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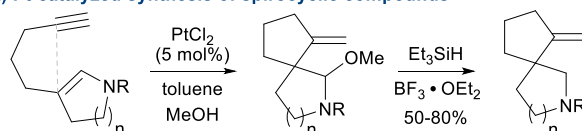
Synthesis of Chiral Polycyclic *N*-Heterocycles via Gold(I)-Catalyzed 1,6-Enyne Cyclization/Intramolecular Nucleophilic Addition

Xu Han,^{a,b} Quentin Gaignard-Gaillard,^{a,b} Pascal Retailleau,^a Vincent Gandon,^{*b,c} Arnaud Voituriez^{*a}

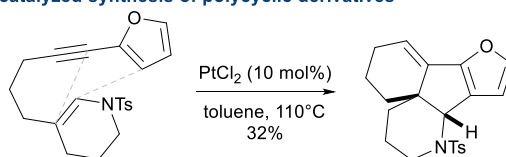
Cycloisomerization of *N*-tethered indole- and dihydropyrrole-arylpropargyl substrates into complex polycycles was investigated by using gold(I) catalysis. Enantioselectivities up to 93% ee were obtained in the asymmetric version of this process. DFT calculations rationalized the reactivity observed for the formation of such complex molecular frameworks.

Transition metal-catalyzed cycloisomerization of enyne substrates is among the most studied transformation in organic synthesis. Numerous products are thus isolable, starting from properly functionalized substrates or different metal complexes.¹ Furthermore, if the synthesized products possess stereogenic centers, the use of chiral complexes could allow the isolation of enantiopure molecules of interest in total synthesis.² Among all polyunsaturated substrates, 1,6-enynes are the most studied, and cyclization can occur with the use of a wide range of catalysts such as palladium, rhodium, iridium, platinum and gold complexes.^{1,2} These (asymmetric) transformations provided a variety of skeletal rearrangements to access functionalized products. In addition, if these transformations are carried out in the presence of external nucleophiles, such as alcohols or electron-rich aryls, new carbon-heteroatom or carbon-carbon bonds can be generated.³ As part of this study, 1,6-enyne cyclization/internal nucleophilic additions will be considered,⁴ starting from enamide derivatives (Scheme 1). In 2004, Dake used enesulfonamide-tethered alkyne substrates, for the synthesis of alkaloid analogues.^{5,1f} Interestingly, spirocyclic molecules can be obtained from properly decorated substrates and using PtCl₂ as catalyst (Scheme 1a). In this transformation, methanol was used to trap the azacarbenium ion, and the addition of silane and boron trifluoride etherate afforded the corresponding spirocycle after reduction of the hemiaminal function.^{5b} Later on, Dake extended this methodology to cyclic enamide/aryl-alkyne

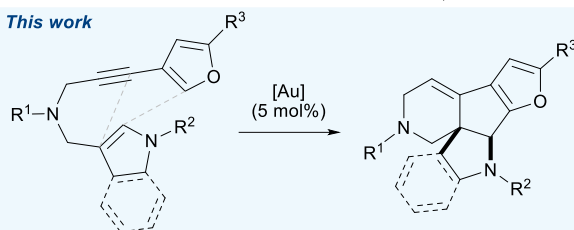
a) Pt-catalyzed synthesis of spirocyclic compounds^{5b}



b) Pt-catalyzed synthesis of polycyclic derivatives^{5c}



c) This work



Scheme 1. Lewis acid-catalyzed cyclization of 1,6-enamide/alkyne substrates.

substrates (Scheme 1b). In this case, the iminium intermediate could be directly trapped by the addition of the heteroaryl group, and after rearomatization that could provide a highly complex polycyclic molecule.^{5c} Au(I)-catalyzed transformations using acyclic enamides were also demonstrated by the same group.^{5d} Inspired by this work, Zhai applied this methodology to *N*-tethered substrates for a platinum-catalyzed diastereoselective transformation. In a very ingenious way, it allowed them to synthesize the natural product nakadomarin A.⁶ With a general interest in asymmetric gold(I) catalysis and its application to total synthesis,⁷ we intended to develop an enantioselective version of this transformation and the extension to 1,6-enyne substrates substituted with either indoles and dihydropyrroles (Scheme 1c). Furthermore, DFT calculations permitted to better understand the key cyclization step via a spirocyclic intermediate.

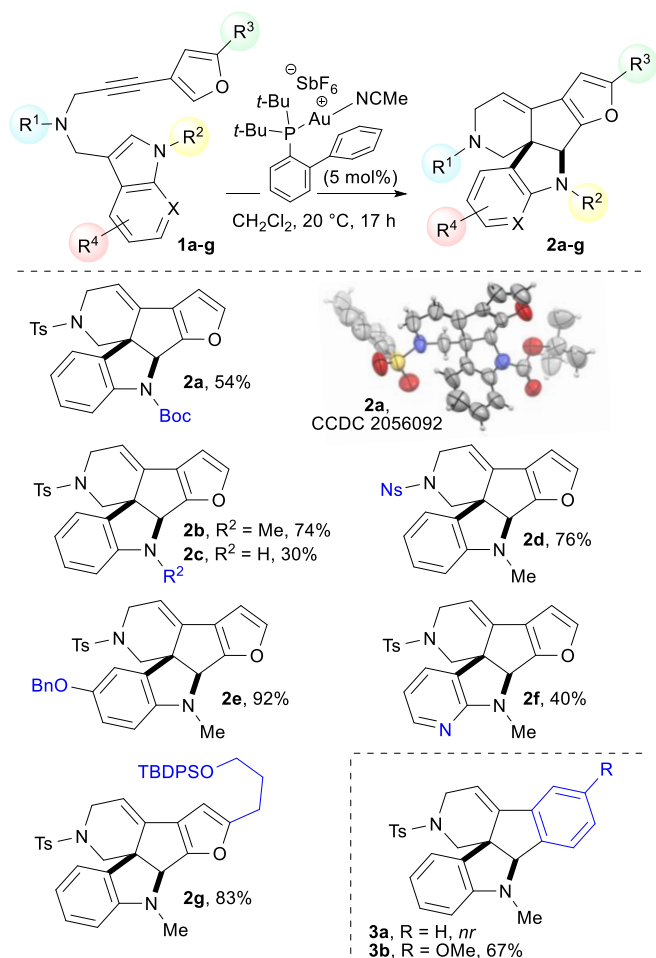
N-tosyl-*N*-arylpropargyl methylindole **1a** was first selected as model substrate to optimize the reaction conditions of the 1,6-enyne cycloisomerization, in the presence of different gold complexes. With the achiral [Au(JohnPhos)(CH₃CN)]SbF₆

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Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data; X-ray crystal structures of **2a** (CCDC 2056092) and **2f** (CCDC 2127769), see DOI: 10.1039/x0xx00000x.



Scheme 2. Gold(I)-catalyzed cyclizations (Ts = tosyl, Ns = nosyl, Boc = *tert*-butoxycarbonyl, Bn = benzyl, TBDPS = *tert*-butyldiphenylsilyl).

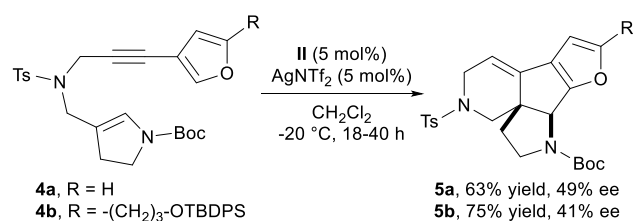
catalyst, in dichloromethane at room temperature, the pentacyclic nitrogen-containing product **2a** was isolated in 54% yield (Scheme 2). Its structure was ascertained by NMR analysis and X-ray diffraction studies. It turned out that the protecting group of the indole nitrogen plays an important role since compound **2b** ($R^2 = \text{Me}$) was isolated in 74% yield and the unprotected indole derivative **2c** ($R^2 = \text{H}$) was produced in only 30% yield. Optimization of the reaction conditions for the formation of this product proved to be unsuccessful. The use of either tosyl- or nosyl-protected propargyl function did not have much influence on the reactivity (76% yield for product **2d**, $R^1 = \text{Ns}$). With electron-rich 5-benzyloxy-1-methyl-indole substrate, the pentacyclic product **2e** was isolated in 92% yield. Interestingly, the methodology could be used for the synthesis of pyrrolo[2,3-*b*]pyridine scaffold, as exemplified with product **2f** (see ESI for X-ray crystal structure determination). Finally, 2-substituted furan substrate furnished **2g** in 83% yield. Following the seminal work of Dake,^{5b} we tentatively engaged phenyl-alkyne derivative in this gold(I)-catalyzed addition/Friedel-Crafts process. Unfortunately, the substrate was inactive, either at room temperature or in refluxing dichloromethane. Introducing electron-donating methoxy-substituent on the aryl group increased its nucleophilicity and allowed to trap the

iminium intermediate, leading to the synthesis of product **3b** in 67% yield. Only one regioisomer of this product has been isolated. Overall, eight highly functionalized alkaloid analogues were synthesized in moderate to good yields. The next step, i.e. the asymmetric version of this cascade cyclization reaction was optimized first with substrate **1a** (Table 1). A systematic screening of chiral gold(I) pre-catalysts revealed that DTBM-MeO-BIPHEP(AuCl)₂ (**I**) and DTBM-SEGPHOS(AuCl)₂ (**II**) gave the most promising results (entries 1-2). We then tested substrates with different *N*-indole protecting groups, since the reactivity of the enamine functionality and the enantioselectivity of the transformation can be radically altered. With *N*-methyl-indole substrate **1b**, the best result (entry 5, 90% yield, 67% ee) was obtained with catalyst (**II**), in the presence of AgNTf₂, with a ratio $[\text{L}^*(\text{AuCl})_2/\text{Ag}] = [1/1]$. The increase of the catalytic activity and the enantioselectivity with the mono-activated chiral *bis*-gold complex has been already demonstrated in the literature.⁸ Finally, decreasing the reaction temperature to 10 °C gave the highest enantioselectivity (entry 6, 99% yield, 93% ee). Among all the silver salts tested $[\text{AgX}]$, with $\text{X} = \text{BF}_4, \text{PF}_6, \text{SbF}_6, \text{OTf}$, AgNTf₂ proved to be the best chlorine scavenger. The silver salt alone could not promote this transformation. Regrettably, this good result could not be transposed to unprotected product **2c** ($R^1 = \text{Ts}$, $R^2 = \text{H}$) or nosyl-substituted **2d** ($R^1 = \text{Ns}$, $R^2 = \text{Me}$) (entries 7-8, 20-50% yield, up to 62% ee).

Table 1. Enantioselective gold(I)-catalyzed cyclization of **1a-g**.

entry	R ¹	R ²	[Au]	Au/Ag ratio	Yield (%) ^a	ee (%) ^b
1	Ts	Boc	(I)	1/2	2a , 24	28
2	Ts	Boc	(II)	1/2	2a , 40	38
3	Ts	Me	(I)	1/2	2b , 35	41
4	Ts	Me	(II)	1/2	2b , 62	60
5	Ts	Me	(II)	1/1	2b , 90	67
6 ^c	Ts	Me	(II)	1/1	2b , 99	93
7 ^c	Ts	H	(II)	1/1	2c , 20	62
8 ^c	Ns	Me	(II)	1/1	2d , 50	45
9 ^{c,d}	Ts	Me	(II)	1/1	2g , 88	45
10 ^e	Ts	Me	(II)	1/1	3b , 35	19

For products **2a-d**, $R^3 = \text{H}$. ^a Isolated yields. ^b Determined by SFC on a chiral stationary phase. ^c At 10 °C for 40 h. ^d $R^3 = -(\text{CH}_2)_3\text{-OTBDPS}$. ^e Starting from substrate **S6**, see ESI.



Scheme 3. Reactivity of dihydropyrrole 3-furan-propargylamine substrates **4**.

Similarly, with chiral gold complexes, reaction rates were disappointing with functionalized substrates **1e-f** (<10% yield). With the optimal reaction conditions, **1g** gave promising results (88% yield, 45% ee) and **3b** was isolated in 35% yield and 19% ee (entries 9-10). We then decided to change the structure of enamine, by replacing the indole part by dihydropyrrole groups (substrates **4a-b**, Scheme 3). Indeed, in the presence of catalytic amounts of chiral gold complex (**II**) and AgNTf_2 in dichloromethane at $-20\text{ }^\circ\text{C}$, substrates **4a,b** furnished the corresponding tetracyclic products **5a,b** in 63-75% yield and up to 49% ee (Scheme 3).

To gain a better understanding of the reaction patterns that enable the formation of polycyclic structures such as compounds **2a-g** and **5a-b**, we undertook DFT computational studies. All optimizations were performed at the B3LYP level of theory^{9a-c} using the Gaussian 16 package.^{9d} 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.¹⁰ The 6-31G(d,p) Pople basis set¹¹ 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-QZVP¹² was used for Au and 6-311+G(2d,p) for the other atoms (see ESI for more details).

Several pathways were envisaged to account for the formation of the polycyclic products in the dihydropyrrole series, all starting from the Johnphos alkyne gold complex **A** selected as reference of the free energies (Scheme 4). Of note, the relative orientation of the dihydropyrrole 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 this rotation TS, the best option is the CCW one, with a modest barrier of 2.9 kcal/mol (vs 3.5 kcal/mol for the CW TS, not shown). The 6-endo-dig cyclization of **A'** to give the spiro complex **B'** is also faster than the transformation of **A** into intermediate **B** (6.3 vs 8.9 kcal/mol). Nevertheless, **B** and **B'** can be connected by a furan rotation TS, the CCW one being the lowest-lying ($\text{TS}_{\text{BB}'\text{-CCW}}$; -16.6 kcal/mol). Even though **B** is more stable than **B'** (-24.3 vs -23.1 kcal/mol), due to geometry constraints, the construction of the polycyclic framework of intermediate **C** by addition of the furan moiety to the iminium framework is only possible from **B'**, hence the importance of taking these rotamers into account in the calculations. This step requires 18.7 kcal/mol of free energy of activation to reach $\text{TS}_{\text{B}'\text{C}}$ (-4.4 kcal/mol). Protodemetalation

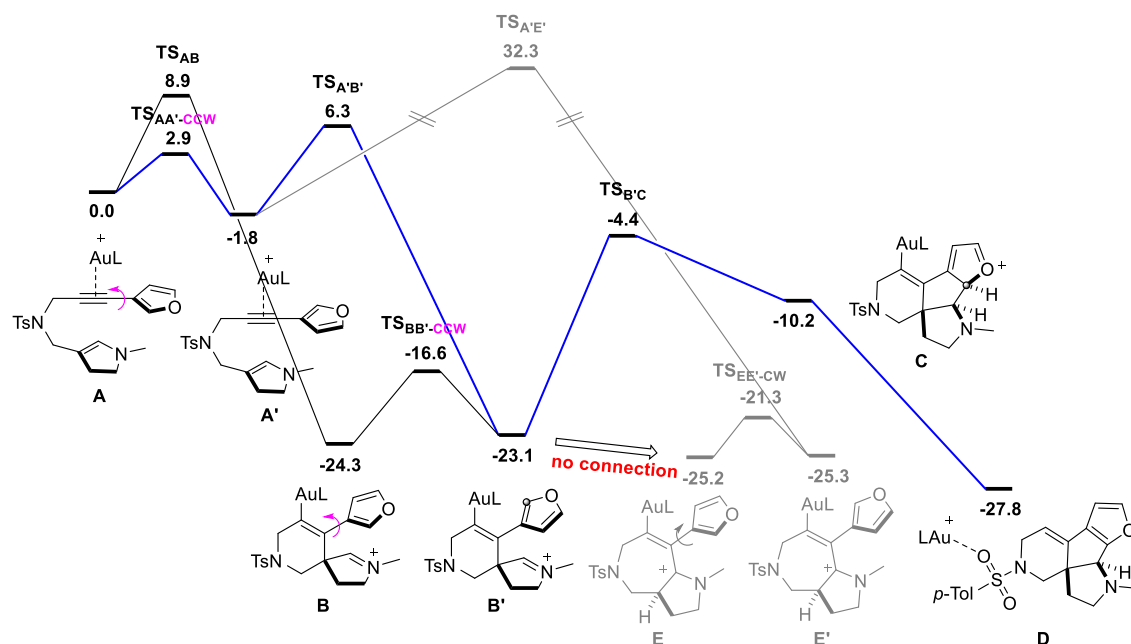
then leads to **D** in a strongly exergonic fashion (-27.8 kcal/mol). We also evaluated the possibility of a 7-endo-dig cyclization/ring contraction as alternate mechanism. However, the formation of the 7-membered complex **E'** from **A'**, by enamine addition to the terminal alkyne carbon and concomitant 1,2-H shift to generate a *N*-stabilized carbocation, faces an unsurmountable barrier to reach $\text{TS}_{\text{A}'\text{E}'}$ (32.3 kcal/mol). Besides, manifold efforts failed to connect rotamers **E** and **E'** to the spiro intermediates **B** and **B'**. Thus, it is the blue pathway in Scheme 4 that is supported by the computations.

In conclusion, we have developed a new gold(I)-catalyzed synthesis of highly functionalized nitrogen-containing polycyclic scaffolds. This method provides easy access to pentacyclic alkaloid-like molecules that are obtained in moderate to good yields and promising enantioselectivities (up to 93% ee) by using a chiral bis(phosphine)digold(I) catalyst. The use of either indole- or dihydropyrrole-tethered *N*-propargylfuran substrates gave access to complex polycyclic framework and we were able to understand this reactivity with the help of DFT calculations.

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Scheme 4. Free energy profile related to the formation of compound **5a/5b** (ΔG_{298} , kcal/mol; L = CyJohnPhos ((2-biphenyl)dicyclohexylphosphine).

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