EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Transformation of Racemic Azlactones into Enantioenriched Dihydropyrroles and Lactones Enabled by Hydrogen-Bond Organocatalysis

Authors: Matej Zabka, Adrian Kocian, Stanislav Bilka, Samuel Andrejcak, and Radovan Sebesta

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201901052

Link to VoR: http://dx.doi.org/10.1002/ejoc.201901052

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201901052

WILEY-VCH

Transformation of Racemic Azlactones into Enantioenriched Dihydropyrroles and Lactones Enabled by Hydrogen-Bond Organocatalysis

Matej Žabka,[a] Adrián Kocian,[a] Stanislav Bilka,[a] Samuel Andrejčák,[a] and Radovan Šebesta*[a]

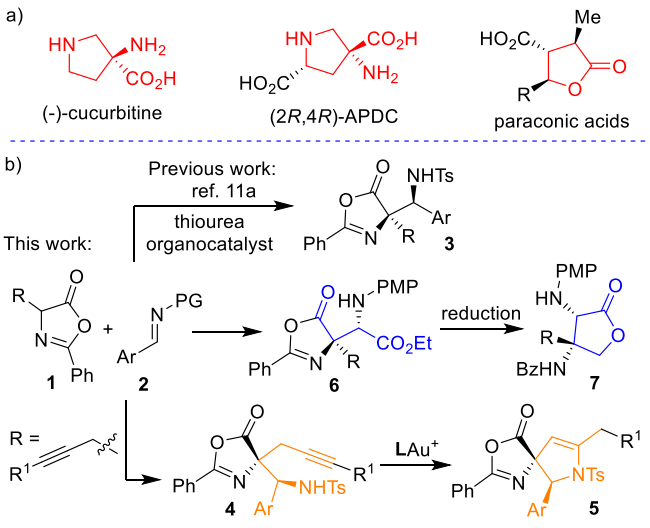
Abstract: Azlactones, a potent building block for the synthesis of complex molecules, have been explored in an organocatalytic Mannich reaction with protected imines. In this study, azlactones containing a propargyl substituent were employed for the first time in organocatalysis so far. The catalytically active species responsible for high enantioselectivity with substrate containing such a small linear substituent is assembled in situ from a bifunctional thiourea, prone to dimerization, and an organic acid, as evidenced by DOSY NMR. The resulting α,β-diamino acid derivatives were subjected to further derivatization: as an example, gold-catalyzed intramolecular hydroamination of alkynes gave chiral spirocyclic dihydropyrrole. Alternatively, related squaramide catalyst enabled a Mannich reaction of azlactones with N-aryl or alkyl glyoxylate imines. Reduction of these adducts gave access to 2,3-diaminobutyrolactones or 2,3-diamino-1,4-diol with a tertiary and a quaternary stereocenter.

Introduction

The synthesis of polyfunctionalized, enantioenriched heterocyclic molecules has been recently in high demand.[1] Such heterocycles are found in current state-of-the-art pharmaceuticals, drug candidates, and agrochemicals.[2] Specifically, chiral pyrrolidines and lactones are found as core skeletons in a number of bioactive compounds and natural products, e.g. (-)-cucurbitine, an amino acid isolated from pumpkin seeds, designed drug (2*R*,4*R*)-APDC, spirooligomer-peptoid hybrids,[3] or paraconic acids – lichen metabolites with antibiotic and antitumor properties (Scheme 1a). The most promising synthetic approach to the heterocycles with multiple stereogenic centers, with regards to cost, time and material used, is the use of cascade catalytic reactions.[4] Various organocatalytic domino strategies efficiently afforded highly substituted pyrrolidines.[5] The combination of organocatalysis with metal-catalyzed reactions proved useful in the assembling of chiral pyrrolidines,[6] or pyrroles.[7] Additionally, stereoselective catalytic synthesis of chiral butenolides and butyrolactones is highly relevant due to their occurrence in natural products and building blocks for synthesis.[8]

Hydrogen-bond donating organocatalysis, due to its flexibility and broad functional group tolerance is among the most versatile strategies for building complex chiral structures.[9] Here, we present a sequential use of hydrogen-bonding organocatalysis and gold(I)-catalysis towards chiral dihydropyrroles. Chiral lactones, on the other hand, were synthesized by the reduction of a highly decorated 2,3-diaminobutane-1,4-dicarboxylate skeleton (Scheme 1b). Versatile functional groups, including an ester, a carboxylic acid, or a protected amine, attached to these heterocycles with quaternary and tertiary stereocenters can be used as handles for further derivatization.

Azlactones have served as valuable building blocks for syntheses of numerous complex molecular scaffolds.[10] We and others have described catalytic methods, starting from racemic azlactones **1** and imines **2**, for accessing enantiopure α,β-diamino acid derivatives **3** (Scheme 1).[11] In this work, we set out to explore the possibility of appending a propargyl moiety to the azlactone, and then use the gold-catalyzed 5-*exo*-dig cyclization of intermediates **4** to afford the spirocyclic dihydropyrroles **5**. Catalysis with gold(I) species,[12] or in combination with organocatalysis, provides a suitable strategy for such hydroamination,[13] which affords variously substituted chiral pyrrolidines. Related spiro-cyclic pyrrolidines were assembled via diverse catalytic domino transformations.[14]



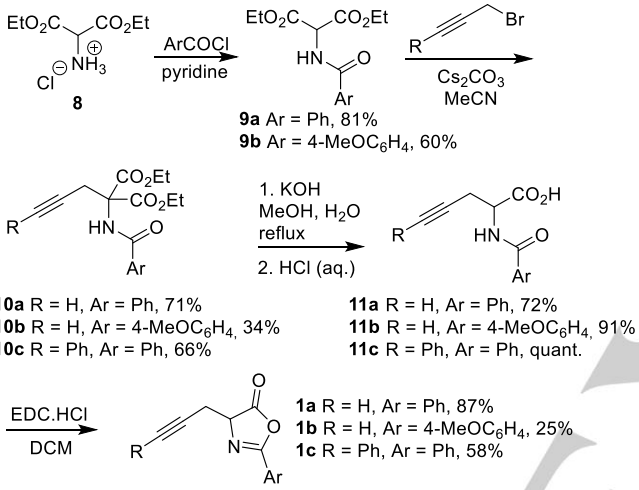
Scheme 1. a) Chiral pyrrolidines and lactones in selected important compounds; b) the context of this work.

[a] Dr. M. Žabka, A. Kocian, S. Bilka, S. Andrejčák, Prof. Dr. R. Šebesta
Department of Organic Chemistry, Faculty of Natural Science
Comenius University in Bratislava
Mlynska dolina, Ilkovičova 6, 84215 Bratislava, Slovakia
E-mail: radovan.sebesta@uniba.sk
Homepage: www.radovansebesta.com

Supporting information for this article is given via a link at the end of the document.

Results and Discussion

The synthesis of the starting azlactone **1a**, with appended propargyl residue, requires the amino acid propargylglycine as a precursor. Considering its cost, we opted for a cheaper alternative, i.e., the synthesis of propargyl azlactones from diethyl aminomalonate (**8**) in four steps (Scheme 2). Acylation with aroyl chloride gave amides **9**, and subsequent enolate alkylation with a suitable propargyl bromide furnished diesters **10**. Basic ester hydrolysis and decarboxylation gave *N*-protected propargylglycines **11**, which were dehydrated upon the action of EDC to give the required azlactones **1**. This approach allowed us to vary the aryl and alkyl-substituents easily.



Scheme 2. Synthesis of propargyl-substituted azlactones **1a**-**c**.

Initially, we screened hydrogen-bonding catalysts **C1**-**C7** for the organocatalytic Mannich reaction between azlactone **1a** and tosyl imine **2a** (Figure 1, Scheme 3). The results of this screening are summarized in Table 1.

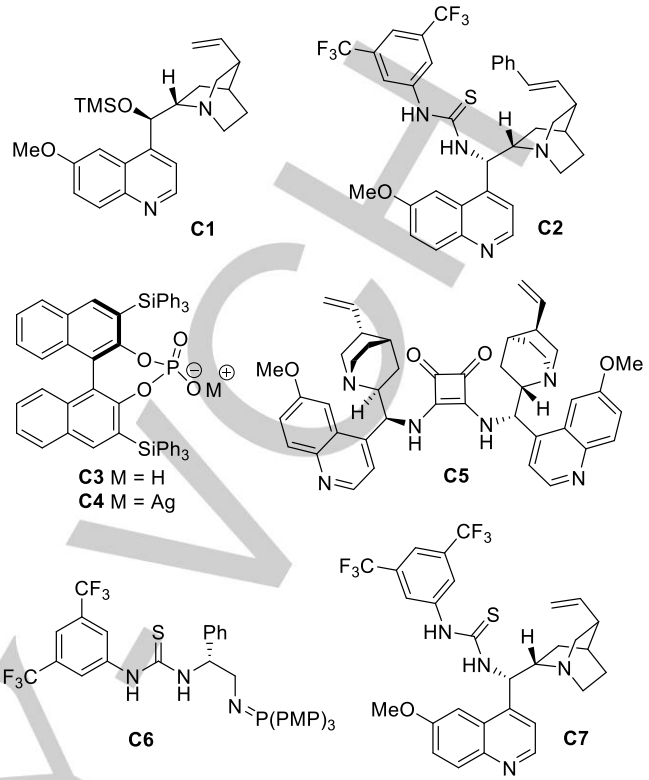
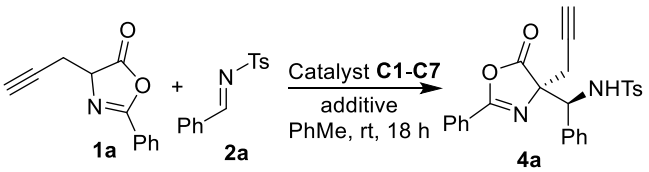


Figure 1. (Organo)catalysts used in this work for the Mannich reaction.

We first screened typical catalysts reported for the Mannich transformations of azlactones and related reactions. Catalysts such as TMS-quinine **C1**, BINOL phosphoric acid silver salt **C4**, dimeric squaramide **C5**, and iminophosphorane **C6** (Figure 1) delivered the required adduct but proved unsuccessful regarding stereoselectivity, particularly enantioselectivity. However, using the bifunctional thiourea catalysts **C2** or **C7**, derived from quinine, and the reaction conditions we reported previously for a related transformation,[11a] we were able to obtain the required adduct **4a** (Scheme 3) in moderate diastereomeric and very good enantiomeric purity of 92:8 e.r. (Table 1, entry 11). Changing the acid co-catalyst or the reaction conditions in any way did not lead to further improvement (Table 1, entries 13-15).



Scheme 3. Initial screening of the hydrogen-bonding catalysts.

Table 1. Catalyst screening in the Mannich reaction.

Entry[a]	Catalyst/(loading mol%)	Yield	d.r.	e.r.
1	**C1**[b] (20)	64	2.7:1	55:45
2	**C2** (5)	70	2.0:1	91:9
3	**C4** (10)	72	1.1:1	52:48
4	**C5** (10)	53	3.0:1	49:51
5	**C6**/10	71	3.0:1	57:43
6	**C7** (10)	52	3.3:1	92:8
7	**C7** (5)	63	2.4:1	89:11
8	**C7** (2.5)	59	2.9:1	92:8
9	**C7** (1)	49	2.8:1	86:14
10	**C7**[c] (10)	62	2.4:1	58:42
11	**C7**[d] (5)	70	3.6:1	92:8
12	**C7**[e] (10)	30f	1:1	-
13	**C7**+$PhB(OH)_2$ (10)	79	2.7:1	90:10
14	**C7**+TsOH (10)	80	2.5:1	91:9
15	**C7**+**C3** (10)	55	3.1:1	90:10

[a] Azlactone (0.24 mmol), imine (0.2 mmol), catalyst (x mol %), $PhCO_2H$ (x mol %), PhMe, rt, 18 h; [b] Et_2O used as a solvent, without $PhCO_2H$; [c] No acidic additive; [d] $PhCF_3$ used as a solvent; [e] Reaction conducted in a ball mill; [f] conversion determined by ^1H NMR.

Catalyst **C7** alone was not able to induce enantioselectivity (Table 1, entry 10). An acidic additive such as benzoic acid was required to improve the selectivity. A complex of thiourea **C7** and benzoic acid is presumed to be formed under the reaction conditions. This assembling of the enantioselective catalytic species was proved by a DOSY NMR study. A 1:1 mixture of **C7** and benzoic acid in benzene-d_6 gave rise to a new set of signals in DOSY spectra. Both components have identical *D* value ($8.1x10^{-6}$ cm^2/s), indicating the formation of a complex (Figure 2). Moreover, the signals of a free benzoic acid and a free catalyst were no longer present. Other organic acids, such as achiral boronic and sulfonic or chiral phosphoric acid also induce the same level of enantioselectivity (Table 1, entries 13 – 15). These results indicate that the acidity of the acidic species does not play a role in reaching high selectivity.

Based on these results, the acid most probably disrupts the equilibrium between the monomeric and dimeric species of the catalyst. The values of diffusion coefficients for the benzoic acid and catalyst from separate samples are slightly higher than predicted and arise due to the equilibria between monomeric and dimeric forms of both species. Another evidence comes from the broad peaks in a 1D ^1H spectrum of the free catalyst, which become sharp upon the addition of the acid, along with the significant downfield shift of the thiourea NH hydrogens to δ 9.5 – 11.5 ppm, indicating a relatively strong binding via H-bond. The subsequent addition of the azlactone did not lead to any change in the appearance of the spectrum of the catalyst-acid complex. The structure of the quinine catalyst dimer has been confirmed and studied previously by NMR.[15] An X-ray crystal structure of **C7** and *m*-chlorobenzoic acid has already been reported, thus supporting our hypothesis.[16]

To get insights into the structure of the complex, we conducted NMR studies of a 1:1 mixture of **C7** and diphenyl phosphate in CD_2Cl_2 at 180 K. To confirm the binding site of the thiourea host and the acid guest, we conducted a 2D ^1H,^{31}P-HMBC experiment.[17]

However, we could not detect any polarization transfer from thiourea protons (or other belonging to the catalyst) to phosphate ^{31}P nucleus via $^{2h}J_{HP}$, most probably due to the formation of an ion pair at low temperature. The dielectric constant of the solvent increases with decreasing temperature, and subsequently, ion pairs are stabilized. At 300 K, again no binding was observed using 2D NOESY or ^1H,^{31}P-HMBC. A single sharp ^{31}P and ^{19}F peaks were observed, indicating the formation of a single species. However, ^1H,^{31}P-HMBC showed at least three other species at low intensity. Only exchange of the phosphate OH hydrogen with the more acidic thiourea hydrogen next to the aryl group was detected (EXSY, 500 ms mixing time).

Titrating a solution of **C7** in either DCM or MeCN with benzoic acid (1 – 10 equiv.) did not cause any change in the ECD spectrum, particularly due to the low concentration required and small association constants. To reinforce this observation, anionic species such as acetate or phosphate, but not neutral molecules, have been reported to bind to oligo(thio)urea foldamers, as observed by the change of ECD signal, thus suggesting very low concentration of the ion pair at room temperature in our case.[18]

Related 1D ^1H NMR experiments with **C3** instead of diphenyl phosphate showed broad NH signals which became slightly sharper upon cooling down to 240 K at δ 11.0 – 11.5 ppm and two species were present according to ^{31}P NMR. However, we did not study this complex further due to significant signal overlap in the aromatic region of the ^1H NMR spectrum.

The hint at why the complex of chiral thiourea and the acid has much higher selectivity comes from the studies of Seidel and co-workers on conjugate base-stabilized carboxylic acids, exploiting the intramolecular activation of carboxylic acids by thiourea binding in asymmetric catalysis.[19] Similarly, the binding of carboxylic acids to Takemoto's bifunctional thiourea and its impact on the catalyst conformation has been described using a combination of VCD and computational methods.[20] In our case, intermolecular binding of the carboxylic acid to thiourea enhances the acidity of the carboxylic proton, which in turn activates the imine towards the addition of the nucleophile. The thiourea or the benzoic acid on their own are most probably not acidic enough to activate such tosyl imines. The thiourea moiety is thus relaying the chiral information across the bound benzoic

acid to the imine. This agrees with our previously calculated transition state at the Hartree-Fock level of theory.[11a]

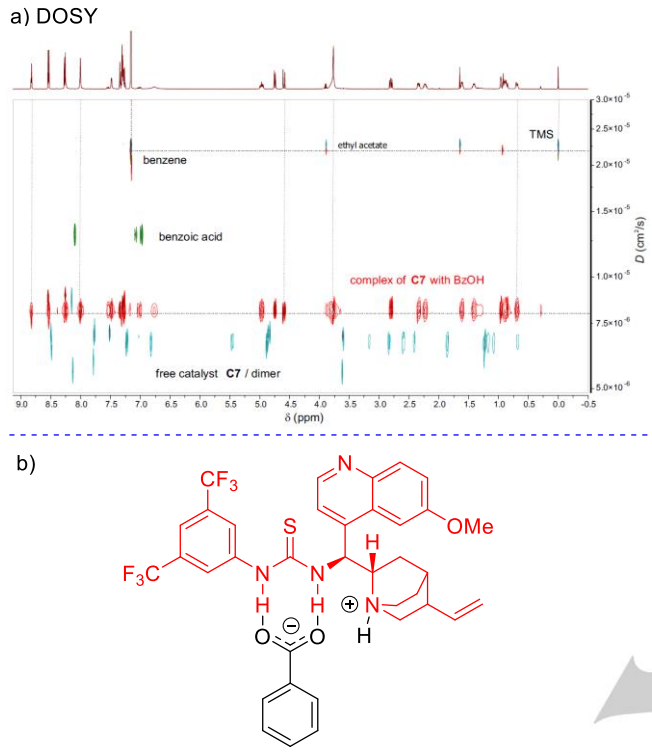


Figure 2. a) Overlaid DOSY NMR spectra of benzoic acid (green), free catalyst **C7** with its dimer (blue), and a 1:1 mixture of **C7** and benzoic acid, resulting in complex formation (red) with its 1D ^{1}H trace, in benzene-d_6 at 298 K, referenced to benzene (2.2x10-5 cm2/s) and TMS; b) proposed structure of the complex **C7**·$PhCO_2H$.

The moderate diastereoselectivity slightly diminishes the practical value of the Mannich reaction with chiral thioureas. This erosion in selectivity might arise from a background reaction with the catalyst. According to the HF calculation, the mutual arrangement of the azlactone and the imine in the TS is synclinal, shown in Figure S1 (see Supporting Information), allowing for the H-bond network between the catalyst and the substrates to develop and give the observed diastereomer. The other possible synclinal arrangement, with the imine rotated by 180°, leading to the other diastereomer, would result in repulsion between the azlactone alkyl group and the aryl group of the imine and is arguably disfavored. The same would be true for one of the antiperiplanar arrangements. However, the antiperiplanar approach leading to the minor diastereomer is still possible, and probably relevant in the reaction. As no H-bond network with the chiral catalyst can develop for this arrangement, the resulting minor diastereomer is racemic, in agreement with the experiment.

With the experimental conditions established to deliver product **4a** in reasonably high enantiomeric purity, we then varied aryl- and alkyl-group on the azlactone and the imine protecting and aryl groups. Three other alkynyl-appended adducts **4b-d** are depicted in Figure 3.

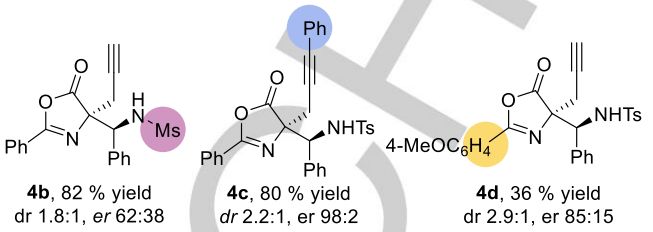
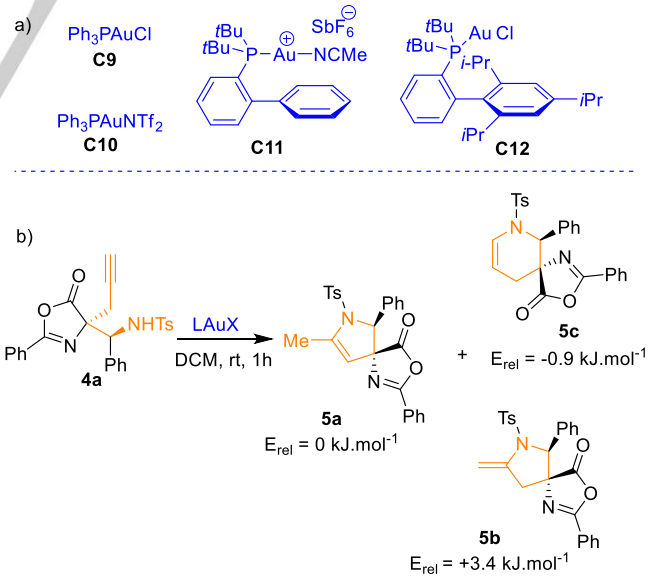


Figure 3. Additional propargyl Mannich products **4b-d** obtained with corresponding azlactones and sulfonyl imines.

With the products of the organocatalytic reaction in hand, we focused on the gold-catalyzed hydroamination reaction. We screened both neutral and cationic phosphine-gold complexes **C9-C12**. The set of screened complexes involved bulky phosphine ligands, such as Echavarren´s catalyst **C11** or **C12** (Scheme 4a). Gold-catalyzed hydroamination of compound **4a** afforded, after a full conversion, a mixture of products **5a-c** (Scheme 4b). Interestingly, an addition of 10 mol% of *p*-TsOH inhibited the reaction. From the inspection of ^{1}H NMR spectra of the crude mixture, we could rule out the presence of **5b**. However, other derivatives were detected. From this mixture, we could isolate as a pure material only the spirocyclic 2,3-dihydro-1*H*-pyrrole derivative **5a**. Result of Au-catalyzed spiro-cyclization are summarized in Table 2.



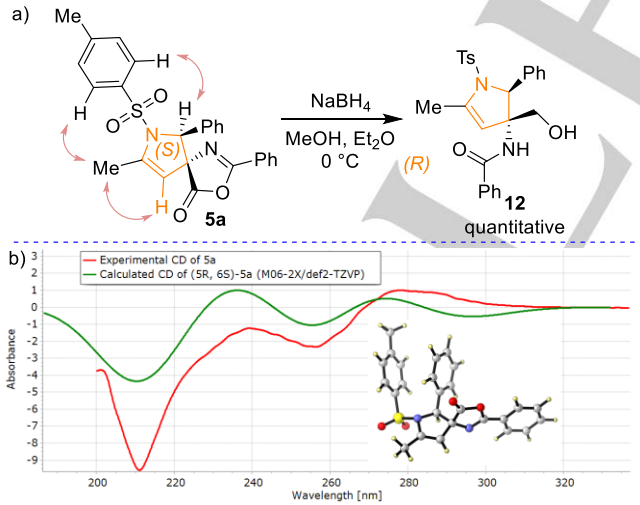
Scheme 4. a) Gold(I) catalysts used in this work; b) The hydroamination reaction; relative energies calculated at M06-2X/TZVP//B3LYP-D3(BJ)/SV(P) level.

Table 2. Gold-catalyzed spiro-cyclization.

Entry	Catalyst/(loading mol%)[a]	Combined yield of **5** (%)[b]	Isolated **5a** (% of the mixture)
1	**C9** (10 mol%)	0	-
2	**C9** (10 mol%), reflux	0	-
3	**C9** (10 mol%), PhMe/DCM 1:1	0	-
4	**C11** (10 mol%)	33	54
5	**C10** (10 mol%)	60	45
6	**C10** (5 mol%)	39	60
7	**C10** (10 mol%)	50	100
8	**C12** (10 mol%), $AgNTf_2$ (10 mol%)	78	0

[a] Catalyst (10 mol %), DCM (0.2 M in **4a**), rt, 2 h; [b] DCM (0.03 M in **4a**), 18 h.

The major product **5a** is a stable isomer also according to the DFT calculations (M06-2X/TZVP//B3LYP-D3(BJ)/SV(P)). NOESY and other 2D NMR methods (DQF-COSY) confirmed its structure (Scheme 5a). The relative and absolute configuration of **5a** was determined by comparison of calculated and experimental CD spectra; see Supporting information for details.



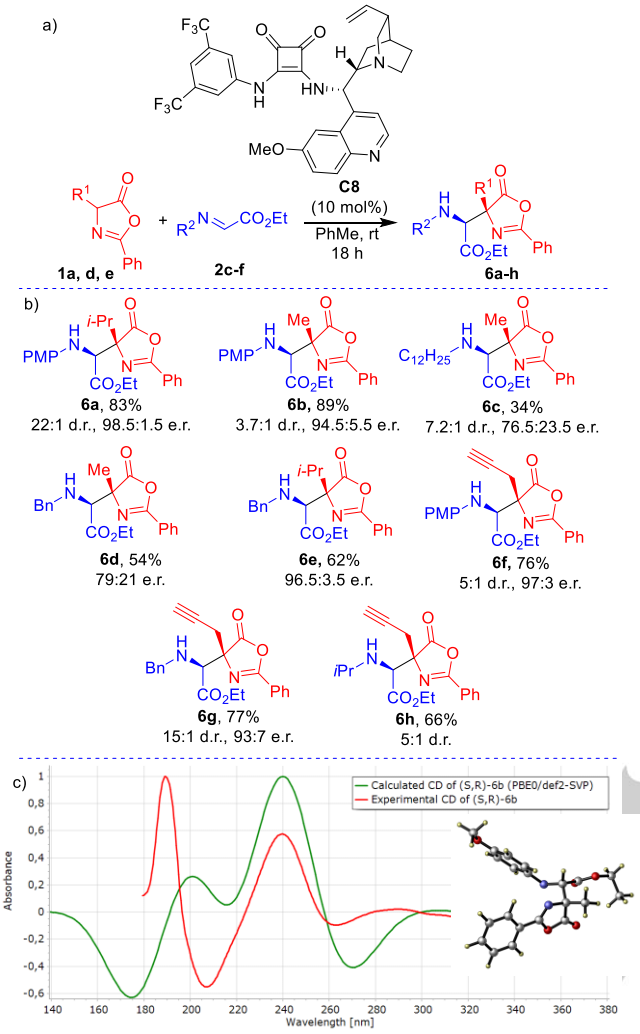
Scheme 5. a) Key NOESY interactions in spirocyclic dihydropyrrole **5a**, and its reduction with sodium borohydride; b) intensity normalized experimental and DFT calculated (M06-2X/def2-TZVP) CD of **5a**.

Spiro-dihydropyrrole **5a** could then be converted to different chiral pyrrolidine derivatives. For example, using sodium borohydride in a mixture of methanol and diethyl ether, we obtained dihydropyrrole **12** in quantitative yield without the need for further purification (Scheme 5). However, the products are labile and acid sensitive.

Attempts to conduct the Mannich reaction and the hydroamination in one-pot process were not reproducible. The gold(I)-catalyzed hydroaminations of **4b** and **4c** did not proceed at all under the conditions used for **4a**, whereas heating the mixture resulted in the decomposition of the starting material.

To enhance the scope of the reaction and access other heterocyclic structures, azlactones **1a, d, e** were reacted with glyoxylate imines **2c**-**e**. Interestingly, a different catalyst was necessary to obtain the corresponding Mannich adducts **6** in high yields and enantiomeric purities (Scheme 6). Catalyst screening revealed that squaramide **C8**, structurally related to thiourea catalyst **C7**, was the most active and selective catalyst affording the product **6a** in 83% yield and 98.5:1.5 e.r. For more details on the catalyst screening, see the Supporting information. Substitution pattern can be altered both on the imine as well as on the azlactone.

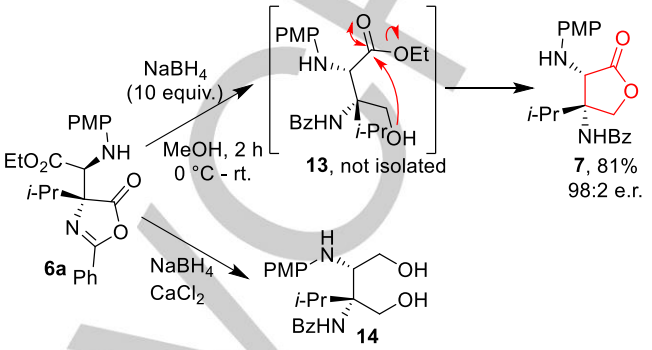
We have probed the reaction conditions using the most effective organocatalyst, squaramide **C8** (see Supporting information for more details on reaction optimization). Toluene was the best solvent for this reaction (Table S1, entry 1). Neither the use of other solvents such as DCM, hexane, *t*BuOMe, THF, nor various additives ($PhCO_2H$, Et_3N, HFIP) had any positive effects. Lowering reaction temperature to 0°C led to adduct **6a** with the highest enantiomer purity (99.5:0.5 e.r., Table S1, entry 2). Adducts **6a**-**h** were obtained in yield ranging 34-89%, with diastereomeric ratios between medium 3.7:1 to excellent 22:1. Enantiomeric purities ranged from 53 to 97% ee with smaller values for methyl substituted azlactone and high values for *i*-propyl substituted azlactones, again hinting at the importance of the amine protecting group size.[11a] Propargyl substituted azlactone also delivered corresponding addition products **6f**-**h** in high enantiomeric purities.



Scheme 6. a) The Mannich reaction of azlactones **1a**, **d**, **e** with glyoxylate imines **2c**-**e**; b) structures of adducts **6a**-**e**; c) comparison of DFT calculated (PBE0/def2-SVP//ωB97XD/6-31G*) and experimental CD spectra for (*S,R*)-**6b**.

We have also performed Au-catalyzed hydroamination on adduct **6f** using $AuNTf_2.PPh_3$ complex. The reaction proceeded with full conversion of the starting material within 2.5 h. Mass spectral analysis confirmed the formation of a hydroamination product (*m/z* 407.1), but pure compounds could not be isolated. The mixture probably contained corresponding spiro-cyclic pyrrolidine and piperidine products, which were however too unstable for purification.

We attempted a reductive opening of the Mannich products. Interestingly, using mild reducing agent $NaBH_4$, we did not isolate the expected hydroxy ester **13**, but after a partial reduction of the azlactone carbonyl, a transesterification with the pending ethoxycarbonyl group afforded lactone **7**. Its enantiomer purity remained high (98:2 e.r.). Complete reduction of adduct **6a** to diol **14** was achieved with $NaBH_4/CaCl_2$ (Scheme 7). The relative configuration of lactone **7** was determined by NOESY and 2D NMR methods (gHMBC, gHSQC). Relative configurations of the Mannich adducts **6a**-**h** were assigned based on the configuration of lactone **7**. The absolute configuration of adduct **6b** was determined by comparison of DFT calculated and experimental ECD spectra (see Supporting information).



Scheme 7. Reductive opening/lactonization and complete reduction of Mannich adduct **6a.**

Conclusions

We have demonstrated that organocatalytic Mannich reaction of azlactones to imines can serve as a useful starting point for the synthesis of valuable chiral spiro-pyrrolidines and lactones. Cinchona-derived thiourea catalyst efficiently catalyzed the Mannich addition of propargyl substituted azlactones to imines. The selective catalytic species is assembled from the thiourea, prone to dimerization, and benzoic acid, as confirmed by DOSY NMR. Our experiments confirmed that the intrinsic acidity of the additive does not play any role, but only in the complex formed there is a functionality acidic enough to activate the imines towards a nucleophilic attack. However, the intermolecular binding of thiourea to the species such as carboxylic or phosphoric acids remains elusive for structural analysis in this context. The corresponding Mannich adduct then underwent Au-catalyzed spiro-cyclization. On the other hand, glyoxylate imines required a cinchona-based squaramide catalyst to afford products in high yield and enantiomeric purity. The reductive opening of this type of Mannich adduct can lead to either chiral lactones or amino diols depending on the choice of the reducing agent. Thus, we have shown that a readily available substrate can be transformed into a variety of complex heterocyclic products by combining complementary types of catalysis or post-functionalization. The work to expand the scope of the transformations is underway.

Experimental Section

General Information

All reactions were carried out in oven-dried glassware under argon. The commercially available chemicals were used without further purification.

Solvents THF, toluene, TBME, and dioxane were distilled from Na/benzophenone; pyridine from KOH; DCM, MeOH, Et_3N, and MeCN from CaH_2 under argon. Thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Kieselgel 60 F_{254}) and visualized by ultraviolet irradiation (254 nm), potassium permanganate, or phosphomolybdic acid stains. Column and flash chromatography were performed on silica gel with particle size 0.040-0.065 and 0.025 mm in diameter. NMR spectra were acquired on Varian NMR System 600 and 300 spectrometers, running at 600 and 300 MHz for ^{1}H, or 150 and 75 MHz for ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) as an internal standard or to the solvent residual signal; $CDCl_3$ (^{1}H: 7.26 ppm, ^{13}C: 77.00 ppm), CD_2Cl_2 (^{1}H: 5.32 ppm), CD_3OD (^{1}H: 3.31 ppm, ^{13}C: 49.00 ppm) or DMSO-d_6 (^{1}H: 2.50 ppm, ^{13}C: 39.52 ppm), respectively. The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; dd, double doublet; ddd, double double doublet; t, triplet; dt, double triplet; q, quartet; dq, double quartet; m, multiplet. IR spectra were measured at Nikolet IS10 spectrometer using a universal ATR crystal sampling plate. HPLC was performed on Daicel Chiralpak AD-H and IA columns with UV detection at 240 nm. Optical rotation measurements were performed on Jasco P-2000 polarimeter. HRMS analyses were performed using a Thermo Scientific LTQ Orbitrap with an ESI source in the positive ion mode. CD data were acquired on Jasco J-815 spectrophotometer using a 10.0 mm cell length quartz cuvette in the solvent stated. Data were collected in continuous scan mode with a data pitch of 0.5 nm, a scanning speed of 100 nm min^{-1} and 4 accumulations. Sample temperature was regulated at 22 °C.

Catalysts **C1**,[21] **C3**,[22] **C4**,[23] **C5**,[24] **C6**,[25] **C7**,[26] **C8**,[27] **C11,** and **C12**[28] were prepared according to the corresponding literature procedures.

Synthesis of Propargyl azlactones

Diethyl 2-benzamidomalonate (**9a**): 2-Aminomalonate hydrochloride (**8**, 5.0 g, 23.6 mmol) was dissolved in pyridine (50 mL). The mixture was cooled to 0 °C, and benzoylchloride (3.31 g, 23.6 mmol) was added dropwise. The mixture was stirred overnight at rt, and the solvent was evaporated under reduced pressure. The mixture was then partitioned between water (50 mL) and TBME (50 mL). The layers were separated, and the aqueous phase was extracted with TBME (2x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **9a** (5.31 g, 81 % yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 – 7.75 (m, 2H), 7.66 – 7.38 (m, 3H), 7.19 (br d, J = 6.9 Hz, 1H), 5.37 (d, J = 6.8 Hz, 1H), 4.40 – 4.22 (m, 4H), 1.32 (t, J = 7.1 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.8 (CO), 166.4 (CO), 133.0 (Cq_{Ar}), 132.1 (CH_{Ar}), 128.6 (CH_{Ar}), 127.3 (CH_{Ar}), 62.7 (CH_2), 56.8 (CH), 14.00 (CH_3). The characterization data match those in the literature.[29]

Diethyl 2-(4-methoxybenzamido)malonate (**9b**): 2-Aminomalonate hydrochloride (**8**, 1.01 g, 5.0 mmol) was dissolved in pyridine (10 mL), cooled to 0 °C, and 4-methoxybenzoylchloride (0.85 g, 5.0 mmol) was added dropwise. The mixture was stirred overnight at rt, and the solvent was evaporated under reduced pressure. Water (40 mL) and EtOH (5 mL) were added to the residue and the solid was filtered. The solid was recrystallized from Et_2O to give **9b** (570 mg) as a white solid. The crystallization mother liquor was concentrated under reduced pressure and the residue purified by column chromatography (hexanes/EtOAc/MeOH 10:10:1) to give additional portion of **9b** (260 mg, 60 % combined yield). ^{1}H NMR (600 MHz, $CDCl_3$):δ 7.84 – 7.78 (m, 2H), 7.02 (d, J = 6.6 Hz, 1H), 6.96 – 6.89 (m, 2H), 5.33 (d, J = 6.8 Hz, 1H), 4.32 and 4.29 (AB of ABX_3, J_{AB} = 10.8 Hz, J_x = 7.1 Hz), 3.86 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.6, 166.3, 162.7, 129.2, 125.3, 113.8, 62.6, 56.8, 55.4, 14.0. Mp: 103 – 104 °C (Et_2O); lit. 103 – 107 °C (Et_2O). The characterization data match those in the literature.[29]

*Diethyl 2-benzamido-2-(prop-2-yn-1-yl)malonate (**10a**): Representative procedure A* (modified procedure from the literature):[30] To a suspension of diethyl 2-benzamidomalonate (**9a**, 5.30 g, 19.0 mmol)and Cs_2CO_3 (6.00 g, 18.4 mmol, 1 eq.) in MeCN (50 mL) was added dropwise propargyl bromide (*w* = 80 % solution in toluene, 4.10 g, 27.6 mmol, 1.5 eq.) and the solution was stirred at rt overnight. The mixture was then filtered under reduced pressure, and the solvent was evaporated under reduced pressure. The residue was again dissolved in EtOAc (60 mL) and washed with water (60 mL). The organic was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc 1:1) gave **10a** (4.30 g, 71 % yield) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 – 7.82 (m, 2H), 7.63 (br s, 1H), 7.56 – 7.52 (m, 1H), 7.50 – 7.42 (m, 2H), 4.37 – 4.26 (m, 4H), 3.41 (d, *J* = 2.6 Hz, 2H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.7 (2x CO), 166.2 (CO), 133.3 (Cq_{Ar}), 132.0 (CH_{Ar}), 128.6 (CH_{Ar}), 127.2 (CH_{Ar}), 78.2 (Cq_{sp}), 71.5 (CH_{sp}), 65.5 (Cq), 63.1 (CH_2), 23.9 (CH_2), 14.0 (CH_3). IR (ATR): 3418, 3280, 2982, 1736, 1662, 1477, 1310, 1205, 710 cm^{-1}. HRMS (ESI+): calcd. for $[C_{17}H_{19}NO_5+H]^+$ ([M+H]$^+$): *m/z* 318.1336, found 318.1324.

*Diethyl 2-(4-methoxybenzamido)-2-(prop-2-yn-1-yl)malonate (**10b**):* Following *Representative procedure A*, starting from diethyl 2-(4-methoxybenzamido)malonate (**9b**, 570 mg, 1.84 mmol) and purification by crystallization (hexanes/EtOAc) gave **10b** (220 mg, 34 % yield) as white needle crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.54 (br s, 1H), 6.97 – 6.90 (m, 2H), 4.35 – 4.23 (m, 4H), 3.86 (s, 3H), 3.40 (d, *J* = 2.6 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 6H).^{13}C NMR (151 MHz, $CDCl_3$, *MZ471*):δ 167.1, 165.9, 162.9, 129.3, 125.7, 114.0, 78.5, 71.6, 65.7, 63.2, 55.7, 24.1, 14.2. IR (ATR): 3417, 3273, 2983, 1733, 1658, 1606, 1485, 1456, 1296, 1260, 1213, 1179, 1029, 1008, 855 cm^{-1}. LR-MS: calcd. for $[C_{18}H_{21}NO_6+Na]^+$ ([M+Na]$^+$): *m/z* 370.1, found 370.1. HRMS (HESI+): calcd. for $[C_{18}H_{21}NO_6+H]^+$ ([M+H]$^+$): *m/z* 348.1447, found 348.1442. Mp.: 69 – 73 °C (hexanes/EtOAc).

*Diethyl 2-benzamido-2-(3-phenylprop-2-yn-1-yl)malonate (**10c**):* Following *Representative procedure A*, starting from diethyl 2-benzamidomalonate (**2a**, 750 mg, 2.68 mmol) and (3-bromoprop-1-yn-1-yl)benzene (784 mg, 4.02 mmol, 1.5 eq.),[31] followed by purification by silica gel column chromatography (hexanes/EtOAc 2:1 – 1:1) gave **10c** (685 mg, 66 % yield) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ7.89 – 7.81 (m, 2H), 7.70 (br s, 1H), 7.60 – 7.40 (m, 3H), 7.36 – 7.20 (m, 5H), 4.41 – 4.24 (m, 4H), 3.63 (s, 2H), 1.29 (t, *J* =7.1 Hz, 6H).IR (ATR): 3390, 2976, 1728, 1661, 1482, 1294, 1111, 1070, 762 cm^{-1}. HRMS (ESI+): calcd. for $[C_{23}H_{23}NO_5+Na]^+$ ([M+Na]$^+$): *m/z* 416.1468, found 416.1460.

*Rac-2-Benzamidopent-4-ynoic acid (**11a**): Representative Procedure B* (modified literature procedure):[32] To a solution of ester **10a** (4.30 g, 13.6 mmol) in MeOH/H_2O (5:1, 250 mL) was added solid KOH (1.66 g, 29.6 mmol, 2.2 eq,) and the mixture was heated at reflux for 2 h and overnight at rt. The solvent was then evaporated under reduced pressure and 2 M aq. HCl was added until pH 1 was reached. The aqueous phase was washed with EtOAc (2x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **11a** (2.14 g, 72 % yield) as a white solid. ^{1}H NMR (600 MHz, CD_3OD): δ7.90 – 7.81 (m, 2H), 7.57 – 7.51 (m, 1H), 7.50 – 7.41 (m, 2H), 4.74 (dd, *J* = 8.1, 5.1 Hz, 1H), 2.89 (ddd, *J* = 17.0, 5.1, 2.7 Hz, 1H), 2.81 (ddd, *J* = 17.0, 8.1, 2.7 Hz, 1H), 2.36 (t, *J* = 2.7 Hz, 1H).^{13}C NMR (151 MHz, $CDCl_3$):δ 173.5 (CO), 170.2 (CO), 135. (Cq_{Ar}), 132.9 (CH_{Ar}), 129.6 (CH_{Ar}), 128.5 (CH_{Ar}), 80.4 (Cq_{sp}), 72.0 (CH_{sp}), 53.2 (CH), 22.2 (CH_2). IR (ATR): 3307, 3029 (broad), 2914, 1712, 1649, 1529, 1420, 1279, 930 cm^{-}

[1]. HRMS (ESI+): calcd. for $[C_{12}H_{11}NO_3+H]^+$ ([M+H]$^+$): *m/z* 218.0812, found 218.0806.

*Rac-2-(4-Methoxybenzamido)pent-4-ynoic acid (**11b**):* Following *Representative Procedure B*, starting from ester **10b** (910 mg, 2.62 mmol) gave **11b** (588 mg, 91 % yield) as a white solid. ^{1}H NMR (600 MHz, CD_3OD): δ 7.89 – 7.78 (m, 2H), 7.04 – 6.94 (m, 2H), 4.72 (dd, *J* = 7.7, 5.4 Hz, 1H), 3.84 (s, 3H), 2.88 (ddd, *J* = 17.1, 5.4, 2.7 Hz, 1H), 2.80 (ddd, *J* = 17.0, 7.9, 2.8 Hz, 1H), 2.35 (t, *J* = 2.6 Hz, 1H).^{13}C NMR (151 MHz, CD_3OD):δ173.6(CO), 169.7 (CO), 164.2 (Cq_{Ar}-OMe), 130.4 (CH_{ar}), 127.1 (Cq_{Ar}), 114.8 (CH_{Ar}), 80.5 (Cq_{sp}), 72.0 (CH_3) 55.9 (CH), 53.1 (CH), 22.3 (CH_2).IR (ATR): 3404, 3202, 2929 (broad), 2120, 1716, 1604, 1540, 1500, 1430, 1250, 1177, 1003, 841 cm^{-1}. HRMS (ESI+): calcd. for $[C_{13}H_{13}NO_4+H]^+$ ([M+H]$^+$): *m/z* 248.0917, found 248.0908.

*Rac-2-Benzamido-5-phenylpent-4-ynoic acid (**11c**):* Following *Representative Procedure B*, starting from ester **10c** (500 mg, 1.27 mmol) gave **11c** (380 mg, quantitative yield) as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.82 (d, *J* = 7.9 Hz, 1H), 7.87 – 7.83 (m, 2H), 7.51 – 7.48 (m, 1H), 7.46 – 7.41 (m, 2H), 4.61 (ddd, *J* = 8.9, 8.0, 5.6 Hz, 1H), 2.97 (dd, *J* = 17.1, 5.6 Hz, 1H), 2.92 (dd, *J* = 17.0, 8.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 172.0 (CO), 166.5 (CO), 133.9 (Cq_{Ar}), 132.5 – 130.6 (m, CH_{Ar}), 129.0 – 128.0 (m, CH_{Ar}), 127.6 – 127.3 (m, CH_{Ar}), 122.9 (Cq_{Ar}), 87.0 (Cq_{sp}), 81.9 (Cq_{sp}), 51.8 (CH), 21.8 (CH_2).IR (ATR): 3280, 2850 (broad), 2610, 1705, 1637, 1528, 1297, 754 cm^{-1}. HRMS (ESI+): calcd. for $[C_{18}H_{15}NO_3+H]^+$ ([M+H]$^+$): *m/z* 294.1125, found 294.1115.

*Rac-2-Phenyl-4-(prop-2-yn-1-yl)oxazol-5(4H)-one (**1a**): Representative Procedure C*: To a suspension of carboxylic acid **11a** (2.00 g, 9.2 mmol) in DCM (50 mL), cooled to 0 °C, was added EDCI.HCl (2.07 g, 11.0 mmol, 1.2 eq.) in portions and the mixture was stirred at 0 °C for 10 min and for 1 h at rt. The solvent was then evaporated under reduced pressure, and the residue dissolved in TBME (50 mL). The organic phase was washed with water (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **1a** (1.60 g, 87 % yield) as a yellow solid. The material was recrystallized from pentane/DCM (3:1) at -20 °C overnight and triturated with pentane to yield the product as yellow needles. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 – 8.02 (m, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.53 – 7.48 (m, 2H), 4.56 (t, *J* = 5.3 Hz, 1H), 2.97 (ddd, *J* = 16.9, 5.1, 2.6 Hz, 1H), 2.89 (ddd, *J* = 16.9, 5.5, 2.6 Hz, 1H), 2.03 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6 (CO), 162.8 (Cq), 133.0 (CH_{Ar}), 128.8 (CH_{Ar}), 128.1 (CH_{Ar}), 125.5(Cq_{Ar}), 77.3 (Cq_{sp}), 71.7 (CH_{sp}), 64.1 (CH), 21.6 (CH_2).IR (ATR): 3287, 1810, 1650, 1449, 1304, 1050, 989, 941, 891 cm^{-1}. HRMS (ESI+): calcd. for $[C_{12}H_9NO_2+H]^+$ ([M+H]$^+$): *m/z* 200.0706, found 200.0698. The characterization data match those in the literature.[33]

*Rac-2-(4-Methoxyphenyl)-4-(prop-2-yn-1-yl)oxazol-5(4H)-one (**1b**):* Following *Representative Procedure C*, starting from carboxylic acid **11b** (558 mg, 2.26 mmol), purification by crystallization (pentane/DCM 3:1) gave **1b** (130 mg, 25 % yield) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 – 7.90 (m, 2H), 7.05 – 6.93 (m, 2H), 4.52 (t, *J* = 5.3 Hz, 1H), 3.88 (s, 3H), 2.94 (ddd, *J* = 16.9, 5.1, 2.6 Hz, 1H), 2.85 (ddd, *J* = 16.9, 5.5, 2.6 Hz, 1H), 2.02 (t, *J* = 2.6 Hz, 1H).^{13}C NMR (125 MHz, $CDCl_3$): δ176.8 (CO), 163.4 (Cq), 162.5 (*Cq*$_{Ar}$-OMe), 130.0 (CH_{Ar}), 117.8 (Cq_{Ar}), 114.2 (CH_{Ar}), 77.6 (Cq_{sp}), 71.6 (CH_3), 64.1 (CH_{sp}), 55.5 (CH), 21.7 (CH_2).IR (ATR): 3269, 2971, 1805, 1646, 1606, 1511, 1420, 1316, 1262, 1053, 873 cm^{-1}. HRMS (ESI+): calcd. for $[C_{13}H_{11}NO_3+H]^+$ ([M+H]$^+$): *m/z* 230.0812, found 230.0804.

*Rac-2-Phenyl-4-(3-phenylprop-2-yn-1-yl)oxazol-5(4H)-one (**1c**):* Following *Representative Procedure C*, starting from carboxylic acid **11c** (505 mg, 1.72 mmol) gave **1c** (276 mg, 58 % yield) as a yellow oil, which was used without any further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 – 8.02 (m, 2H), 7.61 – 7.57 (m, 1H), 7.53 – 7.47 (m, 2H), 7.29 – 7.17 (m, 5H), 4.63 (t, *J* = 5.2 Hz, 1H), 3.19 (dd, *J* = 17.0, 5.1 Hz, 1H), 3.12 (dd, *J* = 17.0, 5.2 Hz, 1H).^{13}C NMR (125 MHz, $CDCl_3$): δ 176.8 (CO), 162.8 (Cq), 133.0 (CH_{Ar}), 131.7 (CH_{Ar}), 128.8 (CH_{Ar}), 128.1 (2xCH_{Ar}), 128.1 (CH_{Ar}), 125.6 (Cq_{Ar}), 122.7 (Cq_{Ar}), 83.8 (Cq_{sp}), 82.6 (Cq_{sp}), 64.5 (CH), 22.7 (CH_2).IR (ATR): 3059, 2917, 1815, 1649, 1489, 1310, 1049, 950, 879 cm^{-1}. HRMS (ESI+): calcd. for $[C_{18}H_{13}NO_2+H]^+$ ([M+H]$^+$): *m/z* 276.1019, found 276.1010.

Synthesis of Alkylazlactones

*Rac-4-Methyl-2-phenyloxazol-5(4H)-one (**1d**): Representative Procedure D* (modified procedure from the literature):[34] To a solution of *rac-N*-benzoylalanine (1.45 g, 7.5 mmol) in DCM (60 mL), cooled to 0 °C, TFAA (2.05 g, 1.36 mL, 9.75 mmol) was added in one portion. The reaction mixture was stirred at 0 °C in an ice bath. After 30 min the ice bath was removed, and mixture was stirred for 2h at rt. The mixture was then washed with saturated aq. $NaHCO_3$ (3x20mL), the organic layer was dried over Na_2SO_4 and solvent evaporated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc 5:1) gave 1d (0.68 g, 52 % yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 – 7.97 (m, 2H), 7.62 – 7.54 (m, 1H), 7.53 – 7.45 (m, 2H), 4.45 (q, *J* = 7.6 Hz, 1H), 1.59 (d, *J* = 7.6 Hz, 3H). The characterization data match the literature data.[34]

*Rac-4-Isopropyl-2-phenyloxazol-5(4H)-one (**1e**):* Following *Representative Procedure D*, starting from *rac-N*-benzoylvaline (1.66 g, 7.5 mmol) and purification by silica gel column chromatography (hexanes/EtOAc 5:1) gave **1e** (1.16 g, 76% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 – 7.96 (m, 2H), 7.65 – 7.42 (m, 3H), 4.29 (d, *J* = 4.5 Hz, 1H), 2.48 – 2.30 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H). The characterization data match the literature data.[34]

Synthesis of Imines

*Ethyl 2-((4-methoxyphenyl)imino)acetate (**2c**): Representative Procedure E* (modified procedure from the literature):[35] Anhydrous $MgSO_4$ was suspended in a solution of 4-methoxyaniline (0.985 g, 8.0 mmol) in DCM. The solution of ethyl glyoxylate in toluene (50% *w/w*, 1.55 g, 8.0 mmol) was added and the mixture was stirred at reflux for 3h. Then the mixture was filtrated under reduced pressure through a short pad of celite. The solids were washed with DCM (2x20mL) and the solvent was evaporated under reduced pressure to afford 2c (1.66 g, quantitative yield) as a yellow oil. The product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$):δ 7.93 (s, 1H), 7.45 – 7.31 (m, 2H), 7.00 – 6.88 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). The characterization data match the literature data.[35]

*Ethyl 2-(dodecylimino)acetate (**2d**):* Following *Representative Procedure E*, starting from *n*-dodecylamine (1.48 g, 1.84 mL, 8.0 mmol), 2d (2.09 g, 97% yield) was obtained as a colorless oil. The product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$):δ 7.69 (t, *J* = 1.5 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.63 (td, *J* = 7.1, 1.4 Hz, 2H), 1.77 – 1.65 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.33 – 1.18 (m, 18H), 0.88 (t, *J* = 6.7 Hz, 3H). The characterization data match the literature data.

*Ethyl 2-(benzylimino)acetate (**2e**):* Following *Representative Procedure E*, starting from benzylamine (0.857g, 0.87mL, 8.0 mmol) to afford **2e** (1.45g, 95% yield) as a colorless oil. The product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$):δ 7.72 (t, *J* = 1.6 Hz, 1H), 7.39 – 7.27 (m, 5H), 4.86 (d, *J* = 1.3 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). The characterization data match the literature data.[35]

*Ethyl 2-(isopropylimino)acetate (**2f**):* Following *Representative Procedure E*, starting from isopropylamine (0.473 g, 0.69 mL, 8.0 mmol) to afford **2f** (1.45 g, 95% yield) as a colorless oil. The product was used without further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.6 (spt, *J* = 6.3 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 6H). The characterization data match the literature data.[36]

Synthesis of Catalyst **C2**

To a solution of (1*S*)-(6-methoxyquinolin-4-yl)((2*S*,4*S*,5*S*)-5-((*E*)-styryl)quinuclidin-2-yl) methanamine[37] (40 mg, 0.10 mmol) in THF (5 mL), cooled to 0 °C, was added a solution of 3,5-bis(trifluoromethyl)phenylisothiocyanate (33 mg, 0.12 mmol, 1.2 eq.) in THF (2 mL) and the solution was stirred at rt overnight. The crude mixture was purified by silica gel column chromatography (DCM/MeOH/Et_3N 10:2:1) to give **C2** (62 mg, 92 % yield) as a white solid. $[\alpha]_D^{20}$ -15.8 (*c* 0.35, $CHCl_3$). ^{1}H NMR (600 MHz, CD_3OD): δ 8.69 (d, *J* = 4.7 Hz, 1H), 8.11 (s, 2H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.61 (dd, *J* = 7.9, 3.1 Hz, 2H), 7.57 – 7.51 (m, 1H), 7.47 – 7.43 (m, 1H), 7.32 (t, *J* = 5.9 Hz, 2H), 7.26 – 7.13 (m, 3H), 6.42 (d, *J* = 15.8 Hz, 1H), 6.29 (dd, *J* = 15.8, 8.0 Hz, 1H), 4.03 (s, 3H), 3.67 (s, 1H), 3.56 (dd, *J* = 17.2, 10.1 Hz, 1H), 3.41 (dd, *J* = 13.9, 10.2 Hz, 1H), 2.95 – 2.84 (m, 2H), 2.57 (s, 1H), 1.79 – 1.69 (m, 3H), 1.63 – 1.55 (m, 1H), 0.98 – 0.92 (m, 1H). ^{13}C NMR (151 MHz, CD_3OD): δ 182.5 (Cq_{Ar}), 159.7 (Cq_{Ar}), 148.3 (CH_{Ar}), 145.2 (Cq_{Ar}), 143.0 (Cq_{Ar}), 138.8 (Cq_{Ar}), 133.8 (CH_{Ar}), 132.7 (q, J_{CF} = 33.4 Hz,Cq),131.6 (CH_{Ar}), 131.2 (CH_{Ar}), 129.5 (CH_{Ar}), 128.1 (CH_{Ar}), 127.1 (CH_{Ar}), 125.6 (q, J_{CF} = 270.7 Hz,Cq),123.8 (CH_{Ar}), 123.6 (CH_{Ar}), 117.8 (CH_{Ar}), 104.2 (CH_{Ar}),61.7 (CH), 57.4 (CH_2), 56.5 (CH_3), 42.9 (CH_2), 40.3 (CH),29.2 (CH), 28.5 (CH_2), 27.8 (CH), 27.0 (CH_2). HRMS (HESI+): calcd. for $[C_{35}H_{32}F_6N_4OS+H]^+$ ($[M+H]^+$): *m/z* 671.2279, found 671.2273.

Mannich Reaction of Propargyl azlactones

General Procedure A: An oven-dried Schlenk tube was charged with imine 2a-b (0.2 mmol), azlactone 1a-c (0.24 mmol, 1.2 equiv.), catalyst (0.02 mmol, 10 mol-%) and acid co-catalyst (0.01 mmol, 10 mol-%) if not stated otherwise. The solvent (1 mL) was then added. After stirring at room temperature for 18 h, the solution was concentrated *in vacuo,* and the residue was purified by silica gel column chromatography (eluent hexanes/EtOAc) to afford the product.

*4-Methyl-N-((S)-((R)-5-oxo-2-phenyl-4-(prop-2-yn-1-yl)-4,5-dihydrooxazol-4-yl)(phenyl)methyl) benzenesulfonamide (**4a**):* Following *General Procedure A*, purification by silica gel column chromatography (hexanes/EtOAc 4:1 – 3:1) gave adduct **4a** as a white solid. R_F = 0.32 (hexanes/EtOAc 3:1). $[\alpha]_D^{20}$ -27.4 (*c* 0.50, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95 – 7.90 (m, 2H), 7.58 – 7.54 (m, 1H), 7.45 (dd, *J* = 11.1, 4.3 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.15 – 7.05 (m, 5H), 6.97 (d, *J* = 8.1 Hz, 2H), 5.44 (d, *J* = 10.8, 1H), 4.77 (d, *J* = 10.9 Hz, 1H), 2.79 – 2.75 (m, 1H), 2.40 (dd, *J* = 16.8, 1.7 Hz, 1H), 2.28 (s, 3H), 1.92 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 177.2 (CO), 163.0 (Cq), 143.2 (Cq_{Ar}), 136.6 (Cq_{Ar}), 134.6 (Cq_{Ar}), 133.2 (Cq_{Ar}), 129.2 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (CH_{Ar}), 128.3 (CH_{Ar}), 128.3 (CH_{Ar}), 127.9 (CH_{Ar}), 127.1 (CH_{Ar}), 125.0 (CH_{Ar}), 76.5 (CH_{sp}), 76.0 (Cq_{sp}), 72.2 (Cq), 61.1 (CH), 25.8 (CH_2), 21.4 (CH_3). IR (ATR): 3300, 3263, 1826, 1649, 1494, 1422, 1319, 1295, 1159, 976 cm^{-1}. LR-MS: calcd. for $[C_{26}H_{22}N_2O_4S+Na]^+$ ($[M+Na]^+$): *m/z* 481.1, found 481.1. HRMS (HESI+): calcd. for $[C_{26}H_{22}N_2O_4S+H]^+$ ($[M+H]^+$): *m/z* 459.1379, found 459.1374. Mp.: 185 – 187 °C (hexanes/EtOAc). HPLC: Daicel IA column, eluent = hexanes/*i*-PrOH 90:10, flow rate = 1.0 mL.min^{-1}; t_R (major) = 14.8 min; t_R (minor) = 18.9 min.

*N-((S)-((R)-5-oxo-2-phenyl-4-(prop-2-yn-1-yl)-4,5-dihydrooxazol-4-yl)(phenyl)methyl) methanesulfonamide (**4b**):* Following *General Procedure A*, purification by silica gel column chromatography (hexanes/EtOAc 3:1 – 1:1) gave adduct **4b** as a white solid. R_F = 0.42 (hexanes/EtOAc 3:1). ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.14 (d, *J* = 10.8 Hz, 1H), 8.10 – 8.03 (m, 2H), 7.78 – 7.70 (m, 1H), 7.70 – 7.60 (m, 3H), 7.48 – 7.38 (m, 3H), 4.87 (d, *J* = 10.8 Hz, 1H), 3.02 – 2.87 (m, 2H, CH_2^A + N*H*), 2.32 (s, 3H), 2.09 (dd, *J* = 16.2, 3.3 Hz, 1H, CH_2^B). ^{13}C NMR (151 MHz, $CDCl_3$): δ 177.1 (CO), 161.5 (Cq), 135.7 (Cq_{Ar}), 133.4 (CH_{Ar}), 129.11 (CH_{Ar}), 129.09 (CH_{Ar}), 128.7 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 125.3 (Cq_{Ar}), 77.4 (Cq), 76.6 (Cq), 74.5 (CH), 61.2 (CH), 41.1 (CH_3), 24.7 (CH_2). HRMS: calcd. for $[C_{20}H_{19}N_2O_4S]^+$ ($[M+H]+$): *m/z* 383.1060, found 383.1055. HPLC: Daicel IA column, eluent = hexanes/ *i*-PrOH 85:15, flow rate = 1.0 mL.min^{-1}; t_R (major) = 10.6 min; t_R (minor) = 12.2 min.

*4-Methyl-N-((S)-((R)-5-oxo-2-phenyl-4-(3-phenylprop-2-yn-1-yl)-4,5-dihydrooxazol-4-yl)(phenyl)methyl)benzenesulfonamide (**4c**):* Following *General Procedure A*, purification by silica gel column chromatography (hexanes/EtOAc 4:1 – 3:1) gave adduct 4c as a white solid. R_F = 0.34 (hexanes/EtOAc 3:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.63 – 7.56 (m, 1H), 7.49 – 7.43 (m, 4H), 7.22 – 7.10 (m, 10H), 7.01 (d, *J* = 8.0 Hz, 2H), 5.43 (d, *J* = 10.8 Hz, 1H), 4.86 (d, *J* = 10.8 Hz, 1H), 3.01 (d, *J* = 16.8 Hz, 1H), 2.63 (d, *J* = 16.7 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 177.4 (CO), 162.9 (Cq), 143.3 (Cq_{Ar}), 136.8 (Cq_{Ar}), 135.0 (Cq_{Ar}), 133.2 (CH_{Ar}), 131.5 (CH_{Ar}), 129.2 (CH_{Ar}), 128.8 (CH_{Ar}), 128.40 (CH_{Ar}), 128.39 (CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 127.1 (CH_{Ar}), 125.1 (Cq_{Ar}), 122.5 (Cq_{Ar}), 84.4 (Cq_{sp}), 81.8 (Cq_{sp}), 76.3 (Cq), 61.1 (CH), 27.0 (CH_2), 21.4 (CH_3). IR (ATR): 3276, 1820, 1650, 1597, 1325, 1292, 1163, 982, 900 cm^{-1}. HRMS (ESI+): calcd. for $[C_{32}H_{26}N_2O_4S+H]^+$ ($[M+H]^+$): *m/z* 536.1686, found 536.1675. MS^2 (ESI+): $[M\text{-}CO]^+$ calcd. *m/z* 507.1737 found 507.1725; $[M\text{-}PhCHNHSO_2Tol+2H]^+$ calcd. *m/z* 276.1019, found 276.1014. HPLC: Daicel IA column, eluent = hexanes/*i*-PrOH 90:10, flow rate = 1.0 mL.min^{-1}; *t* (major) = 22.2 min; *t* (minor) = 29.5 min.

*N-((S)-((R)-2-(4-methoxyphenyl)-5-oxo-4-(prop-2-yn-1-yl)-4,5-dihydrooxazol-4-yl)(phenyl)methyl)-4-methylbenzenesulfonamide (**4d**):* Following *General Procedure A*, purification by silica gel column chromatography (hexanes/EtOAc 3:1 – 1:1) gave adduct **4d** as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.94 – 7.88 (m, 2H), 7.85 – 7.76 (m, 1H), 7.44 – 7.39 (m, 2H), 7.13 – 7.06 (m, 5H), 7.03 – 6.97 (m, 2H), 6.97 – 6.91 (m, 2H), 5.38 (d, *J* = 11.2 Hz, 1H), 4.76 (d, *J* = 10.9 Hz, 1H), 3.87 (s, 3H), 2.76 (dd, *J* = 16.6, 2.6 Hz, 1H), 2.39 (dd, *J* = 16.7, 2.6 Hz, 1H), 2.29 (s, 3H), 1.91 (t, *J* = 2.6 Hz, 1H).). ^{13}C NMR (151 MHz, $CDCl_3$): δ 177.4 (CO), 163.6 (Cq), 143.3 (Cq_{Ar}), 136.7 (Cq_{Ar}), 134.9 (Cq_{Ar}), 130.3 (CH_{Ar}), 129.7 (Cq_{Ar}), 129.2 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 127.8 (CH_{Ar}), 127.1 (CH_{Ar}), 126.5 (CH_{Ar}), 117.2 (Cq_{Ar}), 114.2 (CH_{Ar}), 76.6 (Cq), 75.9 (Cq), 72.2 (CH_{sp}), 61.1 (CH), 55.5 (CH_3), 25.8 (CH_2), 21.4 (CH_3). IR (ATR): 3277, 1820, 1640, 1604, 1509, 1257, 1159, 978, 877 cm^{-1}. HRMS (HESI+): calcd. for $[C_{27}H_{24}N_2O_5S+H]^+$ ($[M+H]^+$): *m/z* 489.1479, found 489.1471. MS^2 (ESI+): $[M\text{-}CO]^+$ calcd. *m/z* 461.1530 found 461.1519; $[M\text{-}C_7H_7SO_2]^+$ calcd. *m/z* 333.1239, found 333.1227; $[M\text{-}PhCHNHSO_2Tol+2H]^+$ calcd. *m/z* 230.0812, found 230.0805. HPLC: Daicel IA column, eluent = hexanes/*i*-PrOH 85:15, flow rate = 1.0 mL.min^{-1}; t_R (major) = 14.4 min; t_R (minor) = 18.9 min.

Gold(I)-Catalyzed Reactions

*(5R,6S)-8-Methyl-2,6-diphenyl-7-tosyl-3-oxa-1,7-diazaspiro[4.4]nona-1,8-dien-4-one (**5a**):* To a solution of **4a** (50 mg, 0.11 mmol) in DCM (4 mL) was added $[Ph_3PAuNTf_2]_2$.PhMe (8.5 mg, 5 mol %) and the solution was stirred at rt for 18 h. The mixture was then concentrated under reduced pressure and the residue purified by silica gel column chromatography (hexanes/EtOAc 3:1 – 2:1) to give 5a (25 mg, 50 % yield). $[\alpha]_D^{20}$ -97.8 (*c*

0.35, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ 7.88 – 7.83 (m, 2H), 7.80 – 7.70 (m, 2H), 7.63 – 7.56 (m, 1H), 7.51 – 7.43 (m, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.28 (m, 5H), 5.33 (s, 1H), 4.73 (pseudo q, *J* = 1.2 Hz, 1H), 2.51 (s, 3H), 2.34 (d, *J* = 1.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.5 (CO), 160.8 (Cq), 148.5 (Cq), 144.4 (Cq_{Ar}), 135.5 (Cq_{Ar}), 134.7 (Cq_{Ar}), 133.2 (CH_{Ar}), 129.9 (CH_{Ar}), 128.8 (CH_{Ar}), 128.7 (Cq_{Ar}), 128.5 (CH_{Ar}), 128.1 (CH_{Ar}), 127.9 (CH_{Ar}), 126.7 (CH_{Ar}), 125.2 (Cq_{Ar}), 106.8 (CH), 80.3 (Cq), 73.8 (CH), 21.7 (CH_3), 16.1 (CH_3). HRMS (HESI+): calcd. for $[C_{26}H_{22}N_2O_4S+H]^+$ ($[M+H]^+$): *m/z* 459.1379, found 459.1372. HPLC: Daicel IA column, eluent = hexanes/*i*-PrOH 85:15, flow rate = 1.0 mL.min^{-1}; t_R (minor) = 12.5 min; t_R (major) = 15.5 min.

*N-((2S,3R)-3-(hydroxymethyl)-5-methyl-2-phenyl-1-tosyl-2,3-dihydro-1H-pyrrol-3-yl)benzamide (**12**).* Azlactone **5a** (25 mg, 0.055 mmol) was dissolved in MeOH (1 mL) and Et_2O (1 mL), and the mixture was cooled to 0 °C. Solid $NaBH_4$ (14 mg, 0.37 mmol, 7 eq.) was added and the mixture was stirred at 0 °C for 10 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (2 mL) and Et_2O (5 mL). The layers were separated, and the mixture was extracted with Et_2O (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure (quantitative yield). The product can be purified by silica gel column chromatography (hexanes/EtOAc 3:1 – 2:1) to give alcohol 12 (2 mg, 8 % yield) as a colorless oil (the product is not stable to silica gel or acidic conditions). ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.58 – 7.48 (m, 4H), 7.48 – 7.19 (m, 6H), 6.94 (d, *J* = 7.9 Hz, 2H), 5.66 (s, 1H), 5.46 (s, 1H), 5.19 (s, 1H, $CH_3C=CH$), 3.90 (dd, *J* = 11.6, 3.7 Hz, 1H, CH_2^A), 2.99 (dd, *J* = 11.2, 5.9 Hz, 1H, CH_2^B), 2.37 (s, 3H, $CH_3C=CH$), 1.98 (s, 3H, $CH_3C_6H_4$), 1.54 – 1.48 (pseudo t, *J* = 6.1 Hz, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$): decomposes in $CDCl_3$.

Mannich Reaction of Alkylazlactones with Glyoxylate Imines

General Procedure B: An oven-dried Schlenk tube was charged with azlactone **1d**-**e** (1 equiv.), imine **2c**-**e** (1 equiv.), catalyst (0.1 equiv.) and Et_3N (0.2 equiv.). PhMe was then added. After stirring at room temperature for 18 h, the solution was diluted with EtOAc (2 mL) and then concentrated in vacuo, and the residue was purified by silica gel column chromatography (eluent hexanes/EtOAc) to afford the product.

*Ethyl (2S)-2-((R)-4-isopropyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)-2-((4-methoxyphenyl)amino) acetate (**6a**):* Following *General Procedure B,* starting with **1e** (129 mg, 0.7 mmol), **2c** (142 mg, 0.7 mmol), C8 (44 mg, 0.07 mmol, 10 mol %), Et_3N (19 µL, 0.14 mmol, 20 mol %) in PhMe (1.7 mL). Purification by silica gel column chromatography (4:1) gave product 6a (156 mg, 58 % yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (m, 2H), 7.64 – 7.55 (m, 1H), 7.54 – 7.45 (m, 2H), 6.80 – 6.72 (m, 4H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 2.59 – 2.47 (m, 1H), 1.12 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.7, 170.5, 162.2, 153.6, 139.8, 133.0, 128.8, 128.2, 128.1, 125.5, 116.7, 114.8, 77.6, 61.5, 61.3, 55.6, 32.1, 17.1, 16.4, 14.0. HRMS (HESI+): calcd. for $[C_{23}H_{26}N_2O_5+H]^+$ ($[M+H]^+$): *m/z* 411.1920, found 411.1916. HPLC: Chiralpak IA column, eluent = hexanes/ *i*-PrOH 85:15, flow rate = 1.0 mL.min^{-1}; t_R (minor) = 6.3 min; t_R (major) = 9.6 min.

*Ethyl (S)-2-((-4-methoxyphenyl)amino)-2-((R)-4-methyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl) acetate (**6b**):* Following *General procedure B,* starting with **1d** (103 mg, 0.59 mmol), **2c** (121 mg, 0.59 mmol), C8 (37 mg, 0.059 mmol), Et_3N (16 µL, 0.117 mmol) in PhMe (1.5 mL). Purification by silica gel column chromatography (4:1) gave product 6b (177 mg, 79 % yield) as a yellowish oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (m, 2H), 7.62 – 7.54 (m, 1H), 7.52 – 7.44 (m, 2H), 6.84 – 6.72 (m, 4H), 4.47- 4.32 (m, 2H), 4.11 – 3.97 (m, 2H), 3.75 (s, 3H), 1.67 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.1, 169.8, 161.8, 153.2, 141.1, 133.0, 128.8, 128.1, 117.4, 115.6, 114.9, 114.7, 76.8, 72.1, 63.4, 62.1, 55.7, 22.2, 13.9. IR (ATR): 3371, 1742, 1647 cm^{-1}. HRMS (HESI+): calcd. for $[C_{21}H_{22}N_2O_5+H]^+$ ($[M+H]^+$): *m/z* 383.1607, found 383.1610. $[\alpha]_D^{20}$ -1.5 (*c* 1.0, $CHCl_3$). HPLC: Chiralpak IA column, hexanes/*i*-PrOH 85:15, flow rate = 1.0 mL.min^{-1}; t_R (minor) = 8.0 min; t_R (major) = 15.1 min.

*Ethyl (S)-2-(dodecylamino)-2-((R)-4-methyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)acetate (**6c**):* Following *General procedure B*, starting with 1d (99 mg, 0.57 mmol), 2d (152 mg, 0.54 mmol), C8 (36 mg, 0.057 mmol), Et_3N (16 µL, 0.113 mmol) in dried PhMe (1.4 mL). Purification by silica gel column chromatography (4:1) gave product 6c (86 mg, 34 % yield) as s colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 – 7.99 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.50 – 7.44 (m, 2H), 4.29 – 4.23 (m, 2H), 3.56 (s, 1H), 2.56 (ddd, *J* = 11.3, 8.0, 6.1 Hz, 1H), 2.40 (ddd, *J* = 11.4, 8.1, 6.3 Hz, 1H), 1.78 (br s, 1H), 1.57 (s, 3H), 1.41-1.13 (m, 23H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 179.3, 171.3, 161.6, 132.8, 128.7, 128.2, 125.8, 72.2, 66.0, 61.3, 48.5, 31.8, 29.8, 29.61, 29.57, 29.6, 29.5, 29.4, 29.3, 27.0, 22.6, 20.9, 14.3, 14.1. IR (ATR): 2922, 2852, 1735, 1651 cm^{-1}. HRMS (HESI+): calcd. for $[C_{26}H_{40}N_2O_4+H]^+$ ($[M+H]^+$): *m/z* 445.3066, found 445.3060. $[\alpha]_D^{20}$ -31.9 (*c* 1.0, $CHCl_3$). HPLC: Chiralpak IA column, eluent = hexanes/*i*-PrOH 90:10, flow rate = 1.0 mL.min^{-1}; t_R (major) = 3.7 min; t_R (minor) = 8.3 min.

*Ethyl (S)-2-(benzylamino)-2-((R)-4-methyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)acetate (**6d**):* Following *General Procedure B*, starting with 1d (120 mg, 0.69 mmol), **2e** (131 mg, 0.54 mmol), **C8** (43 mg, 0.069 mmol) and Et_3N (19 µL, 0.137 mmol) in PhMe (1.7 mL). Purification by silica gel column chromatography (4:1) gave product 6d (113 mg, 45 % yield) as s yellowish oil. ^1H NMR (600 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.59 – 7.54 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.32 – 7.21 (m, 5H), 4.24 (qd, *J* = 7.1, 1.4 Hz, 2H), 3.81 (d, *J* = 13.3 Hz, 1H), 3.64 (d, *J* = 13.3 Hz, 1H), 3.61 (s, 1H), 2.27 (bs, 1H), 1.57 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 179.1, 170.8, 161.6, 138.8, 132.8, 128.7, 128.4, 128.3, 128.2, 127.2, 125.7, 76.8, 72.1, 64.9, 61.4, 52.2, 21.0, 14.3. IR (ATR): 3330, 1733, 1649 cm^{-1}. HRMS (HESI+): calcd. for $[C_{21}H_{22}N_2O_4+H]^+$ ($[M+H]^+$): *m/z* 367.1658, found 367.1650. $[\alpha]_D^{20}$ +1.9 (*c* 1.0, $CHCl_3$). HPLC: Chiralpak IA column, eluent = hexanes/*i*PrOH 90:10, flow rate = 1.0 mL.min^{-1}; t_R (major) = 5.4 min; t_R (minor) = 6.5 min.

*Ethyl (S)-2-(benzylamino)-2-((R)-4-isopropyl-5-oxo-2-phenyl-4,5-dihydrooxazol-4-yl)acetate (**6e**):* Following *General Procedure B*, starting with **1e** (148 mg, 0.72 mmol), **2e** (139 mg, 0.72 mmol), **C8** (46 mg, 0.072 mmol) and Et_3N (20 µL, 0.146 mmol) in PhMe (1.8 mL). Purification by silica gel column chromatography (4:1) gave product **6e** (229 mg, 80 % yield) as a yellowish oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 – 7.98 (m, 2H), 7.61 – 7.53 (m, 1H), 7.51 – 7.42 (m, 2H), 7.30 (m, 5H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.85 (dd, *J* = 12.9, 4.6 Hz, 2H), 3.65 (dd, *J* = 13.1, 6.6 Hz, 1H), 2.51 (septet, *J* = 6.8 Hz, 1H), 2.41 – 2.28 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 171.5, 161.8, 139.0, 132.7, 128.7, 128.5, 128.3, 128.1, 127.2, 125.7, 78.3, 62.7, 61.2, 52.0, 31.9, 16.9, 16.3, 14.2. IR (ATR): 3381, 2969, 1733, 1649 cm^{-1}. HRMS (HESI+): calcd. for $[C_{23}H_{26}N_2O_4+H]^+$ ($[M+H]^+$): *m/z* 395.1971, found 395.1960. $[\alpha]_D^{20}$ +41.2 (*c* 1.0, $CHCl_3$). HPLC: Chiralpak IA column, eluent = hexanes/*i*-PrOH 90:10, flow rate = 1.0 mL.min^{-1}; t_R (major) = 5.2 min; t_R (minor) = 5.7 min.

*Ethyl 2-((4-methoxyphenyl)amino)-2-(5-oxo-2-phenyl-4-(prop-2-yn-1-yl)-4,5-dihydro-oxazol-4-yl)acetate (**6f**):* Light Orange-yellow solid. Melting point: 125 °C. Yield: 76 %. IR (ATR): 3290 (w, N-H); 1814 (s, C=O); 1738 (s, C=O); 1645 (s, C=N); 1512 (s, C=C(Ar)); 1449 (s, CH_2); 1292 (m, C(Ar)-N); 1243 (s, C-O); 1181 (m, C-N); 991 (s, C-H alkene); 700 (s, C(Ar)-H) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.4 Hz, 2H,

major); 8.03 (d, 0.4H, minor); 7.61 (t, *J* = 7.5 Hz, 1H, major); 7.60 (t, 0.2H, minor); 7.50 (t, *J* = 7.8 Hz, 2H, major); 7.49 (t, 0.4H, minor); 6.77 (s, 0.8H, minor); 6.76 (s, 4H, major); 4.52 (d, 0.2H, minor); 4.45 (d, *J* = 11.4 Hz, 1H, major); 4.32 (d, 0.2H, minor); 4.24 (d, *J* = 11.4 Hz, 1H, major); 4.18-4.12 (m, 2H, major); 4.08-4.00 (m, 0.4H, minor); 3.75 (s, 0.6H, minor); 3.73 (s, 3H, major); 3.21 (dd, 0.2H, minor); 3.09 (dd, 1H, *J* = 16.8, 2.5 Hz, 1H, major); 2.96 (dd, *J* = 16.8, 2.5 Hz, 1H, major); 2.95 (dd, 0.2H, minor); 2.02 (t, J = 2.3 Hz, 1H, major); 2.00 (t, 0.2H, minor); 1.18 (t, *J* = 7.1 Hz, 3H, major); 1.07 (t, 0.6H, minor) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 177.4 (major); 177.2 (minor); 169.8 (major); 168.6 (minor); 163.5 (major); 163.2 (minor); 154.2 (major); 153.7 (minor); 140.8 (minor); 139.8 (major); 133.5 (major); 133.4 (minor); 129.0 (minor); 129.0 (major); 128.7 (major); 128.5 (minor); 125.5 (minor); 125.4 (major); 117.6 (major); 116.2 (minor); 115.1 (minor); 114.9 (major); 77.0 (major); 77.0 (minor); 75.1 (minor); 74.5 (major); 72.6 (minor); 72.5 (major); 63.4 (major); 62.8 (minor); 62.4 (minor); 62.1 (major); 55.9 (minor); 55.8 (major); 26.2 (minor); 25.5 (major); 14.3 (major); 14.1 (minor) ppm. HRMS (HESI): *m/z* [M + H]+ calcd for $C_{23}H_{23}N_2O_5$: 407.1601; found: 407.1610. $[\alpha]_D^{20}$ -18.7 (c 1.0, $CHCl_3$). HPLC: Chiralcel OD-H column, eluent = *n*-hexane/*i*-PrOH 90:10, flow rate = 0.5 mL.min^{-1}, 254 nm; t_R(major diastereomer): (minor) = 21.9 min; t_R (major) = 19.8 min. t_R (minor diastereomer): (minor) = 26.4 min; t_R (major) = 24.0 min.

*Ethyl 2-(benzylamino)-2-(3-oxo-5-phenyl-2-(prop-2-yn-1-yl)-3,4-dihydro-2H-pyrrol-2-yl)acetate (**6g**).* Light Orange-yellow solid. Mp 91 °C. Yield: 77 %. IR (ATR): 3296 (w, N-H); 1819 (s, C=O); 1727 (s, C=O); 1648 (s, C=N); 1451 (s, CH_2); 1290 (m, C(Ar)-N); 986 (s, C-H alkene); 694 (s, C(Ar)-H) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$):δ (major diastereomer) 8.03 (d, *J* = 7.4 Hz, 2H); 7.58 (t, *J* = 7.4 Hz, 1H); 7.47 (t, *J* = 7.7 Hz, 2H); 7.32-7.23 (m, 5H); 4.22-4.16 (m, 2H); 3.83 (d, *J* = 13.1 Hz, 1H); 3.70-3.64 (m, 2H); 3.06 (dd, *J* = 16.8; 2.4 Hz, 1H); 2.85 (dd, *J* = 16.8; 2.4 Hz, 1H); 2.33 (bs, 1H); 1.95 (s, 1H); 1.25 (t, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ (major diastereomer) 177.1; 170.5; 162.9; 138.7; 133.0; 128.7; 2x 128.4; 128.3; 127.3; 125.4; 77.1; 74.7; 71.9; 63.9; 61.6; 52.2; 25.2; 14.2 ppm. HRMS (HESI): m/z [M + H]+ calcd for $C_{23}H_{23}N_2O_4$: 391.1652; found: 391.1656. $[\alpha]_D^{20}$ +11.2 (c 1.0, $CHCl_3$). HPLC: Chiralpak IA column, eluent = *n*-hexane/*i*-PrOH 90:10, flow rate = 0.5 mL.min^{-1} 254 nm; t_R(major diastereomer): (minor) = 18.2 min; t_R (major) = 16.2 min.

*Ethyl 2-(isopropylamino)-2-(5-oxo-2-phenyl-4-(prop-2-yn-1-yl)-4,5-dihydrooxazol-4-yl)acetate (**6h**):* Light Orange-yellow solid. Mp 74 °C. Yield: 66 %. IR (ATR): 3288 (w, N-H); 1820 (s, C=O); 1735 (s, C=O); 1648 (s, C=N); 1450 (s, CH_2); 1241 (m, C-O); 1174 (s, C-N); 983 (s, C-H alkene); 694 (s, C(Ar)-H) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$):δ 8.05 (d, *J* = 7.2 Hz, 2H, major); 8.01 (d, 0.4H, minor); 7.59 (t, *J* = 7.7 Hz, 1H, major); 7.58 (t, 0.2H, minor); 7.49 (t, *J* = 7.7 Hz, 2H, major); 7.48 (t, 0.4H, minor); 4.23 (q, *J* = 7.1 Hz, 2H, major); 4.08-4.00 (m, 0.4H, minor); 3.74 (s, 1H, major); 3.73 (s, 0.2H, minor); 3.34 (dd, 0.2H, minor); 3.04 (dd, *J* = 16.7; 2.6 Hz, 1H, major); 2.89 (dd, *J* = 16.8; 2.6 Hz, 1H, major); 2.86 (sept, 0.2H, minor); 2.79 (dd, 0.2H, minor); 2.73 (sept, *J* = 6.2 Hz, 1H, major); 1.97 (t, *J* = 2.6 Hz, 1H, major); 1.95 (t, 0.2H, minor); 1.91 (bs, 1H, major); 1.55 (bs, 0.2H, minor); 1.27 (t, *J* = 7.1 Hz, 3H, major); 1.26 (t, 0.6H, minor); 1.12 (dd, 1.2H, minor); 0.99 (dd, *J* = 6.3; 2.5 Hz, 6H, major) ppm. ^{13}C NMR (151 MHz, $CDCl_3$):δ 177.9; 177.1; 171.2; 170.9; 162.7; 162.4; 2x133.0; 128.8; 128.7; 128.4; 128.2; 2x125.5; 77.5; 77.3; 75.1; 75.0; 72.0; 71.8; 62.8; 62.5; 61.8; 61.5; 48.3; 47.4; 26.1; 25.0; 2x23.6; 22.3; 21.8; 14.2; 13.9 ppm. HRMS (HESI): *m/z* [M + H]+ calcd for $C_{19}H_{23}N_2O_4$: 343.1652; found: 343.1652. $[\alpha]_D^{20}$ +7.7 (c 1.0, $CHCl_3$).

Transformation to Lactone

*N-((3R,4S)-3-isopropyl-4-((4-methoxyphenyl)amino)-5-oxotetrahydrofuran-3-yl)benzamide (**7**):* To a solution of **6a** (41 mg, 0.1 mmol) in anhydrous methanol (2 mL), cooled to 0 °C, was added sodium borohydride (37 mg, 1 mmol). The mixture was stirred at 0 °C for 20 min and at room temperature for 24 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (2 mL) and the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/Et_2O 1:1) to give **7** (30 mg, 81 % yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 – 7.62 (m, 2H, ArH), 7.63 – 7.54 (m, 1H, ArH), 7.47 (t, *J* = 7.7 Hz, 2H, ArH), 6.71 (s, 4H, -C$_6$*H*$_4$OMe), 6.18 (br s, 1H, CON*H*), 5.51 (br s, 1H,C*H*CO), 5.12 (d, *J* = 9.7 Hz, 1H, C*H*$_2^A$O), 4.46 (d, *J* = 9.7 Hz, 1H, C*H*$_2^B$O), 3.86 – 3.74 (br s, 1H, N*H*), 3.71 (s, 3H, OC*H*$_3$), 2.28 (septet, *J* = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 1.11 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3^A$), 1.04 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3^B$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2 (CO lactone), 167.8 (CO amide), 153.4 (OCq$_{PMP}$), 140.8 (NHCq$_{PMP}$), 134.3 (Cq$_{Ph}$), 132.2 (CH$_{Ph}$), 128.9 (CH$_{Ph}$), 126.8 (CH$_{Ph}$), 115.3 (CH$_{PMP}$),115.1 (CH$_{PMP}$), 66.8 (OCH$_2$), 65.4 (Cq), 58.3 (CH), 55.7 (OCH$_3$), 31.7 (CHMe$_2$), 17.8 (CH*Me*^{A}), 16.9 (CH*Me*^{B}). HPLC: Chiralpak IA column, eluent = *n*-hexane/i-PrOH 90:10, flow rate = 1.0 mL.min^{-1}, 254 nm; t_R(major diastereomer): (major) = 7.9 min; t_R (minor) = 10.4 min. t_R (minor diastereomer): (major) = 6.9 min; t_R (minor) = 9.0 min.

*N-((2S,3R)-1-hydroxy-3-(hydroxymethyl)-2-((4-methoxyphenyl)amino)-4-methylpentan-3-yl)benzamide (**14**).* The round bottom flask was filled with $NaBH_4$ (23 mg, 0.61 mmol) and $CaCl_2$ (27 mg, 0.24 mmol), diluted in anh. THF (1.5 mL). Mixture was stirred for 8 hours at 67 °C. Then the azlactone **6a** (50 mg, 0.12 mmol) in anh. THF (1.5 mL) added and mixture was stirred at room temperature for 18 h. Solution was acidified with 5 mL of 10% NH_4Cl, extracted with DCM (3x20 mL) and sat. solution of $NaHCO_3$ (20 mL), dried over Na_2SO_4 and solvent was evaporated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc 1:1) gave product **14** (21 mg, 47% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.85 – 7.82 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.49 – 7.43 (m, 2H), 6.86 – 6.75 (m, 4H), 4.08 (d, *J* = 11.6 Hz, 1H), 3.99 (s, 1H), 3.97 (s, 1H), 3.94 (d, *J* = 11.6 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 1H), 3.65 (d, *J* = 3.4 Hz, 2H), 3.55 (d, *J* = 12.2 Hz, 1H), 3.07 (m, *J* = 13.9, 6.9 Hz, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 168.30, 153.53, 138.85, 133.47, 131.05, 127.76, 126.13, 118.49, 113.84, 76.20, 75.99, 75.78, 65.39, 64.34, 61.73, 59.37, 56.40, 54.60, 27.62, 19.98, 16.19, 15.58, 13.17. HRMS: calcd. for $[C_{21}H_{28}N_2O_4+H]^+$ ([M+H]$^+$): *m/z* 373.2122, found 373.2122.

Acknowledgments

This work was supported by the Slovak Grant Agency VEGA, grant no. VEGA 1/0414/16. We thank Professor Ruth M. Gschwind for suggestions about DOSY and related NMR experiments, and Dr. Juraj Filo for assistance with NMR measurements. We thank Filip Beňovič for some preliminary experiments.

Keywords: hydrogen-bond • organic catalysis • Mannich reaction • hydroamination • dihydropyrroles

[1] L. Albrecht, L. K. Ransborg, K. A. Jørgensen, *Catal. Sci. Technol.* **2012**, *2*, 1089-1098.

[2] E. J. Corey, B. Czakó, L. Kürti, *Molecules and Medicine*, Wiley, Hoboken, **2007**.

[3] J. D. Northrup, G. Mancini, C. R. Purcell, C. E. Schafmeister, *J. Org. Chem.* **2017**, *82*, 13020-13033.

[4] L. F. Tietze, *Domino Reactions: Concepts for Efficient Organic Synthesis*, Wiley-VCH, Weinheim, **2014**.

[5] a) Y. Zhi, K. Zhao, Q. Liu, A. Wang, D. Enders, *Chem. Commun.* **2016**, *52*, 14011-14014; b) G.-H. Chang, C.-Y. Wang, G. Madhusudhan Reddy, Y.-L. Tsai, W. Lin, *J. Org. Chem.* **2016**, *81*, 10071-10080; c) L. Prieto, V. Juste-Navarro, U. Uria, I. Delso, E. Reyes, T. Tejero, L. Carrillo, P. Merino, J. L. Vicario, *Chem. Eur. J.* **2017**, *23*, 2764-2768; d) D. Kowalczyk, Ł. Albrecht, *J. Org. Chem.* **2016**, *81*, 6800-6807.

[6] a) H. D. B., L. Rai‐Shung, *ChemCatChem* **2015**, *7*, 2824-2825; b) L. Næsborg, F. Tur, M. Meazza, J. Blom, K. S. Halskov, K. A. Jørgensen, *Chem. Eur. J.* **2017**, *23*, 268-272.

[7] J. Jin, Y. Zhao, E. M. L. Sze, P. Kothandaraman, P. W. H. Chan, *Adv. Synth. Catal.* **2018**, *360*, 4744-4753.

[8] B. Mao, M. Fañanás-Mastral, B. L. Feringa, *Chem. Rev.* **2017**, *117*, 10502-10566.

[9] a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713-5743; b) S. Beckendorf, S. Asmus, O. G. Mancheño, *ChemCatChem* **2012**, *4*, 926-936; c) O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva, *Org. Biomol. Chem.* **2013**, *11*, 7051-7071; d) T. J. Auvil, A. G. Schafer, A. E. Mattson, *Eur. J. Org. Chem.* **2014**, 2633-2646; e) M. Žabka, R. Šebesta, *Molecules* **2015**, *20*, 15500-15524; f) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253-281; g) F. E. Held, S. B. Tsogoeva, *Catal. Sci. Technol.* **2016**, *6*, 645-667.

[10] a) P. P. de Castro, A. G. Carpanez, G. W. Amarante, *Chem. Eur. J.* **2016**, *22*, 10294-10318; b) A.-N. R. Alba, R. Rios, *Chem. Asian J.* **2011**, *6*, 720-734.

[11] a) M. Žabka, A. Malastová, R. Šebesta, *RSC Adv.* **2015**, *5*, 12890-12893; b) H. Zhang, Z. Yang, B. N. Zhao, G. Li, *J. Org. Chem.* **2018**, *83*, 644-655; c) S. Izumi, Y. Kobayashi, Y. Takemoto, *Org. Lett.* **2016**, *18*, 696-699; d) J. Kikuchi, N. Momiyama, M. Terada, *Org. Lett.* **2016**, *18*, 2521-2523; e) E. P. Ávila, R. M. S. Justo, V. P. Gonçalves, A. A. Pereira, R. Diniz, G. W. Amarante, *J. Org. Chem.* **2015**, *80*, 590-594; f) W.-Q. Zhang, L.-F. Cheng, J. Yu, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 4085-4088; g) S.-H. Shi, F.-P. Huang, P. Zhu, Z.-W. Dong, X.-P. Hui, *Org. Lett.* **2012**, *14*, 2010-2013; h) X. Liu, L. Deng, H. Song, H. Jia, R. Wang, *Org. Lett.* **2011**, *13*, 1494-1497; i) X. Liu, L. Deng, X. Jiang, W. Yan, C. Liu, R. Wang, *Org. Lett.* **2010**, *12*, 876-879; j) D. Uraguchi, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 14088-14089.

[12] a) Y.-F. Yu, C. Shu, T.-D. Tan, L. Li, S. Rafique, L.-W. Ye, *Org. Lett.* **2016**, *18*, 5178-5181; b) S. Fustero, I. Ibáñez, P. Barrio, M. A. Maestro, S. Catalán, *Org. Lett.* **2013**, *15*, 832-835; c) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496-499; d) Y.-F. Yu, C. Shu, B. Zhou, J.-Q. Li, J.-M. Zhou, L.-W. Ye, *Chem. Commun.* **2015**, *51*, 2126-2129.

[13] a) D. M. Barber, A. Ďuriš, A. L. Thompson, H. J. Sanganee, D. J. Dixon, *ACS Catal.* **2014**, *4*, 634-638; b) A. Jean, J. Blanchet, J. Rouden, J. Maddaluno, M. De Paolis, *Chem. Commun.* **2013**, *49*, 1651-1653; c) D. Monge, K. L. Jensen, P. T. Franke, L. Lykke, K. A. Jørgensen, *Chem. Eur. J.* **2010**, *16*, 9478-9484; d) X. Chen, H. Chen, X. Ji, H. Jiang, Z.-J. Yao, H. Liu, *Org. Lett.* **2013**, *15*, 1846-1849.

[14] a) S. Quantao, L. Xiaoyuan, S. Jinhuan, Z. Long, M. Mingxia, Z. Yuanyuan, Z. Yanyan, Z. Ranran, Y. Wenjin, W. Kairong, W. Rui, *Adv. Synth. Catal.* **2015**, *357*, 3187-3196; b) J. H. Li, H. Wen, L. Liu, D. M. Du, *Eur. J. Org. Chem.* **2016**, 2492-2499; c) K. Zhao, Y. Zhi, X. Li, R. Puttreddy, K. Rissanen, D. Enders, *Chem. Commun.* **2016**, *52*, 2249-2252; d) S. Jinhuan, M. Zelin, L. Xiaoyuan, L. Li, S. Zhiqiang, Y. Peiju, L. Yuan, W. Hailin, Y. Wenjin, W. Kairong, W. Rui, *Adv. Synth. Catal.* **2016**, *358*, 3777-3785; e) D. Kowalczyk, J. Wojciechowski, Ł. Albrecht, *Synthesis* **2017**, *49*, 880-890.

[15] a) G. Tárkányi, P. Király, S. Varga, B. Vakulya, T. Soós, *Chem. Eur. J.* **2008**, *14*, 6078-6086; b) P. Király, T. Soós, S. Varga, B. Vakulya, G. Tárkányi, *Magn. Reson. Chem.* **2010**, *48*, 13-19.

[16] R. P. Singh, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2010**, *132*, 9558-9560.

[17] N. Sorgenfrei, J. Hioe, J. Greindl, K. Rothermel, F. Morana, N. Lokesh, R. M. Gschwind, *J. Am. Chem. Soc.* **2016**, *138*, 16345-16354.

[18] R. Wechsel, M. Žabka, J. W. Ward, J. Clayden, *J. Am. Chem. Soc.* **2018**, *140*, 3528-3531.

[19] M. Odagi, H. Araki, C. Min, E. Yamamoto, T. J. Emge, M. Yamanaka, D. Seidel, *Eur. J. Org. Chem.* **2019**, 486-492.

[20] N. M. Kreienborg, C. Merten, *Chem. Eur. J.* **2018**, *24*, 17948-17954.

[21] D. Belmessieri, A. de la Houpliere, E. D. D. Calder, J. E. Taylor, A. D. Smith, *Chem. Eur. J.* **2014**, *20*, 9762-9769.

[22] R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84-86.

[23] M. Raducan, M. Moreno, C. Bour, A. M. Echavarren, *Chem. Commun.* **2012**, *48*, 52-54.

[24] H. B. Jang, H. S. Rho, J. S. Oh, E. H. Nam, S. E. Park, H. Y. Bae, C. E. Song, *Org. Biomol. Chem.* **2010**, *8*, 3918-3922.

[25] M. G. Núñez, A. J. M. Farley, D. J. Dixon, *J. Am. Chem. Soc.* **2013**, *135*, 16348-16351.

[26] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967-1969.

[27] W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450-5453.

[28] A. S. K. Hashmi, B. Bechem, A. Loos, M. Hamzic, F. Rominger, H. Rabaa, *Aust. J. Chem.* **2014**, *67*, 481-499.

[29] F. Varano, D. Catarzi, L. Squarcialupi, M. Betti, F. Vincenzi, A. Ravani, K. Varani, D. Dal Ben, A. Thomas, R. Volpini, V. Colotta, *Eur. J. Med. Chem.* **2015**, *96*, 105-121.

[30] R. J. Brea, M. P. López-Deber, L. Castedo, J. R. Granja, *J. Org. Chem.* **2006**, *71*, 7870-7873.

[31] C. K. Hazra, M. Oestreich, *Org. Lett.* **2012**, *14*, 4010-4013.

[32] N. S. Medran, M. Villalba, E. G. Mata, S. A. Testero, *Eur. J. Org. Chem.* **2016**, *2016*, 3757-3764.

[33] C. Macovei, P. Vicennati, J. Quinton, M.-C. Nevers, H. Volland, C. Créminon, F. Taran, *Chem. Commun.* **2012**, *48*, 4411-4413.

[34] R. S. Z. Saleem, J. J. Tepe, *J. Org. Chem.* **2010**, *75*, 4330-4332.

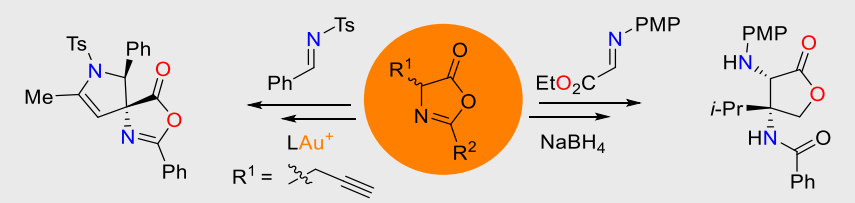
[35] M. Kojima, K. Mikami, *Chem. Eur. J.* **2011**, *17*, 13950-13953.

[36] S. Zhu, J. Dong, S. Fu, H. Jiang, W. Zeng, *Org. Lett.* **2011**, *13*, 4914-4917.

[37] M. S. Manna, S. Mukherjee, *J. Am. Chem. Soc.* **2015**, *137*, 130-133.

Entry for the Table of Contents

FULL PAPER



Racemic azlactones are transformed into valuable chiral heterocycles via asymmetric organocatalytic Mannich reaction followed by Au-catalyzed cyclization or reduction.

Asymmetric organocatalysis

*Matej Žabka, Adrián Kocian, Stanislav Bilka, Samuel Andrejčák, Radovan Šebesta**

Page No. – Page No.

Transformation of Racemic Azlactones into Enantioenriched Dihydropyrroles and Lactones Enabled by Hydrogen-Bond Organocatalysis

*one or two words that highlight the emphasis of the paper or the field of the study