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# Synthesis of Vinylogous Amides by Gold(I)-Catalyzed Cyclization of *N*-Boc-Protected 6-Alkynyl-3,4-dihydro-2*H*-pyridines

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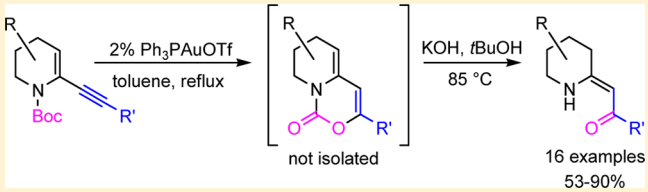
Supporting Information

**ABSTRACT:** The gold(I)-catalyzed cyclization of *N*-Boc-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines, prepared by the Sonogashira coupling of lactam-derived enol triflates or phosphates, provides vinylogous amides, which are useful intermediates in the synthesis of natural compounds. The Au(I)-catalyzed reaction is carried out with $Ph_3PAuOTf$ as a catalyst and proceeds via a 6-*endo*-dig cyclization to form a vinylgold species that after protodeauration generates a cyclic carbamate intermediate. This intermediate is in most cases not isolated, but the addition of a base to the reaction mixture rapidly and quantitatively delivers the target vinylogous amide. The first synthesis of a natural compound from *Sonneratia hainanensis* has been accomplished by this approach.




## INTRODUCTION

Exocyclic vinylogous amides built on pyrrolidine and piperidine rings (Figure 1), form a valuable class of intermediates for the synthesis of a variety of N-heterocyclic compounds. Anisomycin,[1] apomitomycin,[2] mesembrenone,[3] desoxoprosophylline,[4] cassine,[5] pinidinone and related 2,6-piperidine derivatives,[6] deoxyfebrifugine,[7] and sedacryptine[8] are just some examples of natural alkaloids obtained by exploiting the reactivity of these compounds. A number of methods have been established for the preparation of exocyclic vinylogous amides, especially from enolizable lactams. Traditionally, the formation of vinylogous amides relies on the sulfide contraction procedure developed by the Eschenmoser's group.[9] The Knoevenagel-based modification using preformed (alkylthio)alkylideniminium salts[10] or lactam-derived iminium chlorides, lactim ethers, or lactim thioethers[11] provides an alternative to the Eschenmoser procedure. Another general method is the direct condensation of chiral lactim ethers with $\beta$-keto esters in the presence of catalytic nickel acetylacetonate followed by decarboxylation.[6,12,13] Some useful and generally relevant approaches in which the heterocyclic system is built in the last stage of the synthesis include the intramolecular aza-Wittig reaction of $\omega$-azido-$\beta$-dicarbonyl derivatives[14] and the Horner–Wadsworth–Emmons [3 + 2] 1,3-dipolar cycloaddition reaction cascade of 5-azidoaldehyde derivatives.[4,5,15] Also, exocyclic vinylogous amides have been obtained by quite a long sequence from pyridine-2-carboxaldehyde and Grignard reagents.[16]

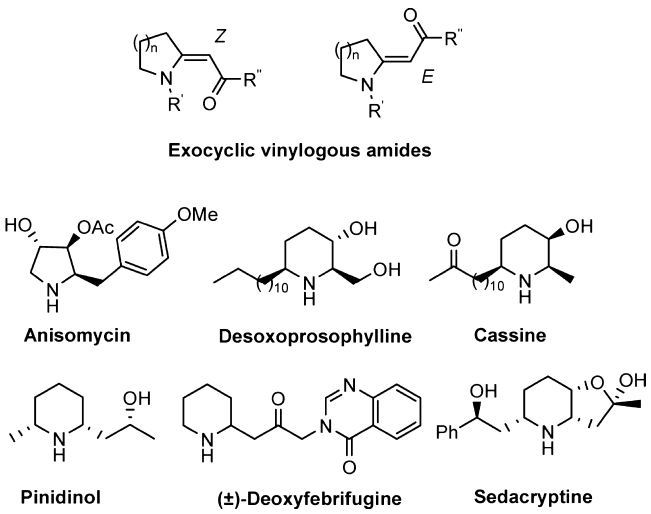
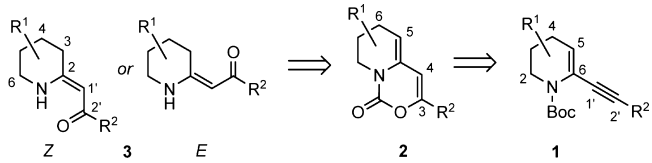



**Figure 1.** Vinylogous amides and some natural compounds prepared from them.

In continuation of our studies of the chemistry and synthetic applications of lactam-derived enol phosphates[17] and triflates,[18] we envisaged that the gold(I)-catalyzed cyclization of *N*-Boc-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines **1** (Scheme 1), obtained by Sonogashira coupling of the above electrophiles

**Scheme 1**

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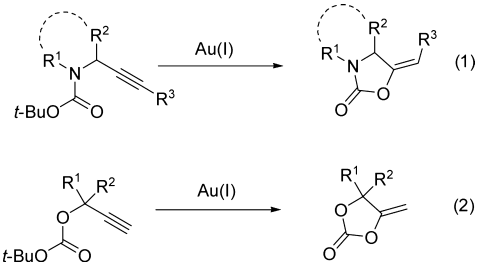
with various alkynes, should provide cyclic urethane intermediates **2**, which could then be easily converted into the target *E* or *Z* vinylogous amides **3**.

As in the similar Au(I)-catalyzed cycloisomerization of *N*-Boc-protected propargylamines to 1,3-oxazolidinones[19,20] (eq 1) as well as in the cyclization of propargyl carbonates[21] (eq 2),



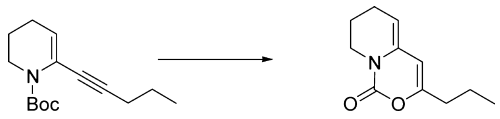

the *tert*-butyl group should be eliminated after carbonyl addition to the alkyne to produce an intermediate vinylgold species.[22] However, whereas in those cases the vinylgold moiety is exocyclic following a 5-*exo*-dig cyclization (with an exception in which a 2-ethynyl-*N*-Boc-pyrrolidine reacted to give a small amount of 6-*endo*-dig product),[19c] we envisaged that the larger bond angle at C6 (120° instead of 109.5°) in enyne **1** should instead force a 6-*endo* pathway, thus providing the six-membered cyclic urethane **2** after protodeauration. Related gold-catalyzed 6-*endo*-dig cyclizations have been observed previously in the case of 2-alkynylphenyl carbonyl derivatives, as in the formation of isocoumarins.[23]

## RESULTS AND DISCUSSION

In order to test our assumption and find the optimal reaction conditions, we first synthesized the simple carbamate **1a** ($R^1$ = H, $R^2$ = *n*Pr) as the model substrate. This was realized by converting *N*-Boc-protected *δ*-valerolactam **5** into the corresponding enol triflate **6a** by treatment with LiHMDS at −78 °C and subsequent trapping of the enolate with *N*-phenyltriflimide (Scheme 2). The enol triflate was not purified but was used directly in the next step, Sonogashira coupling with 1-pentyne, to give enyne **1a** in 71% yield.[24] This compound, as well as most of the other enynes **1** we prepared, proved quite labile when neat, as they started to decompose soon after the chromatographic purification on silica gel. Thus, they were stored in solution or immediately used after their preparation.[25]

The gold-catalyzed cyclization of **1a** was initially carried out in the presence of 2 mol % $Ph_3PAuOTf$ as the catalyst (Table 1) to examine the effect of the solvent and reaction temperature

**Table 1. Gold(I)-Catalyzed Cyclization of 6-Alkynyl-3,4-dihydro-2*H*-pyridine 1a**[a]



**1a** **2a**

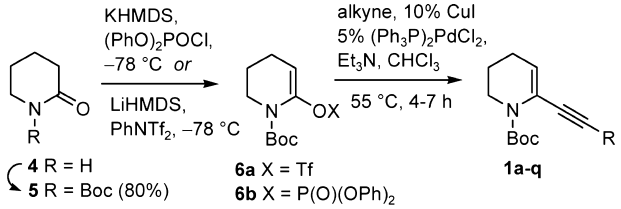
| entry | solvent | catalyst/additive | *T* (°C) | *t* (min) | conv. (%)[b] |
|---|---|---|---|---|---|
| 1 | DCM | 2% $Ph_3PAuOTf$ | 25 | 60 | 20 |
| 2 | DCE | 2% $Ph_3PAuOTf$ | 25 | 60 | 30 |
| 3 | $CH_3CN$ | 2% $Ph_3PAuOTf$ | 82 | 60 | 6 |
| 4 | THF | 2% $Ph_3PAuOTf$ | 67 | 60 | 15 |
| 5 | DME | 2% $Ph_3PAuOTf$ | 85 | 60 | 58 |
| 6 | DCE | 2% $Ph_3PAuOTf$ | 83 | 60 | 84 |
| 7 | toluene | 2% $Ph_3PAuOTf$ | 111 | 20 | >99 |
| 8 | toluene | 2% $Ph_3PAuBF_4$ | 111 | 60 | 9 |
| 9 | toluene | 2% $Ph_3PAuSbF_6$ | 111 | 60 | 69 |
| 10 | toluene | 2% $Ph_3PAuPF_6$ | 111 | 60 | 59 |
| 11 | toluene | – | 111 | 60 | 0 |
| 12 | toluene | 5% $Ph_3PAuCl$ | 111 | 60 | 0 |
| 13 | toluene | 5% AgOTf | 111 | 60 | 15 |
| 14 | toluene | 1% $Ph_3PAuOTf$ | 111 | 60 | 57 |
| 15 | toluene | 1% $Ph_3PAuOTf$/AcOH[c] | 111 | 15 | >99 |
| 16 | toluene | 0.5% $Ph_3PAuOTf$/AcOH[c] | 111 | 60 | 90 |
| 17 | toluene | AcOH[c] | 111 | 60 | 0 |

[a]Typical reaction conditions: a solution of **1a** (1 mmol) in the solvent (5 mL) was added to a solution of the catalyst in the solvent (5 mL), and the mixture was heated as reported. [b]Conversion measured by GLC. [c]2 equiv.

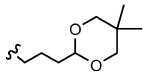
(entries 1−7). The catalyst was prepared by suspending the gold salt ($Ph_3PAuCl$) in a solvent and then adding AgOTf either as a solid or in a solution of the same solvent at a known concentration, causing the immediate precipitation of AgCl. The latter approach was more reproducible and therefore used for the evaluation of the scope of the reaction (vide infra). We were pleased to find that the reaction occurred in both dichloromethane (entry 1) and dichloroethane (entry 2), though slowly, with conversions into **2a** of 20 and 30% (by GLC), respectively, after 1 h at room temperature (after which time the reaction was stopped). Acetonitrile, THF, and DME were much poorer solvents, as the reaction did not proceed at all or the conversion was less than 9% (DME) after 1 h at room temperature. Even when the reactions were carried out in refluxing acetonitrile (81−82 °C; entry 3) and THF (65−67 °C; entry 4) the conversion into compound **2a** was very low, while that in DME (85 °C; entry 5) was barely acceptable (58%), whereas in boiling DCE (83 °C, entry 6) the reaction was almost complete (84%) in 1 h.

Eventually, when the reaction was performed in boiling toluene (110−111 °C; entry 7), we observed the complete conversion of **1a** into **2a** after just 20 min. In this case we tried to isolate **2a** by chromatography, but this cyclic carbamate was in our hand very prone to decomposition. In fact, we were

**Scheme 2**




**1a** R = *n*Pr (from **6a**, 71%)
**1b** R = *n*Bu (59%)
**1c** R = Ph (82%)
**1d** R = $C_6H_4$-*p*-OMe (71%)
**1e** R = *c*Pr (50%)
**1f** R = $CH_2CH_2Ph$ (77%)
**1g** R = $(CH_2)_2C_6H_4$-*p*OMe (79%)
**1h** R = $CH_2CH_2OH$ (83%)
**1i** R = $CH_2CH_2OTIPS$ (from **1h**, 82%)
**1j** R = $CH_2CH_2CH_2OH$ (62%)
**1k** R = $CH_2CH_2CH_2OBn$ (62%)
**1l** R = $CH_2CH_2CH_2OTHP$ (64%)
**1m** R = $CH_2(CH_2)_2CH_2OH$ (72%)
**1n** R = $(CH_2)_3CH_2OTIPS$ (from **1m**, 78%)
**1o** R = $CH_2(CH_2)_3CH_2OH$ (69%)
**1p** R = $CH_2(CH_2)_2CH_2CO_2Me$ (63%)

**1q** R =  (85%)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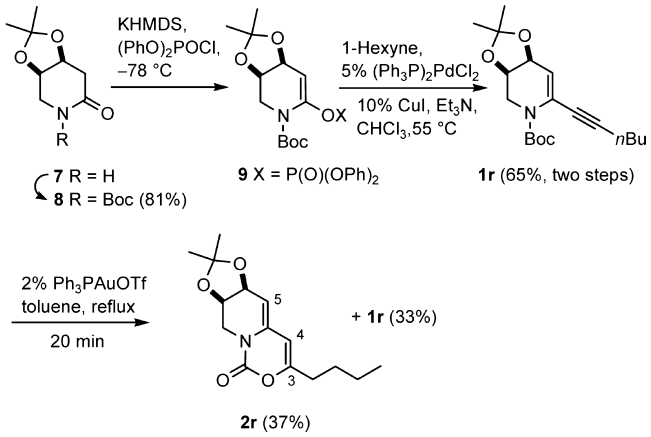
never able to keep neat **2a** for a long time, as quick degradation occurred within minutes. Besides the $Ph_3PAuOTf$ catalyst, we tried also the corresponding tetrafluoroborate (entry 8), hexafluoroantimonate (entry 9), and hexafluorophosphate (entry 10) gold complexes (2 mol %) in refluxing toluene, but all were less competent than $Ph_3PAuOTf$, with $Ph_3PAuSbF_6$ being the best one (69% conversion into **2a** after 1 h). Control experiments were carried out without the catalyst (entry 11), triflate source (entry 12), or gold source (entry 13). In the first two cases, we did not observe the formation of **2a** after 1 h in refluxing toluene. In the last case, a minimal amount of product (15% conversion) was formed in the presence of only a high loading (5%) of AgOTf, arguably because of the catalysis exerted by Ag(I).[26]

When we reduced the loading of $Ph_3PAuOTf$ catalyst to 1 mol % (Table 1, entry 14), the conversion was 57% after 1 h. However, the addition of 2 equiv of acetic acid as a proton source increased the reaction rate, and the conversion into **2a** was complete in just 15 min with 1 mol % catalyst (entry 15) and almost complete (90%) in 60 min with 0.5 mol % $Ph_3PAuOTf$ (entry 16).[27] No reaction at all occurred without catalyst in the presence of acetic acid (entry 17). Despite the lower catalyst amount required in the presence of AcOH, we envisaged that the presence of the latter could not be tolerated by a range of substrates under the reaction conditions, so we opted for a general procedure that uses 2 mol % catalyst without acetic acid in boiling toluene.

Despite its quick decomposition when neat, we were able to assign the structure of **2a** (and thus confirm our initial hypothesis about the reaction outcome) because in the $^1H$ NMR spectrum of **2a** the signal assigned to the vinylic proton (H4) resonates at 5.37 ppm as a singlet (in the 5-*exo*-dig product, it should be a triplet because of the $^3J$ coupling with the methylene hydrogens of the side chain). In one case, intermediate **2r** (prepared by Sonogashira coupling of enol phosphate **9** with 1-hexyne, as reported in Scheme 3) proved

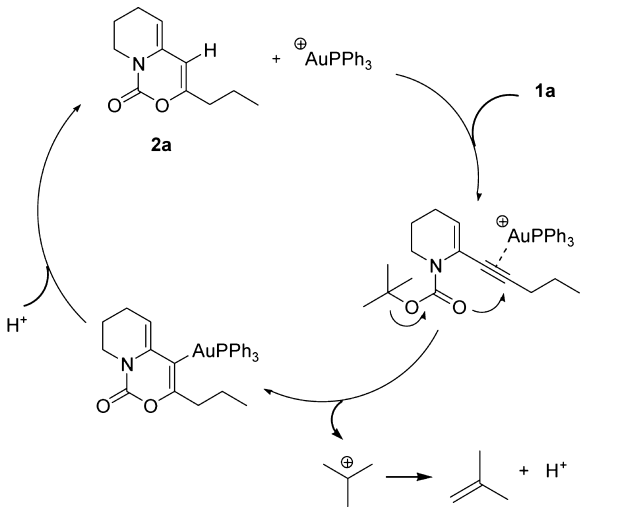
**Scheme 3**




instead more stable and could be purified by flash chromatography on silica gel.[28] Again, in its $^1H$ NMR spectrum, the vinylic proton H4 diagnostically resonates as a singlet at 5.43 ppm, whereas the other olefinic proton (H5) resonates as a doublet at about 4.65 ppm. In both **2a** and **2r**, the $^{13}C$ resonances for C4 as doublets at 99.2 and 99.3 ppm, respectively, are in accordance with the proposed structure of the intermediate.

A mechanism for the formation of cyclic urethane **2a** is depicted in Scheme 4. This is similar to that previously

**Scheme 4**




reported for the formation of 5-methylene-1,3-oxazolidinones from *N*-Boc-protected propargylamines,[19] with the main difference being the step involving oxyauration of the triple bond, which occurs in a 6-*endo* fashion to furnish a neutral *endo* vinylgold species with concurrent or subsequent *tert*-butyl fragmentation to give isobutene. Protodeauration would then provide cyclic urethane **2a** with the concomitant regeneration of the gold(I) catalyst. Compared with the 5-*exo*-dig processes leading to oxazolidinones,[19] the conversion of enyne **1a** into cyclic urethane **2a** requires higher temperatures and longer reaction times when acetic acid is not added. With 1 mol % catalyst ($Ph_3PAuNTf_2$ or $Ph_3PAuSbF_6$), the cyclization of an *N*-Boc-protected 2-alkynylpiperidine in which the side chain is on an $sp^3$ C atom quantitatively generates the corresponding 1,3-oxazolidinone after 1 h at room temperature,[19a] whereas in our case enyne **1a** requires boiling toluene for complete conversion in 20 min in the presence of 2 mol % catalyst. This could be due to greater difficulty of the nucleophilic attack by the carbonyl group at the activated alkyne because of the larger bond angle at C6.

Because of the intrinsic instability of compound **2a**, we decided to hydrolyze this carbamate to the corresponding vinylogous amide **3a** (Scheme 5) in the same reaction vessel after the gold-catalyzed reaction was complete (as monitored by TLC). Among the tested methods, those in which a base (KOH) and a cosolvent (*t*BuOH or MeOH) were added proved to be optimal. With *t*BuOH as the cosolvent and KOH as the base (6 equiv), the reaction was complete after 30 min at 85 °C, whereas with MeOH as the cosolvent and heating at 65 °C the reaction was, as expected, much slower, reaching completion in 2 h. Of the two possible isomers, only one was produced during the hydrolysis step. A NOESY experiment on compound **3a** (and then on all of the other vinylogous amides **3**) showed a correlation between the olefinic proton 1-H′ and the proton(s) on C3 of the ring, consistent with a *Z* geometry of the double bond. This could arise from thermodynamic factors, as the formation of the intramolecular N–H···O hydrogen bond should be favored, as already reported in other cases.[5,6]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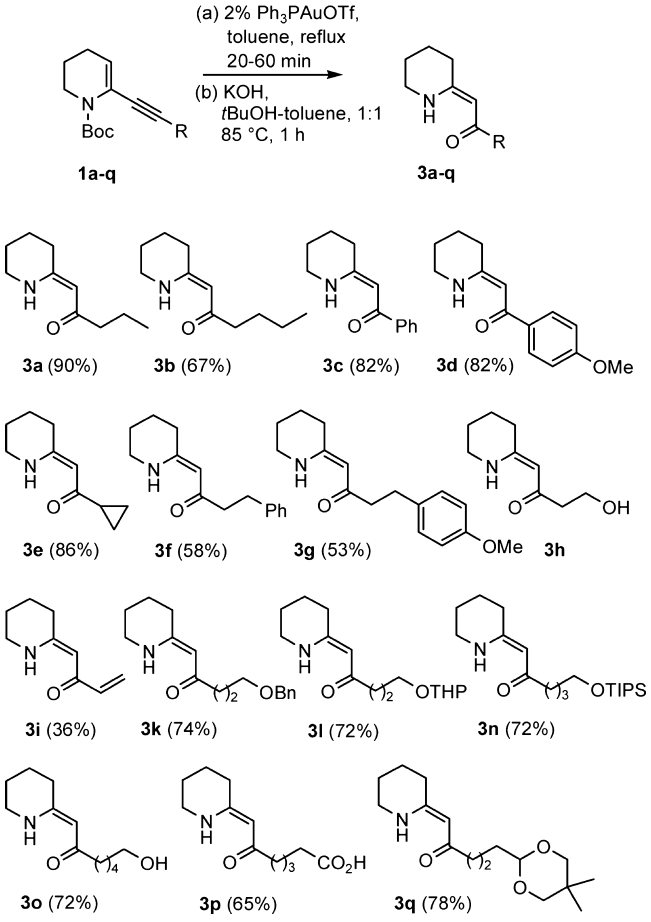
**Scheme 5**




Having assessed the general methodology for the conversion of lactams into vinylogous amides, we next explored the scope of the reaction by coupling lactam-derived enol phosphate **6b** (Scheme 2) to alkynes bearing differently substituted alkyl and aryl groups. Functional groups such as hydroxyl, carbonyl, and carboxyl were chosen, as these are generally present in the side chains of natural piperidines synthesized from vinylogous amides.

For the synthesis of compounds **1g**, **1k**, **1l**, **1p**, and **1q**, the corresponding alkynes were prepared as reported or according to standard procedures. Lactam-derived enol phosphates are generally more stable than the corresponding triflates and are prepared by trapping the corresponding enolates with diphenyl chlorophosphate. Whereas the Sonogashira coupling of lactam-derived enol triflates has been reported,[24] the same reaction with the corresponding enol phosphates (e.g., **6b**) has never been carried out. We found that the conditions we had reported for imide-derived enol phosphates [5% $(Ph_3P)_2PdCl_2$ and 10% CuI in $Et_3N$–$CHCl_3$ at 55 °C][17c] were suitable for successful conversion of **6b** into enynes **1**. In all cases, these enynes were unstable when neat and were either used immediately after a chromatographic purification or stored in the eluent. In some cases (**1e**, **1l**, and **1q**) it was not possible to obtain the enynes in pure form by chromatography, but this did not affect the reaction outcome and rate when they were subjected to the subsequent Au(I)-catalyzed reaction.

The gold(I)-catalyzed cyclization of enynes **1b**–**q** (Scheme 5) was carried out in the presence of 2 mol % catalyst in boiling toluene according to the general procedure, and the subsequent hydrolysis was carried out in situ by addition of KOH (6 equiv) and *t*-BuOH (1:1 ratio with toluene) and then heating at 85 °C. With enynes **1b**–**f** bearing no particular functionality on the side chain, the reaction occurred smoothly to provide vinylogous amides **3b**–**f** with *Z* geometry (as demonstrated by NOE studies) in generally good yields (58–86% over two steps) after chromatography.[29] Of these, vinylogous amide **3c** is of particular interest because it has recently been used to prepare a series of sedamine alkaloids.[9b] In contrast, with enyne **1h** bearing a $\beta$-hydroxy group, the gold-catalyzed cyclization occurred without any problem (as seen by TLC monitoring) but the subsequent hydrolysis step caused either the partial or complete elimination of water, providing the $\alpha,\beta$-unsaturated vinylogous amide **3i**.[30] This occurred also with substrate **1i** prepared by protecting the OH group of **1h** as the TIPS ether.

When instead the reaction was carried out with substrate **1j** (from 4-pentyn-1-ol), the gold-catalyzed cyclization did not occur at all. Even with 5% mol catalyst or in the presence of AcOH, we recovered the unaltered substrate after 1 h in boiling toluene. The same occurred with enyne **1m** derived from 5-hexyn-1-ol. The reason for the unsuitability of a $\gamma$- or $\delta$-hydroxy group as in substrates **1j** and **1m**, respectively, is unclear, but it is possible that an Au(I)-promoted cyclization onto C2′ involving the side-chain OH group takes place to form a vinylgold species in which protodeauration is prevented by coordination of gold to the Boc carbonyl group.[31] In fact, when the OH group was protected as either the benzyl ether (**1k**) or the THP ether (**1l**), the whole process took place smoothly, and vinylogous amides **3k** and **3l** were obtained in 74% and 72% yield, respectively, after chromatography. Similarly, when the reaction was carried out on *O*-TIPS-protected enyne **1n** (in this case obtained directly from **1m**), vinylogous amide **3n** was obtained in 72% yield after chromatography. Interestingly, and reasonably because of the less-favored formation of a seven-membered ring in the competing pathway, the Au(I)-catalyzed reaction of enyne **1o** obtained from 6-heptyn-1-ol did occur, although it was much slower than usual, requiring 2.5 h to reach a complete conversion into **3o** with 6 mol % catalyst. In any case, the above results suggest that protection of the OH group in the side chain is either necessary or preferable.

The ester group of enyne **1p** was compatible with the conditions for the Au(I)-catalyzed reaction, but as expected it was converted into carboxylate in the subsequent basic step. However, carboxylic acid **3p** was obtained in good yield (65%) after an acidic workup and subsequent chromatography. Because aldehydes do not generally tolerate strongly basic conditions, the carbonyl group has to be protected, such as in enyne **1q** prepared from 5,5-dimethyl-2-pent-4-ynyl-[1,3]-dioxane. The cyclic acetal moiety of **1q**, like the tetrahydropyranyl ether in **1l**, proved to be compatible with the reaction conditions, and the sequence provided the corresponding vinylogous amide **3q** in 78% yield.

Having assessed the scope of the reaction, a specific substrate (**1g**) was prepared and subjected to the usual sequence, which provided the corresponding vinylogous amide **3g** (Scheme 5) in 53% yield. We used this as an intermediate for the first synthesis of compound **11**, a natural product isolated as a racemate from the leaves of the Chinese coast mangrove *Sonneratia hainanensis*[32] (Scheme 6). Thus, reduction of the double bond was carried out by catalytic hydrogenation,[9b] providing compound **11** in 73% yield and with $^1H$ and $^{13}C$ NMR spectra identical to those reported for the natural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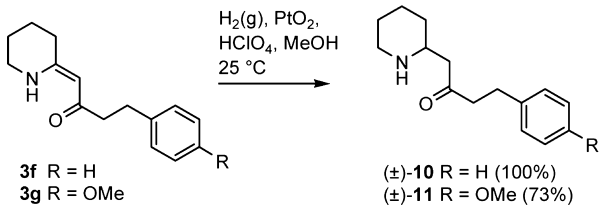
**Scheme 6**




compound.[32] Its unsubstituted analogue **10** was also prepared according to the same route.

## CONCLUSION

We have demonstrated that the gold(I)-catalyzed cyclization of *N*-Boc-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines allows for a facile synthesis of vinylogous amides, which are useful intermediates in the synthesis of natural compounds. The substrates were prepared by Sonogashira coupling of lactam-derived enol triflates and phosphates, which provided the corresponding enynes in good yields. The subsequent Au(I)-catalyzed reaction was carried out with $Ph_3PAuOTf$ as the catalyst and proceeds via a 6-*endo*-dig cyclization to form a vinylgold species that after protodeauration generates a cyclic carbamate intermediate. The intermediate was in most cases not isolated, but the addition of KOH and *t*-BuOH to the reaction mixture at 85 °C rapidly and quantitatively delivered the target vinylogous amide. Although in one particular case the strongly basic conditions caused elimination of water from the side chain, the preparation of a series of products with different substituents and protecting groups on the side chain showed that this methodology has a wide scope and is well-suited for the preparation of natural products embedding a 2-substituted piperidine moiety. Accordingly, the first synthesis of a natural compound from *Sonneratia hainanensis* was accomplished by this approach.

## 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 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 at 50.33 or 100.4 MHz, both in $CDCl_3$ solution. The solvent reference line was set at 7.26 ppm. 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 an Ion Trap LC/MS system with an electrospray ionization (ESI) interface in the positive ion mode. Pent-4-ynyloxymethylbenzene,[33] 1-but-3-ynyl-4-methoxybenzene,[34] and 6-heptyn-1-ol[35] were prepared as reported. Compounds **6a**[18g] and **6b**[36] are known.

**6-(Pent-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1a).** Triflate **6a** (1 mmol) was dissolved in anhydrous THF (0.1 M) under a nitrogen atmosphere. LiCl (1 mmol), diisopropylamine (4 mmol), $Pd(OAc)_2$ (0.05 mmol), $Ph_3P$ (0.1 mmol), CuI (0.1 mmol), and the alkyne (1.5 mmol) were then added, and the resulting mixture was left under stirring at room temperature overnight. Saturated aqueous $NH_4Cl$ (10 mL) was added, and the product was extracted with $Et_2O$ (3 × 10 mL); the combined organic extracts were washed once with brine (15 mL) and dried over anhydrous $K_2CO_3$. After filtration and evaporation of the solvent, crude enyne **1a** was purified by flash chromatography (eluent: petroleum ether/EtOAc, 9:1 containing 1% $Et_3N$; $R_f$ = 0.25) and stored at 4 °C as a 0.1 M solution in the eluent until use.

Colorless oil (177 mg, 71%). $^1$H NMR (200 MHz) $\delta$: 5.41 (t, $J$ = 4.1 Hz, 1H), 3.53−3.39 (m, 2H), 2.23 (t, $J$ = 7.0 Hz, 2H), 2.12−2.04 (m, 2H), 1.76−1.74 (m, 2H), 1.56−1.44 (m, 2H), 1.43 (s, 9H), 0.93 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (50.33 MHz) $\delta$: 153.0 (s), 122.5 (s), 120.9 (d), 87.8 (s), 80.5 (s), 77.7 (s), 43.4 (t), 28.2 (q, 3C), 23.5 (t), 22.6 (t), 21.9 (t), 21.2 (t), 13.5 (q). MS (EI) $m/z$ (%): 249 ([M]$^+$, 55), 193 (45), 148 (90), 121 (85), 57 (100).

**Sonogashira Coupling (General Procedure from Phosphate 6b).** Phosphate **6b** (1 mmol) 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 second portions of alkyne (0.5 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 the mixture was cooled at r.t., water (12 mL) was added, and the product was extracted with $Et_2O$ (3 × 12 mL); the combined organic extracts were dried over anhydrous $K_2CO_3$. After filtration and evaporation of the solvent, crude enyne **1** 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)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1b**).* Colorless oil (155 mg, 59%). $R_f$ = 0.68 (*n*-hexane/EtOAc, 3:1). FCC eluent: *n*-hexane/EtOAc, 20:1 + 1% $Et_3N$. $^1$H NMR (400 MHz) $\delta$: 5.45 (t, $J$ = 4.1 Hz, 1H), 3.55−3.52 (m, 2H), 2.30 (t, $J$ = 6.8 Hz, 2H), 2.15−2.10 (m, 2H), 1.78−1.72 (m, 2H), 1.54−1.38 (m, 4H), 1.48 (s, 9H), 0.90 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (100.4 MHz) $\delta$: 153.2 (s), 122.6 (s), 121.1 (d), 88.1 (s), 80.7 (s), 77.6 (s), 43.5 (t), 30.7 (t), 28.3 (q, 3C), 23.6 (t), 22.7 (t), 22.0 (t), 19.1 (t), 13.6 (q). MS (ESI) $m/z$ (%): 549 ([2M + Na]$^+$, 25), 286 ([M + Na]$^+$, 19).

*6-Phenylethynyl-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1c**).* Pale-yellow solid (232 mg, 82%). $R_f$ = 0.35 (petroleum ether/EtOAc, 95:5). $^1$H NMR (200 MHz) $\delta$: 7.38−7.35 (m, 2H), 7.25−7.20 (m, 3H), 5.60 (t, $J$ = 4.0 Hz, 1H), 3.59−3.54 (m, 2H), 2.13−2.04 (m, 2H), 1.75−1.63 (m, 2H), 1.43 (s, 9H). $^{13}$C NMR (50.33 MHz) $\delta$: 153.0 (s), 131.1 (d, 2C), 128.1 (d, 2C), 127.8 (d), 123.2 (s), 122.5 (s), 122.2 (d), 87.2 (s), 86.8 (s), 80.9 (s), 43.2 (t), 28.1 (q, 3C), 23.6 (t), 22.5 (t). MS (EI) $m/z$ (%): 283, ([M]$^+$, 5), 227 (75), 182 (85), 127 (25), 57 (100).

*6-(4-Methoxyphenylethynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1d**).* White solid (223 mg, 71%). $R_f$ = 0.32 (petroleum ether/EtOAc, 95:5). $^1$H NMR (200 MHz) $\delta$: 7.30 (d, $J$ = 9.0 Hz, 2H), 6.77 (d, $J$ = 9.0 Hz, 2H), 5.56 (t, $J$ = 4.0 Hz, 1H), 3.71 (s, 3H), 3.57−3.52 (m, 2H), 2.19−2.10 (m, 2H), 1.81−1.68 (m, 2H), 1.42 (s, 9H). $^{13}$C NMR (50.33 MHz) $\delta$: 159.2 (s), 153.1 (s), 132.5 (d, 2C), 122.3 (s), 121.9 (d), 115.3 (s), 113.8 (d, 2C), 87.1 (s), 85.2 (s), 80.1 (s), 55.0 (q), 43.2 (t), 28.1 (q, 3C), 23.6 (t), 22.5 (t). MS (EI) $m/z$ (%): 313 ([M]$^+$, 15), 257 (100), 212 (80), 198 (55), 57 (35).

*6-Cyclopropylethynyl-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1e**).* Pale-yellow oil (124 mg, 50%, 81% purity by $^1$H NMR). $R_f$ = 0.45 (petroleum ether/EtOAc, 9:1). $^1$H NMR (200 MHz) $\delta$: 5.39 (t, $J$ = 4.0 Hz, 1H), 3.49−3.44 (m, 2H), 2.11−2.02 (m, 2H), 1.75−1.63 (m, 2H), 1.44 (s, 9H), 1.43−1.42 (m, 1H), 0.76−0.63 (m, 4H). $^{13}$C NMR (50.33 MHz) $\delta$: 153.0 (s), 122.3 (s), 121.3 (d), 90.8 (s), 80.7 (s), 72.8 (s), 43.2 (t), 28.1 (q, 3C), 23.4 (t), 22.5 (t), 8.0 (t, 2C), 0.8 (d). MS (EI) $m/z$ (%): 247 ([M]$^+$, 5), 191 (100), 146 (75), 132 (20), 57 (45).

*6-(4-Phenylbut-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1f**).* Pale-yellow oil (240 mg, 77%). $R_f$ = 0.28 (*n*-hexane/EtOAc, 25:1 + 1% $Et_3N$). $^1$H NMR (400 MHz) $\delta$: 7.31−7.18 (m, 5H), 5.46 (t, $J$ = 4.1 Hz, 1H), 3.57−3.54 (m, 2H), 2.87 (t, $J$ = 7.8 Hz, 2H), 2.60 (t, $J$ = 7.8 Hz, 2H), 2.17−2.12 (m, 2H), 1.80−1.74 (m, 2H), 1.49 (s, 9H). $^{13}$C NMR (100.4 MHz) $\delta$: 153.1 (s), 140.7 (s), 128.4 (d, 2C), 128.3 (d, 2C), 126.2 (d), 122.5 (s), 121.4 (d), 87.3 (s), 80.7 (s), 78.3 (s), 43.5 (t), 35.1 (t), 28.3 (q, 3C), 23.6 (t), 22.7 (t), 21.6 (t). MS (ESI) $m/z$ (%): 645 ([2M + Na]$^+$, 22), 324 ([M + Na]$^+$, 100), 312 ([M + H]$^+$, 9).

*6-[4-(4-Methoxyphenyl)but-1-ynyl]-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1g**).* Pale-yellow oil (270 mg, 79%, 96% purity by $^1$H NMR). $R_f$ = 0.27 (*n*-hexane/EtOAc, 14:1 + 1% $Et_3N$). $^1$H NMR (400 MHz) $\delta$: 7.14 (d, $J$ = 8.6 Hz, 2H), 6.83 (d, $J$ = 8.6 Hz, 2H), 5.46 (t, $J$ = 3.9 Hz, 1H), 3.79 (s, 3H), 3.57−3.53 (m, 2H), 2.81 (t, $J$ = 7.4 Hz, 2H), 2.56 (t, $J$ = 7.4 Hz, 2H), 2.16−2.12 (m,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2H), 1.79−1.73 (m, 2H), 1.49 (s, 9H). $^{13}$C NMR (100.4 MHz) $\delta$: 158.1 (s), 153.1 (s), 132.9 (s), 129.4 (d, 2C), 122.5 (s), 121.4 (d), 113.8 (d, 2C), 87.4 (s), 80.7 (s), 78.3 (s), 55.2 (q), 43.5 (t), 34.2 (t), 28.3 (q, 3C), 23.6 (t), 22.7 (t), 21.9 (t). MS (ESI) $m/z$ (%): 705 ([2M + Na]$^+$, 37), 364 ([M + Na]$^+$, 100), 342 ([M + H]$^+$, 7).

*6-(4-Hydroxybut-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1h**).* Pale-yellow oil (208 mg, 83%). $R_f$ = 0.24 (*n*-hexane/EtOAc, 3:1 + 1% $Et_3N$). $^1$H NMR (400 MHz) $\delta$: 5.48 (t, $J$ = 4.1 Hz, 1H), 3.73 (t, $J$ = 5.7 Hz, 2H), 3.56−3.53 (m, 2H), 2.53 (t, $J$ = 5.7 Hz, 2H), 2.15−2.10 (m, 2H), 1.79−1.75 (m, 2H), 1.47 (s, 9H). $^{13}$C NMR (100.4 MHz) $\delta$: 152.7 (s), 121.8 (s), 120.7 (d), 86.1 (s), 81.0 (s), 79.8 (s), 60.9 (t), 44.0 (t), 28.3 (q, 3C), 23.9 (t), 23.3 (t), 22.6 (t). MS (EI) $m/z$ (%): 251 ([M]$^+$, 7), 194 (23), 150 (32), 125 (15), 57 (45).

*6-(4-Triisopropylsilanoxybut-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1i**).* Imidazole (35 mg, 0.52 mmol) and triisopropylsilyl chloride (40 $\mu$L, 0.19 mmol) were added under a nitrogen atmosphere to a solution of alcohol **1h** (44 mg, 0.17 mmol) in anhydrous DMF (525 $\mu$L). The resulting mixture was heated at 40 °C for 1 h. After the mixture was cooled at room temperature, water was added (6 mL), and the product was extracted with $Et_2O$ (5 × 6 mL). The combined organic extracts were dried over anhydrous $K_2CO_3$. After filtration and evaporation of the solvent, crude **1i** was obtained and purified by flash chromatography (eluent: *n*-hexane/EtOAc, 25:1 + 1% $Et_3N$; $R_f$ = 0.25), affording pure **1i** (58 mg, 82%) as a colorless oil.

$^1$H NMR (400 MHz) $\delta$: 5.47 (t, $J$ = 4.1 Hz, 1H), 3.82 (t, $J$ = 7.4 Hz, 2H), 3.55−3.52 (m, 2H), 2.56 (t, $J$ = 7.4 Hz, 2H), 2.15−2.10 (m, 2H), 1.79−1.73 (m, 2H), 1.49 (s, 9H), 1.05 (m, 21H). $^{13}$C NMR (100.4 MHz) $\delta$: 153.2 (s), 122.4 (s), 121.6 (d), 84.6 (s), 80.8 (s), 78.8 (s), 62.1 (t), 43.4 (t), 28.3 (q, 3C), 23.8 (t), 23.6 (t), 22.7 (t), 17.9 (q, 6C), 11.9 (d, 3C). MS (ESI) $m/z$ (%): 430 ([M + Na]$^+$, 100).

*6-(5-Hydroxypent-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1j**).* Pale-yellow oil (165 mg, 62%). $R_f$ = 0.24 (*n*-hexane/EtOAc, 2:1 + 1% $Et_3N$). $^1$H NMR (400 MHz) $\delta$: 5.47 (t, $J$ = 4.1 Hz, 1H), 3.76 (t, $J$ = 6.1 Hz, 2H), 3.55−3.52 (m, 2H), 2.45 (t, $J$ = 6.8 Hz, 2H), 2.15−2.10 (m, 2H), 1.81−1.72 (m, 4H), 1.48 (s, 9H). $^{13}$C NMR (100.4 MHz) $\delta$: 152.9 (s), 122.3 (s), 121.4 (d), 87.5 (s), 80.8 (s), 78.2 (s), 61.7 (t), 43.7 (t), 31.0 (t), 28.3 (q, 3C), 23.5 (t), 22.7 (t), 16.2 (t). MS (ESI) $m/z$ (%): 553 ([2M + Na]$^+$, 62), 288 ([M + Na]$^+$, 100).

*6-(5-Benzyloxypent-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1k**).* Colorless oil (220 mg, 62%, 75% purity by $^1$H NMR). $R_f$ = 0.82 (petroleum ether/EtOAc, 9:1). $^1$H NMR (200 MHz) $\delta$: 7.41−7.26 (m, 5H), 5.44 (t, $J$ = 4.1 Hz, 1H), 4.52 (s, 2H), 3.59 (t, $J$ = 6.1 Hz, 2H), 3.58−3.52 (m, 2H), 2.45 (t, $J$ = 7.2 Hz, 2H), 2.20−2.08 (m, 2H), 1.93−1.72 (m, 4H), 1.50 (s, 9H). $^{13}$C NMR (50.33 MHz) $\delta$: 152.9 (s), 138.3 (s), 128.2 (d, 2C), 127.4 (d, 2C), 127.1 (d), 122.3 (s), 121.4 (d), 87.4 (s), 80.7 (s), 77.9 (s), 72.8 (t), 68.8 (t), 43.6 (t), 28.8 (t), 28.3 (q, 3C), 23.6 (t), 22.7 (t), 16.2 (t). MS (EI) $m/z$ (%): 355 ([M]$^+$, 5), 298 (30), 254 (40), 121 (100), 91 (50), 57 (45).

*6-[5-(Tetrahydropyran-2-yloxy)pent-1-ynyl]-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1l**).* Colorless oil (223 mg, 64%, 71% purity by $^1$H NMR). $R_f$ = 0.75 (petroleum ether/EtOAc, 4:1). $^1$H NMR (200 MHz) $\delta$: 5.47 (t, $J$ = 4.1 Hz, 1H), 4.55−4.30 (m, 1H), 3.72−3.65 (m, 2H), 3.55−3.52 (m, 4H, 2-H), 2.42 (t, $J$ = 6.8 Hz, 2H), 2.35−2.30 (m, 2H), 1.80−1.40 (m, 10H), 1.48 (s, 9H). $^{13}$C NMR (50.33 MHz) $\delta$: 154.0 (s), 123.3 (s), 121.2 (d), 99.6 (d), 87.5 (s), 81.4 (s), 80.5 (s), 65.8 (t), 62.0 (d), 43.5 (t), 30.5 (t), 28.6 (t), 28.1 (q, 3C), 25.3 (t), 23.4 (t), 22.5 (t), 19.6 (t), 19.3 (t). MS (EI) $m/z$ (%): 349 ([M]$^+$, 1), 165 (100), 121 (73), 57 (85).

*6-(6-Hydroxyhex-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1m**).* Colorless oil (201 mg, 72%). $R_f$ = 0.38 (*n*-hexane/EtOAc, 1:1 + 1% $Et_3N$). $^1$H NMR (400 MHz) $\delta$: 5.46 (t, $J$ = 4.1 Hz, 1H), 3.67 (t, $J$ = 6.1 Hz, 2H), 3.55−3.51 (m, 2H), 2.36 (t, $J$ = 6.8 Hz, 2H), 2.15−2.10 (m, 2H), 1.78−1.73 (m, 2H), 1.72−1.60 (m, 4H), 1.48 (s, 9H). $^{13}$C NMR (100.4 MHz) $\delta$: 153.0 (s), 122.4 (s), 121.3 (d), 87.9 (s), 80.7 (s), 78.0 (s), 62.2 (t), 43.6 (t), 31.8 (t), 28.3 (q, 3C), 24.7 (t), 23.5 (t), 22.7 (t), 19.1 (t). MS (ESI) $m/z$ (%): 581 ([2M + Na]$^+$, 47), 302 ([M + Na]$^+$, 100).

*6-(6-Triisopropylsilanoxyhex-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1n**).* Compound **1n** was prepared as reported for **1i** starting from compound **1m** (75 mg, 0.27 mmol).

Colorless oil (90 mg, 78%). $R_f$ = 0.27 (*n*-hexane/EtOAc, 20:1 + 1% $Et_3N$). $^1$H NMR (400 MHz) $\delta$: 5.46 (t, $J$ = 4.1 Hz, 1H), 3.70 (t, $J$ = 5.9 Hz, 2H), 3.56−3.53 (m, 2H), 2.34 (t, $J$ = 6.6 Hz, 2H), 2.16−2.11 (m, 2H), 1.79−1.73 (m, 2H), 1.66−1.61 (m, 4H), 1.49 (s, 9H), 1.06−1.03 (m, 21H). $^{13}$C NMR (100.4 MHz) $\delta$: 153.2 (s), 122.6 (s), 121.2 (d), 88.0 (s), 80.7 (s), 77.8 (s), 62.8 (t), 43.5 (t), 32.3 (t), 28.3 (q, 3C), 25.2 (t), 23.6 (t), 22.8 (t), 19.3 (t), 18.0 (q, 6C), 12.0 (d, 3C). MS (ESI) $m/z$ (%): 893 ([2M + Na]$^+$, 10), 458 ([M + Na]$^+$, 100).

*6-(7-Hydroxyhept-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1o**).* Pale-yellow oil (202 mg, 69%). $R_f$ = 0.29 (*n*-hexane/EtOAc, 2:1 + 1% $Et_3N$). $^1$H NMR (400 MHz) $\delta$: 5.44 (t, $J$ = 3.9 Hz, 1H), 3.61 (t, $J$ = 6.4 Hz, 2H), 3.53−3.49 (m, 2H), 2.30 (t, $J$ = 6.6 Hz, 2H), 2.14−2.08 (m, 2H), 1.90 (br s, 1H), 1.76−1.70 (m, 2H), 1.59−1.50 (m, 4H), 1.49−1.42 (m, 2H), 1.46 (s, 9H). $^{13}$C NMR (100.4 MHz) $\delta$: 153.1 (s), 122.4 (s), 121.3 (d), 87.9 (s), 80.7 (s), 77.7 (s), 62.5 (t), 43.5 (t), 32.1 (t), 28.2 (q, 3C), 24.9 (t, 2C), 23.4 (t), 22.7 (t), 19.3 (t). MS (ESI) $m/z$ (%): 609 ([2M + Na]$^+$, 52), 316 ([M + Na]$^+$, 100).

*6-(6-Methoxycarbonylhex-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1p**).* Pale-yellow oil (202 mg, 63%). $R_f$ = 0.30 (*n*-hexane/EtOAc, 10:1 + 1% $Et_3N$). $^1$H NMR (400 MHz) $\delta$: 5.46 (t, $J$ = 3.9 Hz, 1H), 3.66 (s, 3H), 3.55−3.52 (m, 2H), 2.35−2.25 (m, 4H), 2.15−2.10 (m, 2H), 1.79−1.70 (m, 4H), 1.61−1.53 (m, 2H), 1.48 (s, 9H). $^{13}$C NMR (100.4 MHz) $\delta$: 173.8 (s), 153.1 (s), 122.5 (s), 121.4 (d), 87.4 (s), 80.7 (s), 78.1 (s), 51.5 (q), 43.5 (t), 33.6 (t), 28.3 (q, 3C), 28.0 (t), 24.2 (t), 23.6 (t), 22.7 (t), 19.1 (t). MS (ESI) $m/z$ (%): 344 ([M + Na]$^+$, 100).

*6-[6-(5,5-Dimethyl-[1,3]dioxan-2-yl)hex-1-ynyl]-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1q**).* Pale-yellow oil (309 mg, 85%, 93% purity by $^1$H NMR). $R_f$ = 0.64 (petroleum ether/EtOAc, 4:1 + 1% $Et_3N$). $^1$H NMR (200 MHz) $\delta$: 5.44 (t, $J$ = 4.0 Hz, 1H), 4.45−4.39 (m, 1H), 3.60−3.48 (m, 4H), 3.44−3.35 (m, 2H), 2.33 (t, $J$ = 6.8 Hz, 2H), 2.18−2.07 (m, 2H), 1.83−1.63 (m, 6H), 1.48 (s, 9H), 1.16 (s, 3H), 0.69 (s, 3H). $^{13}$C NMR (50.33 MHz) $\delta$: 153.1 (s), 122.5 (s), 121.3 (d), 101.7 (d), 87.6 (s), 80.7 (s), 78.0 (s), 77.2 (t, 2C), 43.4 (t), 33.9 (s), 30.1 (t), 28.3 (q, 3C), 23.6 (t), 23.0 (t), 22.7 (t), 21.8 (q, 2C), 19.2 (t). MS (EI) $m/z$ (%): 363 ([M]$^+$, 2), 307 (5), 178 (100), 141 (60), 121 (55), 57 (41).

*(±)-4,5-O-Isopropylidene-4,5-dihydroxy-5,6-dihydro-2-(hex-1-ynyl)-4H-pyridine-1-carboxylic Acid tert-Butyl Ester (**1r**).* Pale-yellow oil (218 mg, 65%). $R_f$ = 0.06 (*n*-hexane/EtOAc, 20:1 + 1% $Et_3N$). $^1$H NMR (400 MHz) $\delta$: 5.61 (d, $J$ = 3.9 Hz, 1H), 4.46 (dd, $J$ = 6.2, 2.3 Hz, 1H), 4.21−4.16 (m, 1H), 3.89 (dd, $J$ = 12.9, 4.1 Hz, 1H), 3.15 (dd, $J$ = 12.9, 8.4 Hz, 1H), 2.31 (t, $J$ = 7.0 Hz, 2H), 1.54−1.46 (m, 2H), 1.47 (s, 9H), 1.45−1.38 (m, 2H), 1.42 (s, 3H), 1.34 (s, 3H), 0.89 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (100.4 MHz) $\delta$: 152.7 (s), 126.2 (s), 118.1 (d), 108.9 (s), 91.1 (s), 81.3 (s), 76.3 (s), 72.5 (d), 69.9 (d), 46.0 (t), 30.4 (t), 28.1 (q, 3C), 27.8 (q), 25.6 (q), 21.9 (t), 19.0 (t), 13.5 (t). MS (ESI) $m/z$ (%): 693 ([2M + Na]$^+$, 19), 358 ([M + Na]$^+$, 100).

**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). A 0.2 M AgOTf solution and a 4 mM $Ph_3PAuCl$ solution, both in anhydrous toluene, were prepared. The AgOTf solution (100 $\mu$L, 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 **1** (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, usually 30 min). After the mixture was cooled at 85 °C (external) and diluted with *tert*-butyl alcohol (10 mL), powdered KOH (6 mmol) was added. The mixture was heated at 85 °C until completion (TLC, usually 1 h) and then cooled at r.t. Water (15 mL) was then added, and the product was extracted with EtOAc (3 × 10 mL); the combined organic extracts were washed once


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with brine (15 mL) and dried over anhydrous $Na_2SO_4$. After filtration and evaporation of the solvent, crude vinylogous amide **3** was purified by flash chromatography to obtain the pure compound.

Intermediate **2a** was isolated by filtration of the mixture resulting from the gold-catalyzed rearrangement over a Celite pad. The solvent was removed under vacuum, and the residue was analyzed without any purification.

Intermediate **2r**, isolated as reported for **2a**, was stable enough to be purified by flash chromatography (eluent: *n*-hexane/EtOAc, 10:1 + 1% $Et_3N$; $R_f$ = 0.09), and the pure **2r** was characterized.

*3-Propyl-7,8-dihydro-6H-pyrido[1,2-c][1,3]oxazin-1-one (**2a**).* Yellow oil (191 mg, 99%). $^1$H NMR (200 MHz) $\delta$: 5.37 (s, 1H), 4.63 (t, $J$ = 4.2 Hz, 1H), 3.80−3.74 (m, 2H), 2.27−2.08 (m, 2H), 1.93−1.84 (m, 2H), 1.71−1.52 (m, 4H), 0.99 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (50.33 MHz) $\delta$: 151.1 (s), 148.6 (s), 132.0 (s), 100.4 (d), 99.2 (d), 42.4 (t), 33.8 (t), 21.2 (t), 20.5 (t), 19.1 (t), 13.2 (q).

*(±)-6,7-O-Isopropylidene-6,7-dihydroxy-3-butyl-7,8-dihydro-6H-pyrido[1,2-c][1,3]oxazin-1-one (**2r**).* Colorless oil (103 mg, 37%). $^1$H NMR (400 MHz) $\delta$: 5.43 (s, 1H), 4.66 (d, $J$ = 4.1 Hz, 1H), 4.55 (t, $J$ = 4.9 Hz, 1H), 4.27−4.23 (m, 1H), 3.98 (dd, $J$ = 13.5, 9.2 Hz, 1H), 3.59 (dd, $J$ = 13.5, 7.4 Hz, 1H), 2.21 (t, $J$ = 7.2 Hz, 2H), 1.57−1.52 (m, 2H), 1.45 (s, 3H), 1.38 (s, 3H), 1.38−1.30 (m, 2H), 0.91 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (100.4 MHz) $\delta$: 154.6 (s), 148.4 (s), 134.1 (s), 109.2 (s), 99.3 (d), 96.3 (d), 70.1 (d), 69.0 (d), 42.6 (t), 31.8 (t), 28.6 (t), 27.9 (q), 26.3 (q), 22.0 (t), 13.7 (q). MS (ESI) $m/z$ (%): 581 ([2M + Na]$^+$, 32), 302 ([M + Na]$^+$, 100).

*(Z)-1-Piperidin-2-ylidene-pentan-2-one (**3a**).*[12c] Pale-yellow oil (151 mg, 90%). $R_f$ = 0.15 (petroleum ether/EtOAc, 4:1). $^1$H NMR (400 MHz) $\delta$: 11.1 (br s, 1H), 4.86 (s, 1H), 3.31 (td, $J$ = 5.9, 1.8 Hz, 2H), 2.35 (t, $J$ = 6.4 Hz, 2H), 2.19 (t, $J$ = 7.4 Hz, 2H), 1.81−1.75 (m, 2H), 1.73−1.65 (m, 2H), 1.64−1.55 (m, 2H), 0.92 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (50.33 MHz) $\delta$: 197.1 (s), 163.9 (s), 92.8 (d), 43.7 (t), 40.7 (t), 28.3 (t), 22.1 (t), 19.6 (t), 19.2 (t), 13.9 (q). MS (ESI) $m/z$ (%): 357 ([2M + Na]$^+$, 100), 190 ([M + Na]$^+$, 18), 168 ([M + H]$^+$, 17). Anal. Calcd for $C_{10}H_{17}NO$ (167.25): C, 71.81; H, 10.25; N, 8.37. Found: C, 71.45, H, 10.32, N 8.17.

*(Z)-1-Piperidin-2-ylidene-hexan-2-one (**3b**).* Pale-yellow oil (121 mg, 67%). $R_f$ = 0.16 (*n*-hexane/EtOAc, 3:1). $^1$H NMR (400 MHz) $\delta$: 11.1 (br s, 1H), 4.86 (s, 1H), 3.31 (td, $J$ = 6.1, 2.3 Hz, 2H), 2.35 (t, $J$ = 6.4 Hz, 2H), 2.21−2.17 (m, 2H), 1.81−1.75 (m, 2H), 1.73−1.66 (m, 2H), 1.59−1.51 (m, 2H), 1.37−1.27 (m, 2H), 0.89 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (100.4 MHz) $\delta$: 197.5 (s), 164.0 (s), 92.9 (d), 41.7 (t), 40.9 (t), 28.6 (t), 28.4 (t), 22.7 (t), 22.3 (t), 19.3 (t), 13.9 (q). MS (ESI) $m/z$ (%): 182 ([M + H]$^+$, 100). Anal. Calcd for $C_{11}H_{19}NO\cdot{}^1/_{10}H_2O$ (183.07): C, 72.17; H, 10.57; N, 7.65. Found: C, 72.09; H, 10.90; N, 7.58.

*(Z)-2-Phenyl-1-piperidin-2-ylidene-ethanone (**3c**).*[9b,12c,13] Yellow solid (165 mg, 82%). $R_f$ = 0.18 (*n*-hexane/EtOAc, 3:1). Mp 57.6−58.2 °C. $^1$H NMR (400 MHz) $\delta$: 11.7 (br s, 1H), 7.86−7.82 (m, 2H), 7.41−7.35 (m, 3H), 5.57 (s, 1H), 3.41 (td, $J$ = 5.9, 2.3 Hz, 2H), 2.51 (t, $J$ = 6.4 Hz, 2H), 1.87−1.81 (m, 2H), 1.80−1.73 (m, 2H). $^{13}$C NMR (100.4 MHz) $\delta$: 187.0 (s), 165.8 (s), 140.7 (s), 130.1 (d), 128.1 (d, 2C), 126.7 (d, 2C), 90.4 (d), 41.1 (t), 28.9 (t), 22.2 (t), 19.3 (t). MS (ESI) $m/z$ (%): 425 ([2M + Na]$^+$, 100), 224 ([M + Na]$^+$, 10), 202 ([M + H]$^+$, 12). Anal. Calcd for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.40, H, 7.54, N 6.58.

*(Z)-2-(4-Methoxyphenyl)-1-piperidin-2-ylidene-ethanone (**3d**).* Yellow solid (190 mg, 82%). $R_f$ = 0.20 (*n*-hexane/EtOAc, 2:1). Mp 230 °C (dec.). $^1$H NMR (400 MHz) $\delta$: 11.6 (br s, 1H), 7.82 (d, $J$ = 8.8 Hz, 2H), 6.88 (d, $J$ = 8.8 Hz, 2H), 5.53 (s, 1H), 3.84 (s, 3H), 3.40 (t, $J$ = 5.7 Hz, 2H), 2.50 (t, $J$ = 6.4 Hz, 2H), 1.86−1.80 (m, 2H), 1.79−1.73 (m, 2H). $^{13}$C NMR (100.4 MHz) $\delta$: 189.3 (s), 165.2 (s), 161.3 (s), 133.3 (s), 128.5 (d, 2C), 113.3 (d, 2C), 89.7 (d), 55.3 (q), 41.1 (t), 28.9 (t), 22.3 (t), 19.4 (t). MS (ESI) $m/z$ (%): 485 ([2M + Na]$^+$, 100), 254 ([M + Na]$^+$, 14), 232 ([M + H]$^+$, 41). Anal. Calcd for $C_{14}H_{17}NO_2$ (231.29): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.44; H, 7.71; N, 6.33.

*(Z)-2-Cyclopropyl-1-piperidin-2-ylidene-ethanone (**3e**).* Yellow oil (142 mg, 86%). $R_f$ = 0.21 (*n*-hexane/EtOAc, 3:1). $^1$H NMR (400 MHz) $\delta$: 11.0 (br s, 1H), 5.03 (s, 1H), 3.30 (td, $J$ = 5.9, 2.3 Hz, 2H), 2.37 (t, $J$ = 6.2 Hz, 2H), 1.80−1.74 (m, 2H), 1.73−1.66 (m, 2H), 1.63−1.56 (m, 1H), 0.93−0.89 (m, 2H), 0.69−0.65 (m, 2H). $^{13}$C NMR (100.4 MHz) $\delta$: 195.9 (s), 163.2 (s), 92.9 (d), 40.9 (t), 28.4 (t), 22.3 (t), 19.5 (d), 19.4 (t), 8.3 (t, 2C). MS (ESI) $m/z$ (%): 353 ([2M + Na]$^+$, 100), 188 ([M + Na]$^+$, 26), 166 ([M + H]$^+$, 32). Anal. Calcd for $C_{10}H_{15}NO$ (165.23): C, 72.69; H, 9.15; N, 8.48. Found: C, 72.33, H, 9.07, N, 8.78.

*(Z)-4-Phenyl-1-piperidin-2-ylidene-butan-2-one (**3f**).* Pale-yellow foam (133 mg, 58%). $R_f$ = 0.31 (*n*-hexane/EtOAc, 3:1). $^1$H NMR (400 MHz) $\delta$: 11.2 (br s, 1H), 7.29−7.14 (m, 5H), 4.88 (s, 1H), 3.33 (td, $J$ = 5.6, 2.3 Hz, 2H), 2.94−2.89 (m, 2H), 2.55−2.51 (m, 2H), 2.35 (t, $J$ = 6.4 Hz, 2H), 1.82−1.76 (m, 2H), 1.75−1.67 (m, 2H). $^{13}$C NMR (100.4 MHz) $\delta$: 195.6 (s), 164.3 (s), 142.2 (s), 128.3 (d, 2C), 128.2 (d, 2C), 125.6 (d), 92.9 (d), 43.4 (t), 41.0 (t), 32.3 (t), 28.5 (t), 22.3 (t), 19.4 (t). MS (ESI) $m/z$ (%): 230 ([M + H]$^+$, 100). Anal. Calcd for $C_{15}H_{19}NO$ (229.32): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.91; H, 8.29; N, 5.89.

*(Z)-4-(4-Methoxyphenyl)-1-piperidin-2-ylidene-butan-2-one (**3g**).* Pale-yellow solid (137 mg, 53%). $R_f$ = 0.28 (*n*-hexane/EtOAc, 1:1). Mp 59.1−60.2 °C. $^1$H NMR (400 MHz) $\delta$: 11.2 (br s, 1H), 7.13 (d, $J$ = 8.8 Hz, 2H), 6.81 (d, $J$ = 8.8 Hz, 2H), 4.87 (s, 1H), 3.77 (s, 3H), 3.32 (td, $J$ = 5.9, 2.3 Hz, 2H), 2.87−2.83 (m, 2H), 2.51−2.46 (m, 2H), 2.34 (t, $J$ = 6.4 Hz, 2H), 1.81−1.75 (m, 2H), 1.73−1.66 (m, 2H). $^{13}$C NMR (100.4 MHz) $\delta$: 195.8 (s), 164.3 (s), 157.6 (s), 134.3 (s), 129.1 (d, 2C), 113.6 (d, 2C), 92.9 (d), 55.2 (q), 43.7 (t), 40.9 (t), 31.4 (t), 28.4 (t), 22.2 (t), 19.3 (t). MS (ESI) $m/z$ (%): 541 ([2M + Na]$^+$, 100), 282 ([M + Na]$^+$, 42), 260 ([M + H]$^+$, 23). Anal. Calcd for $C_{16}H_{21}NO_2$ (259.34): C, 74.10; H, 8.16; N, 5.40. Found: C, 73.84; H, 7.97; N, 5.45.

*(Z)-1-Piperidin-2-ylidene-3-buten-2-one (**3i**).* Starting from **1i**. Pale-yellow oil (54 mg, 36%). $R_f$ = 0.22 (*n*-hexane/EtOAc, 1:1). $^1$H NMR (400 MHz) $\delta$: 11.7 (br s, 1H), 6.27 (dd, $J$ = 17.2, 10.2 Hz, 1H), 6.09 (dd, $J$ = 17.2, 2.1 Hz, 1H), 5.41 (dd, $J$ = 10.2, 2.1 Hz, 1H), 4.97 (s, 1H), 3.37 (td, $J$ = 6.1, 2.1 Hz, 2H), 2.42 (t, $J$ = 6.4 Hz, 2H), 1.84−1.78 (m, 2H), 1.75−1.69 (m, 2H). $^{13}$C NMR (100.4 MHz) $\delta$: 184.8 (s), 166.2 (s), 138.0 (d), 121.8 (t), 93.9 (d), 41.1 (t), 28.5 (t), 22.1 (t), 19.2 (t). MS (ESI) $m/z$ (%): 325 ([2M + Na]$^+$, 100), 152 ([M + H]$^+$, 93). Anal. Calcd for $C_9H_{13}NO$ (151.21): C, 71.49; H, 8.67; N, 9.26. Found: C, 71.72; H, 8.59; N, 8.87.

*(Z)-5-Benzyloxy-1-piperidin-2-ylidene-pentan-2-one (**3k**).* Pale-yellow oil (202 mg, 74%). $R_f$ = 0.23 (petroleum ether/EtOAc, 8:1). $^1$H NMR (400 MHz) $\delta$: 11.1 (br s, 1H), 7.34−7.29 (m, 5H), 4.87 (s, 1H), 4.50 (s, 2H), 3.51 (t, $J$ = 6.6 Hz, 2H), 3.32 (td, $J$ = 6.0, 2.0 Hz, 2H), 2.36−2.28 (m, 4H), 1.97−1.88 (m, 2H), 1.82−1.76 (m, 2H), 1.73−1.67 (m, 2H). $^{13}$C NMR (100.4 MHz) $\delta$: 196.4 (s), 164.2 (s), 138.7 (s), 128.3 (d, 2C), 127.6 (d, 2C), 127.4 (d), 93.0 (d), 72.7 (t), 70.1 (t), 40.9 (t), 38.2 (t), 28.4 (t), 26.3 (t), 22.3 (t), 19.3 (t). MS (ESI) $m/z$ (%): 569 ([2M + Na]$^+$, 100), 296 ([M + Na]$^+$, 66), 274 ([M + H]$^+$, 86). Anal. Calcd for $C_{17}H_{23}NO_2$ (273.37): C, 74.69; H, 8.48; N, 5.12. Found: C, 74.81; H, 8.83; N, 4.83.

*(Z)-1-Piperidin-2-ylidene-5-(tetrahydropyran-2-yloxy)pentan-2-one (**3l**).* Pale-yellow oil (192 mg, 72%). $R_f$ = 0.23 (*n*-hexane/EtOAc, 3:1). $^1$H NMR (400 MHz) $\delta$: 11.1 (br s, 1H), 4.82 (s, 1H), 4.52 (m, 1H), 3.82−3.78 (m, 1H), 3.71−3.65 (m, 1H), 3.44−3.40 (m, 1H), 3.39−3.33 (m, 1H), 3.27−3.24 (m, 2H), 2.31−2.21 (m, 4H), 1.86−1.79 (m, 2H), 1.78−1.70 (m, 2H), 1.69−1.60 (m, 2H), 1.57−1.38 (m, 4H). $^{13}$C NMR (100.4 MHz) $\delta$: 196.3 (s), 163.9 (s), 98.5 (d), 92.8 (d), 67.1 (t), 62.0 (t), 40.8 (t), 38.2 (t), 30.6 (t), 28.3 (t), 26.2 (t), 25.4 (t), 22.2 (t), 19.4 (t), 19.2 (t). MS (ESI) $m/z$ (%): 557 ([2M + Na]$^+$, 14), 535 ([2M + H]$^+$, 16). Anal. Calcd for $C_{15}H_{25}NO_3$ (267.36): C, 67.38; H, 9.42; N, 5.24. Found: C, 67.12; H, 9.34; N, 5.18.

*(Z)-1-Piperidin-2-ylidene-6-triisopropylsilanyloxy-hexan-2-one (**3n**).* Pale-yellow oil (54 mg, 72%). $R_f$ = 0.23 (*n*-hexane/EtOAc, 6:1). $^1$H NMR (400 MHz) $\delta$: 11.1 (br s, 1H), 4.87 (s, 1H), 3.68 (t, $J$ = 6.6 Hz, 1H), 3.34−3.30 (m, 2H), 2.35 (t, $J$ = 6.4 Hz, 2H), 2.22 (t, $J$ = 7.2 Hz, 2H), 1.81−1.76 (m, 2H), 1.73−1.52 (m, 6H), 1.07−1.04 (m, 21H). $^{13}$C NMR (100.4 MHz) $\delta$: 197.1 (s), 163.9 (s), 92.9 (d), 63.2 (t), 41.6 (t), 40.8 (t), 32.8 (t), 28.4 (t), 22.7 (t), 22.2 (t), 19.3 (t), 17.9 (q, 6C), 11.9 (d, 3C). MS (ESI) $m/z$ (%): 729 ([2M + Na]$^+$, 40), 376 ([M + Na]$^+$, 10), 354 ([M + H]$^+$, 100). Anal. Calcd for $C_{20}H_{39}NO_2Si$


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(353.61): C, 67.93; H, 11.12; N, 3.96. Found: C, 67.79; H, 11.34; N, 4.18.

*(Z)-7-Hydroxy-1-piperidin-2-ylidene-heptan-2-one (**3o**).* Pale-yellow oil (152 mg, 72%). $R_f$ = 0.22 (EtOAc). $^1$H NMR (400 MHz) $\delta$: 11.1 (br s, 1H), 4.84 (s, 1H), 3.62 (t, $J$ = 6.4 Hz, 2H), 3.30 (td, $J$ = 5.9, 2.1 Hz, 2H), 2.34 (t, $J$ = 6.4 Hz, 2H), 2.20 (t, $J$ = 7.2 Hz, 2H), 2.00 (br s, 1H), 1.80−1.74 (m, 2H), 1.71−1.65 (m, 2H), 1.63−1.52 (m, 4H), 1.40−1.32 (m, 2H). $^{13}$C NMR (100.4 MHz) $\delta$: 197.0 (s), 164.2 (s), 93.0 (d), 62.6 (t), 41.6 (t), 40.9 (t), 32.5 (t), 28.4 (t), 25.9 (t), 25.5 (t), 22.2 (t), 19.3 (t). MS (ESI) $m/z$ (%): 445 ([2M + Na]$^+$, 100), 234 ([M + Na]$^+$, 9), 212 ([M + H]$^+$, 30). Anal. Calcd for $C_{12}H_{21}NO_2$ (211.30): C, 68.21; H, 10.02; N, 6.63. Found: C, 68.35; H, 10.17; N, 6.88.

*(Z)-6-Oxo-1-piperidin-2-ylidene-heptanoic Acid (**3p**).* Prepared as reported according to the general procedure. Workup: after cooling to r.t., water (15 mL) was added, followed by 1 N HCl to reach pH 3; the product was then extracted with EtOAc (3 × 10 mL), and 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 **3p** was purified by flash chromatography to obtain the pure compound as a pale-yellow oil (146 mg, 65%).

$R_f$ = 0.21 (*n*-hexane/EtOAc, 1:3 + 1% AcOH). $^1$H NMR (400 MHz) $\delta$: 11.1 (br s, 1H), 9.7 (br s, 1H), 4.85 (s, 1H), 3.33 (t, $J$ = 5.9 Hz, 2H), 2.37−2.31 (m, 4H), 2.25−2.21 (m, 2H), 1.81−1.75 (m, 2H), 1.73−1.68 (m, 2H), 1.68−1.63 (m, 4H). $^{13}$C NMR (100.4 MHz) $\delta$: 196.3 (s), 178.2 (s), 165.0 (s), 93.1 (d), 41.0 (t), 40.9 (t), 34.1 (t), 28.4 (t), 25.8 (t), 24.8 (t), 22.1 (t), 19.2 (t). MS (ESI) $m/z$ (%): 473 ([2M + Na]$^+$, 100), 248 ([M + Na]$^+$, 6), 226 ([M + H]$^+$, 9). Anal. Calcd for $C_{12}H_{19}NO_3$ (225.28): C, 63.98; H, 8.50; N, 6.22. Found: C, 64.21; H, 8.21; N, 6.17.

*(Z)-6-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-piperidin-2-ylidene-hexan-2-one (**3q**).* Pale-yellow solid (219 mg, 78%). $R_f$ = 0.24 (*n*-hexane/EtOAc, 1:1). Mp 68.6−70.4 °C. $^1$H NMR (400 MHz) $\delta$: 11.1 (br s, 1H), 4.84 (s, 1H), 4.41 (t, $J$ = 4.9 Hz, 1H), 3.57 (d, $J$ = 11.1 Hz, 2H), 3.39 (d, $J$ = 10.9 Hz, 2H), 3.30 (t, $J$ = 5.7 Hz, 2H), 2.33 (t, $J$ = 6.4 Hz, 2H), 2.21 (t, $J$ = 7.0 Hz, 2H), 1.81−1.74 (m, 2H), 1.72−1.60 (m, 6H, 4-H), 1.17 (s, 3H), 0.69 (s, 3H). $^{13}$C NMR (100.4 MHz) $\delta$: 196.6 (s), 164.1 (s), 102.2 (d), 93.0 (d), 77.2 (t, 2C), 41.5 (t), 40.9 (t), 34.6 (t), 30.1 (s), 28.5 (t), 23.0 (q), 22.3 (t), 21.9 (q), 20.9 (t), 19.4 (t). MS (ESI) $m/z$ (%): 585 ([2M + Na]$^+$, 100), 304 ([M + Na]$^+$, 7), 282 ([M + H]$^+$, 5). Anal. Calcd for $C_{16}H_{27}NO_3$ (281.39): C, 68.29; H, 9.67; N, 4.98. Found: C, 68.35; H, 9.78; N, 5.03.

**(±)-4,5-*O*-Isopropylidene-4,5-dihydroxy-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (8).** $Et_3N$ (320 $\mu$L, 2.29 mmol), di-*tert*-butyl dicarbonate (460 mg, 1 equiv), and DMAP (25 mg, 0.21 mmol) were added to a solution of **7** (356 mg, 2.08 mmol) in anhydrous DCM (12.5 mL) under stirring and a nitrogen atmosphere. The resulting solution was heated under reflux for 6 h, and every 1.5 h a further amount of di-*tert*-butyl dicarbonate (230 mg, 0.5 equiv) was added (in all, 2.5 equiv of di-*tert*-butyl dicarbonate was used). After the mixture was cooled at room temperature, water (15 mL) was added, and the product was extracted with DCM (6 mL). The combined organic extracts were washed with aqueous 5% $KHSO_4$ (15 mL), satd $NaHCO_3$ (15 mL), $H_2O$ (15 mL), and brine (15 mL) and finally dried over anhydrous $Na_2SO_4$. After filtration and evaporation of the solvent, crude **8** was purified by FCC (eluent: *n*-hexane/EtOAc, 1:1; $R_f$ = 0.20), and pure **8** (455 mg, 81%) was obtained as a white solid.

Mp 79.4−80.4 °C. $^1$H NMR (400 MHz) $\delta$: 4.59 (dt, $J$ = 7.8, 2.9 Hz, 1H), 4.45 (dt, $J$ = 7.8, 2.3 Hz, 1H), 4.36 (dd, $J$ = 14.6, 2.3 Hz, 1H), 3.20 (dd, $J$ = 14.6, 2.1 Hz, 1H), 2.75 (dd, $J$ = 16.0, 2.9 Hz, 1H), 2.43 (dd, $J$ = 16.0, 3.3 Hz, 1H), 1.47 (s, 9H), 1.34 (s, 3H), 1.28 (s, 3H). $^{13}$C NMR (100.4 MHz) $\delta$: 168.5 (s), 151.6 (s), 108.9 (s), 82.9 (s), 72.4 (d), 71.5 (d), 46.3 (t), 39.2 (t), 27.8 (q, 3C), 26.0 (q), 24.1 (q). MS (ESI) $m/z$ (%): 565 ([2M + Na]$^+$, 100), 294 ([M + Na]$^+$, 15), 272 ([M + H]$^+$, 4). Anal. Calcd for $C_{13}H_{21}NO_5$ (271.31): C, 57.57; H, 7.80; N, 5.16. Found: C, 57.57; H, 7.98; N, 5.21.

**(±)-3,4-*O*-Isopropylidene-6-(diphenoxyphosphoryloxy)-3,4-dihydroxy-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (9).** A 0.5 M solution of KHMDS in toluene (2.4 mL, 1.20 mmol) was diluted in anhydrous THF (6.3 mL) and cooled at −78 °C. A solution of **8** (218 mg, 0.80 mmol) in anhydrous THF (3.7 mL) was then added dropwise, keeping the temperature below −70 °C, and the resulting mixture was stirred for 1.5 h. Diphenyl chlorophosphate (250 $\mu$L, 1.20 mmol) was slowly added, and after 1 h, the mixture was allowed to warm at 0 °C. Aqueous 10% NaOH (19 mL) was slowly added, and the product was extracted with $Et_2O$ (3 × 15 mL). The combined organic extracts were washed with 10% NaOH (10 mL) and dried over $K_2CO_3$ for 30 min. After filtration and evaporation of the solvent, the crude material was purified over a short pad of silica gel, eluting with *n*-hexane/EtOAc, 2:1 containing 1% $Et_3N$ ($R_f$ = 0.21), affording pure **9** as a colorless oil (399 mg, 99%). This was stored as a ∼1.0 M solution in the same eluent and concentrated under vacuum immediately before use for the next step.

$^1$H NMR (400 MHz) $\delta$: 7.36−7.32 (m, 4H), 7.28−7.17 (m, 6H), 5.31−5.29 (m, 1H), 4.71−4.68 (m, 1H), 4.31−4.27 (m, 1H), 3.91 (dd, $J$ = 13.7, 4.9 Hz, 1H), 3.55 (dd, $J$ = 13.7, 1.9 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 9H), 1.35 (s, 3H). $^{13}$C NMR (100.4 MHz) $\delta$: 153.1 (s), 150.3 (s), 144.2 (s), 144.1 (s), 129.8 (d, 4C), 125.6 (d, 2C), 120.1 (d, 2C), 120.0 (d, 2C), 110.0 (s), 99.6 (d), 73.6 (d), 71.0 (d), 48.7 (t), 28.0 (q, 3C), 27.7 (q), 25.7 (q).

**(±)-4-Phenyl-1-piperidin-2-ylbutan-2-one (10).** Vinylogous amide **3f** (20.9 mg, 0.09 mmol) was dissolved in $CH_3OH$ (4 mL), and $PtO_2$ (1% mol) and 70% $HClO_4$ (7 $\mu$L) were added; the mixture was flushed with $H_2$ and vigorously stirred under a $H_2$ atmosphere for 19 h. The mixture was neutralized using $K_2CO_3$(s) and left under stirring for 30 min. After filtration over a short Celite pad, the solvent was removed under vacuum, and the residue was taken up into DCM (5 mL). The organic phase was washed once with water (5 mL) and dried over anhydrous $Na_2SO_4$. After filtration and evaporation of the solvent, pure amine **10** (21 mg, quantitative) was obtained as a pale-yellow oil.

$R_f$ = 0.30 (EtOAc/MeOH, 2:1). $^1$H NMR (400 MHz) $\delta$: 7.28−7.24 (m, 2H), 7.19−7.14 (m, 3H), 2.99−2.95 (m, 1H), 2.95−2.70 (m, 1H), 2.88 (t, $J$ = 7.4 Hz, 2H), 2.74−2.70 (m, 2H), 2.69−2.62 (m, 1H), 2.44 (d, $J$ = 6.2 Hz, 2H), 2.05−1.95 (br s, 1H), 1.75−1.72 (m, 1H), 1.60−1.50 (m, 2H), 1.42−1.27 (m, 2H), 1.16−1.06 (m, 1H). $^{13}$C NMR (100.4 MHz) $\delta$: 209.5 (s), 140.9 (s), 128.4 (d, 2C), 128.2 (d, 2C), 126.1 (d), 52.4 (d), 50.0 (t), 46.8 (t), 44.8 (t), 32.6 (t), 29.6 (t), 26.0 (t), 24.6 (t). MS (ESI) $m/z$ (%): 232 ([M + H]$^+$, 100). Anal. Calcd for $C_{15}H_{21}NO$ (231.33): C, 77.88; H, 9.15; N, 6.05. Found: C, 77.99; H, 9.08; N, 6.13.

**(±)-4-(4-Methoxyphenyl)-1-piperidin-2-ylbutan-2-one (11).**[32] Compound **11** was prepared as reported for **10** starting from compound **3g** (51 mg, 0.19 mmol). After chromatographic purification, pure **11** was obtained as a pale-yellow oil (36 mg, 73%).

$R_f$ = 0.30 (EtOAc/MeOH, 2:1). $^1$H NMR (400 MHz) $\delta$: 7.06 (d, $J$ = 8.6 Hz, 2H), 6.80 (d, $J$ = 8.6 Hz, 2H), 3.76 (s, 3H), 2.99−2.96 (m, 1H), 2.96−2.88 (m, 1H), 2.81 (t, $J$ = 7.6 Hz, 2H), 2.69−2.66 (m, 2H), 2.66−2.58 (m, 1H), 2.43 (d, $J$ = 6.4 Hz, 2H), 1.77−1.68 (m, 1H), 1.60−1.48 (m, 2H), 1.43−1.27 (m, 2H), 1.15−1.06 (m, 1H). $^{13}$C NMR (100.4 MHz) $\delta$: 209.7 (s), 157.9 (s), 132.9 (s), 129.2 (d, 2C), 113.9 (d, 2C), 55.2 (q), 52.4 (d), 50.1 (t), 46.8 (t), 45.1 (t), 32.6 (t), 28.7 (t), 26.0 (t), 24.6 (t). MS (ESI) $m/z$ (%): 262 ([M + H]$^+$, 100). Anal. Calcd for $C_{16}H_{23}NO_2$ (261.36): C, 73.53; H, 8.87; N, 5.36. Found: C, 73.48; H, 8.92; N, 5.52.

**6-Heptynoic Acid Methyl Ester.** Prepared as reported for 5-hexynoic acid methyl ester[37] starting from 6-heptynoic acid (378 mg, 3.0 mmol). The so-obtained methyl ester was used without further purification in the Sonogashira coupling reaction.

Colorless oil (290 mg, 69%). $R_f$ = 0.41 (*n*-hexane/EtOAc, 10:1). $^1$H NMR (200 MHz) $\delta$: 3.67 (s, 3H), 2.34 (t, $J$ = 7.3 Hz, 2H), 2.21 (td, $J$ = 7.0, 2.6 Hz, 2H), 1.95 (t, $J$ = 2.6 Hz, 2H), 1.82−1.63 (m, 2H), 1.62−1.47 (m, 2H).

**5,5-Dimethyl-2-pent-4-ynyl-[1,3]dioxane.** 5-Hexynal[38] (136 mg, 1.4 mmol) was dissolved in dry toluene (30 mL), and 2,2-dimethyl-1,3-propanediol (190 mg, 1.3 equiv) and *p*-TSA monohydrate (100 mg, 0.5 mmol) were added. The reaction mixture was heated under reflux, and water was removed by Dean−Stark azeotropic distillation. After 15 h, the reaction was quenched by


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addition of water (10 mL), and the product was extracted with $Et_2O$ (3 × 10 mL); the combined organic extracts were washed with aqueous 10% NaOH solution (15 mL) and brine and then dried over anhydrous $Na_2SO_4$. After filtration and evaporation of the solvent, the crude alkyne was purified by flash column chromatography (eluent: petroleum ether/EtOAc, 4:1; $R_f$ = 0.62) to yield 5,5-dimethyl-2-pent-4-ynyl-[1,3]dioxane (133 mg, 70%) as a colorless oil.

$^1$H NMR (200 MHz) $\delta$: 4.38−4.33 (m, 1H), 3.56−3.46 (m, 2H), 3.41−3.27 (m, 2H), 2.20−2.08 (m, 2H), 1.92−1.85 (m, 1H), 1.72−1.50 (m, 4H), 1.10 (s, 3H), 0.63 (s, 3H).

## ■ ASSOCIATED CONTENT

### Supporting Information

Copies of the $^1$H and $^{13}$C NMR spectra of compounds **1a−r**, **2a**, **2r**, **3a−q**, **8−11**, 6-heptynoic acid methyl ester, and 5,5-dimethyl-2-pent-4-ynyl-[1,3]dioxane. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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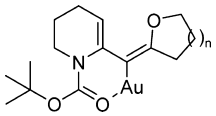
vinylogous amide that we could not isolate. Formation of the exocyclic vinylogous amide moiety was demonstrated by the presence of the diagnostic signals at 9.84 ppm (br s, N*H*) and 5.08 (s, 1′-H) in the $^{1}$H NMR spectrum of the crude reaction mixture and the signals at 201.1 (s, CO) and 96.1 (d, C1′) in the $^{13}$C NMR spectrum.

(29) Two of these vinylogous amides are known: compounds **3a**[12c] and **3c**.[9b,12c,13]

(30) Vinylogous amide **3h** was identified in the crude reaction mixture by its diagnostic $^{1}$H NMR singlet at 4.90 ppm and the side-chain signals at 3.62 (t, $J$ = 7.0 Hz) and 2.38 (t, $J$ = 7.0 Hz) ppm.

(31) This could result in the sequestration of Au(I) and the interruption of any catalytic cycle.

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