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Atroposelective Synthesis of Tetrahydropyrrolo[3,2-*c*]azepine Derivatives Through Gold(I)-Catalyzed Hydroarylation

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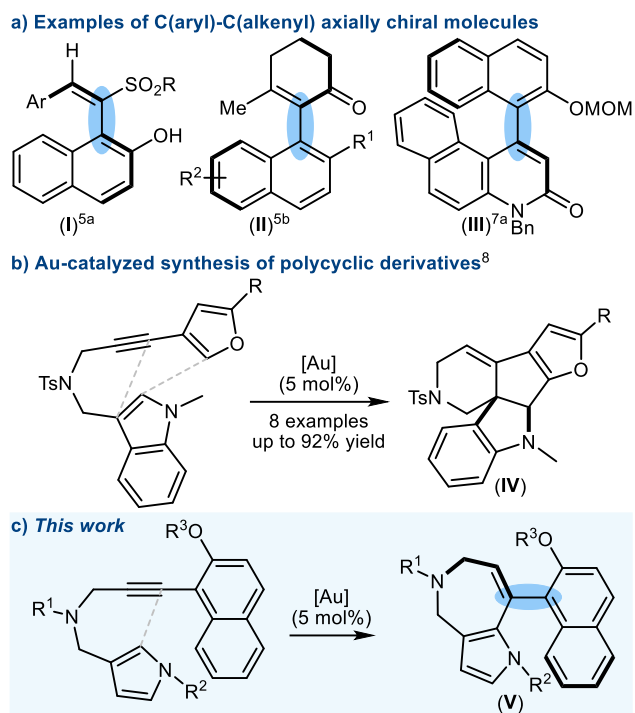
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Abstract. A series of enantioenriched substituted tetrahydropyrrolo[3,2-*c*]azepine products possessing an axial chirality were synthesized in 63-99% yield through a gold(I)-catalyzed hydroarylation. DFT calculations rationalized the reactivity observed for the formation of such complex molecular frameworks and guided our choice in the pyrrole *N*-substituent to isolate configurationally stable compounds.

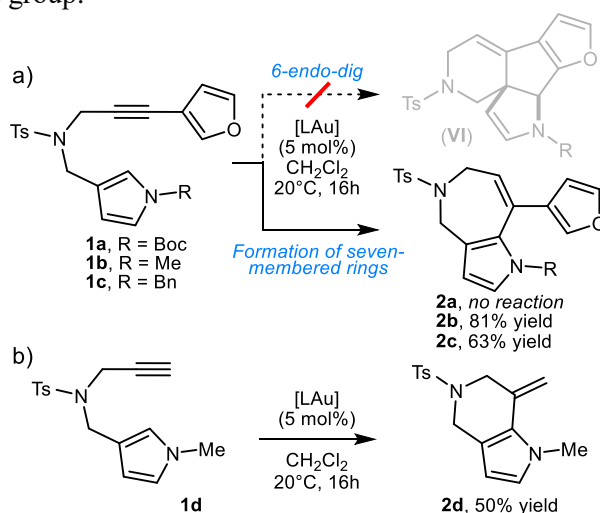
Atropochiral molecules are present in many natural products and active pharmaceutical ingredients.^[1] They are also used in materials science and as ligands and organocatalysts in asymmetric catalysis.^[2] All these various applications have sharpened the interest of the scientific community for these chiral molecules and, as a result, many stereoselective methodologies have been designed and implemented in the last few decades.^[3] Axially chiral compounds are mostly (hetero)biaryl scaffolds. However, nonbiaryl C-C atropisomers are known and attract an increasing attention due to their original molecular diversity and potential applications.^[3d,4] Representative aryl-alkene chiral molecules are shown in Scheme 1a. For instance, enantioenriched sulfone-containing styrenes (**I**) were prepared via an organocatalytic approach involving the formation of vinylidene *ortho*-quinone methide intermediates.^[5a] Chiral 2-aryl-cyclohexenones (**II**) were isolated through an atroposelective palladium-catalyzed Suzuki coupling reaction.^[5b] Because of our interest in asymmetric gold catalysis in recent years,^[6] we were particularly interested in the synthesis of molecule (**III**),^[7a] isolated via an intramolecular hydroalkenylation of alkyne.^[7] In the presence of chiral gold(I) catalysts, this axially chiral compound was isolated in up to 61% ee. Recently, we reported the synthesis of polycyclic molecules (**IV**), shown in Scheme 1b, via a gold-catalyzed hydroarylation approach.^[8] During the optimization of this reaction, we realized that the use of pyrrole derivatives, instead of indole substrates, gave a different reactivity, leading to tetrahydropyrrolo-[3,2-*c*]azepines (**V**) (Scheme 1c). In fact, this reactivity was similar to the work developed by Yu, with the gold-catalyzed synthesis of fused cycloheptafurans.^[9] Given the increasing interest of this skeleton (**V**) and its analogues,^[10] we have studied in depth the synthesis of these compounds. In this paper, we report our efforts in the development of an asymmetric version of this transformation.



Scheme 1. Synthesis of nonbiaryl C-C atropisomers and proposed work.

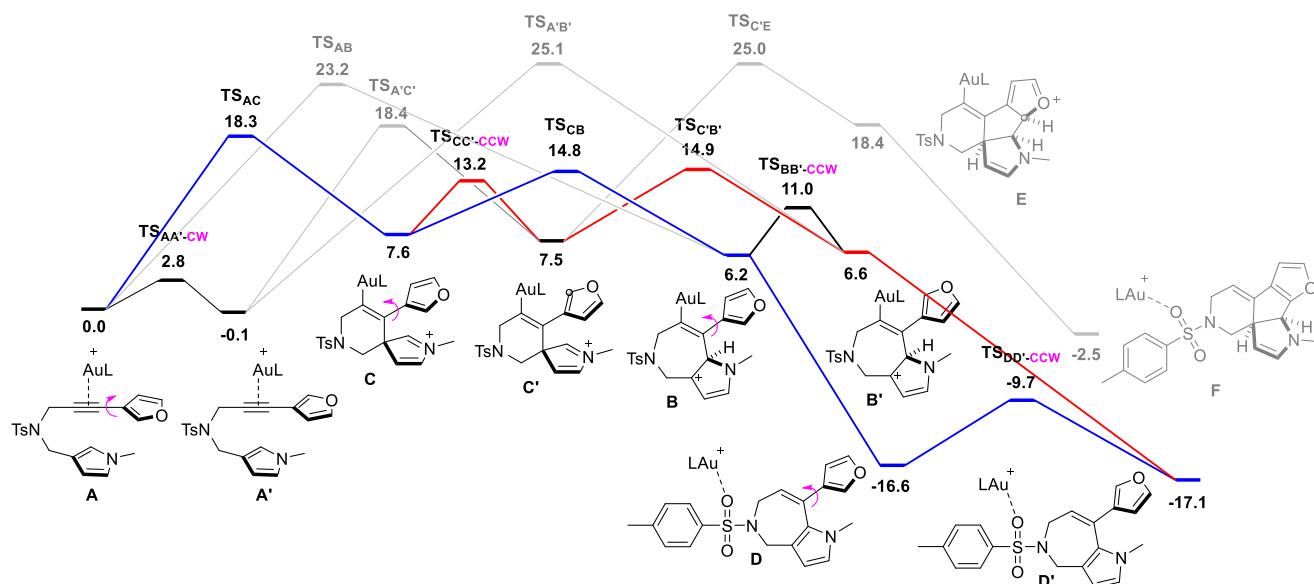
Density functional theory (DFT) calculations were also performed to better understand the key cyclization step catalyzed by cationic gold(I) complexes, and the configurational stability of such complex molecules.

At the beginning of this study we explored the reactivity of *N*-tethered pyrrole-furylpropargyl substrates **1a-c** (Scheme 2a). In the presence of [Au(JohnPhos)(CH₃CN)]SbF₆ catalyst, while the *N*-Boc-pyrrole substrate **1a** proved to be unreactive, we observed the formation of the seven-membered fused tetrahydropyrrolo[3,2-*c*]azepines **2b** and **2c**, starting from *N*-methyl and *N*-benzyl-pyrrole substrates **1b-c**. This reaction was not necessarily expected, since a polycyclic product was isolated from the corresponding indole or dihydropyrrole substrates.^[8] In the present case, with pyrrole derivatives, we never observed any products (**VI**), resulting from a *6-endo-dig* cyclization. In addition, it is important to note that the *N*-methyl pyrrole-propargylamine substrate **1d** gave the *6-exo-dig* cyclization product **2d** in 50% yield (Scheme 2b), as already demonstrated for the furan analogue, in the work of Yu's group.^[9]



Scheme 2. Synthesis of 1,4,5,6-tetrahydropyrrolo[3,2-*c*]azepines. [LAu] = [Au(JohnPhos)(CH₃CN)]SbF₆. Ts = tosyl, Boc = *tert*-butoxycarbonyl.

To gain a better understanding of the reaction mechanism that enables the formation of 1,4,5,6-tetrahydropyrrolo[3,2-*c*]azepines, such as compounds **2b** and **2c**, we undertook a DFT computational study. All optimizations were performed at the B3LYP level of theory^[11a-c] using the Gaussian 16 package.^[11d] The Au atom was described by the LANL2DZ basis set, which includes a double-valence basis set with the Hay and Wadt effective core potential.^[12] The 6-31G(d,p) Pople basis set^[13] was used for the other atoms (C, H, O, N and P). Single point energies were calculated on the optimized structures at 298 K and 1 atm at the M06 level of theory.^[11] The Gaussian basis set def2-QZVP^[14] was used for Au and 6-311+G(2d,p) for the other atoms. Several pathways were envisaged to account for the formation of the 7-membered ring product **2**, starting from the JohnPhos alkyne gold complex **A** selected as reference of the free energies (Scheme 3). Of note, the relative orientation of the pyrrole vs the furan moiety can lead to two conformers **A** and **A'**, connected by a rotation transition state (TS). This rotation may occur in a clockwise (CW) or a counterclockwise (CCW) fashion. For each such rotation TS, only the best option will be presented. This is the CW one that leads to the lowest-lying TS between **A** and **A'**, located a 2.8 kcal/mol on the free energy surface. **A'** is slightly more stable than **A** by 0.1 kcal/mol. The formation of a 6- or a 7-membered ring was computed from **A**. Because of the dearomatization of the pyrrole ring, both pathways start with endergonic steps. Since the 6-*endo*-dig cyclization transition state **TS_{AC}** (18.3 kcal/mol) and the subsequent 1,2-shift transition state **TS_{CB}** (14.8 kcal/mol) lie 4.9 and 8.4 kcal/mol below the 7-*endo*-dig cyclization transition state **TS_{AB}** (23.2 kcal/mol) respectively, the stepwise formation of the 7-membered ring complex **B** through the spiro intermediate **C** seems to be the most likely pathway (in blue). The last step converting **B** into **D** (protodemetalation) is formally a symmetry forbidden 1,3-H shift which cannot be intramolecular.



Scheme 3. Free energy profile related to the formation of **2b** (ΔG_{298} , kcal/mol; L = CyJohnPhos ((2-biphenyl)dicyclohexylphosphine).

It requires an unknown proton shuttle and therefore no transition state can be provided. It is yet a strongly exergonic process, the final complex **D** lying 16.6 kcal/mol below **A**. Complex **D'**, which is a rotamer of **D** easily formed by CCW rotation of the furan moiety via **TS_{DD'}-CCW** (-9.7 kcal/mol), is more stable than **D** by 0.5 kcal/mol. A more direct route to **D'** is shown in red. It involves the formation of rotamer **C'** via **TS_{CC'}-CCW** (13.2 kcal/mol) and then rotamer **B'** after 1,2-shift through **TS_{C'B'}** (14.9 kcal/mol). Since **TS_{CB}** and **TS_{C'B'}** virtually have the same free energy (14.8 vs 14.9 kcal/mol), there is no obvious preference for one route or another. Of note, formation of **B'** or **C'** is more difficult from **A'** (grey lines) than from **A**.

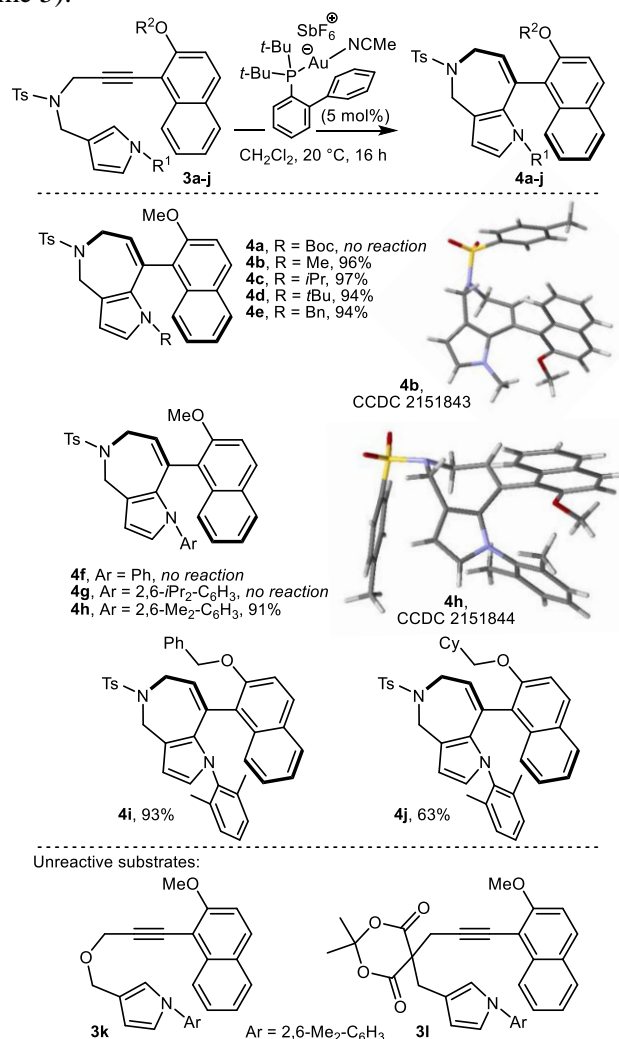
Due to geometry constraints, the construction of the polycyclic framework of intermediate **E** is only possible from **C'** and not from **C**, hence highlighting the importance of taking these rotamers into account in the calculations. However, this step requires 17.5 kcal/mol of free energy of activation to reach **TS_{C'E}** (25.0 kcal/mol), which is twice as much as the free energy demand to reach **TS_{C'B'}** (14.9 kcal/mol). Thus, the calculations predict that the 7-membered ring derivative will prevail over the polycyclic product, which is in line with the experimental observation.

Considering the few methods developed in gold catalysis for the synthesis of tetrahydropyrrolo[3,2-*c*]azepines,^[10] we wondered whether we could isolate nonbiaryl C-C atropisomers, by replacing the 3-furyl substituent by 2-methoxynaphthalene (Scheme 4).

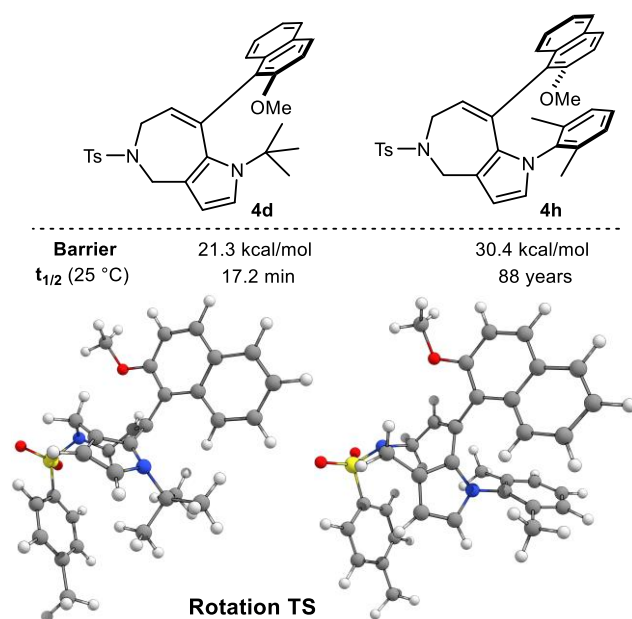
Like for the substrate **1a**, pyrrole *N*-Boc substrate **3a** proved also unreactive, in sharp contrast with substrates **3b-e** that gave the corresponding products **4b-e** in 94-97% yields. This reactivity imposes to find the right balance between the pyrrole nucleophilicity and the steric hindrance of the nucleophile. Indeed, among the three *N*-aryl-pyrrole substrates **3f-h**, the only substrate that proved reactive was substrate **3h**, gratifyingly leading to chiral compound **4h** in 91% yield. The reaction was launched at 80°C in DCE (dichloroethane), and at 110°C in toluene with substrates **3f-g**, without success. Molecular structures of **4b** and **4h** were ascertained by X-ray diffraction studies. With the same *N*-2,6-dimethylphenyl-pyrrole unit, different naphthol substituents were tested (R^2 = benzyl, CH_2 -cyclohexyl). The corresponding compounds **4i-j** were isolated in 65-93% yields. Concerning the mechanistic pathway for the formation of compounds **4**, free energy profile was also investigated (see ESI for details).

With the ambition to extend the substrate scope of our methodology, we finally tried different linkers between alkyne and pyrrole functions, unfortunately without success (Scheme 4, substrates **3k-l**). It is well established that the nature of the tethers deeply influences the reactivity and the selectivity of cycloisomerization reactions.^[15a-b] These differences could be tentatively explained by the hybridization of the hetero-atom present at the tether^[15c] or the trapping of the catalyst by the substrate.^[15d]

At this point of the study, we wondered about the configurational stability of the new axially chiral compounds **4**. To answer this question, rotational barriers and half-life time of molecules **4d** and **4h** were evaluated using DFT calculations^[16] (Scheme 5).



Scheme 4. Gold(I)-catalyzed cyclizations for the formation of tetrahydropyrrolo-[3,2-*c*]azepines (Cy = cyclohexyl).



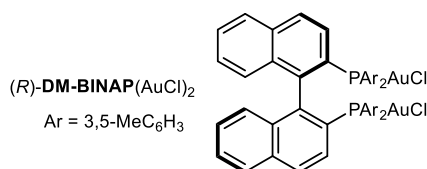
Scheme 5. Computed rotation barriers and corresponding half-life of compounds **4d** and **4h** using the SMD M06-D3/6-31+G(d)//M06-D3/6-31G(d) level of theory.

It turned out that the protecting group of the pyrrole nitrogen plays an important role since **4d** ($R^1 = t\text{Bu}$) has a short half-life, while compound **4h** ($R^1 = 2,6\text{-Me}_2\text{-C}_6\text{H}_3$) proved to be configurationally stable at 25 °C. These half-life times are consistent with our experimental findings, i.e. only enantiomers of **4h** (and the analogues **4i** and **4j**) could be separated by HPLC equipped with a chiral stationary phase. The ease of the rotation of the 2-methoxynaphthyl group of compound **4d** might seem surprising but in this case, the rotation transition state shows that the pyramidalization of the pyrrole nitrogen is possible, allowing the bulky alkyl group to move aside. In contrast, in the rotation transition state of **4h**, the pyrrole nitrogen remains sp^2 hybridized, which promotes a strong steric congestion on the methoxynaphthyl side.

Having in hand configurationally stable atropoisomers, we then tackled the development of the asymmetric version of this reaction, through the use of chiral gold(I) complexes (Table 1). It may be recalled here that the examples of asymmetric gold(I)-catalyzed synthesis of non-centrochiral compounds are quite limited,^[17] especially concerning the atroposelective syntheses.^[7] Recently, we can note the efficient asymmetric gold-catalyzed synthesis of 1,1'-binaphthalene-2,3'-diols by the Alcarazo group.^[7c]

Table 1. Enantioselective gold(I)-catalyzed hydroalkenylation of **3h-j**.

entry	R	X	AgX (x mol%)	Yield (%) ^{a)}	er ^{b)}
1	Me	SbF ₆	5	4h , 40	70:30
2	Me	SbF ₆	10	4h , 90	67:33
3	Me	OTf	10	4h , 95	66.5:33.5
4	Me	NTf ₂	10	4h , 80	67:33
5	Me	BF ₄	10	4h , 85	58.5:41.5
6	Me	PF ₆	10	4h , 99	75:25
7	CH ₂ Ph	PF ₆	10	4i , 65	76:24
8	CH ₂ Cy	PF ₆	10	4j , 65	81.5:18.5



a) Isolated yields. b) Enantiomeric ratio (er) determined by HPLC on a chiral stationary phase.

A screening of chiral precatalysts, silver salts and solvents (entries 1-6) revealed that the bimetallic gold chloride of (*R*)-DM-BINAP ligand, combined with 2 equivalents of AgPF₆ as chloride scavenger in dichloromethane at 20 °C, led to an encouraging 75:25 enantiomeric ratio (entry 6). With other chiral ligands tested, such as DTBM-SEGPHOS, MeO-BIPHEP or MeO-TADDOL phosphoramidite, enantiomeric ratios were lower; see Supporting Information for details). Starting with substrates **3i-j**, with different naphthol substituents, allowed to increase the enantiomeric ratio up to 81.5:18.5 (entries 7-8).

In conclusion, we have developed a synthesis of tetrahydropyrrolo[3,2-*c*]azepines via an (asymmetric) gold(I)-catalyzed hydroalkenylation. By the judicious choice of the *N*-pyrrole protecting group, products **4h-j** proved to be configurationally stable at room temperature. This work represents a rare example of the formation of axially chiral compounds by asymmetric gold catalysis. Investigation of the reaction mechanism using DFT calculations gives us the keys to understand the reactivity currently observed with these substrates.

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