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Advanced Synthesis & Catalysis

Isothiocyanate Strategy for the Synthesis of Quaternary α-Amino Acids Bearing a Spirocyclic Ring System

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Dedicated to the memory of Professor Henryk Krawczyk, our friend and mentor, who passed away too soon

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Abstract: This study demonstrates that isothiocyanates derived from α-substituted α-amino acids are useful building blocks in the heteroannulation reactions with electron-deficient olefins. The developed strategy proceeds in a cascade manner and involves Michael addition followed by a cyclization via nucleophilic addition. Target, spirocyclic heterocycles bearing either a quaternary α-amino acid moiety or α-amino-phosphonate group have been efficiently synthesized in very high yield (up to 99%) and with excellent stereocontrol. The usefulness of heterocycles obtained has been demonstrated in selected transformations.

Keywords: Asymmetric synthesis; Bifunctional catalysis; Isothiocyanates; Quaternary α-amino acids; Pyrrolidine

1 Introduction

Quaternary α-amino acids are an important group of biologically relevant molecules.[1] Such a structural motif is present in various natural products and compounds relevant for the life-science industry (with representative examples **I–III** shown in the Figure 1).[2] Furthermore, the incorporation of quaternary α-amino acid motif into a target molecule results in increased resistance to enzymatic and chemical degradation and, in many cases, enhanced biological properties. Notably, the biological activity of such systems is directly correlated with the absolute stereochemistry of the quaternary stereogenic center. For this reason, the development of methods for their preparation in an enantioselective fashion is of particular importance. Barbituric acid constitutes another structural motif widely distributed in nature that is highly relevant in the contemporary medicinal and organic chemistry. Compounds containing that scaffold possess strong and diverse biological activity (Figure 1, compounds **IV**,**V**).[3] In this context, the spirocyclic architecture present in the biologically relevant barbituric acid derivatives is worth noticing. Surprisingly, the enantioselective methods for their preparation remain limited.[4]

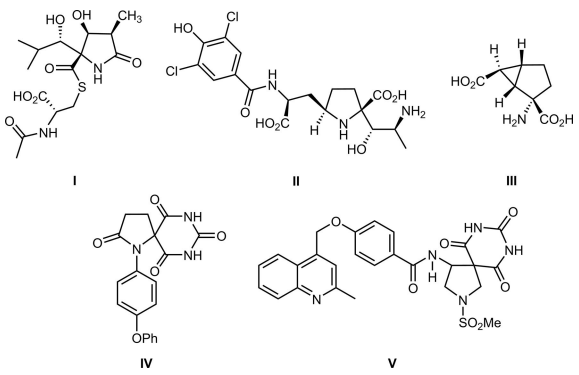
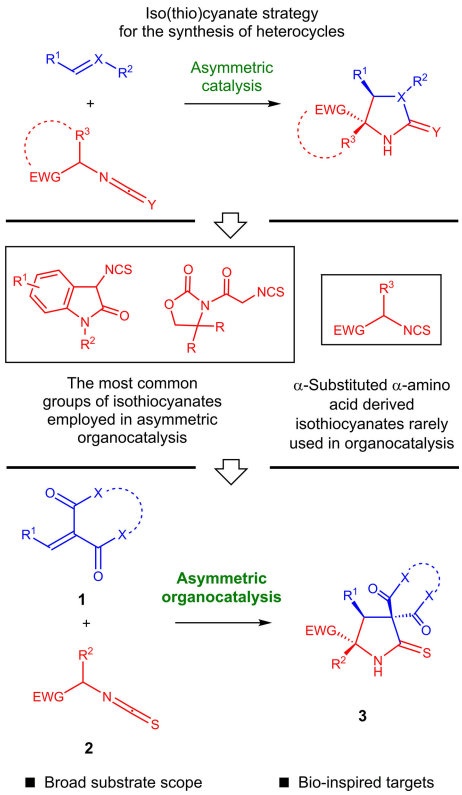


Figure 1. Examples of biologically relevant quaternary α-amino acid and barbituric acid derivatives.

Target-oriented-synthesis of privileged structural motifs is the ultimate goal of the contemporary organic chemistry.[5] This field of research has been recently dominated by the enantioselective approaches with the chiral catalysts used to achieve chiral discrimination.[6] In particular, biomimetic cascade reactivities have recently emerged as a conven-

ient tool to build chemical and stereochemical diversity from simple and readily available starting materials.[7,8] Within this field of research asymmetric organocatalysis has revealed its great potential for the construction of biologically relevant molecules in a single chemical transformation proceeding in a cascade manner.[8] In this context, the immense progress in the development of biomimetic asymmetric strategies leading to α-amino acids and their derivatives is worth noticing.[1,9] Over the years various organocatalytic, stereocontrolled approaches for the preparation of quaternary α-amino acids have been introduced.[9] Among them one particularly visible trend involves the usage of alkyl isothiocyanates bearing an electron-withdrawing moiety in the α-position (Scheme 1, top).[9b,10–13] They readily participate in cascade reactions with various electron-poor C=X and C=C double bonds resulting in the annulation of various heterocyclic systems. Isothiocyanates based on the oxindole scaffold[10] or derived from glycine[11] are commonly employed in such strategies (Scheme 1, middle). Surprisingly, the application of simple isothiocyanates derived from α-substituted α-amino acids in organocatalytic heteroannulations is limited and focuses mainly on their reactions with aldehydes or imines.[12,13]



Scheme 1. Iso(thio)cyanate strategy in the synthesis of heterocycles and the synthetic objectives of our study.

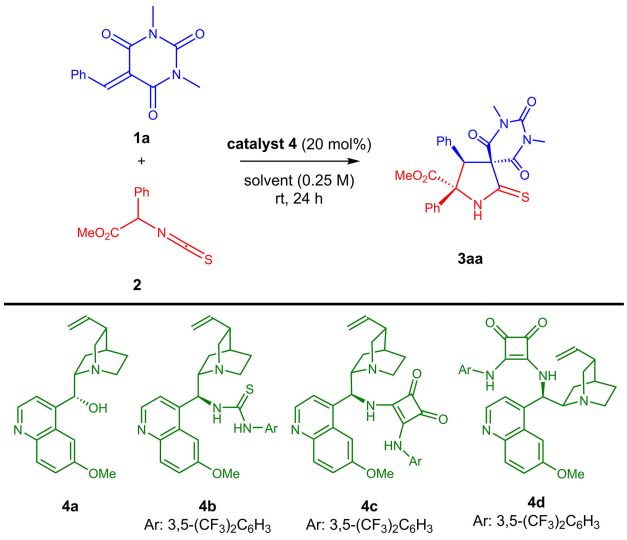
Given the biological and chemical importance of quaternary α-amino acids and their analogues, the task of development of a new approach to this class of compounds was undertaken. We became particularly interested in 2-pyrrolidinethione derivatives containing additional barbiturate or Meldrum's acid moiety in a spirocyclic alignment. In this context it is worth to note that the introduction of two bio-relevant core structures (such as barbituric acid and quaternary amino acid moieties) into one molecule should lead to hybrid molecules with intriguing biological properties. Herein, we present our studies on the application of isothiocyanates derived either from α-substituted α-amino acids or α-aminophosphonates for the synthesis of 2-pyrrolidinethione derivatives bearing spirocyclic ring system (Scheme 1, bottom).

2 Results and Discussion

Optimization studies were performed using dimethyl 5-(benzylidene)barbiturate **1a** and phenylglycine-derived isothiocyanate **2a** as model starting materials (Table 1). Initial experiment was performed in dichloromethane in the presence of quinine **4a** as the catalyst (Table 1, entry 1). We were pleased to observe that under these conditions the annulation of five-membered heterocycle occurred. Disappointingly, the reaction was not stereoselective as **3aa** was formed as almost a racemic mixture of two diastereomers in a close to 1:1 ratio. Therefore, the catalyst screening was initiated (Table 1, entries 1–3). We anticipated that the use of catalysts bearing stronger H-bonding donors such as thiourea or squaramide moieties should be beneficial for the stereochemical reaction outcome. Surprisingly, while the use of thiourea catalyst **4b** (Table 1, entry 2) resulted in similar result when compared to quinine **4a**, the application of squaramide catalyst **4c** (Table 1, entry 3) led to significant improvement in terms of both enantio- and diastereoselectivity. Subsequent solvent screening (Table 1, entries 3–9) indicated that the diastereoselectivity of the elaborated cascade was increased by a simple change of solvent with the reaction performed in toluene providing the best results (Table 1, entry 9). However, longer reaction time was required to achieve full conversion in this case. Notably, the reaction proceeded efficiently with pseudoenantiomeric catalyst **4d** providing access to opposite enantiomer of the product *ent*-**3aa** with comparable results (Table 1, entry 10).

With the optimized reaction conditions in hand, studies on the scope and limitations of the developed heteroannulation reaction were undertaken. Initially, various dimethyl 5-(alkylidene)barbiturates **1** were employed in the developed reaction using **2a** as a model isothiocyanate component (Table 2). To our delight, the reaction proved unbiased towards both

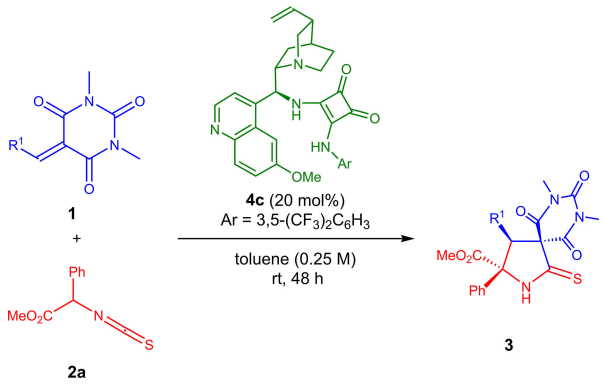
Table 1. Isothiocyanate strategy in the enantioselective synthesis of quaternary α-amino acids **3** – optimization studies.[a]



	solvent	cat.	conv. (yield)[b]	dr[c]	er[d]
1	CH_2Cl_2	**4a**	96	1:1.2	60:40
2	CH_2Cl_2	**4b**	97	1.3:1	51:49
3	CH_2Cl_2	**4c**	57	5.6:1	94:6
4	$CHCl_3$	**4c**	81	6.7:1	95:5
5	AcOEt	**4c**	97	5.3:1	94:6
6	THF	**4c**	93	5.0:1	92.5:7.5
7	MeCN	**4c**	96	1.2:1	73:27
8	Et_2O	**4c**	82	9.7:1	96:4
9[e]	toluene	**4c**	>95(90)	20:1	97:3
10[e]	toluene	**4d**	>95(80)	20:1	6:94

[a] Reactions performed on 0.05 mmol scale using **1a** (1 equiv.) and **2a** (1 equiv.) in 0.2 mL of the CH_2Cl_2.
[b] As determined by ^{1}H NMR of a crude reaction mixture after 24 h (in parenthesis isolated yield is given).
[c] As determined by ^{1}H NMR of a crude reaction mixture after 24 h.
[d] Determined by a chiral stationary phase HPLC.
[e] Reaction carried out for 48 h.

Table 2. Isothiocyanate strategy in the enantioselective synthesis of quaternary α-amino acids **3** – dimethyl 5-(alkylidene)barbiturate **1** scope.[a]



	R^1	yield [%][b]	dr[c]	er[d]
1	Ph (**3aa**)	90	20:1	97:3
2	4-ClC_6H_4 (**3ba**)	77	20:1	97:3
3	3-ClC_6H_4 (**3ca**)	79	>20:1	95:5
4	2-ClC_6H_4 (**3da**)	62	>20:1	98.5:1.5
5	4-$NO_2C_6H_4$ (**3ea**)	52	20:1	82.5:17.5
6	4-$MeOC_6H_4$ (**3fa**)	98	20:1	97.5:2.5
7	2,4-$Cl_2C_6H_3$ (**3ga**)	93	>20:1	99:1
8	1-naphthyl (**3ha**)	56	10:1	98:2
9	2-furyl (**3ia**)	88	>20:1	99:1
10	*i*-Pr (**3ja**)	40	>20:1	96:4
11	(*E*)-β-styryl (**3ka**)	79	6:1	94:6
12[e]	Ph (**3aa**)	86	15:1	99:1

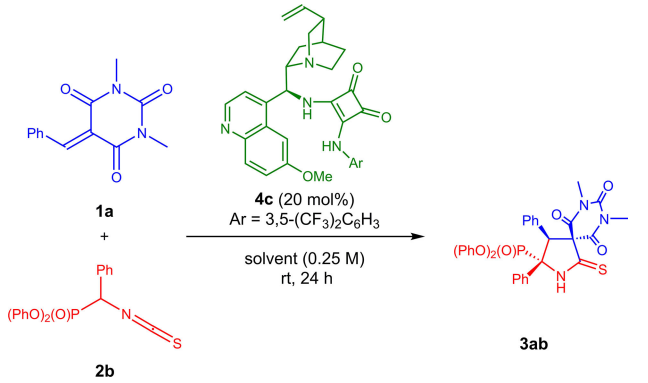
[a] Reactions performed on 0.05 mmol scale using **1** (1 equiv.) and **2a** (1 equiv.) in 0.2 mL of the toluene.
[b] Isolated yields are given.
[c] As determined by ^{1}H NMR of a crude reaction mixture.
[d] Determined by a chiral stationary phase HPLC.
[e] Reaction performed on 3 mmol scale for 72 h. Isolated yield of a single diastereomer is given.

the position (Table 2, entries 2–4) and electronic properties (Table 2, entries 2, 5 vs. 6) of substituents present on the aromatic ring in **1**. Target products **3** were obtained in high yields and in a highly stereoselective fashion in all of the cases. Furthermore, disubstituted aromatic rings and heteroaromatic moieties were also well-tolerated as demonstrated in the synthesis of **3ga**, **3ha** and **3ia** (Table 2, entries 7–9). Interestingly, the reaction proceeded for barbiturates **1j** and **1k** substituted with alkyl and alkenyl groups (Table 2, entries 10, 11). However, in the case of **3ja** (R = *i*-Pr) synthesis, lower yield was observed. Notably, the developed cascade was also efficiently realized on a 60-fold larger scale further increasing the usability of the elaborated protocol (Table 2, entry 12).

Further scope studies were devoted towards the application of isothiocyanates **2** in which the ester moiety was replaced with diphenylphosphonate group. Such a strategy was highly appealing as it provided a facile entry to biologically relevant α-aminophosphonates. However, initial experiment showed that re-optimization of reaction conditions was necessary (Table 3). The application of the aforementioned conditions gave unsatisfactory results (Table 3, entry 1). Therefore, the solvent screening was performed (Table 3, entries 1–4) indicating THF as the best suited solvent for the cascade in terms of diastereoselectivity. To our delight, a substantial increase of the chemical efficiency of the studied reaction was observed when the reaction concentration was increased (Table 3, entry 5). Notably, under these conditions the reaction proceeded with excellent stereocontrol. Unfortunately, alkyl-substituted isothiocyanates **3** were not

reactive enough under the optimized reaction conditions.

Table 3. Isothiocyanate strategy in the enantioselective synthesis of quaternary α-aminophosphonates **3** – optimization studies.[a]



	R	conv. (yield)[b]	dr[c]	er[d]
1	toluene	20	10:1	n.d.
2	MeCN	72	4:1	n.d.
3	1,4-dioxane	17	10:1	n.d.
4	THF	40	>20:1	n.d.
5[e]	THF	100 (99)	>20:1	99:1

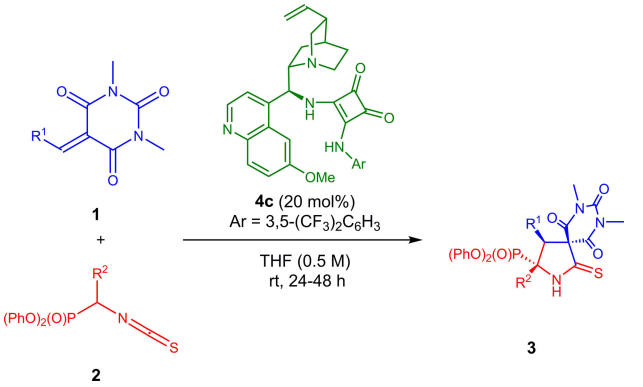
[a] Reactions performed on 0.05 mmol scale using **1a** (1 equiv.) and **2b** (1 equiv.) in 0.2 mL of the toluene.
[b] As determined by ^{1}H NMR of a crude reaction mixture (in parenthesis isolated yield is given).
[c] As determined by ^{1}H NMR of a crude reaction mixture.
[d] Determined by a chiral stationary phase HPLC.
[e] Reaction performed in 0.1 mL of the solvent.

To our delight, the reaction of **2b** with selected barbiturates **1a,b–d,f** proceeded efficiently (Table 4). Both the position (Table 4, entries 2–4) and the electronic properties of substituents on the aromatic ring in **1** (Table 4, entry 2 vs. 5) had no pronounced effect on the reaction outcome. Furthermore, it was found that the nature of R^2 substituent in **2** can be modified as demonstrated in the synthesis of **3ac** and **3ad** (Table 4, entries 6, 7).

In the final part of scope studies the possibility to introduce a different electron-withdrawing group at the double bond in **1** was evaluated (Scheme 2). The reaction with Meldrum's-acid-derived olefin **1l**, performed under un-optimized conditions, proceeded efficiently providing **3la** with high diastereoselectivity, albeit with lower enantioselectivity compared to barbiturate counterpart **1f**.

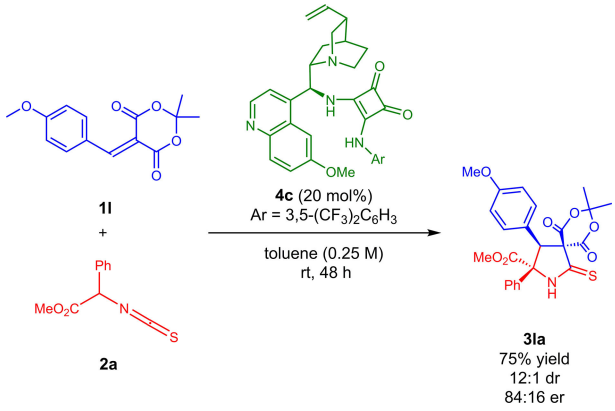
With the scope study accomplished the usefulness of the compounds obtained for the synthesis of various pyrrolidine derivatives was demonstrated (Scheme 3). Oxidative desulfuration of **3aa** realized under standard conditions proceeded efficiently affording

Table 4. Isothiocyanate strategy in the enantioselective synthesis of quaternary α-aminophosphonates **3** – scope studies.[a]



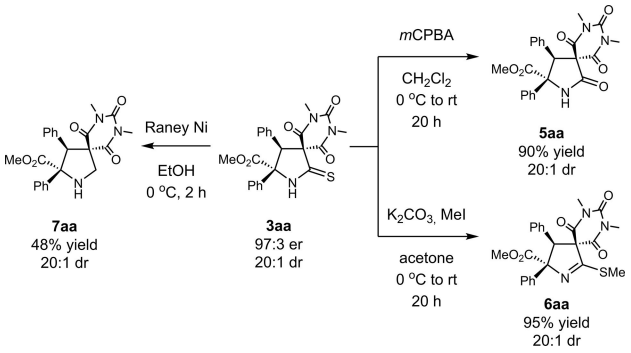
	R^1	R^2	yield [%][b]	dr[c]	er[d]
1	Ph	Ph	**3ab**: 99	>20:1	99:1
2	4-ClC$_6$H$_4$	Ph	**3bb**: 79	10:1	97:3
3	3-ClC$_6$H$_4$	Ph	**3cb**: 84	15:1	96:4
4	2-ClC$_6$H$_4$	Ph	**3db**: 60	20:1	98:2
5	4-MeOC$_6$H$_4$	Ph	**3fb**: 85	>20:1	99:1
6	Ph	4-ClC$_6$H$_4$	**3ac**: 97	>20:1	98:2
7	Ph	4-MeOC$_6$H$_4$	**3ad**: 73	7:1	97:3

[a] Reactions performed on 0.1 mmol scale using **1** (1 equiv.) and **2** (1 equiv.) in 0.2 mL of THF.
[b] Isolated yields are given.
[c] As determined by ^{1}H NMR of a crude reaction mixture.
[d] Determined by a chiral stationary phase HPLC.



Scheme 2. Isothiocyanate strategy in the enantioselective synthesis of quaternary α-amino acids **3** – Meldrum's acid derivative case.

pyrrolidinone **5aa** in high 90% yield. Furthermore, *S*-methylation of **3aa** was readily performed under basic conditions yielding **6aa** in almost quantitative yield. Finally, reductive desulfuration of **3aa** was accomplished using Nickel Raney to give **7aa** in 48% yield. In all cases, stereochemical composition of the starting material **3aa** was fully preserved as **5aa**, **6aa** and **7aa** were obtained as single diastereomers.



Scheme 3. Chemoselective transformations of **3aa**.

The absolute configuration of the products **3** was unequivocally determined by the single crystal X-ray analysis of the products **3aa** and **3ab** (Figure 2).[14]

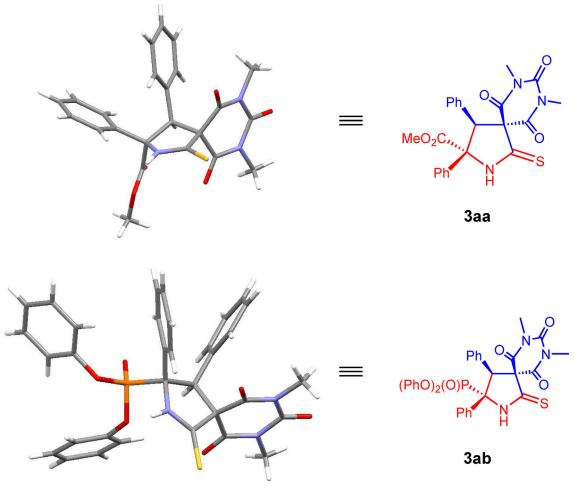
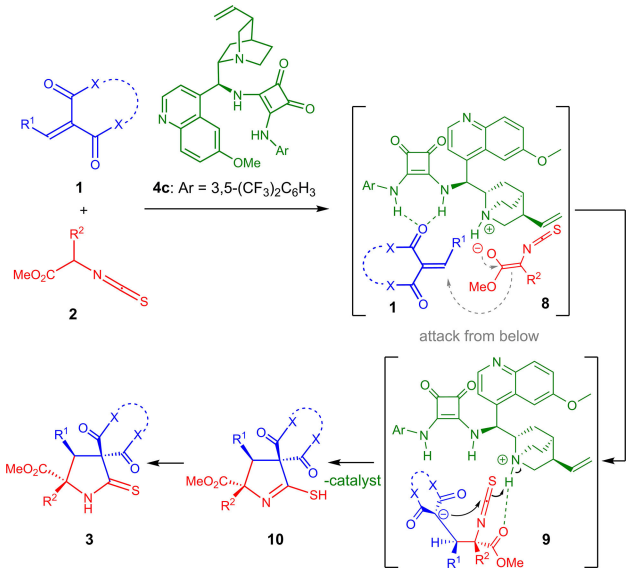


Figure 2. Determination of absolute configuration.

Based on these assignments, a plausible reaction mechanism was proposed (Scheme 4). The elaborated cascade reaction was initiated by two independent processes. Isothiocyanate **2** was deprotonated by **4c** to give anion **8**. Simultaneously, electron-deficient olefin **1** was recognized through the H-bonding interaction with squaramide moiety of the catalyst **4c**. Such a recognition profile of both reactants positioned them correctly in space and forced the enolate **8** to approach **1** in a stereocontrolled fashion. Michael adduct **9** thus obtained underwent intramolecular nucleophilic addition to give **10**. In such a manner, the annulation of five-membered heterocyclic ring was accomplished and the catalyst was liberated. Tautomerization of **10** furnished the cascade yielding **3**.



Scheme 4. Mechanistic considerations.

3 Conclusion

In conclusion, we demonstrated that isothiocyanates **1** derived from α-substituted α-amino acids served as useful building blocks for the synthesis of pyrrolidine-based heterocycles. Their cascade reaction with olefinic barbiturates or Meldrum's acid derivative proceeding in a sequence Michael addition followed by nucleophilic addition resulted in the heteroannulation of 2-pyrrolidinethione ring with spirocyclic architecture. The developed reactivity was expanded for the synthesis of α,α-disubstituted α-aminophosphonates and benefited from excellent chemical and stereochemical efficiency as well as broad substrate scope. Furthermore, usefulness of the products obtained was confirmed in selected transformations.

Experimental Section

NMR spectra were acquired on a Bruker Ultra Shield 700 instrument, running at 700 MHz for ^{1}H, 176 MHz for ^{13}C and 283 MHz for ^{31}P, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). ^{31}P NMR spectra were recorded using 85% H_3PO_4 as external standard. Mass spectra were recorded on a Bruker Maxis Impact spectrometer using electrospray (ES+) ionization (referenced to the mass of the charged species). Optical rotations were measured on a Perkin-Elmer 241 polarimeter and $[\alpha]_D$ values are given in deg·cm·g^{-1}·dm^{-1}; concentration c is listed in g·(100 mL)$^{-1}$. Melting points were determined in open capillaries and are uncorrected. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$. The enantiomeric ratio (er) of the products was determined by chiral

stationary phase HPLC (Daicel Chiralpak IA, IC, ID and IG). Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (Silica gel 60, 230–400 mesh, Fluka) was used. Electron-deficient olefins **1**[15a] and isothiocyanates **2a**[15b] and **2b–d**[15b–d] were prepared according to literature procedures.

Isothiocyanate strategy in the enantioselective synthesis of quaternary α-amino acids 3 – general procedure

In an ordinary 4 mL glass vial, equipped with a Teflon-coated magnetic stirring bar and a screw cap, catalyst **4c** (0.2 equiv., 0.01 mmol, 6.3 mg), corresponding electron-poor olefin **1** (1.0 equiv., 0.05 mmol) and isothiocyanate **2a** (1.0 equiv., 0.05 mmol) were dissolved in toluene (0.2 mL) and stirring was maintained for 48 h at ambient temperature. Pure product **3** was isolated by flash chromatography on silica gel (eluent: CH_2Cl_2).

3aa (3*R*,4*S*)-Methyl 7,9-dimethyl-6,8,10-trioxo-3,4-diphenyl-1-thioxo-2,7,9-triazaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, 20:1 dr), **3aa** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 90% yield (20.3 mg) as a white solid (mp = 230–231 °C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.96 (bs, 1H), 7.35–7.32 (m, 1H), 7.30–7.27 (m, 2H), 7.21–7.18 (m, 3H), 7.06–7.04 (m, 2H), 6.65 (dd, J = 8.2, 0.9 Hz, 2H), 5.30 (s, 1H), 3.77 (s, 3H), 3.30 (s, 3H), 2.94 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.0, 170.5, 167.6, 165.2, 150.0, 134.7, 131.7 (2C), 131.0, 129.2, 129.1, 128.1 (2C), 128.1 (2C), 127.5 (2C), 77.8, 75.2, 60.0, 53.9, 29.6, 29.0. HRMS calculated for $[C_{23}H_{21}N_3O_5S+H^+]$: 452.1275; found: 452.1281. $[\alpha]_D^{22} = -38.1$ (c = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IG column [hexane:*i*-PrOH, 90:10]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 16.4 min., τ_{minor} = 14.1 min., (97:3 er). The reaction was also performed on 0.5 mmol scale providing **3aa** in 90% yield, 20:1 dr, 96:4 er.

3ba (3*R*,4*S*)-Methyl 4-(4-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, 20:1 dr), **3ba** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 77% yield (18.7 mg) as an off-white amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.81 (bs, 1H), 7.38–7.35 (m, 1H), 7.32–7.30 (t, J = 7.7 Hz, 2H), 7.17–7.16 (m, 2H), 7.04–7.03 (m, 2H), 6.64–6.62 (m, 2H),5.39 (s, 1H), 3.77 (s, 3H), 3.32 (s, 3H), 3.01 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 196.5, 170.4, 167.2, 164.8, 150.0, 135.4, 134.5, 133.3 (2C), 129.7, 129.3, 128.3 (2C), 128.2 (2C), 127.5 (2C), 77.0, 75.0, 58.4, 53.9, 29.7, 29.1. HRMS calculated for $[C_{23}H_{20}ClN_3O_5S+H^+]$: 486.0885; found: 486.0888. $[\alpha]_D^{21} = -60.1$ (c = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IG column [hexane:*i*-PrOH, 90:10]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 12.9 min., τ_{minor} = 10.9 min., (97:3 er).

3ca (3*R*,4*S*)-Methyl 4-(3-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, >20:1 dr) **3ca** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 79% yield (19.0 mg) as a white amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.68 (bs, 1H), 7.39–7.37 (m, 1H), 7.32 (dd, J = 11.6, 4.4 Hz, 2H), 7.19 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.17 (d, J = 7.4 Hz, 2H), 7.00 (dd, J = 11.8, 4.1 Hz, 1H), 6.63–6.61 (m, 2H), 5.34 (s, 1H), 3.79 (s, 3H), 3.33 (s, 3H), 3.02 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ196.6, 170.3, 167.2, 164.8, 150.0, 134.4, 133.9, 133.1, 132.0, 130.1, 129.4, 129.3, 129.2, 128.2 (2C), 127.5 (2C), 77.6, 74.9, 58.7, 54.0, 29.8, 29.1. HRMS calculated for $[C_{23}H_{20}ClN_3O_5S+H^+]$: 486.0885; found: 486.0881 $[\alpha]_D^{23} = -36.6$ (c = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IG column [hexane:*i*-PrOH, 90:10]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 13.8 min., τ_{minor} = 11.4 min., (95:5 er).

3da (3*R*,4*R*)-Methyl 4-(2-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, >20:1 dr) **3da** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 62% yield (15.0 mg) as a white amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.91 (bs, 1H), 7.32 (dd, J = 8.1, 1.3 Hz, 2H), 7.31–7.27 (m, 4H), 7.07 (ddd, J = 8.1, 7.4, 1.6 Hz, 1H), 6.72–6.69 (m, 1H), 6.12 (dd, J = 8.1, 1.6 Hz, 1H), 6.04 (s, 1H), 3.81 (s, 3H), 3.34 (s, 3H), 2.82 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ197.2, 170.3, 167.2, 165.0, 150.1, 135.8, 134.7, 133.1, 130.0, 129.7, 129.4, 129.0, 128.6, 127.1 (2C), 125.5, 78.0, 73.9, 54.4, 54.1, 29.6, 28.8, 28.8. HRMS calculated for $[C_{23}H_{20}ClN_3O_5S+H^+]$: 486.0885; found: 486.0894 $[\alpha]_D^{23} = -23.5$ (c = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack ID column [hexane:*i*-PrOH, 80:20]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 22.3 min., τ_{minor} = 20.7 min., (98.5:1.5 er).

3ea (3*R*,4*S*)-Methyl 7,9-dimethyl-4-(4-nitrophenyl)-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, 20:1 dr) **3ea** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 52% yield (12.9 mg) as a white amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.93–7.87 (m, 2H), 7.42–7.38 (m, 1H), 7.36–7.30 (m, 2H), 7.17–7.13 (m, 2H), 6.97–6.94 (m, 2H), 5.65 (s, 1H), 3.80 (s, 3H), 3.35 (s, 3H), 3.06 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 195.7, 170.3, 166.5, 164.2, 149.9, 148.1, 138.6, 134.3, 133.4 (2C), 129.7, 128.4 (2C), 127.4 (2C), 122.9 (2C), 77.5, 74.9, 57.4, 54.1, 30.0, 29.3.HRMS calculated for $[C_{23}H_{21}N_4O_7S+H^+]$: 497.1125; found: 497.1131. $[\alpha]_D^{24} = -35.9$ (c = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IG column [hexane:*i*-PrOH, 90:10]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 24.1 min., τ_{minor} = 21.3 min., (82.5:17.5 er).

3fa (3*R*,4*S*)-Methyl 4-(4-methoxyphenyl)-7,9-dimethyl-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, 20:1 dr) **3fa** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 98% yield (23.6 mg) as a pale yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ8.86 (bs, 1H), 7.36–7.33 (m, 1H), 7.28 (dd, J = 11.6, 4.4 Hz, 2H), 7.18 (d, J = 7.4 Hz, 2H), 6.56 (s, 4H), 5.27 (s, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.30 (s, 3H), 2.97 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.1, 170.5, 167.7, 165.3, 160.0, 150.1, 134.7, 132.9 (2C), 129.1, 128.1 (2C), 127.5 (2C), 122.8, 113.4 (2C), 77.7, 75.2, 59.5, 55.2, 53.8, 29.6, 29.0. HRMS calculated for $[C_{24}H_{23}N_3O_6S+H^+]$: 482.1380; found: 482.1376. $[\alpha]_D^{23} = -56.0$ (c = 1.0, $CHCl_3$). The er was determined by HPLC

using a chiral Chiralpack IG column [hexane: *i*-PrOH, 90:10]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 23.5 min., τ_{minor} = 20.2 min., (97.5:2.5 er).

3ga (3*R*,4*R*)-Methyl 4-(2,4-dichlorophenyl)-7,9-dimethyl-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, >20:1 dr) **3ga** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 93% yield (24.2 mg) as a pale yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.38–7.27 (m, 6H), 6.69 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.08 (d, *J* = 8.7 Hz, 1H), 6.02 (s, 1H), 3.81 (s, 3H), 3.35 (s, 3H), 2.90 (s, 3H).^{13}C NMR (176 MHz, $CDCl_3$) δ 197.0, 170.2, 167.0, 164.8, 150.0, 136.5, 135.4, 134.5, 134.0, 129.5, 129.4, 128.7 (2C), 127.7, 127.1 (2C), 125.9, 78.0, 73.8, 54.1, 53.6, 29.7, 28.9. HRMS calculated for $[C_{23}H_{19}Cl_2N_3O_5S+H^+]$: 520.0495; found: 520.0490.$[\alpha]_D^{25}$ = −50.3 (*c* = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IG column [hexane:*i*-PrOH, 90:10]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 15.5 min., τ_{minor} = 13.8 min., (99:1 er).

3ha (3*R*,4*S*)-Methyl 7,9-dimethyl-4-(naphthalen-1-yl)-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, 10:1 dr) **3ha** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 56% yield (14.0 mg) as a pale yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.84–7.80 (m, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.60 (ddd, *J* = 8.5, 6.8, 1.3 Hz, 1H), 7.52–7.47 (m, 1H), 7.37 (dd, *J* = 11.4, 4.2 Hz, 1H), 7.36–7.17 (m, 4H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.40 (s, 1H), 6.18 (dd, *J* = 7.5, 1.0 Hz, 1H), 3.75 (s, 3H), 3.08 (s, 3H), 2.76 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.3, 170.7, 167.9, 165.6, 149.7, 135.0, 133.9, 132.6, 130.6, 129.7, 129.6, 129.3, 128.3, 127.7, 127.4, 126.1, 126.0, 123.7, 121.9, 78.5, 75.2, 54.0, 54.0, 52.3, 29.8, 29.4, 28.7. HRMS calculated for $[C_{27}H_{23}N_3O_5S+H^+]$: 502.1431; found: 502.1420. $[\alpha]_D^{23}$ = +38.5 (*c* = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IG column [hexane:*i*-PrOH, 90:10]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 18.7 min., τ_{minor} = 23.6 min., (98:2 er).

3ia (3*R*,4*S*)-Methyl 4-(furan-2-yl)-7,9-dimethyl-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, >20:1 dr) **3ia** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 88% yield (19.5 mg) as an off-white amorphous solid.^{1}H NMR (700 MHz, $CDCl_3$) δ 8.82 (bs, 1H), 7.37–7.34 (m, 1H), 7.33–7.30 (m, 2H), 7.22 (ddd, *J* = 7.1, 3.2, 1.9 Hz, 2H), 7.17 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.13–6.11 (m, 1H), 5.65 (s, 1H), 5.59 (d, *J* = 3.4 Hz, 1H), 3.81 (s, 3H), 3.35 (s, 3H), 3.11 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 196.1, 170.1, 167.0, 164.3, 150.4, 145.5, 142.9, 135.0, 129.2, 128.0 (2C), 126.9 (2C), 113.1, 110.8, 76.9, 73.5, 54.0, 52.4, 29.8, 29.2. HRMS calculated for $[C_{21}H_{19}N_2O_6S+H^+]$: 442.1067; found: 442.1063. $[\alpha]_D^{22}$ = + 19.8 (*c* = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IG column [hexane:*i*-PrOH, 90:10]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 16.2 min., τ_{minor} = 18.7 min., (99:1 er).

3ja (3*R*,4*S*)-Methyl 4-isopropyl-7,9-dimethyl-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, >20:1 dr) **3ja** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 40% yield (8.4 mg) as an off-white amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.57–7.53 (m, 2H), 7.45–7.40 (m, 3H), 4.32 (d, *J* = 11.0 Hz, 1H), 3.90 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H), 1.84–1.78 (m, 1H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.60 (d, *J* = 6.5 Hz, 3H).^{13}C NMR (176 MHz, $CDCl_3$) δ 194.1, 171.1, 167.4, 165.2, 150.9, 135.2, 129.3, 128.6 (2C), 128.2 (2C), 78.5, 73.6, 57.5, 53.7, 30.0, 29.5, 26.3, 22.1, 22.1.HRMS calculated for $[C_{20}H_{23}N_3O_5S+H^+]$: 418.1431; found: 418.1427. $[\alpha]_D^{22}$ = −11.5 (*c* = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IC column [hexane:*i*-PrOH, 80:10]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 15.1 min., τ_{minor} = 14.0 min., (96:4 er).

3ka (3*R*,4*S*)-Methyl 7,9-dimethyl-6,8,10-trioxo-3-phenyl-4-((*E*)-styryl)-1-thioxo-2,7,9-triazaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, 6:1 dr) **3ka** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 79% yield (18.9 mg) as a pale yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.42 (dd, *J* = 4.2, 2.4 Hz, 3H), 7.39–7.36 (m, 2H), 7.24 (ddd, *J* = 8.7, 6.1, 3.0 Hz, 3H), 7.16–7.12 (m, 2H), 6.67 (d, *J* = 15.7 Hz, 1H), 5.61 (dd, *J* = 15.7, 10.1 Hz, 1H), 5.11 (d, *J* = 10.1 Hz, 1H), 3.82 (s, 3H), 3.39 (s, 3H), 3.20 (s, 3H).^{13}C NMR (176 MHz, $CDCl_3$) δ 195.8, 170.3, 166.5, 163.8, 150.7, 136.7, 136.1, 134.8, 129.2, 128.8 (2C), 128.5, 128.4 (2C), 126.9 (2C), 126.7 (2C), 121.9, 76.9, 74.6, 54.6, 53.9, 29.9, 29.3. HRMS calculated for $[C_{25}H_{23}N_3O_5S+H^+]$: 478.1431; found: 478.1438. $[\alpha]_D^{22}$ = −46.4 (*c* = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IC column [hexane:*i*-PrOH, 80:20]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 7.4 min., τ_{minor} = 8.7 min., (94:6 er).

3la (3*R*,4*S*)-Methyl 4-(4-methoxyphenyl)-8,8-dimethyl-6,10-dioxo-3-phenyl-1-thioxo-7,9-dioxa-2-azaspiro[4.5]decane-3-carboxylate. Following the general procedure (reaction time 48 h, 12:1 dr) **3la** was isolated by FC on silica gel (eluent: CH_2Cl_2) in 75% yield (17.6 mg) as a pale yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.34–7.31 (m, 1H), 7.29–7.26 (m, 2H), 7.17 (s, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.63–6.58 (m, 2H), 5.32 (s, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 1.76 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 196.7, 170.4, 166.9, 163.1, 160.1, 134.4, 133.4 (2C), 129.2, 128.1 (2C), 127.5 (2C), 122.9, 113.7 (2C), 107.0, 77.8, 73.6, 59.1, 55.3, 53.9, 29.6, 29.1. HRMS calculated for $[C_{24}H_{23}NO_7S+H^+]$: 470.1268; found: 470.1273.$[\alpha]_D^{22}$ = −30.3 (*c* = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IC column [hexane:*i*-PrOH, 80:10]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 23.0 min., τ_{minor} = 16.4 min., (84:16 er).

Isothiocyanate strategy in the enantioselective synthesis of α-aminophosphonates 3 – general procedure

In an ordinary 4 mL glass vial, equipped with a Teflon-coated magnetic stirring bar and a screw cap, catalyst **4c** (0.2 equiv., 0.02 mmol, 6.3 mg), the corresponding dimethyl 5-(alkylidene)barbiturate **1** (1.0 equiv., 0.1 mmol) and isothiocyanate **2** (1.0 equiv., 0.1 mmol) were dissolved in freshly distilled THF (0.2 mL) and stirring was maintained for 24–48 h at ambient temperature. Pure product **3** was isolated by flash chromatography on silica gel (eluent: hexanes:acetone 4:1).

3ab Diphenyl ((3*S*,4*S*)-7,9-dimethyl-6,8,10-trioxo-3,4-diphenyl-1-thioxo-2,7,9-triazaspiro[4.5]decan-3-yl)phosphonate. Following the general procedure (reaction time 24 h, >20:1 dr) **3ab** was isolated by FC on silica gel (eluent: hexanes:acetone 4:1) in 99% yield (61.9 mg) as an off-white solid (mp = 227–228 °C). ^{1}H NMR (700 MHz, $CDCl_3$) δ 11.00–10.88 (m, 1H), 10.04 (s, 1H), 7.31–7.24 (m, 9H), 7.19–7.15 (m, 3H), 7.11–7.09 (m, 2H), 7.07–7.04 (m, 2H), 6.99–6.97 (m, 1H), 6.81–6.76 (m, 2H), 5.74 (d, J = 20.9 Hz, 1H), 3.31 (s, 3H), 3.04 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.5 (d, J = 8.1 Hz), 167.1, 165.1, 150.6 (d, J = 10.0 Hz), 150.3 (d, J = 11.5 Hz), 150.1, 132.2, 130.3, 130.0 (2C), 129.5 (3C), 129.5, 129.3 (d, J = 5.4 Hz, 2C), 128.9, 128.2 (2C), 127.6 (2C), 125.7, 125.3, 120.6 (d, J = 4.4 Hz, 2C), 120.4 (d, J = 4.0 Hz, 2C), 75.3 (d, J = 8.1 Hz), 74.6, 73.7, 58.4, 29.6, 29.1. ^{31}P NMR (283 MHz, $CDCl_3$) δ 10.1. HRMS calculated for [$C_{33}H_{28}N_3O_6PS + H^+$]: 626.1509; found: 626.1517 $[\alpha]_D^{20} = -49.0$ (c = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IA column [hexane:*i*-PrOH, 80:20]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 12.0 min., τ_{minor} = 10.2 min., (99:1 er).

3bb Diphenyl ((3*S*,4*S*)-4-(4-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decan-3-yl)phosphonate. Following the general procedure (reaction time 24 h, 10:1 dr) **3bb** was isolated by FC on silica gel (eluent: hexanes:acetone 4:1) in 79% yield (52.1 mg) as a pale yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.02 (bs, 1H), 7.31–7.27 (m, 4H), 7.25–7.24 (m, 3H), 7.20–7.16 (m, 3H), 7.08–7.06 (m, 2H), 7.05–7.03 (m, 2H), 6.99–6.97 (m, 1H), 6.78–6.74 (m, 2H), 6.68 (d, J = 8.4 Hz, 2H), 5.81 (d, J = 21.0 Hz, 1H), 3.33 (s, 3H), 3.09 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.0 (d, J = 7.9 Hz), 166.7, 164.7, 150.5 (d, J = 10.2 Hz), 150.2 (d, J = 11.2 Hz), 150.0, 135.7, 133.8 (2C), 132.1 (d, J = 4.3 Hz), 130.1 (2C), 129.5 (2C), 129.3 (d, J = 5.5 Hz, 2C), 129.1, 129.0, 128.4 (2C), 127.7, 125.8, 125.4, 120.6 (d, J = 4.4 Hz, 2C), 120.4 (d, J = 3.9 Hz, 2C), 75.2 (d, J = 8.0 Hz), 74.4, 73.5, 56.9, 29.8, 29.2. ^{31}P NMR (283 MHz, $CDCl_3$) δ 10.1. HRMS calculated for [$C_{33}H_{27}ClN_3O_6PS + H^+$]: 660.1119; found: 660.1129. $[\alpha]_D^{20} = -59.6$ (c = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IA column [hexane:*i*-PrOH, 80:20]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 14.7 min., τ_{minor} = 10.0 min., (97:3 er).

3cb Diphenyl ((3*S*,4*S*)-4-(3-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decan-3-yl)phosphonate. Following the general procedure (reaction time 48 h, 15:1 dr) **3cb** was isolated by FC on silica gel (eluent: hexanes:acetone 4:1) in 84% yield (55.4 mg) as a yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.32–7.27 (m, 5H), 7.25–7.22 (m, 3H), 7.18–7.16 (m, 3H), 7.08–7.04 (m, 3H), 7.00–6.96 (m, 1H), 6.80–6.76 (m, 1H), 6.74–6.68 (m, 3H), 5.76 (d, J = 20.8 Hz, 1H), 3.34 (s, 3H), 3.09 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 196.9, 166.7, 164.7, 150.5 (d, J = 10.2 Hz), 150.2 (d, J = 11.4 Hz), 150.0, 133.9, 132.4, 131.9, 130.7, 130.0 (2C), 129.6, 129.6 (2C), 129.4, 129.2 (d, J = 5.5 Hz) (2C), 129.2, 127.6 (2C), 125.8, 125.4, 120.5 (d, J = 4.3 Hz) (2C), 120.4 (d, J = 3.9 Hz) (2C), 75.1 (d, J = 8.0 Hz), 74.5, 73.6, 57.1, 29.8, 29.1. ^{31}P NMR (101 MHz, Chloroform-*d*) δ 10.24. HRMS calculated for [$C_{33}H_{27}ClN_3O_6PS + H^+$]: 660.1119; found: 660.1125. $[\alpha]_D^{24} = -35.0$ (c = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IA column [hexane:*i*-PrOH, 80:20]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 9.2 min., τ_{minor} = 12.9 min., (96:4 er).

3db Diphenyl ((3*S*,4*R*)-4-(2-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decan-3-yl)phosphonate. Following the general procedure (reaction time 48 h, 20:1 dr) **3db** was isolated by FC on silica gel (eluent: hexanes:acetone 4:1) in 60% yield (39.7 mg) as a yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.90 (d, J = 26.3 Hz, 1H), 7.51–7.41 (m, 1H), 7.38 (dd, J = 8.0, 1.3 Hz, 1H), 7.33–7.28 (m, 5H), 7.20–7.16 (m, 1H), 7.14 (tt, J = 11.2, 2.7 Hz, 1H), 7.12–7.08 (m, 2H), 7.00–6.98 (m, 1H), 6.98–6.90 (m, 2H), 6.87–6.84 (m, 2H), 6.77–6.71 (m, 1H), 6.49 (d, J = 20.6 Hz, 1H), 6.01 (dd, J = 8.1, 1.6 Hz, 1H), 3.33 (s, 3H), 2.90 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 198.0, 166.9, 165.6, 150.7 (d, J = 10.1 Hz), 150.1 (d, J = 11.5 Hz), 149.9, 136.5, 133.4, 132.3, 130.5, 130.1 (2C), 130.0 (3C), 129.6 (3C), 129.3, 127.8, 125.7, 125.4 (d, J = 4.9 Hz) (2C), 120.8 (d, J = 4.4 Hz) (2C), 120.6 (d, J = 4.0 Hz) (2C), 74.6, 74.3 (d, J = 7.8 Hz), 73.7, 52.5, 29.7, 28.9. ^{31}P NMR (101 MHz, Chloroform-*d*) δ 9.92. HRMS calculated for [$C_{33}H_{27}ClN_3O_6PS + H^+$]: 660.1119; found: 660.1127. $[\alpha]_D^{24}$ = -20.7 (c = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IA column [hexane:*i*-PrOH, 80:20]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 14.5 min., τ_{minor} = 10.7 min., (98:2 er).

3fb Diphenyl ((3*S*,4*S*)-4-(4-methoxyphenyl)-7,9-dimethyl-6,8,10-trioxo-3-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decan-3-yl)phosphonate. Following the general procedure (reaction time 24 h, >20:1 dr) **3fb** was isolated by FC on silica gel (eluent: hexanes:acetone 4:1) in 85% yield (55.8 mg) as a pale yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.38–7.24 (m, 8H), 7.21–7.14 (m, 3H), 7.07–7.02 (m, 2H), 6.98 (t, J = 7.4 Hz, 1H), 6.70–6.69 (m, 4H), 6.62–6.61 (m, 2H), 5.70 (d, J = 21.0 Hz, 1H), 3.73 (s, 3H), 3.31 (s, 3H), 3.05 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.7 (d, J = 8.1 Hz), 165.2, 160.3, 150.6 (d, J = 10.0 Hz), 150.3 (d, J = 11.3 Hz), 150.1, 133.4 (2C), 132.3 (d, J = 4.2 Hz), 130.0 (2C), 129.5 (2C), 129.3 (d, J = 5.3 Hz, 2C), 128.9, 127.6(2C), 125.7, 125.3, 122.0, 120.6 (d, J = 4.3 Hz, 2C), 120.4 (d, J = 3.8 Hz, 2C), 113.5 (2C), 75.3 (d, J = 8.3 Hz), 74.5, 73.6, 57.9, 55.2, 29.6, 29.1. ^{31}P NMR (283 MHz, $CDCl_3$) δ 10.1. HRMS calculated for [$C_{34}H_{30}N_3O_7PS + H^+$]: 656.1615; found: 656.1610. $[\alpha]_D^{20} = -62.0$ (c = 1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IA column [hexane:*i*-PrOH, 80:20]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major} = 15.4 min, τ_{minor} = 11.9 min, (99:1 er).

3ac Diphenyl ((3*S*,4*S*)-3-(4-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-4-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decan-3-yl)phosphonate. Following the general procedure (reaction time 24 h, >20:1 dr) **3ac** was isolated by FC on silica gel (eluent: hexanes:acetone, 4:1) in 97% yield (64.0 mg) as an off-white amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.32–7.26 (m, 3H), 7.25–7.17 (m, 5H), 7.15–7.13(dtm, 2H), 7.12–7.07 (m, 4H), 7.01–6.99 (m, 1H), 6.82–6.80 (m, 4H), 5.73 (d, J = 20.8 Hz, 1H), 3.31 (s, 3H), 3.08 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.6 (d, J = 8.4 Hz), 167.0, 165.2, 150.5 (d, J = 10.2 Hz), 150.2 (d, J = 11.3 Hz), 150.0, 135.2 (d, J = 2.6 Hz), 132.2 (2C), 131.0 (d, J = 3.9 Hz),

130.8 (d, J=5.5 Hz, 2C), 130.1 (2C), 129.7, 129.6 (2C), 128.4 (2C), 127.7 (2C), 125.8, 125.5, 120.5 (d, J=4.4 Hz, 2C), 120.4 (d, J=3.9 Hz, 2C), 75.2 (d, J=8.1 Hz), 74.2, 73.3, 58.1, 29.7, 29.1. ^{31}P NMR (283 MHz, $CDCl_3$) δ 9.7. HRMS calculated for [$C_{33}H_{27}ClN_3O_6PS+H^+$]: 660.1119; found: 660.1111. $[\alpha]_D^{20}=-67.2$ (c=1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack ID column [hexane:*i*-PrOH, 80:20]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major}=11.3 min., τ_{minor}=15.9 min., (98:2 er).

3ad Diphenyl ((3*S*,4*S*)-3-(4-methoxyphenyl)-7,9-dimethyl-6,8,10-trioxo-4-phenyl-1-thioxo-2,7,9-triazaspiro[4.5]decan-3-yl)phosphonate. Following the general procedure (reaction time 48 h, 7:1 dr) **3ad** was isolated by FC on silica gel (eluent: hexanes:acetone 4:1) in 73% yield (47.9 mg) as a pale yellow amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.33–7.29 (m, 2H), 7.29–7.23 (m, 4H), 7.19 (t, J=7.3 Hz, 1H), 7.13–7.08 (m, 5H), 7.02 (t, J=7.4 Hz, 1H), 6.77 (dd, J=19.2, 7.9 Hz, 4H), 6.72 (d, J=8.5 Hz, 2H), 6.51 (d, J=17.6 Hz, 1H), 5.67 (d, J=20.5 Hz, 1H), 3.76 (s, 3H), 3.31 (s, 3H), 3.04 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.6 (d, J=8.4 Hz), 167.2, 165.3, 160.1, 150.6 (d, J=10.0 Hz), 150.3 (d, J=11.4 Hz), 150.1, 132.2 (2C), 130.7 (d, J=5.5 Hz, 2C), 130.3, 130.1 (2C), 129.6 (2C), 129.5, 128.2 (2C), 125.7, 125.4, 120.6 (d, J=4.4 Hz, 2C), 120.5 (d, J=3.9 Hz, 2C), 113.1(2C), 75.3 (d, J=8.6 Hz), 74.3, 73.4, 58.5, 55.3, 29.6, 29.1. ^{31}P NMR (283 MHz, $CDCl_3$) δ 10.2. HRMS calculated for [$C_{34}H_{30}N_3O_7PS+H^+$]: 656.1615; found: 656.1608. $[\alpha]_D^{20}=-49.1$ (c=1.0, $CHCl_3$). The er was determined by HPLC using a chiral Chiralpack IA column [hexane:*i*-PrOH, 80:20]; column temperature 30 °C; flow rate 1.0 mL/min; τ_{major}=13.6 min., τ_{minor}=11.0 min., (97:3 er).

Synthesis of (3*R*,4*S*)-methyl 7,9-dimethyl-1,6,8,10-tetraoxo-3,4-diphenyl-2,7,9-triazaspiro[4.5]decane-3-carboxylate (5aa)

In an ordinary 4 mL glass vial, equipped with a Teflon-coated magnetic stirring bar and a screw cap solution of **3aa** (1 equiv., 0.1 mmol, 45 mg) in dry CH_2Cl_2 (2 mL) was placed. After cooling in an ice-bath *m*CPBA (4 equiv., 0.4 mmol, 69 mg) was added. After stirring in room temperature for 20 h, reaction mixture was directly subjected to flash chromatography on silica gel (eluent: hexanes:acetone 7:3) giving product **5aa** (20:1 dr) in 90% yield (39.2 mg) as an off-white amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.22–7.12 (m, 5H), 7.11–7.06 (m, 1H), 6.99–6.91 (m, 2H), 6.58 (dd, J=8.2, 0.9 Hz, 2H), 5.00 (s, 1H), 3.68 (s, 3H), 3.20 (s, 3H), 2.76 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.8, 168.6, 167.6, 165.3, 150.2, 135.3, 131.7, 131.2 (2C), 128.9, 128.8, 128.1 (2C), 127.9 (2C), 127.2 (2C), 70.9, 67.0, 59.3, 53.7, 29.3, 28.7. HRMS calculated for [$C_{23}H_{21}N_3O_6+H^+$]: 436.1503; found: 436.1509. $[\alpha]_D^{21}$=-90.8° (c=1.0, $CHCl_3$).

Synthesis of (3*R*,4*S*)-methyl 7,9-dimethyl-1-(methylthio)-6,8,10-trioxo-3,4-diphenyl-2,7,9-triazaspiro[4.5]dec-1-ene-3-carboxylate (6aa)

In an ordinary 4 mL glass vial, equipped with a Teflon-coated magnetic stirring bar and a screw cap solution of **3aa** (1 equiv., 0.1 mmol, 45.0 mg) in dry acetone (2 mL) was placed. After cooling in an ice-bath, K_2CO_3 (1.1 equiv., 0.11 mmol, 15.2 mg) and MeI (1.1 equiv., 0.11 mmol, 15.6 mg) were added. After 20 h of stirring in room temperature reaction mixture was filtered through syringe filter and evaporated giving without any further purification product **6aa** (20:1 dr) in 95% yield (44.2 mg) as an off-white amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.19–7.11 (m, 5H), 7.11–7.07 (m, 1H), 6.98 (dd, J=8.2, 7.5 Hz, 2H), 6.53 (dd, J=8.2, 1.0 Hz, 2H), 5.15 (s, 1H), 3.72 (s, 3H), 3.30 (s, 3H), 2.81 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 172.8, 169.5, 167.5, 165.3, 150.3, 137.4, 132.6, 131.1 (2C), 128.5, 127.9, 127.8 (2C), 127.8 (4C), 88.7, 75.4, 65.4, 53.6, 29.4, 28.7, 15.1.HRMS calculated for [$C_{24}H_{23}N_3O_5S+H^+$]: 466.1431; found: 466.1433. $[\alpha]_D^{19}=-50.9$ (c=1.0, acetone).

Synthesis of (3*R*,4*S*)-methyl 7,9-dimethyl-6,8,10-trioxo-3,4-diphenyl-2,7,9-triazaspiro[4.5]decane-3-carboxylate (7aa)

In an ordinary screw-cap vial equipped with magnetic stirring bar, the **3aa** (90.2 mg, 0.2 mmol) was suspended in EtOH, cooled to 0°C and excess Raney Nickel was added. After stirring for 2 h at 0 °C, mixture was filtered through a short pad of Celite and washed with $CHCl_3$ and concentrated under reduced pressure. Crude product was purified by column chromatography (hexanes:acetone 3:2) affording desired amine **7aa** (20:1 dr) in 48% yield (40.4 mg) as white amorphous solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.27–7.24 (m, 2H), 7.06–7.03 (m, 2H), 7.02–6.97 (m, 4H), 6.95–6.92 (m, 2H), 4.76 (s, 1H), 4.00 (d, J=10.7 Hz, 1H), 3.95 (d, J=10.7 Hz, 1H), 3.74 (s, 3H), 3.39 (s, 2H), 2.57 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 175.0, 170.8, 168.2, 151.3, 138.4, 134.8, 130.8 (2C), 127.9 (2C), 127.8, 127.7 (2C), 127.4, 127.2 (2C), 76.8, 64.5, 64.4, 53.5, 47.5, 29.6, 28.7. HRMS calculated for [$C_{23}H_{23}N_3O_5+H^+$]: 422.1710; found: 422.1717. $[\alpha]_D^{24}=-62.9$ (c=1.0, $CHCl_3$).

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[14] CCDC 1813067 and 1813068 contain the supplementary crystallographic data for this paper. These data can be

obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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