Gold(I)-Catalysed Hydroarylation of Lactam-Derived Enynes as an Entry to Tetrahydrobenzo[g]quinolines

Gold(I)-Catalysed Hydroarylation of Lactam-Derived Enynes as an Entry to Tetrahydrobenzo[*g*]quinolines

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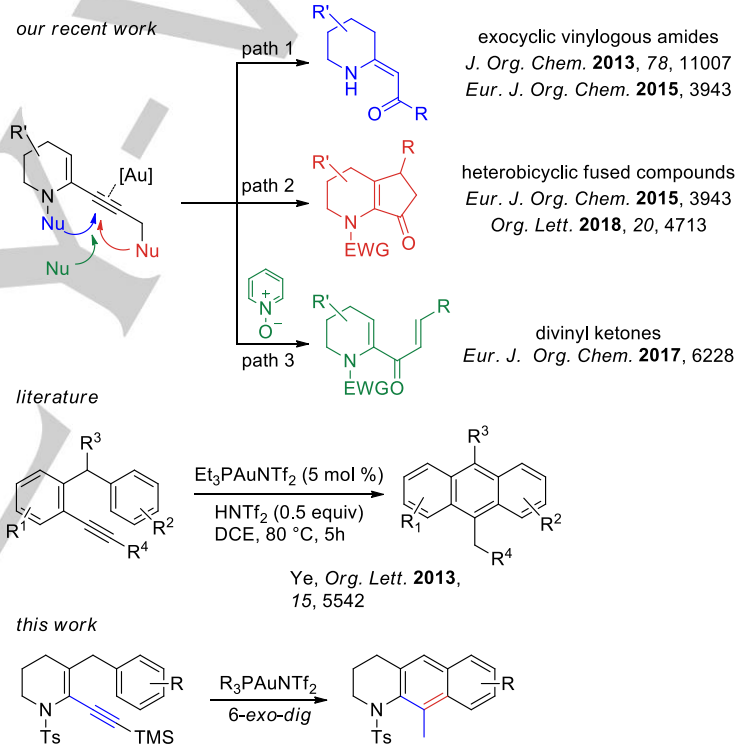
Abstract: The gold(I)-catalysed cyclization of *N*-tosyl-protected 5-benzyl-6-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydropyridines, prepared by the Sonogashira coupling of lactam-derived enol triflates, provides tetrahydrobenzo[*g*]quinolines whose skeleton represents a recurrent motif in natural compounds. The Au(I)-catalysed reaction is carried out with $(C_6F_5)_3PAuCl/AgNTf_2$ as the catalyst system and proceeds via a 6-*exo*-*dig* cyclization to form an exocyclic double bond, which eventually isomerises to the aromatic tetrahydrobenzo[*g*]quinoline. The mode of cyclization is discussed and supported by DFT calculation.

Introduction

Intramolecular hydroarylation of alkynes (or alkenylation of arenes) is a valuable synthetic tool, alternative to Heck or cross-coupling processes, to obtain alkenyl arenes. The recent and rapid advances of gold catalysis in this type of processes offer an easy access to an incredibly highly diversified array of cyclic systems.[1] Au(I) complexes are able to promote hydroarylation with a mechanism comparable to Friedel-Crafts-type electrophilic aromatic substitution, by employing the activated alkyne as electrophile. Carbocyclic polyaromatic compounds,[2] oxygen,[3] nitrogen[4], sulfur[5] and phosphorus[6] heterocyclic polyaromatic compounds have been successfully synthesized.

Among the various *N*-heterocycles, the tetrahydroquinoline and terahydroisoquinoline motif is ubiquitous in natural and pharmaceutical products. Hence, many bioactive compounds based on this scaffold are used as drugs and agrochemicals, and some efforts have been devoted to their synthesis.[7] In particular, tetrahydrobenzoquinolines have been synthesized by cycloaromatization,[8] ring expansion,[9] hydrogenation,[10] and more recently by Au(I)-catalysed formal [4+2] cycloaddition.[11] In continuation of our studies on the chemistry and synthetic applications of lactam-derived enol phosphates and triflates,[12] we recently reported that *N*-protected-2-alkynyl tetrahydropyridines are versatile substrates for gold-catalysed transformations. The gold-activated triple bond of the lactam-derived enyne can be reacted intramolecularly with nucleophiles either part of the protecting group on nitrogen (Scheme 1, path 1),[13] or on the side chain (path 2),[14] or alternatively with external nucleophiles (path 3).[15]



Scheme 1. Background of the work.

We then envisaged that installing a nucleophile on the heterocyclic ring, as a side chain at the adjacent position to the alkyne moiety, would enable the triple bond to undergo an intramolecular hydroarylation after activation by the Au complex. This strategy would afford nitrogen hetero-polycyclic compounds. Similar approaches have already been successfully applied on carbocyclic derivatives. Ye and colleagues reported the gold-catalysed 6-*exo*-*dig* cyclization of *o*-alkynyldiarylmethanes followed by isomerization of the double bond and aromatization to anthracenes.[2b] Phenanthrenes were synthesized by the same authors starting from propargyl biphenyls.[16] More recently, Verma reported the synthesis of phenanthrenes by Ag(I)

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catalysis.[17] To the best of our knowledge, the same approach has never been reported on nitrogen heterocycles.

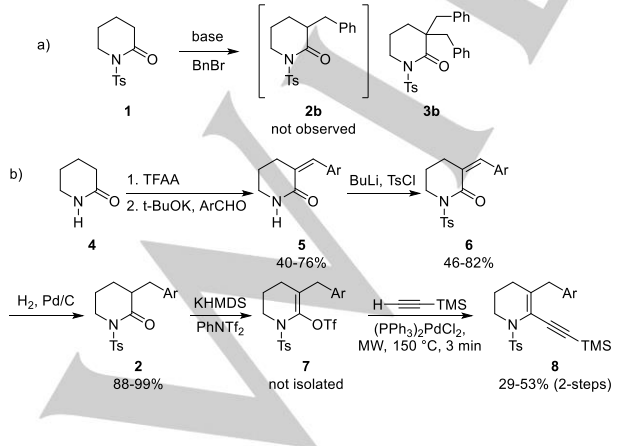
In this paper, we wish to report on the gold-catalysed hydroarylation of lactam-derived *N*-tosyl 5-benzyl-6-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydropyridines. The highly electrophilic $(C_6F_5)_3PAuNTf_2$ complex is employed and the reaction shows complete regioselectivity for the 6-*exo*-*dig* over the 7-*endo*-*dig* cyclization. The reaction is performed without the exclusion of air and moisture in non-anhydrous solvent, and it is chemoselective over the gold-catalysed hydration of the triple bond. The regio- and chemoselectivity are discussed and supported by DFT calculation, as well as the conformational features of the tetrahydrobenzo[*g*]quinoline product.

Results and Discussion

Synthesis of the substrates

The first step in our investigation was the synthesis of 5-benzyl-1-tosyl-6-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydropyridine **8** (Scheme 2, a). We first attempted the introduction of the benzylic side arm relying on the chemistry of enolates, encouraged by literature data according to which the introduction of a methyl group was performed in good yield using MeI as electrophile.[18] To this purpose, 1-tosylpiperidin-2-one **1** was deprotonated with KHMDS and the enolate trapped with benzyl bromide, at -78 °C. Unfortunately, the reaction afforded the double alkylated product **3b** only. We repeated the reaction with different bases (LDA, BuLi), with various temperatures, times and stoichiometric ratios and under Barbier conditions, but **3b** was always the only product identified. Computations[19] settled that the enolate intermediate formed by deprotonation of **2b** is 3.0 kcal mol^{-1} more stable than the enolate derived from **1**. Therefore, the equilibrium is shifted toward the former, and the fast conversion of **2b** into **3b** is justifiable.

We than retuned our strategy and the insertion of the benzyl group was envisaged by an aldol condensation between the lactam **4** and an aromatic aldehyde,[20] followed by protection of the nitrogen and hydrogenation of the double bond (Scheme 2, b). This strategy also allows to perform the synthesis starting from cheap and available aldehydes.



Scheme 2. a) Attempted synthesis of α-benzyl lactam **2b** by alkylation of the corresponding enolate. b) Synthetic pathway towards enyne **8**. TFAA: trifluoroacetic anhydride.

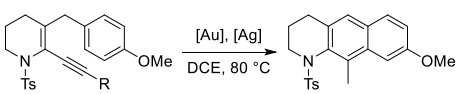
One of the key intermediates of the synthetic strategy proposed in Scheme 2 is the formation of the lactam-derived triflate **7**. Since an electron-withdrawing group is needed on the nitrogen atom of the piperidin-2-one core to form the corresponding triflate,[12a] we reacted **5** with tosyl chloride to introduce a *N*-tosyl group. Hence, after hydrogenation, triflate **7** was prepared by treatment with KHMDS and trapping of the enolate with *N*-phenyl bis(triflimide). The Sonogashira coupling between the vinyl triflate and TMS-acetylene afforded enynes **8** (Scheme 2, b). These compounds, differently from most of the corresponding *N*-Boc enynes,[13a] proved to be quite stable when neat and can be stored for several weeks at 4 °C. The strategy shown in Scheme 2 allowed us to obtain an array of enynes **8** with different electronic features to be tested in the hydroarylation reaction.

The Au-catalysed hydroarylation

In order to test our assumption and find the optimal reaction conditions, we first synthesized enyne **8a**, bearing a *p*-methoxyphenyl as the aryl moiety, as the model substrate. Due to the moderate nucleophilicity of its aryl group, compound **8a** could be considered a suitable substrate to investigate the optimization conditions for the gold-catalysed intramolecular hydroarylation and to find experimental conditions applicable to a variety of α-benzylic lactam-derived enynes.

The gold-catalysed cyclization of **8a** was initially carried out in the presence of 5 mol% of Ph_3PAuCl and 5 mol% of $AgNTf_2$ (Table 1, entry 1). Unfortunately, under these conditions we were unable to detect any cyclization product, but the reaction afforded the terminal alkyne **8a'**, derived from desilylation of the starting material. As reported by Pale, the removal of trimethylsilyl groups from alkynes can be catalysed by Ag salts.[21] Desilylation was indeed observed in the presence of $AgNTf_2$ alone (entry 11), while it did not occur when we reacted **8a** with a gold chloride complex alone (entry 12): in this case, the starting material was recovered unaltered. To promote the hydroarylation, we moved to different ligands on the gold complex and found some conversion to product **9a** with JohnPhosAuCl/$AgNTf_2$ (entry 2). The cationic complex JohnPhosAu(MeCN)SbF_6, on the other hand, was not effective (entry 3).

Table 1. Gold(I)-catalysed hydroarylation of **8a**.[a]



8a R = TMS
8a' R = H

9a

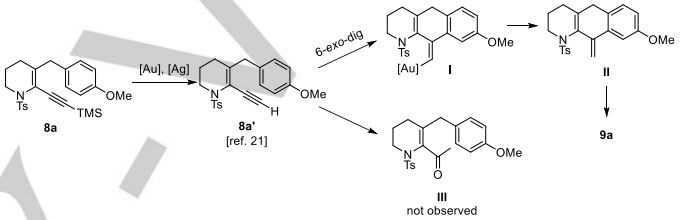
entry	[Au]	[Ag]	Time (h)	additive	yield[b]
1	Ph_3PAuCl	$AgNTf_2$	4.5	-	-

2	JohnPhosAuCl	$AgNTf_2$	7	-	9%
3	JohnPhosAu(MeCN)SbF_6	-	6	-	-
4	(2,4-*t*-$Bu_2PhO)_3PAuCl$	$AgNTf_2$	4	-	38% (37%)
5	$(MeO)_3PAuCl$	$AgNTf_2$	2	-	52% (45%)
6	$(MeO)_3PAuCl$	AgOTf	23	-	17%
7	$(C_6F_5)_3PAuCl$	$AgNTf_2$	2	-	62% (57%)
8	$(C_6F_5)_3PAuCl$	AgOTf	17	-	10%
9	$(C_6F_5)_3PAuCl$	$AgNTf_2$	0.5	$HNTf_2$ 0.5 eq	16%
10	-	-	0.5	$HNTf_2$ 0.5 eq	15%
11	-	$AgNTf_2$	5	-	-
12	$(C_6F_5)_3PAuCl$	-	5	-	-[c]
13[d]	$(C_6F_5)_3PAuCl$	$AgNTf_2$	3	-	39%
14[e]	$(C_6F5)_3PAuCl$	$AgNTf_2$	3	-	18%

[a] All reactions were performed at 80 °C in 1,2-dichloroethane (DCE) with 5 mol% LAuCl and 5 mol% AgX. [b] Determined by ^1H NMR at 600 MHz, using nitromethane as an internal standard (yields of isolated product in brackets). If not otherwise specified, quantitative removal of the trimethylsilyl group was observed. [c] No desilylation was observed. [d] Toluene as solvent. [e] Cyclopentyl methyl ether as solvent.

With a more electron-withdrawing phosphite ligand the yield improved (entry 4). In order to keep the electronic properties, while reducing the bulkiness of the Au complex, we then tried trimethylphosphite as ligand (entry 5). In fact, we considered that also steric hindrance could play a role in the cyclization of these encumbered substrates, and we were delighted to observe an increase in the yield of **9a** with $(MeO)_3PAuCl$ (entry 5, 52% in 2 h). The choice of the proper Ag salt is crucial, as when we performed the reaction under the same conditions but using AgOTf we observed a drop in the yield (entry 6). On the basis of these results, we aimed at increasing the electrophilicity of the gold complex and we synthesized $(C_6F_5)_3PAuCl$, a complex which has been reported to perform well in the hydroarylation of *o*-propargyl biaryls.[16] The use of this strongly electron-poor ligand in combination with $AgNTf_2$ led to an increase in the yield of **9a** (entry 7), while AgOTf revealed again to be less suitable (entry 8). In his gold-catalysed synthesis of anthracenes, Ye reported that the addition of the strong Brønsted acid $HNTf_2$ to the reaction medium had a beneficial effect on the final yield.[2b] When we added $HNTf_2$, we observed a fast consumption of the starting material, but the yield was low (entry 9), suggesting that the substrate is subject to decomposition in acidic conditions, even if some of it is converted into the hydroarylation product. This was further confirmed when we reacted compound **8a** in the presence of $HNTf_2$ only (entry 10). The reaction was performed also in two different solvents, toluene and cyclopentyl methyl ether (entries 13-14), but in these cases the yields were lower.

The addition of the Brønsted acid was originally meant to convert the methyl ketone **III** (Scheme 3), arising from the possible gold-catalysed hydration of the triple bond, to the desired hydroarylation product.[2b] However, differently from what reported by Ye, we never detected the formation of the ketone **III**, even if the reaction was performed in non-anhydrous DCE. The proposed mechanism for the hydroarylation involves the desilylation of the alkyne as first step, that occurs *in situ* prior to hydroarylation. Indeed, monitoring of the reaction progress showed the preliminary and complete conversion of **8a** into the terminal alkyne **8a'** and soon after the formation of **9a** (Scheme 3). Isolating **8a'** and reacting it in the gold-catalysed conditions led to a comparable yield of the hydroarylation product. The alkenyl gold intermediate **I** undergoes protodeauration to the *exo* intermediate **II**, which rapidly aromatizes to the final product **9a**.



Scheme 3. Possible reaction pathways for enyne **8a** under gold catalysis conditions.

In principle, both carbon atoms of the triple bond in the enyne substrate can undergo the hydroarylation reaction. Since we observed instead complete regioselectivity for the 6-*exo-dig* cyclization over the 7-*endo-dig*, we investigated the mechanism by DFT calculation. Computational studies on substrate 6-ethynyl-1-tosyl-5-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydropyridine (see Scheme 4), by interaction with the complex tris(2,4-di-*tert*-buthylphenyl)phosphite gold chloride, confirmed the preference for the 6-*exo-dig* cyclization. According to the Natural Bond Orbital analysis,[22] the charges on the triple bond are -0.41 on the terminal carbon and 0.13 on the other carbon (Figure 1). Au is slightly asymmetrically bonded to the

alkyne: the distance from the terminal carbon is 2.19 Å, whereas the other Au-C bond is 2.53 Å.

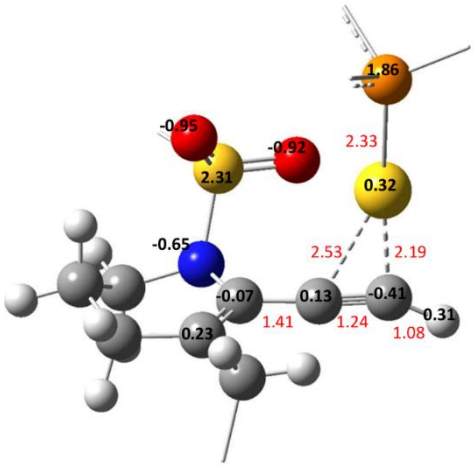
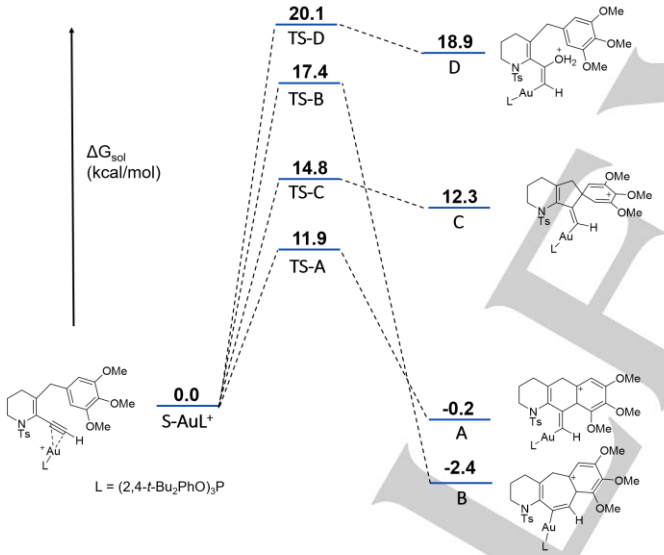
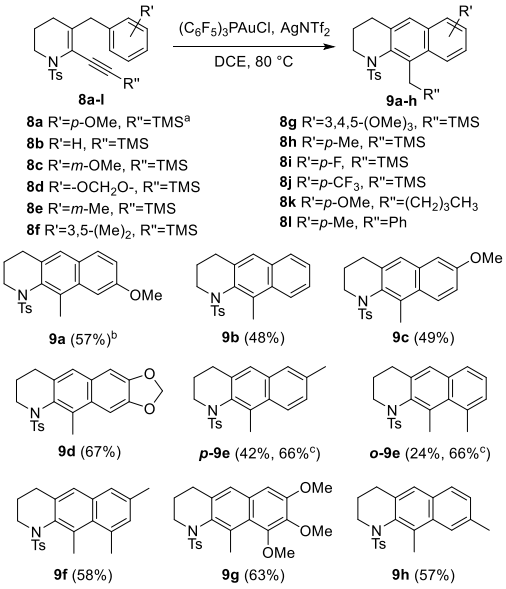


Figure 1. NBO charges (black) and bond distances (red, in Angstrom) for S-AuL$^+$ reactant in Scheme 4. For sake of clarity, only part of the molecule is shown. The overall molecule is reported in the Supporting Information.



Scheme 4. Free energy profile for the possible reaction steps. Energetics were calculated at M06/def2TZVP-PCM level, at M06/6-31G(d) geometries. See Experimental Section for more details

Four competitive processes are conceivable. The reaction with the lower free energy barrier (11.9 kcal mol^{-1}) leads to the 6-*exo-dig* cyclization (**TS-A** in Scheme 4). The C-C bond formation distance in the transition structure is 2.19 A. The intermediate **A** is almost isoergic with the reactant (+0.2 kcal mol^{-1}). This is in agreement with the experimental results which showed complete selectivity for the 6-*exo-dig* product. The cyclization to form the seven-membered ring (**TS-B**) leads to the thermodynamically most stable intermediate (**B**), -2.4 kcal mol^{-1} below the reactant. However, this reaction is characterized by a rather high barrier, compared to the other competitive steps, of 17.4 kcal mol^{-1}, which makes this reaction about 1000 times slower than **TS-A**. The C-C distance for the nascent σ bond is 2.21 A, similar to those for **TS-A**. We hypothesize that the high barrier is due to the deformation energy necessary to move the Au complex form the terminal to the adjacent carbon of the alkyne. Moreover, the NBO charges in Figure 1 show a slightly negative value on the terminal carbon of the alkyne (-0.41, or -0.1 with H summed into carbon), and a slightly positive value (0.13) on the adjacent carbon. Therefore, the terminal carbon has less electrophilic character, which is coherent with the higher barrier. These results are consistent with the theoretical study on transition metal-catalysed cycloisomerizations of propargyl biphenyls to anthracenes.[23] A 5-*exo-dig* attack on the *ipso* carbon of the aryl ring is also possible, leading to the *spiro* intermediate **C**. This reaction has an energy barrier of 14.8 kcal mol^{-1} and it is about 100 time slower than **TS-A**. Furthermore, the *spiro* intermediate **C** does not have any hydrogen that could be easily lost to form stable compounds, therefore it cannot evolve any further. In addition, it is thermodynamically less stable than the reactant (+12.3 kcal mol^{-1}) and the reverse reaction is fast because of the very low barrier of about 2.5 kcal mol^{-1}. Last, the hydration of the triple bond was taken into account (**TS-D**). Because of the high barrier of this step (20.1 kcal mol^{-1}), this reaction has a much smaller rate constant than the other steps. The reason of the high barrier is the loss of entropy due to the bimolecular process $\Delta S^{\ddagger}$(353 K) = -57.87 cal mol^{-1} K^{-1}, that raises the free energy barrier by about 11 kcal mol^{-1} compared to the potential energy. Even considering the amount of water that could be present in the reaction medium, which is not anhydrous, the reaction is estimated to be extremely slow. This is in line with the experimental results, which do not show any hydration product.



Scheme 5. Substrate scope of the gold-catalysed hydroarylation. All reactions were performed at a 0.1 M concentration, with 5 mol% Au complex and 5 mol% Ag salt. [a] TMS in the starting material is converted to H in the product. [b] Yields of isolated product are reported. [c] Overall yield of the two regioisomers.

Having assessed the best conditions for the gold-catalysed hydroarylation, we turned our attention to the study of the scope of the reaction, applying the optimized conditions to a variety of enynes, as shown in Scheme 5. The reaction works well with strong electron-donating substituents on the aryl ring, such as methoxy or dioxole groups, as well as weakly electron-donating methyl groups. The electron-neutral phenyl ring is also suitable. On the other hand, when we reacted the *p*-fluorophenyl or the *p*-(trifluoromethyl)phenyl derivatives **8i** and **8j**, we did not observe the corresponding hydroarylation product. Even substrates **8k** and **8l**, bearing an alkyl and a phenyl group respectively on the alkyne moiety, failed to convert into the corresponding tetrahydrobenzo[*g*]quinolines. When different regioisomers of the hydroarylation product are possible, the regioselectivity is dictated by both electronic and steric factors. *m*-Methoxy- and dioxole-substituted enynes **8c** and **8d** afforded the product with complete regioselectivity for the *para* position, while in the case of *m*-methyl derivative **8e** a mixture of *ortho* and *para* products was obtained.

Structural analysis of the tetrahydrobenzo[*g*]quinolines

The ^{1}H NMR spectrum of the tetrahydrobenzo[*g*]quinoline products presents an unexpected pattern which is worth of deeper investigation. The signals attributed to the protons in the CH_2 groups of the heterocyclic ring are split, indicating that the two protons are not equivalent. This feature is exemplified in the spectrum of **9a**, reported in Figure 2, **I**, and is not found in the spectra of all the other intermediates, in which every CH_2 group appears as a single peak integrating for two protons (see the SI for the spectra of the intermediates).

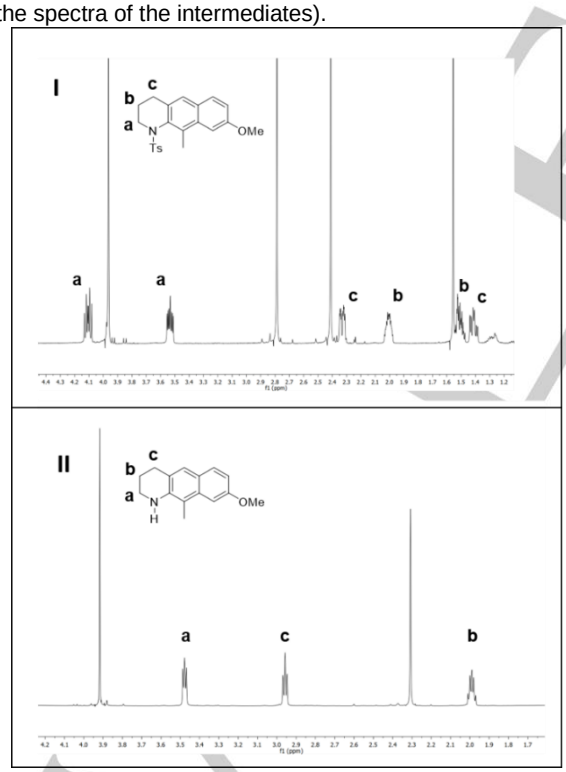


Figure 2. The aliphatic zone in the ^{1}H NMR spectra of **9a** (**I**) and **10a** (**II**). The assignments were confirmed by COSY and HMQC analysis. See the SI for the full-size spectra.

We hypothesized that the rigidity of the aromatic bicyclic structure could reduce the conformational freedom of the fused heterocyclic ring. The steric clash between the *N*-tosyl group and the neighbouring methyl group[24] may hamper the pyramidal inversion of the tri-substituted nitrogen atom, preventing the *N*-enantiomers from being averaged in the NMR timescale. Slow inversion of the pyramidal nitrogen was previously reported also by Kleinpeter in some *N*-arylsulfonyl morpholines.[25] They used the coalescence temperatures, the chemical shift differences and the coupling constants to estimate the free energy barriers of ring interconversion, which were in the range of 9.2-10.3 kcal mol^{-1}. By DFT method, we calculated a free energy conformational barrier for **9a** of 18.9 kcal mol^{-1} (see the SI for the figure of the relevant transition structure). On the other hand, when the tosyl group was replaced by a hydrogen, the free energy barrier dropped to 4.2 kcal mol^{-1}. On the basis of these results, we decided to remove the *N*-tosyl group of **9a** by means of the radical anion sodium naphthalenide,[26] obtaining the secondary amine **10a**. The ^{1}H NMR spectrum of **10a** (Figure 2, **II**) clearly shows that the protons of the CH_2 groups are not split anymore, as rapid interconversion between the two enantiomers is now allowed. Both enantiomers of **9a** are found in the crystal structure, which is reported in Figure 3.

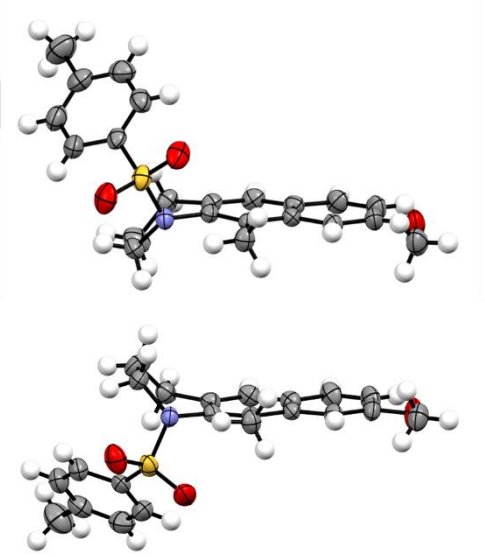


Figure 3. ORTEP diagram of the two enantiomers in the crystal structure of **9a**. Ellipsoids are displayed at a 50% probability level. Element colours: grey (C), white (H), red (O), violet (N), yellow (S).

Conclusions

In this paper, we have shown the feasibility of the Au(I)-catalysed intramolecular hydroarylation of heterocyclic enynes for the synthesis of tetrahydrobenzo[*g*]quinolines, a common motif in natural and pharmaceutical compounds. The reaction is run in open-air conditions in non-anhydrous solvent, and it shows complete regio- and chemoselectivity. The selectivity of the cyclization was elucidated by DFT calculation. The rigidity of the

tetrahydrobenzo[*g*]quinoline structure, combined with the steric bulkiness of the *N*-tosyl group, dramatically slows down the interconversion between the two enantiomers on the chiral nitrogen atom.

Nitrogen heterocycles are of great interest for the total synthesis of biologically active compounds. This work, in continuation of our previous research, extends the range of nitrogen-containing molecular scaffolds that are accessible in few steps starting from very simple lactam precursors.

Experimental Section

Synthetic procedures and characterization of all the intermediates, copies of the NMR spectra of new compounds, DFT geometries and energies, crystallographic details are available in the Supporting Information. CCDC code 1962707 contains the supplementary crystallographic data for **9a**.

Theoretical Method: All stationary points on the energy hypersurface, i.e. minima and first order saddle points, corresponding to transition structures (TS),[27] were determined by gradient procedures within the Density Functional Theory (DFT)[28] and making use of the M06.[29] This functional was expected to perform acceptably on the basis of literature studies.[23, 30] Reactants, transition structures, and intermediates have been optimized in the gas phase with the 6-31G(d)[31] basis set whereas, for Au only, the SDD effective core potential was used.[32] The nature of the critical points was checked by vibrational analysis. The energies were then refined by single-point energy computations with def2TZVP basis set,[33] using the polarizable continuum model (PCM). This theory level is indicated as M06/def2TZVP-PCM//M06/6-31G(d). Since the experimental part of the work was carried out in the liquid phase, solvent (1,2-dichloroethane) was simulated using the polarized continuum method, within the SMD[34] and IEF-PCM schemes.[35] The M06/6-31G(d) thermochemical corrections were added to the M06/def2TZVP PCM relative energies to obtain the Gibbs free energies. According to the experimental section, the Gibbs free energies reported, were estimated at T = 353 K. Quantum mechanical calculations were carried out by using the GAUSSIAN09 system of programs. Ultrafine integration grid and two-electron integral accuracy of 10-12 were used in all the computations.

General information: Flasks and all equipment used for the generation and reaction of moisture-sensitive compounds were dried by electric heat gun under nitrogen. Anhydrous THF was obtained by distillation over $LiAlH_4$, followed by distillation over Na-benzophenone; anhydrous DME was obtained by distillation over Na-benzophenone; anhydrous toluene was purchased from Sigma Aldrich or Acros Organics; Et_3N was distilled over CaH_2; *t*-BuOK was sublimated under vacuum. All other reagents were used as received, without further purification. Flash column chromatography was performed over silica gel (40-63 µm, 230-400 mesh); R_f values refer to TLC carried out on silica gel plates. ^1H NMR and ^{13}C NMR spectra were recorded on a Jeol ECZR600, on a Bruker AVIII400 UltraShield Plus or on a Bruker Avance 200, in $CDCl_3$, using residual solvent peak as an internal standard ($CHCl_3$, ^1H: 7.26 ppm, ^{13}C: 77.16 ppm). Multiplicity is reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), m (multiplet), br (broad). GC-MS spectra were recorded at an ionizing voltage of 70 eV. ESI-MS spectra were acquired on a Waters ZQ mass spectrometer equipped with ESCI source. All spectra were recorded in ESI+ mode, using appropriate values of capillary and cone voltages. HRMS analysis were run on a high resolving power hybrid mass spectrometer (HRMS) Orbitrap Fusion (Thermo Scientific, Rodano, Italy), equipped with an a ESI ion source. The samples were analysed in acetonitrile solution using a syringe pump at a flow rate of 5 µL/min. The tuning parameters adopted for the ESI source were: source voltage 4.0 kV. The heated capillary temperature was maintained at 275°C. The mass accuracy of the recorded ions (vs. the calculated ones) was ±2.5 mmu (milli-mass units). Microanalysis were carried out on an elemental analyser. Preparative HPLC was performed on a SunFire™ Prep C18 (5 µm, 10x150 mm) column, with a Waters 2998 photodiode array detector.

General procedure for gold-catalysed hydroarylation: To a 0.1 M solution of the enyne (1.0 eq, 0.1-0.5 mmol) in 1,2-dichloroethane the gold catalyst (5 mol %) and the silver co-catalyst (5 mol %) were added. The mixture was stirred at 80 °C until complete conversion (TLC monitoring), then the solvent was removed under vacuum and the crude product was purified by flash column chromatography.

8-methoxy-10-methyl-1-tosyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (9a): White solid, 57% yield, mp 155-156 °C (PE). R_f 0.25 (8:2 PE/Et_2O). ^1H NMR (600 MHz) δ (ppm): 7.64 (d, 1H, *J* = 8.8 Hz), 7.45 (d, 2H, *J* = 8.2 Hz), 7.32 (d, 1H, *J* = 2.3 Hz), 7.25 (s, 1H), 7.20 (d, 2H, *J* = 8.0 Hz), 7.16 (dd, 1H, *J* = 8.9 Hz, 2.4 Hz), 4.11 (dt, 1H, *J* = 13.8 Hz, 8.4 Hz), 3.96 (s, 3H), 3.55-3.51 (m, 1H), 2.79 (s, 3H), 2.41 (s, 3H), 2.33 (ddd, 1H, *J* = 14.6 Hz, 4.8 Hz, 2.8 Hz), 2.04-1.98 (m, 1H), 1.54-1.47 (m, 1H), 1.41 (td, 1H, *J* = 13.3 Hz, 5.5 Hz). ^{13}C NMR (150 MHz) δ (ppm): 157.5 (Cq), 143.6 (Cq), 137.0 (Cq), 134.1 (Cq), 133.9 (Cq), 133.5 (Cq), 133.4 (Cq), 129.7 (CH), 129.2 (CH), 127.7 (CH), 127.6 (Cq), 123.8 (CH), 118.6 (CH), 104.1 (CH), 55.5 (CH_3), 45.9 (CH_2), 26.4 (CH_2), 24.1 (CH_2), 21.7 (CH_3), 16.7 (CH_3). HRMS (ESI) *m/z*: calcd. for $C_{22}H_{23}NO_3SNa^+$ 404.1291; found 404.1297.

10-methyl-1-tosyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (9b): White solid, 48% yield, mp 131-132 °C (MeOH). R_f 0.19 (9:1 PE/Et_2O). ^1H NMR (600 MHz) δ (ppm): 8.08 (d, 1H, *J* = 8.3 Hz), 7.74 (d, 1H, *J* = 7.6 Hz), 7.54-7.47 (m, 2H) superimposed to 7.46 (d, 2H, *J* = 7.69 Hz), 7.32 (s, 1H), 7.20 (d, 2H, *J* = 7.6 Hz), 4.15-4.10 (m, 1H), 3.57-3.51 (m, 1H), 2.83 (s, 3H), 2.41 (s, 3H), 2.40-2.35 (m, 1H), 2.07-2.00 (m, 1H), 1.55-1.43 (m, 2H). ^{13}C NMR (150 MHz) δ (ppm): 143.7 (Cq), 137.0 (Cq), 136.0 (Cq), 134.8 (Cq), 133.5 (Cq), 132.9 (Cq), 132.3 (Cq), 129.7 (CH), 127.7 (CH), 127.7 (CH), 126.2 (CH), 125.6 (CH), 125.4 (CH), 124.0 (CH), 45.9 (CH_2), 26.7 (CH_2), 24.0 (CH_2), 21.7 (CH_3), 16.5 (CH_3). HRMS (ESI) *m/z*: calcd. for $C_{21}H_{21}NO_2SNa^+$ 374.1191; found 374.1186.

7-methoxy-10-methyl-1-tosyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (9c): White solid, 49% yield, mp 166-167 °C (MeOH). R_f 0.24 (8:2 hexane/EtOAc). ^1H NMR (400 MHz) δ (ppm): 7.98 (d, 1H, *J* = 9.2 Hz), 7.46 (d, 2H, *J* = 8.0 Hz), 7.21-7.15 (m, 4H), 7.04 (d, 1H, *J* = 2.8 Hz), 4.15-4.05 (m, 1H), 3.92 (s, 3H), 3.55-3.48 (m, 1H), 2.79 (s, 3H), 2.41 (s, 3H), 2.36-2.31 (m, 1H), 2.06-1.98 (m, 1H), 1.56-1.41 (m, 2H). ^{13}C NMR (100 MHz) δ (ppm): 157.9 (Cq), 143.6 (Cq), 137.1 (Cq), 136.7 (Cq), 134.8 (Cq), 133.6 (Cq), 131.6 (Cq), 129.7 (2CH), 128.1 (CH), 127.7 (2CH), 127.1 (CH), 123.0 (CH), 117.8 (CH), 105.9 (CH), 55.4 (CH_3), 45.9 (CH_2), 26.7 (CH_2), 24.0 (CH_2), 21.7 (CH_3), 16.4 (CH_3). Elemental analysis (%): calcd for $C_{22}H_{23}NO_3S\cdot{}^1/_4H_2O$ C 68.46, H 6.14, N 3.63; found C 68.21, H 6.13, N 3.45.

5-methyl-6-tosyl-6,7,8,9-tetrahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-*g*]quinoline (9d): White solid, 67% yield, mp 175-177 °C (hexane/EtOAc). R_f 0.14 (9:1 PE/EtOAc). ^1H NMR (600 MHz) δ (ppm): 7.45 (d, 2H, *J* = 8.3 Hz), 7.36 (s, 1H), 7.20 (d, 2H, *J* = 8.3 Hz), 7.14 (s, 1H), 7.01 (s, 1H), 6.05 (s, 2H), 4.10 (dt, 1H, *J* = 13.8 Hz, 8.6 Hz), 3.50 (ddd, 1H, *J* = 13.4 Hz, 8.3 Hz, 4.5 Hz), 2.72 (s, 3H), 2.41 (s, 3H), 2.32-2.27 (m, 1H), 2.03-1.96 (m, 1H), 1.55-1.46 (m, 1H), 1.41 (td, 1H, *J* = 13.3 Hz, 5.4 Hz). ^{13}C NMR (150 MHz) δ (ppm): 147.7 (Cq), 147.6 (Cq), 143.6 (Cq), 137.0 (Cq), 134.3 (Cq), 133.7 (Cq), 132.5 (Cq), 129.6 (CH), 129.6 (Cq), 129.3 (Cq), 127.7 (CH), 123.3 (CH), 103.7 (CH), 102.1 (CH), 101.2 (CH_2), 45.8 (CH_2), 26.3 (CH_2), 24.0 (CH_2), 21.7 (CH_3), 16.8 (CH_3). HRMS (ESI) *m/z*: calcd. for $C_{22}H_{21}NO_4SNa^+$ 418.1084; found 418.1087.

7,10-dimethyl-1-tosyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (*p*-9e): Separated from regioisomer ***o*-9e** by HPLC (9:1 MeCN/H_2O, 2.5 ml/min). White solid, 42% yield (66% total yield of two isomers), mp 188-190 °C. R_f 0.45 (8:2 PE/Et_2O). ^{1}H NMR (600 MHz) δ (ppm): 7.97 (d, 1H, *J* = 8.6 Hz), 7.50 (s, 1H), 7.44 (d, 2H, *J* = 8.3 Hz), 7.35 (dd, 1H, *J* = 8.6 Hz, 1.4 Hz), 7.22 (s, 1H), 7.19 (d, 2H, *J* = 7.9 Hz), 4.11 (td, 1H, *J* = 13.8 Hz, 8.6 Hz), 3.53 (ddd, 1H, *J* = 13.1 Hz, 8.3 Hz, 4.1 Hz), 2.80 (s, 3H), 2.51 (s, 3H), 2.41 (s, 3H), 2.36-2.32 (m, 1H), 2.05-1.98 (m, 1H), 1.54-1.47 (m, 1H), 1.42 (td, 12.9 Hz, 4.8 Hz). ^{13}C NMR (150 MHz) δ (ppm): 143.6 (Cq), 137.0 (Cq), 136.1 (Cq), 135.8 (Cq), 134.7 (Cq), 132.7 (Cq), 132.5 (Cq), 131.1 (Cq), 129.7 (CH), 127.8 (CH), 127.7 (CH), 126.7 (CH), 125.3 (CH), 123.4 (CH), 45.9 (CH_2), 26.7 (CH_2), 24.0 (CH_2), 21.7 (CH_3), 21.7 (CH_3), 16.4 (CH_3). HRMS (ESI) *m/z*: calcd. for $C_{22}H_{23}NO_2SNa^+$ 388.1347, found 388.1345.

9,10-dimethyl-1-tosyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (*o*-9e): Separated from regioisomer ***p*-9e** by HPLC (9:1 MeCN/H_2O, 2.5 ml/min). White solid, 24% yield (66% total yield of two isomers). R_f 0.45 (8:2 PE/Et_2O). ^{1}H NMR (600 MHz) δ (ppm): 7.55 (d, 1H, *J* = 8.3 Hz), 7.47 (d, 2H, *J* = 8.3 Hz), 7.33-7.29 (m, 1H), 7.28-7.26 (m, 2H), 7.20 (d, 2H, *J* = 7.6 Hz), 4.16-4.10 (m, 1H), 3.48 (ddd, 1H, *J* = 13.1 Hz, 8.3 Hz, 4.8 Hz), 2.97 (s, 3H) superimposed to 2.97 (s, 3H), 2.41 (s, 3H), 2.36 (ddd, 1H, *J* = 14.5 Hz, 5.2 Hz, 2.8 Hz), 1.54-1.48 (m, 1H), 1.43 (td, 1H, *J* = 13.2 Hz, 6.0 Hz). ^{13}C NMR (150 MHz) δ (ppm): 143.6 (Cq), 137.1 (Cq), 136.7 (Cq), 136.7 (Cq), 135.3 (Cq), 135.0 (Cq), 140.0 (Cq), 133.7 (Cq), 129.7 (CH), 129.6 (CH), 127.7 (CH), 126.8 (CH), 125.8 (CH), 125.1 (CH), 45.7 (CH_2), 26.6 (CH_2), 26.2 (CH_3), 24.0 (CH_2), 21,9 (CH_3), 21.8 (CH_3). HRMS (ESI) *m/z*: calcd. for $C_{22}H_{23}NO_2SNa^+$ 388.1347, found 388.1343.

7,9,10-trimethyl-1-tosyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (9f): White solid, 58% yield, mp 202-203 °C (MeCN). R_f 0.28 (9:1 PE/Et_2O). ^{1}H NMR (600 MHz) δ (ppm): 7.46 (d, 2H, *J* = 8.2 Hz), 7.32 (s, 1H), 7.18 (d, 2H, *J* = 8.1 Hz) superimposed to 7.17 (s, 1H), 7.12 (s, 1H), 4.12 (ddd, 1H, *J* = 13.8 Hz, 8.8 Hz, 7.8 Hz), 3.50-3.45 (m, 1H), 2.95 (s, 3H), 2.93 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 2.33 (ddd, 1H, *J* = 14.5 Hz, 5.3 Hz, 2.8 Hz), 2.04-1.98 (m, 1H), 1.54-1.47 (m, 1H), 1.42-1.36 (m, 1H). ^{13}C NMR (150 MHz) δ (ppm): 143.5 (Cq), 137.1 (Cq), 136.5 (Cq), 136.4 (Cq), 135.4 (Cq), 135.2 (Cq), 134.3 (Cq), 134.2 (Cq), 131.9 (CH), 131.8 (Cq), 129.6 (CH), 127.7 (CH), 125.8 (CH), 124.5 (CH), 45.8 (CH_2), 26.6 (CH_2), 26.1 (CH_3), 24.0 (CH_2), 21.7 (CH_3), 21.2 (CH_3). HRMS (ESI) *m/z*: calcd. for $C_{23}H_{25}NO_2SNa^+$ 402.1504; found 407.1500.

7,8,9-trimethoxy-10-methyl-1-tosyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (9g): White solid, 63% yield, mp 166-167 °C (*i*-Pr_2O). R_f 0.36 (8:2 PE/EtOAc). ^{1}H NMR (600 MHz) δ (ppm): 7.51 (d, 2H, *J* = 7.9 Hz), 7.21 (d, 2H, *J* = 7.9 Hz), 7.14 (s, 1H), 6.83 (s, 1H), 4.14-4.08 (m, 1H), 3.96 (s, 3H), 3.96 (s, 6H), 3.49-3.44 (m, 1H), 2.92 (s, 3H), 2.41 (s, 3H), 2.34-2.30 (m, 1H), 2.06-1.99 (m, 1H), 1.52-1.47 (m, 2H). ^{13}C NMR (150 MHz) δ (ppm): 152.9 (Cq), 151.5 (Cq), 143.5 (Cq), 142.4 (Cq), 137.2 (Cq), 135.8 (Cq), 134.8 (Cq), 133.1 (Cq), 130.8 (Cq), 129.6 (CH), 127.7 (CH), 123.7 (Cq), 123.0 (CH), 102.8 (CH), 61.6 (CH_3), 61.2 (CH_3), 55.9 (CH_3), 45.7 (CH_2), 26.6 (CH_2), 24.0 (CH_2), 24.0 (CH_2), 21.7 (CH_3), 19.2 (CH_3). HRMS (ESI) *m/z*: calcd. for $C_{24}H_{27}NO_5SNa^+$ 464.1508; found 464.1505.

8,10-dimethyl-1-tosyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (9h): White solid, 57% yield, mp 178-179 °C (hexane). R_f 0.36 (8:2 PE/Et_2O). ^{1}H NMR (600 MHz) δ (ppm): 7.85 (s, 1H), 7.63 (d, 1H, *J* = 8.3 Hz), 7.45 (d, 2H, *J* = 8.3 Hz), 7.32 (dd, 1H, *J* = 8.3, 1.4 Hz), 7.27 (s, 1H), 7.19 (d, 2H, *J* = 8.3 Hz), 4.14-4.08 (m, 1H), 3.53 (ddd, 1H, *J* = 13.1, 7.9, 4.1 Hz), 2.80 (s, 3H), 2.56 (s, 3H), 2.41 (s, 3H), 2.37-2.33 (m, 1H), 2.05-1.98 (m, 1H), 1.55-1.48 (m, 1H), 1.44 (td, 1H, *J* = 13.1, 5.5 Hz). ^{13}C NMR (150 MHz) δ (ppm): 143.6 (Cq), 137.1 (Cq), 135.2 (Cq), 135.0 (Cq), 134.1 (Cq), 135.6 (Cq), 133.0 (Cq), 130.5 (Cq), 129.7 (CH), 128.3 (CH), 128.3 (CH), 127.7 (CH), 127.5 (CH), 124.6 (CH), 123.8 (CH), 45.9 (CH_2), 26.6 (CH_2), 24.1 (CH_2), 22.2 (CH_3), 21.7 (CH_3), 16.5 (CH_3). HRMS (ESI) *m/z*: calcd. for $C_{22}H_{23}NO_2SNa^+$ 388.1347; found 388.1349.

Synthesis of 8-methoxy-10-methyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (10a): The *N*-tosyl deprotection was performed according to a literature procedure.[26a] A solution of **9a** (1.0 eq, 0.2 mmol) in anhydrous DME (0.1 M) was cooled down to -78 °C. A 1.0 M solution of Na and naphthalene (6.0 eq) in anhydrous DME was prepared. The colour of sodium naphthalenide is dark green. The solution of sodium naphthalenide was slowly added to the solution of **9a** at -78 °C until the dark green colour was persistent. The mixture was stirred at -78 °C for 30 min, then it was allowed to warm to room temperature, H_2O was added and the mixture was extracted three times with EtOAc; the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum. The crude product was purified by flash column chromatography to afford pure **10a** as an off-white solid. 75% yield, mp 114-116 °C (hexane). R_f 0.40 (9:1 PE/EtOAc). ^{1}H NMR (600 MHz) δ (ppm): 7.52 (d, 1H, *J* = 8.8 Hz), 7.28 (s, 1H), 7.08 (d, 1H, *J* = 2.1 Hz), 6.85 (dd, 1H, *J* = 8.8, 2.2 Hz), 3.92 (s, 3H), 3.49-3.47 (m, 2H), 2.96 (d, 2H, *J* = 6.4 Hz), 2.31 (s, 3H), 1.99 (quin, 2H, *J* = 6.2 Hz). ^{13}C NMR (150 MHz) δ (ppm): 157.6 (Cq), 141.2 (Cq), 133.5 (Cq), 129.5 (CH), 125.8 (CH), 122.8 (Cq), 122.0 (Cq), 113.4 (CH), 109.9 (Cq), 101.4 (CH), 55.3 (CH_2), 42.8 (CH_2), 28.3 (CH_2), 22.3 (CH_2), 11.5 (CH_3). HRMS *m/z*: calcd. for 250.1208, found 250.1211.

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FULL PAPER

The gold(I)-catalysed cyclization of *N*-tosyl-protected 5-benzyl-6-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydropyridines, prepared by Sonogashira coupling of lactam-derived enol triflates, provides tetrahydrobenzo[*g*]quinolones. The Au(I)-catalysed reaction is carried out with $(C_6F_5)_3PAuCl/AgNTf_2$ and proceeds via a 6-*exo*-*dig* cyclization to the aromatic tetrahydrobenzo[*g*]quinolines. The mode of cyclization is discussed and supported by DFT calculation.

Gold Catalysis

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Gold(I)-Catalysed Hydroarylation of Lactam-Derived Enynes as an Entry to Tetrahydrobenzo[*g*]quinolines