5- endo-dig Cyclization of O-Propargyl Mandelic Acid Amides towards 2,5-Dihydrofurans

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5-*endo-dig* Cyclization of O-propargyl mandelic acid amides towards 2,5-dihydrofurans

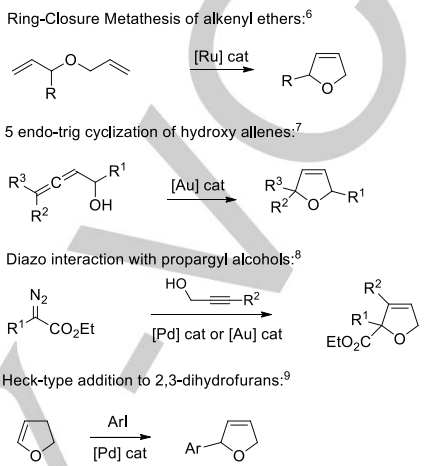
Lilia Ben Gaied,[a] Nicolas Fincias,*[b] Julian Garrec*[b] and Laurent El Kaïm*[b]

Dedication ((optional))

Abstract: O-Propargyloxyamides obtained through boric acid triggered Passerini reaction followed by propargylation cyclize in the presence of potassium *tert*-butylate to afford 2,5-dihydrofurans. The mechanism of the reaction has been studied in relation with DFT calculation and the results compared with the behavior of analogous N-propargylamide derivatives.

Introduction

Compared to 2,3-dihydrofurans, tetrahydrofurans or furans, 2,5-dihydrofurans are certainly the least represented in terms of biological activity as well as occurrence in natural products.[1] However, the interest for these compounds has grown significantly in the last twenty years and 2,5-dihydrofurans now appear as major synthetic intermediates for the preparation of other members of the furan family. They can be easily isomerized to their more stable 2,3-isomer,[2] converted to tetrahydrofurans[3] or oxidized either to furans[4] or butyrolactones,[5] a skeleton widely encountered in natural products. The wealth of this chemistry is mainly associated with the disclosure of direct accesses to these compounds thanks to the development of metathesis of alkenyl ethers[6] (Scheme 1). Besides this ruthenium carbenoid based transformation, many other preparations of 2,5-dihydrofurans are associated with metal triggered cyclization of alkyne or allenyl derivatives. These transformations take advantage of the π-Lewis electrophilic properties of various metals in order to activate nucleophilic attacks on double and triple bonds. Thus many silver or gold catalyzed formations of 2,5-hydrofurans from both hydroxyallenes and hydroxyalkynes have been reported.[7] The interaction of diazo compounds with propargylic alcohols affords as well a direct access to dihydrofuran under palladium or gold catalysis.[8] Alternatively, 2,3-dihydrofurans can be arylated towards substituted 2,5-dihdyrofurans under Heck type reactions.[9] (Scheme 1).



Scheme 1. Usual approaches towards 2,5-dihydrofurans

Though the formation of 2,5-dihydrofurans through anionic 5-endo-dig cyclization of O-propargylic ethers (which may be considered as an example of Conia ene cyclization)[10] appears as a very attractive method due to an easy formation of propargylic ethers, the scope of nucleophiles that can be involved in the cyclization is often limited by the use of a Lewis acid as catalyst in order to raise the electrophilicity of the alkyne. Indeed while O-propargyl hydroxypyrimidinediones could cyclise in a 5-endo mode in the presence of $AgSbF_6$[11] or $FeCl_3$ [12] (Scheme 2), more simple O-propargylketoesters failed to cyclize in a tandem $Rh_2(esp)_2/ZnI_2$ addition-cyclization sequence from diazo compounds (in contrast to the related O-homopropargylketoesterr which led to efficient formation of tetrahydrofurans via 5-exo-dig Conia-ene cyclization).[13] Besides these metal triggered cyclizations, few anionic 5-*endo-dig* cyclizations have been described on propiolate esters.[14] In these cases, the reaction is favoured by the electron-poor nature of the triple bond. For simple alkynes and more reactive O-propargyl anionic species formed in the absence of π-electrophilic Lewis acids, [1,2] or [2,3]-Wittig rearrangement towards hydroxy alkynes and allenes are usually observed (Scheme 2).[15]

Considering these limitations and the few number of metal-free 5-endo-dig cyclizations of O-propargyl ethers,[16] we decided to start a combined experimental and theoretical approach towards anionic cyclization of O-propargyl-mandelic secondary amides enolate. Indeed, the ability to obtain these compounds from benzaldehyde in a 2-step Passerini/O-propargylation sequence opens the way for easy preparation of various aryl analogues allowing a better tuning of the reactivity of the anions (Scheme 2).

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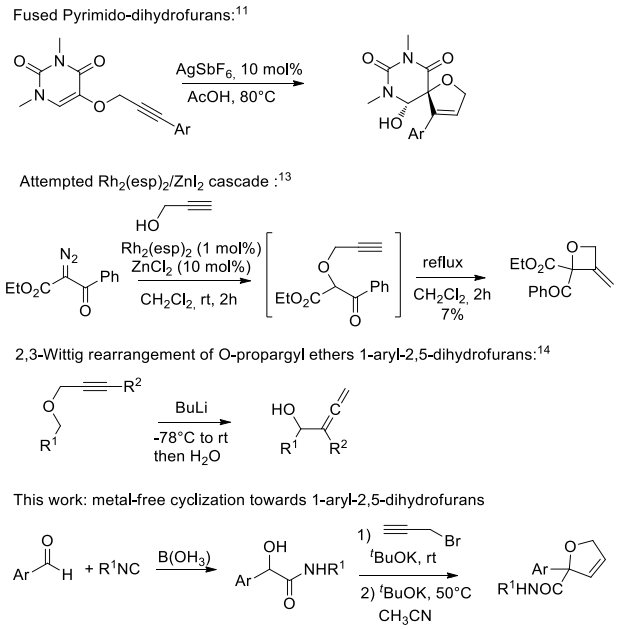
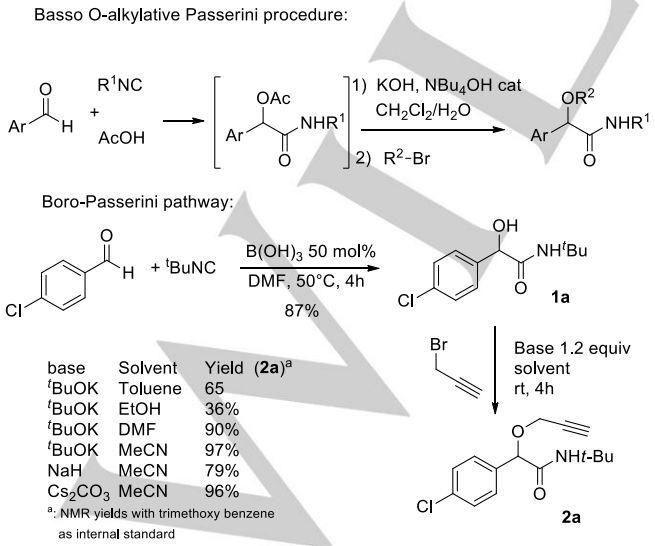


Scheme 2. 5-endo-dig cyclization of propargyl ethers

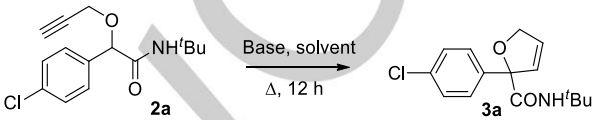
Results and Discussion

The Passerini reaction is a convenient three-component access to α-acyloxy amides from aldehydes, isocyanides and carboxylic acids.[17] Though the preparation of the requisite O-propargyl amide derivatives could be envisioned using a three-step one -pot Passerini/saponification/alkylation procedure settled by Basso et al (Scheme 3),[18] we preferred to form directly the starting α-hydroxyamides using a previously reported boronic acid triggered Passerini coupling.[19] Thus, following a slightly modified procedure (working at 50°C in DMF instead of rt), we could obtain hydroxyamide **1a** in a 87% isolated yield from 4-chlorobenzaldehyde and *tert*-butyl isocyanide (Scheme 3).



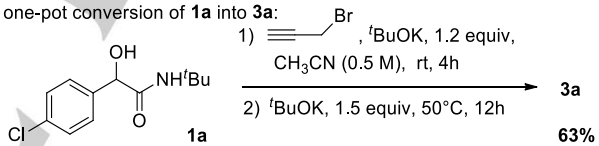
Scheme 3. O-alkylative Passerini procedures[20]

Due to an internal hydrogen bonding, these amides are expected to be more acidic than simple secondary alcohols and their O-alkylation is known to proceed efficiently under basic conditions (NaH/DMF or KOH in dichloromethane/water mixture under phase transfer conditions).[21] With the objective of reaching a potential one-pot alkylation/cyclization procedure, various conditions were tested for the O-propargylation of **1a**. ^{t}BuOK or Cs_2CO_3 which afforded an almost quantitative yield of **2a** in acetonitrile (Scheme 3), were then evaluated as bases for the following step.



Base (equiv)	Solvent[a]	yield[b]
^{t}BuOK (0.5)	MeCN	52%
^{t}BuOK (0.5)	MeCN (80°C)	51%[c]
^{t}BuOK (1.5)	MeCN	63% (**62% isolated**)
^{t}BuOK (1.5)	Toluene	12%
^{t}BuOK (1.5)	DMF	53%
^{t}BuOK (1.5)	DMSO	63%
^{t}BuOK (1.5)	EtOH	0%
NaH (1.5)	MeCN	56%
Cs_2CO_3 (1.5)	MeCN	0%
^{t}BuOK (1.5)	MeCN (0.1 M)	63%

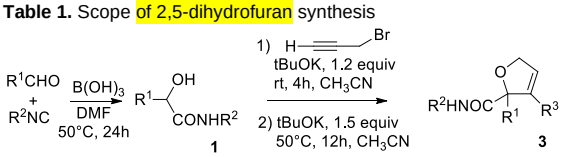
[a]unless indicated temperature was 50°C and the concentration 0.5M; [b]yield given by NMR with 1,3,5-trimethoxybenzene as internal standard; [c]the reaction was over in 6h

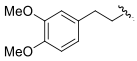
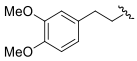


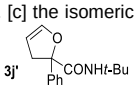
Scheme 4. Optimized formation 2,5-dihydrofuran **3a**

While no reaction occurred at room temperature using *t*-BuOK (0.5 equiv) in acetonitrile, we could observe the expected cyclization with the same basic conditions heating at 50°C for 12 hours (Scheme 4). Cs_2CO_3 which gave quantitative yields in the alkylation step was not basic enough to trigger the cyclization. Raising the amount of base to 1.5 equiv afforded a slight increase in yields. Sodium hydride as well as other solvents (DMF, toluene, EtOH, DMSO) all proved less efficient or convenient than the ^{t}BuOK/CH_3CN couple. These conditions could be easily adapted to offer a one-pot two-step conversion of **1a** into **3a**. After room temperature propargylation of **1a** in the presence of 1.2 equiv of ^{t}BuOK in CH_3CN, further base was added after 4 hours and the temperature raised at 50°C for the following 12 hours to afford **3a** in 63% isolated yield. These conditions were selected to perform the preparation of the various 2,5-dihydrofurans displayed in Table 1.

Table 1. Scope of 2,5-dihydrofuran synthesis

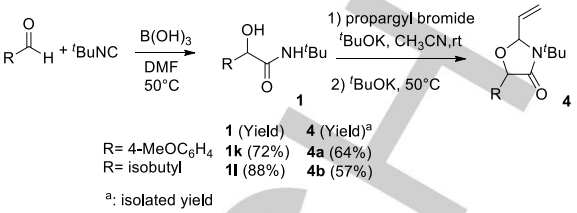


Entry	R^1	R^2	**1** (yield)[a]	**3** (yield)[a]
1	4-ClC_6H_4	^{t}Bu	**1a** (87%)	**3a** (63%)
2	4-ClC_6H_4	Cy	**1b** (85%)	**3b** (63%)
3	4-ClC_6H_4		**1c** (95%)	**3c** (42%)
4	4-FC_6H_4	^{t}Bu	**1d** (80%)	**3d** (31%)[b]
5	4-FC_6H_4	Cy	**1e** (96%)	**3e** (67%)
6	3-pyridyl	^{t}Bu	**1f** (82%)	**3f** (56%)
7	3-pyridyl	Cy	**1g** (86%)	**3g** (52%)
8	3-pyridyl		**1h** (82%)	**3h** (44%)
9	2-furyl	Cy	**1i** (72%)	**3i** (62%)
10	Ph	^{t}Bu	**1j** (70%)	**3j** (25%)[c]

[a] Isolated yields after column chromatography on silica gel. [b] a 50% conversion was observed. [c] the isomeric 2,3-dihydrofuran **3j'** was also obtained in 29% yield. 

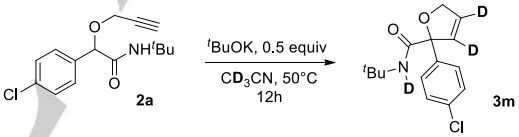
For most reactions of table 1, the alkylation step was almost quantitative (checked by an NMR of an aliquot before adding more base and heating) and the cyclization led to the dihydrofurans **3** in moderate to good yield. Except for phenyl substituted O-propargyl amide **1j**, which led to an equimolar mixture of 2,3 and 2,5-dihydrofurans **3j** and **3j'**, all amides **1** afforded 2,5-dihydrofurans without any trace of 2,3 isomer visible in the NMR of the crude mixture (Table 1, entries 1-9). No other side product could be isolated. The reaction seems to be strongly affected by the electronic nature of the starting aldehyde. The cyclization was less effective with electron-rich aromatic aldehyde. In the case of 4-methoxy-substituted Passerini adduct **1l**, the expected dihydrofuran was not isolated but we could recover oxazolinone **4a** obtained in a 60% isolated yield (Scheme 5). The analogous oxazolinone **4b** was also formed when the Passerini/Propargylation/Cyclization sequence was attempted with isobutyraldehyde (Scheme 5). Both **4a** and **4b** were isolated as single diastereomers but their stereochemistry could not be determined.

O-alkylative Passerini procedure:



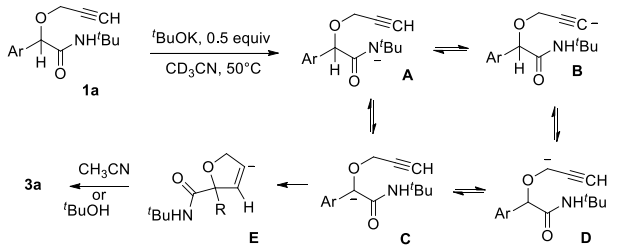
Scheme 5. Attempted O-propargylation/cyclization sequence for **1k** and **1l**

The formation of 2,3 and 2,5 regioisomeric dihydrofurans together with oxazolinones according to the nature of the starting aldehyde is indicative of the importance of the deprotonation step under basic treatment. The most related cyclizations displaying similar potential competing deprotonations have been reported using N-propargyl Ugi adducts instead of Passerini ones.[22] Pyrrolines were then formed instead of dihydrofurans. Whereas for the nitrogen analogues, the potential 2,3-Wittig reaction is not an issue, the formation of 2,3-pyrrolines as major regioisomers is even more puzzling in the light of our results. In order to gain further indications on the reaction mechanism, O-propargyl Passerini adduct **1a** was treated under our optimized cyclization conditions using ^{t}BuOK as a base but replacing CH_3CN by deuterated acetonitrile. Under these conditions, the trisdeuterated dihydrofyran **3m** was obtained in 58 % yield.



Scheme 5. Attempted O-propargylation/cyclization sequence of **1k** and **1l**

This last example gives some good indications on the mechanism probably involved in the cyclization step. Starting **2a** possesses several acidic centers, besides the NH amide and the CH benzylic positions, one can also imagine the potential deprotonation of the terminal CH alkyne as well as the two propargylic CH bonds. From the reaction performed in deuterated acetonitrile and the fact that the cyclization works efficiently with less than one equivalent of base, it may be reasoned that the three monoanionic species **A**, **B** and **C** exist in equilibrium after treatment with ^{t}BuOK (Scheme 6). Even if no deuterium exchange has been observed at this position, anion **D** might be also expected to be formed as an intermediate towards allene derivatives. While **A** and **B** may lead to proton exchanges with the solvent, **C** may cyclize in a 5-endo-dig fashion to form the vinyl anion **E** which is protonated either by the solvent or *t*-BuOH from the added base to form **3a**. A further experiment made placing **3a** in deuterated acetonitrile under the cyclization conditions showed that the terminal alkyne position fully exchanges its proton with deuterium before the cyclization step (no deuteration of the vinyl positions of **3a** but conversion of the NH into ND).



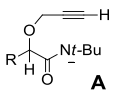
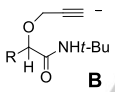
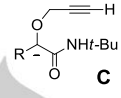
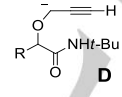
Scheme 6. Anionic species involved in the reaction mechanism

Whenever the benzylic position becomes less acidic either by using electron-rich starting aromatic aldehydes (Passerini adduct **1k**) or when the anion is less stabilized by conjugation (Passerini adduct **1l** made from an aliphatic aldehyde), the formation of anionic intermediate **C** together with its cyclization become less efficient and the O-propargyl moiety may ultimately isomerize into an allenyl ether which is probably involved in the cyclization process towards **4a** and **4b** as well as the formation of the regioisomeric 2,3-dihydrofuran **3j'** (Table 1, entry 10).

To confirm these elements, molecular modeling employing density functional theory (DFT) calculations was undertaken to examine the relative energies of the various anions presented above in CH_3CN together with the feasibility of the 5-endo-dig cyclization.

The relative stability of different carbanions that may be generated during the deprotonation of *O*-propargyloxy-amide were evaluated by comparing their energy in acetonitrile as a solvent cage (Table 2).

Table 2. Relative energies (kcal/mol) of the four different anionic species for *O*-propargyloxy-amide with different substituent (R). Energy of anion **A** was set as reference for easier comparison.

	 A	 B	 C	 D
R=Ph	0	4.6	0.9	12.0
R=4-(MeO)Ph	0	4.2	4.0	11.6
R=4-ClPh	0	5.1	-1.0	12.4
R=Me	0	-0.7	13.0	7.2

Amide anions **A** appear as the most stable in most of the substitution patterns examined. As expected, the relative stability of species **C** leading to the 5-*endo* cyclization adduct is greatly influenced by the substitution of the enolic position. When this carbon is substituted with a phenyl or a *p*-chlorophenyl group, anion **C** and anion **A** have close energies indicating that both compounds may be present in solution. However the higher stability of **C** for the chloro substituted analogue is associated with an exclusive formation of the 2,5-isomer in similar amount. In the case of the phenyl ring, the lower amount of **C** in the medium probably gives more space for the propargyl-allenyl isomerization to occur leading to important amount of the 2,3-isomer.[23] When the enolic carbon is substituted with a *p*-methoxybenzene or a methyl group, the energy of compound **C** is too high for an efficient deprotonation at this position in the presence of the NH-amide unless a dianionic species is involved. This analysis is further confirmed with the lack of 5-endo cyclization observed with both **1k** and **1l**.

The higher acidity of the NH-amide raises further questions on the reaction mechanism. Indeed, amide anion **A** could be expected to cyclize onto the alkyne moiety in a 6-exo-dig fashion to afford morpholine derivatives. Related 6-exo-dig cyclizations have been recently reported by Miranda et al working on N-propargyl Ugi adducts derived from aliphatic aldehydes and aromatic isocyanides.[24]

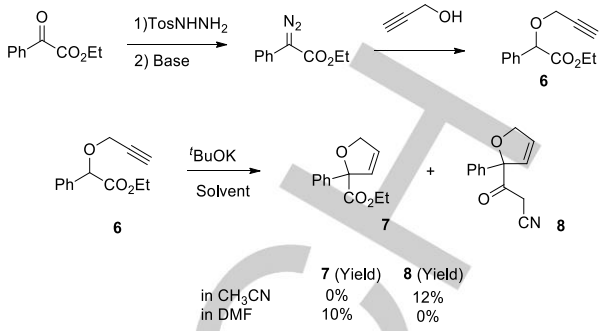
In order to answer these questions, we have modelled the full 5-endo and 6-exo reaction pathways.[25]

The chosen structural model was compound **1j**. The corresponding potential energy surfaces (PES) are represented in Fig. 1. For both mechanisms, deprotonation before cyclization and reprotonation after cyclization are always facile processes (thermodynamically favorable) with energy drops in the range [−18, −14] kcal/mol. It is worth stressing that the value of these energy is pretty independent from the mechanism considered. The main difference in the energetics of the two chemical pathways lies in the cyclization step itself. The 5-*endo* cyclization is clearly more favorable, both on the kinetic and thermodynamic point of view, with a barrier of $\Delta_{5\text{-endo cycl.}}E^{\ddagger} \approx 15$ kcal/mol and an energy difference between cyclized and uncyclized forms of $\Delta_{5\text{-endo cycl.}}E \approx -10$ kcal/mol. The corresponding values For the 6-exo pathway are $\Delta_{6\text{-exo cycl.}}E^{\ddagger} \approx 22$ kcal/mol and $\Delta_{6\text{-exo cycl.}}E \approx +7$ kcal/mol, respectively. Hence, the differences in activation and reaction energies between the two cyclization steps are $\Delta_{5\text{-endo}\rightarrow 6\text{-exo}}\Delta_{cycl.}E^{\ddagger} \approx 7$ kcal/mol and $\Delta_{5\text{-endo}\rightarrow 6\text{-exo}}\Delta_{cycl.}E \approx 17$ kcal/mol, respectively. This is consistent with our experimental observation that only dihydrofurans are formed from compound **1j**.

A close inspection of our optimized transition state structures reveals that the preference for the 5-*endo* mechanism originates from a steric conflict involving the *t*-Bu group attached to the amide group of **1j** in the case of the 6-*exo* approach. Indeed, the 6-exo cyclization requires the terminal carbon atom of the alkyne moiety to get very close to the *t*Bu group, which is detrimental to the energetics of the chemical step. We provide more detailed molecular representations showing this specific steric hindrance in the supporting information part together with a comparison of the 5-*endo*/6-*exo* cyclization of the N-Me analogue showing that the latter cyclization may become easier (ref SI in Fig. S1).

While the use of the Passerini reaction affords a fast synthetic pathway towards dihydrofurans, our study clearly shows that the presence of a secondary amide moiety may complicate the cylization due to competing deprotonations. Thus, we decided to examine the behavior of alternative starting materials replacing

secondary amides by tertiary amides or esters. Due to poorly efficient O-propargylation of ethyl mandelate under our conditions, we decided to prepare O-propargyl ester **6** using a BF_3 triggered reaction of diazoester **5** as reported by Just et al (Scheme 7).[26] When **6** was treated under our optimized cyclization conditions, the expected 2,5-dihydrofuran **7** was not formed but we could isolate out of the complex mixture the 2,5-dihydrofuran **8** obtained in a low 12% yield (Scheme 7). The formation of **8** demonstrates the sensitivity of the ester moiety to the reaction conditions. Indeed, the latter may undergo a nucleophilic attack of the acetonitrile derived anion after cyclization. A potential formation of a ketene from **6** may be also considered.



Scheme 7. Cyclization of ester **6**

The hydroxy amide **9** was next prepared. As its propargylation could be achieved much more easily than the ester analogue **6**, a one-pot version was directly attempted as previously

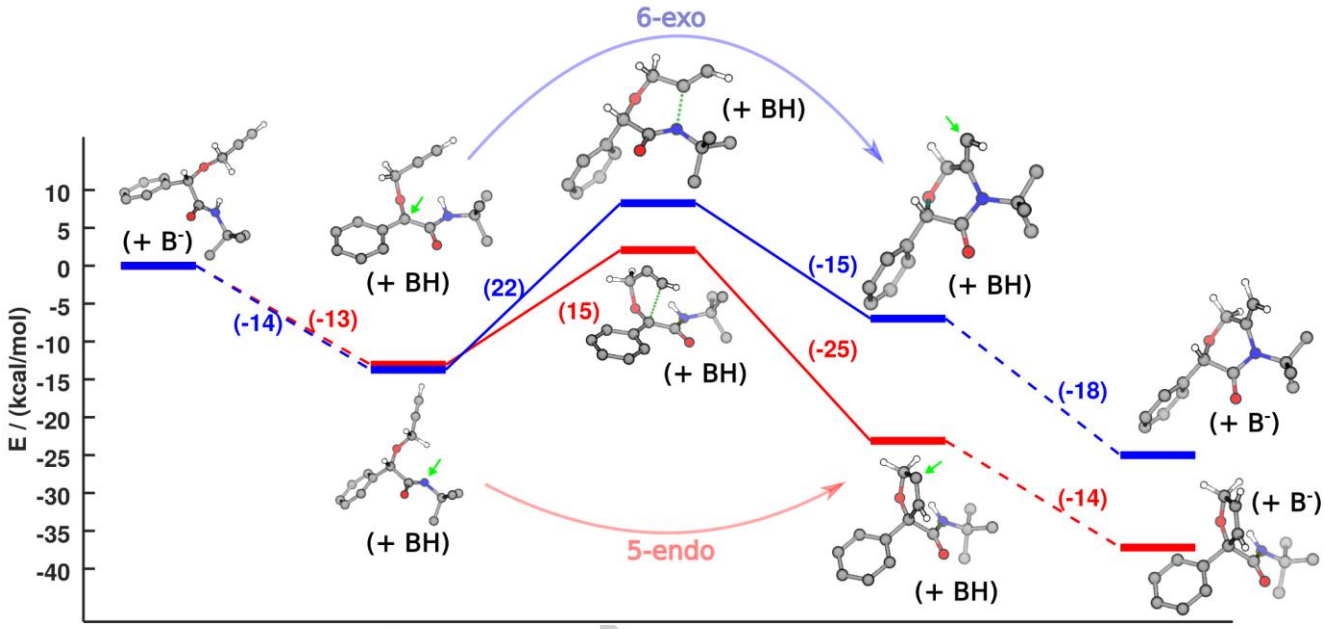
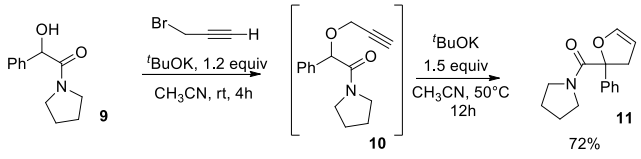


Figure 1: Comparison of the potential energy surfaces of the 5-endo and 6-exo mechanisms in acetonitrile, depicted in red and blue, respectively. Optimized molecular structures derived from compound 1a' are represented for all stationary points of the two pathways. H-atoms the Ar and tBu groups are hidden for the sake of clarity. On each energy level, B^- and BH correspond to, respectively, a deprotonated and normal acetonitrile molecule taken at infinite separation. Deprotonation and protonation steps are shown as dashed lines on the pathways. Cyclization steps are represented with plain lines. Anionic sites on meta-stable structures are highlighted with a green arrow.

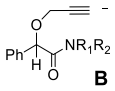
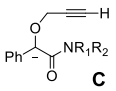
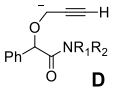
described for our NH-amides **1**. While the substitution pattern of **9** is close to the one of **1k**, to our surprise we didn't observe any 2,5-dihydrofuran but the sole formation of the 2,3-dihydrofuran **11** isolated in a good 72% yield (Scheme 8).



Scheme 8. Cyclization of amide **9**

According to the trend observed in our study and confirmed by the modelling with NH amides, this behavior should be indicative of a less acidic α-amide CH position. Indeed, the presence of two alkyl groups on the nitrogen should prevent the amide benzylic anion **C** (Table 3) to reach a flat geometry leading to a higher energy of the latter and thus more time for the propargyl-allene isomerization to occur. In opposition to this analysis, the modeling of the geometry[27] and energies of the various anions potentially formed from **10** failed to bring convincing elements to explain the more selective formation of 2,3-dihydrofuran as anion **C** is more stabilized for the pyrrolidone moiety than for the NHtBu group. A more detailed study on the isomerization of the propargyl moiety will probably be required for a better understanding of this effect.

Table 3. Relative energies (kcal/mol) of the different anionic species in acetonitrile generated from **9** and **1k**. Energies of anion **B** were set to 0 kcal.mol^{-1} for relative energy comparison

	 **B**	 **C**	 **D**
H, R_2 = *t*-Bu	**0**	**-3.7**	**7.4**
R_1,R_2 =$(CH_2)_4$	**0**	**-8.2**	**8.8**

Conclusions

We have performed a combined experimental and theoretical study on the formation of 2,5-dihydrofuran under basic treatment of O-propargyl amides. The formation of dihydrofurans under transition metal-free cyclization of O-propargyl derivatives is much less documented than the related cyclization of the nitrogen analogues towards pyrrolidines due to the potential competing 2,3-wittig rearrangement well described in the literature. While the 2,3-wittig rearrangement is not observed with our substrates, we have explained and confirmed with DFT modeling the selectivity of the process. Most noteworthy is the ability to extend these cyclizations to other substrates than Passerini adducts as shown by our last cyclizations performed with ester **6** or tertiary amide **9**.

Experimental Section

Computational methods: All electronic structure calculations were performed by means of density functional theory (DFT) using the M062X functional[27] with the 6-31G(d,p) basis set.[29-31] as implemented in the Gaussian 09 suite of programs[32] The molecular system was embedded in a dielectric cavity mimicking the acetonitrile solvent (polarizable continuum model (PCM)[33]).

All relevant reactants, products and transition states (TS) geometries were optimized then and characterized by standard normal mode analysis. For each TS, the single mode corresponding to an imaginary frequency was used to define an intrinsic reaction coordinates (IRC)[34] and proceed downhill toward the reactants an prod- ucts of the elementary step. It is worth noting that we did not attempts to search transition states corresponding to proton transfers as all relevant protonation/deprotonations steps in the various chemical pathways where all highly exothermic and thus considered as rather facile processes (see main text fordiscussion).
Graphical representation of the molecules were made with the software VMD.[35]

General Considerations: NMR spectra were recorded at 298 K using a Bruker AVANCE 400 spectrometer. 1H NMR spectra were recorded at 400 MHz and residual solvent peaks were used as an internal reference (CDCl3 δ 7.26). Data are reported as follows: chemical shift in ppm, apparent multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, m = multiplet or overlap of non-equivalent resonances), coupling constants, integration. 13C NMR spectra were recorded at 100 MHz and residual solvent peaks were used as an internal reference (CHCl3 δ 77.16). Data are reported as follows: chemical shift in ppm, multiplicity deduced from DEPT experiments (CH3, CH2, CH, Cq), apparent multiplicity, coupling constants and integration where relevant. Analytical TLC was performed with Merck silica gel plates, pre-coated with silica gel 60 F254 (0.2 mm). Visualisation was performed using UV fluorescence (λmax = 254 nm or 360 nm) and staining with *p*-anisaldehyde, potassium permanganate or vanillin TLC stain solutions, followed by heating. Flash chromatography employed VWR (230–400 mesh) silica gel. Reactions were conducted under a positive pressure of dry nitrogen or argon in oven-dried or flame dried glassware, and at ambient room temperature, unless specified otherwise. Anhydrous solvents were either obtained from commercial sources or dried with a MBRAUN Solvent Purification System SPS-800. Petroleum ether refers to the 40-60 °C boiling fraction. Commercially available chemicals were used as purchased, or where specified, purified by standard techniques. IR spectra were recorded on a Perkin Elmer Spectrum 65 FT-IR Spectrometer. Melting points were measured on a Stuart SMP3 melting point apparatus and are uncorrected. High resolution mass spectra were recorded on an Agilent 1100 series LC-MS (with a 6310 ion trap) under electrospray ionization (ESI). For compounds containing bromine, the mass of 79Br was used. Monowave 300 produced by Anton Paar was used for the microwave conditions.

General procedure for the synthesis of α-hydroxyamides:

The corresponding aldehyde (2.00 mmol), isocyanide (1.00 equiv.) and boric acid (1.00 equiv.) were dissolved in 0.4 mL of DMF and the resulting mixture was stirred at 50°C for 24h. The crude solution was then diluted with 10 mL of EtOAc and washed with 80 mL of brine. The aqueous solution was further extracted with 2x10 mL of EtOAc ; the combined organic layers were washed a last time with 60 mL of brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure.α-Hydroxyamides were purified by flash column chromatography with the corresponding eluent.

N-(tert-butyl)-2-(4-chlorophenyl)-2-hydroxyacetamide (1a): Following general procedure with p-chlorobenzaldehyde and tert-butyl isocyanide. **1a** was obtained as a white solid (m.p. 150-153 °C) in 87% isolated yield (421 mg, 1.74 mmol) after column chromatography (PE:EtOAc = 80/20 to 70/30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 9.0 Hz, 2H), 5.90 (s,

1H), 4.79 (d, *J* = 3.7 Hz, 1H), 3.78 (d, *J* = 3.7 Hz, 1H), 1.24 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 138.4, 134.4, 129.0, 128.2, 73.5, 51.6, 28.7. HRMS: expected: 241.0870, found: 241.0870. IR (thin film) cm^{-1} 3363, 3233, 2969, 1644, 1535, 1407, 1284, 1229, 1189, 1103, 1087, 1068, 842.

2-(4-chlorophenyl)-N-cyclohexyl-2-hydroxyacetamide (1b): Following general procedure with p-chlorobenzaldehyde and cyclohexyl isocyanide. **1b** was obtained as a white solid (m.p. 126-128 °C) in 85% yield (455 mg, 1.70 mmol) after column chromatography (PE:EtOAc = 80/20 to 70/30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 4H), 6.01 (d, *J* = 8.3 Hz, 1H), 4.87 (s, 1H), 3.65 (tdd, *J* = 10.7, 6.7, 4.1 Hz, 1H), 3,65 (s br, 1H), 1.87-1.70 (m, 2H), 1.69-1.44 (m, 3H), 1.39-1.16 (m, 2H), 1.04 (ddt, *J* = 18.0, 10.9, 3.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 138.2, 134.43, 129.0, 128.2, 73.4, 48.5, 32.9, 32.9, 25.4, 24.8, 24.7. HRMS: expected: 267.1026, found: 267.10.23. IR (thin film): cm^{-1} 3291, 2929, 2854, 1746, 1647, 1529, 1489, 1089, 736.

2-(4-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-2-hydroxyacetamide (1c): Following general procedure with para-chlorobenzaldehyde and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene, **1c** was obtained as a dark yellow oil in 95% yield (665 mg, 1.90 mmol) after column chromatography (CH_2Cl_2: MeOH = 100/0 to 95/5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.58 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.26 (d, *J* = 5.3 Hz, 1H), 4.99 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.66-3.44 (m, 2H), 2.76 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 149.0, 147.7, 138.0, 134.4, 129.0, 128,1, 120.7, 111.7, 111.2, 73.4, 55.9, 55.9, 40.7, 35.1. HRMS: expected: 349.1081, found: 349.1085. IR (thin film): cm^{-1} 3336, 3059, 2933, 2835, 1652, 1511, 1258, 1233, 1142, 1083, 1021.

***N*-(*tert*-butyl)-2-(4-fluorophenyl)-2-hydroxyacetamide (1d)**: Following general procedure with *p*-fluorobenzaldehyde and tert-butyl isocyanide. **1d** was obtained as a white solid (m.p. 154-156 °C) in 80% yield (360 mg, 1.60 mmol) after column chromatography (EP:EtOAc = 80/20 to 70/30). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.34-7.23 (m, 2H), 7.04-6.93 (m, 2H), 5.85 (s, 1H), 4.80 (d, *J* = 3.6 Hz, 1H), 3.70 (d, *J* = 3.6 Hz, 1H), 1.25 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 162.8 (d, *J* = 247.0 Hz), 135.8 (d, *J* = 3.1 Hz), 128.6 (d, *J* = 8.2 Hz), 115.8 (d, *J* = 21.7 Hz), 73.5, 51.6, 28.7. HRMS: expected: 225.1165, found: 225.1154. IR (thin film): cm^{-1} 3361, 3237, 2972, 1641, 1536, 1508, 1219, 846.

N-cyclohexyl-2-(4-fluorophenyl)-2-hydroxyacetamide (1e): Following general procedure with *p*-fluorobenzaldehyde and cyclohexyl isocyanide, **1e** was obtained as a white solid (m.p. 92-95 °C) in 96% yield (482 mg, 1.92 mmol) after column chromatography (PE:EtOAc = 90/10 to 70/30). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.25-7.15 (m, 2H), 6.90 (m, 2H), 6.54 (s, 1H), 4.78 (s, 1H), 4.68 (s, 1H), 3.75-3.35 (m, 1H), 1.81-1.46 (m, 5H), 1.33-0.92 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 162.6 (d, *J* = 246.6 Hz), 135.8 (d, *J* = 3.1 Hz), 128.5 (d, *J* = 8.2 Hz), 115.4 (d, *J* = 21.5 Hz), 73.3, 48.2, 32.9, 32.8, 25.4, 24.7. HRMS: expected: 251.1322, found: 251.1332. IR (thin film): cm^{-1} 3296, 2930, 2855, 1647, 1604, 1508, 1223, 1071, 839.

N-(tert-butyl)-2-hydroxy-2-(pyridin-3-yl) acetamide (1f): Following general procedure with pyridine-3-carboxaldehyde and *tert*-butyl isocyanide, **1f** was obtained as a yellow oil in 82% yield (342 mg, 1.64 mmol) after column chromatography (CH_2Cl_2: MeOH = 100/0 to 95/5). ^{1}H NMR (400 MHz $CDCl_3$) δ 8.38 (d, *J* = 2.2 Hz, 1H), 8.29 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.80-7.60 (m, 1H), 7.20 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 6.79 (s, 1H), 4.84 (s, 1H), 1.26 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 148.4, 147.6, 136.8, 135.0, 123.8, 71.8, 51.2, 28.7. HRMS: expected: 208.1212, found: 209,1287 (M+H). IR (thin film): cm^{-1} 3296, 2967, 2929, 1879, 1654, 1521, 1221, 1077, 709.

N-cyclohexyl-2-hydroxy-2-(pyridin-3-yl) acetamide (1g): Following general procedure with pyridine-3-carboxaldehyde and cyclohexyl isocyanide, **1g** was obtained as a yellow oil in 86% yield (403 mg, 1.72 mmol) after column chromatography (CH_2Cl_2: MeOH = 100/0 to 95/5). ^{1}H NMR (400 MHz $CDCl_3$) δ 8.41 (s, 1H), 8.25 (d, *J* = 4.8 Hz, 1H), 7.71 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.17 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 2H), 4.93 (s, 1H), 3.61 (td, *J* = 14.4, 7.0 Hz, 1H), 1.88-1.45 (m, 6H), 1.36-0.92 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 148.2, 147.5, 136.8, 135.0, 123.7, 71.44, 48.1, 32.9, 32.9, 25.4, 24.8, 24.8.
HRMS: expected: 234.1368, found: 109.0523 (M+H-C(O)NHCy) .
IR (thin film): cm^{-1} 3271, 2928, 2853, 1647, 1589, 1523, 1077, 1029, 708.

N-(3,4-dimethoxyphenethyl)-2-hydroxy-2-(pyridin-3-yl)acetamide (1h):
Following general procedure with pyridine-3-carboxaldehyde and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene, **1h** was obtained as a red solid (m.p. 93-95 °C) in 82% yield (519 mg, 1.64 mmol) after column chromatography (CH_2Cl_2: MeOH = 98/2 to 90/10). ^{1}H NMR (400 MHz $CDCl_3$) δ 8.35 (d, *J* = 2.1 Hz, 1H), 8.29 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.61 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.17 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.92 (t, *J* = 6.0 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 6.64-6.53 (m, 2H), 4.94 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.44 (qd, *J* = 7.0, 3.3 Hz, 2H), 2.68 (td, *J* = 7.0, 1.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 149.0, 148.8, 147.7, 147.7, 136.2, 134.8, 131.0, 123.8, 120.7, 111.9, 111.4, 71.7, 55.9, 55.9, 40.5, 35.2. HRMS: expected: 316.1423, found: 316.1419. IR (thin film): cm^{-1} 3284, 3054, 2936, 2835, 1657, 1511, 1458, 1421, 1259, 1233, 1024, 730, 706.

N-cyclohexyl-2-(furan-2-yl)-2-hydroxyacetamide (1i): Following general procedure with furan-2-carbaldehyde and cyclohexyl isocyanide, **1i** was obtained as a brown solid (m.p. 85-87 °C) in 72% yield (322 mg, 1.44 mmol) after column chromatography (PE:EtOAc = 100:00 to 85:15). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.33 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.32 (dt, *J* = 3.3, 0.8 Hz, 1H), 6.29 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.03 (d, *J* = 8.3 Hz, 1H), 5.00 (d, *J* = 3.7 Hz, 1H), 3.81 – 3.65 (m, 2H), 1.94-1.74 (m, 1H), 1.73-1.46 (m, 2H), 1.43-0.97 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 152.0, 143.0, 110.7, 108.5, 67.6, 48.7, 32.9, 32.9, 25.4, 24.7, 24.7. HRMS: expected: 223.1208, found: 223.1201.
IR (thin film): cm^{-1} 3292, 2928, 2853, 1646, 1529, 1448, 1146, 1057, 734.

N-(tert-butyl)-2-hydroxy-2-phenylacetamide (1j): Following general procedure with benzaldehyde and *tert*-butyl isocyanide, **1j** was obtained as a white solid (m.p. 89-93 °C) in 70% yield (290 mg, 1.40 mmol) after column chromatography (PE:EtOAc = 100:00 to 85:15). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.51-7.35 (m, 5H), 5.88 (s, 1H), 4.94 (d, *J* = 3.5 Hz, 1H), 3.77 (d, *J* = 3.2 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 139.9, 129.0, 128.6, 126.9, 74.2, 51.6, 28.7. HRMS: expected: 207.1259 found: 207.1253. IR (thin film): cm^{-1} 3353, 3243, 2965, 2921, 1638, 1530, 1451, 1229, 735.

N-(tert-butyl)-2-hydroxy-2-(4-methoxyphenyl)acetamide (1k):
Following general procedure with *p*-methoxy benzaldehyde and *tert*-butyl isocyanide, **1k** was obtained as a white solid (m.p. 94-96 °C) in 82% yield (389 mg, 1.64 mmol) after column chromatography

(PE:EtOAc = 90:10 to 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 9.0, 2.5 Hz, 2H), 6.95 (dd, *J* = 9.0, 2.5 Hz, 2H), 5.85 (s, 1H), 4.91 (d, *J* = 3.2 Hz, 1H), 3.87 (t, *J* = 1.4 Hz, 3H), 3.69 (t, *J* = 2.7 Hz, 1H), 1.38 (t, *J* = 1.4 Hz, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 159.8, 132.1, 128.3, 114.3, 73.8, 55.4, 51.5, 28.7. HRMS: expected: 237.1365, found: 237.1365. IR (thin film): cm^{-1} 3380, 2966, 1652, 1510, 1245, 1174, 1065, 1032, 734.

N-(tert-butyl)-2-hydroxy-4-methylpentanamide (1l):
Following general procedure with isobutyraldehyde and *tert*-butyl isocyanide, **1l** was obtained as a white solid (m.p. 83-85 °C) in 88% yield (330 mg,1.76 mmol) after column chromatography (PE:EtOAc = 90:10 to 70:30. ^{1}H NMR (400 MHz $CDCl_3$) δ 6.11 (s, 1H), 3.94 (ddd, *J* = 9.7, 5.2, 3.4 Hz, 1H), 2.61-2.37 (m, 1H), 1.76 (dddd, *J* = 13.3, 11.5, 6.6, 3.3 Hz, 1H), 1.61-1.36 (m, 2H), 1.30 (s, 9H), 0.90 (d, *J* = 3.0 Hz, 3H), 0.88 (d, *J* = 2.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 70.9, 51.0, 44.1, 28.8, 24.6, 23.6, 21.5. HRMS: expected: 187.1572, found: 187.1562. IR (thin film): cm^{-1} 3356, 3252, 2955, 1642, 1533, 1229, 1085.

General procedure for the synthesis of O-propargyloxy-acetamides 2a:
N-(tert-butyl)-2-(4-chlorophenyl)-2-hydroxyacetamide **1a** (1,00 mmol) was dissolved in 2,0 mL of MeCN, and *t*-BuOK (1.20 equiv) was added. The solution was stirred at r.t. for 20 min and alkylating reagent (1.20 equiv.) was added dropwise. The solution was kept stirring at r.t. for 2h. The reaction mixture was quenched with sat. NH_4Cl solution, and the aqueous solution was extracted with 3x10 mL of EtOAc. The organic layer was washed with 20 mL of brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (PE/EtOAc= 95:05 to 80:20).

N-(tert-butyl)-2-(4-chlorophenyl)-2-(prop-2-yn-1-yloxy)acetamide (2a):
Following general procedure using propargyl bromide as alkylating reagent, **2a** was obtained as a yellow solid (m.p. 93-96 °C) in 96% yield (269 mg, 0.96 mmol) after column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 4H), 6.51 (s, 1H), 4.81 (s, 1H), 4.18 (dd, *J* = 15.8, 2.4 Hz, 1H), 3.92 (dd, *J* = 15.8, 2.4 Hz, 1H), 2.43 (t, *J* = 2.4 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 135.4, 134.5, 128.9, 128.8, 79.9, 78.2, 75.9, 56.4, 51.2, 28.8. HRMS: expected: 279.1026, found: 179.0264 (M-C(O)NH*t*Bu). IR (thin film): cm^{-1} 3408, 3298, 2968, 1673, 1518, 1489, 1083.

General procedure for the one-pot synthesis of 2,5 dihydrofurans and isoxazoles:
The corresponding α-hydroxyamide (0.50 mmol) was dissolved in 1.00 mL of acetonitrile, *t*-BuOK (1.20 equiv.) was added and the solution was stirred for 20 min. Then, propargylbromide (1.20 equiv.) was added and the solution was stirred for another 2 h at r.t. To the previous solution was added an extra amount of *t*-BuOK (1.50 equiv.) and the solution was stirred for 22h at 50°C. The reaction mixture was quenched with sat. NH_4Cl solution, and the aqueous solution was extracted with 3x10 mL of EtOAc. The organic layer was washed with 20 mL of brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography with the suited eluent.

N-(tert-butyl)-2-(4-chlorophenyl)-2,5-dihydrofuran-2-carboxamide (3a):
Following general procedure with N-(tert-butyl)-2-(4-chlorophenyl)-2-hydroxyacetamide, **3a** was obtained as a colourless oil in 61% yield (85 mg, 0.31 mmol) after column chromatography (PE/EtOAc = 95:05 to 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.34 (m, 2H), 7.24-7.18 (m, 2H), 6.73 (s, 1H), 6.17 (dt, *J* = 6.1, 2.5 Hz, 1H), 5.92 (dt, *J* = 6.1, 1.6 Hz, 1H), 4.88-4.63 (m, 2H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 139.9, 133.7, 130.6, 128.4, 127.2, 126.7, 94.1, 76.0, 50.9, 28.8. HRMS: expected: 279.1026, found 279.1014. IR (thin film): cm^{-1} 3397, 2966, 2923, 2860, 2195, 1665, 1511, 1488, 1223, 1073, 757.

2-(4-chlorophenyl)-N-cyclohexyl-2,5-dihydrofuran-2-carboxamide (3b):
Following general procedure with 2-(4-chlorophenyl)-N-cyclohexyl-2-hydroxyacetamide, **3b** was obtained as a pale yellow oil in 63% yield (96 mg, 0.32 mmol) after column chromatography (PE/EtOAc = 95:05 to 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.36 (m, 2H), 7.26-7.20 (m, 2H), 6.92-6.68 (m, 1H), 6.18 (dt, *J* = 6.1, 2.5 Hz, 1H), 5.93 (dt, *J* = 6.1, 1.6 Hz, 1H), 4.75 (td, *J* = 2.7, 1.6 Hz, 2H), 3.78-3.42 (m, 1H), 1.88-1.72 (m, 2H), 1.71-1.47 (m, 3H), 1.42-0.98 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 139.7, 133.7, 130.5, 128.4, 127.2, 126.8, 94.1, 76.0, 47.9, 33.1, 33.0, 25.5, 24.8, 24.8. HRMS: expected: 305.1183, found: 179.0259 (M - C(O)NHCy). IR (thin film): cm^{-1} 3406, 3329, 2927, 2852, 1658, 1507, 1488, 1071.

2-(4-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-2,5-dihydrofuran-2-carboxamide (3c):
Following general procedure with 2-(4-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-2-hydroxyacetamide, **3c** was obtained as a yellow oil in 47% yield (82 mg, 0.24 mmol) after column chromatography (PE/EtOAc = 85:15). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.42-7.26 (m, 2H), 7.26-7.11 (m, 2H), 6.92 (t, *J* = 6.0 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 1H), 6.60-6.55 (m, 2H), 6.15 (dt, *J* = 6.1, 2.4 Hz, 1H), 5.89 (dt, *J* = 6.1, 1.6 Hz, 1H), 4.64 (qdd, *J* = 13.2, 2.5, 1.6 Hz, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 3.40 (dp, *J* = 16.5, 6.6 Hz, 2H), 2.66 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 149.0, 147.7, 139.5, 133.8, 131.2, 130.2, 128.4, 127.1, 126.9, 120.8, 111.9, 111.3, 94.1, 76.0, 55.9 (d, *J* = 10.6 Hz), 40.3, 35.2. HRMS: expected: 387.1237 found: 387.1243. IR (thin film): cm^{-1} 3406, 3055, 2933, 2857, 1665, 1510, 1260, 1234, 1022, 732.

N-(tert-butyl)-2-(4-fluorophenyl)-2,5-dihydrofuran-2-carboxamide (3d):
Following general procedure with N-(tert-butyl)-2-(4-fluorophenyl)-2-hydroxyacetamide **3d** was obtained as a colourless oil in 31% yield (41 mg, 0.16 mmol) after column chromatography (PE/EtOAc= 100:0 to 85/15). 50% of starting material was recovered after column chromatography. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.51-7.33 (m, 2H), 6.94 (m, 2H), 6.86-6.69 (m, 1H), 6.18 (dt, *J* = 6.1, 2.4 Hz, 1H), 5.93 (dt, *J* = 6.1, 1.6 Hz, 1H), 4.91-4.60 (m, 2H), 1.28 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 162.4 (d, *J* = 246.0 Hz), 137.2 (d, *J* = 3.1 Hz), 130.8, 127.5 (d, *J* = 8.2 Hz), 126.6, 115.1 (d, *J* = 21.4 Hz), 94.2, 75.9, 50.9, 28.8. HRMS: expected: 263.1322, found: 163.0555 (M-C(O)NH*t*Bu). IR (thin film): cm^{-1} 3401, 2970, 1775, 1677, 1506, 1227, 836.

N-cyclohexyl-2-(4-fluorophenyl)-2,5-dihydrofuran-2-carboxamide (3e):
Following general procedure with N-cyclohexyl-2-(4-fluorophenyl)-2-hydroxyacetamide **3e** was obtained as a yellow oil in 67% yield (84 mg, 0.34 mmol) after column chromatography (PE/EtOAc = 95:05 to 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.17 (m, 3H), 7.04-6.89 (m, 2H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.20 (dt, *J* = 6.1, 2.5 Hz, 1H), 5.95 (dt, *J* = 6.1, 1.6 Hz, 1H), 4.76 (dt, *J* = 2.7, 1.3 Hz, 2H), 3.77-3.53 (m, 1H), 1.91-1.43 (m, 7H), 1.42-0.98 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 162.5 (d, *J* = 246.2 Hz), 137/0, 130.6, 127.6 (d, *J* = 8.3 Hz), 126.7, 115.2 (d, *J* = 21.5 Hz), 94.2, 75.9, 47.8, 33.1, 33.1, 25.5, 24.9,

24.8. HRMS: expected: 289.1478, found: 163.0555 (M-C(O)NHCy). IR (thin film): cm^{-1} 3407, 3332, 2927, 2853, 2321, 1773, 1659, 1501, 1229, 1069, 833.

N-(tert-butyl)-2-(pyridin-3-yl)-2,5-dihydrofuran-2-carboxamide (3f):

Following general procedure with N-(tert-butyl)-2-hydroxy-2-(pyridin-3-yl) acetamide, **3f** was obtained in 56% yield (69 mg, 0.28 mmol) after column chromatography (PE/EtOAc = 85:15) .^{1}H NMR (400 MHz $CDCl_3$) δ 8.79 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.56 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.88 (ddd, *J* = 8.0, 2.3, 1.6 Hz, 1H), 7.29 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 6.86 (s, 1H), 6.30 (dt, *J* = 6.1, 2.5 Hz, 1H), 6.08 (dt, *J* = 6.1, 1.6 Hz, 1H), 4.89 (qdd, *J* = 13.2, 2.5, 1.6 Hz, 2H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 149.0, 147.2, 136.9, 133.6, 130.2, 127.1, 123.1, 93.1, 76.1, 51.0, 28.7. HRMS: expected: 246.1368, found: 146.0601 (M-C(O)NH*t*Bu). IR (thin film): cm^{-1} 3411, 2946, 2893, 1775, 1669, 1511, 1074, 710.

N-cyclohexyl-2-(pyridin-3-yl)-2,5-dihydrofuran-2-carboxamide (3g):

Following general procedure with N-cyclohexyl-2-hydroxy-2-(pyridin-3-yl) acetamide **3g** was obtained as a dark yellow solid (m.p. 118-121 °C) in 52% yield (71 mg, 0.26 mmol) after column chromatography (PE/EtOAc= 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.3 Hz, 1H), 8.55-8.39 (m, 1H), 7.79 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.18 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.20 (dt, *J* = 6.1, 2.5 Hz, 1H), 5.97 (dt, *J* = 6.1, 1.6 Hz, 1H), 4.93-4.65 (m, 2H), 3.63 (dddd, *J* = 10.6, 8.5, 6.7, 4.2 Hz, 1H), 1.93-1.41 (m, 5H), 1.41-0.96 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 149.0, 147,2, 136.8, 133.6, 130.0, 127.2, 123.1, 93.0, 76.1, 47.9, 33.0, 33.0, 25.5, 24.8, 24.8. HRMS: expected: 272.1525 found: 272.1530. IR (thin film): cm^{-1} 3403, 3318, 3043, 2927, 2853, 1655, 1580, 1510, 1072, 707.

N-(3,4-dimethoxyphenethyl)-2-(pyridin-3-yl)-2,5-dihydrofuran-2-carboxamide (3h):

Following general procedure with N-(3,4-dimethoxyphenethyl)-2-hydroxy-2-(pyridin-3-yl) acetamide **3h** was obtained as a light brown colored oil in 44% yield (78 mg, 0.22 mmol) after column chromatography (PE/EtOAc= 85:15 to 65:35). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73-8.65 (m, 1H), 8.43 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.72 (ddd, *J* = 8.0, 2.4, 1.6 Hz, 1H), 7.16 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 6.99 (t, *J* = 6.1 Hz, 1H), 6.73-6.66 (m, 1H), 6.64-6.52 (m, 2H), 6.19 (dt, *J* = 6.1, 2.4 Hz, 1H), 5.94 (dt, *J* = 6.1, 1.6 Hz, 1H), 4.90-4.59 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.42 (ddd, *J* = 12.7, 6.9, 5.8 Hz, 2H), 2.68 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 149.0, 148.9, 147.7, 147.1, 136.6, 133.6, 131.1, 127.3, 123.1, 120.7, 111.9, 111.3, 93.1, 76.2, 55.9, 55.8, 40.3, 35.2. HRMS: expected: 354.1580, found: 354.1580. IR (thin film): cm^{-1} 3353, 2937, 2836, 1663, 1510, 1260, 1234, 1024, 730.

N-cyclohexyl-[2,2'-bifuran]-2(5H)-carboxamide (3i):

Following general procedure with N-cyclohexyl-2-(furan-2-yl)-2-hydroxyacetamide **3i** was obtained as a brown solid (m.p. 113-116 °C) in 62% yield (82 mg, 0.31 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.24 (qd, *J* = 3.3, 1.4 Hz, 2H), 6.09 (dt, *J* = 6.1, 2.4 Hz, 1H), 6.04 (dt, *J* = 6.1, 1.5 Hz, 1H), 4.75 (qdd, *J* = 13.1, 2.4, 1.6 Hz, 2H), 3.71 (tdt, *J* = 10.6, 8.1, 3.9 Hz, 1H), 1.98-1.48 (m, 5H), 1.43-1.00 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 152.8, 142.8, 128.5, 128.0, 110.4, 108.2, 90.5, 76.1, 47.9, 33.0, 25.5, 24.8, 24.8. HRMS: expected: 261.1365, found: 261.1357. IR (thin film): cm^{-1} 3353, 2928, 2854, 1658, 1514, 1154, 1062, 757, 738 .

N-(tert-butyl)-2-phenyl-2,5-dihydrofuran-2-carboxamide (3j'):

Following general procedure with N-(tert-butyl)-2-hydroxy-2-phenylacetamide **3j** was obtained as a colourless oil in 25% yield (32 mg, 0.13 mmol) after column chromatography (contaminated with around 10% of an inseparable impurity). The 2,3-hydrofuran **3j'** isomer was also isolated as a colourless oil in 29% isolated yield (35 mg, 0.14 mmol)

3j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.39 (m, 2H), 7.29-7.23 (m, 2H), 7.23-7.16 (m, 1H), 6.77 (s, 1H), 6.22 (dt, J = 6.1, 2.5 Hz, 1H), 5.93 (dt, J = 6.0, 1.6 Hz, 1H), 4.82-4.68 (m, 2H), 1.28 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 141.3, 130.8, 128.4, 127.8, 126.5, 125.7, 94.7, 75.9, 50.9, 28.8.

3j': ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.42 (m, 2H), 7.31-7.23 (m, 2H), 7.24-7.16 (m, 1H), 6.52 (s, 1H), 6.33 (q, *J* = 2.4 Hz, 1H), 4.92 (q, *J* = 2.6 Hz, 1H), 3.48 (dt, *J* = 16.0, 2.5 Hz, 1H), 2.78 (dt, *J* = 15.9, 2.4 Hz, 1H), 1.24 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 143.1, 142.1, 128.3, 127.7, 125.0, 101.0, 90.2, 51.0, 41.1, 28.6. HRMS: expected: 245.1416, found: 245.1414. IR (thin film): cm^{-1} 3414, 2967, 2868, 1675, 1511, 1451, 1226, 1046, 698.

3-(tert-butyl)-5-(4-methoxyphenyl)-2-vinyloxazolidin-4-one (4a):

Following general procedure with N-(tert-butyl)-2-hydroxy-2-(4-methoxyphenyl)acetamide, **4a** was obtained as a colourless oil in 64% yield (88 mg, 0.32 mmol) after column chromatography (PE/EtOAc = 100:00 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.05 – 6.88 (m, 2H), 6.07 (ddd, *J* = 17.1, 10.1, 7.7 Hz, 1H), 5.78 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.57 (d, *J* = 17.1 Hz, 1H), 5.48 (d, *J* = 10.2 Hz, 1H), 5.21 (d, *J* = 1.5 Hz, 1H), 3.85 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 159.9, 136.8, 129.1, 128.2, 119.8, 114.1, 90.2, 78.7, 55.3, 54.8, 28.0. HRMS: expected 275.1521, found: 175.0747 (M-C(O)NH*t*Bu). IR (thin film): cm^{-1} 2932, 2855, 1698, 1512, 1248, 1175, 1031, 732.

3-(tert-butyl)-5-isobutyl-2-vinyloxazolidin-4-one (4b):

Following general procedure with N-(tert-butyl)-2-hydroxy-4-methylpentanamide **4b** was obtain as a colourless oil in 57% yield (64 mg, 0.29 mmol) after column chromatography (PE/EtOAC = 100:00 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.1, 10.1, 7.7 Hz, 1H), 5.56-5.51 (m, 1H), 5.46 (dt, *J* = 17.1, 0.8 Hz, 1H), 5.38 (dt, *J* = 10.1, 0.7 Hz, 1H), 4.29 (ddd, *J* = 9.3, 3.3, 1.5 Hz, 1H), 1.94-1.79 (m, 1H), 1.70 (ddd, *J* = 14.1, 8.7, 3.3 Hz, 1H), 1.57-1.47 (m, 1H), 1.45 (s, 9H), 1.01-0.85 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 136.7, 119.2, 89.8, 75.6, 54.4, 41.0, 27.9, 24.7, 23.3, 21.8. HRMS: expected: 225.1729, found: 225.1730. IR (thin film): cm^{-1} 2957, 2872, 1699, 1394, 1366, 1215, 936.

ethyl 2-phenyl-2-(prop-2-yn-1-yloxy)acetate (6):

ethyl 2-oxo-2-phenylacetate (4.00 mmol) was treated with *p*-toluene sulfonylhydrazide (1.05 equiv.) in 20 mL of MeOH. The solution was stirred at r.t. for 12h, the solvent was removed under reduced pressure giving a pale yellow oil which was dissolved in 20 mL EtOAc and washed with 3x 10 mL of water to removed the remaining hydrazide. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure affording the ethyl-2-phenyl-2-(2-tosylhydrazineylidene)acetate quantitatively. Hydrazone was engaged in next step without purification.

ethyl (E)-2-phenyl-2-(2-tosylhydrazineylidene)acetate was treated with triethylamine (1.20 equiv.) in dichloromethane (20 mL, 0.40M) for 24h. 40 mL Were then added to the solution and the organic layer was washed with 3 x 20 mL, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give ethyl 2-diazo-2-phenylacetate, which was directly engaged in next step.

To a solution ethyl 2-diazo-2-phenylacetate in dichloromethane (40 mL, 0.1M) was added propargyl alcohol (10.00 equiv) and the solution was stirred for 5 min. Boron trifluoride diethyl etherate

complex (0.10 equiv.) was then added: the solution started to bubble gently: the reaction was stirred for 2h at r.t. until no more bubbling was observed. The reaction was quenched with 10 mL of water, the organic layer was washed with 3x 20 mL of water, dried over $MgSO_4$ and the solvent was removed under vacuum to afford a yellow oil which was purified by column chromatograph giving ethyl 2-phenyl-2-(prop-2-yn-1-yloxy)acetate as a deep yellow oil in 67% yield (585 mg, 2.67 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.47 (m, 2H), 7.47-7.35 (m, 3H), 5.24 (s, 1H), 4.41 – 4.12 (m, 4H), 2.54 (t, *J* = 2.4 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 135.5, 129.0, 128.7, 127.6, 78.7, 75.7, 61.4, 56.2, 14.1. HRMS: expected: 218.0943, found: 218.0946. IR (thin film): cm^{-1} 3284, 2983, 2902, 1737, 1206, 1178, 1094, 1024, 695.

ethyl 2-phenyl-2,5-dihydrofuran-2-carboxylate (7):
ethyl 2-phenyl-2-(prop-2-yn-1-yloxy)acetate (0.50 mmol) was treated with *t*-BuOK (1.10 equiv.) in DMF (1.00 mL). The solution was stirred for 24h at 50°C. The solution was quenched with water diluted with 15 mL EtOAc, and the organic layer was washed with 3 x 20 mL of water, dried over $MgSO_4$, the solvent was removed under vacuum and the crude was purified by column chromatography (PE/EtOAc = 100:00 to 85:15) affording 3 ethyl 2-phenyl-2,5-dihydrofuran-2-carboxylate as a colourless oil in 12% yield (13 mg, 0.06 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (tt, *J* = 5.8, 1.4 Hz, 2H), 7.33-7.18 (m, 3H), 6.15 (ddt, *J* = 23.9, 6.1, 2.5 Hz, 1H), 6.07-5.95 (m, 1H), 4.91-4.69 (m, 2H), 4.27-3.97 (m, 2H), 1.17 (td, *J* = 7.1, 2.3 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 140.5, 129.0, 128.5, 128.5, 128.1, 125.4, 93.8, 76.1, 61.6, 14.2. IR (thin film): cm^{-1} 3097, 2996, 2917, 2852, 1776, 1731, 1234, 1095, 1032, 695.

3-oxo-3-(2-phenyl-2,5-dihydrofuran-2-yl)propanenitrile (8):
ethyl 2-phenyl-2-(prop-2-yn-1-yloxy)acetate (0.50 mmol) was treated with *t*-BuOK (1.10 equiv.) in MeCN (1.00 mL). The solution was stirred for 24h at 50°C. The solution was quenched with water diluted with 15 mL EtOAc, and the organic layer was washed with 3 x 20 mL of water, dried over $MgSO_4$, the solvent was removed under vacuum and the crude was purified by column chromatography (PE/EtOAc = 100:00 to 85:15) affording 3-oxo-3-(2-phenyl-2,5-dihydrofuran-2-yl)propanenitrile as a dark red oil in 10% yield (11 mg , 0.05 mmol) as a dark red oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 2H), 7.36-7.23 (m, 3H), 6.14 (dt, *J* = 6.1, 2.5 Hz, 1H), 6.01 (dt, *J* = 6.1, 1.6 Hz, 1H), 5.00-4.72 (m, 2H), 3.83 (d, *J* = 19.7 Hz, 1H), 3.53 (d, *J* = 19.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 138.4, 129.0, 128.6, 128.5, 128.3, 124.9, 113.6, 98.3, 76.4, 28.2. HRMS: expected: 213.0790, found: 145.0653 (M-C(O)CH_2CN). IR (thin film): cm^{-1} 3062, 2918, 2861, 1730, 1308, 1067, 741, 699..

2-hydroxy-2-phenyl-1-(pyrrolidin-1-yl)ethan-1-one (9)
methyl 2-hydroxy-2-phenylacetate (2.00 mmol) was treated with pyrrolidine (1.50 equiv.) in presence of *p*-toluene sulfonic acid (0.10 equiv.) in toluene (10 mL, 2.0 M). The solution was stirred at 100°C overnight. Solvent was removed under vacuum and the crude solid was dissolved in 30 mL EtOAc and washed with 3x 10 mL of water. The organic layer was dried over $MgSO_4$, the solvent was removed under vacuum affording 2-hydroxy-2-phenyl-1-(pyrrolidin-1-yl)ethan-1-one as a white solid (96-99 °C) in 90% yield (369 mg, 1.80 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 5H), 4.97 (d, *J* = 5.9 Hz, 1H), 4.69 (d, *J* = 6.0 Hz, 1H), 3.63 – 3.23 (m, 3H), 2.91 – 2.63 (m, 1H), 1.90 – 1.55 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 139.0, 128.9, 128.5, 127.8, 72.7, 46.6, 45.9, 25.9, 23.8. HRMS: expected: 205.1103, found: 205.1102. IR (thin film): cm^{-1} 3390, 2972, 2878, 1632, 1450, 1382, 1190, 1067, 702.

(2-phenyl-2,3-dihydrofuran-2-yl)(pyrrolidin-1-yl)methanone (11):
2-hydroxy-2-phenyl-1-(pyrrolidin-1-yl)ethan-1-one (0.50 mmol) was treated with *t*-BuOK (1.10 equiv.) in MeCN (1.00 mL). The solution was stirred for 24h at 50°C. The solution was quenched with water diluted with 15 mL EtOAc, and the organic layer was washed with 3 x 20 mL of water, dried over $MgSO_4$, the solvent was removed under vacuum and the crude was purified by column chromatography (PE/EtOAc = 100:00 to 85:15) affording (2-phenyl-2,3-dihydrofuran-2-yl)(pyrrolidin-1-yl)methanone as a colorless oil in 72% yield (88mg , 0.36 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.14 (m, 5H), 6.32 (q, *J* = 2.5 Hz, 1H), 4.86 (q, *J* = 2.6 Hz, 1H), 3.99 (dt, *J* = 16.0, 2.5 Hz, 1H), 3.60-3.31 (m, 3H), 2.93 (ddd, *J* = 11.5, 7.5, 4.3 Hz, 1H), 2.47 (dt, *J* = 15.9, 2.4 Hz, 1H), 1.78-1.40 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 142.9, 142.5, 128.6, 127.4, 124.1, 100.1, 91.3, 47.5, 47.1, 42.3, 26.4, 23.4. HRMS: expected: 243.1259, found: 243.1258. IR (thin film): cm^{-1} 3395, 2968, 2871, 1637, 1423, 1146, 1042, 965, 700.

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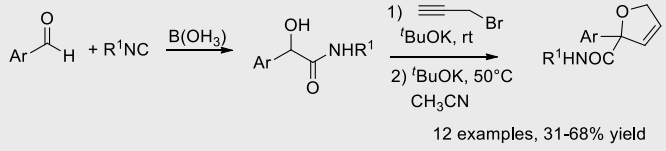

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