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ABSTRACT

Controlled preparation of 2,5-dihydro-1*H*-pyrroles, 3,6-dihydro-2*H*-pyrans, and pyrroles has been achieved through switchable chemo- and regioselectivity in the metal-catalyzed heterocyclization reactions of allenic amino alcohols. The gold-catalyzed cycloisomerization reaction of α-amino-β-hydroxyallenes was effective as 5-*endo* cyclization by addition of the amino functionality to the distal allene carbon to yield enantiopure 2,5-dihydro-1*H*-pyrroles; whereas their palladium-catalyzed cyclizative coupling reactions furnished 3,6-dihydro-2*H*-pyrans through a chemo- and regioselective 6-*endo* cycloetherification. In opposition, the gold-catalyzed heterocyclization reaction of β-amino-γ-hydroxyallenes exclusively generated pyrrole

derivatives. These results could be explained through a chemo- and regioselective 5-*exo* aminocyclization to the central allene carbon, followed by aromatization. Chemo- and regioselectivity depend on both the linker elongation as well as the type of catalyst. This behaviour can be justified by means of Density Functional Theory calculations.

Table of Contents (TOC)
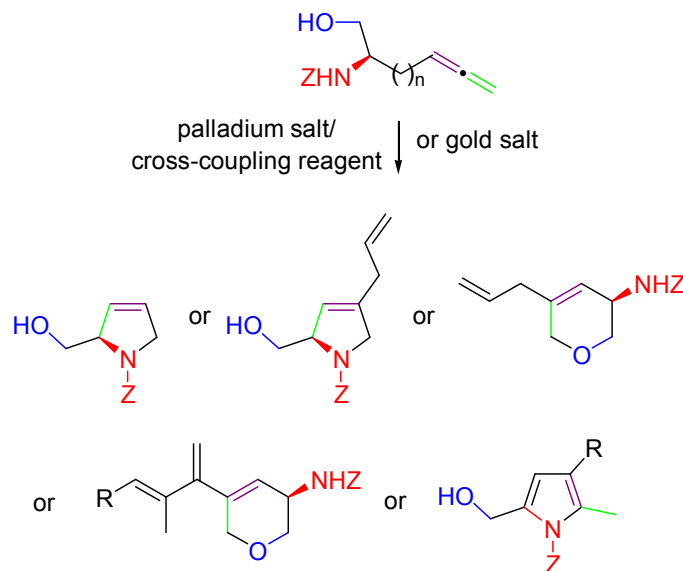
INTRODUCTION

Cycloisomerization reactions have been developed as the most efficient, atom-economical synthetic strategy to build up heterocycles. In particular, catalytic intramolecular addition of a pendant Y–H group to an allene moiety avoids by-product formation of classical substitution reactions.[1] How to control chemoselectivity to get the desired adducts over unwanted isomers is the principal issue in these cyclization reactions.

Despite that this performance has previously been reported for allenols and allenamines, related transformations for hydroxy allenamines are undeveloped; probably because of additional chemoselectivity problems. An interesting case of

2

selectivity arises in allenic amino alcohols, because two potentially reactive moieties, namely, alcohol and amine, are present in the same substrate. In 2009, the Krause group reported the gold-catalyzed[2] 5-*endo* cycloisomerization of *N*-(buta-2,3-dienyl)hydroxylamines to give *N*-hydroxypyrrolines.[3] Apart from the above mentioned aminocyclization reaction, there exist too few reports on the heterocyclization reactions of allenic amino alcohols. Even so, the switchable[4] synthesis of different heterocycles from the same starting allenic amino alcohol is very attractive, but very difficult because each moiety could react to afford diversely sized oxa- or azacycles. Besides, it may also benefit the understanding of the reaction mechanisms.[5] We envisioned that a metal-catalyzed heterocyclization reaction of α-amino-β-hydroxyallenes would produce different 3-, 4-, 5- or 6-membered heterocycles. Depending on both the chemoselectivity (aminocyclization versus oxycyclization) as well as the regioselectivity (*endo-trig* versus *endo-dig* versus *exo-dig* versus *exo-trig* attack) either of the eight possible cycloisomerization adducts could be the reaction products (Scheme 1). In consideration of the importance of both aminocyclization and cycloetherification reactions, we decided to examine the influence of different metal activators on the heterocyclization reaction.

Scheme 1. Possible Cycloisomerizations that Can Take Place in α-Amino-β-hydroxyallenes
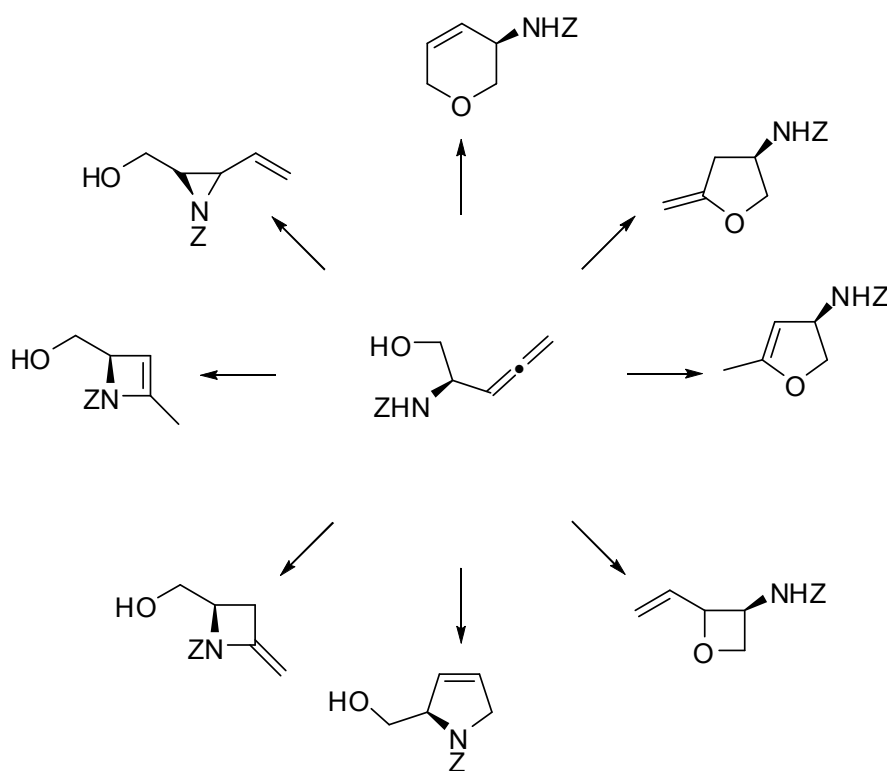
RESULTS AND DISCUSSION

To explore the effects of various complexes on the metal-catalyzed heterocyclization reaction of allenic amino alcohols, α-amino-β-hydroxyallene **1a** and β-amino-γ-hydroxyallenes **2a,b** were synthesized in optically pure form. Starting allene **3** was made from the corresponding alkyne by treatment with paraformaldehyde in the presence of diisopropylamine and copper(I) bromide (Crabbé reaction) using our previously described methodology.[6] Starting allenes **4a,b** were obtained from Garner's aldehyde via the coupling with propargyl bromides promoted by indium, followed by protection of the hydroxyl functionality in the form of methyl ether.[7] Precursors for the heterocycle formation, enantiopure allenic amino alcohols **1a** and **2a,b** were smoothly

obtained in excellent yields by $BiCl_3$-catalyzed aminal cleavage (Scheme 2). Unfortunately, we faced significant difficulties at the purification stage in the case of highly polar substrates **2a,b**. Chromatography, even with neutralized silica gel or alumina, resulted in decomposition products. Consequently, we devised a one-pot sequence from oxazolidine-derived allenes **4a,b** avoiding the purification of β-amino-γ-hydroxyallenes **2a,b**. Thus, it was our hope that the resulting crude products displayed sufficient purity to be engaged in the metal-catalyzed cyclization step.

Scheme 2. Preparation of Enantiopure Allenic Amino Alcohols 1 and 2
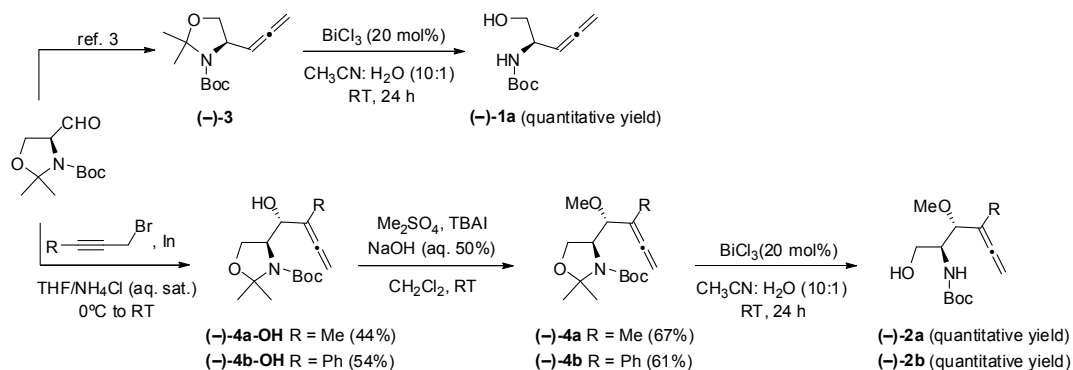
Next, we targeted on the use of metal catalysis to the selective preparation of heterocycles starting from allenic amino alcohols. Initially, it was hoped that a catalytic activation strategy could be developed through the use of noble metal salts. In the investigation of the reaction conditions, α-amino-β-hydroxyallene **1a** was chosen as the model substrate. Firstly, the effect of the catalyst on the model reaction was examined. Fortunately, a variety of gold and platinum catalysts were applied with success to α-amino-β-hydroxyallene **1a**. These reactions were completely selective for the formation of 2,5-dihydro-1*H*-pyrrole **5a** (Table 1). When the reaction was catalyzed by $[PtCl_2(CH_2=CH_2)]_2$ or $PtCl_2/AgOTf$, comparable results of azacycle **5a** were obtained (Table 1). However, the addition of Gagosz' catalyst $[(Ph_3P)AuNTf_2]$ provided lower yield of the cycloisomerization product (Table 1). To our delight, the use of a gold(III)-

based catalyst, such as AuCl$_3$, enhanced the hydroamination reaction.   Thus, 2,5-

dihydro-1H-pyrrole **5a** could be isolated after purification by column chromatography

in 77% yield after AuCl$_3$ treatment. A screening of solvents (toluene, polyethylene

glycol 400, 1,2-dichloroethane) revealed that the reaction is best performed in

dichloromethane. The above outcome could be rationalized invoking a 5-*endo*

cycloisomerization by chemo- and regiospecific addition of the amino group to the

terminal allene carbon.[8]

Table 1 Selective aminocyclization reaction of α-amino-β-hydroxyallene 1a under

modified metal-catalyzed conditions
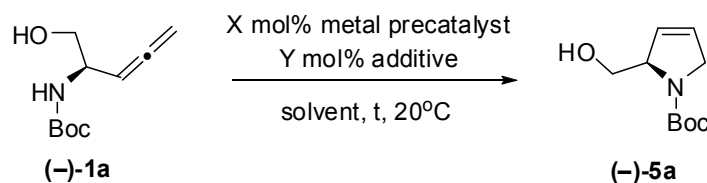
| entry	metallic salt (X mol%)	additive (Y mol%)	solvent/t (h)	yield[d]
1	PtCl$_2$ (5)	AgOTf (5)	CH$_2$Cl$_2$ /23	59
2	[PtCl$_2$(CH$_2$=CH$_2$)]$_2$ (5)	TDMPP[a] (10)	CH$_2$Cl$_2$/23	52
3	[(Ph$_3$P)AuNTf$_2$] (5)	-	DCE[b]/3	20
4	AuCl$_3$ (5)	-	toluene/5	68
5	AuCl$_3$ (5)	-	PEG-400[c]/4	49
6	AuCl$_3$ (5)	-	DCE /3	75
7	AuCl$_3$ (5)	-	CH$_2$Cl$_2$/3	77

[a]TDMPP = tris(2,6-dimethoxyphenyl)phosphine. [b]DCE = 1,2-Dichloroethane. [c]PEG = Polyethylene

glycol 400. [d]Yield of pure, isolated product with correct analytical and spectral data.

A need of modern organic synthesis is to investigate how different types of

molecules can be created from the same starting material merely through catalyst choice.

6

Thus, having found a solution for the selective allenic aminocyclization, our next aim was to study the catalyst-controlled chemoselective heterocyclization of allenic amino alcohols in order to obtain oxacycles. Our initial investigations on Pd-catalyzed chemodifferentiation reactions focused on the heterocyclization of α-amino-β-hydroxyallene **1a** with allyl bromide.[9] Worthy of note, under PdCl$_2$ catalysis the reaction took place, affording 3,6-dihydro-2*H*-pyran-3-amine derivative **6a** in fair yield (Scheme 3). Disappointingly, along with cyclic ether **6a**, dihydropyrrole **7a** was also obained as minor product. Fortunately, isomeric heterocycles **6a** and **7a** could be easily separable by flash chromatography. The formation of dihydropyran **6a** can be somehow explained through a chemoselective 6-e*ndo-trig* allenic oxycyclization followed by cross-coupling.

Scheme 3. Palladium-Catalyzed Preparation of Dihydropyran 6a and Dihydropyrrole 7a
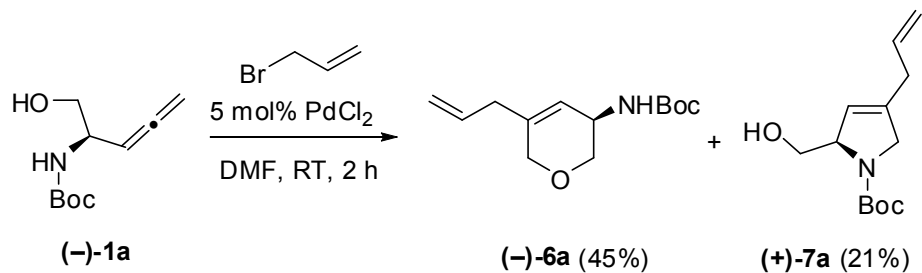
We thought it would be of interest to apply to α-amino-β-hydroxyallene **1a** our previously developed palladium-catalyzed heterocyclization/cross-coupling sequence between α-allenols and α-allenic esters.[10] Gratifyingly, it was observed that these reaction conditions using α-allenic esters **8** were compatible with substrate **1a**, resulting in the formation of the desired oxacycles **9** in fair yields with complete regio- and chemoselectivity (Scheme 4). The ^{1}H NMR spectra of the crude reaction mixtures show the presence of oligomeric material but did not reveal the formation of any cyclization/cross-coupling adducts different to products **9**.

7

Scheme 4. Palladium-Catalyzed Preparation of Dihydropyrans 9. PMP = 4-MeOC₆H₄

8a R = Ph
8b R = PMP

(−)-9a R = Ph (44%)
(−)-9b R = PMP (47%)

(−)-1a
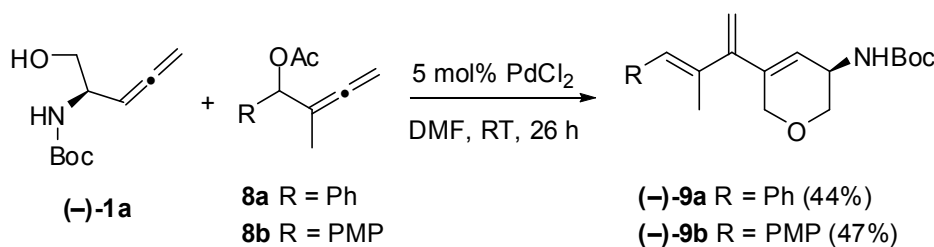
Lanthanide amido complexes have shown remarkable success in catalyzing both hydroamination[11] and hydroalkoxylation reactions.[12] The above precedents suggest that lanthanide-based catalysts may be effective for the cycloisomerization reaction of allenic amino alcohols. In marked contrast, it was found that the *N*-Boc cleavage of α-amino-β-hydroxyallene **1a** occurred using lanthanum bis(trimethylsilyl)amide as promoter (Scheme 5). Of note, the allene moiety in product **1b** remained intact despite its inherent reactivity. To the best of our knowledge, such controlled reactivity has not been reported before.

Scheme 5. Lanthanum-Catalyzed Preparation of α-Amino-β-hydroxyallene 1b

(−)-1a

(+)-1b (quantitative yield)
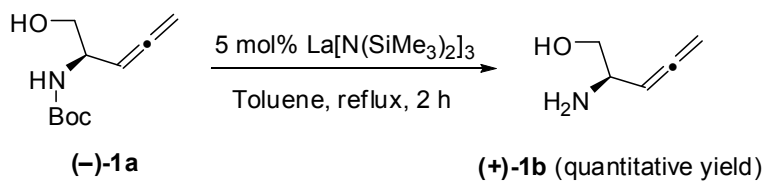
To address the selectivity issue on the metal-catalyzed heterocyclization reaction of allenic amino alcohols, we further investigated additional substrate **1b**. We were pleased to observe that α-amino-β-hydroxyallene **1b** also worked well under the above optimized catalytic conditions of Table 1 and Schemes 3 and 4. Thus, gold-catalyzed cycloisomerization and palladium-catalyzed cyclization/coupling reactions lead to the controlled formation of heterocycles **5b–7b** and **10a,b** in slightly higher yields (Scheme

8

6). Dendralenic products **10** are potential precursors for more complex structures through the diene-transmissive Diels–Alder reaction.[13]

Scheme 6. Chemo- and Regiocontrol in the Metal-Catalyzed Heterocyclization Reactions of α-Amino-β-hydroxyallene 1b
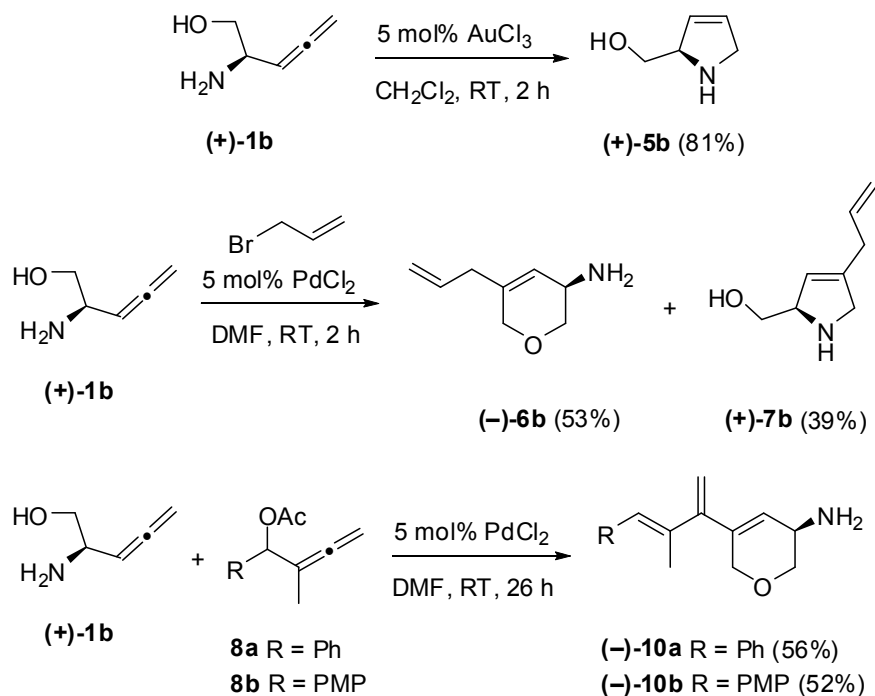
Next, we focused on finding a heterocyclization procedure for functionalized allenes **2a,b** that could be both regio- and chemoselective. β-Amino-γ-hydroxyallenes **2a,b** have diverse reactive sites, at which two different transformations (*N*-cyclization *versus O*-cyclization) can take place. Gold(I)-based complexes were the best catalysts among several complexes screened (AuCl₃, PtCl₂, PdCl₂, PtCl₂(CH₂=CH₂)]₂). A number of gold(I) catalysts were tested to reveal that [(Ph₃P)AuNTf₂] was the catalyst of choice. The best result was obtained from a reaction of **2a** using [(Ph₃P)AuNTf₂] (5 mol %) in dichloromethane, producing *tert*-butyl 5-(hydroxymethyl)-2,3-dimethyl-1*H*-pyrrole-1-carboxylate **11a** in 53% isolated yield (Scheme 7). When the present reaction was conducted with allenic amino alcohol **2b**, pyrrole derivative **11b** was also

exclusively produced (Scheme 7). Unfortunately, extensive decomposition was observed on sensitive pyrroles **11** during purification by flash chromatography, which may be responsible for the moderate isolated yields. The gold-catalyzed heterocyclization reaction of β-amino-γ-hydroxyallenes **2** shows the same chemoselectivity but different regioselectivity as that observed under gold catalysis for α-amino-β-hydroxyallenes **1**, that is, the initial cyclization takes place by selective nucleophilic addition of the amino group to the activated central allene carbon. By contrast, the cyclization of β-amino-γ-hydroxyallenes **2a,b** was not as rewarding when they were treated with allyl bromide using a Pd–based catalytic system. Palladium salts, which were effective for the oxycyclization reaction of allenic amino alcohols **1a,b**, gave rise to complex reaction mixtures. These results clearly show that the metal-catalyzed aminocyclization is preferred over cycloetherification for β-amino-γ-hydroxyallenes **2**. Pyrrole formation could be explained through a 5-*exo* cyclization by chemo- and regioselective attack of the amino group to the central allene carbon, followed by elimination of methanol with concomitant aromatization.

Scheme 7. Gold-Catalyzed Preparation of Pyrroles 11

(–)-2a
**(–)-2b**

11a R = Me (53%)
11b R = Ph (40%)
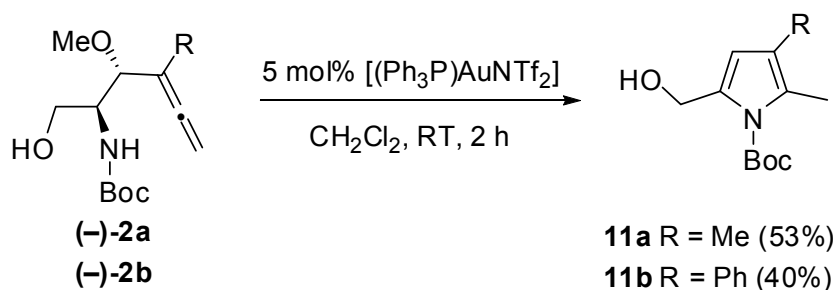
A possible mechanism for the catalytic achievement of 2,5-dihydro-1*H*-pyrroles **5** involving a gold-based carbophilic π-acid may proceed through initial coordination of the metal to the distal double bond of α-amino-β-hydroxyallenes **1** leading to species **1-Au**. Next, chemo- and regioselective 5-*endo*-trig allenic aminoauration forms

zwitterionic dihydropyrroles **12**. Loss of HCl in intermediates **12** generates neutral alkenylmetal species **13**. Protonolysis of the carbon–gold bond of **13** liberates 2,5-dihydro-1*H*-pyrroles **5** with concomitant regeneration of the Au(III) catalytic species (Scheme 8).

Scheme 8. Mechanistic Explanation for the Gold-Catalyzed Cycloisomerization Reaction of α-Amino-β-hydroxyallenes 1
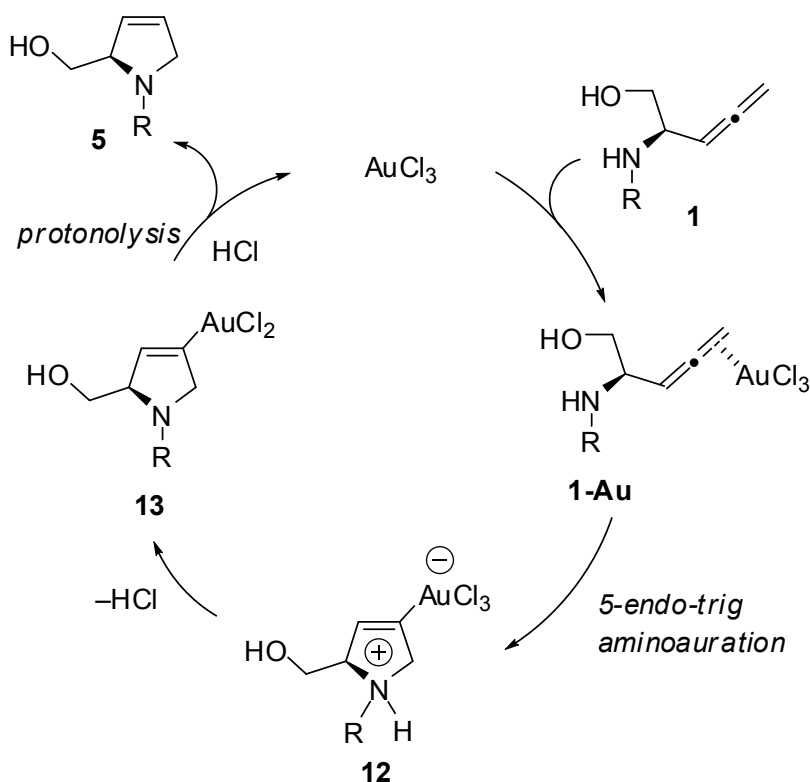
A mechanistic hypothesis for the achievement of 3,6-dihydro-2*H*-pyrans **9** and **10** from α-amino-β-hydroxyallenes **1** is outlined in Scheme 9. Chemo- and regiocontrolled palladium(II)-catalyzed oxypalladacyclization of the amino-β-hydroxyallene molecule **1** produces a palladadihydropyran species **14**, which then suffers a cross-coupling reaction with the α-allenic ester **8**. Alkenyl palladium(II) species **14** reacted with the central allene carbon of **8** in a regioselective fashion giving rise to intermediates **15**. Subsequently, buta-1,3-dienyl 3,6-dihydro-2*H*-pyran-3-amines **9** and **10** are formed as

single *E*-isomers through *trans*-β-deacetoxypalladation. The metal catalyst is reformed

at the same time. Notably, the heteropalladation of α-amino-β-hydroxyallenes **1** to form

the corresponding 3,6-dihydropyranyl palladium species **14** is totally chemoselective

toward the allenol functionality. We did not observe the formation of azacycles from the

aminocyclization of the allenamine functionality in **1**.

Scheme 9. Mechanistic Explanation for the Palladium-Catalyzed

Oxycyclization/Cross-Coupling Sequence between α-Amino-β-hydroxyallenes 1

and α-Allenic esters
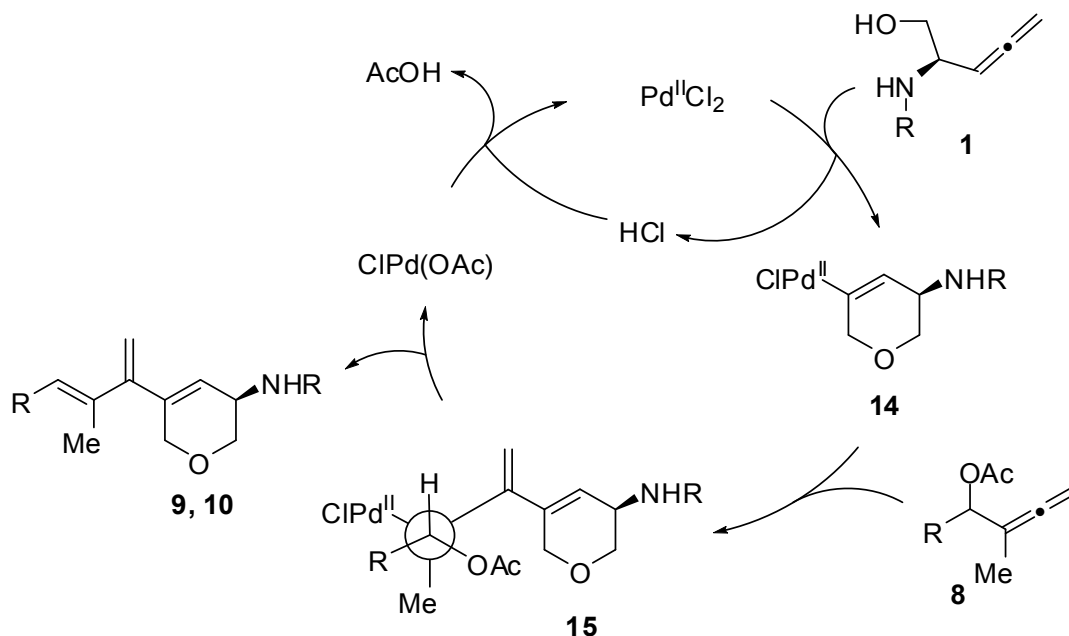
Scheme 10 outlines a mechanistic proposal for the achievement of pyrroles **11** from

allenic amino alcohols **2**. Initial Au^I-coordination to the 1,2-diene moiety gave an

allenegold complex **2-Au**, which suffers a chemo- and regioselective 5-*exo*

aminocyclization reaction to give the intermediate auradihydropyrrolium **16**. Loss of

proton generates neutral species **17**, which followed by protonolysis of the carbon–gold

bond afforded dihydropyrroles **18** with concurrent regeneration of the gold catalyst.

Heterocycles **18** then suffer a methanol elimination to give the pyrrole products **11**.

12

Scheme 10. Mechanistic Explanation for the Gold-Catalyzed Aminocyclization reaction of β-Amino-γ-hydroxyallenes 2
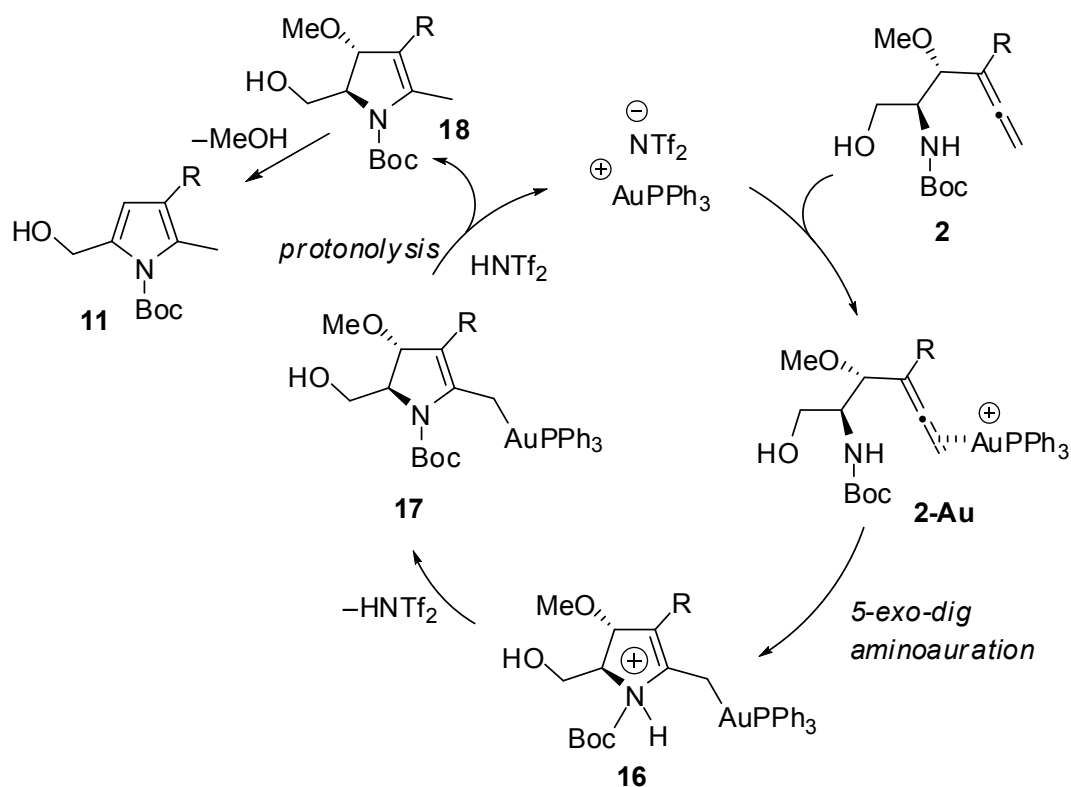
In order to get further insights into the chemo- and regioselectivity, as well as the reaction pathway, a density functional theory (DFT) study has been performed.

As a model reaction, we have selected precursor **1b**. Table 2 summarizes the activation barriers and relative energies for the possible heterocyclization steps for both the amino and alcohol functionalities, from the allene–metal complexes **1b-Au$_D$** and the less stable **1b-Au$_P$**. These complexes are formed by coordination of the distal and proximal alkene bonds of the allene to the catalyst, respectively.

Table 2. Relative free-energy values [M06/def2-QZVP/PCM, in kcal mol^{-1}] for the possible Au-catalyzed heterocyclization steps of **1b**.

Complex		Mode	$\Delta G^{\#}$	ΔG
1b-Au$_D$	aminocyclizations	4-*exo-dig-*	3.7	-13.4
		5-*endo-trig-*	2.6	-17.7
	oxycyclizations	5-*exo-dig-*	8.6	-12.2
		6-*endo-trig-*	6.1	-2.3
1b-Au$_P$	aminocyclizations	3-*exo-trig-*	7.8	-15.0
		4-*endo-dig-*	13.3	-9.1
	oxycyclizations	5-*endo-dig-*	10.8	-10.5
		4 *exo-trig-*	12.8	6.8

According to the calculated values, the lowest-energy transition structure for the Au(III)-catalyzed heterocyclization is found for **TS1$_{5\text{-endo-trig}}$**, which belongs to the 5-*endo-trig* cyclization.[1,14] Moreover, it drives to the most stable Au σ-alkenyl zwitterionic intermediate **I$_{5\text{-endo-trig}}$**. Other plausible transition structures for the intramolecular nucleophilic attack of the alcohol or amine on the triggered allene, show higher barriers than **TS1$_{5\text{-endo-trig}}$** ($\Delta\Delta G^{\#}$ = 1.1–10.7 kcal mol^{-1}). The formation of the heterocyclization intermediates is exergonic for all; only one exception is found, as the strained attack of the β-allenol group onto the central allene position, 4-*exo-trig* cyclization, is slightly endergonic. In fact, the formation of the most stable Au σ-alkenyl intermediate **I$_{5\text{-endo-trig}}$** is the most exergonic process (-17.7 kcal mol^{-1}), pointing to a moderately irreversible character of this heterocyclization mode.

These results agree with the experimentally observed selective formation of 3-pyrroline **5b** and would propose a kinetic and thermodynamic control of the chemo- and regioselective intramolecular aminocyclization. However, according to previous estimation of the reaction mechanism by us[15] and others,[16] the rate-determining step would be the 1,3-H migration to form the product which is assisted by the metal-complex and proceeds stepwise: release of HCl and Au–C bond excision by protonolysis with HCl to end the cycle and restore the active catalyst.[17]

14

For the formation of **5b**, the loss of HCl from $I_{5\text{-endo-trig}}$ produces the neutral complex $I2_{5N}$-**Au** in an endergonic process (ΔG = +16.2 kcal mol^{-1}). To end, protonolysis of the C-Au bond yields **5b-Au** via the transition state $TS3_{5N}$-**Au** with an activation energy of $\Delta G^{\#}$ = +4.9 kcal mol^{-1}. Thus, according to the calculated higher energy barriers, the 1,3-H migration would be the bottleneck of the Au-catalyzed formation of **5b** (Figure 1).
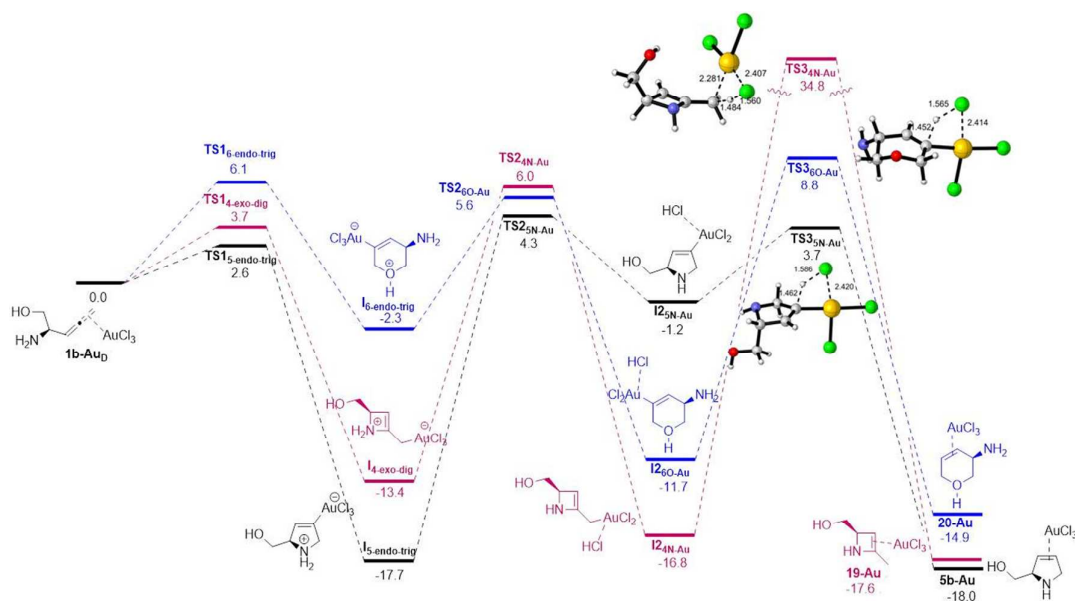
Figure 1. Calculated free-energy profile [M06/def2-QZVP/PCM, in kcal mol^{-1}] for some plausible Au-catalyzed reactions of **1b**.

For the Pd-catalyzed process, the calculations also suggest that, the 5-*endo-trig* heterocyclization by nucleophilic attack of the α-amino moiety to the terminal allene carbon of the most stable complex, **1b-Pd$_D$** (by 0.8 kcal mol^{-1}) (*via* **TS1$_{5\text{-endo-trig}}$**) (Table 3), is the favored ring-closure step both from the kinetic and thermodynamic perspectives, in view of the higher activation energy barriers ($\Delta\Delta G^{\#}$ = 4.8–18.1 kcal mol^{-1}) and the lower exergonicity ($\Delta\Delta G$ = 3.7–25.7 kcal mol^{-1}) computed for other plausible heterocyclizations. Notably, the *endo-trig* cyclization by nucleophilic attack of

15

the β-alcohol on the terminal allene carbon, through **TS1$_{6\text{-}endo\text{-}trig}$**, also shows a low

activation barrier, although 4.8 kcal/mol higher, which unfortunately contrasts with the

experimental observations.

Table 3. Relative free-energy values [M06/def2-QZVP/PCM, in kcal mol^{-1}] for the

possible Pd-catalyzed heterocyclization steps of **1b**.

Complex		Mode	$\Delta G^{\#}$	ΔG
1b-Pd$_D$	aminocyclizations	4-*exo-dig-*	9.7	-9.2
		5-*endo-trig-*	2.3	-12.9
	oxycyclizations	5-*exo-dig-*	15.8	-8.1
		6-*endo-trig-*	7.1	4.1
1b-Pd$_P$	aminocyclizations	3-*exo-trig-*	11.7	-8.1
		4-*endo-dig-*	19.9	-7.7
	oxycyclizations	5-*endo-dig-*	19.0	-3.0
		4 *exo-trig-*	20.4	12.8

On other hand, the results depicted in Scheme 6 suggest that the selectivity of the

Pd-catalyzed process depends on the nature of the coupling alkene. Thus, in the

presence of allyl bromide, the kinetically favored formation of the **I$_{5\text{-}endo\text{-}trig}$** and **I$_{6\text{-}endo\text{-}trig}$**

alkenyl intermediates would undergo a cross-coupling reaction to form **7b** and **6b**,

respectively, while in the presence of α-allenic ester, the formation of the oxacycles **10**

takes place with complete regio- and chemoselectivity. To account for these

observations and apparent discrepancies, we have performed a deeper analysis.

The cross-coupling with allyl bromide from the alkenyl intermediate **I$_{6\text{-}endo\text{-}trig}$** takes

place as follows (Figure 2). After loss of HCl through **TS2$_6$** (+6.0 kcal mol^{-1} above **1b-**

Pd$_D$), the Pd-coordinated HCl is easily moved by the entering allyl bromide in a

probable fast ligand-interchange displacement mechanism to yield the palladium

complex **I3$_{6Br}$**. This step is slightly endergonic ($\Delta G = -0.9$ kcal mol^{-1}) and has a low

activation barrier (1.2 kcal mol^{-1}). This species evolves into complex **I4$_{6Br}$** *via* the nearly

planar four-membered transition structure **TS4$_{6Br}$**, a saddle point related to the insertion

of the allylic halide C=C bond into the Pd-alkenyl bond to yield a σ-C–Pd intermediate

I4$_{6Br}$ and the formation of a new carbon–carbon bond. This intermediate is formed in a

highly exergonic step (–30.1 kcal mol^{-1}) with a low activation barrier (2.8 kcal mol^{-1}). A

final elimination step yields the complexed dihydropyran **6b-Pd** in a exergonic step (by

–8.8 kcal mol^{-1}) through **TS5$_{6Br}$** (–18.0 kcal mol^{-1}). Overall, the reaction is highly

exergonic and the cyclization and coupling steps constitute the bottleneck of the

transformation.

Earlier computational results on palladium-catalyzed reactions have revealed that,

in presence of an unsaturated reactant, the cross-coupling from the alkenyl intermediate

is favored over a proton shift process to yield protonolysis products.[12d,18] Expectedly,

the competitive protonolysis step from **I2$_6$** involves a less favored process both from

kinetic and thermodynamic viewpoints, since our calculations reveal a higher activation

barrier (transition structure 11.9 kcal mol^{-1} above **1b-Pd$_D$**) and less exergonicity (–14.4

kcal/mol) than the coupling-process, in agreement with the experimental absence of the

protonolysis product.

The formation of the 3-pyrroline **7b** follows the equivalent pathway after azacyclization

(Figure 2), namely, loss of HCl, ligand displacement from the metal coordination sphere,

insertion of the C=C bond of the allylic halide into Pd–alkyl bond to yield a σ-C–Pd

intermediate, and finally, a β-elimination step. Firstly, the lower activation barrier for

the HCl release is likely due to the lower steric distortion needed to attain the transition

state, whereas the higher stability of **I2$_5$** is due to the strong H-bond of the formed HCl

with the amine group. This complex can coordinate the allyl bromide to produce the

allyl-palladium complex **I3$_{5Br}$**, 0.5 kcal mol^{-1} less stable than **I3$_{6Br}$**, through a transition

structure **TS3$_{5Br}$** showing an energy 0.4 kcal mol^{-1} higher than the dihydropyran

counterpart (**TS3$_{6Br}$**). This intermediate species evolves into complex **I4$_{5Br}$** by formation of the new carbon–carbon bond via the transition state **TS4$_{5Br}$**, 0.4 kcal mol^{-1} less stable than **TS4$_{6Br}$**. Finally, the elimination step leads to the complexed 3-pyrroline **7b-Pd** in a exergonic step (by –11.7 kcal mol^{-1}) by overcoming a low activation barrier.

If we compare the free energy profiles for the formation of **6b** and **7b**, a similar profile for the cross-coupling process is found. However, the rate-determining step for **6b** is the cyclization, although very close to the coupling event, while for **7b** the cross-coupling is proposed as the rate determining step, involving a transition structure only 0.1 kcal mol^{-1} higher than the heterocyclization for **6b**. These results are supported by the competitive formation of **6b** and **7b**.
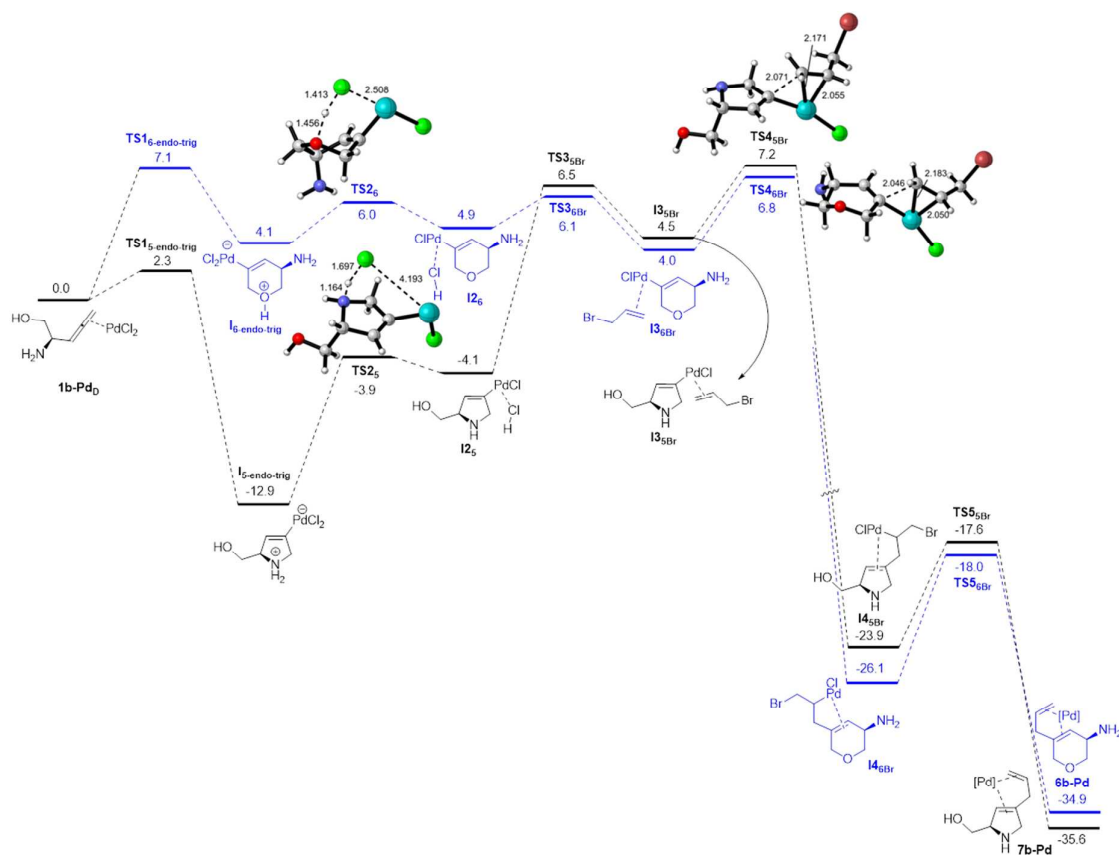
Figure 2. Calculated free-energy profile [M06/def2-QZVP/PCM, in kcal mol^{-1}] for the Pd-catalyzed heterocyclization/cross-coupling reaction of **1b** with allyl bromide to form **6b** (blue) and **7b** (black).

Following the same analysis for the cross-coupling reaction with the α-allenic esters **8** to afford the dihydropyrans **10** (R = Ph), the calculations reveal critical differences between the formation of the dihydropyran and 3-pyrroline frameworks.

Recently, results on the palladium-catalyzed cross-coupling process between two different allenes (allenol and α-allenic ester) to form dihydropyrans were reported.[18] The computational analysis of the reaction mechanisms suggested a kinetic control of the chemo- and regioselective intramolecular cyclization. Moreover, the calculations accounted for the absence of the plausible homo-coupling, other cross-coupling modes or Pd–C protonolysis products.

The alkenyl palladium(II) intermediate **I2$_6$** can coordinate an α-allenic ester ligand to form the allene-Pd complex **I3$_{6AI}$** (Figure 3) through an associative mechanism step involving a very low energy barrier (0.9 kcal mol^{-1}) *via* **TS3$_{6AI}$**. This species evolves into complex **I4$_{6AI}$** *via* the transition state **TS4$_{6AI}$**, which shows the incipient formation of a C-C bond with the central carbon of the allene (C–C distance = 2.107 Å). This step proceeds with a low energy barrier ($\Delta G^{\#}$ = 2.7 kcal mol^{-1}) and is strongly exergonic (ΔG = –37.7 kcal mol^{-1}), thus suggesting an irreversible process. It should be noted that **TS4$_{6AI}$** shows a C(sp^2)-H...π interaction[19] with the aromatic core (2.504 Å). Other conformations for **TS4$_{6AI}$** and **I4$_{6AI}$** lacking this interaction are 2.8 and 2.7 kcal mol^{-1} higher in energy, respectively (see additional computational results in the Supporting Information).

Finally, a *trans*-β-deacetoxypalladation step drives to the formation of the *trans*-buta-1,3-dienyl-dihydropyran **10a-Pd**, η^4-coordinated to Pd[II]. This step takes place through the transition structure **TS5$_{6AI}$**, which shows a C–O cleavage (2.146 Å) and the initial coordination of the ester to the metal (2.951 Å), with an energy 19.8 kcal mol^{-1} below **1b-Pd$_D$**. The overall process is highly exergonic (–30.1 kcal mol^{-1}).

19

A close inspection of the cross-coupling process from de azacyclic intermediate **I2$_5$**

reveals crucial differences. The corresponding computed reaction profiles are depicted

in Fig. 3, which collects the relative free energy values calculated at 298 K (ΔG_{298}).

Thus, our calculations put forward that the formation of **I3$_{5AI}$** is kinetic (by 1.9 kcal mol^{-1})

and thermodynamically disfavored (by 5.3 kcal mol^{-1}) over the formation of the

oxacycle **I3$_{6AI}$**. Then, the coupling step occurs *via* the transition state **TS4$_{5AI}$**, involving

the C-C bond formation (2.043 Å), with a free energy 5.5 kcal mol^{-1} higher in energy

than **TS4$_{6AI}$** in a strong exergonic transformation ($\Delta G_{298} = -39.0$ kcal mol^{-1}). It should

be noted that **TS4$_{5AI}$** shows a C(sp^3)-H…π (2.798, 3.211 Å), weaker than a C(sp^2)-H…π

in **TS4$_{6AI}$**, which could account for, in part, the higher energy. Finally, we locate the

transition state **TS5$_{5AI}$**, a saddle point associated with the *trans*-β-deacetoxypalladation

step, which leads to the complexed dihydropyrrole product, **21-Pd**. Therefore, based on

the computed data, it can be concluded that the formation of **10a** seems to be the most

favored process for the palladium-catalyzed heterocyclization/cross-coupling sequence

between α-allenols and α-allenic esters, taking place with regio- and chemoselectivity,

which nicely agrees with the experimental findings.
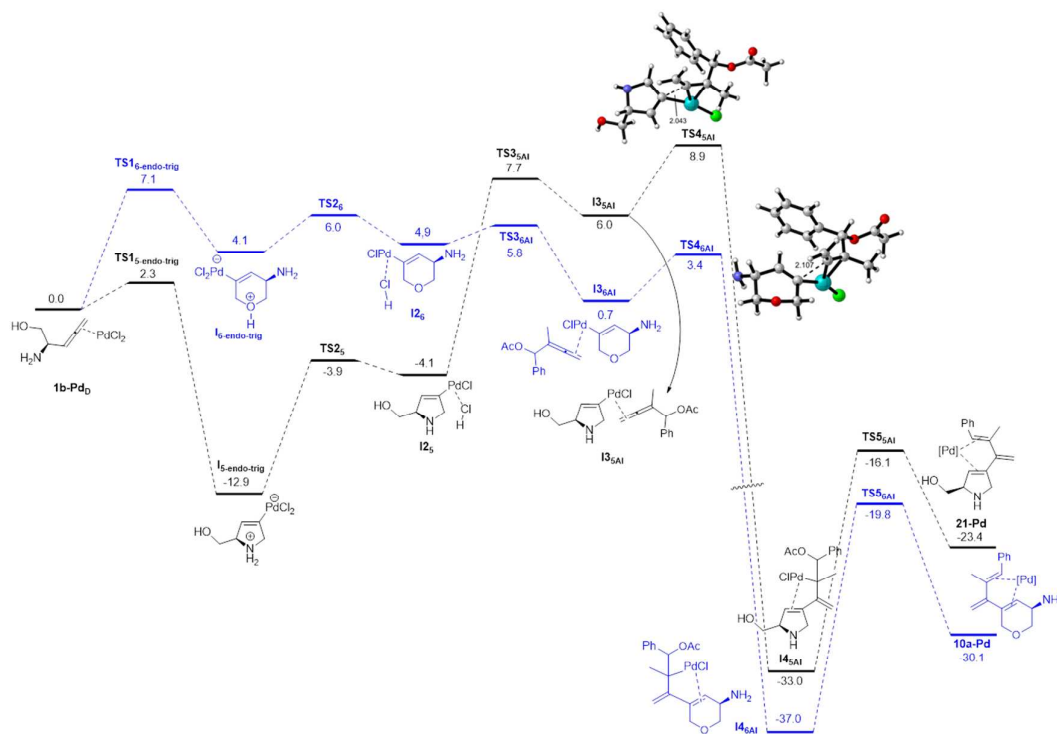
Figure 3. Comparison of the free-energy profiles [M06/def2-QZVP/PCM, in kcal mol⁻¹] for the Pd-catalyzed heterocyclization/cross-coupling reaction of **1b** with α-allenic acetate **8a** to yield **10a** (blue) and the undetected dihydropyrrole product **21** (black).

To account for the differences found between the coupling reagents, we have performed a NBO analysis of the coupling processes of allyl bromide and α-allenic acetates. In the intermediate complexes **I3**, the σ-donating (from the endocyclic C_C sp² lone pair partially overlapping the 5s orbital on palladium) and π-backdonating (a highly polarized dπ-to-pπ donation from the metal to the empty pπ orbital on C_C) interactions between the heterocyclic scaffold and the catalyst generate a short Pd−endocyclic carbon bond and a high Wiberg bond order (these values exceed the maximum value of 0.5 for a σ bond, see additional computational results in the Supporting Information). This effect is also reflected in the analysis of partial NPA charges, which shows a less NPA negative charge at the PdCl fragment with increasing

C_C-Pd bond order. Hence, the charge flow from the π–backbonding interaction of the metal to the alkene/allene moiety should be lower and the interaction weaker. For the coupling process with α-allenic acetate, a comparison of the NBO analysis for **I3$_{6Al}$** and **I3$_{5Al}$**, reveals a higher NPA charge at the catalyst (-0.10 vs $+0.01e$), a lower NPA positive charge at the allene fragment ($+0.13$ vs $+0.03e$, respectively), and lower Wiberg bond orders for the Pd–C-allene interactions for **I3$_{5Al}$** (0.222 and 0.198 vs 0.186 and 0.155, respectively), which is also confirmed by the lower interaction energy for **I3$_{5Al}$** than for **I3$_{6Al}$** ($\Delta E_2 = 7.7$ kcal mol^{-1}). Additionally, in the coupling transition state, **TS4$_{5Al}$**, the analysis also reveals a weaker interaction energy than for **TS4$_{6Al}$** ($\Delta E_2 = 6.2$ kcal mol^{-1}) between the donor π orbital and the empty developing orbital on the endocyclic C_C atom.

In contrast, a comparison of the NBO analysis for **I3$_{6Br}$** and **I3$_{5Br}$**, shows a similar negative NPA charge at the catalyst (-0.11 vs $-0.12e$), an analogous NPA positive charge at the incoming alkene fragment ($+0.17$ vs $+0.19e$, respectively), and equivalent Wiberg bond orders for the Pd-alkene interaction (0.246 and 0.218 vs 0.264 and 0.244, respectively). This similarity is reflected by the small difference of interaction energy (slightly lower for **I3$_{5Br}$**, $\Delta E_2 = 1.3$ kcal mol^{-1}). Expectedly, the coupling transition structures also reveal similar values for the interaction energy between the donor orbital and the empty developing orbital on the endocyclic C atom. In summary, the results suggest that the interplay of electronic effects at the heterocycle and coupling reagent controls the competitive formation of dihydropyrans and dihydropyrroles in the Pd-catalized heterocyclization/cross-coupling reactions of allenic amino alcohols.

CONCLUSIONS

In conclusion, the controlled preparation of 2,5-dihydro-1*H*-pyrroles, 3,6-dihydro-2*H*-pyrans, and pyrroles has been achieved through swithchable chemo- and regioselectivity in the metal-catalyzed heterocyclization reactions of allenic amino alcohols. Chemo- and regioselectivity depend on both the linker elongation as well as the type of catalyst. Furthermore, in order to justify this different demeanor, Density Functional Theory calculations have been implemented.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 MHz spectrometers. NMR spectra were recorded in CDCl$_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or CDCl$_3$ (^{13}C, 77.0 ppm). Low and high resolution mass spectra were performed on a QTOF LC–MS spectrometer using the electrospray mode (ES) unless otherwise stated. Specific rotation [α]$_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in grams per 100 mL. All commercially available compounds were used without further purification. Flash chromatography was performed by using silica gel 60 (230−400 mesh) or neutral alumina. Products were identified by TLC (silica gel). UV light (λ = 254nm) and a solution of phosphomolybdic acid in EtOH (1 g of phosphomolybdic acid hydrate, 100 mL EtOH) was used to develop the plates.

Computational Details. The calculations were performed with the Gaussian 09 suite of programs.[20] The structures were optimized with Truhlar´s dispersion-corrected meta hybrid exchange-correlation functional M06. This hybrid functional has been recommend for structures involving transition metals.[21,22] The quadruple-ζ quality plus polarization def2-QZVP basis set of Ahlrichs and coworkers[23] have been applied for all atoms except Au and Pd, which were treated with the SDD ECPs.[24] The stationary

23

points were characterized by means of harmonic analysis. For all the transition structures, the normal mode related to the imaginary frequency corresponds to the nuclear motion along the reaction coordinates under study. Additionally, in some cases, we carried out intrinsic reaction coordinate calculations (IRC) to verify that the transition structures connect with reactants and products. The Polarizable Continuum Model (PCM)[25] was applied to consider the solvents effects. Finally, to estimate the changes in the Gibbs energies in the presence of CH_2Cl_2 or DMF as solvent, single-point calculations on the optimized geometries were carried out. The natural bond orbital analysis (NBO)[26] were performed on the optimized structures.

General Procedure for the Deprotection of Allenyloxazolidines **3, 4a, and 4b. Preparation of *N*-Boc Allenic Amino Alcohols 1a, 2a, and 2b.** The corresponding allenyloxazolidine **3**, **4a**, or **4b** (1.00 mmol) was dissolved in acetonitrile/water (10 mL, 95:5) and the solution was cooled to 0 °C. $BiCl_3$ (0.05 mmol) was added and the mixture was stirred at RT until disappearance of the starting material (TLC, typically 14–24 h). The reaction mixture was poured into a satd. aq. solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford allenic amino alcohols **1a**, **2a**, and **2b**. Further purification was not necessary. Spectroscopic and analytical data for compounds **1a**, **2a**, and **2b** follow.

***N*-Boc Allenic Amino Alcohol (–)-1a.** From 100 mg (0.42 mmol) of allenyloxazolidine (–)-**3**, compound (–)-**1a** (87 mg, quantitative yield) was obtained as a colorless oil; $[\alpha]_D = -16.2$ (*c* 1.2, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ: 1.43 (s, 9H), 2.86 (br s, 1H), 3.62 (dd, 1H, *J* = 11.1, 5.5 Hz), 3.70 (dd, 1H, *J* = 11.1, 4.1 Hz), 4.23 (br s, 1H), 4.90 (dd, 2H, *J* = 6.7, 3.4 Hz), 4.99 (d, *J* = 7.5 Hz), 5.23 (dd, 1H, *J* =

12.0, 6.5 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$, 25 ^{o}C) δ: 207.2, 156.0, 89.8, 79.8, 78.5, 65.4,

50.7, 28.3; IR (CHCl$_3$, cm^{-1}): ν 3401, 3343, 1959, 1692, 1170; HRMS (ES): calcd for

C$_{10}$H$_{17}$NO$_3$ [M]$^+$: 199.1208; found: 199.1212.

N-Boc Allenic Amino Alcohol (–)-2a. From 100 mg (0.34 mmol) of

allenyloxazolidine (–)-**4a**, compound (–)-**2a** (86 mg, quantitative yield) was obtained as

a colorless oil; [α]$_D$ = –85.5 (*c* 0.5, CH$_2$Cl$_2$); ^{1}H-NMR (300 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 1.43

(s, 9H), 1.66 (t, *J* = 3.1 Hz, 3H), 2.98 (s, 3H), 3.60 (dd, *J* = 11.4, 4.0 Hz, 1H), 3.73 (d, *J*

= 6.5 Hz, 1H), 3.88 (m, 2H), 4.56 (d, *J* = 1.8 Hz, 2H), 5.02 (d, *J* = 8.5 Hz, 1H); ^{13}C-

NMR (75 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 207.8, 155.9, 96.5, 83.9, 79.1, 74.8, 62.5, 56.8, 53.3,

28.5 (3C), 13.5; IR (CHCl$_3$, cm^{-1}): ν 3447, 1958, 1695, 1172; HRMS (ES): calcd for

C$_{13}$H$_{23}$NO$_4$ [M]$^+$: 257.1627; found: 257.1628.

N-Boc Allenic Amino Alcohol (–)-2b. From 100 mg (0.28 mmol) of

allenyloxazolidine (–)-**4b**, compound (–)-**2b** (89 mg, quantitative yield) was obtained as

a colorless oil; [α]$_D$ = –23.5 (*c* 0.8, CH$_2$Cl$_2$); ^{1}H-NMR (300 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 1.44

(s, 9H), 2.98 (s, 3H), 3.49 (dd, *J* = 11.3, 2.7 Hz, 1H), 3.99 (m, 2H), 4.67 (br s, 1H), 4.88

(m, 2H), 5.53 (d, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 2H), 7.72

(d, *J* = 7.6 Hz, 2H); ^{13}C-NMR (75 MHz, C C$_6$D$_6$, 25 ^{o}C) δ: 208.8, 156.0, 134.4, 129.0

(2C), 127.5, 127.1 (2C), 104.6, 82.4, 80.0, 79.1, 61.8, 57.6, 54.0, 28.5 (3C); IR (CHCl$_3$,

cm^{-1}): ν 3437, 1940, 1703, 1174; HRMS (ES): calcd for C$_{18}$H$_{25}$NO$_4$ [M]$^+$: 319.1784;

found: 319.1773.

Procedure for the La^{III}-Catalyzed Cleavage of *N*-Boc Allene 1a. Preparation

of Allenic Amino Alcohol 1b. La[N(SiMe$_3$)$_2$]$_3$ (0.05 mmol) was added to a stirred

solution of the *N*-Boc allenic amino alcohol **1a** (200 mg, 1.0 mmol) in toluene (10.0

mL) under argon. The resulting mixture was stirred at reflux temperature until

disappearance of the starting material (TLC, 2 h). The reaction was then filtered through a celite plug before being concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes (1:2) gave analytically pure adduct **1b**.

Allenic Amino Alcohol (+)-1b. From 200 mg (1.0 mmol) of *N*-Boc allenic amino alcohol (–)-**1a**, compound (+)-**1b** (99 mg, quantitative yield) was obtained as a colorless oil; $[\alpha]_D$ = +9.4 (*c* 0.5, CHCl$_3$); ^{1}H-NMR (300 MHz, CDCl$_3$, 25 ^{o}C) δ: 4.19 (dd, 1H, *J* = 8.5, 5.6 Hz), 4.42 (dd, 1H, *J* = 13.7, 6.9 Hz), 4.57 (t, 1H, *J* = 8.3 Hz), 4.97 (dt, 2H, *J* = 6.4, 1.7 Hz), 5.22 (dd, 1H, *J* = 13.3, 6.7 Hz), 5.32 (br s, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$, 25 ^{o}C) δ: 208.1, 90.6, 78.8, 70.1, 51.6; IR (CHCl$_3$, cm^{-1}): ν 3279, 1956, 1228; HRMS (ES): calcd for C$_5$H$_9$NO $[M]^+$: 99.0684; found: 99.0688.

General Procedure for the Indium-Promoted Reaction between 3-Substituted Prop-2-ynyl Bromides and Garner's Aldehyde. Preparation of α-Allenic Alcohols 4a-OH and 4b-OH. 1-Bromo-2-butyne or 1-bromo-3-phenyl-2-propyne (3.0 mmol) was added to a well stirred suspension of Garner's aldehyde (1.0 mmol) and indium powder (6.0 mmol) in THF/NH$_4$Cl (aq. sat.) (1:5, 5 mL) at 0 ^{o}C. After disappearance of the starting material (TLC) the mixture was extracted with ethyl acetate (3 x 5 mL). The organic extract was washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure. Flash chromatography of the residue on deactivated silica gel using ethyl acetate/hexanes mixtures gave analytically pure compounds.

α-Allenol (–)-4a-OH. From 680 mg (2.96 mmol) of Garner's aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound (–)-**4a-OH** (374 mg, 44%) as a colorless oil; $[\alpha]_D$ = –41.3 (*c* 1.2, CH$_2$Cl$_2$); ^{1}H-NMR (300 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 4.63 (m, 2H), 3.70 (m, 4H), 3.36 (t, *J* = 9.8 Hz, 1H), 1.85 (t, *J* = 3.1 Hz, 3H), 1.36 (m, 15H); ^{13}C-NMR (75 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 207.9, 155.2, 98.8, 97.4, 79.0, 75.0, 74.8, 63.2, 46.8, 28.8, 28.5 (3C), 19.9, 13.7; IR (CHCl$_3$,

cm^{-1}): ν 3478, 1957, 1738; HRMS (ES): calcd for C$_{15}$H$_{25}$NO$_4$ [M]$^+$: 283.1784; found: 283.1771.

α-Allenol (–)-4b-OH. From 500 mg (2.18 mmol) of Garner's aldehyde, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound (–)-**4b-OH** (411 mg, 54%) as a colorless oil; [α]$_D$ = –39.1 (c 1.0, CH$_2$Cl$_2$); ^{1}H-NMR (300 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 7.35 (m, 2H), 7.17 (m, 3H), 5.16 (m, 2H), 3.99 (m, 4H), 1.43 (m, 15H); ^{13}C-NMR (75 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 208.1, 154.9, 132.0, 128.7 (2C), 128.2, 127.2 (2C), 109.1, 99.4 (2C), 80.0, 72.0, 63.3, 48.0, 28.5, 28.4 (3C), 20.2; IR (CHCl$_3$, cm^{-1}): ν 3476, 1971, 1735; HRMS (ES): calcd for C$_{20}$H$_{27}$NO$_4$ [M]$^+$: 345.1940; found: 345.1929.

General Procedure for the Synthesis of Methoxy Allenes 4. Tetrabutyl ammonium iodide (cat), 50% aqueous sodium hydroxide (18 mL) and dimethyl sulfate (0.60 mmol) were sequentially added at room temperature to a solution of the corresponding α-allenol (0.92 mmol) in dichloromethane (18 mL). The reaction was stirred until disappearance of the starting material (TLC). Then aqueous ammonia (30%) was added (2.5 mL), before being partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 x 15 mL), the combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure. Flash chromatography of the residue on deactivated silica gel using ethyl acetate/hexanes mixtures gave analytically pure compounds.

Methoxy Allene (–)-4a. From 175 mg (0.62 mmol) of α-allenol (–)-**4a-OH**, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound (–)-**4a** (124 mg, 67%) as a colorless oil; [α]$_D$ = –38.9 (c 0.9, CH$_2$Cl$_2$); ^{1}H-NMR (300 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 4.54 (m, 2H), 3.79 (m, 4H), 3.21 (s, 3H), 1.49 (m, 18H); ^{13}C-NMR (75 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 207.9, 155.1, 98.8, 97.4, 79.0, 74.9, 75.0,

63.2, 56.8, 46.8, 28.8, 28.4 (3C), 19.8, 13.7; IR (CHCl$_3$, cm^{-1}): ν 1956, 1737; HRMS

(ES): calcd for C$_{16}$H$_{27}$NO$_4$ [M]$^+$: 297.1940; found: 297.1921.

Methoxy Allene (–)-4b. From 170 mg (0.49 mmol) of α-allenol (–)-**4b-OH**, and

after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave

compound (–)-**4b** (107 mg, 61%) as a colorless oil; [α]$_D$ = –37.1 (*c* 1.5, CH$_2$Cl$_2$); ^{1}H-

NMR (300 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 7.43 (m, 2H), 7.22 (m, 3H), 5.14 (m, 2H), 4.04 (m,

4H), 3.30 (d, *J* = 9.3 Hz, 3H), 1.37 (m, 15H); ^{13}C-NMR (75 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 208.0,

154.9, 131.9, 128.6 (2C), 128.2, 127.2 (2C), 109.0, 99.3 (2C), 79.9, 71.9, 63.2, 57.3,

48.0, 28.4, 28.3 (3C), 20.2; IR (CHCl$_3$, cm^{-1}): ν 1955, 1739; HRMS (ES): calcd for

C$_{21}$H$_{29}$NO$_4$ [M]$^+$: 359.2097; found: 359.2077.

General Procedure for the Au^{III}-Catalyzed Cyclization of α-Amino-β-

hydroxyallenes 1. Preparation of 2,5-Dihydro-1*H*-pyrroles 5. AuCl$_3$ (0.025 mmol)

was added to a stirred solution of the appropriate allenic amino alcohol **1** (0.50 mmol)

in dichloromethane (5 mL) under argon. The resulting mixture was stirred at RT until

disappearance of the starting material (TLC, typically 3 hours). The reaction was then

quenched with brine (0.5 mL), the mixture was extracted with ethyl acetate (3 x 5 mL),

and the combined extracts were washed twice with brine. The reaction was concentrated

under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl

acetate mixtures gave adducts **5**. Spectroscopic and analytical data for pure forms of **5**

follow.

2,5-Dihydro-1*H*-pyrrole (–)-5a. From 44 mg (0.221 mmol) of *N*-Boc allenic

amino alcohol (–)-**1a**, and after chromatography of the residue using hexanes/ethyl

acetate (4:1) as eluent gave compound (–)-**5a** (34 mg, 77%) as a colorless oil; [α]$_D$ = –

58.1 (*c* 0.7, CHCl$_3$); ^{1}H-NMR (300 MHz, CDCl$_3$, 25 ^{o}C) δ: 1.50 (s, 9H), 3.11 (br s, 1H),

3.58 (dd, 1H, *J* = 11.2, 7.0 Hz), 3.79 (dd, 1H, *J* = 11.4, 2.3 Hz), 4.09 (ddt, 1H, *J* = 15.6,

5.4, 2.2 Hz), 4.21 (d, 1H, J = 15.4 Hz), 4.71 (br s, 1H), 5.63 (d, 1H, J = 4.4 Hz), 5.83 (s,

1H); ^{13}C-NMR (75 MHz, CDCl$_3$, 25 ^{o}C) δ: 156.6, 126.7, 126.6, 80.6, 67.6, 67.3, 54.2,

28.4 (3C); IR (CHCl$_3$, cm^{-1}): ν 3247, 1748, 1207; HRMS (ES): calcd C$_{10}$H$_{17}$NO$_3$ [M]$^+$:

199.1208; found: 199.1205.

2,5-Dihydro-1H-pyrrole (+)-5b. From 31 mg (0.31 mmol) of α-amino-β-

hydroxyallene (+)-**1b**, and after chromatography of the residue using hexanes/ethyl

acetate (2:1) as eluent gave compound (+)-**5b** (25 mg, 81%) as a colorless oil; [α]$_D$ =

+5.4 (c 0.5, CHCl$_3$); ^{1}H-NMR (300 MHz, CDCl$_3$, 25 ^{o}C) δ: 3.83 (m, 1H), 4.25 (dd, 1H,

J = 8.5, 5.1 Hz), 4.40 (ddt, 1H, J = 15.6, 3.0, 2.1 Hz), 4.61 (t, 1H, J = 8.6 Hz), 4.74 (m,

1H), 5.91 (dt, 1H, J = 5.9, 2.9 Hz), 6.06 (ddd, 1H, J = 5.9, 3.7, 2.1 Hz); ^{13}C-NMR (75

MHz, CDCl$_3$, 25 ^{o}C) δ: 130.9, 128.9, 68.7, 64.6, 54.8; IR (CHCl$_3$, cm^{-1}): ν 3325, 1247;

HRMS (ES): calcd C$_5$H$_9$NO [M]$^+$: 99.0684; found: 99.0687.

General Procedure for the Pd^{II}-Catalyzed Cyclization of α-Amino-β-

hydroxyallenes 1 in Presence of Allyl bromide. Preparation of Dihydropyrans 6

and Dihydropyrroles 7. Palladium(II) chloride (0.005 mmol) was added to a stirred

solution of the corresponding allenic amino alcohol **1** (0.10 mmol) and allyl bromide

(0.25 mmol) in N,N-dimethylformamide (1.0 mL). The reaction was stirred under argon

atmosphere until disappearance of the starting material (TLC, 2 h). Water (0.5 mL) was

added before being extracted with ethyl acetate (3 x 4 mL). The organic phase was

washed with water (2 x 2 mL), dried (MgSO$_4$) and concentrated under reduced pressure.

Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave

analytically pure adducts **6** and **7**.

Preparation of Dihydropyran (−)-6a and Dihydropyrrole (+)-7a. From 40 mg

(0.20 mmol) of α-amino-β-hydroxyallene (−)-**1a**, and after chromatography of the

residue using hexanes/ethyl acetate (4:1) as eluent, 22 mg (45%) of the less polar

compound (–)-**6a** and 10 mg (21%) of the more polar compound (+)-**7a** were obtained.

Dihydropyran (–)-6a. Colorless oil; $[\alpha]_D = -47.8$ (*c* 0.7, CHCl$_3$); ^{1}H-NMR (300

MHz, CDCl$_3$, 25 ^{o}C) δ: 1.45 (s, 9H), 2.67 (d, 2H, *J* = 6.8 Hz), 3.66 (dd, 1H, *J* = 11.4,

3.0 Hz), 3.79 (d, 1H, *J* = 12.0 Hz), 4.01 (m, 2H), 4.78 (d, 1H, *J* = 8.2 Hz), 5.08 (m, 2H),

5.59 (s, 1H), 5.75 (ddt, 1H, *J* = 16.4, 9.4, 6.9 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$, 25 ^{o}C) δ:

155.1, 139.6, 134.5, 119.6, 117.2, 79.4, 69.4, 67.6, 44.2, 37.3, 28.4 (3C); IR (CHCl$_3$,

cm^{-1}): ν 3301, 1737, 1215; HRMS (ES): calcd C$_{13}$H$_{21}$NO$_3$ [*M*]$^+$: 239.1521; found:

239.1531.

Dihydropyrrole (+)-7a. Colorless oil; $[\alpha]_D = +26.7$ (*c* 0.4, CHCl$_3$); ^{1}H-NMR

(300 MHz, CDCl$_3$, 25 ^{o}C) δ: 1.49 (s, 9H), 2.84 (d, 2H, *J* = 6.6 Hz), 3.56 (dd, 1H, *J* =

11.4, 7.2 Hz), 3.75 (dd, 1H, *J* = 11.4, 2.2 Hz), 4.04 (m, 2H), 4.70 (br s, 1H), 5.09 (s,

1H), 5.14 (m, 1H), 5.30 (m, 1H), 5.81 (m, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$, 25 ^{o}C) δ:

156.6, 139.2, 134.1, 120.4, 117.2, 80.6, 68.1, 67.6, 55.8, 33.2, 28.5; IR (CHCl$_3$, cm^{-1}): ν

2992, 1754, 1188; HRMS (ES): calcd C$_{13}$H$_{21}$NO$_3$ [*M*]$^+$: 239.1521; found: 239.1523.

Preparation of Dihydropyran (–)-6b and Dihydropyrrole (+)-7b. From 50

mg (0.50 mmol) of α-amino-β-hydroxyallene (+)-**1b**, and after chromatography of the

residue using hexanes/ethyl acetate (4:1) as eluent, 37 mg (53%) of the less polar

compound (–)-**6b** and 28 mg (39%) of the more polar compound (+)-**7b** were obtained.

Dihydropyran (–)-6b. Colorless oil; $[\alpha]_D = -16.2$ (*c* 0.4, CHCl$_3$); ^{1}H-NMR (300

MHz, CDCl$_3$, 25 ^{o}C) δ: 2.90 (d, 2H, J = 6.6 Hz), 3.77 (m, 1H), 4.22 (dd, 1H, *J* = 8.5, 5.2

Hz), 4.25 (m, 1H), 4.57 (t, 1H, *J* = 8.6 Hz), 4.74 (m, 1H), 5.13 (m, 2H), 5.53 (m, 1H),

5.81 (m, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$, 25 ^{o}C) δ: 144.3, 133.6, 122.7, 117.5, 69.0,

64.8, 56.5, 33.1; IR (CHCl$_3$, cm^{-1}): ν 3278, 1231; HRMS (ES): calcd C$_8$H$_{13}$NO [M]$^+$: 139.0997; found: 139.0998.

Dihydropyrrole (+)-7b. Colorless oil; [α]$_D$ = +10.4 (*c* 0.3, CHCl$_3$); ^{1}H-NMR (300 MHz, CDCl$_3$, 25 ^{o}C) δ: 2.99 (d, 2H, J = 6.2 Hz), 4.03 (m, 1H), 4.05 (dd, 1H, *J* = 8.5, 7.0 Hz), 4.54 (t, 1H, *J* = 8.5 Hz), 4.70 (m, 1H), 5.10 (m, 2H), 5.19 (m, 1H), 5.70 (m, 1H), 5.76 (m, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$, 25 ^{o}C) δ: 139.3, 134.3, 128.8, 117.1, 69.8, 50.0, 48.2, 32.7; IR (CHCl$_3$, cm^{-1}): ν 2920, 1188; HRMS (ES): calcd C$_8$H$_{13}$NO [M]$^+$: 139.0997; found: 139.1006.

General Procedure for the Pd^{II}-Catalyzed Cyclization of α-Amino-β-hydroxyallenes 1 in Presence of α-Allenic Acetates 8. Preparation of Dihydropyrans 9 and 10. Palladium(II) chloride (0.005 mmol) was added to a stirred solution of the appropriate allenic amino alcohol **1** (0.10 mmol) and the correspondinge α-allenic acetate **8** (0.30 mmol) in *N,N*-dimethylformamide (1.0 mL). The reaction was stirred under argon atmosphere until disappearance of the starting material (TLC). Water (0.5 mL) was added before being extracted with ethyl acetate (3 x 4 mL). The organic phase was washed with water (2 x 2 mL), dried (MgSO$_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure 3,6-dihydro-2*H*-pyran-3-amine derivatives **9** and **10**.

Dihydropyran (–)-9a. From 50 mg (0.25 mmol) of *N*-Boc allenic amino alcohol (–)-**1a**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound (–)-**9a** (38 mg, 44%) as a colorless oil; [α]$_D$ = –1.2 (*c* 1.3, CHCl$_3$); ^{1}H-NMR (300 MHz, CDCl$_3$, 25 ^{o}C) δ: 1.46 (s, 9H), 2.01 (d, 3H, *J* = 1.3 Hz), 3.79 (m, 2H), 4.22 (m, 2H), 4.85 (d, 1H, *J* = 8.1 Hz), 5.01 (d, 1H, *J* = 1.0 Hz), 5.17 (d,

31

1H, J = 1.12 Hz), 5.84 (d, 1H, J = 4.3 Hz), 6.52 (s, 1H), 7.30 (m, 5H); ^{13}C-NMR (75

MHz, CDCl$_3$, 25 ^{o}C) δ: 155.2, 150.0, 140.2, 137.6, 136.5, 129.7, 129.1 (2C), 128.1 (2C),

126.7, 123.2, 112.5, 79.6, 69.4, 67.3, 44.2, 28.4 (3C), 17.0; IR (CHCl$_3$, cm^{-1}): ν 3343,

1709, 1236; HRMS (ES): calcd C$_{17}$H$_{19}$NO$_3$ [M – isobutene + H]$^+$: 286.1443; found:

286.1451.

Dihydropyran (–)-9b. From 50 mg (0.25 mmol) of *N*-Boc allenic amino alcohol

(–)-**1a**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as

eluent gave compound (–)-**9b** (44 mg, 47%) as a colorless oil; [α]$_D$ = –17.1 (*c* 0.6,

CHCl$_3$); ^{1}H-NMR (300 MHz, CDCl$_3$, 25 ^{o}C) δ: 1.45 (s, 9H), 2.00 (d, 3H, J = 1.2 Hz),

3.81 (m, 2H), 3.83 (s, 3H), 4.24 (m, 2H), 4.85 (d, 1H, J = 8.3 Hz), 4.99 (s, 1H), 5.14 (s,

1H), 5.82 (d, 1H, J = 4.1 Hz), 6.45 (s, 1H), 6.90 (d, 2H, J = 8.8Hz), 7.25 (d, 2H, J = 8.7

Hz); ^{13}C-NMR (75 MHz, CDCl$_3$, 25 ^{o}C) δ: 159.3, 158.3, 150.2, 134.9, 131.7, 130.3

(2C), 129.2, 127.1, 123.1, 113.6 (2C), 112.2, 81.4, 69.0, 67.4, 55.3, 44.2, 28.4 (3C),

17.0; IR (CHCl$_3$, cm^{-1}): ν 3237, 1718, 1195; HRMS (ES): calcd C$_{22}$H$_{29}$NO$_4$ [M]$^+$:

371.2097; found: 371.2099.

Dihydropyran (–)-10a. From 50 mg (0.5 mmol) of α-amino-β-hydroxyallene

(+)-**1b**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as

eluent gave compound (–)-**10a** (68 mg, 56%) as a colorless oil; [α]$_D$ = –5.7 (*c* 1.4,

CHCl$_3$); ^{1}H-NMR (300 MHz, CDCl$_3$, 25 ^{o}C) δ: 1.98 (d, 3H, J = 1.4 Hz$_3$), 4.02 (ddd, 1H,

J = 14.7, 4.2, 2.3 Hz), 4.28 (dd, 1H, J = 8.6, 5.0 Hz), 4.58 (ddd, 1H, J = 14.7, 2.7, 1.6

Hz), 4.62 (t, 1H, J = 8.7 Hz), 4.87 (m, 1H), 5.11 (s, 1H), 5.27 (s, 1H), 5.83 (q, 1H, J =

1.7 Hz), 6.48 (s, 1H), 7.32 (m, 5H); ^{13}C-NMR (75 MHz, CDCl$_3$, 25 ^{o}C) δ: 146.1, 143.4,

137.4, 136.7, 129.3, 129.0 (2C), 128.2 (2C), 126.8, 125.9, 115.1, 68.6, 65.2, 55.1, 18.1;

IR (CHCl$_3$, cm^{-1}): ν 3454, 1236; HRMS (ES): calcd C$_{16}$H$_{19}$NO [M]$^+$: 241.1467; found: 241.1475.

Dihydropyran (–)-10b. From 50 mg (0.5 mmol) of α-amino-β-hydroxyallene (+)-**1b**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound (–)-**10b** (71 mg, 52%) as a colorless oil; [α]$_D$ = –1.8 (*c* 1.2, CHCl$_3$); ^{1}H-NMR (300 MHz, CDCl$_3$, 25 ^{o}C) δ: 1.05 (d, 3H, J = 1.3 Hz), 3.83 (s, 3H), 4.01 (ddd, 1H, J = 14.7, 4.2, 2.3 Hz), 4.28 (dd, 1H, J = 8.6, 5.1 Hz), 4.57 (ddd, 1H, J = 14.7, 2.7, 1.6 Hz), 4.61 (t, 1H, J = 8.7 Hz), 4.86 (m, 1H), 5.09 (s, 1H), 5.24 (s, 1H), 5.81 (q, 1H, J = 1.7 Hz), 6.41 (s, 1H), 6.90 (d, 2H, J = 8.8 Hz), 7.26 (d, 2H, J = 7.1 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$, 25 ^{o}C) δ: 163.2, 146.3, 143.6, 135.0, 130.2 (2C), 130.0, 128.8, 125.8, 114.8, 113.7 (2C), 68.7, 65.2, 55.3, 55.2, 18.0; IR (CHCl$_3$, cm^{-1}): ν 3461, 1228; HRMS (ES): calcd C$_{17}$H$_{21}$NO$_2$ [M]$^+$: 271.1572; found: 271.1580.

General Procedure for the Au^I-Catalyzed Cyclization of β-Amino-γ-hydroxyallenes 2. Preparation of Pyrroles 11. [(Ph$_3$P)AuNTf$_2$] (0.05 mmol) was added to a stirred solution of the corresponding allenic amino alcohol **2** (1.0 mmol) in dichloromethane (4.0 mL) under argon. The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC, typically 2 h). After filtration through a pad of Celite, the mixture was extracted with dichloromethane (3 x 10 mL), and the combined extracts were washed twice with brine. The organic layer was dried (MgSO$_4$) and concentrated under reduced pressure. Chromatography (deactivated silica gel or neutral alumina) of the residue eluting with ethyl acetate/hexanes mixtures gave adducts **11**.

Pyrrole 11a. From 70 mg (0.27 mmol) of β-amino-γ-hydroxyallene **2a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave

compound **11a** (32 mg, 53%) as a colorless oil; ^{1}H-NMR (300 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 5.85 (s, 1H), 4.68 (s, 2H), 3.47 (br s, 1H), 2.11 (s, 3H), 1.82 (s, 3H), 1.22 (s, 9H); ^{13}C-NMR (75 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 151.3, 134.9, 127.4, 118.3, 115.4, 83.5, 58.8, 27.7 (3C), 13.6, 11.2 (CH$_3$); IR (CHCl$_3$, cm^{-1}): ν 3441, 2927, 1733, 1366, 1327, 1139; HRMS (ES): calcd C$_{12}$H$_{19}$NO$_3$ [*M*]$^+$: 225.1365; found: 225.1368.

Pyrrole 11b. From 85 mg (0.18 mmol) of β-amino-γ-hydroxyallene **2b**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound **11a** (20 mg, 40%) as a colorless oil; ^{1}H-NMR (300 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 7.35 (m, 2H),7.26 (m, 3H), 6.16 (s, 1H), 4.67 (s, 2H), 2.27 (s, 3H), 1.22 (s, 9H); ^{13}C-NMR (75 MHz, C$_6$D$_6$, 25 ^{o}C) δ: 151.3, 136. 5, 135.6, 129.2 (2C), 128.9, 128.8 (2C), 126.7, 125.8, 114.1, 84.0, 58.7, 27.7 (3C), 14.7; IR (CHCl$_3$, cm^{-1}): ν 3394, 2977, 1737, 1366, 1327, 1132; HRMS (ES): calcd C$_{17}$H$_{21}$NO$_3$ [*M*]$^+$: 287.1521; found: 287.1535.

ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra of new compounds, additional computational results, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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