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Enantioselective Gold-Catalyzed Pictet−Spengler Reaction

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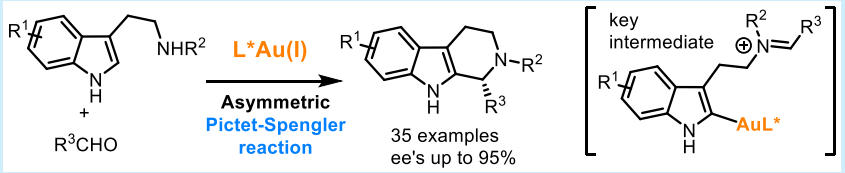
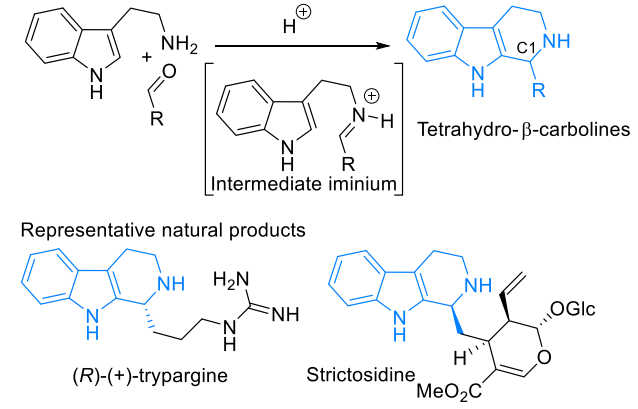
Supporting Information



ABSTRACT: Cationic chiral Au(I) complexes catalyze asymmetric Pictet−Spengler reactions between tryptamines and arylaldehydes. The resulting tetrahydro-β-carbolines are obtained with wide functional group tolerance in high yield and with high enantioselectivities (up to 95%). Aldehydes bearing polar or protic functions are well tolerated. The reaction features a hitherto unknown C2-auration of the indole as the key step, supported by density functional theory calculations.

The Pictet−Spengler reaction is the acid-catalyzed condensation of β-arylethylamines with aldehydes, leading to tetrahydroisoquinolines[1] or tetrahydro-β-carbolines (TH-β-Cs)[2] through the intermediacy of an iminium. With more than a century of intense research, the Pictet−Spengler reaction has now proved to be one of the most efficient and reliable method for the synthesis of tetrahydro-β-carbolines, a major class of heterocyclic compounds (Scheme 1).[3] Some of these derivatives are natural products, such as (*R*)-tryptargine or strictosidine. Numerous compounds embedding this structural unit are endowed with wide and interesting biological activities and are currently available as drugs or drug candidates.[3b]

Scheme 1. Structure and Natural Occurrence of Tetrahydro-β-carbolines



Numerous efforts have been made by synthetic chemists to control the absolute stereochemistry of C1.[4] Enantioselective approaches to tetrahydro-β-carbolines include the reduction of dihydro-β-carbolines, using Ru or Rh chiral complexes via asymmetric transfer hydrogenation reactions[5] or biocatalyzed reductions.[6] However, the Pictet−Spengler reaction is unarguably the leading synthetic strategy for the efficient synthesis of chiral tetrahydro-β-carbolines.[7] Beyond diastereoselective Pictet−Spengler reactions, enantioselective variants of the reaction can be catalyzed by Pictet−Spenglerase enzymes,[8] or by Brønsted acid organocatalysis.[9] Jacobsen, Seidel, List, and Hiemstra have developed elegant enantioselective Pictet−Spengler reactions using chiral thioureas[10] or chiral phosphoric acids[11] as catalysts, which have found numerous applications in total synthesis.[11d,12] Each of these methods has its strengths and weaknesses in the nature of the aldehyde used, the substituting pattern of the tryptamine, or the electronic environment around the indole ring. However, in the context of such an important synthetic transformation, one must note that no enantioselective strategies using organometallic catalysis have been reported.

In the course of a project aiming at the synthesis of polycyclic indole derivatives,[13] we extensively used the chiral phosphoric-acid-catalyzed Pictet−Spengler reaction to prepare key tetrahydro-β-carboline moieties that were cyclized to more

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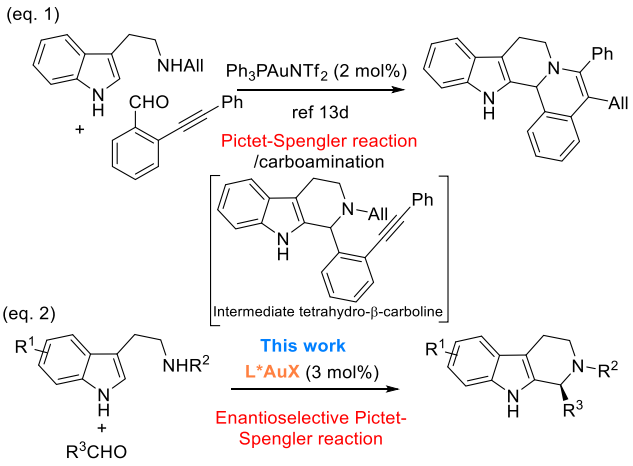
complex polycyclic compounds using palladium[13a,b] or gold catalysis.[13c,d] During the study of the carboamination of *N*-allyltetrahydro-*β*-carbolines to alkynes, we incidentally identified Au(I) complexes as efficient catalysts for the Pictet–Spengler reaction and developed a sequence combining this step with the carboamination cyclization (Scheme 2, eq 1).[13d]

Scheme 2. Gold-Catalyzed Synthesis of TH-*β*-Cs



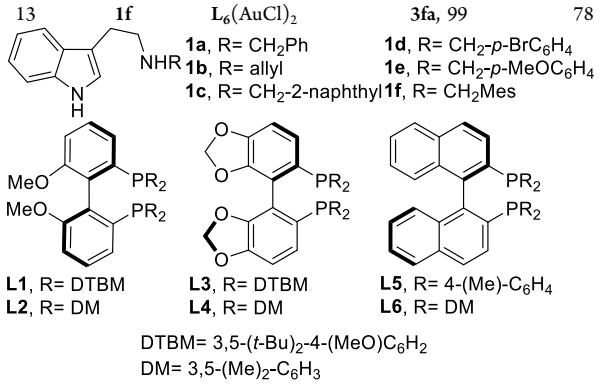
Precedence in the field was shown using achiral Au(I)[14] or Au(III)[15] complexes, but it was not clear from the literature the role that gold complexes could play in such a reaction, traditionally catalyzed by acids. In this Letter, we demonstrate that chiral Au(I) complexes efficiently catalyze enantioselective Pictet–Spengler reactions (Scheme 2, eq 2) and report our efforts in determining the scope of the reaction and understanding its mechanism.

We initiated this work by establishing a suitable catalytic system. After we checked that tryptamine itself did not react under these conditions,[16] we prepared a series of tryptamines **1** with diverse substituents to test under different catalytic conditions. We first engaged *N*-benzyl tryptamine **1a** in a Pictet–Spengler reaction with benzaldehyde **2a** in the presence of the Gagosz's catalyst $Ph_3PAuNTf_2$ **4**[17] in dichloromethane (DCM) and molecular sieves,[18] leading to the expected product **3aa** in 90% yield (Table 1, entry 1). By anticipation that the use of chiral neutral Au(I) complexes necessitates a silver activation, we checked that the silver salt $AgNTf_2$ was not catalytically active (entry 2). We next selected the DTBM–MeO–BIPHEP chiral ligand providing the digold complex $\mathbf{L_1}(AuCl)_2$ (3 mol %), using $AgNTf_2$ (5.8 mol %) as a chloride abstractor and screened tryptamines **1a–f** (entries 3–8). Tryptamines **1b** and **1c** bearing an allyl and a naphthylmethyl group led to moderate enantiomeric excesses (*ee*'s) (entries 4 and 5), whereas all other tryptamines substituted by a benzyl-type protecting group led to an average 75% *ee* in good yield (entries 3 and 6–8). The best enantiomeric excess was obtained with a CH_2Mes group, leading to 83% *ee* (entry 8). We further screened a series of chiral diphosphines (entries 9–13)[19] that identified (DM)–SEGPHOS $\mathbf{L_4}$ as the best chiral ligand, delivering a 93% *ee* (entry 11).[20]

The optimal conditions were then applied to a series of aromatic aldehydes using $\mathbf{L_4}(AuCl)_2$ as the precatalyst and **1f** as the tryptamine partner on a 0.3 mmol scale (Scheme 3). Benzaldehyde afforded **3fa** in 97% yield and with 92% *ee*. Aldehydes bearing a substituent in the para position led to excellent results with a good tolerance toward halide, alkyl, and

Table 1. Optimization of the Reaction[a]

entry	1	catalyst	yield (%)[b]	ee[c]
1[d]	**1a**	$Ph_3PAuNTf_2$ **4**	**3aa**, 90	
2	**1a**	$AgNTf_2$	**3aa**, 0	
3	**1a**	$\mathbf{L_1}(AuCl)_2$	**3aa**, 99	75
4	**1b**	$\mathbf{L_1}(AuCl)_2$	**3ba**, 90	57
5	**1c**	$\mathbf{L_1}(AuCl)_2$	**3ca**, 50	52
6	**1d**	$\mathbf{L_1}(AuCl)_2$	**3da**, 88	74
7	**1e**	$\mathbf{L_1}(AuCl)_2$	**3ea**, 80	75
8	**1f**	$\mathbf{L_1}(AuCl)_2$	**3fa**, 84	83
9	**1f**	$\mathbf{L_2}(AuCl)_2$	**3fa**, 82	91
10	**1f**	$\mathbf{L_3}(AuCl)_2$	**3fa**, 32	80
11	**1f**	$\mathbf{L_4}(AuCl)_2$	**3fa**, quant.	93
12	**1f**	$\mathbf{L_5}(AuCl)_2$	**3fa**, 82	79
13	**1f**	$\mathbf{L_6}(AuCl)_2$	**3fa**, 99	78



[a]Reactions were run using **1** (0.1 mmol) and **2a** (0.2 mmol) in DCM (1 mL) at rt. [b]Isolated yields. [c]Determined by chiral high-performance liquid chromatography (HPLC). [d]No silver salt added.

aryl substituents (**3fb–ff**). Suitable crystals of compound **3fe** allowed us to determine the absolute configuration of the stereogenic center as *R*.[21] The presence of an electron-donating group led to a drop in the *ee* to 73% in **3fg**. Aldehyde **2h**, including a boronic acid function, led to **1fh** with 88% *ee*. The reaction performed from terephthalaldehyde **2i** led to **3fi** with an excellent 95% *ee* and in 86% yield. Remarkably, there was no trace of difunctionalization despite the presence of a second aldehyde function. Finally, against all odds, the reaction tolerated the highly electrophilic nitrone function, reputed reactive toward Au(I) complexes.[22] The corresponding tetrahydro-*β*-carboline **3fj** was isolated in excellent yield and with 72% *ee*. Ortho-substituted aromatic aldehydes were next screened. Halide substituents were found to be compatible with the established conditions, although a better *ee* was obtained with the less sterically demanding fluorine atom, leading to **3fl** in 87% *ee*. On the contrary, mesomeric electron-withdrawing groups such as cyanide or nitro resulted in lower *ee*'s. Aldehydes substituted at the meta position by either halogens or trifluoromethyl groups resulted in excellent *ee*'s, >90% for **3fo–fq**. Despite a significant drop of the *ee* to 61%, the reaction was compatible with an unprotected phenol function, leading to compound **3fr** in 92% yield. When the reaction was performed with a dialdehyde (*m*-phthalaldehyde **2s**), **3fs** was isolated with an excellent 95% *ee* with, again, no

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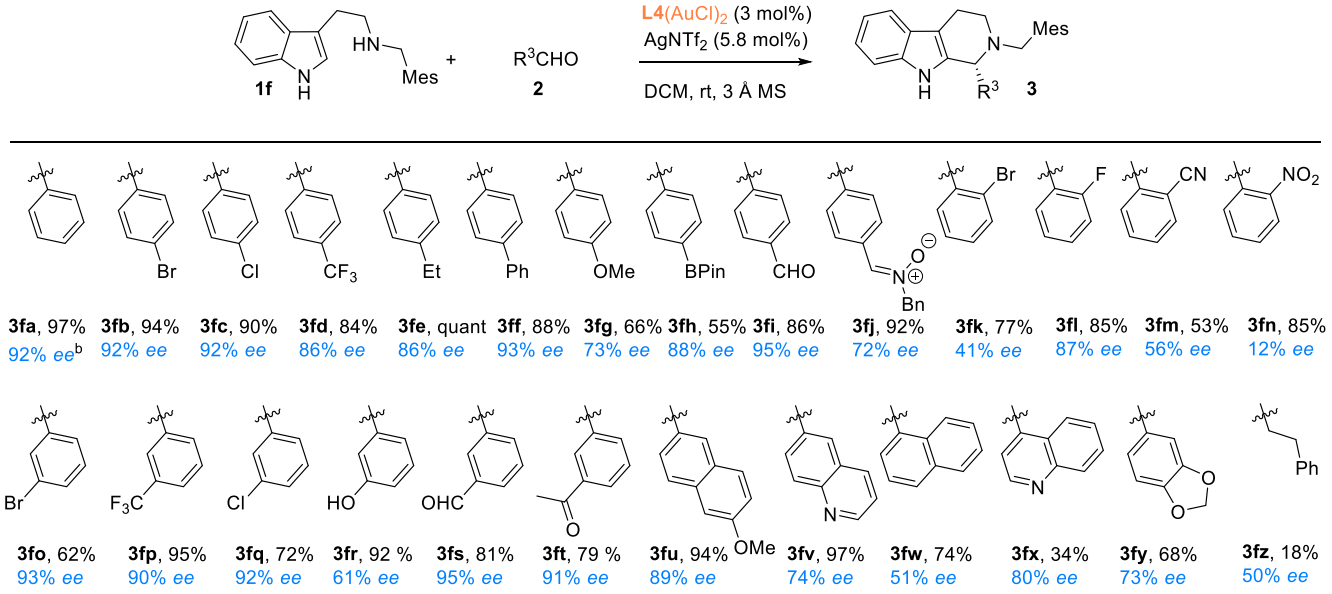
Scheme 3. Scope of Aldehydes in the Gold-Catalyzed Enantioselective Pictet–Spengler Reaction with Tryptamine 1f[a]



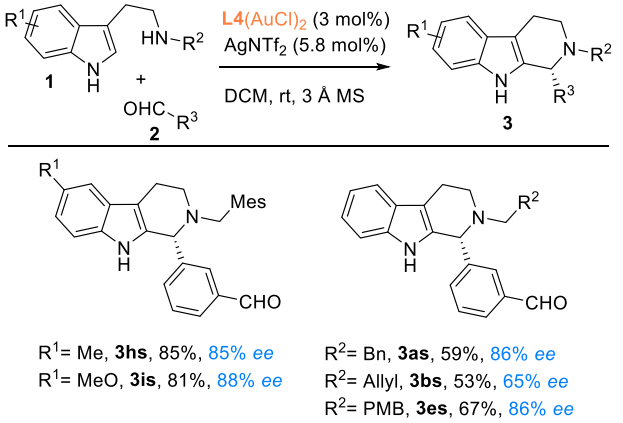
[a]Reactions were run using **1f** (0.3 mmol), **2** (0.6 mmol), and powdered activated 3 Å molecular sieves (300 mg) in DCM (3 mL) at rt. [b]Product **3fa** was obtained in 89% yield and with 83% ee when the reaction was performed on a 1 mmol scale of tryptamine **1f**.

trace of difunctionalization. In a similar manner, with 3-acetylbenzaldehyde **2t**, the gold-catalyzed functionalization proved totally selective for the aldehyde over the ketone function. Bicyclic aldehydes were next screened, and it was shown that 2-naphthaldehyde **2u** or 6-quinolinecarboxaldehyde **2v** was well tolerated, leading to 89 and 74% *ee*, respectively. Compound **3fw** was obtained with a moderate 51% *ee* from 1-naphthaldehyde. Interestingly, though, its aza-analoguous 4-quinolinecarboxaldehyde **2x** led to **2fx** in a moderate 34% yield but with excellent 80% *ee*. Finally, the piperonaldehyde led to **3fy** with 73% *ee*, introducing the 1,3-benzodioxole scaffold present in numerous indolic drugs such as tadalafil.[23] Finally aliphatic aldehydes were screened, pointing out the limitation of this methodology to aromatic aldehydes. Indeed, with 3-phenylpropanal **2z**, the corresponding tetrahydro-β-carboline **3fz** was obtained in a low 18% yield and with 50% *ee*. Other tryptamines bearing either a substituent on the indole ring or another group on the nitrogen were next used under the optimized conditions (Scheme 4). The reaction tolerated a methyl and a methoxy group at position five of the indole ring using **2s** as the aldehyde, leading to **3hs** and **3js** with good enantioselectivities.

When the reaction was performed from *N*-benzyltryptamine **3a**, the product **3as** was obtained with excellent 86% *ee*, which dropped to 65% *ee* using an allyl group. A *p*-methoxy substituent proved very similar to a benzyl group, leading to **3es** with 86% *ee* and in 67% yield.

The mechanism of the Pictet–Spengler reaction is controversial in regards to the nature of the addition of the indole ring to the iminium ***ii*** (Scheme 5).[24] However, regardless of the exact mechanism for the cyclization, all known Pictet–Spengler reactions initially undergo the formation of an iminium ***ii*** from a hemiaminal ***i*** and an acidic catalyst, with this step generating water (Scheme 5, eq 1). The mechanistic issue associated with the Au(I)-catalyzed version of this reaction stands in (1) the mechanistic pathway for the formation of the iminium and water from the hemiaminal, while the reaction is seemingly performed in the absence of

Scheme 4. Additional Scope



protons and the role of the Au(I) complex during this step (Scheme 5, eq 2) and (2) the nature of the intermediates (likely involving covalent bonding with the chiral gold complex to explain such high levels of enantioselectivity). Our hypothesis is that the coordination of the π-Lewis acid Au(I) complex to the indole ring from **A** via C2 modifies the acidity of the proton at C2, thereby allowing an intramolecular dehydration from intermediate **B** to **C** (Scheme 5, eq 3).[25] However, very little is known about the actual auration of indoles, with most of the examples being extremely specific.[26,27] The catalytic cycle would then consist of the formation of the key iminium **C** from the tryptamine **1**, aldehyde **2**, and the gold catalyst through intermediate **A**. The addition of the indole ring to the iminium would occur via the direct addition of C2 to lead to **D** (or, alternatively, the C3 addition). After a deauration step regenerating the catalytic species, the product would be obtained (Scheme 6).

The Au(I)-catalyzed Pictet–Spengler reaction of tryptamine **1f** with benzaldehyde using $AuPPh_3^+$ as a model catalyst was studied by means of density functional theory (DFT) computations. (See the Supporting Information for details

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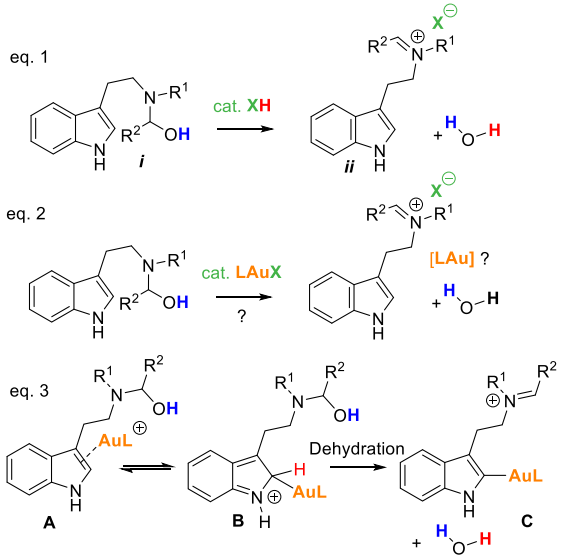
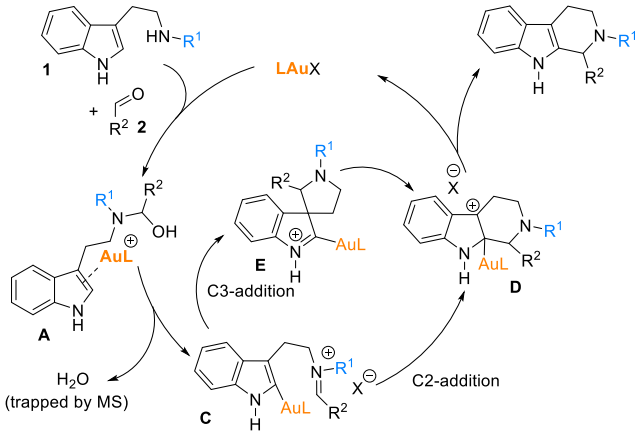
Scheme 5. Putative and Proposed Mechanistic Steps for the Formation of the Key Iminium



Scheme 6. Mechanistic Proposal



and additional computations.) The investigations started by the computational analysis of the initial steps of the reaction from the hemiaminal **B**. Here we focus on the process of dehydration and the formation of the final product. Figure 1 shows the results obtained on the computed mechanism that was postulated in Scheme 6. All energies are Gibbs free energies at 298 K including a solvent correction for dichloromethane. The hemiaminal complex **B**, located at −0.7 kcal/mol, displays the Au(I) fragment at the C2 position of the indole moiety. The dehydration process involving the C2−H bond to form iminium **C** requires 22.7 kcal/mol of free energy of activation, that is, 22.0 kcal/mol from the reference system. Subsequently, intermediate **C** may form the spiro complex **E** via C3 attack to the iminium. This virtually thermoneutral spiroindolization requires only 3.3 kcal/mol of free energy of activation. It is thus easily reversible. Importantly, a C3 to C2 C−C bond migration that would form a six-member ring **D** could not be modeled, which is consistent with previous observations in the field of organocatalyzed Pictet−Spengler reactions.[24] Alternatively, intermediate **C** can also be directly cyclized from the C2 position to give **D** at the expense of a moderate energy barrier of 4.8 kcal/mol. This step is appreciably exergonic by 16.6 kcal/mol. Finally, intermediate **D** releases the catalyst and the observed product, lying at −5.7 kcal/mol on the free-energy surface.

In conclusion, we have developed a new route to chiral tetrahydro-β-carbolines with high enantioselectivities using Au(I) catalysis. Although limited to aromatic aldehydes, the reaction tolerates a large number of reactive functions with high chemoselectivity. The Au(I) complex serves as an activator by binding to the indole ring, thereby allowing the formation of the key iminium with concomitant metalation at C2 of the indole ring. We expect that this new reactivity will pave the way to new strategies in the growing field of gold catalysis applied to heterocyclic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03656.

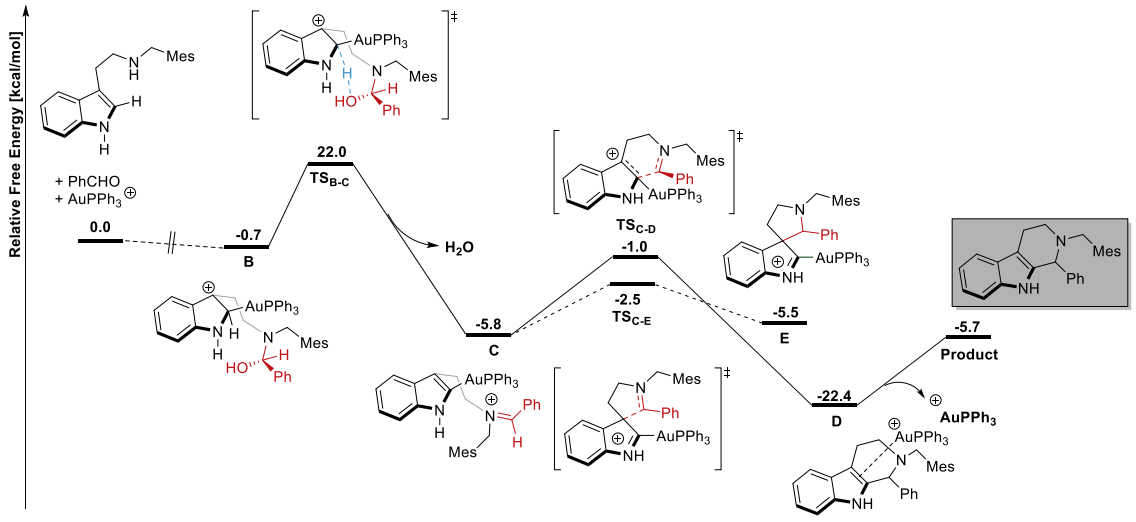


Figure 1. Computed dehydration pathway and final steps to the product.

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Details of the experimental procedures, nuclear magnetic resonance spectra, HPLC, and spectroscopical and computational data (PDF)

Accession Codes

CCDC 1915147−1915149 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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