Synthesis M. Saktura et al. Feature

Aminocatalytic Synthesis of Uracil Derivatives Bearing a Bicyclo[2.2.2]octane Scaffold via a Doubly Cycloadditive Reaction Cascade

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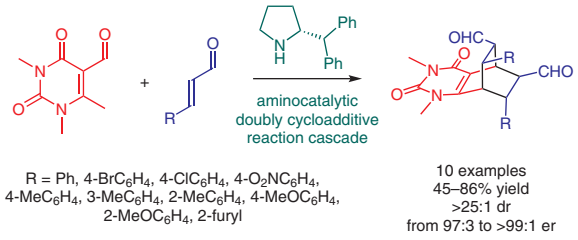
Dedicated to Professor Grzegorz Mlostoń on the occasion of his 70th birthday



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Abstract Aminocatalytic synthesis of highly enantiomerically enriched uracil derivatives bearing a bicyclo[2.2.2]octane scaffold is described. The developed strategy utilizes 1,3,6-trimethyl-5-formyluracil and α,β-unsaturated aldehydes as starting materials and has been realized employing various aminocatalytic activation strategies operating in a synergistic manner. The reaction cascade can be described as doubly cycloadditive as it consists of two consecutive Diels–Alder cycloadditions allowing for a facile construction of the bicyclo[2.2.2]octane scaffold. Notably, both steps proceed with dearomatization of the partially aromatic uracil moiety. Excellent stereoselectivity of the reaction cascade is ensured by the use of 2-(diphenylmethyl)pyrrolidine as aminocatalyst.

Key words asymmetric synthesis, organocatalysis, aminocatalysis, uracil, bicyclic compounds, Diels–Alder cycloaddition

Bridged bicyclic compounds, their chemistry and biology constitute important research areas given the wide occurrence of such structural motifs in natural products and compounds relevant in the life sciences.[1,2] Their structural rigidity defines alignment of substituents making them suitable for biological applications. In particular, bicyclo[2.2.2]octane and related scaffolds (Figure 1, top panel, left) constitute important representatives of this class of compounds with interesting properties. For instance, (–)-atiserene is a diterpenoid isolated from the tropical tree *Erythroxylon monogynum* and mitindomide exhibits antitumor activity (Figure 1, bottom panel).

Uracil is a pyrimidine derivative (Figure 1, top panel, right), very common in nature due to the presence as nucleobase in ribonucleic acid (RNA).[3] Furthermore, it can be found in many bioactive molecules with selected representatives depicted below in the bottom panel of Figure 1. 5-Flourouracil is an antitumor agent, sorivudine possesses antiviral properties, and elagolix is a GnRH antagonist (Figure 1, bottom panel).

The design and development of novel and stereocontrolled synthetic strategies leading to organic compounds of biological relevance constitute fundamental tasks in the contemporary organic chemistry. Recently, their realization is strictly combined with the rapid evolution of catalytic methods involving chiral reaction promotors.[4] Within this field of research, asymmetric organocatalysis has provided

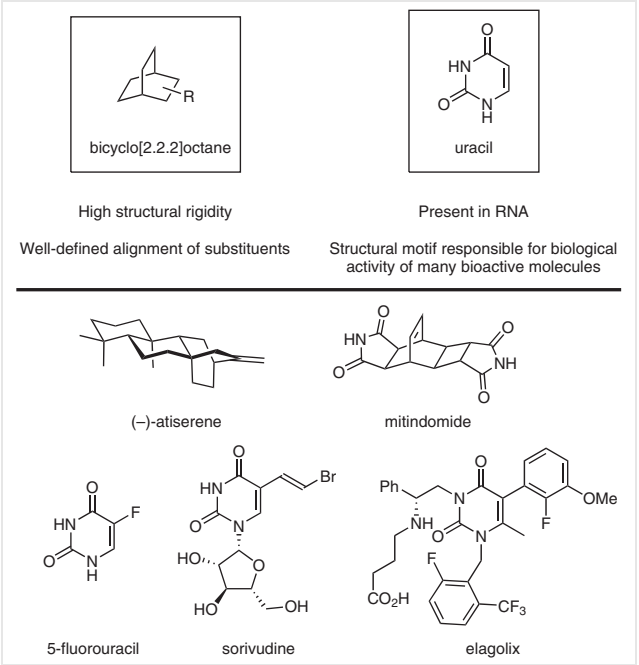

Figure 1 The importance of bicyclo[2.2.2]octane, uracil, and their derivatives

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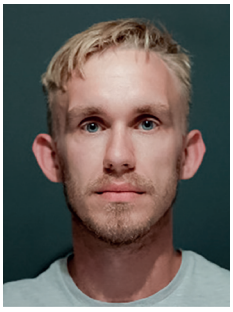
novel solutions within the last 20 years.[5–10] Owing to the implementation of innovative reactivity concepts (with well-defined approaches to control stereochemical reaction outcomes), asymmetric organocatalysis has significantly expanded the arsenal of modern synthetic methods.[6,7] Among such concepts, vinylogy – allowing for a transfer of either nucleophilic or electrophilic properties of a given position through the neighboring conjugated π-system – occupies a prominent position.[6,8–10] Following this principle, unique reactivities have been identified and described. Many of these rely on the usage of polyenamines and related polyenolates as nucleophiles, dienes, or dienophiles (Figure 2, top panel).[6,8–10] The diversity of such reactants resulting in building chemical and stereochemical complexity is astonishing. Within this research area, dearomative formation of such reaction intermediates using (hetero)aromatic

Biographical Sketches

Maciej Saktura studied chemistry at Lodz University of Technology, where he obtained his M.Sc. under the guidance of Prof. Tadeusz Gajda in 2016. Upon graduation he decided to change his scientific interests to organocatalysis and started his Ph.D. studies under the guidance of Prof. Łukasz Albrecht at the same university. His current research focuses on the application of asymmetric organocatalysis in cycloaddition reactions, and functionalizations of polyene systems.



Sebastian Frankowski was born in 1992 in Łódź (Poland). He studied chemistry at Lodz University of Technology, where he obtained his M. Sc. degree in 2016. In the same year he joined Łukasz Albrecht's group and started his Ph.D. studies at the same university. His current research focuses mainly on new cycloadditions for asymmetric synthesis.

Bartlomiej Joachim studied at Lodz University of Technology, where he obtained his B.Sc. under the guidance of Professor Łukasz Albrecht in 2019. After graduation, he started his M.Sc. studies in the same group.

Łukasz Albrecht was born in Łódź, Poland. He obtained his M.Sc. degree (2004), Ph.D. (2009), and habilitation (2015) from the Lodz University of Technology, Poland. He was appointed a full professor in 2019. In 2009–2012 he stayed as a postdoctoral researcher with Professor Karl Anker Jørgensen at the Center for Catalysis, Aarhus University, Denmark working on new applications of asymmetric organocatalysis. Since 2013 he is a group leader at the Institute of Organic Chemistry, Lodz University of Technology, Poland.

compounds as their precursors constitutes a powerful strategy for the functionalization of the specific positions in their side-chains (Figure 2, bottom panel).[10]

Recently, we have developed a new strategy for the synthesis of bicyclo[2.2.2]lactones (Scheme 1, top panel).[11] It was based on dienamine-mediated [4+2] cycloaddition between α,β-unsaturated aldehydes and corresponding coumalates. In continuation of our efforts towards the development of vinylogous organocatalytic synthetic strategies leading to bicyclic compounds, we turned our attention to 1,3,6-trimethyl-5-formyluracil (**1**) (Scheme 1, bottom panel).[12] Its use seemed particularly attractive as it should lead to the formation of uracil hybrids **3** bearing a bicyclo-[2.2.2]octane ring system via a doubly cycloadditive reaction cascade consisting of two consecutive Diels–Alder cycloadditions (for a detailed reaction mechanism, see Scheme 2, vide infra). It was anticipated that dearomatized dienamine intermediate **5** (derived from **1** and **4**) should be able to participate as an electron-rich diene in the initial Diels–Alder cycloaddition. α,β-Unsaturated aldehydes **2** were selected as model dienophiles as their ability to undergo Diels–Alder cycloaddition under iminium ion activation is well recognized.[13] The second Diels–Alder cycloaddition of the cascade was expected to involve the formation of trienamine intermediate **6** acting as a diene reacting with dienophile **7** to construct bicyclo[2.2.2]octane scaffold. Notably, at the outset of our studies both cycloadditions were expected to proceed with temporary dearomatization of uracil moiety.

Herein, we present our studies on the development of doubly cycloadditive reaction cascade allowing for a construction of uracil hybrids **3** bearing a bicyclo[2.2.2]octane scaffold. The developed protocol benefits from operational simplicity and utilizes readily available starting materials.

Optimization studies were initiated using 1,3,6-trimethyl-5-formyluracil (**1**) and cinnamaldehyde (**2a**) as model reactants (Table 1). To our delight, the devised, doubly cycloadditive cascade proved to be possible to realize in the presence of diphenylprolinol trimethylsilyl ether **4a** in dichloromethane (Table 1, entry 1). However, the reaction yield was not satisfactory. Therefore, the additive screening was initiated (entries 2–6). While in the presence of acidic additive no reaction was observed (entry 2), the use of basic co-catalyst allowed to improve the yield (entries 3–6) with the use of sodium acetate providing the best result (entry 6). Importantly, at this stage attempts to isolate **3a** in a pure form were undertaken and proved unsuccessful. Therefore, the derivatization of **3a** via a Wittig olefination with ylide **8** was performed. Diolefin **9a** thus obtained proved stable under flash chromatography conditions and such protocol was utilized throughout the study. Furthermore, we were pleased to observe that **9a** was obtained as single diastereoisomer and with excellent enantioselectivity. In order to further improve the result in terms of yield, the catalyst screening was performed (entries 6–10). Surprisingly, among catalysts **4** tested, simple 2-diphenylmethylpyrrolidine (**4e**) allowed to significantly improve the yield and diastereoselectivity of the cascade, while maintaining the excellent enantioselectivity of the process (entry 10). Subsequently, the solvent screening was performed (entries 10–15). It was found that the reaction proceeded most efficiently in chlorinated solvents (entries 10–12) with dichloromethane affording **9a** in 74% isolated yield (entry 10). Further studies focused on the concentration (compare entries 10, 16, 17) and temperature effects (compare entries

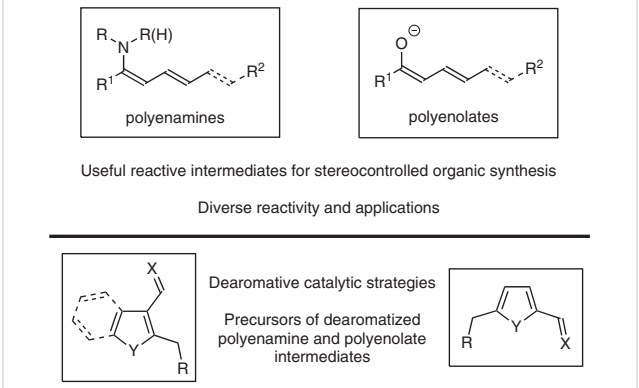
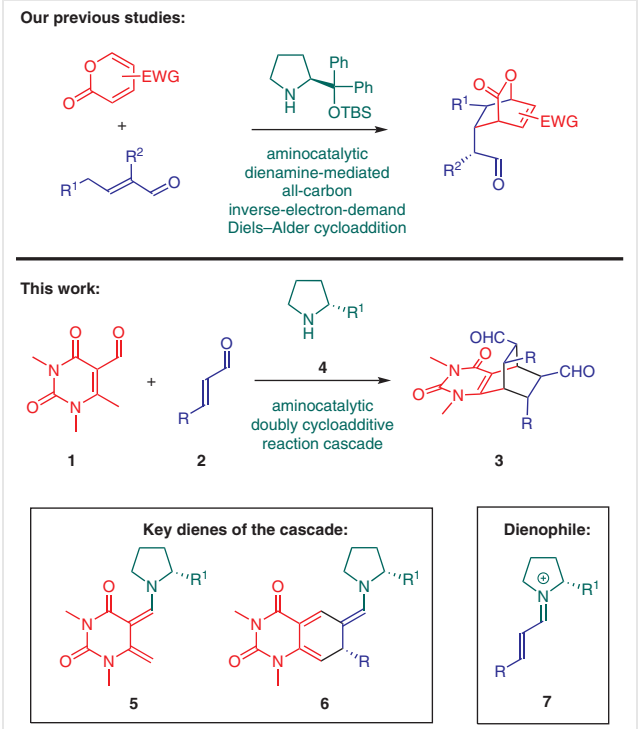


Figure 2 Polyenamines and polyenolates as useful synthons in organic synthesis



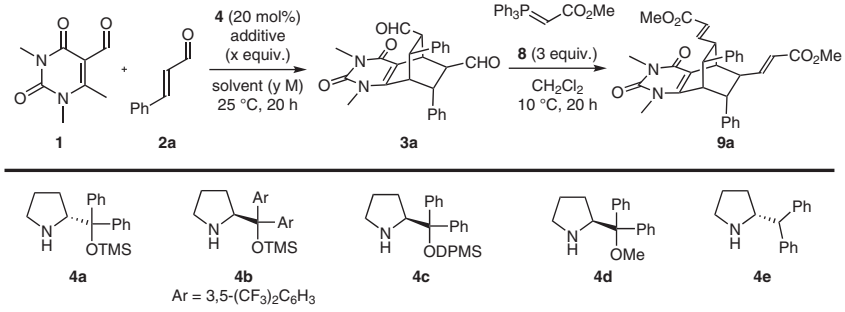
Scheme 1 Organocatalytic synthesis of bicyclo[2.2.2]lactones and synthetic objectives of present studies

10 and 18) did not improve results, thus indicating entry 10 as the best conditions for the developed cascade.

With the optimized reaction conditions for the doubly cycloadditive reaction cascade in hand, the scope of the methodology was studied (Table 2). Therefore, various α,β-unsaturated aldehydes **2** were allowed to react with 1,3,6-trimethyl-5-formyluracil (**1**). In all of the cases, for the ease of isolation and enantiomeric excess determination, crude cycloadducts **3** were subjected to the Wittig olefination with ylide **8** to give **9**. The reaction proceeded smoothly for a wide variety of enals **2** with different electronic properties and positions of substituents on the aromatic ring. Enals **2b–i** containing either electron-withdrawing (Table 2, entries 2–4) or -donating substituents (entries 5–9) were well tolerated. Slightly lower yield was obtained in the case of reaction involving **2d** bearing strong electron-withdrawing substituent in the *para*-position (entry 4). Furthermore, the position of the substituent had no significant influence on the stereochemical reaction outcome (compare entries 5–7 and 8, 9). However, in the case of *ortho*-substituted derivatives a decrease in the yield was observed (entries 7, 9). Heteroaromatic substituents proved also possible to be present in **2** as demonstrated in the synthesis of **9j** (entry 10). Delightfully, excellent diastereo- and enantioselectivities of the doubly cycloadditive cascade were obtained in all of the cases. However, no reactivity was observed when aliphatic α,β-unsaturated aldehydes **2** were employed.

The absolute configuration of stereogenic centers in **3h** was established by the chemical correlation (Scheme 2, to the left).[12] The stereochemistry of remaining products was assigned by analogy assuming that all **3** were obtained in

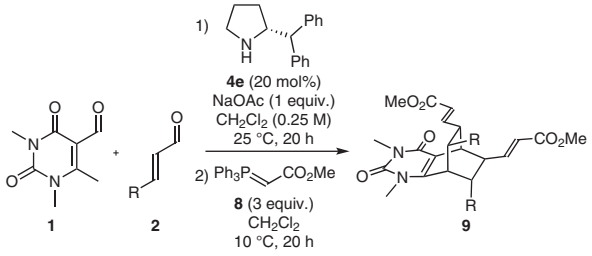
Table 1 Optimization Studies on the Asymmetric Organocatalytic Doubly Cycloadditive Cascade Reactions Involving 1,3,6-Trimethyl-5-formyluracil (**1**)[a]



Entry	Catalyst	Additive (x equiv.)	Solvent (concentration [M])	Temp (°C)	NMR yield (%)[b]	dr[c]	er[d]
1	**4a**	–	CH_2Cl_2 (0.25)	25	42	>25:1	n.d.
2	**4a**	$PhCO_2H$ (0.4)	CH_2Cl_2 (0.25)	25	<5	n.d.	n.d.
3	**4a**	NMM (0.4)	CH_2Cl_2 (0.25)	25	41	3:1	n.d.
4	**4a**	$NaHCO_3$ (0.4)	CH_2Cl_2 (0.25)	25	44	>25:1	n.d.
5	**4a**	NaOAc (0.4)	CH_2Cl_2 (0.25)	25	53	7:1	n.d.
6	**4a**	NaOAc (1)	CH_2Cl_2 (0.25)	25	49 (45)	11.5:1	>99:1
7	**4b**	NaOAc (1)	CH_2Cl_2 (0.25)	25	<5	n.d.	n.d.
8	**4c**	NaOAc (1)	CH_2Cl_2 (0.25)	25	48 (42)	8.5:1	2:98
9	**4d**	NaOAc (1)	CH_2Cl_2 (0.25)	25	68 (60)	>25:1	>1:99
10	**4e**	NaOAc (1)	CH_2Cl_2 (0.25)	25	82 (74)	>25:1	99:1
11	**4e**	NaOAc (1)	$CHCl_3$ (0.25)	25	63	>25:1	n.d.
12	**4e**	NaOAc (1)	$ClCH_2CH_2Cl$ (0.25)	25	82 (72)	>25:1	>99:1
13	**4e**	NaOAc (1)	THF (0.25)	25	40	2:1	n.d.
14	**4e**	NaOAc (1)	MeCN (0.25)	25	<5	n.d.	n.d.
15	**4e**	NaOAc (1)	MeOH (0.25)	25	12	n.d.	n.d.
16	**4e**	NaOAc (1)	CH_2Cl_2 (0.125)	25	74 (68)	>25:1	>99:1
17	**4e**	NaOAc (1)	CH_2Cl_2 (0.5)	25	82 (72)	>25:1	>99:1
18	**4e**	NaOAc (1)	CH_2Cl_2 (0.25)	40	65 (46)	>25:1	>99:1

[a] All reactions were performed in a 0.1 mmol scale using **1** (1.0 equiv.) and **2a** (2.2 equiv.).
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture for the reaction performed in the presence of 1,3,5-tris(trifluoromethyl)benzene (1.0 equiv.). In parenthesis isolated yield is given.

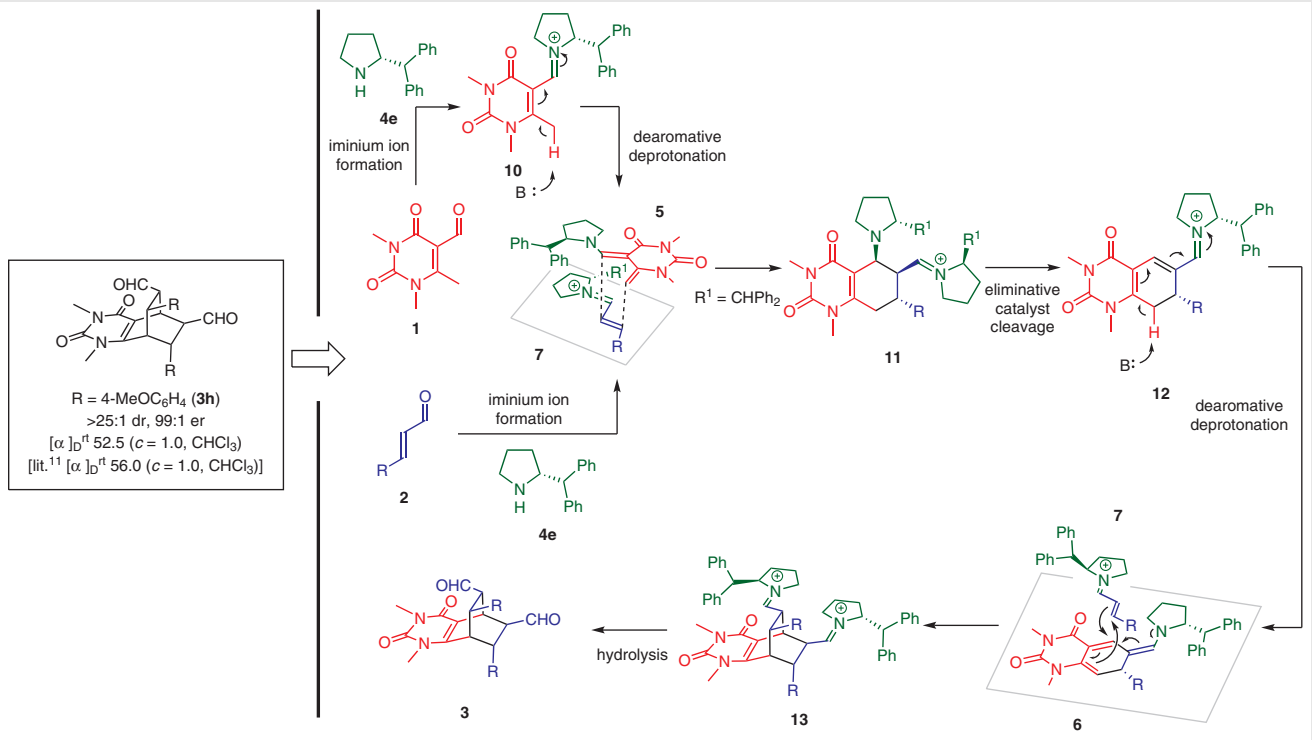
Table 2 Asymmetric Organocatalytic Doubly Cycloadditive Cascade Involving 1,3,6-Trimethyl-5-formyluracil (**1**)[a]



Entry	R	Yield (%)[b]	dr[c]	er[d]
1	Ph (**9a**)	74	>25:1	99:1
2	4-BrC_6H_4 (**9b**)	58	>25:1	97:3
3	4-ClC_6H_4 (**9c**)	52	>25:1	>99:1
4[e]	4-O_2NC_6H_4 (**9d**)	45	>25:1	>99:1
5	4-MeC_6H_4 (**9e**)	86	>25:1	>99:1
6	3-MeC_6H_4 (**9f**)	83	>25:1	>99:1
7	2-MeC_6H_4 (**9g**)	58	>25:1	>99:1
8	4-MeOC_6H_4 (**9h**)	62	>25:1	99:1
9	2-MeOC_6H_4 (**9i**)	52	>25:1	99:1
10	2-furyl (**9j**)	73	>25:1	99:1

[a] All reactions were performed in a 0.1 mmol scale using **1** (1.0 equiv.) and **2** (2.2 equiv.) in 0.4 mL of CH_2Cl_2.
[b] Isolated yields of **9** are given.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined by chiral UPC^2 analysis of **9**.
[e] Reaction performed using **2d** (4.0 equiv.) at 40 °C for 48 h.

the reaction proceeding according to the same mechanistic scenario and that the subsequent Wittig olefination does not influence the stereochemical reaction outcome. Given the assigned configuration, a plausible reaction mechanism is proposed (Scheme 2, to the right). The developed doubly cycloadditive reaction cascade is initiated by two activation processes. The first one involves activation of 1,3,6-trimethyl-5-formyluracil (**1**) via its condensation with aminocatalyst **4e** and subsequent dearomative deprotonation under basic conditions. The second one leads to the formation of iminium ion **7** in the reversible reaction of **2** with **4e**. With the two reactants **5** and **7** formed, the initial *endo*-selective [4+2] cycloaddition occurs with the approach of both chiral reactants controlled by the bulky diphenylmethyl substituent present in the 2 position of the pyrrolidine ring in both **5** and **7**. The reaction proceeds with the rearomatization of the pyrimidine ring yielding iminium ion **11** that undergoes eliminative cleavage of catalyst **4e**. Subsequently, the dearomative deprotonation of **12** occurs to afford trienamine intermediate **6**. Notably, two distal double bonds in trienamine **6** are in *s-cis* conformation making them perfectly suitable for the second Diels–Alder reaction. This step is again doubly stereocontrolled as both reactants (diene **6** and dienophile **7**) are chiral. This important feature is responsible for the proper alignment of iminium ion **7** with respect to **6** in order to avoid disfavored steric interaction between bulky moieties in pyrrolidine rings present in both **7** and **6**, thus resulting in the second *endo*-selective cycloaddition. Hydrolysis of diiminium ion **13** thus obtained regenerates the catalyst **4e** and terminates the catalytic cycle.



Scheme 2 Asymmetric, organocatalytic doubly cycloadditive cascade involving 1,3,6-trimethyl-5-formyluracil (**1**) – mechanistic considerations

In conclusion, an organocatalytic, asymmetric route to uracil hybrids bearing bicyclo[2.2.2]octane scaffold was developed. The strategy was based on two consecutive Diels–Alder reactions enabling the construction of the bicyclo-[2.2.2]octane ring system. Notably, dienes for both of these reactions were formed via dearomative deprotonations of the corresponding uracil derivatives. The stereochemical reaction outcome was governed by simple 2-diphenylmethylpyrrolidine (**4e**) acting as the aminocatalyst.

NMR spectra were acquired on a Bruker Ultra Shield 700 instrument, running at 700 MHz for ^{1}H and 176 MHz for ^{13}C, 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). 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 PerkinElmer 241 polarimeter and $[\alpha]_D$ values are given in deg·cm·g^{-1}·dm^{-1}; concentration *c* is listed in g·(100 mL)$^{-1}$. Analytical TLC was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation. The enantiomeric ratios (er) of the products were determined by chiral stationary phase UPC^2 (Daicel Chiralpak IA, IB, IG column). Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (Silica Gel 60; 35–70 µm, Sigma Aldrich) was used. α,β-Unsaturated aldehydes **2** were prepared according to literature procedure.[14a]

1,3,6-Trimethyl-5-formyluracil (1)

1,3,6-Trimethyl-5-formyluracil (**1**) was prepared according to literature procedure.[14b] To a flame-dried 25 mL flask equipped with a stirring bar were added 1,3,6-trimethyluracil[14b] (924 mg, 6 mmol) and DMF (3 mL). The resulting suspension was stirred for 5 min in an ice-cold bath. Subsequently, $POCl_3$ (3 mL) was added dropwise and the reaction mixture was stirred in an ice-cold bath for 20 min. Next, the mixture was placed in an oil bath (at 120 °C) and stirring was maintained for 3 h. Then the dark-brown suspension was brought to r.t. and subsequently H_2O (15 mL) was added. The resulting mixture was extracted with $CHCl_3$ (4 × 20 mL) and the combined organic layers were washed with H_2O (2 × 10 mL) and dried (anhyd $MgSO_4$). After evaporation under reduced pressure, the crude brown residue was purified using column chromatography on silica gel (eluent: hexanes/EtOAc 80:20 to 70:30) to obtain pure **1**; yield: 305 mg (28%); white, amorphous solid.

^{1}H NMR (700 MHz, $CDCl_3$): δ = 10.27 (s, 1 H), 3.52 (s, 3 H), 3.40 (s, 3 H), 2.78 (s, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 190.1, 162.73, 160.6, 151.3, 108.1, 31.9, 28.1, 16.1.

Asymmetric Organocatalytic Doubly Cycloadditive Cascade Reaction; General Procedure

In an ordinary 4 mL glass vial, equipped with a Teflon-coated magnetic stirring bar and a screw cap, the corresponding aldehyde **2** (0.22 mmol, 2.2 equiv.), 1,3,6-trimethyl-5-formyluracil (**1**; 18.2 mg, 0.10 mmol, 1 equiv.), and NaOAc (8.2 mg, 0.10 mmol, 1 equiv.) were dissolved in CH_2Cl_2 (0.4 mL) and the catalyst **4e** (4.7 mg, 0.02 mmol, 0.2 equiv) was added and the mixture was stirred for 20 h at 25 °C. After this time, the mixture was diluted with CH_2Cl_2 (0.4 mL), cooled to 10 °C and the ylide **8** (100 mg, 0.3 mmol, 3 equiv.) was added and stirring was maintained at 10 °C for 20 h. Pure products **9** were isolated as single diastereoisomers by flash chromatography on silica gel (eluent: hexanes/EtOAc from 4:1 to 3:1).

Dimethyl (2*E*,2′*E*)-3,3′-[(5*R*,7*S*,8*S*,9*S*,10*S*)-1,3-Dimethyl-2,4-dioxo-7,9-diphenyl-1,2,3,4,5,6,7,8-octahydro-5,8-ethanoquinazoline-6,10-diyl]diacrylate (9a)

Following the general procedure, **9a** was isolated by FC on silica gel in) as an off-white semi-solid (>25:1 dr); yield: 40.1 mg (74%); $[\alpha]_D^{25}$ –15.2 (*c* 1.0, $CHCl_3$).

The er was determined by UPC^2 using a Chiralpak IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; t_R = 3.28 min (major), t_R = 4.05 min (minor) (>99:1 er).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.47–7.43 (m, 2 H), 7.38–7.35 (m, 1 H), 7.34–7.31 (m, 2 H), 7.22–7.19 (m, 3 H), 7.18 (dd, *J* = 15.8, 5.9 Hz, 1 H), 6.81–6.77 (m, 2 H), 6.71 (dd, *J* = 15.7, 6.8 Hz, 1 H), 5.92 (dd, *J* = 8.3, 1.6 Hz, 1 H), 5.90 (dd, *J* = 8.3, 1.6 Hz, 1 H), 3.76 (s, 3 H), 3.71–3.70 (m, 1 H), 3.68 (s, 3 H), 3.47 (s, 3 H), 3.24–3.21 (m, 1 H), 3.20 (t, *J* = 1.8 Hz, 1 H), 3.18 (d, *J* = 7.7 Hz, 1 H), 3.08 (s, 3 H), 2.78 (d, *J* = 7.2 Hz, 1 H), 2.76–2.73 (m, 1 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 166.7, 166.6, 160.4, 154.3, 152.2, 149.5, 147.2, 142.3, 138.2, 129.5 (2 C), 129.4 (2 C), 128.3 (2 C), 128.0, 127.7, 127.0 (2 C), 123.1, 121.3, 110.0, 51.9, 51.7, 50.9, 49.2, 47.7, 42.0, 37.8, 37.4, 31.2, 28.7.

HRMS: *m*/*z* calcd for [$C_{32}H_{32}N_2O_6$ + H$^+$]: 541.2333; found: 541.2346.

Dimethyl (2*E*,2′*E*)-3,3′-[(5*R*,7*S*,8*S*,9*S*,10*S*)-7,9-Bis(4-bromophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6,7,8-octahydro-5,8-ethanoquinazoline-6,10-diyl]diacrylate (9b)

Following the general procedure, **9b** was isolated by FC on silica gel as a white semi-solid (>25:1 dr); yield: 40.2 mg (58%); $[\alpha]_D^{25}$ –27.9 (*c* 1.0, $CHCl_3$).

The er was determined by UPC^2 using a Chiralpak IA column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; t_R = 3.50 min (major), t_R = 3.80 min (minor) (97:3 er).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.60–7.57 (m, 2 H), 7.38–7.35 (m, 2 H), 7.20–7.17 (m, 2 H), 7.11 (dd, *J* = 15.8, 6.0 Hz, 1 H), 6.70–6.68 (m, 2 H), 6.66 (dd, *J* = 15.8, 6.8 Hz, 1 H), 5.90–5.86 (m, 2 H), 3.76 (s, 3 H), 3.70–3.69 (m, 1 H), 3.68 (s, 3 H), 3.46 (s, 3 H), 3.14–3.11 (m, 2 H), 3.10 (s, 3 H), 3.06 (dd, *J* = 7.7, 1.5 Hz, 1 H), 2.73 (d, *J* = 7.4 Hz, 1 H), 2.67 (dd, *J* = 7.8, 5.7 Hz, 1 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 166.6, 166.4, 160.2, 153.5, 152.1, 148.8, 146.5, 141.0, 137.1, 132.7 (2 C), 132.6 (2 C), 129.9 (2 C), 128.7 (2 C), 123.4, 122.1, 121.8, 121.7, 110.1, 52.0, 51.8, 50.3, 49.2, 47.3, 41.7, 37.9, 37.3, 31.3, 28.7.

HRMS: *m*/*z* calcd for [$C_{32}H_{30}Br_2N_2O_6$ + H$^+$]: 697.0543; found: 697.0538.

Dimethyl (2*E*,2′*E*)-3,3′-[(5*R*,7*S*,8*S*,9*S*,10*S*)-7,9-Bis(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6,7,8-octahydro-5,8-ethanoquinazoline-6,10-diyl]diacrylate (9c)

Following the general procedure, **9c** was isolated by FC on silica gel as a white semi-solid (>25:1 dr); yield: 32.0 mg (52%); $[\alpha]_D^{25}$ –4.1 (*c* 1.0, $CHCl_3$).

The er was determined by UPC^2 using a Chiralpak IA column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; t_R = 3.21 min (major), t_R = 3.48 min (minor) (>99:1 er).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 2 H), 7.26–7.24 (m, 2 H), 7.22–7.19 (m, 2 H), 7.14–7.10 (m, 1 H), 6.76–6.73 (m, 2 H), 6.66 (dd, *J* = 15.7, 6.8 Hz, 1 H), 5.90–5.87 (m, 2 H), 3.76 (s, 3 H), 3.71–3.69 (m, 1 H), 3.68 (s, 3 H), 3.46 (s, 3 H), 3.15–3.13 (m, 1 H), 3.12 (t, *J* = 1.7 Hz, 1 H), 3.10 (s, 3 H), 3.09–3.07 (m, 1 H), 2.77–2.74 (m, 1 H), 2.69–2.66 (m, 1 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 166.6, 166.4, 160.2, 153.6, 152.1, 148.8, 146.5, 140.5, 136.6, 134.1, 133.8, 129.8 (2 C), 129.6 (2 C), 129.6 (2 C), 128.4 (2 C), 123.4, 121.6, 110.1, 52.0, 51.8, 50.3, 49.3, 47.4, 41.6, 37.9, 37.8, 31.3, 28.7.

HRMS: *m*/*z* calcd for [$C_{32}H_{30}Cl_2N_2O_6$ + H^+]: 609.1554; found: 609.1562.

Dimethyl (2*E*,2′*E*)-3,3′-[(5*R*,7*S*,8*S*,9*S*,10*S*)-1,3-Dimethyl-7,9-bis(4-nitrophenyl)-2,4-dioxo-1,2,3,4,5,6,7,8-octahydro-5,8-ethanoquinazoline-6,10-diyl]diacrylate (9d)

Following the modified general procedure (4 equiv. of 4-nitrocinnamaldehyde, reaction time 48 h, 40 °C), **9d** was isolated by FC on silica gel as a yellow semi-solid (>25:1 dr); yield: 28.2 mg (45%); $[\alpha]_D^{25}$ –23.0 (*c* 1.0, $CHCl_3$).

The er was determined by UPC^2 using a Chiralpak IA column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; t_R = 4.22 min (major), t_R = 4.57 min (minor) (>99:1 er).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 8.38–8.31 (m, 2 H), 8.14–8.10 (m, 2 H), 7.52 (d, *J* = 8.5 Hz, 2 H), 7.12 (dd, *J* = 15.8, 6.0 Hz, 1 H), 7.03–6.97 (m, 2 H), 6.67 (dd, *J* = 15.7, 6.9 Hz, 1 H), 5.94–5.88 (m, 2 H), 3.79–3.78 (m, 1 H), 3.77 (s, 3 H), 3.69 (s, 3 H), 3.48 (s, 3 H), 3.25–3.22 (m, 2 H), 3.17 (dd, *J* = 7.4, 1.7 Hz, 1 H), 3.14 (s, 3 H), 2.95–2.92 (m, 1 H), 2.78–2.74 (m, 1 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 166.3, 166.1, 160.0, 152.5, 151.9, 148.9, 147.8, 147.8, 147.7, 145.5, 145.3, 129.2 (2 C), 128.0 (2 C), 124.8 (2 C), 124.8 (2 C), 124.0, 122.3, 110.3, 52.1, 51.9, 50.7, 49.3, 46.4, 42.4, 38.0, 37.3, 31.4, 28.8.

HRMS: *m*/*z* calcd for [$C_{32}H_{30}N_4O_{10}$ + H^+]: 631.2035; found: 631.2043.

Dimethyl (2*E*,2′*E*)-3,3′-[(5*R*,7*S*,8*S*,9*S*,10*S*)-1,3-Dimethyl-2,4-dioxo-7,9-di(*p*-tolyl)-1,2,3,4,5,6,7,8-octahydro-5,8-ethanoquinazoline-6,10-diyl]diacrylate (9e)

Following the general procedure, **9e** was isolated by FC on silica gel as a white semi-solid (>25:1 dr); yield: 49.1 mg (86%); $[\alpha]_D^{25}$ –22.0 (*c* 1.0, $CHCl_3$).

The er was determined by UPC^2 using a Chiralpak IA column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; t_R = 3.08 min (major), t_R = 3.29 min (minor) (>99:1 er).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.25–7.22 (m, 2 H), 7.21–7.19 (m, 2 H), 7.16 (dd, *J* = 15.8, 5.9 Hz, 1 H), 7.00 (br d, *J* = 7.8 Hz, 2 H), 6.71–6.67 (m, 3 H), 5.90 (dd, *J* = 10.2, 1.6 Hz, 1 H), 5.88 (dd, *J* = 10.1, 1.6 Hz, 1 H), 3.75 (s, 3 H), 3.68–3.67 (m, 1 H), 3.67 (s, 3 H), 3.46 (s, 3 H), 3.19–3.13 (m, 3 H), 3.08 (s, 3 H), 2.74–2.68 (m, 2 H), 2.39 (s, 3 H), 2.26 (s, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 166.8, 166.7, 160.4, 154.5, 152.3, 149.7, 147.4, 139.3, 137.7, 137.4, 135.2, 130.1 (2 C), 129.9 (2 C), 128.2 (2 C), 126.9 (2 C), 123.0, 121.2, 110.0, 51.8, 51.7, 50.5, 49.3, 47.9, 41.6, 37.9, 37.4, 31.2, 28.6, 21.1, 21.0.

HRMS: *m*/*z* calcd for [$C_{34}H_{36}N_2O_6$ + H^+]: 569.2646; found: 569.2654.

Dimethyl (2*E*,2′*E*)-3,3'-[(5*R*,7*S*,8*S*,9*S*,10*S*)-1,3-Dimethyl-2,4-dioxo-7,9-di(*m*-tolyl)-1,2,3,4,5,6,7,8-octahydro-5,8-ethanoquinazoline-6,10-diyl]diacrylate (9f)

Following the general procedure, **9f** was isolated by FC on silica gel as a white semi-solid (>25:1 dr); yield: 47.0 mg (83%); $[\alpha]_D^{25}$ –17.1 (*c* 1.0, $CHCl_3$).

The er was determined by UPC^2 using a Chiralpak IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; t_R = 3.08 min (major), t_R = 3.59 min (minor) (>99:1 er).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 1 H), 7.20–7.16 (m, 2 H), 7.15–7.12 (m, 1 H), 7.11–7.07 (m, 2 H), 7.00 (br d, *J* = 7.5 Hz, 1 H), 6.70 (dd, *J* = 15.7, 6.7 Hz, 1 H), 6.60 (s, 1 H), 6.56 (d, *J* = 7.5 Hz, 1 H), 5.93 (dd, *J* = 15.8, 1.8 Hz, 1 H), 5.89 (dd, *J* = 15.7, 1.4 Hz, 1 H), 3.76 (s, 3 H), 3.70–3.69 (m, 1 H), 3.67 (s, 3 H), 3.47 (s, 3 H), 3.21–3.15 (m, 3 H), 3.09 (s, 3 H), 2.75–2.72 (m, 2 H), 2.40 (s, 3 H), 2.23 (s, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 166.8, 166.6, 160.4, 154.5, 152.2, 149.7, 147.4, 142.3, 139.1, 139.0, 138.2, 129.4, 129.3, 129.2, 128.7, 128.4, 128.1, 125.2, 123.6, 123.0, 121.2, 110.0, 51.9, 51.7, 50.8, 49.1, 47.7, 41.9, 37.9, 37.4, 31.2, 28.7, 21.8, 21.51.

HRMS: *m*/*z* calcd for [$C_{34}H_{36}N_2O_6$ + H^+]: 569.2646; found: 569.2648.

Dimethyl (2*E*,2′*E*)-3,3′-[(5*R*,7*S*,8*S*,9*S*,10*S*)-1,3-Dimethyl-2,4-dioxo-7,9-di(*o*-tolyl)-1,2,3,4,5,6,7,8-octahydro-5,8-ethanoquinazoline-6,10-diyl]diacrylate (9g)

Following the general procedure, **9g** was isolated by FC on silica gel as a white semi-solid (>25:1 dr). 58% (32.8 mg); $[\alpha]_D^{25}$ –40.8 (*c* 1.0, $CHCl_3$).

The er was determined by UPC^2 using a Chiralpak IG column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; t_R = 3.66 min (major), t_R = 3.97 min (minor) (>99:1 er).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.50–7.47 (m, 1 H), 7.38–7.34 (m, 1 H), 7.29–7.24 (m, 3 H), 7.07–7.03 (m, 2 H), 7.03–7.00 (m, 1 H), 6.67 (dd, *J* = 15.7, 6.6 Hz, 1 H), 6.65–6.63 (m, 1 H), 5.92 (dd, *J* = 15.8, 1.8 Hz, 1 H), 5.87 (dd, *J* = 15.7, 1.3 Hz, 1 H), 3.79–3.78 (m, 1 H), 3.78 (s, 3 H), 3.66 (s, 3 H), 3.53 (dd, *J* = 7.9, 1.4 Hz, 1 H), 3.48 (s, 3 H), 3.35 (br t, *J* = 7.2 Hz, 1 H), 2.94–2.92 (m, 1 H), 2.92 (s, 3 H), 2.88–2.84 (m, 1 H), 2.71 (t, *J* = 1.6 Hz, 1 H), 2.29 (s, 3 H), 1.65 (s, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 166.8, 166.6, 160.4, 154.5, 152.2, 149.5, 147.5, 140.0, 136.9, 135.8, 135.5, 132.0, 131.2, 128.0, 127.3, 127.0, 126.8, 126.8, 124.8, 123.0, 121.0, 110.0, 51.9, 51.7, 48.7, 47.7, 45.8, 37.4, 36.9, 36.4, 30.9, 28.7, 20.0, 19.2.

HRMS: *m*/*z* calcd for [$C_{34}H_{36}N_2O_6$ + H^+]: 569.2646; found: 569.2651.

Dimethyl (2*E*,2′*E*)-3,3′-[(5*R*,7*S*,8*S*,9*S*,10*S*)-7,9-Bis(4-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6,7,8-octahydro-5,8-ethanoquinazoline-6,10-diyl]diacrylate (9h)

Following the general procedure, **9h** was isolated by FC on silica gel as a white semi-solid (>25:1 dr); yield: 37.2 mg (62%); $[\alpha]_D^{25}$ –24.2 (*c* 1.0, $CHCl_3$).

The er was determined by UPC^2 using a Chiralpak IA column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; t_R = 3.26 min (major), t_R = 3.45 min (minor) (99:1 er).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.24–7.22 (m, 2 H), 7.16 (dd, *J* = 15.8, 5.9 Hz, 1 H), 6.99–6.94 (m, 2 H), 6.75–6.71 (m, 4 H), 6.69 (dd, *J* = 16.0, 7.1 Hz, 1 H), 5.92–5.86 (m, 2 H), 3.85 (s, 3 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.68–3.67 (m, 1 H), 3.67 (s, 3 H), 3.46 (s, 3 H), 3.15–3.10 (m, 3 H), 3.09 (s, 3 H), 2.72–2.70 (m, 1 H), 2.70–2.67 (m, 1 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 166.8, 166.7, 160.4, 159.2, 159.0, 154.5, 152.3, 149.6, 147.4, 134.3, 130.1, 129.4 (2 C), 128.1 (2 C), 123.0, 121.2, 114.8 (2 C), 114.7 (2 C), 109.9, 55.5, 55.4, 51.9, 51.7, 50.2, 49.4, 48.2, 41.1, 38.1, 37.3, 31.3, 28.7.

HRMS: *m*/*z* calcd for [$C_{34}H_{36}N_2O_8$ + H^+]: 601.2544; found: 601.2546.

Dimethyl (2*E*,2′*E*)-3,3′-[(5*R*,7*S*,8*S*,9*S*,10*S*)-7,9-bis(2-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6,7,8-octahydro-5,8-ethanoquinazoline-6,10-diyl]diacrylate (9i)

Following the general procedure, **9i** was isolated by FC on silica gel as a white semi-solid (>25:1 dr); yield: 31.3 mg (52%); $[\alpha]_D^{25}$ –62.0 (*c* 1.0, $CHCl_3$).

The er was determined by UPC^2 using a Chiralpak IG column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; t_R = 4.20 min (major), t_R = 4.86 min (minor) (99:1 er).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.44–7.41 (m, 1 H), 7.36–7.33 (m, 1 H), 7.19 (dd, *J* = 15.8, 5.6 Hz, 1 H), 7.14–7.08 (m, 2 H), 6.97–6.94 (m, 1 H), 6.77 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.71–6.69 (m, 1 H), 6.69–6.65 (m, 2 H), 5.94 (dd, *J* = 15.8, 1.8 Hz, 1 H), 5.87 (dd, *J* = 15.7, 1.4 Hz, 1 H), 3.81 (s, 3 H), 3.76 (s, 3 H), 3.71–3.69 (m, 1 H), 3.65 (s, 3 H), 3.58 (d, *J* = 8.5 Hz, 1 H), 3.45 (s, 3 H), 3.37 (s, 3 H), 3.26 (t, *J* = 7.3 Hz, 1 H), 3.14 (t, *J* = 1.6 Hz, 1 H), 3.12–3.09 (m, 1 H), 3.07 (s, 3 H), 2.77–2.74 (m, 1 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 167.0, 166.9, 160.6, 157.9, 156.8, 155.9, 152.4, 150.0, 148.2, 130.2, 128.6, 128.3, 127.4, 126.5, 125.8, 122.6, 121.0, 120.9, 120.7, 110.9, 110.8, 109.3, 55.5, 55.1, 51.8, 51.6, 47.3, 44.9, 44.5, 37.4, 35.4, 34.2, 30.8, 28.5.

HRMS: *m*/*z* calcd for [$C_{34}H_{36}N_2O_8$ + H^+]: 601.2544; found: 601.2550.

Dimethyl (2*E*,2′*E*)-3,3′-[(5*R*,7*S*,8*S*,9*S*,10*R*)-7,9-Di(furan-2-yl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6,7,8-octahydro-5,8-ethanoquinazoline-6,10-diyl]diacrylate (9j)

Following the general procedure, **9j** was isolated by FC on silica gel as a white semi-solid (>25:1 dr); yield: 38.0 mg (73%); $[\alpha]_D^{25}$ –13.9 (*c* 1.0, $CHCl_3$).

The er was determined by UPC^2 using a Chiralpak IA column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; t_R = 2.81 min (major), t_R = 2.92 min (minor) (99:1 er).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 1.5 Hz, 1 H), 7.26–7.23 (m, 1 H) 7.10 (dd, *J* = 15.7, 6.6 Hz, 1 H), 6.68 (dd, *J* = 15.7, 6.8 Hz, 1 H), 6.41 (dd, *J* = 3.2, 1.9 Hz, 1 H), 6.29 (d, *J* = 3.3 Hz, 1 H), 6.23 (dd, *J* = 3.2, 1.9 Hz, 1 H), 5.95 (dd, *J* = 5.3, 1.5 Hz, 1 H), 5.93 (dd, *J* = 5.3, 1.5 Hz, 1 H), 5.89 (d, *J* = 3.3 Hz, 1 H), 3.76 (s, 3 H), 3.70 (t, *J* = 2.2 Hz, 1 H), 3.69 (s, 3 H), 3.60–3.58 (m, 1 H), 3.41 (s, 3 H), 3.30–3.27 (m, 1 H), 3.26 (s, 3 H), 3.05–3.01 (m, 1 H), 2.82–2.79 (m, 1 H), 2.59–2.56 (m, 1 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 166.7, 166.6, 160.4, 154.8, 153.3, 152.4, 152.2, 148.6, 146.8, 143.1, 142.3, 123.4, 121.6, 110.8, 110.7, 109.7, 108.2, 106.3, 51.9, 51.7, 46.9, 43.8, 41.8, 38.0, 36.7, 36.3, 31.2, 28.6.

HRMS: *m*/*z* for [$C_{28}H_{28}N_2O_8$ + H^+]: 521.1918; found: 521.1932.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707313.

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