EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

Title: Silver-Catalyzed Diastereoselective Synthesis of Spirocyclic Pyrrolidine-Lactones by 1,3-Dipolar Cycloaddition

Authors: Eduardo García-Mingüens, Oľga Caletková, Dušan Berkeš, Carmen Nájera, and Jose Miguel Sansano

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000915

Link to VoR: https://doi.org/10.1002/ejoc.202000915

WILEY-VCH

WILEY-VCH

FULL PAPER

Silver-Catalyzed Diastereoselective Synthesis of Spirocyclic Pyrrolidine-Lactones by 1,3-Dipolar Cycloaddition

Eduardo García-Mingüens,[a][b][c] Oľga Caletková,[d] Dušan Berkeš,*[d] Carmen Nájera,*[b] and José M. Sansano.*[a][b][c]

Dedicated to the memory of Prof. Rolf Huisgen.

[a] Mr. E. García-Mingüens, Prof. C. Nájera, and Prof. J. M. Sansano.
Departamento de Química Orgánica. Facultad de Ciencias.
Universidad de Alicante, 03080-Alicante, Spain.
E-mail: jmsansano@ua.es, https://cvnet.cpd.ua.es/curriculum-breve/en/sansano-gil-jose-miguel/10547.
[b] Centro de Innovación en Química Avanzada (ORFEO-CINQA)
[c] Instituto de Síntesis Orgánica (ISO).
Universidad de Alicante, 03080-Alicante, Spain.
[d] Dr. O. Caletková, Prof. D. Berkeš.
Department of Organic Chemistry, Slovak University of Technology in Bratislava, Slovakia.

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

Abstract: The preparation of two enantiomerically enriched amino lactones as chiral starting substrates for asymmetric 1,3-dipolar cycloadditions is described. They act as precursors of the chiral imino lactones, which form in situ the corresponding azomethine ylides. They react with with electrophilic alkenes under silver catalysis to afford spirolactone-pyrrolidines products. The sequential method consisting in one-pot imine-formation→cycloaddition is optimized and compared with the multicomponent process. The scope of the reaction is studied as well as the stereochemical outcomes and the mechanistic details using DFT calculations and X-ray diffraction analysis.

Introduction

Spirocyclic pyrrolidines are commonly present in natural products (for example **1**-**3**) and are considered as advanced building blocks in the discovery of biologically important drugs (molecules **4**-**6**)[1] (Figure 1). The particular balance in their conformational rigidity and flexibility allow exclusive biological effects in nature.[2] The 1,3-dipolar cycloadditions (1,3-DCs) involving intermediate azomethine ylides[3] are one of the best processes employed by scientists, even by nature, [4] to achieve these types of scaffolds.[5] The asymmetric synthesis of the molecules containing this stereogenic quaternary centre can be accessed in catalytic enantioselective processes[6] or in diastereoselective routes[3] using chiral auxiliaries attached to the substrates.

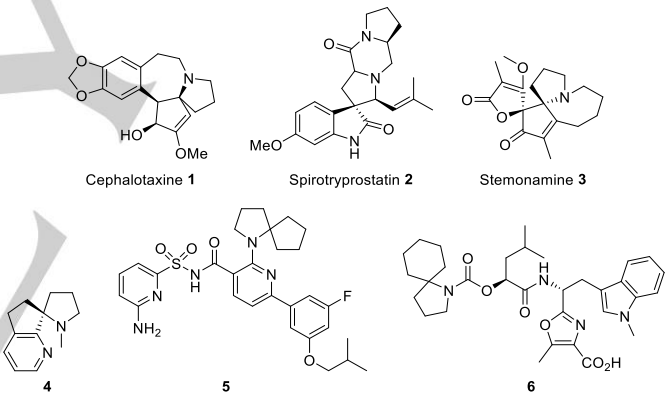
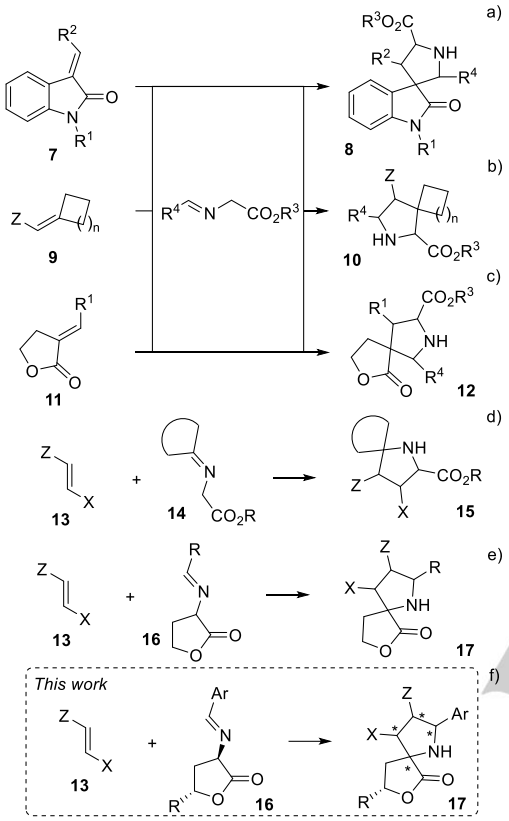


Figure 1. Natural and synthetic biologically active compounds containing spirocyclic pyrrolidines.

Addressing our attention in the reported methodologies for the elaboration of these types of molecular arrangements **8**, **10**, **12**, **15** and **17**, Scheme 1 shows the two main approaches. Firstly, an exocyclic alkene (**7**, **9** or **11**) is used as dipolarophile (Scheme 1a-c), and a second alternative involves exocyclic imines **14** or iminolactones **16** as 1,3-dipole precursors (Scheme 1d and e).[3] For example, alkylidene oxindoles **7** have been widely used (Scheme 1a),[4a, 7] but ethyl 2-cyclopropylidene acetate[8] belonging to the family of compounds **9** (Scheme 1b) and α-methylene/alkylidene-γ-butyrolactone[9] (Scheme 1c) were not so extensively studied. Concerning the structure of 1,3-dipole, 1,8-diazafluorenone,[10] ninhydrin, 1,2,3-phenalenetrione[11] and others[3] allowed to obtain skeletons **15** (Scheme 1d). However, homoserine lactone **16** derived 1,3-dipole has been used in multiple non-asymmetric processes with several common dipolarophiles,[12] methyleneindolinone derivatives,[13] arylidenemalonates.[14] In the case of enantioselective silver(I)-catalyzed 1,3-DC with common dipolarophiles[15][16], 3-methyl-4-nitro-5-alkenyl-isoxazole,[17] and nitroalkenes[18] were published.

In addition, in the presence of chiral organocatalysts such as several α,β-unsaturated butenolides,[19] 4-benzylidene-pyrazol-5(4H)-ones,[20] and in a two-step process consisted with nitroalkenes, have been used.[21]

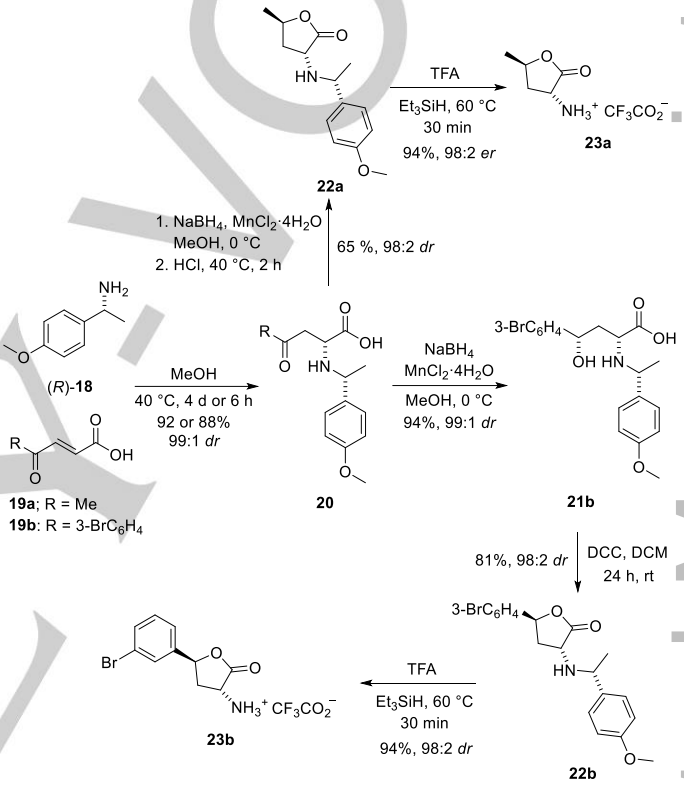
Due to the notable interest of this last lactone 1,3-dipole precursor, we will focus this work in the study in the transfer of chirality from the original enantiomerically enriched homoserine lactone derivatives **16** towards the spirocyclic pyrrolidine-lactones **17** (Scheme 1f) using a silver catalysed 1,3-DC process operating under mild conditions.



Scheme 1. Different approaches to synthesize spirocyclic pyrrolidines using 1,3-DC with azomethine ylides.

Results and Discussion

The synthesis of enantiomerically enriched aminolactone **23a** was reported by us following the chemical sequence depicted in Scheme 2.[22] The sequence started with a crystallisation-induced asymmetric transformation (CIAT)-aza-Michael addition of amine (*R*)-**18** to 3-acetylacrylic acid **19a** affording enantiomerically pure (99:1 *dr*) adduct **20a** in 92% yield. Next, a smooth *syn*-stereoselective reduction was performed with sodium borohydride in MeOH in the presence of $MnCl_2{\cdot}4H_2O$[22] giving, after acidic lactonization, intermediate **22a** in good yield (65%) and high diastereoselectivity (98:2 *dr*). The removal of the chiral auxiliary was accomplished by a mild reductive debenzylation with trifluoroacetic acid as the solvent and triethylsilane as the reducing agent. Chiral lactone **23a** was isolated in 94% yield and 98:2 *dr*. The preparation of the 3-bromophenyl analogue was reported by the first time employing a similar pathway starting with the CIAT-aza-Michael addition but requiring 6 h instead of the 4 d needed for the obtention of **20a**. Thus, intermediate product **20b** was isolated in 88% yield and 99:1 *dr*. In this case, the *syn*-stereoselective reduction was identically performed. However, the cyclization of **21b** under acidic media allows the both *cis*- and *trans*-lactones formation.[23] So, the γ-hydroxy-α-amino acid **21b** (obtained in 94% yield and 99:1 *dr*) was lactonized using DCC in dichloromethane at room temperature, furnishing *trans*-lactone **22b** in 81% yield and 98:2 *dr*. Finally, **23b** was isolated as it was described for **23a** with identical results.

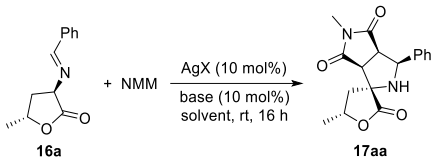


Scheme 2. Synthesis of chiral aminolactones **23**.

The diastereoselective 1,3-DC was optimized using iminolactone **16a** with *N*-methylmaleimide (NMM) as a benchmark reaction (Table 1). Imine **16a** was quantitatively prepared from **23a** using benzaldehyde and triethylamine (one equiv each) in dichloromethane at room temperature 19 h. The use of AgOAc (10 mol%) with triethylamine, in toluene revealed an excellent conversion of **17aa** in 87/13 *dr* (Table 1, entry 1). THF, *tert*-butyl methyl ether (TBME) and dichloromethane were tested affording good diastereomeric ratios, being dichloromethane selected for the next optimization analyses (Table 1, entries 2-4). The effect of silver salt nature was also very important. Whilst AgF and Ag_2CO_3 afforded very disappointing results in terms of conversion (Table 1, entries 5 and 7), silver hexafluoroantimonate gave a 92% of conversion and 88:12 *dr* (Table 1, entry 6). 1,4-Diazabicyclo[2.2.2]octane (DABCO) and diisopropylethylamine (DIPEA) were assessed affording lower diastereoselectivities than the corresponding one generated in the reaction performed with triethylamine (Table 1, entries 8 and 9). The reaction is not completed after 16 h in the absence of base

and AgOAc as the catalyst is crucial for the development of this diastereoselective transformation (Table 1, entries 10 and 11). Also, the lowering of the catalyst loading to a 7 mol% was not appropriate (Table 1, entry 12). Taking advantage that the imine **16a** is generated in DCM, the sequential one pot-imine formation followed by the cycloaddition was studied. Thus, to the reaction mixture containing the preformed (during 17 h and non-isolated) imino lactone **16a**, the dipolarophile and the catalytic system were added and the new mixture was stirred during 16 h. The result was identical to the stepwise method described in entry 4 of Table 1. The reaction was completely inhibited by lowering the temperature at 4 ºC (ice bath) furnishing to very poor conversions (<20%) and no noticeable increment of the *dr* was detected (not shown in Table 1).

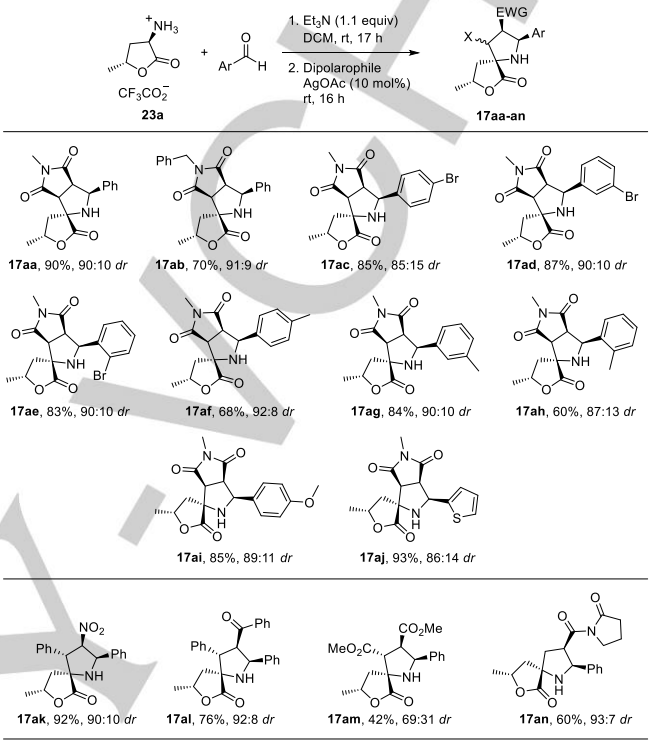
Table 1. Optimization of the reaction parameters of the synthesis of compound **17aa**.



entry	AgX	solvent	base	Conv. (%)[a]	*dr* [a]
1	AgOAc	PhMe	Et_3N	>98	87:13
2	AgOAc	THF	Et_3N	90	89:11
3	AgOAc	TBME	Et_3N	90	88:12
4	AgOAc	DCM	Et_3N	>98	92:8
5	AgF	DCM	Et_3N	58	n.d.
6	$AgSbF_6$	DCM	Et_3N	92	88:12
7	Ag_2CO_3	DCM	Et_3N	29	nd
8	AgOAc	DCM	DABCO	90	86:14
9	AgOAc	DCM	DIPEA	>98	83:17
10	AgOAc	DCM	---	90	90:10
11	---	DCM	Et_3N	20	n.d.
12	AgOAc[b]	DCM	Et_3N	78	92:8
13	AgOAc[c]	DCM	Et_3N	>98	92:8

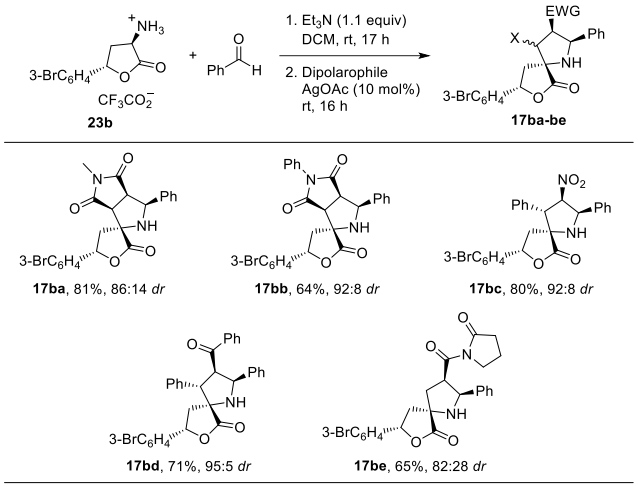
[a] Determined by ^1H NMR of the crude reaction mixture. [b] Reaction performed with 7 mol% of both AgOAc and triethylamine. [c] Sequential one-pot reaction starting from salt **23a** and 1.1 equiv of triethylamine.

Using this sequential method (Table 1, entry 13), the scope of the reaction with several aldehydes and dipolarophiles was surveyed (Scheme 3). NMM and *N*-benzylmaleimide afforded cycloadducts **17aa** and **17ab** in similar diastereoselectivities but in 90 and 70% yields, respectively. Using, NMM as dipolarophile, the presence of a substituent in the aromatic ring of the imino moiety did not affect neither in the yield nor in the diastereomeric ratio. For example, the ranges of yields (87-83% or 60-84%) and *dr* (85:15 - 90:10 or 87:13 - 92:8) obtained for the series of bromoarenes **17ac**-**17ae** and tolyl derivatives **17af**-**17ah** justified this fact. The presence of an electron-donating group (OMe) in the aromatic ring provided spiranic system **17ai** in 85% yield and 89:11 *dr*. In addition, slightly lower diastereoselectivity (86:14) and an excellent yield (93%) were achieved in the example run with 2-thiophenecarboxaldehyde (**17aj**). Next, different dipolarophiles were assayed (Scheme 3). In the case of β-nitrostyrene, compound **17ak** was isolated in excellent yield (93%) and good diastereoselectivity (90:10). Chalcone was an appropriate electron-deficient alkene able to run the diastereoselective 1,3-DC in both high yield (76%) and diastereoselectivity (92:8). Whilst dimethyl fumarate gave spiropyrrolidine **17am** in modest yield (43%) and diastereoselectivity (69:31), *N*-acryloylpyrrolidin-2-one provided the best result (**17an**) in terms of diastereomeric ratio (93:7) of this series.



Scheme 3. Synthesis spirocyclic pyrrolidine-lactones **17** through the sequential method from **23a**.

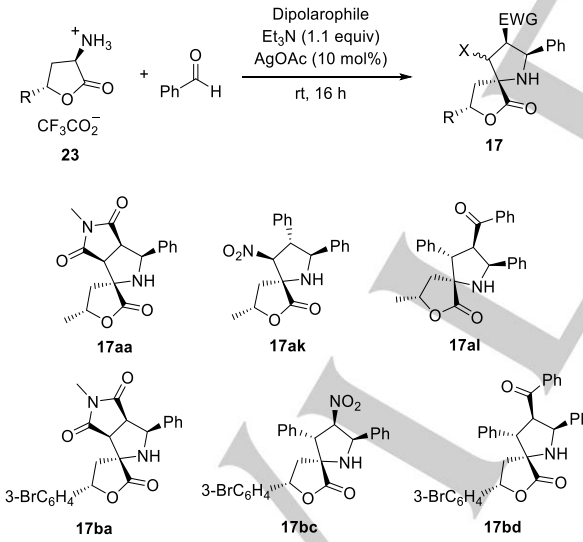
The analysis of the presence of a bulkier group (3-bromophenyl) in the stereogenic centre of the amino lactone was next assessed, using the sequential 1,3-DC with assorted dipolarophiles keeping benzaldehyde as common reagent in all examples (Scheme 4). In general, similar diastereoselectivities and yields to those reported in Scheme 3 for **23a** were observed. It is noticeable the good result obtained with *N*-phenylmaleimide, which was not suitable in the reaction with **23a**. Product **17bb** was isolated in 64% yield and a 92:8 *dr*. β-Nitrostyrene and chalcone furnished the best results for **17bc** and **17bd**, respectively, being the last one the highest diastereoselectivity determined in all the series (95:5). *N*-Acryloylpyrrolidin-2-one furnished the corresponding cycloadduct in good yield (63%) but with lower diastereoselectivity (82:18).



Scheme 4. Synthesis spirocyclic pyrrolidine-lactones **17** through the sequential method from **23b**.

Strict multicomponent reaction was also attempted. The mixture of **23**, benzaldehyde, triethylamine (1.1 equiv), the dipolarophile and AgOAc (10 mol%) were put together at the same time having a moderate success (Table 2). NMM, β-nitrostyrene and chalcone gave very good yields and very high diastereoselectivities, slightly higher than the analogous products obtained in the reaction employing the sequential method. Other different dipolarophiles attempted, such as acrylates, fumarates, conjugated ketones and 1,2-bis(phenylsulfonyl)ethylene furnished very low conversions (<25%). The reactions using non-aromatic aldehydes were not successful at all.

Table 2. Multicomponent 1,3-DC involving amino lactones **23**.



entry	23	dipolarophile	17	Yield (%)[a]	*dr* [b]
1	**23a**	NMM	**17aa**	90	90:10
2	**23a**	β-nitrostyrene	**17ak**	78	92:8
3	**23a**	chalcone	**17al**	71	95:5
4	**23b**	NMM	**17ba**	90	90:10
5	**23b**	β-nitrostyrene	**17bc**	79	95:5
6	**23b**	chalcone	**17bd**	82	95:5

[a] Isolated yields after flash chromatography. [b] Determined by ^{1}H NMR of the crude reaction mixture.

The diastereomeric ratios reported in all the work were determined by measurements of the integrals in the ^{1}H NMR spectra of both crude and purified materials. Also, the mixture of diasteroisomers of **17aa** was analysed by HPLC using columns with several chiral stationary phases demonstrating a full match between the ratios determined by the two instrumental techniques. The absolute configuration was assigned by X-ray diffraction analysis of compound **17ak** (Figure 2). [24] Complementary bidimensional or nOe NMR experiments and the values of the coupling constants helped to ensure the identical absolute configuration of the rest of the isolated molecules **17**. According to the standard nomenclature of the *endo*/*exo* approach of the dipolarophile towards the 1,3-dipole, the process occurred in a diastereoselective *endo*-approach with an all-*cis*- and 2,4,5-*cis*-arrangements for maleimides and the rest of dipolarophiles, respectively. The study of the biological properties of these new molecules **17** is underway.

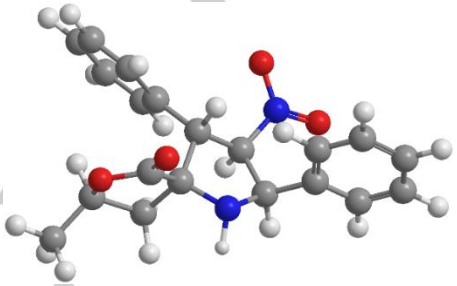


Figure 2. X-Ray diffraction pattern of product **17ak**.

The less and the most favourable *endo*-approaches (Figure 3a) has been calculated using DFT modelling at B3LYP basic level. From these results **TSA** and **TSC** corresponded to the transition states that originated the minor *endo*-diastereoisomers of **17** and **TSB** and **TSD** generated the most abundant *endo*-cycloadducts (Figure 3b). In all of them a weak interaction of the nitrogen atom of the NMM with the silver cation was defined. The energy gaps between **TSA**-**TSC** and **TSB**-**TSD** are of 2.0 and 2.6 kcal·mol^{-1}, respectively (Figure 3c) and the stability of the final cycloadducts is very closed to each other, specially, for the major and minor *endo*-**17aa** spirocyclic pyrrolidines. Despite the long distance existing between the reactive area of the transition state and the chiral information position the diastereoselection is very high.[25] The steric interaction of the maleimide with the methyl or the arene moiety bonded to the stereogenic centre seemed to be similar and enough to favour one of the two *endo*-approaches. However, the extra higher energy gap observed in the **TSB**-couple would be caused by the weak π-stacking interaction of the two aromatic rings observed in the most favoured approach in **TSD**. The importance of the silver cation (see above in entry 11 of Table 1) for the catalytic 1,3-DC process is based in the control of the geometry of the dipole and also by the notable secondary stereoelectronic interaction with the dipolarophile (in these examples is NMM). The increment of the reactivity of both components bonded to the metal sphere confirmed the dual catalytic character of the silver(I) species.

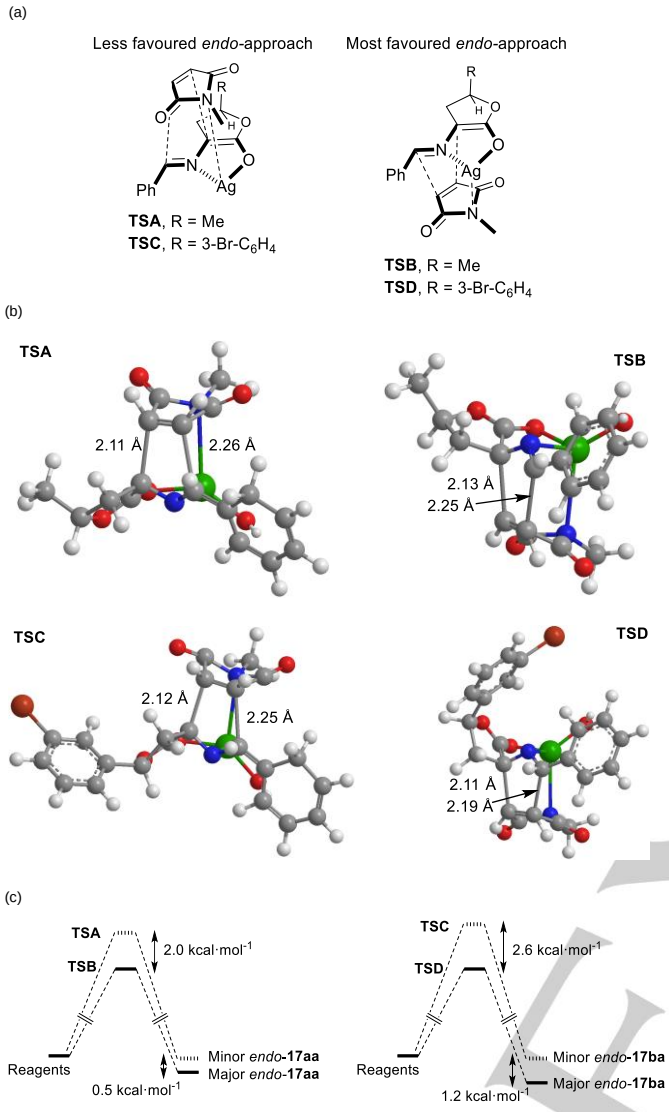


Figure 3. (a) Representation of the less favoured and most favoured approaches of the NMM to the imino lactone for the synthesis of **17aa** and **17ab**. (b) Calculated transition states **TSA**, **TSB**, **TSC** and **TSD** at B3LYP basic level. (c) Plot of relative energy profiles *versus* the reaction course.

Conclusions

In conclusion, the catalytic diastereoselective 1,3-dipolar cycloaddition occurred when chiral amino lactones, aromatic aldehydes and dipolarophiles were allowed to react in the presence of substoichiometric amounts of silver acetate. The resulting spirocyclic pyrrolidine-lactones were obtained in high yields and diasteroselectivities as *endo*-cycloadducts. The multicomponent version is highly dependent on the nature of the dipolarophiles. These components were also crucial for the generation of both high *dr* and yields. Silver cation had a paramount relevance to achieve the expected cycloadducts, which can be considered as new chiral building blocks for general organic synthesis. Many silver-catalyzed 1,3-DC have been reported but never was remarked the extremely high functional group tolerance of this cation and its salts. The experimental outcomes were supported by computational analyses. Almost synchronous transitions states showed small (but enough) steric interactions between the substituents of the stereogenic centre and the NMM during the less favoured approach. Besides, a weak π-stacking interaction between the two aromatic moieties of the system stabilized the most favoured *endo*-approach for the cases of the 3-bromophenyl derivatives.

Experimental Section

General: All commercially available reagents and solvents were used without further purification, and only aldehydes were also distilled prior to use. Compound **23a** was prepared according to the literature.[22] Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates, and the spots were visualized under UV light (λ = 254 nm). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. HPLC analyses were performed in a JASCO 2000 series machine. Optical rotations were measured on a JASCO P-1030 polarimeter with a thermally jacketed 5 cm cell at approximately 25 ˚C and concentrations (*c*) are given in g/100 mL. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT) are listed and wavenumbers are given in cm^{-1}. NMR spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ as solvent and TMS as internal standard (0.00 ppm) unless otherwise stated. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet or unresolved and br s = broad signal. All coupling constants (*J*) are given in Hertz (Hz) and chemical shifts in ppm. ^{13}C NMR spectra were referenced to $CDCl_3$ at 77.16 ppm. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in *m/z* are given with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were measured on an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95S. Vibrational Circular Dichroism (VCD) studies were accomplished in a Jasco FVS-6000 and X-ray crystal structure was determined using a Bruker CCD-Apex.

*General procedure for the preparation of amino lactone **23b**.*

m-Bromoacetophenone (32.24 g, 0.162 mol) and the glyoxylic acid monohydrate (14.9 g, 0.162 mol) were refluxed for 24 h in the mixture of acetic acid (80 mL) and conc. aq. HCl (36%, 3 mL). The mixture was concentrated *in vacuo* and extracted between 400 mL of 10% aq. Na_2CO_3 solution and ethyl acetate (3 x 150 mL). Organic layers were discarded, and the water layer was acidified with conc. aq. HCl to pH 2-3, and the formed suspension was further extracted with diethyl ether (3 x 200 mL), combined organic phases were dried over $MgSO_4$, filtrated and concentrated. Obtained crude acid was crystallized from ethyl acetate to obtain **19b** (22.36 g, 55%).

Acid **19b** (30 g, 0.118 mol) was dissolved in methanol (600 mL) and (*R*)-1-(4-methoxyphenyl)ethylamine (*R*)-**18** (1.1 eq., 19.56 g, 0.129 mol) was added to the solution. Reaction mixture was stirred for 6 hours at 40 °C and the reaction was monitored

by HPLC. The suspension was filtered off, washed with methanol (150 mL) and diethyl ether (150 mL) and dried *in vacuo*, obtaining **20b** (42 g, 88%).

$MnCl_2 \cdot 4H_2O$ (0.2 eq., 2.44 g, 12.31 mmol) was dissolved in methanol (600 mL) and compound **20b** (25 g, 61.50 mmol) was added. Mixture was cooled to 0-5 °C in the ice bath and $NaBH_4$ (3 eq., 6.98 g, 184.50 mmol) was added in portions over the period of 1 h. The reaction mixture was stirred at this temperature for additional 1 h and methanol was removed under reduced pressure. Residual solids were suspended in a mixture of water (50 mL) and 10% aq. K_2CO_3 (50 mL) and after 15 min. of stirring, solids were filtered off. Filtrate was acidified with 1M aq. HCl to pH 6.5 while forming thick suspension. This was filtered off, washed with water (100 mL), ethanol (100 mL), diethyl ether (100 mL) and dried to obtain crude product **21b** as white solid (23.65 g, 94%).

Acid **21b** (23.65 g, 57.92 mmol) was added to the solution of DCC (1.5 eq., 17.92 g, 86.89 mmol) in DCM (500 mL) and the mixture was stirred for 24 h at rt. The resulting suspension was filtered off and the filtrate was concentrated under the reduced pressure. The crude product was purified by column chromatography (Hex:EtOAc;3:1 to 1:1). The desired lactone **22b** was obtained as a colorless oil (18.25 g, 81%).

Triethylsilane (1 eq., 44.6 mmol, 5.2 g, 7.1 mL) was added to the lactone **21b** (17.4 g, 44.6 mmol) and the mixture was dissolved in TFA (130 mL). Reaction mixture was stirred at 60 °C for 30 min. and concentrated under the reduced pressure. The residue was triturated with cold diethyl ether, filtered and dried isolating pure **21b** (15.27 g, 94%).

General Procedure for the diastereoselective 1,3-DC.

Sequential one-pot method: To a suspension of (3*R*,5*R*)-5-methyl-2-oxotetrahydrofuran-3-aminium 2,2,2-trifluoroacetate **23a** or (3*R*,5*S*)-5-(3-bromophenyl)-2-oxotetrahydrofuran-3-aminium 2,2,2-trifluoroacetate **23b** (0.3 mmol) and the corresponding aldehyde (0.3 mmol) in dichloromethane was added triethylamine dropwise. The solution was stirred for 17 hours. Next, silver acetate (10 mol%) and the dipolarophile were added to the crude mixture. The reaction was stirred 17 hours. The crude mixture was filtered through celite and washed with brine three times. The combined organic layers were dried over magnesium sulphate ($MgSO_4$) and concentrated under *vacuum*. The purification step depends on the product (see characterization data).

Multicomponent method: To a suspension of (3*R*,5*R*)-5-methyl-2-oxotetrahydrofuran-3-aminium 2,2,2-trifluoroacetate **23a** or (3*R*,5*S*)-5-(3-bromophenyl)-2-oxotetrahydrofuran-3-aminium 2,2,2-trifluoroacetate **23b** (0.3 mmol) (0.3 mmol) and the corresponding aldehyde (0.3 mmol) in dichloromethane was added triethylamine (0.33 mmol) dropwise. Next, silver acetate (10 mol%) and the dipolarophile were added to the crude mixture. The reaction was stirred 17 hours. The crude mixture was filtered through celite and washed with brine three times. The combined organic layers were dried over magnesium sulphate ($MgSO_4$) and concentrated under *vacuum*. The purification step depends on the product (see characterization data).

[(*E*)-4-(3-Bromophenyl)-4-oxobut-2-enoic acid (19b). White solid (22.36 g, 55% yield); mp: 154 – 156 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 6.92 (d, *J* = 15.5 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.77 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.86 – 7.98 (m, 2H), 8.14 (m, 1H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 123.5, 127.5, 130.7, 132.0, 132.2, 137.1, 137.8, 138.2, 170.1, 188.0 ppm; HRMS (HESI): *m/z* $[M-H]^-$ calcd. for $C_{10}H_6BrO_3$: 252.95058, found: 252.95056.

(*R*)-4-(3-Bromophenyl)-2-{[(*R*)-1-(4-methoxyphenyl)ethyl]amino}-4-oxobutanoic acid (20b). White solid (42 g, 88% yield, 99:1 *dr*); mp: 186-187 °C; $[\alpha]_D^{25}$: -42.3 (*c* 1, MeOH:5% aq. HCl, 9:1); ^{1}H NMR (300 MHz, acetone-d6/DCl) δ_H 1.82 (d, *J* = 6.9 Hz, 3H), 3.78 (s, 3H), 3.92 (m, 2H), 4.17 (dd, *J* = 6.5, 4.6 Hz, 1H), 4.83 (q, *J* = 6.8 Hz, 1H), 6.94-7.02 (m, 2H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.58-7.66 (m, 2H), 7.77 (m, 1H), 7.92-8.04 (m, 2H) ppm; ^{13}C NMR (75 MHz, acetone-d_6/DCl) δ_C 20.7, 53.3, 53.3, 55.6, 59.3, 115.2, 123.1, 128.1, 128.2, 130.8, 131.4, 131.6, 137.1, 161.2, 169.3, 195.1 ppm; HRMS (HESI): *m/z* $[M+H]^+$ calcd. for: $C_{19}H_{21}BrNO_4$: 406.06485, found: 406.06528.

(2*R*,4*S*)-4-(3-Bromophenyl)-4-hydroxy-2-{[(*R*)-1-(4-methoxyphenyl)ethyl]amino}-butanoic acid (21b). White solid (23.65 g, 94%, 99:1 *dr*) mp: 192-193 °C; $[\alpha]_D^{25}$: -14.6 (*c* 1, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ_H 1.76 (d, *J* = 6.8 Hz), 2.06-2.22 (m, 2H), 3.73-3.80 (m, 4H), 4.53 (q, *J* = 6.8 Hz, 1H), 4.79 (dd, *J* = 9.2, 4.0 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 2H), 7.17-7.31 (m, 2H), 7.34-7.55 (m, 4H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ_C 20.5, 39.3, 56.1, 57.1, 59.2, 70.8, 115.9, 123.3, 125.6, 128.0, 129.6, 130.6, 131.4, 131.7, 147.1, 161.9, 169.7 ppm; HRMS (HESI): *m/z* $[M+H]^+$ calcd. for: $C_{19}H_{23}BrNO_4$: 408.08050, found: 408.08092.

(3*R*,5*S*)-5-(3-Bromophenyl)-3-{[(*R*)-1-(4-methoxyphenyl)ethyl]amino}dihydrofuran-2(3*H*)-one (22b). Colorless oil (18.3 g, 81% yield, 98:2 *dr*); $[\alpha]_D^{25}$: 106.6 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.37 (d, *J* = 6.6 Hz, 3H), 2.01 (ddd, *J* = 13.1, 8.1, 4.0 Hz, 1H), 2.22 (m, 1H), 3.44 (t, *J* = 8.1 Hz, 1H), 3.80 (s, 3H), 4.00 (q, *J* = 6.6 Hz, 1H), , 5.47 (dd, *J* = 7.9, 4.0 Hz, 1H), 6.83-6.89 (m, 2H), 7.17-7.29 (m, 3H), 7.07-7.12 (m, 1H), 7.31-7.35 (m, 1H), 7.40-7.44 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 24.8, 38.8, 54.5, 55.4, 57.2, 77.5, 114.0, 123.0, 123.6, 128.1, 128.2, 130.5, 131.4, 136.8, 141.8, 159.0, 177.1 ppm; HRMS (HESI): *m/z* $[M+H]^+$ calcd. for: $C_{19}H_{21}BrNO_3$: 390.06993, found: 390.06996.

(3*R*,5*S*)-5-(3-Bromophenyl)-2-oxotetrahydrofuran-3-aminium 2,2,2-trifluoroacetate (23b). White solid (15.27 g, 94% yield, 98:2 *dr*); mp: 138-140 °C; $[\alpha]_D^{25}$: 29.2 (*c* 1, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ_H 2.77 (ddd, *J* = 13.4, 9.3, 2.6 Hz, 1H), 2.84 (ddd, *J* = 13.4, 9.4, 8.6 Hz, 1H), 4.40 (t, *J* = 9.7 Hz, 1H), 5.83 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.57 – 7.53 (m, 2H); ^{13}C NMR (151 MHz, CD_3OD) δ_C 34.7, 48.5, 79.1, 118.2 (q, *J* = 292.9 Hz), 124.0, 125.1, 129.4, 131.9, 132.9, 142.4, 163.1 (q, *J* = 34.5 Hz), 173.3 ppm; HRMS (HESI): *m/z* $[M\text{-}CF_3COO^-]^+$ calcd. for: $C_{10}H_{11}BrNO_2^+$: 255.99677, found: 255.99682.

(3*S*,3'*R*,3a'*S*,5*R*,6a'*R*)-5,5'-Dimethyl-3'-phenylhexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(5'*H*)-trione (17aa). White solid (84.6 mg, 90% yield, 90:10 *dr*); without purification; mp: 234 °C; $[\alpha]_D^{25.7}$ = -51.7 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.56 (d, *J* = 5.1 Hz, 3H, CH_3), 1.94 (t, *J* = 11,4 Hz, 1H, CH_2), 2.70 (m, 1H, CH_2), 2.91 (s, 3H, NCH_3), 3.37 (d, *J* = 6.7 Hz, 1H, CCH), 3.62 (bs, 1H, NCHC*H*), 4.64 (d, *J* = 6.8 Hz, 1H, NCH), 4.81 (bs, 1H, C*H*CH_3), 7.38 (bs, 5H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 20.5 (CH*C*H_3), 25.3 (NCH_3), 46.3 (CH_2), 51.0

(*C*HCO), 54.6 (*C*HCO), 64.7 (NCH), 69.8 (NC), 73.6 (*C*HCH$_3$), 127.0, 128.5, 128.6, 135.8 (ArC), 174.2 (CO), 174.6 (CO), 175.1 (CO) ppm; IR (ATR) υ_{max}: 3025, 2981, 2926, 1770, 1697, 1438, 1389, 1286, 1201 cm^{-1}; MS (EI): *m/z* 314 (M$^+$, 8%), 270 (27), 256 (18), 255 (100), 242 (14), 241 (22), 156 (11); HRMS calcd. for $C_{17}H_{18}N_2O_4$: 314.1267; found: 314.1278.

(3*S*,3'*R*,3a'*S*,5*R*,6a'*R*)-5'-Benzyl-5-methyl-3'-phenylhexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(5'*H*)-trione (17ab). White solid (116.8 mg, 70% yield, 91:9 *dr*); without purification; mp: 221 °C; $[\alpha]_D^{28.1}$ = -67.9 (*c* 1.0, -67.9 CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.53 (d, *J* = 6.1 Hz, 3H, CH$_3$), 2.10 (t, *J* = 11.5 Hz, 1H, CCH$_2$), 2.69 (dd, *J* = 11.5, 4.1 Hz, 1H, CCH$_2$), 3.40 (d, *J* = 7.5 Hz, 1H, CCH), 3.61 (t, *J* = 7.9 Hz, 1H, NCHC*H*), 4.44 (d, *J* = 14.0 Hz, 1H, NCH$_2$), 4.62 (d, *J* = 14.0 Hz, 1H, NCH$_2$), 4.71-4.80 (m, 2H, NCH, CHCH$_3$), 7.12-7.36 (m, 10H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 20.3 (CH*C*H$_3$), 43.1 (NCH$_2$), 44.6 (C*C*H$_2$), 50.1 (*C*HCO), 54.2 (*C*HCO), 65.0 (NCH), 70.1 (NC), 74.5 (*C*HCH$_3$), 127.3, 128.3, 128.8, 129.0, 129.3, 133.7, 135.3 (ArC), 173.1 (CO), 173.6 (CO), 174.0 (CO) ppm; IR (ATR) υ_{max}: 1771, 1699, 1402, 1337, 1205, 1171 cm^{-1}; MS (EI): *m/z* 390 (M$^+$,13%), 373 (20), 346 (30), 345 (10), 332 (23), 331 (100), 318 (10), 170 (10), 156 (11), 91 (29); HRMS calcd. for $C_{23}H_{22}N_2O_4$: 390.1580; found: 390.1576.

(3*S*,3'*R*,3a'*S*,5*R*,6a'*R*)-3'-(4-Bromophenyl)-5,5'-dimethylhexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(5'*H*)-trione (17ac). White solid (99.8 mg, 85% yield, 85:15 *dr*); without purification; mp: 218°C; $[\alpha]_D^{24.6}$ = -73.4 (*c* 0.5, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.55 (d, *J* = 6.1 Hz, 3H, CH$_3$), 1.99 (m, 1H, CH$_2$), 2.68 (m, 1H, CH$_2$), 2.91 (s, 3H, CH$_3$), 3.37 (d, *J* = 7.6 Hz, 1H, CCH), 3.62 (t, *J* = 7.7 Hz, 1H, NCHC*H*), 4.63 (d, *J* = 7.7 Hz, 1H, NCH), 4.83 (m, 1H, C*H*CH$_3$), 7.23 (m, 1H, ArH), 7.50 (m, 3H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 20.5 (CH*C*H$_3$), 25.5 (NCH$_3$), 46.0 (CH$_2$), 50.4 (*C*HCO), 54.3 (*C*HCO), 64.1 (NCH), 69.8 (NC), 73.7 (*C*HCH$_3$), 128.8, 131.8 (ArC), 174.3 (CO) ppm; IR (ATR) υ_{max}: 3309, 2981, 2915, 1778, 1693, 1195, 1106 cm^{-1}; MS (EI): *m/z* 394 (M$^+$,11%), 392 (M$^+$,11), 350 (14), 349 (14), 348 (29), 336 (16), 335 (97), 334 (23), 333 (100), 322 (12), 321 (16), 320 (10), 319 (11), 281 (10), 241 (17), 236 (11), 115 (13), 89 (10); HRMS calcd. for $C_{17}H_{17}BrN_2O_4$: 393.0371; found: 393.0352.

(3*S*,3'*R*,3a'*S*,5*R*,6a'*R*)-3'-(3-Bromophenyl)-5,5'-dimethylhexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(5'*H*)-trione (17ad). White solid (102.3 mg, 87% yield, 90:10 *dr*); without purification; mp: 230 °C; $[\alpha]_D^{30.6}$ = -111.62 (*c* 0.7, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.54 (d, *J* = 6.1 Hz, 3H, CH$_3$), 1.89 (dd, *J* = 12.3, 11.0 Hz, 1H, CH$_2$), 2.67 (dd, *J* = 12.5, 4.6 Hz, 1H, CH$_2$), 2.90 (s, 3H, CH$_3$), 3.35 (d, *J* = 7.6 Hz, 1H, CCH), 3.59 (t, *J* = 7.7 Hz, 1H, NCHC*H*), 4.57 (d, *J* = 7.7 Hz, 1H, NCH), 4.57-4.83 (m, 1H, C*H*CH$_3$), 7.45-7.52 (4H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 20.5 (CH*C*H$_3$), 25.4 (NCH$_3$), 46.2 (CH$_2$), 50.5 (CHCO), 54.2 (CHCO), 63.9 (NCH), 69.6 (NC), 73.5 (*C*HCH$_3$), 122.7, 125.7, 130.0, 130.2, 131.6, 138.2 (ArC), 174.0 (CO), 174.4 (CO), 174.9 (CO) ppm; IR (ATR) υ_{max}: 3313, 2978, 1760, 1698 cm^{-1}; MS (EI): *m/z* 394 (M$^+$, 10%), 392 (M$^+$, 10%), 350 (36), 349 (13), 348 (32), 336 (16), 335 (100), 334 (21), 333 (100), 322 (11), 321 (14), 320 (11), 241 (13), 236 (10), 115 (13); HRMS calcd. for $C_{17}H_{17}BrN_2O_4$: 390.0372; found: 390.0360.

(3*S*,3'*R*,3a'*S*,5*R*,6a'*R*)-3'-(2-Bromophenyl)-5,5'-dimethylhexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(5'*H*)-trione (17ae). White solid (97.5 mg, 83% yield, 90:10 *dr*); Precipitation CHCl$_3$/*n*-Hexane; mp: 211 °C; $[\alpha]_D^{28.7}$ = -80.9 (*c* 0.58, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.55 (d, *J* = 6.1 Hz, 3H, CH$_3$), 2.02 (t, *J* = 12.5 Hz, 1H, CH$_2$), 2.79 (dd, *J* = 12.5, 4.5 Hz, 1H, CH$_2$), 2.86 (s, 3H, CH$_3$), 3.41 (d, *J* = 7.6 Hz, 1H, CCH), 3.98 (t, *J* = 7.7 Hz, 1H, NCHC*H*), 4.80 (d, *J* = 7.7 Hz, 1H, NCH), 4.60-4.87 (m, 1H, C*H*CH$_3$), 7.20-7.24 (m, 1H, ArH), 7.30-7.34 (m, 1H, ArH), 7.46-7.49 (m, 1H, ArH), 7.60-7.63 (m, 1H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 20.5 (CH*C*H$_3$), 25.4 (NCH$_3$), 45.6 (CH$_2$), 47.5 (*C*HCO), 53.5 (*C*HCO), 63.2 (NCH), 69.2 (NC), 73.6 (*C*HCH$_3$), 123.6, 127.0, 127.8, 129.9, 132.8, 135.2 (ArC), 173.7 (C=O), 174.4 (C=O), 174.7 (C=O) ppm; IR (ATR) υ_{max}: 1771, 1697, 1434, 1284, 755 cm^{-1}; MS (EI): *m/z* 350 (M$^+$ -CO$_2$, 22%), 348 (M$^+$ -CO$_2$, 22%), 336 (13), 335 (79), 334 (15), 333 (82), 314 (18), 313 (100), 241 (24), 115 (11); HRMS calcd. for $C_{17}H_{17}BrN_2O_4$ (–CO$_2$): 350.0430; found: 350.0453.

(3*S*,3'*R*,3a'*S*,5*R*,6a'*R*)-5,5'-Dimethyl-3'-(*p*-tolyl)hexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo [3,4-c]pyrrole]-2,4',6'(5'*H*)-trione (17af). White solid (67 mg, 68 % yield, 92:8 *dr*); Precipitation CHCl$_3$/*n*-Hexane; mp: 233 °C; $[\alpha]_D^{31.5}$ = -100.7 (*c* 0.82, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.54 (d, *J* = 6.1 Hz, 3H, CH$_3$), 1.92 (dd, *J* = 12.4, 11.0 Hz, 1H, CH$_2$), 2.35 (s, 3H, CCH$_3$) 2.67 (dd, *J* = 12.5, 4.7 Hz, 1H, CH$_2$), 2.90 (s, 3H, NCH$_3$), 3.35 (d, *J* = 7.7 Hz, 1H, CCH), 3.58 (t, *J* = 7.8 Hz, 1H, NCHC*H*), 4.58 (d, *J* = 8 Hz, 1H, NCH), 4.73-4.85 (m, 1H, C*H*CH$_3$), 7.16-7.23 (m, 4H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 20.5 (CH*C*H$_3$), 21.4 (C*C*H$_3$), 25.3 (NCH$_3$), 46.2 (CH$_2$), 51.0 (NCHPh*C*H), 54.6 (NC*C*H), 64.6 NCHPh), 69.7 (NC), 73.6 (*C*HCH$_3$), 126.8, 129.3, 132.6, 138.2 (ArC), 174.3, 174.7, 175.2 (C=O) ppm; IR (ATR) υ_{max}: 1770, 1693, 1200 cm^{-1}; MS (EI): *m/z* 328 (M$^+$, 13%), 284 (23), 270 (19), 269 (100), 255 (11), 241 (17); HRMS calcd. for $C_{18}H_{20}N_2O_4$: 328.1423; found: 328.1416.

(3*S*,3'*R*,3a'*S*,5*R*,6a'*R*)-5,5'-Dimethyl-3'-(*m*-tolyl)hexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo [3,4-*c*]pyrrole]-2,4',6'(5'*H*)-trione (17ag). White solid (82.6 mg, 84 % yield, 90:10 *dr*); Precipitation CHCl$_3$/Et$_2$O; mp: 165 °C; $[\alpha]_D^{29.5}$ = -85.1 (*c* 0.52, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.53 (d, *J* = 6.1 Hz, 3H, CH$_3$), 2.13 (t, *J* = 11.5 Hz, 1H, CH$_2$), 2.30 (s, 3H, CCH$_3$) 2.73 (dd, *J* = 12.4, 3.9 Hz, 1H, CH$_2$), 2.88 (s, 3H, NCH$_3$), 3.46 (t, *J* = 7.5 Hz, 1H, CCH), 3.68 (t, *J* = 7.8 Hz, 1H, NCHC*H*), 4.73 (d, *J* = 8.0 Hz, 1H, NCH), 4.76-4.86 (m, 1H, C*H*CH$_3$), 7.14-7.16 (m, 3H, ArH), 7.24-7.28 (m, 1H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 20.3 (CH*C*H$_3$), 21.6 (CCH$_3$), 25.4 (NCH$_3$), 45.2 (CH$_2$), 50.5 (*C*HCO), 54.2 (*C*HCO), 64.7 (NCH), 69.8 (NC), 74.1 (*C*HCH$_3$), 124.2, 127.8, 128.5, 129.5, 134.6, 138.3 (ArC), 173.9 (CO), 174.3 (CO), 174.6 (CO) ppm; IR (ATR) υ_{max}: 1769, 1697, 1198 cm^{-1}; MS (EI): *m/z* 328 (13), 284 (24), 270 (19), 269 (100), 256 (10), 255 (13), 241 (14); HRMS calcd. for $C_{18}H_{20}N_2O_4$: 328.1423; found: 328.1425.

(3*S*,3'*R*,3a'*S*,5*R*,6a'*R*)-5,5'-Dimethyl-3'-(*o*-tolyl)hexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo [3,4-*c*]pyrrole]-2,4',6'(5'*H*)-trione (17ah). White solid (59 mg, 60% yield, 87:13 *dr*); Precipitation CHCl$_3$/Et$_2$O; mp: 165°C; $[\alpha]_D^{26.2}$ = -68.5 (*c* 0.71, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.55 (d, *J* = 6.1 Hz, 3H, CH$_3$), 1.97 (dd, *J* = 12.3, 11.0 Hz, 1H, CH$_2$), 2.44 (s, 3H, CCH$_3$) 2.74 (dd, *J* = 12.5, 4.6 Hz, 1H, CH$_2$), 2.85 (s, 3H, NCH$_3$), 3.39 (d, *J* = 7.7 Hz, 1H, CCH), 3.69 (t, *J* = 7.9 Hz, 1H, NCHC*H*), 4.7 (d, *J*

= 8.1 Hz, 1H, NCH), 4.77-4.87 (m, 1H, C*H*CH_3), 7.20-7.35 (m, 4H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 19.8 (CH_3), 20.5 (CH_3), 25.3 (NCH_3), 45.9 (CH_2), 48.5 (*C*HCO), 54.2 (*C*HCO), 61.1 (NCH), 69.2 (NC), 73.6 (*C*HCH_3), 124.8, 126.4, 128.2, 130.5, 134.2, 135.6 (ArC), 173.8 (CO), 174.6 (CO), 175.0 (CO) ppm; IR (ATR) υ_{max}: 3022, 2977, 2932, 1773, 1699, 1434, 1285, 1198, 1095 cm^{-1}; MS (EI): *m/z* 320 (16), 278 (43), 276 (22), 261 (100), 248 (18), 247 (22), 209 (11), 164 (10), 96 (12); HRMS calcd. for $C_{18}H_{20}N_2O_4$: 328.1423; found: 328.1430.

(3*S*,3'*R*,3a'*S*,5*R*,6a'*R*)-3'-(4-Methoxyphenyl)-5,5'-dimethylhexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(5'*H*)-trione (17ai). White solid (87.8 mg, 85% yield, 89:11 *dr*); Precipitation $CHCl_3$/*n*-Hexane; mp: 184 °C; $[\alpha]_D^{24.6}$ = -151.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.54 (d, *J* = 6.1 Hz, 3H, CH_3), 2.03 (t, *J* = 11.6 Hz, 1H, CH_2), 2.68 (dd, *J* = 12.5, 4.5 Hz, 1H, CH_2), 2.86 (s, 3H, NCH_3), 3.38 (t, *J* = 7.7 Hz, 1H, CCH), 3.60 (t, *J* = 7.8 Hz, 1H, NCHC*H*), 3.81 (s, 3H, OCH_3), 4.65 (d, *J* = 8.1 Hz, 1H, NCH), 4.73-4.83 (m, 1H, C*H*CH_3), 6.9 (d, *J* = 8.7 Hz, 1H, ArH), 7.26 (d, *J* = 8.7 Hz, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 20.4 (CH*C*H_3), 25.4 (NCH_3), 45.9 (CH_2), 50.7 (*C*HCO), 54.5 (*C*HCO), 55.4 (OCH_3), 64.5 (NCH), 69.7 (NC), 73.8 (*C*HCH_3), 114.0, 127.0, 128.3, 159.7 (ArC), 174.1 (CO), 174.4 (CO), 174.9 (CO) ppm; IR (ATR) υ_{max}: 2981, 2911, 1774, 1693, 1245 cm^{-1}; MS (EI): *m/z* 344 (M^+, 30%), 300 (26), 299 (13), 286 (20), 285 (100), 273 (16), 271 (10), 270 (22), 233 (43), 188 (17), 187 (13), 173 (13), 134 (10), 121 (12); HRMS calcd. for $C_{18}H_{20}N_2O_5$: 344.1372; found: 344.1375.

(3*S*,3'*R*,3a'*S*,5*R*,6a'*R*)-5,5'-Dimethyl-3'-(thiophen-2-yl)hexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(5'*H*)-trione (17aj). White solid (89.3 mg, 93% yield, 86:14 *dr*); Precipitation $CHCl_3$/*n*-Hexane; mp: 154 °C; $[\alpha]_D^{24.6}$ = -119.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.54 (d, *J* = 6.1 Hz, 3H, CH_3), 1.99 (dd, *J* = 12.1, 11.1 Hz, 1H, CH_2), 2.64 (dd, *J* = 12.4, 4.6 Hz, 1H, CH_2), 2.93 (s, 3H, NCH_3), 3.36 (d, *J* = 7.6 Hz, 1H, CCH), 3.61 (t, *J* = 7.8 Hz, 1H, NCHC*H*), 4.73-4.83 (m, 1H, C*H*CH_3), 4.91 (d, *J* = 8.0 Hz, 1H, NCH), 7.03 (dd, *J* = 5.0, 3.6 Hz, 1H, ArH), 7.12 (d, *J* = 3.6 Hz, 1H, ArH), 7.30 (dd, *J* = 5.1 Hz, 1.1 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 20.4 (CH*C*H_3), 25.5 (NCH_3), 46.0 (CH_2), 51.0 (*C*HCO), 54.4 (*C*HCO), 69.6 (NCH), 73.7 (NC), 125.4, 125.7, 127.2, 138.6 (ArC), 173.8 (CO), 174.3 (CO), 174.5(CO) ppm; IR (ATR) υ_{max}: 2981, 1770, 1693, 1203 cm^{-1}; MS (EI): *m/z* 320 (M^+, 16%), 278 (44), 276 (22), 275 (11), 262 (16), 261 (100), 247 (22), 209 (11), 164 (10), 96 (12); HRMS calcd. for $C_{15}H_{16}N_2O_4S$: 320.0831; found: 320.0829.

(2*S*,3*S*,4*S*,5*S*,8*R*)-8-Methyl-3-nitro-2,4-diphenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (17ak). White solid (82.4 mg, 92% yield, 90:10 *dr*); Precipitation $CHCl_3$/*n*-Hexane; mp: 177 °C; $[\alpha]_D^{28.6}$ = 65.4 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.22 (d, *J* = 6.2 Hz, 1H, CH_3), 1.97 (dd, *J* = 13.2, 9,3 Hz, 1H, CH_2), 2.59 (dd, *J* = 13.2, 6.2 Hz, 1H, CH_2), 3.17 (dp, *J* = 9.3, 6.2 Hz, 1H, C*H*CH_3), 4.57 (d, *J* = 8.8 Hz, 1H, CCH), 4.98 (d, *J* = 8.3 Hz, 1H, NCH), 5.84 (t, *J* = 8.5 Hz, 1H, $CHNO_2$), 7.32-7.48 (m, 10 H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 21.5 (CH_3), 40.2 (CH_2), 57.6 CCHPh), 65.5 (NCH), 70.6 (NC), 74.8 (*C*HCH_3), 93.0 ($CHNO_2$), 127.0, 127.8, 129.0, 129.1, 129.2, 129.6, 132.8, 134.8 (ArC), 177.3 (CO) ppm; IR (ATR) υ_{max}: 2979, 1769, 1551 cm^{-1}; MS (EI): *m/z* 306 (M^+ -NO_2, 23%), 263 (17), 262 (72), 261 (18), 260 (18), 246 (35), 233 (14), 232 (56), 220 (11), 219 (32), 203 (12), 202 (12), 194 (16), 193 (100), 178 (14), 156 (13), 117 (12), 116 (13), 115 (52), 91 (23), 77 (10); HRMS calcd. for $C_{20}H_{20}N_2O_4$: 352.1423; found: 352.1423.

(2*R*,3*S*,4*R*,5*S*,8*R*)-3-Benzoyl-8-methyl-2,4-diphenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (17al). White solid (93.8 mg, 76% yield, 92:8 *dr*); Precipitation $CHCl_3$/*n*-Hexane; mp: 194 °C; $[\alpha]_D^{27.7}$ = 64.6 (*c* 0.82, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.21 (d, *J* = 6.2 Hz, 3H, CH_3), 2.03 (dd, *J* = 13.0, 9.7 Hz, 1H, CH_2), 2.71 (dd, *J* = 13.0, 6.1 Hz, 1H, CH_2), 2.98-3.07 (m, 1H, $CHCH_3$), 4.56 (d, *J* = 11.8 Hz, 1H, CCH), 4.94 (dd, *J* = 11.7, 9.8 Hz, 1H, CHCO), 5.05 (d, *J* = 9.8 Hz, 1H, NCH), 7.10-7.12 (m, 3H, ArH), 7.24-7.36 (m, 9H, ArH), 7.47-7.51 (m, 1H, ArH), 7.69-7.71 (m, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 21.6 (CH_3), 41.7 (CH_2), 54.6 (*C*HCOPh), 55.0 (CCHPh), 64.6 (NCH), 70.9 (NC), 74.4 (*C*HCH_3), 127.8, 127.9, 128.2, 128.3, 128.7, 129.1, 133.3, 135.2, 137.4, 139.1 (ArC), 179.1 (*C*O), 196.2 (COPh) ppm; IR (ATR) υ_{max}: 3358, 3082, 3031, 2973, 2935, 1757, 1678, 1664 cm^{-1}; MS (EI): *m/z* 263 (21), 262 (100), 234 (19), 223 (14), 209 (13), 208 (14), 207 (12), 204 (11), 203 (81), 161 (12), 131 (11), 117 (16), 115 (11), 105 (32), 91 (10), 77 (25); HRMS calcd. for $C_{27}H_{25}NO_3$: 411.1834; found: 411.1812.

Dimethyl (2*R*,3*S*,4*S*,5*S*,8*R*)-8-methyl-6-oxo-2-phenyl-7-oxa-1-azaspiro[4.4]nonane-3,4-dicarboxylate (major diastereoisomer) (17am). White foam (43.7 mg, 42% yield, 69:31 *dr*); precipitation CH_2Cl_2/*n*-Hexane; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: major diastereoisomer: 1.47 (d, *J* = 6.2 Hz, 3H, CHC*H*$_3$, major diastereoisomer), 1.50 (d, *J* = 6.3Hz, 1.5H, CH_3, minor diastereoisomer), 1.95 (dd, *J* = 13.5, 8.9 Hz, 1H, CH_2, major diastereoisomer), 2.09 (dd, *J* = 13.0, 9.2 Hz, 0.4 H, CH_2, minor diastereoisomer), 2.67 (dd, *J* = 13.5, 6.7 Hz, 1H, CH_2, major diastereoisomer), 2.89 (dd, *J* = 13.0, 8.0 Hz, 0.4H, CH_2, minor diastereoisomer), 3.20 (s, 3H, CO_2CH_3, major diastereoisomer), 3.65 (s, 1.24, 3H, CO_2CH_3, minor diastereoisomer), 3.73 (s, 1.70H, CO_2CH_3, CCH, minor diastereoisomer), 3.75 (s, 3H, CO_2CH_3, major diastereoisomer), 3.79-3.94 (m, 2H, NCHC*H*, CCH, major diastereoisomer), 4.31-4.40 (m, 1.4 H, CH2 major diastereoisomer, CH_2 minor diastereoisomer), 4.69 m (1H, NCH, major diastereoisomer), 4.74-4.89 (m, 1H, NCH, minor diastereoisomer) 7.29-7.54 (m, 7.2 H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: major diastereoisomer: 22.0, 41.4, 51.8, 52.6, 52.8, 57.6, 63.6, 68.7, 74.7, 127.3, 127.4, 128.4, 128.6, 129.0, 138.9, 170.4, 170.8, 177.4; Minor diastereoisomer: 21.0, 45.4, 52.9, 54.2, 54.7, 67.4, 70.4, 74.4, 139.0, 170.7, 173.1, 176.4 ppm; IR (ATR) υ_{max}: 2950, 1761, 1729, 1201, 1163 cm^{-1}; MS (EI): *m/z* 316 (M^+ -CH_3O, 24%), 303 (26), 271 (14), 256 (22), 244 (48), 243 (15), 242 (14), 216 (24), 212 (40), 203 (20), 196 (15), 187 (57), 178 (12), 177 (100), 170 (14), 157 (16), 156 (41), 143 (21), 141 (97), 115 (26) ; HRMS calcd. for $C_{18}H_{21}NO_6$ –($C_2H_3O_2$): 288.1236; found: 288.1237.

(2*R*,3*S*,5*R*,8*R*)-8-Methyl-3-(2-oxopyrrolidine-1-carbonyl)-2-phenyl-7-oxa-1-azaspiro[4.4] nonan-6-one (17an). White solid (61.6 mg, 60% yield, 93:7 *dr*); Precipitation $CHCl_3$/*n*-Hexane; mp: °C; $[\alpha]_D^{30.4}$ = 45.34 (*c*, 0.6 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.48 (d, *J* = 6.1 Hz, 3H, CH_3), 1.69-1.84 (m, 1H), 1.93 (m, 1H), 2.09-2.26 (m, 2H), 2.35-2.44 (m, 1H), 2.49-2.56 (m, 1H), 2.65 (bs, 1H), 2.71-2.78 (m, 1H), 2.84-2.92 (m, 1H), 3.45-3.54 (m, 1H), 4.50-4.61 (m, 1H), 4.70-4.74 (m, 2H), 7.24-7.29 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 16.9 (CH_2), 20.8 (CH_3), 33.6 (CH_2), 37.5 (CH_2),

44.8 (CH_2), 45.6 (CH_2), 50.7 (*C*HCON), 64.7 (NCH), 67.1 (NC), 74.2 ($CHCH_3$), 127.4, 128.0, 128.2, 139.3 (ArC), 171.8 (CO), 175.1 (CO), 178.5 (CO) ppm; IR (ATR) υ_{max}: 1770, 1730, 1680, 1373, 1212 cm^{-1}; MS (EI): *m/z* 299 (27), 298 (M^+ -CO_2, 95%), 284 (19), 283 (100), 230 (58), 213 (15), 203 (29), 198 (21), 186 (29), 185 (18), 184 (12), 170 (28), 161 (10), 158 (30), 157 (22), 156 (32), 143 (19), 131 (10), 118 (14), 116 (14), 91 (11); HRMS calcd. for $C_{19}H_{22}N_2O_4$: 342.1580; found: 342.1569.

(3*S*,3'*R*,3a'*S*,5*S*,6a'*R*)-5-(3-Bromophenyl)-5'-methyl-3'-phenylhexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(5'*H*)-trione (17ba). White solid (110.6 mg, 81% yield, 86:14 *dr*); washed with chloroform:Et_2O; mp: 210 °C; $[\alpha]_D^{25.2}$ = -53.4 (*c* 0.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.24 (t, *J* = 11.8 Hz, 1H, CH_2), 2.90 (s, 3H, NCH_3), 2.98 (m, 1H, CH_2), 3.52 (d, *J* = 7.4Hz, 1H, CCH), 3.66 (t, *J* = 7.6 Hz, 1H, NCHC*H*), 4.65 (d, *J* = 7.6 Hz, 1H, NCH), 5.61 (dd, *J* = 11.0, 4.6 Hz, CH_2C*H*), 7.30-7.56 (m, 9H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 25.4 (CH_3), 46.8 (CH_2), 50.8 (*C*HCO), 54.4 (*C*HCO), 64.7 (NCH), 69.5 (NC), 76.9 (OCHAr), 123.1, 124.6, 127.0, 128.6, 129.1, 130.7, 132.3, 135.6, 139.6 (ArC), 174.1 (CO), 174.6 (CO), 174.6 (CO) ppm; IR (ATR) υ_{max}: 1785, 1698, 1183 cm^{-1}; MS (EI): *m/z* 412 (M^+ -CO_2, 95%), 410 (100), 409 (29), 331 (17), 299 (11), 272 (48), 255 (26), 254 (19), 242 (26), 241 (66), 156 (18), 143 (15), 130 (12), 116 (10), 115 (26), 103 (16), 78 (12); HRMS calcd. for $C_{22}H_{19}BrN_2O_4$: 454.0528; found: 454.0490.

(3*S*,3'*R*,3a'*S*,5*S*,6a'*R*)-5-(3-Bromophenyl)-3',5'-diphenylhexahydro-2*H*,4'*H*-spiro[furan-3,1'-pyrrolo[3,4-*c*]pyrrole]-2,4',6'(5'*H*)-trione (17bb). White solid (99.8 mg, 64% yield, 92:8 *dr*); washed with chloroform:Et_2O; mp: 195 °C; $[\alpha]_D^{26.4}$ = -56.9 (*c* 0.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.28 (t, *J* = 11.7 Hz, 1H, CH_2), 2.98 (dd, *J* = 12.9, 4.4 Hz, 1H, CH_2), 3.65 (m, 1H, CCH), 3.76 (m, 1H, NCHC*H*), 4.74 (d, *J* = 7.4 Hz, 1H, NCH), 5.58 (m, 1H, CH_2C*H*) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 46.5 (CH_2), 50.7 (*C*HCO), 54.2 (*C*HCO), 65.0 (NCH), 70.1 (NC), 123.0, 124.8, 126.4, 127.1, 128.6, 128.9, 129.2, 129.2, 130.4, 131.4, 132.3, 135.3, 139.5 (ArC), 173.0 (CO), 174.0 (CO), 174.7 (CO) ppm; IR (ATR) υ_{max}: 1780, 1705, 1205, 1182 cm^{-1}; MS (EI): *m/z* 475 (27), 474 (98), 473 (44), 472 (100), 471 (19), 393 (13), 335 (12), 334 (57), 326 (11), 317 (21), 316 (21), 304 (19), 303 (31), 299 (13), 252 (11), 156 (32), 143 (26), 117 (17), 115 (30), 103 (19), 91 (12); HRMS calcd. for $C_{27}H_{21}BrN_2O_4$ – CO_2: 472.0786 ; found: 472.0690.

(2*S*,3*S*,4*S*,5*S*,8*S*)-8-(3-Bromophenyl)-3-nitro-2,4-diphenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (17bc). White solid (116 mg, 80% yield, 92:8 *dr*); Crystallization EtOAc; mp: 168 °C; $[\alpha]_D^{28.7}$ = 98.0 (*c* 0.57, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.30 (dd, *J* = 13.4, 9.9 Hz, 1H, CH_2), 2.88 (d, 13.4, 6.5 Hz, 1H, CH_2), 3.83 (dd, *J* = 9.8, 6.5 Hz, 1H, CHO), 4.66 (d, *J* = 8.9 Hz, 1H, CCH), 4.99 (d, *J* = 8.3 Hz, 1H, NCH), 5.87 (t, *J* = 8.6 Hz, 1H, $CHNO_2$), 7.00 (m, 1H, ArH), 7.13-7.22 (m, 2H, ArH), 7.41-7.49 (m, 12H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 41.4 (CH_2), 57.4 (C*C*HPh), 65.5 (NCH), 70.2 (NC), 77.8 (OCHAr), 92.7 ($CHNO_2$), 122.9, 124.2, 127.1, 127.9, 128.8, 129.0, 129.3, 129.5, 129.8, 130.5, 132.0, 132.7, 134.8, 140.4 (ArC), 176.9 (CO) ppm; IR (ATR) υ_{max}: 1773, 1551, 1180 cm^{-1}; MS (EI): *m/z* 450 (20), 448 (21), 232 (33), 220 (20), 219 (100), 193 (64), 115 (30), 91 (10); HRMS calcd. for $C_{25}H_{21}BrN_2O_4$ –(NO_2) : 446.0756; found: 446.0776.

(2*R*,3*S*,4*R*,5*S*,8*S*)-3-Benzoyl-8-(3-bromophenyl)-2,4-diphenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (17bd). White solid (130.0 mg, 71% yield, 95:5 *dr*); Precipitation DCM:Et_2O; mp: 147 °C; $[\alpha]_D^{28.7}$ = 98.0 (*c* 0.64, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.38 (dd, *J* = 13.3, 10.2 Hz, 1H, CH_2), 3.00 (dd, *J* = 13.3, 6.4 Hz, 1H, CHCO), 4.66 (d, *J* = 11.6 Hz, 1H, CCH), 4.98-5.12 (m, 2H, NCH, $CHNO_2$), 7.00-7.03 (m, 1H, ArH), 7.47-7.52 (m, 16 H, ArH), 7.71-7.74 (m, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 42.5 (CH_2), 54.5 (C*C*HPh), 54.8 (*C*HCOPh), 64.5 (NCH), 70.6 (NC), 77.2 (OCHAr), 122.7, 124.3, 127.8, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 129.3, 130.4, 131.7, 133.4, 134.9, 137.3, 138.8, 140.9 (ArC), 178.6 (CO), 196.0 (COPh) ppm; IR (ATR) υ_{max}: 1759, 1677, 1217, 1184 cm^{-1}; MS (EI): *m/z* 510 (10), 509 (19), 508 (10), 507 (29), 404 (50), 402 (50), 345 (48), 343 (48), 301 (17), 299 (27), 242 (18), 240 (18), 235 (38), 233 (38), 223 (48), 222 (36), 220 (19), 219 (20), 218 (28), 217 (11), 209 (43), 208 (57), 207 (74), 193 (20), 191 (19), 105 (100), 91 (21), 89 (21); HRMS calcd. for $C_{32}H_{26}BrNO_3$ –($C_8H_5O_3$): 402.0857; found: 402.0835.

(2*R*,3*S*,5*R*,8*S*)-8-(3-Bromophenyl)-3-(2-oxopyrrolidine-1-carbonyl)-2-phenyl-7-oxa-1-azaspiro[4.4]nonan-6-one (17be). White solid (87.1 mg, 65% yield, 82:18 *dr*); washed with Et_2O; mp: 112°C; $[\alpha]_D^{28.7}$ = 26.1 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.37-1.42 (m, 1H), 1.51-1.54 (m, 1H), 1.71-1.85 (m, 4H), 2.80-2.96 (m, 3H), 3.48-3.57 (m, 1H), 4.75-4.87 (m, 2H), 5.37 (dd, *J* = 7.8 Hz, 1H, CH_2C*H*) 7.25-7.47 (m, 9H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 17.1 (CH_2), 33.8 (CH_2), 37.5 (CH_2), 45.2 (CH_2), 45.8 (CH_2), 50.6 (*C*HCON), 64.8 (NCH), 67.1 (NC), 77.8 (OCHAr), 123.0, 124.5, 127.6, 128.5, 129.1, 130.6, 132.1, 138.6, 140.4 (ArC), 171.5 (CO), 175.4 (CO), 177.5 (CO) ppm; IR (ATR) υ_{max}: 1771, 1729, 1685, 1363, 1212 cm^{-1}; MS (EI): *m/z* 441 (M^+ -CO_2, 25%), 440 (100), 439 (28), 438 (100), 355 (12), 353 (14), 345 (12), 343 (12), 327 (20), 325 (25), 230 (41), 225 (77), 224 (22), 223 (80), 222 (14), 185 (20), 184 (43), 170 (16), 156 (62), 142 (47), 91 (14), 89 (10); HRMS calcd. for $C_{24}H_{23}BrN_2O_4$ –(CO_2): 438.0943; found: 438.0938.

Associated content

The Supporting Information is available free of charge on the ACS Publications website at DOI: Computational details including energies, and cartesian coordinates, together with experimental details, characterization data, and NMR spectra for new compounds and X-RD analysis is supplied.

Acknowledgements

We gratefully acknowledge financial support from the Spanish Ministerio de Economía y Competitividad (MINECO) Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (pro-jects CTQ2013-43446-P, CTQ2014-51912-REDC, CTQ2016-76782-P, CTQ2016-81797-REDC and CTQ2016-76155-R), the Generalitat Valenciana (PROMETEOII/2014/017), the University of Alicante. This research was also supported by the Slovak Research and Development Agency under contract VEGA 1/0489/19. We also thank Dr. T. Soler her

help in the X-ray diffraction analysis (SSTTI, University of Alicante).

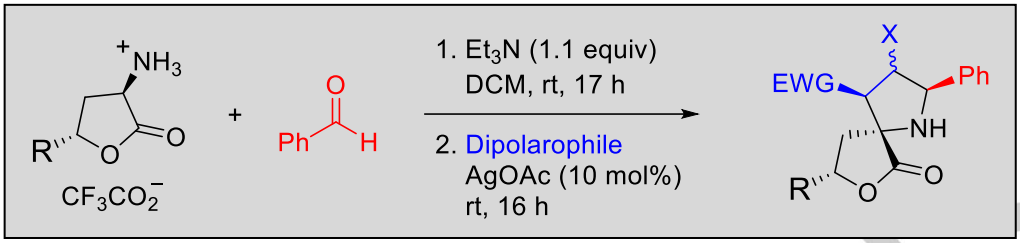
Keywords: Dipolar cycloaddition • diastereoselective • silver • spirolactones • spiropyrrolidines

WILEY-VCH

FULL PAPER

Entry for the Table of Contents

Enantiomerically pure spirocyclic pyrrolidines are prepared through highly diastereoselective dipolar cycloaddition using chiral aminolactones. Silver acetate has a crucial role as catalyst in these dipolar cycloadditions involving fleeting azomethine ylides. Silver shows dual catalysis activating the dipole and the dipolarophile simultaneously. Silver cation controls the geometry of the dipole and the *endo*-approach *via* a concerted but asynchronous process. Final products incorporated a high functional group density, a new quaternary sterogenic centre and a spiranic unit connecting a pyrrolidine and a lactone. This two units have, separately, biologically interesting applications, so the study of some antiviral properties are in progress.



[1] a) K. P. Melnykov, A. N. Artemenko, B. O. Ivanenko, Y. M. Sokolenko, P. S. Nosik, E. N. Ostapchuk, O. O. Grygorenko, D. M. Volochnyuk, S. V. Ryabukhin, *ACS Omega* **2019**, *4*, 7498-7515; b) B. A. Chalyk, M. V. Butko, O O. Yanshyna, K. S. Gavrilenko, T. V. Druzhenko, P. K. Mykhailiuk, *Chem. Eur. J.* **2017**, *23*, 16782-16786.
[2] a) E. Chupakhin, O. Babich, A. Prosekov, L. Asyakina, M. Krasavin, *Molecules* **2019**, *24*, 4165-4202;
[3] a) L. Maiuolo, V. Algieri, F. Olivito, A. De Nino, *Catalysts* **2020**, *10*, 1-27, doi:10.3390/catal10010065; b) C. Nájera, J. M. Sansano, *Pure Appl. Chem*. **2019**, *91*, 575-596; c) A. V. Gulevskaya, J. I. Nelina-Nemtseva, *Chem. Heterocycl. Comp*. **2018**, *54*, 1084-1107; d) I. Arrastia, A. Arrieta, F. P. Cossío, Eur. J. Org. Chem. **2018**, 5889-5904; e) X. Fang, C.-J. Wang, *Org. Biomol. Chem.* **2018**, *16*, 2591-2601; f) H. A. Dondas, M. G. Retamosa, J. M. Sansano, *Synthesis* **2017**, *49*, 2819-2851.
[4] a) S. M. Gueret, S. Thavam, R. J. Carbajo, M. Potowski, N. Larsson, G. Dahl, A. Dellsen, T. N. Grossmann, A. T. Plowright, E. Valeur, M. Lemurell, H. Waldmann, *J. Am. Chem. Soc.* **2020**, *142*, 4904-4915. b) M. Baunach, C. Hertweck, *Angew. Chem. Int. Ed*. **2015**, *54*, 12550-12552.
[5] a) A. Padwa, *Arkivoc* **2018**, *part iv*, 23-49; b) G. Pandey, D. Dey, S. K. Tiwari, *Tetrahedron Lett*. **2017**, *58*, 699-705.
[6] a) J. Adrio, J. C. Carretero, *Chem. Commun*. **2019**, *55*, 11979-11991; b) B. Bdiri, B.-J. Zhao, Z.-M. Zhou, *Tetrahedron: Asymmetry* **2017**, *28*, 876-899; c) A. Padwa, S. Bur, *Chem. Heterocycl. Comp*. **2016**, *52*, 616-626; d) T. Hashimoto, K. Maruoka, *Chem. Rev*. **2015**, *115*, 5366-5412.
[7] a) Y. Yi, Y.-Z. Hua, H.-J. Lu, L.-T. Liu, M.-C. Wang, *Org. Lett*. **2020**, *22*, 2527-2531; b) J. H. Siitonen, S. Lira, M. Yousufuddin, L. Kurti, *Org. Biomol. Chem*. **2020**, *18*, 2051-2053, and references cited therein.
[8] T. Liu, Q. Li, Z. He, J. Zhang, C Wang, *Chin. J. Catal*. **2015**, *36*, 68–77.
[9] Q.-H. Li, T.-L. Liu, L. Wei, X. Zhou, H.-Y. Tao, C.-J. Wang, *Chem. Commun*. **2013**, *49*, 9642-9644.
[10] R. Grigg, T. Mongkolaussavaratana, C. A. Pounds, S. Sivagnanam, *Tetrahedron Lett*. **1990**, *31*, 7215-7218.
[11] a) R. Grigg, J. F. Malone, T. Mongkolaussavaratana, S. Thianpatanagul, *Tetrahedron* **1989**, *45*, 3849-3862; b) R. Grigg, J. F. Malone, T. Mongkolaussavaratana, S. Thianpatanagul, *J. Chem. Soc., Chem. Commun*. **1986**, 421-422.
[12] a) R. Grigg, C. Kilner, M. A. B. Sarker, C. Orgaz de la Cierva, H. A. Dondas, *Tetrahedron* **2008**, *64*, 8974–8991; b) R. Grigg, M. A. B. Sarker, *Tetrahedron* **2006**, *62*, 10332–10343.
[13] L. Wang, X.-M. Shi, W.-P. Dong, L.-P. Zhua, R. Wang, *Chem. Commun*. **2013**, *49*, 3458-3460.
[14] L.-W. Tang, C. Li, B.-J. Zhao, L. Lan, M. Zhang, Z.-M. Zhou, *Tetrahedron* **2017**, *73*, 923-930.
[15] T.-L. Liu, Z.-L. He, H.-Y. Tao, C.-J. Wang, *Chem. Eur. J*. **2012**, *18*, 8042-8046.
[16] H.-C. Liu, H.-Y. Tao, H. Cong, C.-J. Wang, *J. Org. Chem*. **2016**, *81*, 3752−3760.
[17] K. Liu, Y. Xiong, Z.-F. Wang, H.-Y. Tao, C.-J. Wang, *Chem. Commun*. **2016**, *52*, 9458-9461.
[18] A. Cayuelas, R. Ortiz, C. Nájera, J. M. Sansano, O. Larrañaga, A. de Cózar, F. P. Cossío, *Org. Lett*. **2016**, *18*, 2926-2929.
[19] D. Kowalczyk-Dworak, Ł. Albrecht, *Org. Biomol. Chem*. **2019**, *17*, 2624-2629.
[20] N. Chen, L. Zhu, L. Gan, Z. Liu, R. Wang, X. Cai, X. Jiang, *Eur. J. Org. Chem*. **2018**, 2939–2943.
[21] X. Fang, X.-Q. Dong, C.-J. Wang, *Tetrahedron Lett*. **2014**, *55*, 5660–5662.
[22] D Valachová, B. Ferko, E. Puchľová, O. Caletková, D. Berkeš, A. Kolarovič, P. Jakubec, *Synthesis* **2019**, *51*, 4568-4575.
[23] D. Berkeš, A. Kolarovič, R. Manduch, P. Baran, F. Považanec, *Tetrahedron-Asymmetry* **2005**, *16*, 1927-1934.
[24] The structural data submitted to the CCDC corresponds to the following assigned deposition number: 2000052.
[25] A similar result was observed in the case of small chiral auxiliaries bonded in the dipolarophile. C. Nájera, M. G. Retamosa, J. M. Sansano, *Tetrahedron: Asymmetry* **2006**, *17*, 1985-1989.