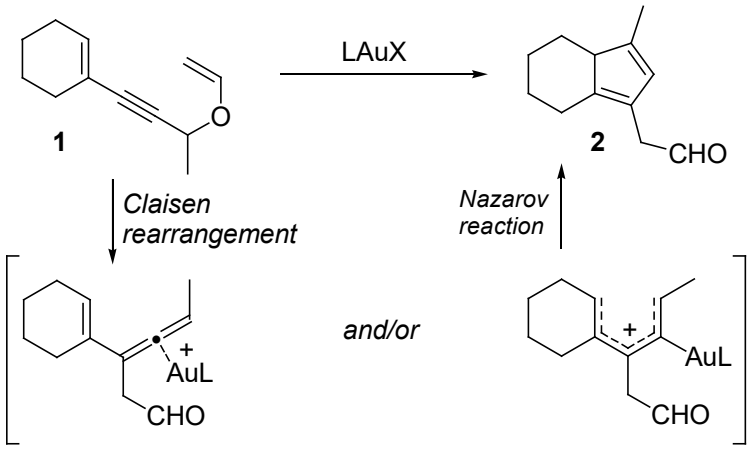
26) DFT calculations were carried out with the Gaussian16 set of programs and the M06 functional. For computational details, see the Supplementary Information.
27) Reviews on counterion effects in homogeneous gold catalysis: (a) Jia, M.; Bandini, M. *ACS Catal*. **2015**, *5*, 1638-1652. (b) Schießl, J.; Schulmeister, J.; Doppiu, A.; Wçrner, E.; Rudolph, M.; Karch, R.; Hashmi, A. S. K. *Adv. Synth. Catal*. **2018**, *360*, 2493−2502. See also, (c) Lu, Z.; Han, J.; Okoromoba, O. E.; Shimizu, N.; Amii, H.; Tormena, C. F.; Hammond, G. B.; Xu, B. *Org. Lett*. **2017**, *19*, 5848−5851.

Figure 1

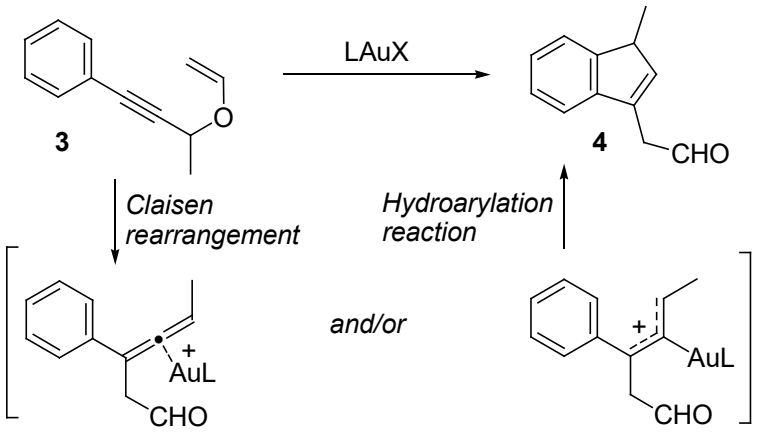


Scheme 1

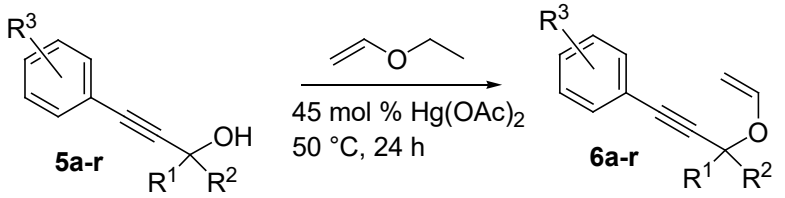
(a) Previous work: tandem gold(I)-catalyzed Claisen rearrangement/Nazarov reaction



(b) This work: tandem gold(I)-catalyzed Claisen rearrangement/hydroarylation reaction

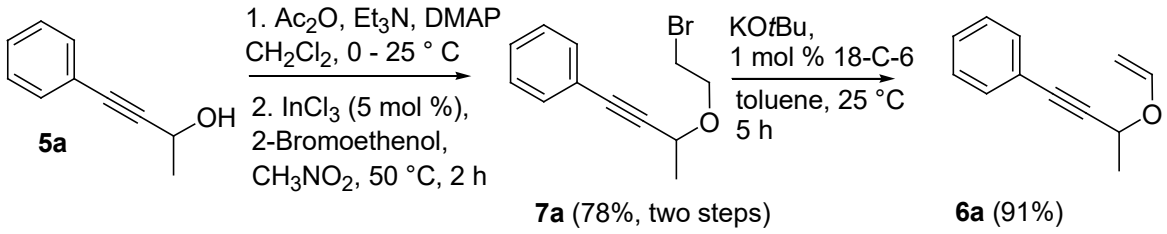


Scheme 2



6a R^1 = Me, R^2 = R^3 = H
6b R^1 = Me, R^2 = H, R^3 = *p*-Me
6c R^1 = Me, R^2 = H, R^3 = *o*-Me
6d R^1 = Me, R^2 = H, R^3 = *m*-Me
6e R^1 = Me, R^2 = H, R^3 = *p*-MeO
6f R^1 = Me, R^2 = H, R^3 = *m*-MeO
6g R^1 = Me, R^2 = H, R^3 = *p*-CH_2NHBoc
6h R^1 = Me, R^2 = H, R^3 = *p*-CH_2OBn
6i R^1 = Me, R^2 = H, R^3 = *p*-$CH(-OCH_2CH_2O-)$
6j R^1 = Me, R^2 = H, R^3 = *p*-Br
6k R^1 = Me, R^2 = H, R^3 = *m*-F
6l R^1 = Me, R^2 = H, R^3 = *p*-CO_2Me
6m R^1 = *n*-Pr, R^2 = R^3 = H
6n R^1 = Bn, R^2 = R^3 = H
6o R^1 = R^2 = Me, R^3 = H
6p R^1 = Me, R^2 = *i*-Bu, R^3 = H
6q R^1 = Ph, R^2 = R^3 = H
6r R^1 = *m,p*-$Cl_2C_6H_3$, R^2 = R^3 = H

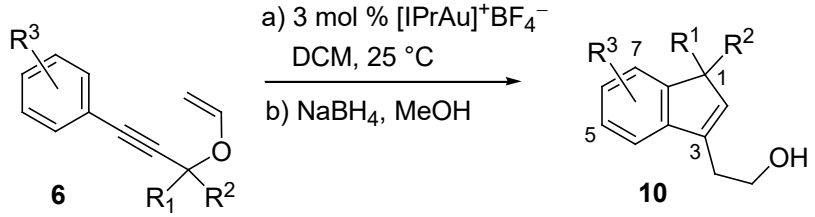
Scheme 3

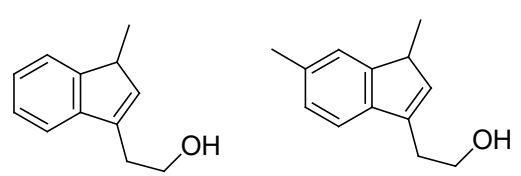


7a (78%, two steps)

6a (91%)

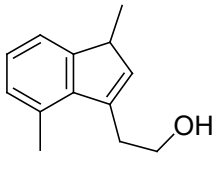
Scheme 4



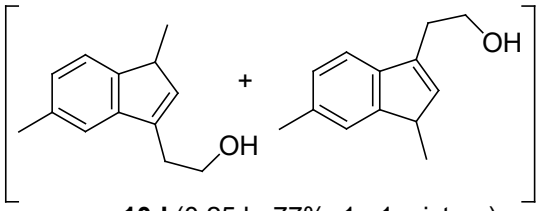


10a (0.4 h, 80%)

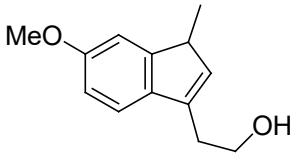
10b (0.25 h, 89%)



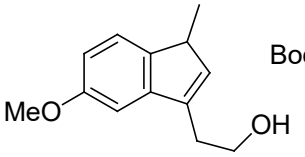
10c (1.5 h, 71%)



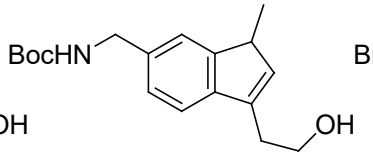
10d (0.25 h, 77%, 1 : 1 mixture)



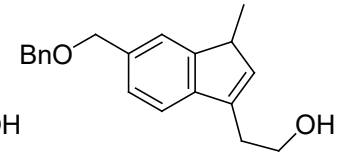
10e (0.25 h, 79%)



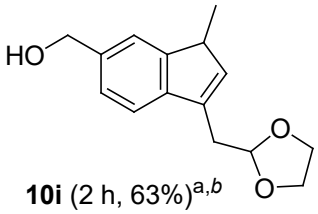
10f (0.25 h, 74%)



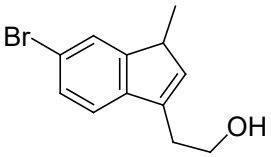
10g (0.25 h, 62%)



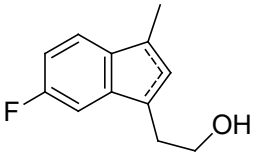
10h (0.8 h, 75%)[a]



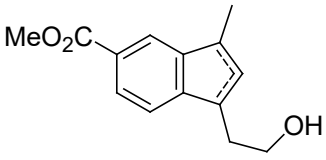
10i (2 h, 63%)[a,b]



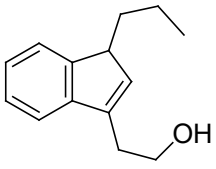
10j (6 h, 56%)



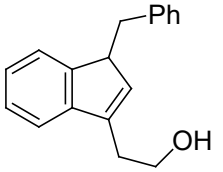
10k (16 h, 74%)[c]
(1.2 : 1 mixture)



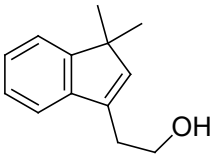
10l (7 h, 72 %)[d]
(ca. 1 : 1 mixture)



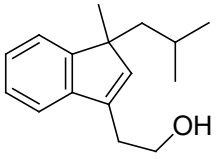
10m (1 h, 70%)[a]



10n (2 h, 69%)[a,b]



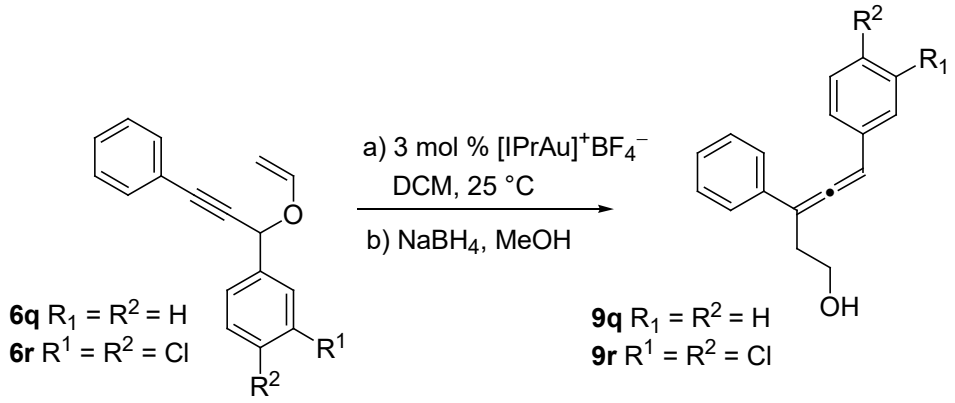
10o (3.5 h, 93%)



10p (16 h, 92%)[b]

[a]Commercial $[IPrAuCH_3CN]BF_4$ was used; [b]6 Mol % of the catalyst was used;
[c]In mixture with 7-F isomer (15%); [d]Reaction carried out at 40 °C

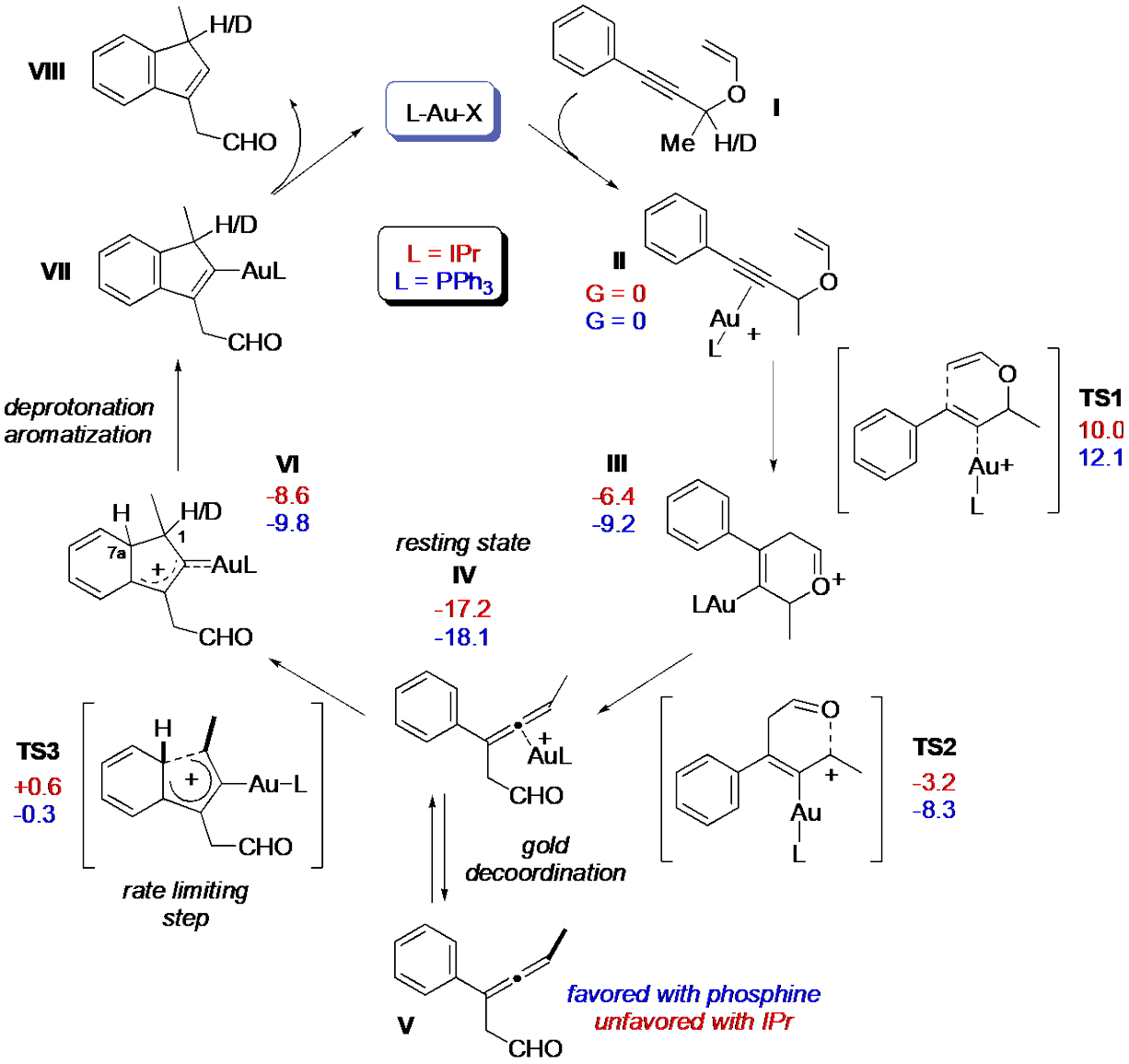
Scheme 5



6q $R_1 = R^2 = H$
6r $R^1 = R^2 = Cl$

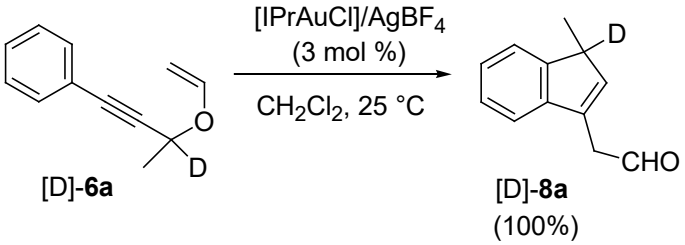
9q $R_1 = R^2 = H$
9r $R^1 = R^2 = Cl$

Scheme 6

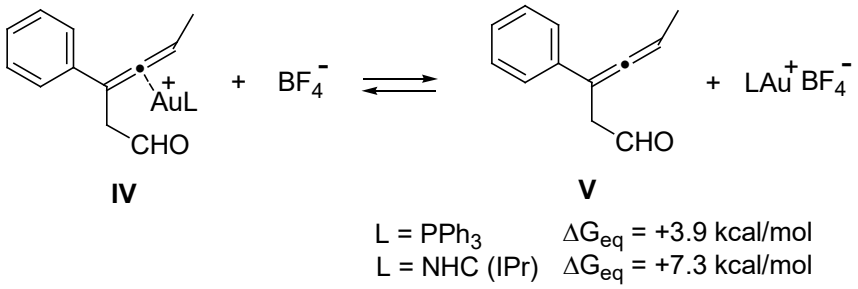


Schematic representation of the thermodynamics associated with the tandem process. Energies in kcal/mol are calculated relative to **II** (in blue for Ph_3P ligand, in red for IPr ligand)

Scheme 7



Scheme 8



Scheme 9.