Gold-catalyzed Synthesis of Exocyclic Vinylogous Amides and β-Amino Ketones. A Detailed Study on the 5-*exo*/6-*endo dig* Selectivity, Methodology and Scope

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Dedicated to Prof. Antonio Guarna on the occasion of his retirement

Abstract: The gold(I)-catalyzed reaction of *N*-Boc-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines, which affords synthetically useful vinylogous amides (*β*-enaminones), has been studied in detail in order to optimize the reaction conditions, enlarge the scope and have insights into the mechanism and the structural features that selectively favor the 6-*endo dig* oxyauration of the triple bond. Experimental studies and DFT calculations demonstrate that the 6-*endo dig* approach is exclusive with substituted alkynes, whereas with terminal alkynes the 5-*exo dig* cyclization prevails despite the large angle (120°) at C6. The same selectivity is observed with *N*-Cbz-protected 2-alkynyl piperidines. With these, β-amino ketones are obtained as a consequence of the 6-*endo dig* attack to a substituted triple bond. *Sedamine* alkaloids are easily obtained by this approach.

Introduction

Vinylogous amides (β-enaminones) constitute an important class of valuable intermediates in the synthesis of heterocyclic and natural compounds.[1] They also possess important therapeutic potential against the multidrug resistance (MDR) of cancer cells,[2] and epilepsy.[3] For these reasons, many efforts have been put in the quest for new methods that efficiently provide them.[3,4] Among exocyclic vinylogous amides, those built on a piperidine ring are versatile intermediates in the preparation of many *N*-heterocycles[5] and natural alkaloids (Figure 1), such as desoxoprosophylline,[6] cassine,[7] pinidinone,[8] deoxyfebrifugine,[9] norallosedamine[10] and others.[11] The synthesis of other related alkaloids such as sedamine[12] and 5-hydroxy sedamine,[13] halosaline[14] and pelletierine[15] could also be easily envisaged by exploiting the reactivity of such vinylogous amides.

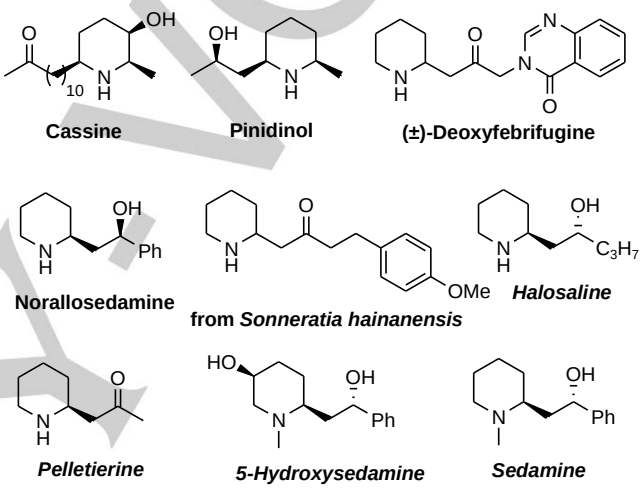
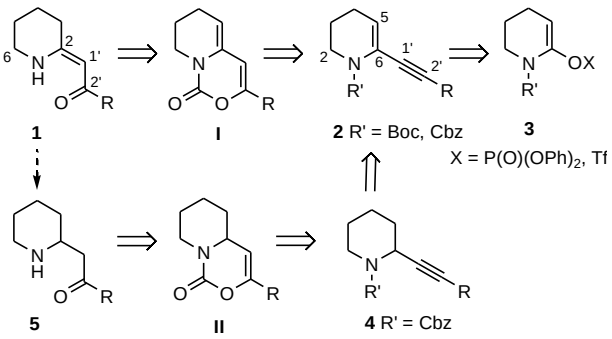


Figure 1. Naturally occurring alkaloids prepared from vinylogous amides and some related compounds.

Recently we have reported on a new approach to the synthesis of exocyclic vinylogous amides **1** in which the key step was the gold(I)-catalyzed rearrangement of *N*-Boc enynes **2** (Scheme 1).[11] *N*-Boc enynes **2** were obtained by the Sonogashira coupling of lactam-derived enol phosphates and triflates **3** to a variety of terminal alkynes.[11]



Scheme 1. Retrosynthetic analysis.

The gold(I)-catalyzed step, which was carried out in the presence of 2-3 mol % of $Ph_3PAuOTf$ in refluxing toluene,

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included a 6-*endo dig* attack to the activated triple bond by the Boc carbonyl oxygen of the enyne to form a labile cyclic urethane intermediate (**I**). Because of its instability, this intermediate could not be usually isolated and thus its hydrolysis was carried out *in situ* to afford the corresponding vinylogous amide **1** in good yields (generally no less than 70%, irrespective of the R residue) and as the Z isomer only.

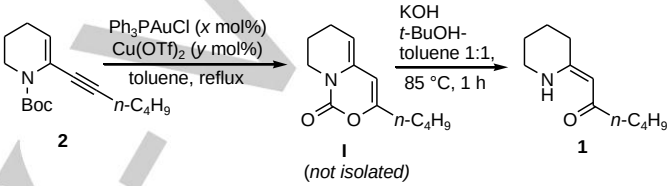
In view of possible applications of the methodology to large scale syntheses, we wanted to further lower down the catalyst loading. Moreover, concerning the scope of the reaction, this was limited to the alkyne chain and so we decided to explore the compatibility of various functional groups on the piperidine ring with the reaction conditions, as well as to explore the reactivity of 7-alkynyl-2,3,4,5-tetrahydro-azepine derivatives. Furthermore, we envisaged that a further extension of the scope could be attained by the replacement of the *N*-Boc protection with a *N*-Cbz group, which would in theory result in C1' substituted vinylogous amides deriving from a carbodeauration step.[16]

A key point of our previous work was that with substrates such as *N*-Boc enynes **2** the exclusive formation of products deriving from a 6-*endo dig* oxyauration step was observed, whereas for *N*-Boc propargylamines and 2-alkynyl *N*-Boc-substituted pyrrolidines and piperidines[17-19] only the 5-*exo dig* approach has been reported.[20] Also based on other reports from the literature, it seemed to us reasonable that in our case the alternative 5-*exo dig* mechanism was disfavored by the larger bond angle at C6 (due to the presence of the endocyclic double bond), which caused also a much lower reactivity of substrates **2** in comparison to the corresponding saturated compounds.[18,19] However, the strikingly different results reported for the latter substrates prompted us to carry out further investigations, including theoretical calculations, to unveil the role of the C6 hybridization, and other possible structural features of these substrates, in the 6-*endo*/5-*exo dig* preference during the gold-catalyzed cyclization of enynes **2**. Finally, since all natural compounds potentially derived from exocyclic vinylogous amides (Figure 1) are β-amino ketones (or alcohols obtained from β-amino ketones), we decided also to explore the gold(I)-catalyzed cycloisomerization of 2-alkynylpiperidines **4** (Scheme 1) as an alternative synthetic route in which reduction of the double bond to afford the β-amino ketone **5** is carried before (and not) after the gold-catalyzed step.

Results and Discussion

In gold(I)-catalyzed processes the catalyst is generally used at a percentage varying from 1 to 5% mol,[21] even though some exceptions have also been reported.[22] The active gold(I) catalysts are generally prepared *in situ* by anion exchange between LAuX (X = Cl, Br) and a silver salt (AgY) so that the highly coordinating anion X^- can be eliminated as AgX. Beside the fact that the silver does play a role in some gold(I)-catalyzed processes,[23] there are issues related to the decay/decomposition of the active gold catalyst that have recently been pointed out.[24,25] This is what we actually observed in our previous study on the gold(I)-catalyzed rearrangement of *N*-Boc-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines, and for this reason we then used 2-3 mol % of the catalyst to achieve a complete conversion in a reasonable time.[11] In a study on the anion metathesis reported by Bezzenine-Lafollée and Gandon,[24] it was found that by slowing down the rate of the anion exchange, for example by changing the source of the weakly coordinating anion from silver to copper salts, the decomposition of the catalyst could be prevented. This was due to the slow release of the active LAu^+ species in the solution over a longer period of time.[26] Among the various catalytic systems, $Cu(OTf)_2$ proved to be the best, and so we decided to evaluate these new conditions to attain a lower catalyst loading (Table 1).

Table 1. Gold(I)-catalyzed reaction of enyne **2** in the presence of $Cu(OTf)_2$.[a]



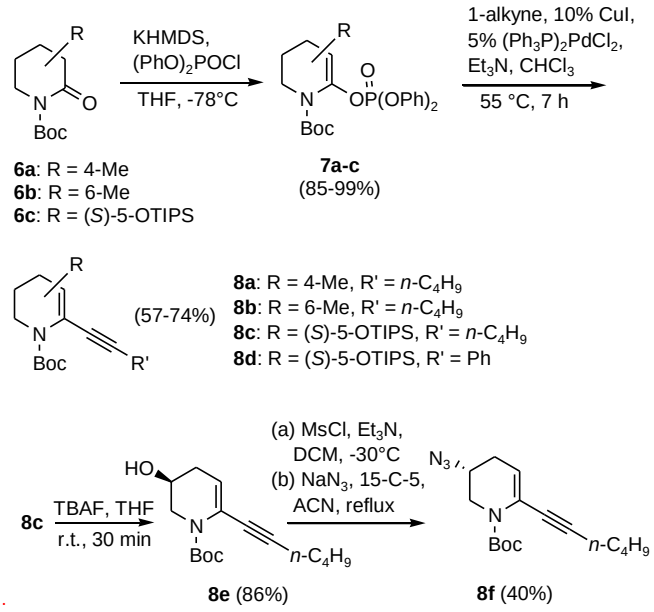
2 **I** (*not isolated*) **1**

Entry	Ph_3PAuCl mol %	$Cu(OTf)_2$ mol %	Time (h)	**I** (%)[b]	**1** (%)[c]
1	0.5	10	0.5	100	70
2	0.5	5	0.5	100	72
3	0.2	5	3.5	76	-
4	0.1	5	6.5	70	-
5	0	10	2.5	40	-

[a] Reactions carried out on a 0.5 mmol scale under inert atmosphere. [b] Conversion measured by ^{1}H NMR. [c] Yield after chromatographic purification.

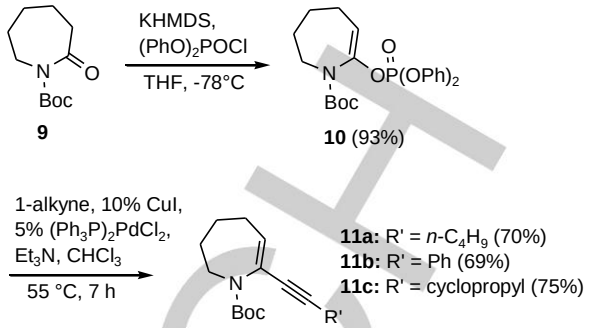
We carried out the reaction in refluxing toluene on compound **2** as a model substrate and lowered the gold(I) relative amount to 0.5% mol since the first experiment and added $Cu(OTf)_2$ in a 20:1 molar ratio (entry 1). We were delighted to find out that in only 30 minutes the starting material was completely consumed and corresponding vinylogous amide **1** was obtained after alkaline hydrolysis of intermediate **I** in the usual 70% yield after purification. The same result was obtained with a 10:1 molar ratio by lowering the quantity of $Cu(OTf)_2$ to 5% mol (entry 2), whereas with lower amounts of Ph_3PAuCl the reaction never went to completion (entries 3 and 4), even by prolonging the reaction time up to 6.5 h (entry 4). Not unexpectedly, $Cu(OTf)_2$ alone at 10% mol had some catalytic properties[24,27] but the reaction required 2.5 h to reach 40% of conversion (entry 5), so the cationic gold(I) is the true catalyst. Based on these results, we decided to use Ph_3PAuCl at 0.5% mol together with 5% mol of $Cu(OTf)_2$ as the new catalytic system for the next gold(I)-catalyzed experiments.

The synthesis of substrates bearing functional groups on the piperidine ring, as well as larger heterocyclic rings, was carried out in order to expand the scope of the reaction.



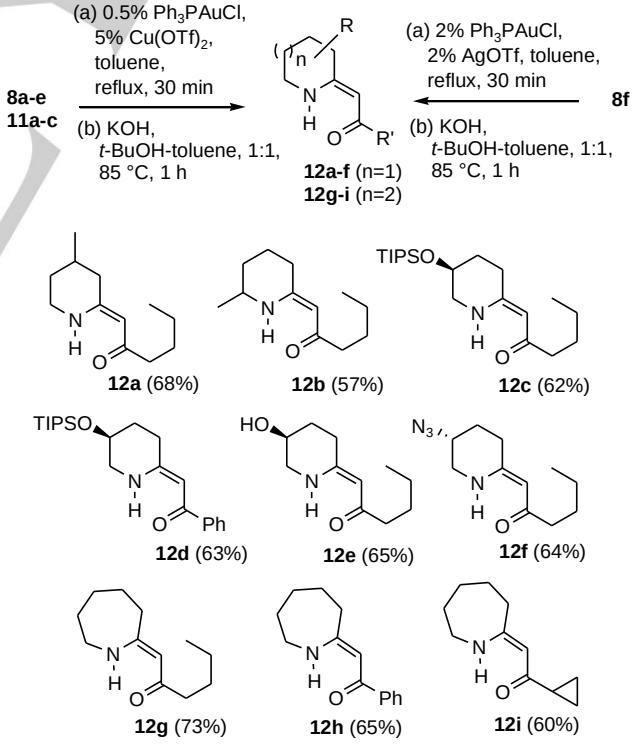
Scheme 2. Synthesis of compounds **8a-f**.

We were in particular interested in assessing the compatibility of OH groups, usually present in natural compounds prepared from β-enaminones, and N-containing groups. Lactams **6a**[28] and **6b**[29] were obtained by oxidation of the corresponding racemic *N*-Boc protected methylpiperidines,[30,31] whereas lactam **6c** (Scheme 2) was prepared from (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone[32,33] and using standard chemistry for the final two protection steps on the 5-hydroxy-δ-valerolactam.[33] The enol phosphates **7a-c** were obtained in good yields by treatment of **6a-c** with KHMDS at -78 °C and trapping the enolate *in situ* by addition of diphenyl chlorophosphate; the purification was performed on a very short silica pad and the products used as substrates in the next Sonogashira coupling with 1-hexyne (to give **8a-c**, yields 57-74%) or phenylacetylene (to give **8d**, yield 69%). As we have already reported for analogous substrates, enynes **8a-d** were not stable when neat and were stored in solution in the presence of Et_3N (1% v/v). Part of enyne **8c** was deprotected to restore the free hydroxyl group and a portion of **8e** was transformed into the corresponding azide **8f**, by treatment with mesyl chloride followed by substitution with NaN_3. More enynes (Scheme 3) were obtained starting from *N*-Boc ε-caprolactam[34] (**9**) and coupling enolphosphate **10** with 1-hexyne (to give **11a**), phenylacetylene (to give **11b**) and cyclopropylacetylene (to give **11c**) under the usual Sonogashira conditions.



Scheme 3. Synthesis of compounds **11a-c**.

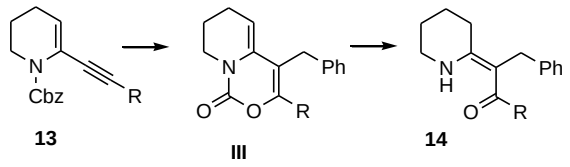
All enynes **8a-f** and **11a-c** were successfully used for the synthesis of the corresponding vinylogous amides with the gold-copper catalytic system (Scheme 4). With **8f** only the reaction was best carried out by using the Ph_3PAuCl-AgOTf system to provide the corresponding vinylogous amide **12f** (which contains a masked amino group on the piperidine ring) in good yield after purification. As we reported in our previous work, the cyclic intermediates were not stable and thus the hydrolysis was performed *in situ* at 80 °C by addition of KOH and *tert*-butanol.[35] In all cases, the vinylogous amides were obtained in good yields over the two steps (57-73%).



Scheme 4. Synthesis of compounds **12a-i**.

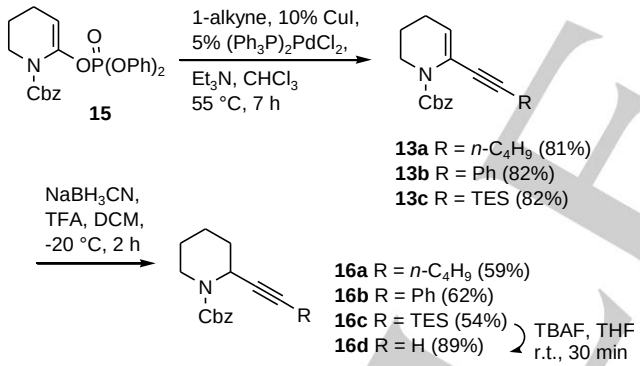
To further expand the scope of the reaction, we then decided to focus our attention on different substrates in which a

carbobenzyloxy replaces the *t*-butyloxy group. According to the reaction mechanism, in the case of *N*-Boc substrates, once the carbonyl oxygen of the Boc group attacks the gold-activated triple bond, the so formed *t*-butyl cation decomposes in isobutylene and H^+, generating the most important proton-source for the protodeauration step. Since carbodeauration has been demonstrated with those substrates able to generate a carbocation (mainly allylic),[16] we decided to verify if this process would be possible in our case with a benzyl carbocation derived from a *N*-Cbz protection, affording thus vinylogous amides **14** bearing a C1' substituent (Scheme 5).



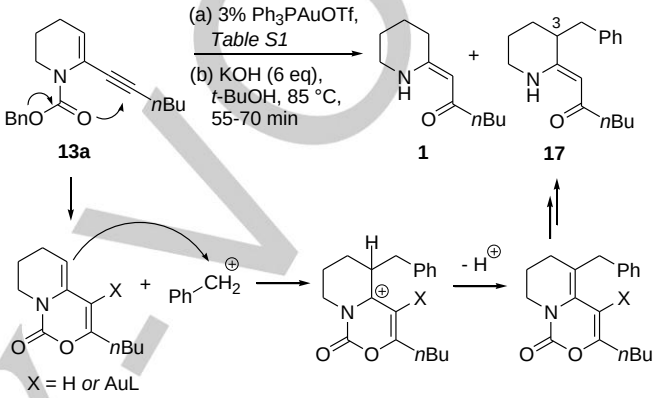
Scheme 5. Planned synthesis of **14**.

The synthesis of *N*-Cbz enyne **13a** (Scheme 6), as the model substrate, was carried out by Sonogashira coupling between the *N*-Cbz enol phosphate **15**[36] and 1-hexyne. As the analogous *N*-Boc compound, also **13a** proved unstable when neat and was stored in solution in the presence of Et_3N.



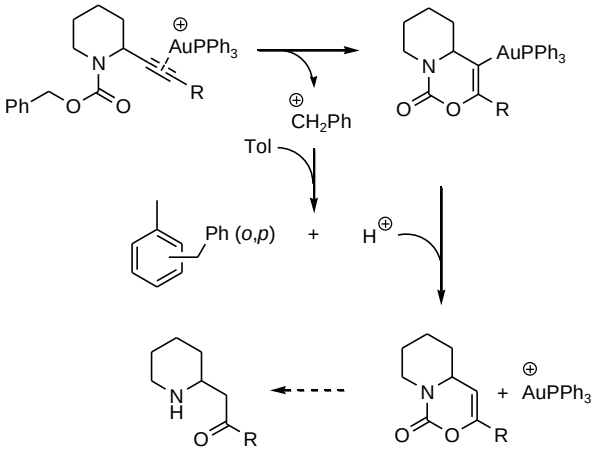
Scheme 6. Synthesis of compounds **13a-c** and **16a-d**.

Compound **13a** was then used in the gold(I)-catalyzed process under the usual conditions (Scheme 7) but the reaction failed to go to completion even by prolonging the reaction time up to 4.5 h, as well as to provide, after hydrolysis, compound **14** deriving from carbodeauration. Whatever the conditions used, the reaction took place via a 6-*endo dig* oxyauration process and, together with the unreacted starting material, we only obtained a mixture of vinylogous amides **1** and **17** (Table S1 in the Supporting Information), the former deriving from protodeauration and the latter from an electrophilic addition of the benzylic carbocation to the piperidine double bond (before or after the protodeauration step) and consequent release of a proton. Moreover, *o*-benzyltoluene and *p*-benzyltoluene were detected in ^{1}H-NMR of the crude mixture, both deriving from an electrophilic aromatic substitution on toluene which therefore represents an additional proton source in the process. Compounds **1** and **17** were not separated by chromatography, but the structure of **17** was easily assigned by ^{1}H NMR analysis of the mixture, in which a diagnostic ABX system associated to the two benzylic protons (dd at 3.06 ppm, J = 13.5, 4.7 Hz and dd at 2.73, J = 13.5, 10.2 Hz), and 3-H (m at 2.64-2.58 ppm) is present.



Scheme 7. Au(I)-catalyzed reaction of **13a**.

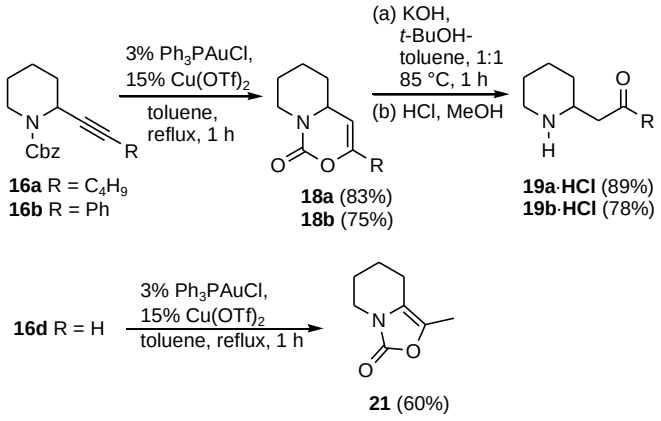
Based on these results, we decided to reduce the double bond of **13a** (to obtain **16a**) so that no benzylic addition could occur and, by exploiting toluene as a proton source, products formally deriving from the double bond reduction of the vinylogous amides **1** (i.e. β-amino ketones) could instead be obtained (Scheme 8).



Scheme 8. Planned synthesis of β-amino ketones.

As mentioned above, this would represent an alternative synthetic route to β-amino ketones in which reduction of the double bond is carried out before the gold-catalyzed step. For example, a series of natural products which included various

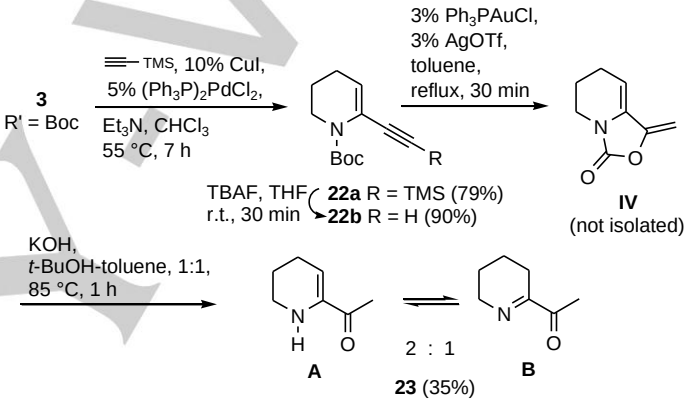
Sedamine alkaloids has been obtained from β-amino ketone **19b** (Scheme 9),[10] and the latter itself is a natural compound (norsedaminone).[37] The selective reduction was performed at low temperature with $NaBH_3CN$ under acidic conditions[38] and afforded compound **16a** in good yield (Scheme 6).



Scheme 9. Synthesis of compounds **19a-b** and **21**.

We were glad to observe that the subsequent gold-catalyzed step afforded only compound **18a**, that derived from the 6-*endo dig* approach, whereas we were unable to find any signal in the ^{1}H NMR spectrum of the crude reaction mixture attributable to the 5-*exo dig* isomer (Scheme 9).[39] To confirm our findings, we decided to synthesize compound **16b** by means of a Sonogashira coupling of **15** with phenylacetylene followed by reduction of the double bond of **13b** as already described (Scheme 6). Compound **18b** is a known compound[40] and since it was synthesized by a [4+2] cycloaddition of *N*-acyliminium ion with phenylacetylene, its structure was undoubtedly assigned. Treatment of **16b** with Ph_3PAuCl and $Cu(OTf)_2$ under the usual conditions afforded only **18b** (Scheme 9), with spectroscopic data identical to those reported in the literature.[41] A further confirmation of both structures of **18a** and **18b** came from the hydrolysis under basic conditions which afforded β-amino ketones **19a** and **19b** which, being quite volatile, were converted into their HCl salts in good overall yield (89 and 78%, respectively).

These results seemed in contrast with the data previously reported in the literature for *N*-Boc protected propargylamines, in which only 5-*exo dig* products were obtained even though the 6-*endo dig* approach was equally possible. Also when heterocyclic substrates were employed, i.e. *N*-Boc-2-ethynylpyrrolidine,[18,19] *N*-Boc-2-ethynylpiperidine[19] and *N*-Boc-2-ethynylazepane,[19] 5-*exo dig* products were obtained,[20] but all of them had a terminal alkyne moiety. Since in our case all substrates possessed a substituted alkyne appendage, we wondered whether an analogy with the gold(I)-catalyzed propargylic ester migration would exist. In the latter, the 1,2-process is favored for terminal alkynes whereas the 1,3-rearrangement becomes a competing, or even the leading, path for internal ones.[42] The synthesis of the substrate with a terminal alkyne was therefore required; this was carried out by Sonogashira coupling of phosphate **15** with triethylsilylacetylene (to give **13c**) followed by reduction of the double bond (to give **16c**) and deprotection with TBAF (to give **16d**, Scheme 6). It should be highlighted that, in case our hypothesis were correct, treatment of **16d** with gold-catalyst would afford the same product obtained by Gagosz and Buzas starting from the analogous *N*-Boc substrate.[19] We were delighted to verify that **16d**, under the usual gold catalysis conditions, afforded only compound **21** (Scheme 9), which derives from a 5-*exo dig* approach, followed by the isomerization of the double bond to the endocyclic position.[43] Furthermore an experiment performed with unsaturated *N*-Boc compound **22** (Scheme 10) afforded known compound **23**,[44] that derives from the 5-*exo dig* intermediate. These results all together show that the 6-*endo*/5-*exo dig* selectivity we observe with our substrates depends on whether the triple bond is internal or terminal.



Scheme 10. Synthesis of compound **23**.

To get further insights into the reason for the distinguished selectivity with terminal or internal alkynes, and to ascertain whether the large N-C_{sp2}-C_{sp} angle has a role in the high 6-*endo* preference with those substrates possessing an internal triple bond, DFT calculations were carried out with the Gaussian 09 suite of programs (see Computational Methods section). Since the 5-*exo*/6-*endo* selectivity trend does not depend on the alkoxycarbonyl moiety, the *N*-Cbz protection was chosen and compounds **13b**, **13d**, **16b** and **16d** (Figure 2) were selected as model substrates for the cyclization reaction, as examples of the four possible combinations of saturated/unsaturated rings and substituted/unsubstituted alkynes. Triphenyl-phosphine-gold(I) cation was used as reaction catalyst, and the study was centered on the cyclization step, which is the regiodetermining step.

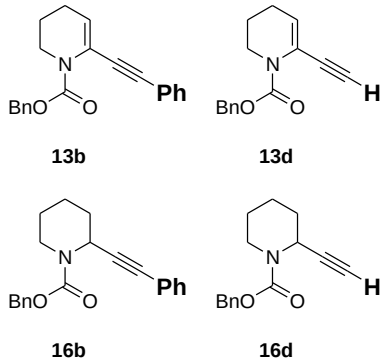


Figure 2. Model substrates for DFT studies.

Given the very different steric hindrance at the two carbons of the triple bond in terminal alkynes (**13d** and **16d**), it would seem reasonable to hypothesize at first sight, that steric effects were important for the observed 5-*exo* regioselectivity in these substrates, since gold atom could preferably be placed on the least substituted terminal position during oxygen attack. But, being potentially important, this effect alone would not explain the regioselectivity found in internal alkynes (**13b** and **16b**), since both carbon atoms are sterically quite similar in those cases. Thus, the four alkyne-gold(I) complexes were computed (only the unsaturated ones **V-Ph** and **V-H** are shown in Figure 3), and not surprisingly, the complexes evidenced clear structural differences regarding the alkyne/gold complexation.

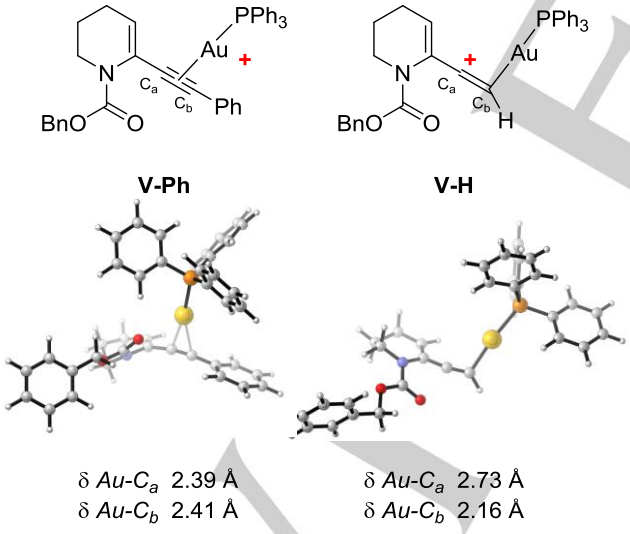


Figure 3. Structure of complexes **V-Ph** and **V-H**.

Specifically, in **V-H**, gold coordination induces a weakening of the triple bond (δ C_a-C_b = 1.23 Å) and a strong asymmetry of the C-Au bonds ($\delta_{(Ca\text{-}Au)}$ = 2.73 Å, $\delta_{(Cb\text{-}Au)}$ = 2.16 Å), forming a complex that can be considered to some extent as a vinyl cation. The computed natural population atomic charges at both carbon atoms are +0.203e (C_a) and -0.480e (C_b), confirming that the positive charge of the complex is centered at C_a. These values are in agreement with those computed for a simple unsubstituted propargylic acetate,[42b] although in our case the positive charge on C_a is even higher (+0.203e vs. +0.063e), the Ca-Au bond length longer (2.73 vs. 2.514 A) and the C_b-Au bond length shorter (2.16 vs. 2.239 Å). On the other hand, the alkyne/gold complex **V-Ph** shows a much more symmetrical structure, with nearly identical Au-C distances (Figure 3), and NPA charges (C_a = -0.056 e, C_b = -0.002 e). In this case, the positive charge is centered in the gold atom (Au = +0.437e in **V-Ph** *vs* +0.365e in **V-H**).

As a result of the higher positive character of the internal C_a carbon atom in **V-H**, the oxygen attack takes place exclusively at that position, an experimental fact that could be confirmed computationally with substrates **13d** and **16d**. We found that the 5-*exo dig* cyclization occurs with a very low barrier (3.9 kcal/mol for **TS13-H-5-*exo***) or, in the case of the corresponding saturated compound **16b**, with essentially no activation barrier (**TS16-H-5-*exo***, Figure 4).

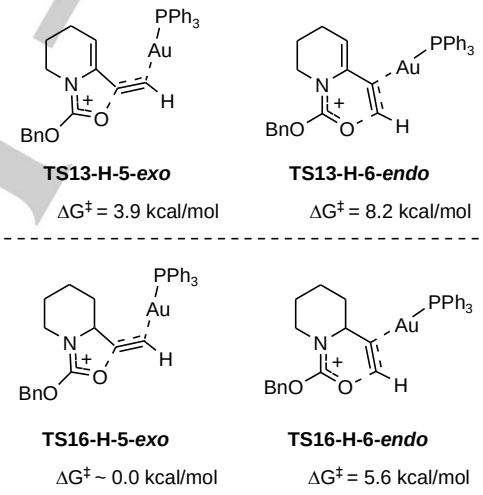


Figure 4. Transition state structures and energies for terminal alkynes.

In fact, no convergence or convergence to the starting material was observed during the transition state search in the latter case, in spite of the use of different functionals (B3LYP, M06, BHandHLYP) and basis sets. To further analyze this issue, a potential scan for the O-C bond formation was performed, confirming that it is a downhill process without appreciable activation energy. On the other hand, the transition states for the regioisomeric 6-*endo* cyclizations were located, presenting low but measurable activation energies (8.2 and 5.6 kcal/mol, Figure 4), which are *ca.* 4-5 kcal/mol higher than the 5-*exo* processes. This energy difference is able to explain the absolute experimental preference for the 5-membered cyclic products, in agreement with the preferred 1,2-acyl shift for propargylic acetates having an unsubstituted alkyne moiety.[42b]

On the other hand, the transition structures for the reaction of the internal triple bonds are in agreement with the experimental

preference for the C_b attack. Thus, the lowest computed activation energies were 7.8 kcal/mol for the unsaturated ring (**TS13-Ph-6-*endo***, Figure 5) and 8.4 kcal/mol for **TS16-Ph-6-*endo***. It is interesting to note, that the *endo*/*exo* selectivity is predicted to be better for **13** ($\Delta\Delta G^{\ddagger}_{exo\text{-}endo}$ = 2.5 kcal/mol) than for **16** ($\Delta\Delta G^{\ddagger}_{exo\text{-}endo}$ = 1.3 kcal/mol). This effect can be attributed to the increase in the N-C-C_a angle induced by the presence of the double bond, from 113º (**16d**, N-C_{sp3}-C_a) to 119º (**13d**, N-C_{sp2}-C_a), a factor that plays against the formation of the smaller 5-membered ring.

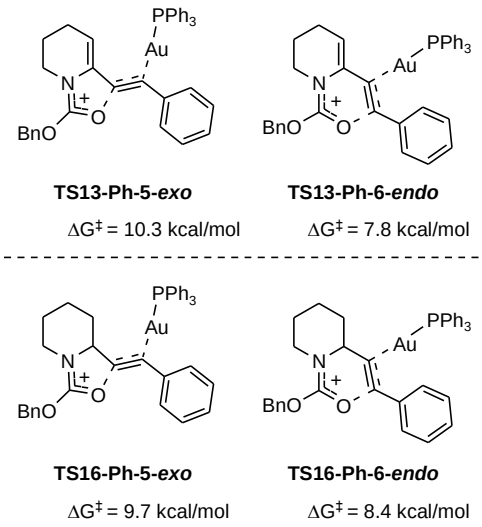


Figure 5. Transition state structures and energies for internal alkynes.

The data gathered in Figures 3 and 5 are not informative enough about the exact reason for the 6-*endo* selectivity with internal alkynes, since C_a and C_b possess very similar electronic properties and their bonding distances with the gold atom are virtually equal (Figure 3). Thus, we envisioned an indirect way to analyze the geometrical factors that determine the reactivity of the internal alkynes, by utilizing symmetrical computational substrates (Figure 6).

For example, in the model system **VI**, the triple bond is symmetrically substituted, and both carbons (C_a and C_b) are absolutely identical, reducing to the mere geometrical preference the factors that affect the formation of one ring or another. Interestingly, the activation energy is lower for the 6-*endo* cyclization by 4.4 kcal/mol, indicating that in principle, the preference for the 6-membered ring is purely geometrical, and could be generalized to any type of internal alkynes, regardless the substituent at the terminal position. It is worth to mention that a similar preference, but to a lesser extent ($\Delta\Delta G^{\ddagger}$ = 2.3 kcal/mol) was found for the computational model **VII**, possessing saturated rings, in agreement with the general lower selectivity of this type of substrates (*vide supra*).

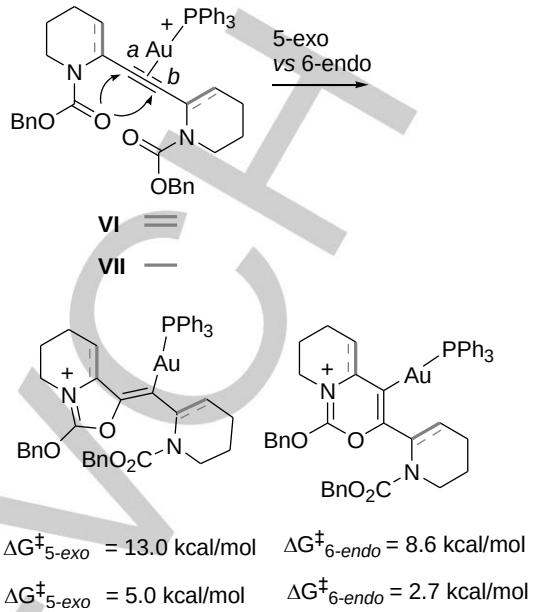


Figure 6. Comparison of the activation energies for the 5-*exo* and 6-*endo* dig pathways.

Conclusions

In this work we have studied in detail the gold(I)-catalyzed cyclization of *N*-Boc-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines, which provides synthetically useful exocyclic vinylogous amides, with three objectives in mind. First, in view of large scale application of the methodology, we wanted to optimize the reaction conditions in order to reduce as much as possible the amount of gold-catalyst. This has been realized by using $Cu(OTf)_2$ as the triflate source, which allowed us to charge the reaction vessel with 0.5 mol % of Au(I) without affecting the reaction rate. Secondly, we expanded the scope of the reaction to substituted and different N-heterocycles to assess the tolerance to the reaction conditions by some functional groups usually present in natural compounds easily prepared by these vinylogous amides. Third goal was to assess the structural features that selectively favors the 6-*endo dig* oxyauration of the triple bond. We found that a 6-*endo dig* approach is exclusive with substituted alkynes, whereas with terminal alkynes the 5-*exo dig* cyclization prevails despite the large angle (120°) at C6. Analogous selectivity is observed with *N*-Cbz-protected 2-alkynyl piperidines. These, after hydrolysis of the cyclic intermediates, furnish β-amino ketones as a consequence of a 6-*endo dig* attack to the internal triple bond. DFT calculations showed that with both types of substrates, the oxyauration step has low or almost no barrier when involves the internal position of a terminal triple bond, thus determining a 5-*exo dig* process. By contrast, the 6-*endo dig* approach is always favored with substituted alkynes, this preference being purely geometrical and irrespective of the type of substitution, thus providing either

β-enaminones or their reduced equivalents β-amino ketones in a robust, reliable and convenient way.

Experimental Section

General. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; R_f values refer to TLC carried out on 0.25-mm silica gel plates (F_{254}), with the same eluent as indicated for the column chromatography. ^{1}H NMR spectra were recorded at 200 or 400 MHz and ^{13}C NMR spectra were recorded at 50.33 or 100.4 MHz, both in $CDCl_3$ solution, unless otherwise specified. Solvent reference line was set at 7.26 ($CDCl_3$) or 4.79 ppm (D_2O). Mass spectra were either recorded at an ionizing voltage of 70 eV or carried out by direct inlet of a 10 ppm solution in CH_3OH on a LCQ Fleet™ Ion Trap LC/MS system with an electrospray ionization (ESI) interface in the positive mode. Microanalyses were carried out with an elemental analyzer. Compounds **6a**,[28] **6b**,[29] **10**,[34] **15**[36] and 5-hydroxy-δ-valerolactam[32] were prepared as reported. *All enynes **2**, **8**, **11**, **13**, and **22**, as well as intermediates **16** decompose when neat and must be stored in solution in the presence of Et_3N (1% v/v)*.

Computational Methods

The structures were optimized by using density functional theory (DFT) with the BHandHLYP[45] and the 6-31G* (LANL2DZ for Au) basis set as implemented in Gaussian 09.[46] The B3LYP functional was also evaluated, affording similar results to BHandHLYP, but some of the lowest-in-energy transition states (**TS13-H-5-*exo*** and **TS16-H-5-*exo***) did not converge properly with the former. The energy values shown in Figures 3[47] and 4 also include single-point refinements at M06-2X/6-311++G**(SDD) level of theory[48] on the previously optimized structures, to better account for the dispersion forces of such large systems. The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies. The intrinsic reaction coordinates (IRC)[49] were followed to verify the energy profiles connecting each TS to the correct associated local minima. Natural bond orbital (NBO) analysis[50] has been performed to evaluate the NPA atomic charges.

(5*S*)-2-Oxo-5-triisopropylsilanyloxy-piperidine-1-carboxylic acid *tert*-butyl ester (6c). 5-Hydroxy-δ-valerolactam[32] (680 mg, 5.9 mmol) was dissolved in anhydrous DMF (12 mL); imidazole (1.21 mg, 17.7 mmol) and triisopropylsilyl chloride (1.27 mL, 5.9 mmol) were added to this solution that, after the addition, was warmed at 40 °C. A second equivalent of triisopropylsilyl chloride (1.27 mL, 5.9 mmol) was added in portions over 8 h and the reaction left under stirring at 40 °C overnight. After cooling to room temperature, water was added (120 mL), the product extracted with Et_2O (4 x 50 mL) and the combined organic phases were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (eluent: EtOAc; R_f 0.27), affording pure 5-triisopropylsilanyloxypiperidin-2-one as a colorless oil (1.36 g, 85%). $[\alpha]_D^{21}$ = – 11.3 (*c* 1.12, $CHCl_3$). ^{1}H NMR (400 MHz) δ (ppm): 7.05 (br s, 1 H, N-H), 4.17-4.12 (m, 1 H, 5-H), 3.41-3.37 (m, 1 H, 6-H), 3.23-3.19 (m, 1 H, 6-H'), 2.56 (dt, *J* = 17.6, 7.6 Hz, 1 H, 3-H), 2.27 (dt, *J* = 17.6, 6.1 Hz, 1 H, 3-H'), 1.90-1.86 (m, 2 H, 4-H), 1.05-0.98 (m, 21 H, TIPS). ^{13}C NMR (100.4 MHz) δ (ppm): 172.1 (s, C2), 64.1 (d, C5), 49.4 (t, C6), 29.0 (t, C3), 27.5 (t, C4), 17.9 (q, 6 C, CH_3 TIPS), 12.1 (d, 3 C, *C*H TIPS). MS (ESI) *m/z* (%): 565 ([2M+Na]$^+$, 100), 543 ([2M+1]$^+$, 16). $C_{14}H_{29}NO_2Si$ (271.47): calcd C, 61.94; H, 10.77; N, 5.16. Found: C, 61.72; H, 10.50; N, 4.91. 5-Triisopropylsilanyloxypiperidin-2-one (1.3 g, 4.79 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL); to this solution Et_3N (740 μL, 5.27 mmol), di-*t*-butyl dicarbonate (1.1 g, 4.79 mmol) and DMAP (59 mg, 0.48 mmol) were added and the resulting mixture was heated under reflux. After 2 h, a second equivalent of di-*t*-butyl dicarbonate (1.1 g, 4.79 mmol) was added and, after the reaction was completed (TLC; 5 h), the mixture was cooled to room temperature, water was added (40 mL) and the layers separated; the aqueous one was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were washed with aq. 5% $KHSO_4$ (40 mL), satd $NaHCO_3$ (40 mL), water (40 mL), brine (40 mL) and finally dried over anhydrous Na_2SO_4. The solvent was filtered and evaporated and the crude purified by flash chromatography (eluent: *n*-hexane-EtOAc, 8:1; R_f 0.12), affording pure **6c** as a colorless oil (1.44 g, 81%). $[\alpha]_D^{20}$ = +10.0 (*c* 0.92, $CHCl_3$). ^{1}H NMR (400 MHz) δ (ppm): 4.26-4.21 (m, 1 H, 5-H), 3.73 (dd, *J* = 13.1, 4.7 Hz, 1 H, 6-H), 3.62 (dd, *J* = 13.1, 3.5 Hz, 1 H, 6-H'), 2.75-2.67 (m, 1 H, 3-H), 2.40 (dt, *J* = 17.2, 5.9 Hz, 1 H, 3-H'), 1.98-1.92 (m, 1 H, 4-H), 1.91-1.84 (m, 1 H, 4-H'), 1.48 (s, 9 H, C(CH_3)$_3$), 1.10-0.95 (m, 21 H, TIPS). ^{13}C NMR (100.4 MHz) δ (ppm): 170.8 (s, C2), 152.3 (s, *C*=O), 82.7 (s, *C*(CH_3)$_3$), 64.4 (d, C5), 52.5 (t, C6), 31.0 (t, C3), 29.1 (t, C4), 27.9 (q, 3 C, CH_3 Boc), 17.8 (q, 6 C, CH_3 TIPS), 12.0 (d, 3 C, *C*H TIPS). MS (ESI) *m/z* (%): 766 (33), 765 ([2M + Na]$^+$, 100), 394 ([M + Na]$^+$, 7). $C_{19}H_{37}NO_4Si$ (371.59): calcd C, 61.41; H, 10.04; N, 3.77. Found: C, 61.25; H, 9.98; N, 3.91.

(±)-6-(Diphenoxyphosphoryloxy)-4-methyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (7a). A 0.5 M solution of KHMDS in toluene (6.4 mL, 3.2 mmol) was diluted in anhydrous THF (18 mL) and cooled at – 78 °C. A solution of **6a**[28] (455 mg, 2.13 mmol) in anhydrous THF (10 mL) was then added dropwise, keeping the temperature below – 70 °C, and the resulting mixture was stirred for 1.5 h. Diphenylchlorophosphate (663 μL, 3.2 mmol) was slowly added, and after 1 h, the mixture was allowed to warm at 0 °C and quenched by the addition of aqueous 10% NaOH (50 mL). The product was extracted with Et_2O (3 x 40 mL) and the combined organic extracts were washed once with aqueous 10% NaOH (28 mL) and dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, the crude material was purified over a short pad of silica gel (eluent: *n*-hexane/EtOAc 7:1 + 1% Et_3N; R_f 0.13), affording pure **7a** as a colourless oil (800 mg, 85%). ^{1}H NMR (400 MHz) δ (ppm): 7.37-7.31 (m, 4 H, Ar), 7.25-7.17 (m, 6 H, Ar), 5.01-4.99 (m, 1 H, 5-H), 3.61-3.50 (m, 2 H, 2-H), 2.45-2.38 (m, 1 H, 4-H), 1.87-1.79 (m, 1 H, 3-H), 1.43 (s, 9 H, C(CH_3)$_3$), 1.41-1.33 (m, 1 H, 3-H'), 1.01 (d, *J* = 6.0 Hz, 3 H, CH_3). ^{13}C NMR (100.4 MHz) δ (ppm): 153.1 (s, *C*=O), 150.6 (s, Ph), 150.5 (s, Ph), 140.0 (s, C6), 129.7 (d, 4 C, C_{Ar}), 125.4 (d, Ph), 125.3 (d, Ph), 120.09 (d, Ph), 120.08 (d, Ph), 120.04 (d, Ph), 120.03 (d, Ph), 105.3 (d, C5), 81.7 (s, *C*(CH_3)$_3$), 44.1 (t, C2), 31.1 (d, C4), 28.1 (q, 3 C, C(CH_3)$_3$), 27.8 (t, C3), 21.3 (q, CH_3). MS (ESI) *m/z* (%): 913 ([2M+Na]$^+$, 100), 468 ([M+Na]$^+$, 20), 446 ([M+1]$^+$, 35).

(±)-6-(Diphenoxyphosphoryloxy)-2-methyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (7b). Prepared as reported for **7a**, starting from **6b**[29] (362 mg, 1.7 mmol) and obtaining, after purification (eluent: *n*-hexane-EtOAc 6:1 + 1% Et_3N; R_f 0.12), pure **7b** (658 mg, 87%) as clear yellowish oil. ^{1}H NMR (400 MHz) δ (ppm): 7.38-7.28 (m, 4 H, Ph), 7.26-7.12 (m, 6 H, Ph), 5.11 (q, *J* = 3.5 Hz, 1 H, 5-H), 4.67-4.53 (m, 1 H, 2-H), 2.21-2.10 (m, 2 H, 4-H), 1.77-1.66 (m, 1 H, 3-H), 1.63-1.57 (m, 1 H, 3-H'), 1.43 (s, 9 H, C(CH_3)$_3$), 1.15 (d, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (100.4 MHz) δ (ppm): 153.2 (s, *C*=O), 150.5 (s, Ph), 150.4 (s, Ph), 138.3 (s, C6), 129.7 (d, 4 C, Ph), 125.4 (d, Ph), 125.3 (d, Ph), 120.12 (d, Ph), 120.10 (d, Ph), 119.98 (d, Ph), 119.93 (d, Ph), 99.3 (d, C5), 81.6 (s, *C*(CH_3)$_3$), 49.2 (d, C2), 28.1 (q, 3 C, C(CH_3)$_3$), 27.1 (t, C4), 18.6 (t, C3), 15.7 (q, CH_3). MS (ESI) *m/z* (%): 913 ([2M+Na]$^+$, 100), 468 ([M+Na]$^+$, 41), 446 ([M+1]$^+$, 27).

(3*S*)-6-(Diphenoxyphosphoryloxy)-3-triisopropylsilanyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (7c). Prepared as reported for **7a**, starting from **6c** (1.44 g, 3.87 mmol) and obtaining,

after purification (eluent: *n*-hexane/EtOAc 5:1 + 1% Et_3N; R_f 0.50), pure **7c** (2.33 g, 99%) as pale yellow oil. ^{1}H NMR (400 MHz) δ (ppm): 7.37 (m, 4 H, *Ph*), 7.27-7.25 (m, 4 H, *Ph*), 7.21-7.18 (m, 2 H, *Ph*), 5.06-5.04 (m, 1 H, 5-H), 4.11-4.06 (m, 1 H, 3-H), 3.71 (dd, *J* = 12.9, 3.1 Hz, 1 H, 2-H), 3.51 (dd, *J* = 12.9, 7.4 Hz, 1 H, 2-H'), 2.51-2.43 (m, 1 H, 4-H), 2.16-2.08 (m, 1 H, 4-H'), 1.44 (s, 9 H, C(C*H*$_3$)$_3$), 1.13-1.01 (m, 21 H, TIPS). ^{13}C NMR (100.4 MHz) δ (ppm): 153.0 (s, *C*=O), 150.5 (s, 2 C, C_{Ar}), 140.0 (s, C6), 129.7 (d, 4 C, C_{Ar}), 125.4 (d, 2 C, C_{Ar}), 120.0 (d, 4 C, C_{Ar}), 97.8 (d, C5), 81.6 (s, *C*(CH$_3$)$_3$), 65.2 (d, C3), 51.2 (t, C2), 32.4 (t, C4), 28.0 (q, 3 C, *C*H$_3$ Boc), 17.9 (q, 6 C, *C*H$_3$ TIPS), 12.1 (d, 3 C, *C*H TIPS). MS (ESI) *m/z* (%): 1229 ([2M+Na]$^+$, 100), 792 ([M+Na]$^+$, 7).

General Procedure for Sonogashira Coupling. Phosphate (**7a-c**, **10**,[34] **15**[36]) was dissolved in an anhydrous 3:1 Et_3N/$CHCl_3$ mixture (0.13 M), and the alkyne (1 mmol), CuI (0.1 mmol), and $(Ph_3P)_2PdCl_2$ (0.05 mmol) were added. The resulting solution was heated at 55 °C (external) for 2 h, after which time a second portion of alkyne (0.5 mmol), CuI (0.05 mmol) and $(Ph_3P)_2PdCl_2$ (0.025 mmol) were added, if necessary. The mixture was heated at 55 °C until completion (TLC, usually in 4-7 h). After cooling to room temperature, water (12 mL) was added and the product extracted with Et_2O (3 x 12 mL); the combined organic extracts were dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, crude enyne (**8a-d**, **11a-c**, **13a-c**) was purified by flash chromatography (eluent containing 1% Et_3N) and stored at 4 °C as a 0.1 M solution in the eluent until use.

(±)-6-Hex-1-ynyl-4-methyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (8a). Pale yellow oil (205 mg, 74%). R_f 0.12 (*n*-hexane/EtOAc 30:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 5.34 (d, *J* = 3.5 Hz, 1 H, 5-H), 3.59 (ddd, *J* = 12.9, 7.0, 3.1 Hz, 1 H, 2-H), 3.46 (ddd, *J* = 12.9, 8.2, 2.7 Hz, 1 H, 2-H'), 2.36-2.30 (m, 1 H, 4-H), 2.30 (t, *J* = 7.0 Hz, 2 H, 3'-H), 1.88-1.83 (m, 1 H, 3-H'), 1.55-1.46 (m, 2 H, 4'-H), 1.49 (s, 9 H, C(C*H*$_3$)$_3$), 1.44-1.36 (m, 3 H, 5'-H and 3-H), 1.00 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 0.90 (t, *J* = 7.4 Hz, 3 H, 6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.1 (s, *C*=O), 126.7 (d, C5), 121.4 (s, C6), 88.3 (s, C1'), 80.7 (s, *C*(CH$_3$)$_3$), 77.6 (s, C2'), 42.2 (t, C2), 30.9 (t, C3), 30.7 (d, C4), 29.0 (t, C3'), 28.3 (q, 3 C, *C*H$_3$ Boc), 22.0 (q, *C*H$_3$), 21.0 (t, C4'), 19.1 (t, C5'), 13.6 (q, C6'). MS (ESI) *m/z* (%): 577 ([2M+Na]$^+$, 100), 300 ([M+Na]$^+$, 30). MS/MS (ESI of [M+Na]$^+$) *m/z* (%): 300 (4), 244 (100).

(±)-6-Hex-1-ynyl-2-methyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (8b). Yellow oil (160 mg, 58%). R_f 0.18 (*n*-hexane/EtOAc 30:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 5.44 (t, *J* = 3.7 Hz, 1 H, 5-H), 4.56-4.49 (m, 1 H, 2-H), 2.30 (t, *J* = 7.0 Hz, 2 H, 3'-H), 2.15-2.09 (m, 2 H, 4-H), 1.83-1.73 (m, 1 H, 3-H), 1.62-1.55 (m, 1 H, 3-H'), 1.49 (s, 9 H, C(C*H*$_3$)$_3$), 1.55-1.38 (m, 4 H, 4'-H and 5'-H), 1.11 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$), 0.90 (t, *J* = 7.3 Hz, 3 H, 6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.0 (s, *C*=O), 119.9 (d, C5), 119.8 (s, C6), 87.6 (s, C1'), 80.6 (s, *C*(CH$_3$)$_3$), 78.3 (s, C2'), 46.8 (d, C2), 30.7 (t, C4'), 28.3 (q, 3 C, *C*H$_3$ Boc), 27.0 (t, C3), 22.1 (t, C5'), 19.8 (t, C4), 19.1 (t, C3'), 15.9 (q, *C*H$_3$), 13.6 (q, C6'). MS/MS (ESI of [M+Na]$^+$) *m/z* (%): 300 (3), 244 (100).

(3*S*)-6-Hex-1-ynyl-3-triisopropylsilanyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (8c). Yellow oil (279 mg, 64%). R_f 0.36 (*n*-hexane/EtOAc 20:1 + 1% Et_3N). $[\alpha]_D^{19}$ = +37.9 (*c* 0.77, $CHCl_3$). ^{1}H NMR (400 MHz) δ (ppm): 5.40 (t, *J* = 4.0 Hz, 1 H, 5-H), 4.05-3.99 (m, 1 H, 3-H), 3.84 (dd, *J* = 12.4, 3.0 Hz, 1 H, 2-H), 3.21 (dd, *J* = 12.4, 8.4 Hz, 1 H, 2-H'), 2.44 (dt, *J* = 18.9, 5.2 Hz, 1 H, 4-H), 2.31 (t, *J* = 7.0 Hz, 2 H, 3'-H), 2.08 (ddd, *J* = 18.9, 6.3, 4.0 Hz, 1 H, 4-H'), 1.53-1.46 (m, 2 H, 4'-H), 1.48 (s, 9 H, C(C*H*$_3$)$_3$), 1.44-1.39 (m, 2 H, 5'-H), 1.07-1.04 (m, 21 H, TIPS), 0.90 (t, *J* = 7.3 Hz, 3 H, 6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 152.9 (s, *C*=O), 122.2 (s, C6), 119.2 (d, C5), 88.7 (s, C1'), 80.7 (s, *C*(CH$_3$)$_3$), 77.3 (s, C2'), 65.2 (d, C3), 49.8 (t, C2), 34.5 (t, C4), 30.7 (t, C3'), 28.1 (q, 3 C, *C*H$_3$ Boc), 22.0 (t, C4'), 19.1 (t, C5'), 18.0 (q, 6 C, *C*H$_3$ TIPS), 13.6 (q, C6'), 12.1 (d, 3 C, *C*H TIPS). MS (ESI) *m/z* (%): 909 ([2M+K]$^+$, 43), 893 ([2M+Na]$^+$, 100), 458 ([M+Na]$^+$, 26).

(3*S*)-6-Phenylethynyl-3-triisopropylsilanoxy-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (8d). Yellow oil (314 mg, 69%). R_f 0.13 (*n*-hexane/EtOAc 20:1 + 1% Et_3N). $[\alpha]_D^{27}$ = +22.5 (*c* 2.03, $CHCl_3$). ^{1}H NMR (400 MHz) δ (ppm): 7.45-7.32 (m, 2 H, Ph), 7.33-7.27 (m, 3 H, Ph), 5.60 (t, *J* = 4.1 Hz, 1 H, 5-H), 4.13-4.08 (m, 1 H, 3-H), 3.87 (dd, *J* = 12.5, 2.7 Hz, 1 H, 2-H), 3.36 (dd, *J* = 12.5, 8.0 Hz, 1 H, 2-H'), 2.53 (dt, *J* = 19.1, 5.3 Hz, 1 H, 4-H), 2.18 (ddd, *J* = 19.1, 5.6, 4.1 Hz, 1 H, 4-H'), 1.49 (s, 9 H, C(C*H*$_3$)$_3$), 1.11-1.02 (m, 21 H, TIPS). ^{13}C NMR (100.4 MHz) δ (ppm): 153.0 (s, *C*=O), 131.3 (d, 2 C, Ph), 128.3 (d, 2 C, Ph), 128.0 (d, Ph), 123.3 (s, C6), 122.1 (s, Ph), 120.5 (d, C5), 87.8 (s, C1'), 86.3 (s, C2'), 81.1 (s, *C*(CH$_3$)$_3$), 65.1 (d, C3), 50.0 (t, C2), 34.7 (t, C4), 28.2 (q, 3 C, *C*H$_3$ Boc), 18.0 (q, 6 C, *C*H$_3$ TIPS), 12.3 (d, 3 C, *C*H TIPS). MS (ESI) *m/z* (%): 933 ([2M+Na]$^+$, 100), 478 ([M+Na]$^+$, 12), 456 ([M+1]$^+$, 11).

6-Trimethylsilanylethynyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (22a). Colorless oil (229 mg, 82%). R_f 0.63 (Petroleum ether/EtOAc 9:1 + 1% Et_3N). ^{1}H NMR (200 MHz) δ (ppm): 5.63 (t, *J* = 4.0 Hz, 1 H, 5-H), 3.57-3.52 (m, 2 H, 2-H), 2.16 (td, *J* = 6.9, 4.1 Hz, 2 H, 4-H), 1.83-1.71 (m, 2 H, 3-H), 1.52 (s, 9 H, C(C*H*$_3$)$_3$), 0.19 (s, 9 H, Si(C*H*$_3$)$_3$). ^{13}C NMR (50.33 MHz) δ (ppm): 153.2 (s, C=O), 124.0 (s, C6), 122.5 (d, C5), 101.9 (s, C2'), 91.9 (s, C1'), 81.4 (s, *C*(CH$_3$)$_3$), 43.2 (t, C2), 28.3 (q, 3 C, *C*H$_3$ Boc), 23.7 (t, C3), 22.7 (t, C4), -0.1 (q, 3 C, Si(*C*H$_3$)$_3$). MS *m/z* (%): 279 ([M]$^+$, 23), 223 (92), 206 (15), 179 (87), 178 (100), 164 (72), 57 (56).

6-Hex-1-ynyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (13a). Colorless oil (720 mg, 81%). R_f 0.11 (*n*-hexane/EtOAc 20:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 7.42-7.27 (m, 5 H), 5.52 (t, *J* = 3.9 Hz, 1 H, 3-H), 5.20 (s, 2 H, C*H*$_2$Ph), 3.65-3.62 (m, 2 H, 6-H), 2.21-2.13 (m, 4 H, 4-H and 3'-H), 1.82-1.75 (m, 2 H, 5-H), 1.45-1.31 (m, 4 H, 4'-H and 5'-H), 0.87 (t, *J* = 7.0 Hz, 3 H, 6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.9 (s, C=O), 136.4 (s, Ph), 128.3 (d, 2 C, Ph), 127.9 (d, 2 C, Ph), 127.8 (d, Ph), 122.2 (s, C6), 121.9 (d, C5), 89.1 (s, C1'), 77.1 (s, C2'), 67.5 (t, *C*H$_2$Ph), 44.0 (t, C2), 30.6 (t, C4'), 23.5 (t, C4), 22.6 (t, C3), 22.0 (t, C5'), 18.9 (t, C3'), 13.6 (q, C6'). MS (ESI) *m/z* (%): 617 ([2M+Na]$^+$, 100), 320 ([M+Na]$^+$, 12), 298 [M+1]$^+$, 31).

6-Phenylethynyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (13b). Pale yellow oil (260 mg, 82%). R_f 0.21 (*n*-hexane/EtOAc 20:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 7.42-7.39 (m, 2 H, Ph), 7.29-7.23 (m, 8 H, Ph), 5.73 (t, *J* = 4.1 Hz, 1 H, 5-H), 5.24 (s, 2 H, C*H*$_2$Ph), 3.73-3.70 (m, 2 H, 2-H), 2.25 (td, *J* = 6.8, 4.1 Hz, 2 H, 4-H), 1.88-1.83 (m, 2 H, 3-H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.9 (s, C=O), 136.2 (s, Ph), 131.4 (d, 2 C, Ph), 128.4 (d, 2 C, Ph), 128.1 (d, 2 C, Ph), 128.04 (d, 2 C, Ph), 128.02 (d, Ph), 127.9 (d, Ph), 123.4 (d, C5), 123.1 (s, C6), 122.0 (s, Ph), 88.1 (s, C1'), 86.1 (s, C2'), 67.8 (t, *C*H$_2$Ph), 44.0 (t, C2), 23.7 (t, C3), 22.5 (t, C4). MS (ESI) *m/z* (%): 657 ([2M+Na]$^+$, 100), 318 [M+1]$^+$, 30).

6-Triethylsilanylethynyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (13c). Colorless oil (709 mg, 82%). R_f 0.25 (*n*-hexane/EtOAc 20:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 7.42-7.40 (m, 2 H, Ph), 7.39-7.28 (m, 3 H, Ph), 5.70 (t, *J* = 4.1 Hz, 1 H, 5-H), 5.21 (s, 2 H, C*H*$_2$Ph), 3.65-3.62 (m, 2 H, 2-H), 2.18 (td, *J* = 6.6, 4.1 Hz, 2 H, 4-H), 1.82-1.72 (m, 2 H, 3-H), 0.96 (t, *J* = 8.0 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$), 0.57 (q, *J* = 8.0 Hz, 6 H, Si(C*H*$_2$CH$_3$)$_3$). ^{13}C NMR (100.4 MHz) δ (ppm): 153.9 (s, C=O), 136.5 (s, Ph), 128.3 (d, 2 C, Ph), 127.8 (d, 2 C, Ph), 127.7 (d, Ph), 124.5 (s, C6), 122.0 (d, C5), 102.2 (s, C2'), 90.6 (s, C1'), 67.3 (t, *C*H$_2$Ph), 43.8 (t, C2), 23.6 (t, C3), 22.5 (t, C4), 7.4 (q, 3 C, Si(CH$_2$*C*H$_3$)$_3$),

4.3 (t, 3 C, Si(CH_2CH_3)$_3$). MS (ESI) *m/z* (%): 733 ([2M+Na]$^+$, 100), 356 [M+1]$^+$, 30).

7-Hex-1-ynyl-2,3,4,5-tetrahydroazepine-1-carboxylic acid *tert*-butyl ester (11a). Colorless oil (194 mg, 70%). R_f 0.24 (eluent: *n*-hexane/EtOAc 20:1 + 1% Et_3N). ^{1}H NMR (200 MHz) δ (ppm): 5.81 (t, *J* = 6.6 Hz, 1 H, 6-H), 3.42 (t, *J* = 5.3 Hz, 2 H, 2-H), 2.28 (t, *J* = 6.8 Hz, 2 H, 3'-H), 2.19-2.10 (m, 2 H, 5-H), 1.78-1.66 (m, 2 H, 4-H), 1.66-1.35 (m, 6 H, 3-H, 4'-H and 5'-H), 1.46 (s, 9 H, C(CH_3)$_3$), 0.89 (t, *J* = 6.9 Hz, 3 H, 6'-H). ^{13}C NMR (50.33 MHz) δ (ppm): 153.6 (s, C=O), 131.0 (s, C7), 127.8 (d, C6), 87.3 (s, C2'), 80.0 (s, *C*(CH_3)$_3$), 78.5 (s, C1'), 47.2 (t, C2), 30.7 (t, C4'), 29.6 (t, C3), 28.3 (q, 3 C, C(*C*H_3)$_3$), 27.5 (t, C4), 23.8 (t, C3'), 22.0 (t, C5), 19.0 (t, C5'), 13.5 (q, C6'). MS *m/z* (%): 277 ([M]$^+$, 4), 221 (61), 179 (68), 162 (65), 148 (57), 135 (87), 57 (100).

7-Phenylethynyl-2,3,4,5-tetrahydroazepine-1-carboxylic acid *tert*-butyl ester (11b). Yellow oil (205 mg, 69%). R_f 0.21 (eluent: *n*-hexane/EtOAc 20:1 + 1% Et_3N). ^{1}H NMR (200 MHz) δ (ppm): 7.44-7.37 (m, 2 H, *Ph*), 7.32-7.28 (m, 3 H, *Ph*), 6.02 (t, *J* = 6.6 Hz, 1 H, 6-H), 3.54-3.49 (m, 2 H, 2-H), 2.29-2.20 (m, 2 H, 5-H), 1.83-1.72 (m, 2 H, 4-H), 1.58-1.45 (m, 2 H, 3-H), 1.48 (s, 9 H, C(CH_3)$_3$). ^{13}C NMR (50.33 MHz) δ (ppm): 153.3 (s, C=O), 132.4 (d, *Ph*), 131.1 (d, 2 C, *Ph*), 128.1 (d, 2 C, *Ph*), 127.8 (d, C6), 127.3 (s, *Ph*), 123.0 (s, C7), 87.5 (s, C2'), 86.4 (s, C1'), 80.1 (s, *C*(CH_3)$_3$), 47.2 (t, C2), 29.4 (t, C3), 28.2 (q, 3 C, C(*C*H_3)$_3$), 27.6 (t, C4), 23.6 (t, C5). MS *m/z* (%): 297 ([M]$^+$, 3), 241 (100), 197 (67), 196 (99), 182 (47), 169 (54).

7-Cyclopropylethynyl-2,3,4,5-tetrahydroazepine-1-carboxylic acid *tert*-butyl ester (11c). Colorless oil (196 mg, 75%). R_f 0.30 (eluent: *n*-hexane/EtOAc 20:1 + 1% Et_3N). ^{1}H NMR (200 MHz) δ (ppm): 5.81 (t, *J* = 6.5 Hz, 1 H, 6-H), 3.44-3.39 (m, 2 H, 2-H), 2.18-2.09 (m, 2 H, 5-H), 1.77-1.66 (m, 2 H, 4-H), 1.52-1.40 (m, 2 H, 3-H), 1.47 (s, 9 H, C(CH_3)$_3$), 1.37-1.24 (m, 1 H, 3'-H), 0.83-0.64 (m, 4 H, 4'-H). ^{13}C NMR (50.33 MHz) δ (ppm): 153.5 (s, C=O), 131.0 (d, C6), 127.7 (s, C7), 90.2 (s, C2'), 80.0 (s, *C*(CH_3)$_3$), 73.9 (s, C1'), 47.3 (t, C2), 29.6 (t, C5), 28.4 (q, 3 C, C(*C*H_3)$_3$), 27.5 (t, C4), 23.8 (t, C3), 8.2 (t, 2 C, C4'), -0.1 (d, C3'). MS *m/z* (%): 261 ([M]$^+$, 10), 205 (100), 204 (41), 160 (44), 57 (43).

(3*S*)-6-Hex-1-ynyl-3-hydroxy-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (8e). To a solution of **8c** (740 mg, 1.7 mmol) in anhydrous THF (82 mL), under N_2 atmosphere, 1 M TBAF solution in THF (1.94 mL, 1.94 mmol) was slowly added. After 30 min the solvent was evaporated under *vacuum* and the residue was taken up in Et_2O (82 mL). The solvent was evaporated again and the residue was purified by flash chromatography (*n*-hexane/EtOAc 2:1 + 1% Et_3N; R_f 0.24) to afford pure **8e** (410 mg, 86%). $[\alpha]_D^{22}$ = – 10.6 (*c* 0.97, $CHCl_3$). ^{1}H NMR (400 MHz) δ (ppm): 5.40 (t, *J* = 3.9 Hz, 1 H, 5-H), 4.07-4.02 (m, 1 H, 3-H), 3.56 (AB system, J_{AB} = 12.8 Hz, 1 H, 2-H), 3.54 (AB system, J_{AB} = 12.8 Hz, 1 H, 2-H'), 2.53 (br s, 1 H, O*H*), 2.44 (dt, *J* = 19.1, 4.3 Hz, 1 H, 4-H), 2.29 (t, *J* = 7 Hz, 2 H, 3'-H), 2.09 (dt, *J* = 19.1, 4.7 Hz, 1 H, 4-H'), 1.54-1.45 (m, 2 H, 4'-H), 1.47 (s, 9 H, C(CH_3)$_3$), 1.44-1.36 (m, 2 H, 5'-H), 0.89 (t, *J* = 7.4 Hz, 3 H, 6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.8 (s, *C*=O), 122.4 (s, C6), 118.6 (d, C5), 88.8 (s, C1'), 81.2 (s, *C*(CH_3)$_3$), 77.0 (s, C2'), 64.3 (d, C3), 49.2 (t, C2), 32.8 (t, C4), 30.6 (t, C4'), 28.2 (q, 3 C, *C*H_3 Boc), 22.0 (t, C3'), 19.0 (t, C5'), 13.6 (q, C6'). MS (ESI) *m/z* (%): 597 ([2M+K]$^+$, 24), 581 ([2M+Na]$^+$, 100), 302 ([M+Na]$^+$, 21).

6-Ethynyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (22b). Prepared as reported for **8e**, starting from **22a** (279 mg, 1.0 mmol) and obtaining, after purification by flash chromatography (eluent: petroleum ether/EtOAc 9:1; R_f 0.50), pure **22b** (205 mg, 99%) as a colorless oil. ^{1}H NMR (200 MHz) δ (ppm): 5.65 (t, *J* = 4.0 Hz, 1 H, 5-H), 3.59-3.54 (m, 2 H, 2-H), 2.93 (s, 1 H, 2'-H), 2.21-2.12 (m, 2 H, 4-H), 1.84-1.72 (m, 2 H, 3-H), 1.50 (s, 9 H, C(CH_3)$_3$). ^{13}C NMR (50.33 MHz) δ (ppm): 152.9 (s, C=O), 123.8 (s, C6), 121.5 (d, C5), 81.5 (s, C1'), 80.6 (s, *C*(CH_3)$_3$), 75.9 (d, C2'), 43.4 (t, C2), 28.3 (q, 3 C, *C*H_3 Boc), 23.6 (t, C3), 22.5 (t, C4). MS *m/z* (%): 207 ([M]$^+$, 22), 151 (65), 134 (29), 107 (81), 106 (71), 92 (41), 79 (12), 57 (100), 41 (26).

(3*R*)-6-Hex-1-ynyl-3-azido-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (8f). To a solution of **8e** (280 mg, 1.00 mmol) and triethylamine (180 µL, 1.3 mmol) in anhydrous CH_2Cl_2 (1.44 mL), cooled to –30 °C, MsCl (103 µL, 1.3 mmol) was added dropwise. After 5 min the cooling bath was removed and the reaction mixture was left under stirring for 2 h at room temperature. Then aqueous $KHSO_4$ 5% (6 mL) was added dropwise and, after 10 min, the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with water (3 x 10 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (*n*-hexane/EtOAc 4:1 + 1% Et_3N; R_f 0.20), to afford the mesylate (307 mg, 86%) as a pale yellow oil. ^{1}H NMR (400 MHz) δ (ppm): 5.36 (t, *J* = 3.9 Hz, 1 H, 5-H), 5.01-4.98 (m, 1 H, 3-H), 4.06 (dd, *J* = 13.7, 5.9 Hz, 1 H, 2-H), 3.43 (dd, *J* = 13.7, 1.9 Hz, 1 H, 2-H'), 2.99 (s, 3 H, C*H*$_3$ Ms), 2.56 (dm, *J* = 19.9 Hz, 1 H, 4-H), 2.38 (dm, *J* = 19.9 Hz, 1 H, 4-H'), 2.28 (t, *J* = 7.0 Hz, 2 H, 3'-H), 1.52-1.43 (m, 2 H, 4'-H), 1.46 (s, 9 H, C(CH_3)$_3$), 1.42-1.36 (m, 2 H, 5'-H), 0.87 (t, *J* = 7.0 Hz, 3 H, 6'-H). The intermediate mesylate (301 mg, 0.84 mmol) was dissolved in anhydrous CH_3CN (2 mL) and to the resulting solution 15-crown-5 (34 µL, 0.17 mmol) and NaN_3 (82 mg, 1.26 mmol) were added under N_2 atmosphere. The mixture was heated under reflux for 6 h and then stirred at room temperature for 12 h. After filtration through a silica/celite 1:1 pad, the filtrate was concentrated under *vacuum* and the residue purified by flash chromatography (*n*-hexane/EtOAc, 30:1 + 1% Et_3N; R_f 0.14), affording pure **8f** (120 mg, 47%) as a pale yellow oil. $[\alpha]_D^{21}$ = – 21.0 (*c* 1.16, $CHCl_3$). ^{1}H NMR (400 MHz) δ (ppm): 5.37 (t, *J* = 3.9 Hz, 1 H, 5-H), 3.80-3.74 (m, 1 H, 3-H), 3.66-3.57 (m, 2 H, 2-H), 2.47 (ddd, *J* = 19.5, 6.2, 3.9 Hz, 1 H, 4-H), 2.86 (t, *J* = 7 Hz, 2 H, 3'-H), 2.15 (dt, *J* = 19.5, 4.7 Hz, 1 H, 4-H'), 1.53-1.44 (m, 2 H, 4'-H), 1.48 (s, 9 H, C(CH_3)$_3$), 1.43-1.35 (m, 2 H, 5'-H), 0.88 (t, *J* = 7.0 Hz, 3 H, 6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.0 (s, *C*=O), 122.9 (s, C6), 117.2 (d, C5), 89.2 (s, C1'), 81.4 (s, *C*(CH_3)$_3$), 76.7 (s, C2'), 54.4 (d, C3), 46.3 (t, C2), 30.5 (t, C4), 29.4 (t, C4'), 28.1 (q, 3 C, *C*H_3 Boc), 21.9 (t, C3'), 18.9 (t, C5'), 13.5 (q, C6'). MS (ESI) *m/z* (%): 631 ([2M + Na]$^+$, 100), 343 ([M + K]$^+$, 8), 327 ([M + Na]$^+$, 35).

Gold-Catalyzed Rearrangement and Hydrolysis Procedure. A volume of the enyne solution containing 1 mmol of substrate was concentrated and dried under *vacuum* (no heating) for 30 min and then dissolved in anhydrous toluene (5 mL). In a two neck round bottom flask containing Ph_3PAuCl (0.005 mmol) in anhydrous toluene (5 mL), $Cu(OTf)_2$ (0.05 mmol) was added under nitrogen atmosphere. After 15 min. the solution of enyne was added and the resulting mixture was heated under reflux until the starting material disappeared (TLC, usually 30 min.). After cooling at 85 °C (external) and dilution with *tert*-butyl alcohol (10 mL), powdered KOH (6 mmol) was added. The mixture was heated at 85 °C until completion (TLC, usually 15 min.) and then cooled at r.t. Water (15 mL) was then added, and the product was extracted with EtOAc (3 x 10 mL); the combined organic extracts were washed once with brine (15 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude vinylogous amide (**12a-e, 12g-i**) was purified by flash chromatography to obtain the pure compound.

(±)-1-(4-Methylpiperidin-2-ylidene)-hexan-2-one (12a). Pale yellow solid (133 mg, 68%). R_f 0.23 (*n*-hexane/EtOAc 7:1). Mp 52.6-54.1 °C. ^{1}H NMR (400 MHz) δ (ppm): 11.09 (bs, 1 H, N-*H*), 4.81 (s, 1 H, 1'-H), 3.39-3.34 (m, 1 H, 6-H), 3.28-3.21 (m, 1 H, 6'-H), 2.33-2.79 (m, 1 H, 3-H'), 2.15 (t, *J* = 7.4 Hz, 2 H, 3'-H), 1.98 (dd, *J* = 17.1, 10.5 Hz, 1 H, 3-H'), 1.82-1.73 (m, 2 H, 4-H and 5-H'), 1.55-1.48 (m, 2 H, 4'-H), 1.40-1.24 (m, 3 H, 5-H and 5'-H), 0.96 (d, *J* = 6.3 Hz, 3 H, C*H*$_3$), 0.85 (t, *J* = 7.0 Hz, 3 H,

6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 197.4 (s, C2'), 163.6 (s, C2), 92.8 (d, C1'), 41.5 (t, C6), 40.7 (t, C3), 36.7 (t, C5), 30.1 (d, C4), 28.5 (t, C3'), 25.8 (t, C4'), 22.6 (t, C5'), 21.2 (q, *C*H$_3$), 13.8 (q, C6'). MS (ESI) *m/z* (%): 413 ([2M + Na]$^+$, 100), 196 ([M + 1]$^+$, 44). MS/MS (ESI of [M + 1]$^+$) *m/z* (%): 178 (5), 112 (100). $C_{12}H_{21}NO$ (195.30): calcd C, 73.80; H, 10.84; N, 7.17. Found: C, 73.75; H, 10.97; N, 7.30.

(±)-1-(6-Methylpiperidin-2-ylidene)-hexan-2-one (12b). Orange oil (111 mg, 57%). R_f 0.13 (*n*-hexane/EtOAc 7:1). ^{1}H NMR (400 MHz) δ (ppm): 11.06 (bs, 1 H, N-*H*), 4.81 (s, 1 H, 1'-H), 3.45-3.37 (m, 1 H, 6-H), 2.31-2.26 (m, 2 H, 3-H), 2.17 (t, *J* = 7.5 Hz, 2 H, 3'-H), 1.91-1.84 (m, 1 H, 5-H), 1.80-1.72 (m, 1 H, 4-H), 1.63-1.49 (m, 3 H, 4-H' and 4'-H), 1.36-1.24 (m, 3 H, 5-H' and 5'-H), 1.20 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$), 0.86 (t, *J* = 7.4 Hz, 3 H, 6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 197.3 (s, C2'), 163.6 (s, C2), 92.5 (d, C1'), 47.3 (d, C6), 41.5 (t, C3), 30.6 (t, C5), 28.3 (t, C4'), 28.1 (t, C3), 22.6 (t, C5'), 22.5 (q, *C*H$_3$), 18.9 (t, C4), 13.9 (q, C6'). MS (ESI) *m/z* (%): 413 ([2M + Na]$^+$, 100), 218 ([M + Na]$^+$, 17), 196 ([M + 1]$^+$, 65). MS/MS (ESI of [M + 1]$^+$) *m/z* (%): 111 (100), 94 (3). $C_{12}H_{21}NO$ (195.30): calcd C, 73.80; H, 10.84; N, 7.17. Found: C, 73.61; H, 10.93; N, 7.14.

(5*S*)-1-(5-Triisopropylsilanyloxypiperidin-2-ylidene)-hexan-2-one (12c). Yellow oil (219 mg, 62%). R_f 0.24 (*n*-hexane/EtOAc 10:1). $[\alpha]_D^{20}$ = – 25.4 (*c* 0.98, $CHCl_3$). ^{1}H NMR (400 MHz) δ (ppm): 11.02 (br s, 1 H, N-*H*), 4.99 (br s, 1 H, 1'-H), 4.17-4.12 (m, 1 H, 5-H), 3.48 (dd, *J* = 13.2, 4.0 Hz, 1 H, 6-H), 3.21 (dd, *J* = 13.2, 5.8 Hz, 1 H, 6-H'), 2.64 (ddd, *J* = 17.5, 7.8, 5.9 Hz, 1 H, 3-H), 2.31 (ddd, *J* = 17.5, 7.1, 5.9 Hz, 1 H, 3-H'), 2.21-2.18 (m, 2 H, 3'-H), 1.91-1.84 (m, 1 H, 4-H), 1.80-1.71 (m, 1 H, 4-H'), 1.57-1.55 (m, 2 H, 4'-H), 1.37-1.25 (m, 2 H, 5'-H), 1.10-0.96 (m, 21 H, TIPS), 0.88 (t, *J* = 7.4 Hz, 3 H, 6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 197.9 (s, C2'), 163.0 (s, C2), 93.1 (d, C1'), 64.7 (d, C5), 48.3 (t, C6), 41.6 (t, C3), 28.4 (t, C4), 28.3 (t, C3'), 25.4 (t, C4'), 22.6 (t, C5'), 17.9 (q, 6 C, *C*H$_3$ TIPS), 13.9 (q, C6'), 12.1 (d, 3 C, *C*H TIPS). MS (ESI) *m/z* (%): 729 ([2M + Na]$^+$, 69), 707 ([2M + 1]$^+$, 14), 706 ([2M]$^+$, 33), 354 ([M + 1]$^+$, 100). MS/MS (ESI of [M$^+$ + 1]) *m/z* (%): 354 (4), 270 (5), 180 (100), 162 (9). $C_{20}H_{39}NO_2Si$ (353.61): calcd C, 67.93; H, 11.12; N, 3.96. Found: C, 67.63; H, 11.21; N, 3.77.

(5*S*)-1-Phenyl-2-(5-triisopropylsilanoxypiperidin-2-ylidene)ethanone (12d). Yellow oil (119 mg, 63%). R_f 0.10 (*n*-hexane/EtOAc 10:1). $[\alpha]_D^{24}$ = – 12.3 (*c* 1.49, $CHCl_3$). ^{1}H NMR (400 MHz) δ (ppm): 11.61 (bs, 1 H, N-*H*), 7.85-7.83 (m, 2 H, Ph), 7.40-7.35 (m, 3 H, Ph), 5.62 (s, 1 H, 1'-H), 4.23-4.20 (m, 1 H, 5-H), 3.56 (dt, *J* = 13.3, 2.9 Hz, 1 H, 6-H), 3.30 (ddd, *J* = 13.3, 5.3, 2.0 Hz, 1 H, 6-H'), 2.80 (ddd, *J* = 17.4, 8.0, 6.1 Hz, 1 H, 4-H), 2.45 (dt, *J* = 17.4, 6.2 Hz, 1 H, 4-H'), 1.95-1.89 (m, 1 H, 3-H), 1.88-1.81 (m, 1 H, 3-H'), 1.12-1.04 (m, 21 H, TIPS). ^{13}C NMR (100.4 MHz) δ (ppm): 187.2 (s, C2'), 165.0 (s, C2), 140.5 (s, Ph), 130.2 (d, Ph), 128.1 (d, 2 C, Ph), 126.8 (d, 2 C, Ph), 90.1 (d, C1'), 64.6 (d, C5), 48.6 (t, C6), 28.3 (t, C4), 25.9 (t, C3), 18.0 (q, 6 C, *C*H$_3$ TIPS), 12.2 (d, 3 C, *C*H TIPS). MS (ESI) *m/z* (%): 769 ([2M + Na]$^+$, 100), 746 ([2M]$^+$, 72), 374 ([M + 1]$^+$, 66). $C_{22}H_{35}NO_2Si$ (373.60): calcd C, 70.73; H, 9.44; N, 3.75. Found: C, 70.59; H, 9.72; N, 3.91.

(5*S*)-1-(5-Hydroxypiperidin-2-ylidene)-hexan-2-one (12e). Yellow oil (128 mg, 65%). R_f 0.19 (*n*-hexane/EtOAc 3:1). $[\alpha]_D^{23}$ = – 16.5 (*c* 1.34, $CHCl_3$). ^{1}H NMR (400 MHz) δ (ppm): 10.95 (bs, 1 H, N-*H*), 4.89 (s, 1 H, 1'-H), 4.29 (bs, 1 H, O-*H*), 4.08-4.02 (m, 1 H, 5-H), 3.44 (br d, *J* = 13.3 Hz, 1 H, 6-H), 3.17 (dd, *J* = 13.3, 5.5 Hz, 1 H, 6-H'), 2.57 (ddd, *J* = 17.5, 7.4, 5.8 Hz, 1 H, 3-H), 2.30 (dt, *J* = 17.5, 6.6 Hz, 1 H, 3-H'), 2.13 (t, *J* = 7.8 Hz, 2 H, 3'-H), 1.89-1.83 (m, 1 H, 4-H), 1.76-1.69 (m, 1 H, 4-H'), 1.53-1.45 (m, 2 H, 4'-H), 1.32-1.22 (m, 2 H, 5'-H), 0.85 (t, *J* = 7.4 Hz, 3 H, 6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 197.5 (s, C2'), 163.8 (s, C2), 92.8 (d, C1'), 63.3 (d, C5), 47.6 (t, C6), 41.5 (t, C3), 28.6 (t, C3'), 27.2 (t, C4), 25.4 (t, C4'), 22.5 (t, C5'), 13.8 (q, C6'). MS (ESI) *m/z* (%): 417 ([2M + Na]$^+$, 100), 220 ([M + Na]$^+$, 14), 198 ([M + 1]$^+$, 17). MS/MS (ESI of [M + 1]$^+$) *m/z* (%): 198 (22), 180 (100), 162 (34), 113 (58), 95 (21). $C_{11}H_{19}NO_2$ (197.27): calcd C, 66.97; H, 9.71; N, 7.10. Found: C, 67.37; H, 10.00; N, 7.03.

1-Azepan-2-ylidenehexan-2-one (12g). Colorless oil (142 mg, 73%). R_f 0.25 (eluent: *n*-hexane/EtOAc 3:1). ^{1}H NMR (200 MHz) δ (ppm): 11.0 (s br, 1 H, N-*H*), 4.96 (s, 1 H, 1'-H), 3.36-3.28 (m, 2 H, 7-H), 2.32-2.19 (m, 4 H, 3-H and 3'-H), 1.68-1.28 (m, 10 H, 4-H, 5-H, 6-H, 4'-H and 5'-H), 0.90 (t, *J* = 7.2 Hz, 3 H, 6'-H). ^{13}C NMR (50.33 MHz) δ (ppm): 198.7 (s, C2'), 169.6 (s, C2), 93.6 (d, C1'), 44.2 (t, C7), 41.9 (t, C3'), 34.9 (t, C3), 30.6 (t, C6), 29.5 (t, C5), 28.5 (t, C4'), 26.0 (t, C4), 22.7 (t, C5'), 14.0 (q, C6'). MS *m/z* (%): 195 ([M]$^+$, 23), 138 (100), 111 (35). $C_{12}H_{21}NO$ (195.30): calcd C, 73.80; H, 10.84; N, 7.17. Found: C, 74.01; H, 10.90; N, 7.03.

2-Azepan-2-ylidene-1-phenylethanone (12h). Yellow oil (140 mg, 65%). R_f 0.22 (eluent: *n*-hexane/EtOAc 3:1). ^{1}H NMR (200 MHz) δ (ppm): 11.54 (br s, 1 H, N-*H*), 7.90-7.82 (m, 2 H, *Ph*), 7.42-7.35 (m, 3 H, *Ph*), 5.67 (s, 1 H, 1'-H), 3.45-3.37 (m, 2 H, 7-H), 2.47-2.42 (m, 2 H, 3-H), 1.80-1.60 (m, 6 H, 4-H, 5-H and 6-H). ^{13}C NMR (50.33 MHz) δ (ppm): 188.1 (s, C2'), 171.3 (s, C2), 140.6 (s, *Ph*), 130.3 (d, *Ph*), 128.0 (d, 2 C, *Ph*), 126.8 (d, 2 C, Ph), 91.0 (d, C1'), 44.4 (t, C7), 35.3 (t, C3), 30.5 (t, C6), 29.3 (t, C5), 25.8 (t, C4). MS *m/z* (%): 215 ([M]+, 81), 214 (100), 186 (22), 105 (24). $C_{14}H_{17}NO$ (215.29): calcd C, 78.10; H, 7.96; N, 6.51. Found: C, 77.92; H, 7.90; N, 6.24.

2-Azepan-2-ylidene-1-cyclopropylethanone (12i). Colorless oil (108 mg, 60%). R_f 0.31 (eluent: *n*-hexane/EtOAc 3:1). ^{1}H NMR (200 MHz) δ (ppm): 10.89 (br s, 1 H, N-*H*), 5.12 (s, 1 H, 1'-H), 3.34-3.26 (m, 2 H, 7-H), 2.34-2.29 (m, 2 H, 3-H), 1.78-1.54 (m, 7 H, 4-H, 5-H, 6-H and 3'-H), 0.99-0.90 (m, 2 H, 4'-H), 0.82-0.66 (m, 2 H, 4'-H'). ^{13}C NMR (50.33 MHz) δ (ppm): 197.1 (s, C2'), 168.7 (s, C2), 93.6 (d, C1'), 44.2 (t, C7), 35.0 (t, C3), 30.6 (t, C6), 29.5 (t, C5), 26.0 (t, C4), 19.8 (d, C3'), 8.61 (t, 2 C, C4'). MS *m/z* (%): 179 ([M]$^+$, 80), 138 (100). $C_{11}H_{17}NO$ (179.26): calcd C, 73.70; H, 9.56; N, 7.81. Found: C, 73.44; H, 9.82; N, 8.05.

1-(1,4,5,6-Tetrahydropyridin-2yl)ethanone (23).[44] Pale yellow oil (22 mg, 35%). ^{1}H NMR (200 MHz) δ (ppm) [2:1 mixture of isomers A and B]: 5.61 (t, *J* = 4.4 Hz, 1 H, 2-H, A), 4.19 (br s, 1 H, N-H, A), 3.84-3.79 (m, 2 H, 5-H, B), 3.14 (t, *J* = 5.3 Hz, 2 H, 5-H, A), 2.38-2.31 (m, 2 H, 2-H, B), 2.33 (s, 3 H, C*H*$_3$, B), 2.31-2.20 (m, 2 H, 3-H, A), 2.26 (s, 3 H, C*H*$_3$, A), 1.85-1.73 (m, 2 H, 4-H, A), 1.73-1.54 (m, 4 H, 3-H, 4-H, B).

(5*R*)-1-(5-Azidopiperidin-2-ylidene)-hexan-2-one (12f). A volume of the enyne solution containing 1 mmol of substrate was concentrated and dried under vacuum (no heating) for 30 min and then dissolved in anhydrous toluene (5 mL). A 0.2 M AgOTf solution and a 4 mM Ph_3PAuCl solution, both in anhydrous toluene, were prepared. The AgOTf solution (100 µL, 0.02 mmol) was added at r.t. to the 4 mM Ph_3PAuCl solution (5 mL, 0.02 mmol) under stirring and a nitrogen atmosphere, and a white precipitate immediately formed. The solution of enyne **8f** (1.0 mmol) in anhydrous toluene (5 mL) was then added, and the resulting mixture was heated under reflux until the starting material disappeared (TLC, 30 min). The mixture was cooled at 85 °C (external) and diluted with *tert*-butyl alcohol (10 mL); powdered KOH (6 mmol) was added and the mixture heated at 85 °C until completion (TLC, 10 min.). After cooling at room temperature, water (15 mL) was then added, and the product extracted with EtOAc (3 × 10 mL); the combined organic extracts were washed once with brine (15 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude vinylogous amide **12f** was purified by flash chromatography (*n*-hexane/EtOAc 3:1; R_f 0.24) to obtain the pure compound (142 mg, 64%) as a colorless oil. $[\alpha]_D^{23}$ = – 11.5 (*c* 0.92, $CHCl_3$). ^{1}H NMR (400 MHz) δ (ppm): 10.99 (br s, 1 H, N-*H*), 4.93 (s, 1 H, 1'-H), 3.89-3.83 (m, 1 H, 5-H), 3.49 (ddd, *J* = 13.3, 4.7, 2.3 Hz, 1 H, 6-H), 3.23 (ddd, *J* = 13.3, 6.2, 1.9 Hz, 1 H, 6-H'), 2.55 (ddd, *J* = 17.6, 7.8, 5.9 Hz, 1 H, 3-H), 2.36 (ddd, *J* = 17.6, 7.4, 6.3 Hz, 1

H, 3-H'), 2.22-2.18 (m, 2 H, 3'-H), 2.03-1.95 (m, 1 H, 4-H), 1.85-1.76 (m, 1 H, 4-H'), 1.57-1.50 (m, 2 H, 4'-H), 1.35-1.28 (m, 2 H, 5'-H), 0.88 (t, *J* = 7.4 Hz, 3 H, 6'-H) ppm. ^{13}C NMR (100.4 MHz) δ (ppm): 198.5 (s, C2'), 161.4 (s, C2), 93.5 (d, C1'), 54.4 (d, C5), 44.5 (t, C6), 41.7 (t, C3), 28.3 (t, C3'), 25.4 (t, C4), 24.6 (t, C4'), 22.6 (t, C5'), 13.9 (q, C6'). MS (ESI) *m/z* (%): 467 ([2M + Na]$^+$, 100), 245 ([M + Na]$^+$, 38), 223 ([M + 1]$^+$, 18). MS/MS (ESI of [M + 1]$^+$) *m/z* (%): 166 (94), 110 (32), 93 (100), 81 (93). $C_{11}H_{18}N_4O$ (222.29): calcd C, 59.44; H, 8.16; N, 25.20. Found: C, 59.83; H, 7.82; N, 24.98

2-Hex-1-ynylpiperidine-1-carboxylic acid benzyl ester (16a). Enyne **13a** (217 mg, 0.73 mmol) was dissolved in anhydrous CH_2Cl_2 (36 mL) and $NaBH_3CN$ (275 mg, 4.37 mmol) was added; the mixture was vigorously stirred at r. t. for 20 min and then cooled at – 50 °C. A solution of TFA (561 μL, 7.28 mmol) in anhydrous CH_2Cl_2 (4.9 mL) was added dropwise keeping the temperature constant during the addition. The mixture was then allowed to warm at – 20 °C and left under stirring until completion (TLC; 2-3 h). The reaction was then quenched by addition of satd $NaHCO_3$ (40 mL) and, after separation of the phases, the product was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed once with satd $NaHCO_3$ (40 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude **16a** was obtained and purified by flash chromatography (eluent: *n*-hexane/EtOAc 20:1; R_f 0.11) to afford pure **16a** as a colourless oil (129 mg, 59%). ^{1}H NMR (400 MHz) δ (ppm): 7.36-7.28 (m, 5 H, Ph), 5.18-5.08 (m, 1 H, 2-H), 5.14 (s, 2 H, C*H*$_2$Ph), 3.98 (br d, *J* = 12.5 Hz, 1 H, 6-H), 3.11 (br t, *J* = 12.3 Hz, 1 H, 6-H'), 2.19 (td, *J* = 6.8, 2.0 Hz, 2 H, 3'-H), 1.81-1.56 (m, 5 H, 3-H, 4-H and 5-H), 1.51-1.36 (m, 5 H, 4'-H, 5'-H and 5-H'), 0.91 (t, *J* = 7.2 Hz, 3 H, 6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 155.1 (s, C=O), 136.9 (s, Ph), 128.4 (d, 2 C, Ph), 127.9 (d, 2 C, Ph), 127.7 (d, Ph), 84.8 (s, C1'), 77.7 (s, C2'), 67.1 (t, *C*H$_2$Ph), 44.6 (t, C6), 40.5 (d, C2), 31.0 (t, C4'), 30.9 (t, C3), 25.4 (t, C5), 21.9 (t, C5'), 19.9 (t, C4), 18.3 (t, C3'), 13.6 (q, C6'). MS (ESI) *m/z* (%): 621 ([2M+Na]$^+$, 100), 322 ([M+Na]$^+$, 17), 300 [M+1]$^+$, 4). $C_{19}H_{25}NO_2$ (299.41): calcd C, 76.22; H, 8.42; N, 4.68. Found: C, 76.33; H, 8.82; N, 4.40.

2-Phenylethynylpiperidine-1-carboxylic acid benzyl ester (16b). Prepared as reported for **16a**, starting from **13b** (151 mg, 0.47 mmol) and obtaining, after purification by flash chromatography (eluent: *n*-hexane/EtOAc 20:1; R_f 0.21), pure **16b** (93 mg, 62%) as a pale yellow oil. ^{1}H NMR (400 MHz) δ (ppm): 7.43-7.29 (m, 10 H, Ph), 5.38 (br s, 1 H, 2-H), 5.17 (s, 2 H, C*H*$_2$Ph), 4.05 (br d, *J* = 12.3 Hz, 1 H, 6-H), 3.21 (br t, *J* = 11.9 Hz, 1 H, 6-H'), 1.90-1.83 (m, 2 H, 3-H), 1.77-1.67 (m, 3 H, 5-H and 4-H), 1.51-1.42 (m, 1 H, 5-H'). ^{13}C NMR (100.4 MHz) δ (ppm): 155.0 (s, C=O), 136.7 (s, Cbz), 131.7 (d, 2 C, Ph), 128.5 (d, Ph), 128.2 (d, 2 C, Ph), 128.1 (d, 2 C, Cbz), 127.9 (d, 2 C, Cbz), 127.7 (d, Cbz), 122.9 (s, Ph), 84.4 (s, C1'), 77.2 (s, C2'), 67.2 (t, *C*H$_2$Ph), 45.0 (t, C6), 40.7 (d, C2), 30.8 (t, C3), 25.3 (t, C5), 20.0 (t, C4). MS (ESI) *m/z* (%): 661 ([2M+Na]$^+$, 100), 342 ([M+Na]$^+$, 10), 320 [M+1]$^+$, 3). $C_{21}H_{21}NO_2$ (319.40): calcd C, 78.97; H, 6.63; N, 4.39. Found: C, 78.79; H, 6.41; N, 4.84.

2-Triethylsilanylethynylpiperidine-1-carboxylic acid benzyl ester (16c). Prepared as reported for **16a**, starting from **13c** (702 mg, 1.97 mmol) and obtaining, after purification by flash chromatography (eluent: *n*-hexane/EtOAc 20:1; R_f 0.31), pure **16c** (383 mg, 54%) as a colorless oil. ^{1}H NMR (400 MHz) δ (ppm): 7.36-7.28 (m, 5 H, Ph), 5.25-5.09 (m, 1 H, 2-H), 5.14 (s, 2 H, C*H*$_2$Ph), 4.01 (br d, *J* = 11.3 Hz, 1 H, 6-H), 3.20-3.05 (br m, 1 H, 6-H'), 1.90-1.74 (m, 2 H, 3-H), 1.70-1.60 (m, 3 H, 5-H and 4-H), 1.48-1.33 (m, 1 H, 5-H'), 0.97 (t, *J* = 7.8 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$), 0.59 (q, *J* = 7.8 Hz, 6 H, Si(C*H*$_2$CH$_3$)$_3$). ^{13}C NMR (100.4 MHz) δ (ppm): 155.0 (s, C=O), 136.8 (s, Ph), 128.4 (d, 2 C, Ph), 127.9 (d, 2 C, Ph), 127.6 (d, Ph), 104.8 (s, C2'), 86.3 (s, C1'), 67.1 (t, *C*H$_2$Ph), 45.2 (t, C6), 40.5 (d, C2), 30.7 (t, C3), 25.3 (t, C5), 19.8 (t, C4), 7.4 (q, 3 C, Si(CH$_2$CH$_3$)$_3$), 4.4 (t, 3 C, Si(CH$_2$CH$_3$)$_3$). MS (ESI) *m/z* (%): 737 ([2M+Na]$^+$, 100), 380 ([M+Na]$^+$, 10), 358 [M+1]$^+$, 3). $C_{21}H_{31}NO_2Si$ (357.56): calcd C, 70.54; H, 8.74; N, 3.92. Found: C, 70.24; H, 8.46; N, 4.24.

2-Ethynylpiperidine-1-carboxylic acid benzyl ester (16d). Prepared as reported for **8e**, starting from **16c** (341 mg, 0.95 mg) and obtaining, after purification by flash chromatography (eluent: *n*-hexane/EtOAc 20:1; R_f 0.18), pure **16d** (207 mg, 89%) as a colorless oil. ^{1}H NMR (400 MHz) δ (ppm): 7.39-7.29 (m, 5 H, Ph), 5.18-5.12 (m, 1 H, 2-H), 5.15 (s, 2 H, C*H*$_2$Ph), 4.03 (br d, *J* = 11.7 Hz, 1 H, 6-H), 3.12 (br t, *J* = 12.3 Hz, 1 H, 6-H'), 2.30 (d, *J* = 2.3 Hz, 1 H, 2'-H), 1.83-1.74 (m, 2 H, 3-H), 1.71-1.65 (m, 3 H, 5-H and 4-H), 1.46-1.35 (m, 1 H, 5-H'). ^{13}C NMR (100.4 MHz) δ (ppm): 155.0 (s, C=O), 136.6 (s, Ph), 128.4 (d, 2 C, Ph), 127.9 (d, 2 C, Ph), 127.8 (d, Ph), 81.6 (s, C1'), 72.3 (d, C2'), 67.2 (t, *C*H$_2$Ph), 44.2 (t, C6), 40.5 (d, C2), 30.3 (t, C3), 25.1 (t, C5), 19.7 (t, C4). MS (ESI) *m/z* (%): 509 ([2M+Na]$^+$, 100), 266 ([M+Na]$^+$, 37), 244 [M+1]$^+$, 7). $C_{15}H_{17}NO_2$ (243.30): calcd C, 74.05; H, 7.04; N, 5.76. Found: C, 73.79; H, 7.41; N, 5.84.

3-Butyl-5,6,7,8-tetrahydro-4a*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (18a). In a two neck round bottom flask containing Ph_3PAuCl (5.4 mg, 0.011 mmol) in toluene (1.8 mL), $Cu(OTf)_2$ (20 mg, 0.055 mmol) was added under nitrogen atmosphere. A solution of alkyne **16a** (108 mg, 0.36 mmol) in toluene (1.8 mL) was added and the resulting mixture was heated under reflux until the starting material disappeared (TLC, 1.5-2 h). After cooling, water (5 mL) was added and the product extracted with EtOAc (3 x 5 mL); the combined organic extracts were washed once with brine (5 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude material was purified by flash chromatography (eluent: *n*-hexane/EtOAc 5:1; R_f 0.23) to afford pure **18a** as a colourless oil (63 mg, 83%). ^{1}H NMR (400 MHz) δ (ppm): 4.64 (d, *J* = 2.8 Hz, 1 H, 4-H), 4.43 (dd, *J* = 13.2, 1.6 Hz, 1 H, 8-H), 3.78 (d, *J* = 11.2 Hz, 1 H, 4a-H), 2.67 (td, *J* = 12.8, 2.8 Hz, 1 H, 8-H'), 2.07 (t, *J* = 7.6 Hz, 2 H, 1'-H), 1.89-1.85 (m, 1 H, 7-H), 1.75-1.72 (m, 2 H, 6-H and 7-H'), 1.58-1.41 (m, 4 H, 5-H, 6-H' and 2'-H), 1.39-1.27 (m, 3 H, 5-H' and 3'-H), 0.89 (t, *J* = 7.2 Hz, 3 H, 4'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 150.2 (s, C1), 150.0 (s, C3), 98.6 (d, C4), 55.0 (d, C4a), 45.1 (t, C8), 34.2 (t, C5), 32.0 (t, C1'), 28.0 (t, C2'), 25.0 (t, C7), 24.2 (t, C6), 22.0 (t, C3'), 13.7 (q, C4'). MS (ESI) *m/z* (%): 441 ([2M+Na]$^+$, 100), 419 ([2M+1]$^+$, 25), 210 ([M+1]$^+$, 9). $C_{12}H_{19}NO_2$ (209.28): calcd C, 68.87; H, 9.15; N, 6.69. Found: C, 69.05; H, 9.13; N, 6.54.

3-Phenyl-5,6,7,8-tetrahydro-4a*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (18b).[40] Prepared as reported for **18a**, starting from **16b** (90 mg, 0.28 mmol) and obtaining, after purification by flash chromatography (eluent: *n*-hexane/EtOAc 5:1; R_f 0.19), pure **18b** (48 mg, 75%) as a colorless oil. ^{1}H NMR (400 MHz) δ (ppm): 7.63-7.61 (m, 2 H, Ph), 7.39-7.32 (m, 3 H, Ph), 5.42 (d, *J* = 3.2 Hz, 1 H, 4-H), 4.50 (d, *J* = 13.6 Hz, 1 H, 8-H), 3.99 (d, *J* = 10.4 Hz, 1 H, 4a-H), 2.76 (td, *J* = 12.5, 2.9 Hz, 1 H, 8-H'), 1.95-1.92 (m, 1 H, 6-H), 1.83-1.80 (m, 1 H, 5-H), 1.75-1.72 (m, 1 H, 7-H), 1.64-1.46 (m, 3 H, 5-H', 6-H' and 7-H'). ^{13}C NMR (100.4 MHz) δ (ppm): 149.6 (s, C1), 147.3 (s, C3), 131.8 (s, Ph), 129.2 (d, Ph), 128.4 (d, 2 C, Ph), 124.5 (d, 2 C, Ph), 98.7 (d, C4), 55.3 (d, C4a), 45.2 (t, C8), 33.9 (t, C5), 25.0 (t, C7), 24.2 (t, C6). MS (ESI) *m/z* (%): 481 ([2M+Na]$^+$, 100), 459 ([2M+1]$^+$, 36), 230 ([M+1]$^+$, 32).

1-Piperidin-2-ylhexan-2-one (19a). Compound **18a** (60 mg, 0.29 mmol) was dissolved in toluene (2.9 mL); the solution was diluted with *t*-butanol (2.9 mL) and powdered KOH (65 mg, 1.16 mmol) was then added. The mixture was heated at 85 °C (external) for 45 min. After cooling, water (6 mL) was added and the product extracted with EtOAc (3 x 6 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration, the solvent was concentrated under *vacuum* (caution! The product is volatile!) and the residue purified by flash chromatography

(eluent: EtOAc/MeOH 1:1; R_f 0.13). The fractions were concentrated to a small volume under *vacuum* and, due to the volatility of the product, only a small portion was dried under *vacuum* for the characterization as free amine. Colorless oil. R_f 0.13 (EtOAc/MeOH 1:1). ^{1}H NMR (400 MHz) δ (ppm): 3.01 (d, *J* = 11.7 Hz, 1 H, 6-H), 2.98-2.91 (m, 1 H, 2-H), 2.66 (td, *J* = 11.7, 2.7 Hz, 1 H, 6-H'), 2.48 (d, *J* = 5.9 Hz, 2 H, 1'-H), 2.38 (t, *J* = 7.4 Hz, 2 H, 3'-H), 2.33 (br s, 1 H, N-*H*), 1.78-1.72 (m, 1 H, 5-H), 1.63-1.49 (m, 3 H, 3-H and 4'-H), 1.47-1.24 (m, 5 H, 4-H, 5-H' and 5'-H), 1.21-1.12 (m, 1 H, 3-H'), 0.89 (t, *J* = 7.4 Hz, 3 H, 6'-H). ^{13}C NMR (100.4 MHz) δ (ppm): 210.9 (s, C=O), 52.4 (t, C1'), 49.5 (t, C3'), 46.7 (t, C6), 43.2 (d, C2), 32.4 (t, C3), 25.9 (t, C4'), 25.8 (t, C5), 24.6 (t, C4), 22.3 (t, C5'), 13.8 (q, C6'). MS (ESI) *m/z* (%): 184 ([M+1]$^+$, 100). The largest portion was cooled in ice bath and HCl 1.25 M in MeOH (500 μL) was added under stirring. After 30 min, the solvent was evaporated; the crude dissolved in a small volume of acetone and the product precipitated by adding Et_2O. The white solid was filtered, washed with cold Et_2O and dried under *vacuum*, affording pure **19a** hydrochloride as a white solid (57 mg, 89%). **19a·HCl.** M.p. 115.2-116.6 °C. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.52-3.43 (m, 1 H, 2-H), 3.34 (dm, *J* = 13.2 Hz, 1 H, 6-H), 3.01-2.91 (m, 2 H, 6-H' and 1'-H), 2.87-2.80 (m, 1 H, 1'-H'), 2.50 (t, *J* = 7.6 Hz, 2 H, 3'-H), 1.87-1.77 (m, 3 H, 3-H and 5-H), 1.65-1.38 (m, 5 H, 3-H', 4-H and 4'-H), 1.24 (sextuplet, *J* = 7.2 Hz, 2 H, 5'-H), 0.82 (t, *J* = 7.2 Hz, 3 H, 6'-H). $C_{11}H_{22}ClNO$ (219.75): calcd C, 60.12; H, 10.09; N, 6.37. Found: C, 60.05; H, 9.98; N, 6.51.

1-Phenyl-2-piperidin-2-ylethanone (19b).[10] Prepared as reported for **19a** and **19a·HCl**, starting from **18b** (45 mg, 0.19 mmol) and obtaining, after purification by flash chromatography (eluent: EtOAc/MeOH 1:1; R_f 0.07), a small sample of free amine **19b** and pure **19b·HCl** (36 mg, 78%) as a white solid, after treatment with HCl 1.25 M in MeOH.

19b.[10] R_f 0.05 (EtOAc/MeOH 2:1). ^{1}H NMR (400 MHz) δ (ppm): 7.96-7.93 (m, 2 H, Ph), 7.59-7.54 (m, 1 H, Ph), 7.47-7.43 (m, 2 H, Ph), 3.38 (br s, N-*H*), 3.24-3.04 (m, 4 H, 3-H and 6-H), 2.74 (td, *J* = 11.7, 2.7 Hz, 1 H, 2-H), 1.86-1.80 (m, 1 H, 5-H), 1.73-1.62 (m, 2 H, 1'-H), 1.59-1.38 (m, 3 H, 4-H and 5-H'). ^{13}C NMR (100.4 MHz) δ (ppm): 199.3 (s, C=O), 136.9 (s, Ph), 133.3 (d, Ph), 128.6 (d, 2 C, Ph), 128.1 (d, 2 C, Ph), 52.9 (t, C1'), 46.3 (t, C6), 44.7 (d, C2), 31.9 (t, C3), 25.2 (t, C5), 24.3 (t, C4). MS (ESI) *m/z* (%): 204 ([M+1]$^+$, 100).

19b·HCl.[37] ^{1}H NMR (400 MHz, D_2O) δ (ppm): 7.98-7.92 (m, 2 H, *Ph*), 7.70-7.63 (m, 1 H, *Ph*), 7.55-7.48 (m, 2 H, *Ph*), 3.73-3.63 (m, 1 H, 2-H), 3.57-3.48 (m, 1 H, 1'-H), 3.44-3.33 (m, 2 H, 6-H and 1'-H'), 3.05 (td, *J* = 12.4, 2.8 Hz, 1 H, 6-H'), 1.99-1.91 (m, 1 H, 5-H), 1.91-1.80 (m, 2 H, 3-H), 1.70-1.49 (m, 3 H, 4-H and 5-H').

1-Methyl-5,6,7,8-tetrahydro-oxazolo[3,4-*a*]pyridin-3-one (21). Prepared as reported for **18a**, starting from **16d** (100 mg, 0.41 mmol) and obtaining, after purification by flash chromatography (eluent: *n*-hexane/EtOAc 3:1; R_f 0.07), pure **21** (38 mg, 60%) as a white waxy solid. M.p. 45.6-46.4 °C. ^{1}H NMR (400 MHz) δ (ppm): 3.51 (t, *J* = 6.0 Hz, 2 H, 5-H), 2.43 (t, *J* = 6.4 Hz, 2 H, 8-H), 1.98 (s, 3 H, C*H*$_3$), 1.83-1.76 (m, 2 H, 6-H), 1.71-1.64 (m, 2 H, 7-H). ^{13}C NMR (100.4 MHz) δ (ppm): 155.6 (s, C=O), 130.4 (s, C1), 117.2 (s, C9), 40.5 (t, C5), 22.4 (t, C8), 20.0 (t, C6), 19.3 (t, C7), 9.8 (q, *C*H$_3$). MS (ESI) *m/z* (%): 329 ([2M+Na]$^+$, 100), 176 ([M+Na]$^+$, 37). $C_8H_{11}NO_2$ (153.18): calcd C, 62.73; H, 7.24; N, 9.14. Found: C, 63.05; H, 6.98; N, 8.91.

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[1] For recent examples see: a) R. Li, X. Wang, Z. Wei, C. Wu, F. Shi, *Org. Lett.* **2013**, *15*, 4366-4369; b) G. S. Buchanan, H. Dai, R. P. Hsung, A. I. Gerasyuto, C. M. Scheinebeck, *Org. Lett.* **2011**, *13*, 4402-4405; c) A. I. Gerasyuto, R. P. Hsung, *J. Org. Chem.* **2007**, *72*, 2476-2484; d) R. P. Hsung, L.-L. Wei, H. M. Sklenicka, C. J. Douglas, M. J. McLaughlin, J. A. Mulder, L. J. Yao, *Org. Lett.* **1999**, *1*, 509-512; e) E. Gayon, M. Szymczyk, H. Gérard, E. Vrancken, J.-M. Campagne, *J. Org. Chem.* **2012**, *77*, 9205-9220; f) A. Noole, M. Borissova, M. Lopp, T. Kanger, *J. Org. Chem.* **2011**, *76*, 1538-1545; g) A. Abdukader, Q. Xue, A. Lin, M. Zhang, Y. Cheng, C. Zhu, *Tetrahedron Lett*. **2013**, *54*, 5898-5900; h) J. Huang, Y. Liang, W. Pan, Y. Yang, D. Dong, *Org. Lett*. **2007**, *9*, 5345-5348.

[2] N. N. Salama, N. D. Eddington, D. Payne, T. L. Wilson, K. R. Scott, *Curr. Med. Chem.* **2004**, *11*, 2093-2103; b) I. O. Edafiogho, S. B. Kombian, K. V. V. Ananthalakshmi, N. N. Salama, N. D. Eddington, T. L. Wilson, M. S. Alexander, P. L. Jackson, C. D. Hanson, K. R. Scott, *J. Pharm. Sci*. **2007**, *96*, 2509-2531.

[3] I. O. Edafiogho, M. G. Qaddoumi, K. V. V. Ananthalakshmi, O. A. Phillips, S. B. Kombian, *Eur. J. Med. Chem*. **2014**, *76*, 20-30.

[4] For the most recent syntheses see: a) N. D. Koduri, Z. Wang, G. Cannell, K. Cooley, T. Mesfin Lemma, K. Miao, M. Nguyen, B. Frohock, M. Castaneda, H. Scott, D. Albinescu, S. R. Hussaini, *J. Org. Chem*. **2014**, *79*, 7405-7414; b) H.-D. Vu, J. Renault, T. Roisnel, N. Gouault, P. Uriac, *Eur. J. Org. Chem*. **2014**, 4506-4514; c) M. C. Martin, D. V. Patil, S. France, *J. Org. Chem*. **2014**, *79*, 3030-3039; d) P.-Q. Huang, W. Ou, K.-J. Xiao, A.-E. Wang, *Chem. Commun*. **2014**, *50*, 8761-8763; e) D. L. Priebbenow, C. Bolm, *RSC Adv*. **2013**, *3*, 10318-10322. See also ref. [11] and references therein.

[5] For recent examples see: a) S. K. Ghosh, G. S. Buchanan, Q. A. Long, Y. Wei, Z. F. Al-Rashid, *Tetrahedron* **2008**, *64*, 883-893; b) F. Josefík, M. Svobodová, V. Bertolasi, P. Šimůnek, *Beilstein J. Org. Chem*. **2013**, *9*, 1463–1471; c) F. Josefík, M. Svobodová, V. Bertolasi, P. Šimůnek, V. Macháček, N. Almonasy, E. Černošková, H. M. Sklenicka, R. P. Hsung, *J. Organomet. Chem*. **2012**, *699*, 75-81.

[6] C. Herdeis, J. Telser, *Eur. J. Org. Chem*. **1999**, 1407-1414.

[7] C. Herdeis, P. Küpper, S. Plé, *Org. Biomol. Chem*. **2006**, *4*, 524-529.

[8] S. Fréville, P. Delbecq, V. M. Thuy, H. Petit, J. P. Célérier, G. Lhommet, *Tetrahedron Lett*. **2001**, *42*, 4609-4611.

[9] J. P. Michael, C. B. de Koning, D. P. Pienaar, *Synlett* **2006**, 383-386.

[10] B. A. D. Neto, A. A. M. Lapis, A. B. Bernd, D. Russowsky, *Tetrahedron* **2009**, *65*, 2484-2496.

[11] A. Oppedisano, C. Prandi, P. Venturello, A. Deagostino, G. Goti, D. Scarpi, E. G. Occhiato, *J. Org. Chem*. **2013**, *78*, 11007-11016.

[12] a) G. Satyalakshmi, K. Suneel, D. B. Shinde, B. Das, *Tetrahedron: Asymmetry* **2011**, *22*, 1000-1005; b) S. Fustero, D. Jiménez, J. Moscardó, S. Catalán, C. del Pozo, *Org. Lett.* **2007**, *9*, 5283-5286.

[13] R. W. Bates, N. F. M. Aslam, C. H. Tang, O. Simon, *Tetrahedron* **2014**, *70*, 2134-2140.

[14] a) P. R. Krishna, B. K. Reddy, P. Srinivas, *Tetrahedron* **2012**, *68*, 841-845; b) W. A. Maio, S. Sinishtaj, G. H. Posner, *Org. Lett.* **2007**, *9*, 2673-2676.

[15] a) W.-H. Chiou, G.-T. Chen, C.-L. Kao, Y.-K. Gao, *Org. Biomol. Chem.* **2012**, *10*, 2518-2520; b) T. K. Beng, R. E. Gawley, *J. Am. Chem. Soc.* **2010**, *132*, 12216-12217.

[16] Carbodeauration process was studied with allylic cations generated *in situ*. See: a) M. C. Blanco Jaimes, V. Weingand, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2013**, *19*, 12504-12511; b) A. S. K. Hashmi, C. Lothshütz, R. Döpp, M. Ackermann, J. de Buck Becker, M. Rudolph, C. Scholz, F. Rominger, *Adv. Synth. Catal.* **2012**, *354*, 133-147.

[17] R. Robles-Machín, J. Adrio, J. C. Carretero, *J. Org. Chem*. **2006**, *71*, 5023-5026.

[18] E.-S. Lee, H.-S. Yeom, J.-H. Hwang, S. Shin, *Eur. J. Org. Chem*. **2007**, 3503-3507.

[19] A. Buzas, F. Gagosz, *Synlett* **2006**, 2727-2730.

[20] In the case of *N*-Boc-2-ethynylpyrrolidine, whereas Gagosz and Buzas reported the formation of the 5-*exo dig* product only, Shin *et al*. referred on the formation of a mixture 3:1 of 5-*exo dig* vs 6-*endo dig* compounds; however, catalyst, solvent and reaction times were different.

[21] a) D. Malhotra, L.-P. Liu, M. S. Mashuta, G. B. Hammond, *Chem. Eur. J.* **2013**, *19*, 4043-4050; b) C. H. Oh, J. H. Kim, B. K. Oh, J. R. Park, J. H. Lee, *Chem. Eur. J.* **2013**, *19*, 2592-2596; c) E. Rettenmeier, A. M. Schuster, M. Rudolph, F. Rominger, C. A. Gade, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2013**, *52*, 5880-5884; d) N. Ghosh, S. Nayak, B. Prabagar, A. K. Sahoo, *J. Org. Chem.* **2014**, *79*, 2453-2462; e) L. Pawar, F. C. Pigge, *Tetrahedron Lett.* **2013**, *54*, 6067-6070; f) W. Rao, P. W. H. Chan, *Chem. Eur. J.* **2014**, *20*, 713-718; g) O. Seppänen, M. Muuronen, J. Helaja, *Eur. J. Org. Chem.* **2014**, 4044-4052.

[22] a) R. Cai, D. Wang, Y. Chen, W. Yan, N. R. Geise, S. Sharma, H. Li, J. L. Petersen, M. Li, X. Shi, *Chem. Commun*. **2014**, *50*, 7303-7305; b) P. Nun, R. S. Ramón, S. Gaillard, S. P. Nolan, *J. Organomet. Chem*. **2011**, *696*, 7-11; c) M. Kumar, G. B. Hammond, B. Xu, *Org. Lett*. **2014**, *16*, 3452-3455.

[23] D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc*. **2012**, *134*, 9012-9019.

[24] A. Guérinot, W. Fang, M. Sircoglou, C. Bour, S. Bezzinine-Lafolléè, V. Gandon, *Angew. Chem. Int. Ed.* **2013**, *52*, 5848-5852.

[25] M. Kumar, J. Jasinski, G. B. Hammond, B. Xu, *Chem. Eur. J.* **2014**, *20*, 3113-3119.

[26] More catalytic systems were reported in a more recent paper. See: W. Fang, M. Presset, A. Guérinot, C. Bour, S. Bezzinine-Lafolléè, V. Gandon, *Chem. Eur. J.* **2014**, *20*, 5439-5446.

[27] Á. Sinai, Á. Mészáros, T. Gáti, V. Kudar, A. Palló, Z. Novák, *Org. Lett*. **2013**, *15*, 5654-5657.

[28] S. Hanessian, E. Therrien, J. Zhang, W. van Otterlo, Y. Xue, D. Gustafsson, I. Nilsson, O. Fjellström, *Bioorg. Med. Chem. Lett*. **2009**, *19*, 5429–5432.

[29] K. Tchabanenko, R. M. Adlington, A. R. Cowley, J. E. Baldwin, *Org. Lett*. **2005**, *7*, 585-588.

[30] E. G. Occhiato, C. Prandi, A. Ferrali, A. Guarna, P. Venturello, *J. Org. Chem.* **2003**, *68*, 9728-9741.

[31] M. C. Kozlowski, Z. Xu, A. G. Santos, *Tetrahedron* **2001**, *57*, 4537-4542.

[32] C. Herdeis, *Synthesis* **1986**, 232-233.

[33] D. Scarpi, L. Bartali, A. Casini, E. G. Occhiato, *Eur. J. Org. Chem.* **2013**, 1306-1317.

[34] a) F. Lepifre, S. Clavier, P. Bouyssou, G. Coudert, *Tetrahedron* **2001**, *57*, 6969-6975; b) K. C. Nicolaou, G.-Q. Shi, K. Namoto, F. Bernal, *Chem. Comm.* **1998**, 1757-1758.

[35] Other attempts at opening the urethane ring by using reducing agents such as DIBAL-H or Super-H at low temperature failed and produced complex mixtures of by-products only.

[36] E. G. Occhiato, A. Casini, A. Guarna, D. Scarpi, *Eur. J. Org. Chem.* **2011**, 6544-6552.

[37] J. F. Stevens, H. Hart, H. Hendriks, T. M. Malingré, *Phytochemistry* **1992**, *31*, 3917-3924.

[38] J. D. Ha, J. H. Cha, *J. Am. Chem. Soc.* **1999**, *121*, 10012-10020.

[39] We tried the same approach with a similar, saturated *N*-Boc protected alkyne, but the reduction of the double bond of the enyne was troublesome due to the sensitivity of the *N*-Boc group to TFA and gave only poor yields. However by submitting the scarce amount of reduced substrate so obtained to the gold-catalyzed reaction, only the 6-*endo* compound was obtained.

[40] S. Suga, Y. Tsutsui, A. Nagaki, J. Yoshida, *J. Bull. Chem. Soc. Jpn* **2005**, *78*, 1206-1217.

[41] Degradation of this compound took place to a very small extent in $CDCl_3$ solution during spectroscopic characterization (see Supporting Information).

[42] a) A. González Pérez, C. Silva López, J. Marco-Contelles, O. Nieto Faza, E. Soriano, A. R. de Lera, *J. Org. Chem.* **2009**, *74*, 2982-2991; b) E. Soriano, J. Marco-Contelles, *Chem. Eur. J.* **2008**, *14*, 6771-6779; See also: c) A. Correa, N. Marion, L. Fensterbank, M. Malacria, S. P. Nolan, L. Cavallo, *Angew. Chem., Int. Ed*. **2008**, *47*, 718-721.

[43] This was expected because Gagosz employed DCM at r.t. whereas we used refluxing toluene.

[44] T. J. Harrison, G. R. Dake, *J. Org. Chem.* **2005**, *70*, 10872-10874.

[45] BHandHLYP was used as implemented in Gaussian09 ($0.5*E_X^{HF} + 0.5*E_X^{LSDA} + 0.5*\Delta E_X^{Becke88} + E_C^{LYP}$).

[46] Gaussian09, Revision D.01. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.

[47] 3D-structures have been represented with CyLview software: CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org).

[48] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215-241.

[49] C. Gonzalez, H.B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523-5527.

[50] J. P. Foster, F. Weinhold, *J. Am. Chem. Soc.* **1980**, *102*, 7211-7218.

[51] E. G. Occhiato, A. Trabocchi, A. Guarna, *J. Org.Chem*. **2001**, *66*, 2459-2465.

[52] M. Cieslikiewicz, A. Bouet, S. Jugé, M. Toffano, J. Bayardon, C. West, K. Lewinski, I. Gillaizeau, *Eur. J. Org. Chem*. **2012**, 1101-1106.