ACCESSING CHIRAL DIHYDRO- AND TETRAHYDROQUINAZOLINE-2,4-DIONES *VIA* [4+2]-CYCLOADDITIONS: FROM PIONEERING STUDIES TO ASYMMETRIC ORGANOCATALYZED SYNTHESES

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Abstract. *Quinazoline-2,4-diones represent a prominent class of 5,6-fused-uracil derivatives which have attracted appreciable attention in the field of medicinal chemistry owing to their peculiar structure and multifaceted pharmacological profile. Within this heterocyclic class, the subdomain of chiral functionalized dihydro- and tetrahydroquinazoline derivatives, embedding in-cycle stereogenic elements, has emerged as an intriguing, yet underestimated, class of compounds, whose challenging structure and potential usefulness as drug-like pharmacophores has stimulated the development of versatile and efficient strategies toward their synthesis. After notable pioneering studies dating back to early 1980s, accessing these compounds in racemic format, substantial stagnation of innovative enantioselective synthesis procedures to access these ring systems occurred, thus precluding their exploitation in medicinal chemistry programmes. Quite recently, the implementation of asymmetric, organocatalytic strategies towards these products, and based on stepwise [4+2]-cycloadditions has renewed the interest toward this fascinating class of chiral compounds, possibly paving the way to the study of their biological activities in the years to come. This account highlights strategies to the chemical synthesis of chiral dihydro- and tetrahydroquinazoline-2,4-dione ring systems in both racemic and enantioenriched formats via [4+2]-cyclization between elusive uracil-based ortho-quinodimethane dienes and suitable dienophile components.*

Contents

1. Introduction

Nitrogen-containing heterocycles represent the largest class of heterocyclic compounds found in natural products and pharmaceuticals, and possess considerable therapeutic potential.[1] From a chemist perspective, their structure has often triggered the development of numerous synthetic methods, thus placing them among the protagonists in chemical sciences.[2] Among *N*-heterocycles, the pyrimidine-2,4(1*H*,3*H*)-dione scaffold **1**, better known as uracil (Figure 1a), is a key structure in life chemistry, being one of the five primary nucleobases making up the RNA/DNA-based genetic code and the structural core of a wide variety of other natural products.[3] The uracil core **1** is also a notable pharmacophore in medicinal chemistry, since it is present in many commercial drugs and bioactive molecules (Figure 2a). Antiviral and antitumor are the two most represented activities exerted by uracil analogues; however, herbicidal, insecticidal, and bactericidal activities have also been demonstrated for these compounds.[4]

Therefore, it is not surprising that the search for novel uracil derivatives has been carried out since the beginning of the last century, and even today there is great interest in the development of novel synthetic strategies to access such derivatives with increasing structural complexity and promising biological activities.

From a structural point of view, uracil is a flat molecule, featuring two main tautomeric forms, the poorly aromatic amide tautomer **1**, also called the “lactam tautomer”, and the imidic acid tautomer **1a** called the

"lactim tautomer" with a more pronounced aromatic character.[5] Both tautomeric forms exist at neutral pH, with the lactam structure being the most stable, predominant form (Figure 1a). The aromaticity of uracil is still a debated matter among chemists, and several computational studies seem to demonstrate its aromatic behavior: indeed, the zwitterionic resonance structure **1b** (Figure 1a) shows an increased π-electron delocalization within the ring, imparting some degree of aromaticity to the uracil core.[5]

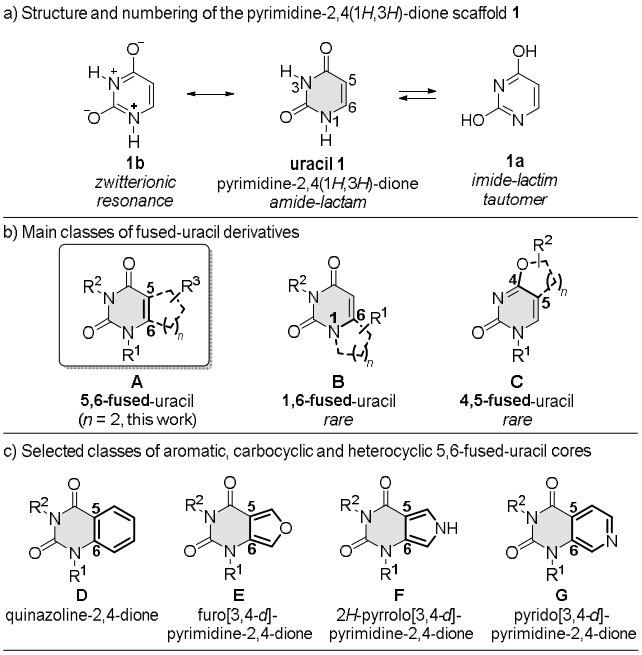


Figure 1. a) Structure and numbering of the pyrimidine-2,4(1*H*,3*H*)-dione core **1**. b) Main classes of fused-uracil derivatives. c) Selected examples of carbocycle- and heterocycle-5,6-fused-uracil scaffolds.

Chemical modifications of the uracil ring often maintain the pyrimidindione core, which is enriched with flexible aromatic/aliphatic chains and/or sugar moieties at the N1, N3, C5, and C6 atoms; it can also be fused with flanking carbo- and heterocycles, which generally are flattened and Csp^2-rich rings. The resultant fused carbo- or hetero(poly)cyclic systems, also known as "fused-uracil" derivatives, constitute an important sub-class of heterocycles, possessing a wide variety of attractive pharmacological effects, spanning from antiviral, antiallergic, antihypertensive, to anti-tumor activities (Figure 2b).[6]

In particular, according to the bond involved in the "fusion" with the pyrimidine core, 5,6-, 1,6-, and 4,5-fused-uracil derivatives **A**, **B**, and **C** can be distinguished (Figure 1b); among them, only rare examples of uracil analogues of type **B** and **C** have been reported so far,[7] while 5,6-fused systems of type **A**, featuring an aromatic carbo- or heterocycle fused to the 5,6-bond of the uracil ring, have been the focus of much more targeted syntheses, as demonstrated by the numerous drug-related molecules of pharmaceutical interest in which they appear as core structures.[6] Probing examples include quinazoline-2,4-diones **D**,[8] furo[3,4-*d*]uracils **E**,[9] 2*H*-pyrrolo[3,4-*d*]uracils **F**,[10] and pyrido[3,4-*d*]uracils[11] **G**, among others (Figure 1c).

Also, an issue of primary importance when dealing with bioactive, drug-like heterocyclic scaffolds, concerns their stereochemistry.[12] Indeed, several natural and non-natural uracil and fused-uracil derivatives are chiral, enantiopure molecules, embedding one or more stereogenic elements (*e.g.* stereogenic carbon atoms or chiral axes) mainly "out-of-cycle" and within the appendages bound at either nitrogen N1 or N3.

Figure 2 shows emblematic examples of chiral drugs or advanced drug candidates featuring such structural motifs; for instance, elagolix,[13] a uracil-based drug recently approved to manage endometriosis-induced pain, possesses a stereocenter within the phenylethyl chain attached at N3, while

sorivudine,[14] an antiviral drug behaving as nucleoside analogue, brings a chiral sugar moiety at N1 (Figure 2a). Interestingly, quinazoline-2,4-dione derivative PD 0305970,[15] a Pfizer's antibacterial drug candidate, carries the chiral information in the pyrrolidine substituent appended at the fused phenyl ring, while a synthetic precursor of the Amgen's anti-cancer agent sotorasib possesses a Csp^2–N1 chiral axis (Figure 2b).[16]

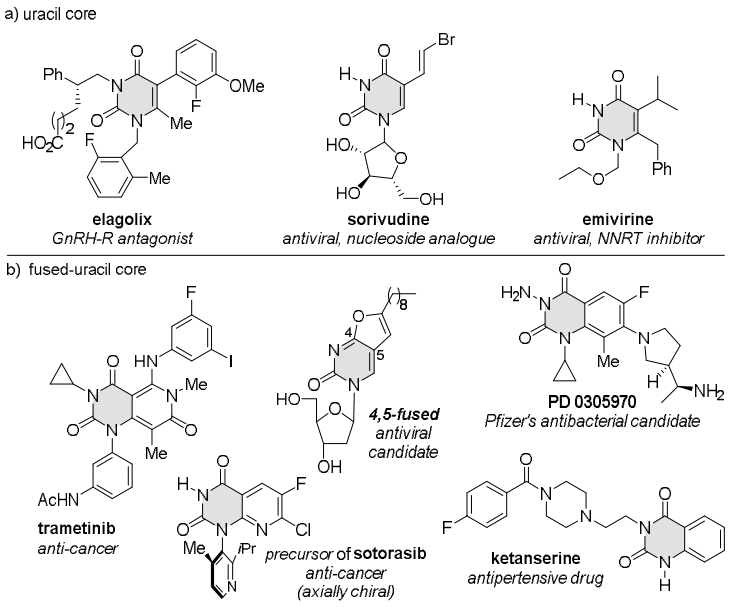
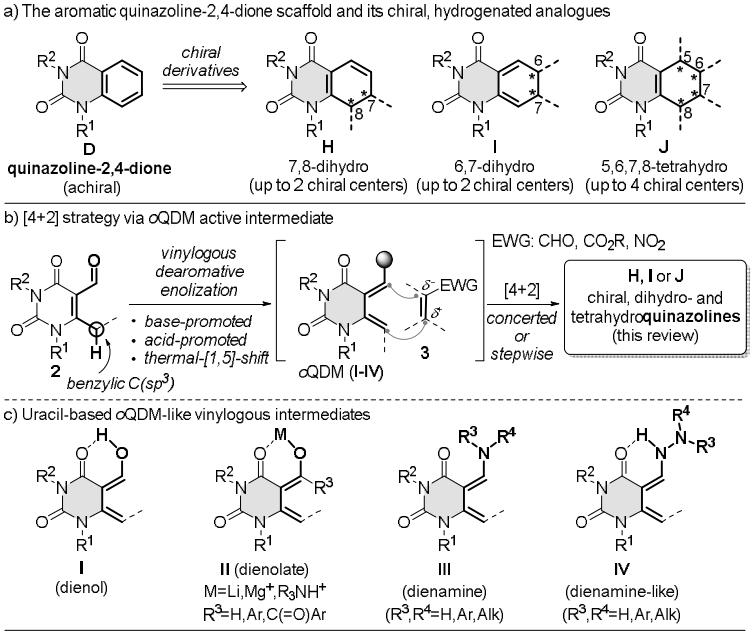


Figure 2. a) Selected examples of drugs or advanced drug candidates embedding a uracil core and b) a fused-uracil core.

Circumscribing better 5,6-fused-uracils, and specifically considering 5,6-carbocycle-fused derivatives, quinazoline-2,4-diones of type **D** (Figure 1c and Scheme 1a), featuring the pyrimidine-2,4-dione core fused with an aromatic 6-membered carbocyclic arene, occupy a preeminent position, given the wide array of pharmacological properties they exhibit, spanning from anticancer, diuretic, anti-inflammatory, to anticonvulsant and antihypertensive activities.[8] The majority of these drug-like molecules maintain the flat, full Csp^2 architecture of the parent pharmacophore **D**, while the corresponding 7,8-dihydro-, 6,7-dihydro- and 5,6,7,8-tetrahydro forms **H**, **I**, and **J** (Scheme 1a) are much less frequent products, even though partial or total carbocycle saturation may in principle lead to the creation of up to four contiguous stereocenters, with the evident attracting opportunity to deviate from full ring planarity and introduce *in-cycle* stereogenic centers. Such challenging structures have drawn attention of organic chemists for over 40 years (*vide infra*), though the lack of versatile and suitable asymmetric procedures to access these systems has hampered the development of these pharmacophores until a few years ago. The very recent exploitation of asymmetric organocatalytic strategies to construct ring systems of type **H**, **I**, and **J** has allowed the "re-discovery" of this fascinating class of compounds, with the interesting perspective to interrogate them for biological activities in the years to come.

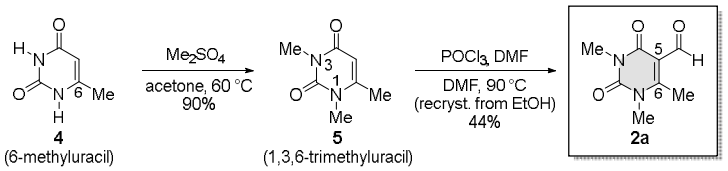
From a synthetic perspective, a clever strategy to forge the chiral backbone of hydrogenated quinazoline-2,4-dione derivatives **H-J** envisaged the construction of the carbocyclic unit through either concerted or stepwise [4+2]-cycloaddition[17] between 1,3-disubstituted 6-methyluracil carbaldehydes of type **2** and suitable electron-poor dienophiles **3** (Scheme 1b). Of note, the reactivity of the benzylic Csp^3 site of carbaldehyde **2** is influenced by the π-extended carbonyl system according to the vinylogy principle, thus possibly engaging in remote functionalization upon vinylogous enolization to a diene intermediate and entrapment with dienophile substrates.[18] However, vinylogous enolization here is quite challenging, since it involves the unfavourable loss

of the aromatic character of the starting heterocyclic ring, affording highly reactive, elusive intermediates **I-IV** which feature a temporarily dearomatized *ortho*-quinodimethane (*o*QDM) framework (Scheme 1c). Such vinylogous, dearomative enolization can be accessed by different strategies, according to the way the π-system within **2** is activated. Dienol **I** and metal/ammonium dienolates **II** can be obtained directly from aldehydes **2** by either thermal bond rearrangement, or acid-/base-promoted enolization of the carbonyl system, while dienamine-type *o*QDMs **III** and **IV** require a preliminary transformation of the formyl carbonyl to imine, hydrazone, or iminium ion moieties, prior to enolization.



Scheme 1. a) Structure and numbering of chiral, hydrogenated quinazoline-2,4-dione derivatives. b) [4+2]-Cycloaddition of uracil carbaldehyde **2** and suitable electron-poor dienophiles **3**. c) Uracil-based *o*QDM-like intermediates **I-IV**.

In this context, 1,3,6-trimethyluracil-5-carbaldehyde **2a** (Scheme 2) represents the first and probably the most exploited uracil pronucleophile of type **2**, its first synthesis and use dating back to 1971.[19] As described in Scheme 2, **2a** was easily accessed from the parent 6-methyluracil **4** *via* a two-step sequence involving a first, almost quantitative methylation at both nitrogen atoms, furnishing trimethyluracil **5**, followed by a thermal Vilsmeier-Haack formylation at C5. After recrystallization from ethanol, **2a** could be isolated in a useful 44% yield (40% overall yield).



Scheme 2. Synthesis of 1,3,6-trimethyluracil pronucleophile **2a** from 6-methyluracil **4**.

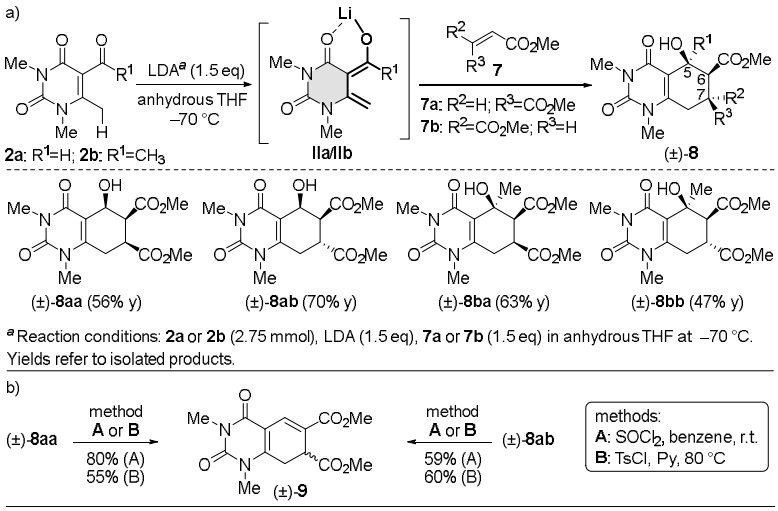
This account highlights the different strategies, pursued in the past 40 years, to access differently functionalized chiral dihydro- and tetrahydroquinazoline-2,4-dione scaffolds of type **H-J** *via*

[4+2]-cycloadditions between substituted uracil carbaldehydes of type **2** and suitable dienophiles **3** (Scheme 1b). Considering the nature of the [4+2]-annulation involved in the reported syntheses, this account has been divided in two major chapters namely: *i.* non-asymmetric methodologies leading to racemic derivatives and, *ii.* catalytic, enantioselective [4+2]-cycloadditions leading to chiral, enantioenriched targets. A special focus will be devoted to the peculiar mechanisms involved in the generation of the active, *o*QDM diene intermediates from **2**, whose nature (*e.g.* dienol **I**, dienolate **II**, dienamines **III** and **IV**) characterizes the corresponding paragraphs within each chapter.[20]

2. Synthesis of chiral racemic dihydro- and tetrahydroquinazoline-2,4-diones *via* [4+2]-cycloadditions

2.1. [4+2]-Cycloadditions involving metal *o*QDM dienolates

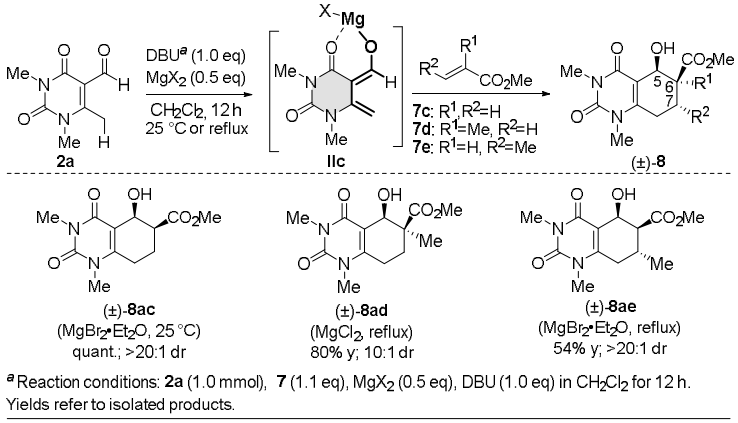
The first, pioneering work on the synthesis of chiral, 5,6,7,8-tetrahydroquinazoline derivatives of type **J** (Scheme 1a) *via* based-promoted [4+2]-cycloaddition was reported by Senda and co-workers in 1980 (Scheme 3).[21] Treatment of 1,3,6-trimethyluracil-5-carbaldehyde **2a** or the corresponding methyl ketone **2b** with LDA (1.5 eq) in THF at −70 °C, followed by the addition of a slight excess of an electron-poor dienophile such as dimethylmaleate **7a** or dimethylfumarate **7b**, resulted in the formation of the corresponding tetrahydroquinazoline-2,4-diones of type (±)-**8** embedding three contiguous stereocenters, in good yields (47-70%) and complete diastereoselectivities. The reaction was proposed to proceed *via* a base-promoted vinylogous, dearomative enolization of diene **2** enabling formation of the corresponding lithium *Z*-dienolate **IIa** or **IIb** featuring a stabilizing, intramolecular interaction between the lithium ion and the C4 carbonyl. The following *endo*-Diels-Alder reaction of **II** with **7a** or **7b** gave the corresponding racemic cycloadducts (±)-**8** as single diastereoisomers (Scheme 3a). The relative configuration of **8aa** and **8ab** was assigned as 5,6-*cis*/6,7-*cis* and 5,6-*cis*/6,7-*trans*, respectively, by ^{1}H-NMR analyses and observing that treatment of **8aa** and **8ab** with either thionyl chloride in benzene at room temperature or *p*-toluenesulfonyl chloride in pyridine at 80 °C, gave the same 7,8-dihydroquinazoline (±)-**9** in good yields (Scheme 3b).



Scheme 3. Senda's first synthesis of chiral quinazolines (±)-**8** from 1,3,6-trimethyluracil aldehyde **2a** or ketone **2b**, *via* lithium dienolates **IIa** and **IIb**.

A similar procedure was implemented a decade later, in 1992, by the group of Noguchi,[22] with the aim of improving and expanding the scope and reactivity of metal *o*QDMs **II** in [4+2]-cycloadditions with dienophiles bearing only one electron-withdrawing substituent (Scheme 4). To avoid the strong basic environment resulting from the use of LDA, a short survey was performed, by screening different metal salts coupled with DBU to favor the "soft vinylogous enolization" of **2a** and generate the corresponding metal *o*QDMs of type **II**. Among the different systems tested, magnesium salts gave the best results; indeed,

treatment of **2a** and methylacrilate **7c**, 2-methylacrilate **7d**, or *E*-methylcrotonate **7e** with sub-stoichiometric $MgBr_2 \cdot OEt_2$ or $MgCl_2$ (0.5 eq) and DBU (1.0 eq) (in CH_2Cl_2 for 12 h) yielded the corresponding chiral fused-uracil derivatives (±)-**8ac**-**8ae** in moderate-to-high isolated yields (54% to >99%) and high diastereoselectivities (up to >20:1 dr) in favor of the 5,6-*cis* configured isomers (6,7-*trans* for **8ae**).



Scheme 4. Noguchi's synthesis of chiral, tetrahydroquinazoline derivatives (±)-**8ac-8ae** from **2a** *via* the corresponding magnesium dienolate *o*QDM **IIc**.

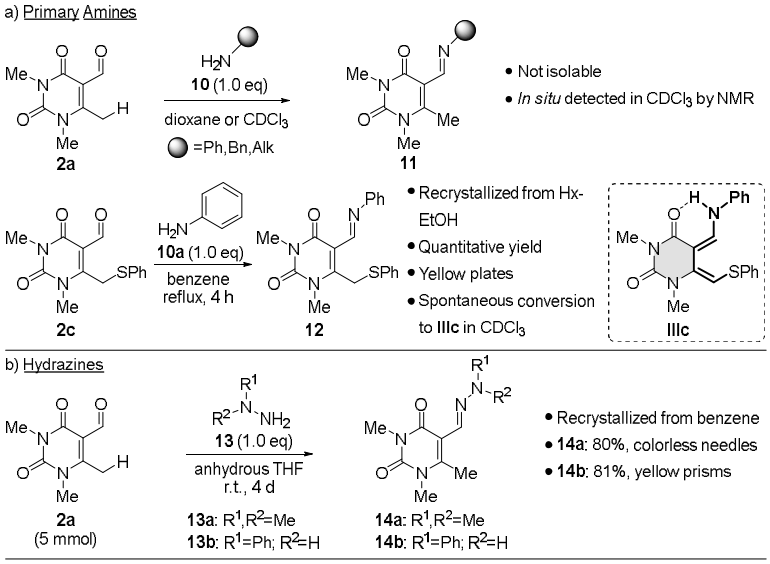
2.2. [4+2]-Cycloadditions involving *o*QDM dienamines

Starting from 6-methyluracil carbaldehyde **2a**, the use of suitable primary (or secondary) amines or hydrazines is particularly attractive for the generation of active dienamine-like *o*QDMs of type **III** and **IV** to be employed as useful diene partners in [4+2]-cyclizations (Scheme 1c). By interacting with the carbonyl moiety of **2a**, the amine would enable formation of the resulting imine (iminium ion or hydrazone) intermediate with subsequent generation of the corresponding dienamine species **III** *via* either base-catalyzed, dearomative, vinylogous enolization or, alternatively, *via* thermal [1,5]-hydrogen shift of the benzylic Csp^3–H to the imine Nsp^2 (*vide infra*). The issue of generating imine congeners from uracil carbaldehyde **2a**, though attracting, turned out to be quite challenging, as testified by great efforts by the Noguchi's group along this direction.

Preliminary investigations on the reaction of **2a** with primary amines in some refluxing solvents, under dehydrating conditions, resulted quite disappointing, as no imine products could be isolated.[23] Fortunately, it was later found that, with a series of primary aryl- and alkylamines of type **10** in either dioxane or $CDCl_3$ at room temperature, the corresponding aldimines **11** could actually be generated *in situ*, though they were too unstable to be isolated (Scheme 5a). Interestingly, a stable, crystalline aldimine **12** was later isolated by reacting 6-(phenylthiomethyl)uracil carbaldehyde **2c** with aniline **10a** in benzene at reflux.[24] It was observed that in $CDCl_3$, aldimine **12** spontaneously isomerized to the corresponding dienamine *o*QDM **IIIc**, as demonstrated by ^{1}H-NMR analysis of the reaction mixture. Other important findings by Noguchi and co-workers concern the preparation and reactivity of uracil-based hydrazone derivatives **14** (Scheme 5b).[23] Thus, it was found that the reaction of *N*,*N*-dimethylhydrazine **13a** or phenylhydrazine **13b** with **2a** in anhydrous THF, at room temperature, yielded the corresponding crystalline hydrazones **14a** and **14b** in good yields (80% and 81% yields of isolated products, respectively). These imine or hydrazone intermediates proved to be viable substrates as active diene partners in a series of racemic [4+2]-cycloadditions, as shown below.

The first example on the use of primary amines as promoters of [4+2]-cycloaddition reactions does not concern the synthesis of quinazolin-2,4-dione derivatives, but rather that of chiral, heterocyclic 5,6-fused uracil scaffolds **15** (Table 1). Although these targets are beyond the focus of this account, they represent the first reported example of a [4+2]-cyclization involving an *in situ*-generated uracil-based aldimine scaffold and a dienophile in an unexpected hetero-Diels-Alder transformation. Indeed, in 1988 Noguchi and co-workers, in

their efforts to isolate the above mentioned uracil aldimines **11** from 1,3,6-trimethyluracil-5-carbaldehyde **2a** (Scheme 5a), serendipitously found that an equimolar mixture of **2a** and benzylamine **10b** in anhydrous THF, kept for 5 days at room temperature, upon standing afforded the dimeric fused-uracil (±)-**15ab** as a yellow crystalline product (74% isolated yield), which featured a 6,7-dihydropyrido[3,4-*d*]pyrimidine core containing a stereocenter at C6 (Table 1, entry 1).[23] Similarly, other primary amines such as aniline **10a**, butylamine **10c**, allylamine **10d**, 3-aminomethylpyridine **10e**, ethyl glycinate **10f**, and glycinonitrile **10g**, all proved feasible substrates, giving the corresponding cycloadducts in high isolated yields (56-96%, Table 1, entries 2-7) and complete regioselectivity.



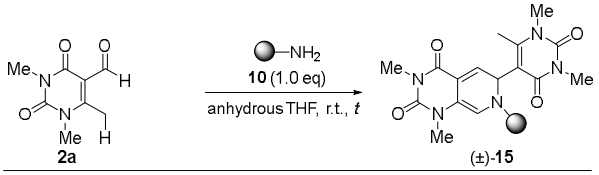
Scheme 5. Accessing uracil-based aldimine and hydrazone pronucleophiles **11**, **12**, and **14**.

For this reaction, the authors proposed the mechanistic pathway illustrated in Scheme 6. Initially, thermal [1,5]-hydrogen shift within **2a** generates dienol *o*QDM intermediate **Ia**, probably favoured by the formation of an intramolecular hydrogen bond between enol OH and the carbonyl oxygen at C4. At the same time, aldimine **11** is formed by addition of the primary amine to the formyl carbonyl of a second molecule of **2a**. Hence, the key [4+2]-hetero-Diels-Alder (HDA) occurs between diene **Ia** and aldimine **11** behaving as a dienophile, affording the non-isolable 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine-2,4-dione intermediate (±)-**16**. Then, conversion to the isolated product (±)-**15** is enabled by vinylogous dehydration involving the benzylic Csp^3–H proton at C8, and the alcohol functionality at C5. Of note, the structure of products **15** poses two interesting issues: *i*. they represent a rare example of "stable" *o*QDM backbone, and *ii*. the regiochemistry of the key [4+2]-hetero-Diels-Alder cycloaddition between **2a** and **11** is certainly not obvious, as it implies connection of the *ipso* carbon of **Ia** to the electron poor imine carbonyl of **11**, as well as coupling of the electron-rich *γ*-carbon of the dienol to the imine Nsp^2 (Scheme 6). Whereas the authors acknowledged the different regiochemical outcome as compared to similar [4+2]-cycloadditions involving *o*QDM intermediates, they failed to give any definitive explanation, asserting that the process was controlled by the electron-donating properties of the hydroxyl group of the dienol *o*QDM species.

Later in 1990, the same group accomplished the synthesis of chiral, hydrogenated quinazoline-2,4-dione scaffolds embedding up to four contiguous stereocenters, by developing a Diels-Alder-like [4+2]-cycloaddition between dienamine *o*QDM intermediates of type **III**, derived from condensation of 1,3,6-trimethyluracil-5-carbaldehyde **2a** with several primary amines **10**, and maleimide **17** as the dienophile (Scheme 7).[24] As a model reaction, **2a** was allowed to react with aniline **10a** and *N*-methylmaleimide **17** in a one-pot, three-component modality, in dioxane at room temperature. After 6 h, the *endo*-cycloadduct (±)-**18aa**

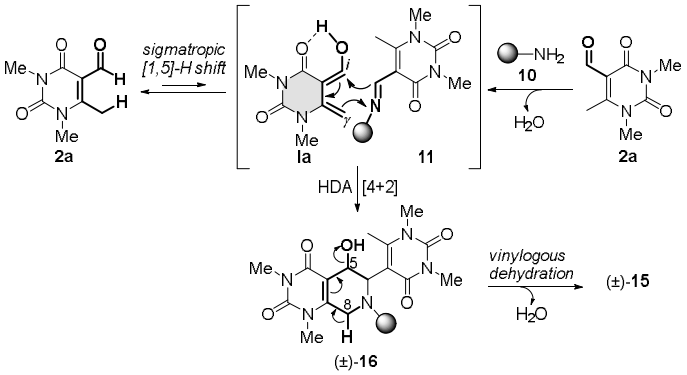
could be isolated in a 90% yield as a single isomer. Other primary amines such as benzylamine **10b**, ethyl glycinate **10f**, and cyclohexylamine **10h**, proved to be viable substrates with **2a**, yielding the corresponding adducts (±)-**18** in high isolated yields (73% to 98%) as single isomers. A similar behavior was observed using 6-morpholinomethyl-substituted carbaldehyde **2d**, whose reaction with aniline **10a** under the same conditions afforded the corresponding *endo*-product (±)-**18da** featuring four contiguous stereocenters in 90% yield. Finally, under a modified protocol (two-step conditions in refluxing benzene for 4 h), preformed 6-(phenylthiomethyl)-substituted imine **12** also reacted with **17** to furnish the corresponding adduct (±)-**18ca** as a sole isomer in a 68% isolated yield. Interestingly, both (±)-**18da** and (±)-**18ca** possess the same 5,6-*cis*-7,8-*trans* relative configuration, meaning that all these [4+2]-cycloadditions involving dienamine **III** proceeded with high *endo*-selectivity.

Table 1. Noguchi's one-step hetero-Diels-Alder cycloaddition.



Entry[a]	—NH2	t (d)	Product	Yield (%)
1	$PhCH_2$-NH_2 (**10b**)	5	(±)-**15ab**	74
2	Ph-NH_2 (**10a**)	7	(±)-**15aa**	74
3	*n*-Bu-NH_2 (**10c**)	5	(±)-**15ac**	96
4	Allyl-NH_2 (**10d**)	5	(±)-**15ad**	78
5	Py-CH_2-NH_2 (**10e**)	5	(±)-**15ae**	81
6	EtO_2C-CH_2-NH_2 (**10f**)	5	(±)-**15af**	95
7	CN-CH_2-NH_2 (**10g**)	7	(±)-**15ag**	56

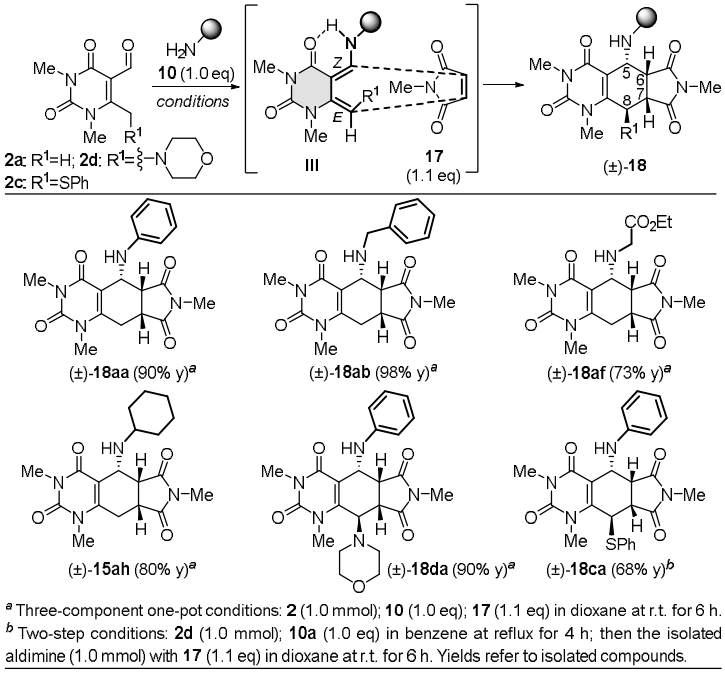
[a] Reaction conditions: **2a** (3.0 mmol); **10** (1.0 eq) in anhydrous THF at r.t. for the indicated time. Yields refer to isolated products.



Scheme 6. Proposed mechanism for the HDA reaction between **2a** and *in situ* generated aldimine **11**.

This pioneering work was indeed anticipated in 1989 by the same group, who reported the unprecedented diastereoselective [4+2]-cycloaddition between preformed uracil-based dimethylaminohydrazone **14a** (or the

6-morpholinomethyl congener **14c**) and *N*-methylmaleimide **17**, to afford highly adorned chiral derivatives (±)-**19a** or (±)-**19c** in high isolated yields (95%, 76% yields, respectively, Scheme 8a).[25] Of note, both targets were obtained as single isomers, implying a highly diastereoselective reaction pathway that the authors described as a two-step sequence. First, a thermal [1,5]-hydrogen shift within the hydrazone π-system of **14a** or **14c** afforded the corresponding dienamine *o*QDM intermediates **IVa/IVc**, featuring a favorable intramolecular hydrogen bond between the hydrazine N–H and the uracil C–4 carbonyl. Then, a diastereoselective [4+2]-cycloaddition occurs with electron-poor dienophile **17**, affording the tricyclic fused-uracil derivatives (±)-**19a** and (±)-**19c** in 95% and 76% isolated yields, respectively. The exclusive formation of tricycle (±)-**19c** as a single isomer, possessing four adjacent stereocenters with a 5,6-*cis*-7,8-*trans* relative configuration, calls for the selective enolization of hydrazone **14c** which generates the corresponding dienamine *o*QDM intermediates **IVc** with a defined *Z,E*-configuration of the double bonds. Also, the efficient deamination of (±)-**19a** by treatment with HCl in ethanol afforded the corresponding dihydroquinazoline congener (±)-**20a** (92% yield), which could also be dehydrogenated with Pd/C in refluxing dioxane to furnish the corresponding hexahydropyrrolo[3,4-*g*]quinazoline **21** in a good 85% yield (Scheme 8b).

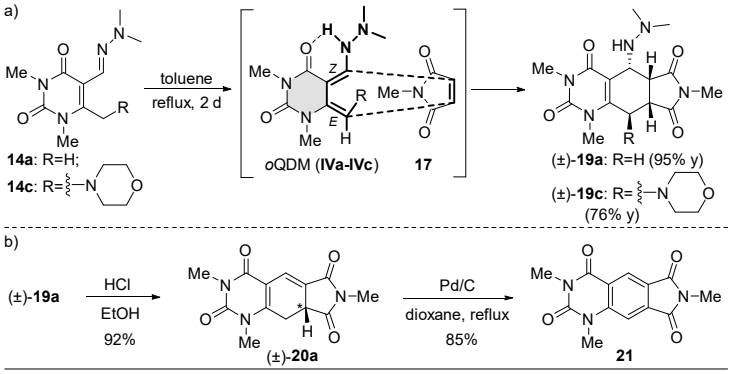


[a] Three-component one-pot conditions: **2** (1.0 mmol); **10** (1.0 eq); **17** (1.1 eq) in dioxane at r.t. for 6 h.
[b] Two-step conditions: **2d** (1.0 mmol); **10a** (1.0 eq) in benzene at reflux for 4 h; then the isolated aldimine (1.0 mmol) with **17** (1.1 eq) in dioxane at r.t. for 6 h. Yields refer to isolated compounds.

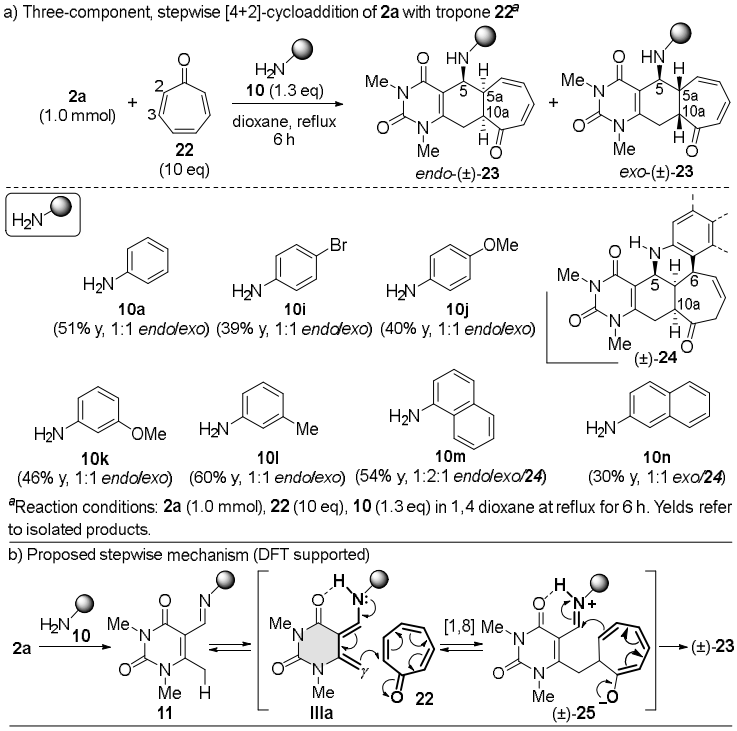
Scheme 7. Noguchi's direct [4+2]-cycloadditions involving *in situ*-formed uracil-based imines.

The scope of such transformation was later expanded by the same group in 1995, reporting a regioselective, three-component [4+2]-cycloaddition between **2a** and 7-membered tropone **22** in the presence of a series of primary aromatic amines **10a-10i-n** (Scheme 9a).[26] Under thermal control in dioxane at reflux and regardless of the nature of the aryl substituents within the amine component, an almost equimolar mixture of *endo*- and *exo*-cycloadducts (±)-**23** featuring a chiral, cyclohepta[*g*]quinazoline core were obtained in generally moderate yields (30-60% combined yields), and outstanding regioselectivity on the 2,3-double bond of tropone dienophile **22**. With the aid of semi-empirical DFT calculations, a stepwise process was suggested, as depicted in Scheme 9b. Here, the *in situ* condensation of primary amine **10** with the formyl moiety of **2a** generates the corresponding imine **11**, which isomerizes to the *o*QDM diene **III** by thermal [1,5]-hydrogen shift. This dienamine intermediate selectively adds to the C2 of **22** *via* a vinylogous 1,8-Michael-type reaction to generate betaine intermediate **25,** which then undergoes an intramolecular, bis-vinylogous Mannich-type

ring closure to afford products **23**. Of note, with 1- and 2-naphthylamines **10m** and **10n**, a third, pentacyclic product (±)-**24** was also obtained, derived from the intramolecular 1,6-conjugate addition of the naphthyl aromatic moiety to the *δ*-position (C6 within **24**) of the seven-membered ketone.



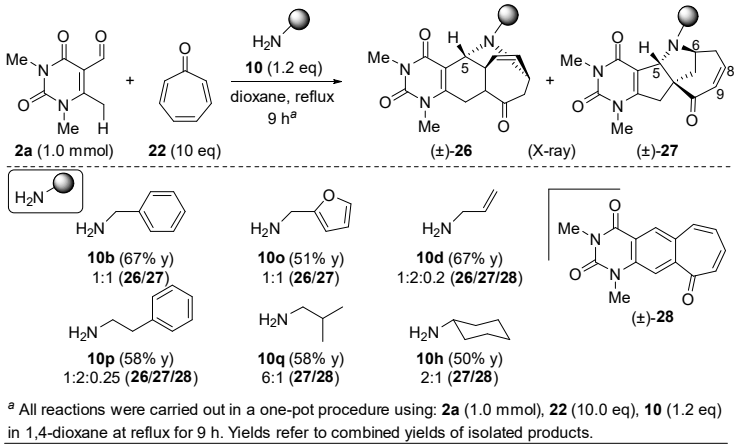
Scheme 8. Noguchi's [4+2]-cycloadditions involving preformed, uracil-based hydrazones **14a** and **14c** with *N*-methylmaleimide **17**.



Scheme 9. Primary amine-promoted stepwise, three-component [4+2]-cycloadditions between **2a** and tropone **22**.

When alkylamines were used in place of aromatic amines, the reaction of **2a** with tropone **22** behaved differently (Scheme 10).[27] In fact, in the presence of benzylamine **10b** in 1,4-dioxane under reflux, the

[4+2]-cycloaddition of **2a** with **22** failed to give the expected *endo*- and *exo*-quinazolines (±)-**23** as final products, which instead reacted giving two novel isomeric products namely, the 2,5-ethanopyrido[2,3-*f*]quinazoline (±)-**26** and the 6,10a-methanopyrimido-[4',5':4,5]cyclopenta[1,2-*b*]azocine (±)-**27** in 34% and 33% isolated yield, respectively (Scheme 10). Other primary alkylamines, including 2-furylmethylamine **10o**, allylamine **10d**, and phenylethylamine **10p**, performed similarly in terms of yield and selectivity, while isobutylamine **10q** and cyclohexylamine **10h** produced the azocine derivative (±)-**27** predominantly (58% and 50% yields respectively), along with a small amount of the achiral, quinazoline derivative (±)-**28**, which was also detected in minor amounts in the reactions performed with **10d** and **10p**.



[a] All reactions were carried out in a one-pot procedure using: **2a** (1.0 mmol), **22** (10.0 eq), **10** (1.2 eq) in 1,4-dioxane at reflux for 9 h. Yields refer to combined yields of isolated products.

Scheme 10. Noguchi's [4+2]-cycloadditions of **2a** and tropone **22**, promoted by primary aliphatic amines.

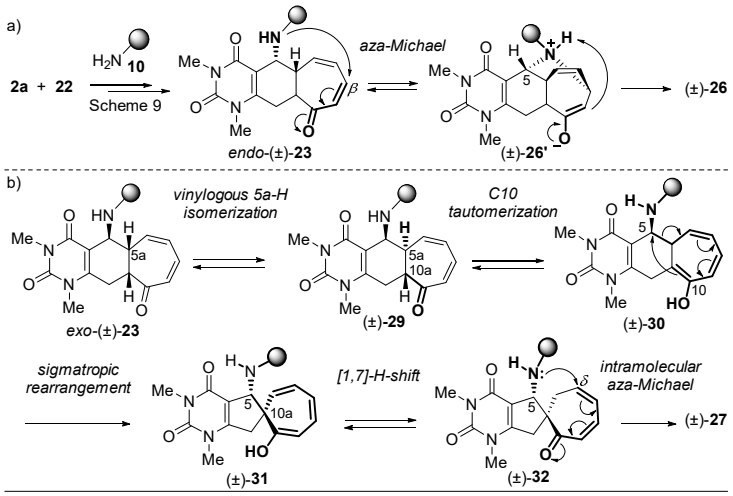
Theoretical DFT calculations corroborated a plausible stepwise mechanism, as described in Scheme 11; this includes a first [4+2]-cycloaddition reaction of **2a** with **22**, promoted by the primary alkylamine, as described in Scheme 9b, which affords mixtures of the expected *endo* and *exo* cycloadducts (±)-**23** featuring a secondary alkylamino group at the stereogenic C5. Then, *endo*-(±)-**23** overreacts *via* an intramolecular *aza*-Michael reaction operated by the alkylamino group which attacks the *β*-position of the seven-membered unsaturated ketone leading to product (±)-**26** (Scheme 11a). On the other hand, *exo*-(±)-**23** was envisaged to be the most likely precursor of azocine (±)-**27**; as described in Scheme 11b, compound **23** undergoes a first vinylogous isomerization at C5a enabling the formation of 5a,10a-*trans*-fused derivative (±)-**29**, that readily tautomerizes to the corresponding enol (±)-**30**. This enol undergoes a 1,7-sigmatropic rearrangement, to afford the spiro system (±)-**31** which then isomerizes to spirocycle (±)-**32** bearing a seven-membered *α,β,γ,δ*-unsaturated ketone system. Finally, an intramolecular aza-Michael reaction operated by the alkylamino group to the *δ*-position of the seven-membered unsaturated ketone affords azocine (±)-**27**.

A similar, three-component approach was proposed by Noguchi and co-workers, focusing on the regioselective [4+2]-cycloaddition of **2a** with the seven-membered 8,8-dicyanoheptafulvene **33**, promoted by several primary, aromatic amines of type **10** (Scheme 12).[28] After 6 h at reflux in 1,4-dioxane, the reaction yielded the corresponding tetrahydrocyclohepta[*g*]quinazoline derivatives (±)-**34** in moderate isolated yields (45-56%), and with high diastereoselectivity (from 8:1 to >10:1) in favor of the *exo*-(5,5a-*trans*,5a,10a-*cis*)-configured stereoisomer.

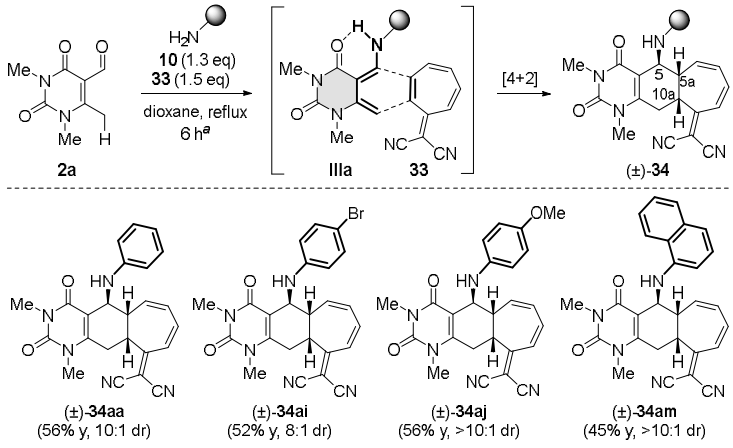
3. Catalytic enantioselective synthesis of chiral dihydro- and tetrahydroquinazoline-2,4-diones

The above described processes represent early examples of [4+2]-cycloadditions where the activation of the *π*-system of a uracil-based aldehyde pro-diene is enabled by the use of stoichiometric amounts of either strong bases or primary amines (or hydrazines), leading to the formation of highly reactive dienolate or dienamine *o*QDM systems. These elusive and highly reactive intermediates are intercepted by suitable

electron-poor dienophiles, to forge 5,6-fused uracil derivatives with high diastereoselectivities, yet in racemic format. These remarkable pioneering works, however, suffer from several major drawbacks: *i.* the non-asymmetric nature of the reactions, which afforded racemic products; *ii.* the modest efficiency and low applicability to diversely functionalized substrates, and *iii.* the lack of catalytic activation modalities. Quite surprisingly, only in recent years the implementation of asymmetric, organocatalytic strategies has enabled access to chiral, enantiopure dihydro- and tetrahydro-quinazoline-2,4-diones with high efficiency and stereocontrol. These novel advancements have rekindled the interest toward this fascinating class of chiral heterocyclic compounds, opening the way to further studies in this field.



Scheme 11. DFT-supported mechanism of the [4+2]-cycloadditions of **2a** and tropone **22**, promoted by primary aliphatic amines.



[a]All reactions were carried out using: **2a** (1.0 mmol), **33** (1.5 eq), and **10** (1.3 eq) in 1,4-dioxane at reflux for 6 h. Yields refer to combined yields of isolated products; dr refers to the ratio of compound **34** with its C5-epimer (not shown).

Scheme 12. Scope of the [4+2]-cycloaddition of **2a** with 8,8-dicyanoheptafulvene **33**, promoted by a series of aromatic amines.

Today, organocatalysis is one of the most thriving research domains in contemporary organic synthesis, and a series of catalytic activation modalities has been discovered[29] (*e.g.* covalent and noncovalent activation modalities), which rendered previously undisclosed chemical transformations possible.[30]

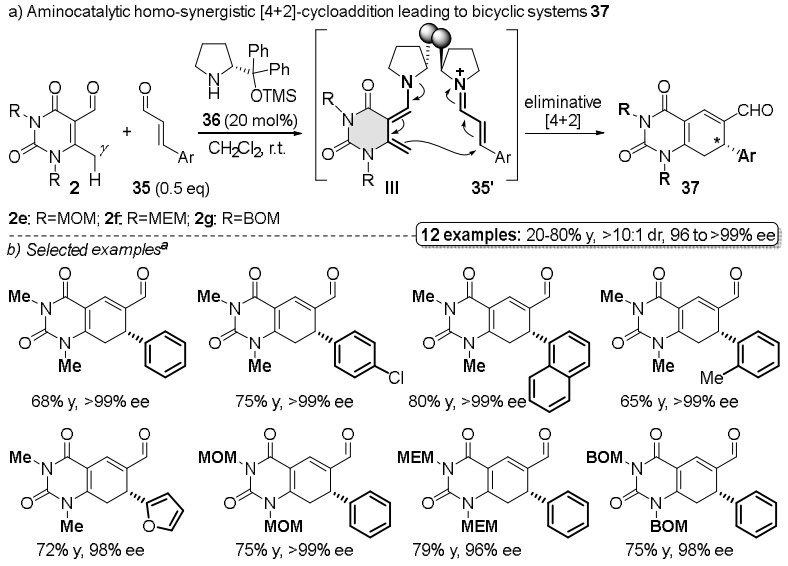
In this context, over the past decade, the strategic partnership between vinylogy and asymmetric organocatalysis has gained momentum in directing the desymmetrization of "flat" (hetero)aromatic cycles into unprecedented, chiral and enantioenriched chemotypes.[18] In the following sections, the discovery of recent organocatalytic asymmetric procedures is described, which led to the creation of novel chiral, enantioenriched quinazoline-2,4-dione targets featuring *in-cycle* stereogenic units.

3.1. Aminocatalytic strategies

Among the organocatalytic strategies developed so far to generate chiral, *o*QDM intermediates from suitable uracil-based pro-dienes of type **2**, those catalyzed by a chiral, secondary amine (aminocatalysis) is one of the most pursued.[31] Indeed, by interacting with the carbonyl moiety of **2**, the catalytic amine gives an iminium ion intermediate, which may then be converted to the corresponding chiral dienamine *o*QDM *via* a dearomative, vinylogous enolization.[18] Such intermediates represent chiral versions of the aforementioned dienes of type **III** (Schemes 7-12), thus promoting [4+2]-cyclization processes in an enantioselective format. It is worth noting that, in the previously described report of 1988,[23] Noguchi asserted that the reaction of 1,3,6-trimethyluracil-5-carbaldehyde **2a** with achiral secondary amines such as diethylamine or piperidine afforded a product, whose nature though, remained uncertain. In that pioneering work, Noguchi skimmed over the issue of the covalent activation, thus of carbonyl compounds by secondary amines, anticipating by more than a decade the activation strategy that would later become the basis of asymmetric, covalent aminocatalysis.

The first example of asymmetric synthesis of enantiopure 5,6-fused-uracil derivates was reported by Zanardi and co-workers in 2020,[32] implementing a divergent aminocatalytic [4+2]-cross-cycloaddition between remotely enolizable 6-methyluracil-5-carbaldehydes **2** and *β*-aryl enals **35** (Schemes 13 and 14).

Using the Hayashi prolinol **36** as the catalyst of choice, two novel bicyclic and tricyclic fused-uracil derivatives, **37** and **38**, were chemoselectively accessed in generally good yields, and a high level of enantiocontrol (Scheme 13).

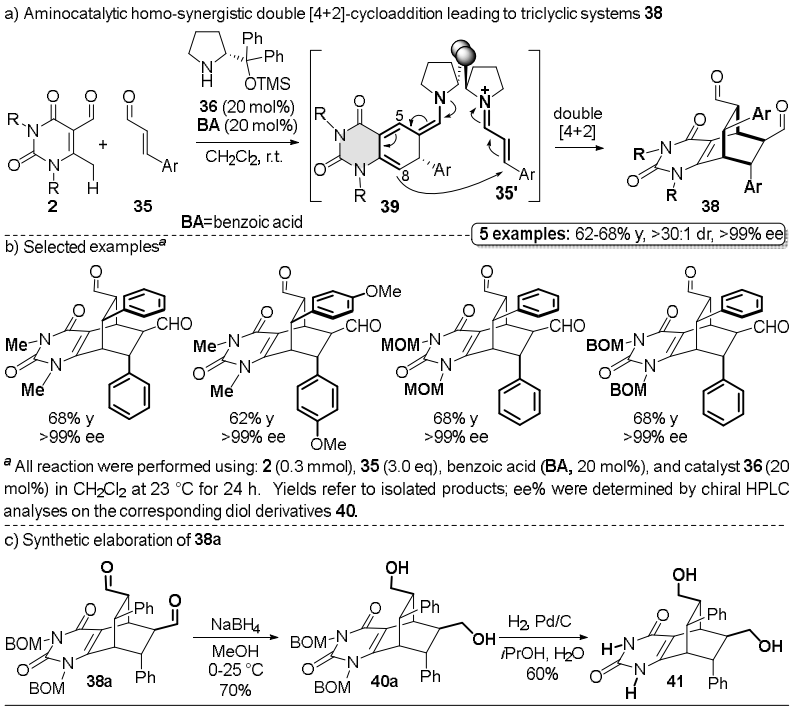


[a] All reactions were carried out using: **2** (0.4 mmol), **35** (0.5 eq), **36** (20 mol%) in CH_2Cl_2, and 23 °C for 24 h. Yields refer to isolated products. Enantiomeric excesses (ee%) were determined by chiral HPLC.

Scheme 13. Zanardi's aminocatalytic, eliminative [4+2]-cycloaddition leading to chiral, enantiopure 7,8-dihydroquinazoline derivates **37**.

In particular, the reaction of 1,3,6-trimethyluracil-5-carbaldehyde **2a** with a series of aromatic *α,β*-unsaturated aldehydes **35** catalyzed by prolinol **36** (20 mol%), in CH_2Cl_2 at room temperature for 24 h, afforded the corresponding 7,8-dihydroquinazoline-2,4-diones **37** in generally good yields (up to 80%) and very high enantioselectivities (up to >99% ee). Furthermore, novel pro-dienes of type **2**, differently substituted at the N1 and N3 atoms with methoxymethyl- (MOM, **2e**), methoxyethoxymethyl- (MEM, **2f**), and benzyloxymethyl- (BOM, **2g**) appendages, respectively, proved also viable substrates, affording the corresponding cycloadducts **37ea**, **37fa**, and **37ga** in comparable yields and stereoselectivities (Scheme 13).[32]

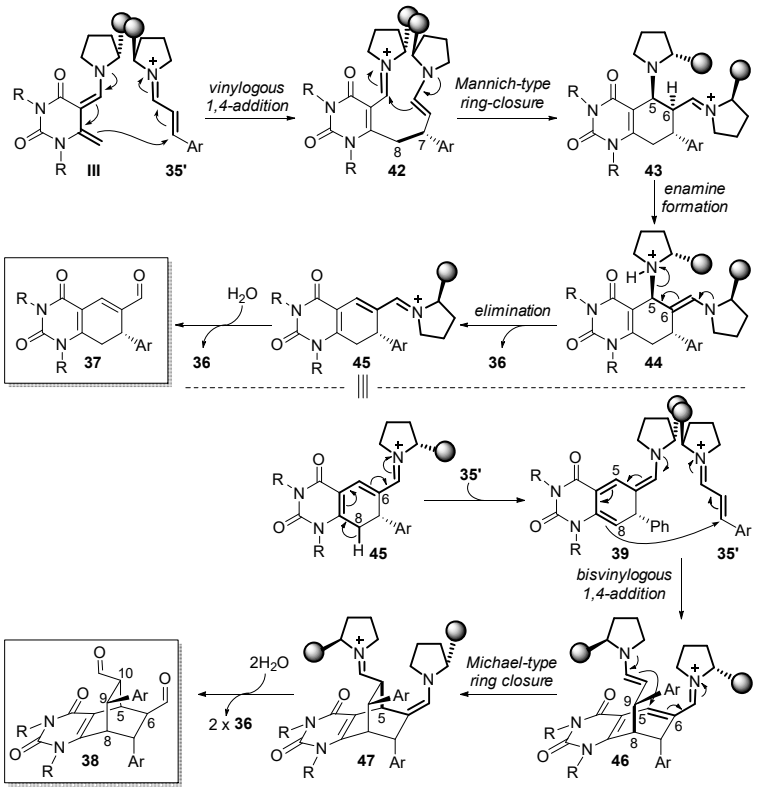
Interestingly, working with excess enal **35** (3.0 equiv) in the presence of benzoic acid **BA** (20 mol%) as the co-catalyst together with prolinol **36**, the reaction performed double [4+2]-annulation, producing chiral, enantiopure tricyclic dienals **38** (Scheme 14), featuring a bicyclo[2.2.2]octane scaffold fused with the uracil ring. Tricycles **38** were obtained in good, isolated yields (62-68%) and complete diastereoselectivities (>30:1 dr), along with minor amounts of the parent bicycles (6:1 **38**/**37**). To expand the molecular diversity of the accessed targets, further chemical elaborations were implemented, including the reduction of both aldehyde carbonyl groups within **38** into the corresponding bis-alcohols **40** (*e.g.* **38ga**, Scheme 14c), and the reductive removal of BOM groups within the uracil ring to afford the corresponding 1,3-unsubstituted tricycle analogue **41** with a good 60% isolated yield.[32]



Scheme 14. Aminocatalytic, homo-synergistic, double [4+2]-cycloaddition catalyzed by Hayashi's prolinol **36**, leading to chiral, enantiopure tricyclic derivates **38**.

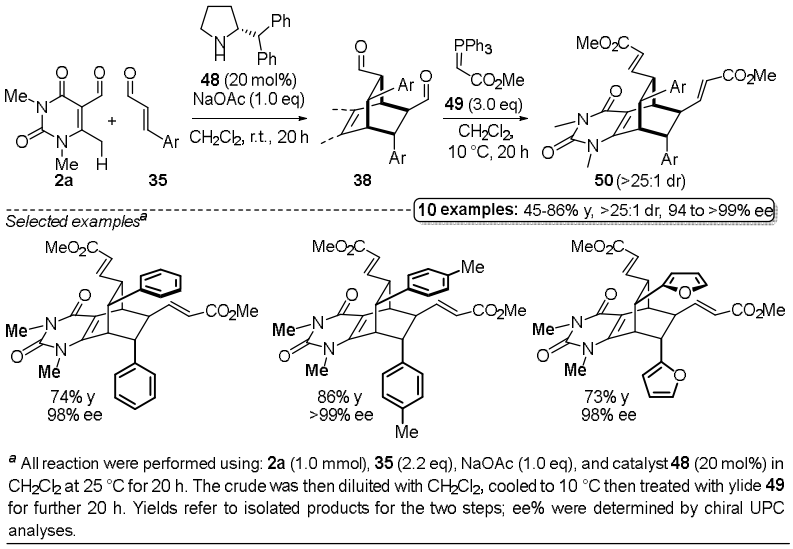
In-depth DFT calculations and control experiments corroborated a dual, homo-synergistic approach, where both the aldehyde partners **2** and **35** were concomitantly activated by the amine catalyst into the corresponding dienamine *o*QDM **III** and iminium ion species **35'**, respectively (Scheme 15). Indeed, according to computational analysis, bicycles **37** were forged via a stepwise, eliminative [4+2]-cycloaddition involving three key steps: *i.* a doubly stereoinduced, vinylogous Michael-type *γ*-addition of chiral dienamine **III** to the *β*-carbon of iminium ion **35'**, to afford non-isolable product **42** and securing the C7–C8 bond of the product embedding the stereocenter at C7; *ii.* a rate-determining, intramolecular Mannich-type addition to generate the

tetrahydroquinazolin-2,4-dione iminium ion intermediate **43**, entrapping one molecule of the catalyst at C5 as a tertiary amine; and finally, *iii.* a conjugate elimination of the catalyst, leading to the formation of the corresponding bicyclic compound **45**. This *α,β*-unsaturated iminium ion represents a point of divergence of the entire process: in fact, in the absence of any acidic co-catalyst, product **37** is formed by simple hydrolysis of the iminium ion functionality with concomitant regeneration of the catalyst. Alternatively, intermediate **45** can isomerize to trienamine **39** *via* C8–H deprotonation, triggering a two-step sequence which involves a first, stereoselective, bis-vinylogous Michael addition to the *β*-carbon of iminium ion **35'** securing the C8–C9 within adduct **46**, followed by a rate-determining, Michael-type ring closure, affording the tricyclic iminium/enamine intermediate **47**, direct precursor of **38**. Of note, this second [4+2]-cycloaddition generates four new stereogenic centers with complete absolute stereocontrol.



Scheme 15. DFT supported mechanism for the aminocatalytic, homo-synergistic eliminative [4+2]-cycloaddition between **2** and **35**, leading to either bicyclic derivatives **37** or bicyclo[2.2.2]octane compounds **38**.

In the same period, a similar double [4+2]-cycloaddition was reported by Albrecht and co-workers (Scheme 16).[33] In this instance, 2-diphenylmethylpyrrolidine catalyst **48** in the presence of a basic additive (sodium acetate) was used to promote the double [4+2]-cycloaddition between methyl-substituted uracil **2a** and a series of aromatic enals **35**, affording the corresponding tricyclic products **38** which were *in situ* converted to the corresponding *α,β*-unsaturated esters **50** *via* Wittig olefination with ylide **49**. The overall process performed well, affording products **50** in good overall yields (45-86%), and almost complete diastereo- and enantioselectivities (>25:1 dr; 94% to >99% ee). Also in this case, the authors postulated a stepwise mechanism similar to the one previously described in Scheme 15.



[a] All reaction were performed using: **2a** (1.0 mmol), **35** (2.2 eq), NaOAc (1.0 eq), and catalyst **48** (20 mol%) in CH_2Cl_2 at 25 °C for 20 h. The crude was then diluited with CH_2Cl_2, cooled to 10 °C then treated with ylide **49** for further 20 h. Yields refer to isolated products for the two steps; ee% were determined by chiral UPC analyses.

Scheme 16. Albrecht's aminocatalytic, asymmetric entry to tricyclic fused-uracil **50** *via* double [4+2]-cycloaddition of **2a** with aromatic enals **35**, catalyzed by prolinol **48** in a basic environment.

Another recent enantioselective entry to complex 5,6-fused-uracil architectures was devised by the group of Jørgensen in 2021, based on a covalent aminocatalytic strategy. The synthesis was part of an extensive experimental and computational survey aimed at developing an enantioselective access to *trans*-Diels-Alder products bearing the bicycle[4.1.0]heptane (Norcarane) scaffold (Scheme 11).[34] Among the variegated set of polycycles reported, chiral enantiopure fused-uracil **54** appeared as a single entry.

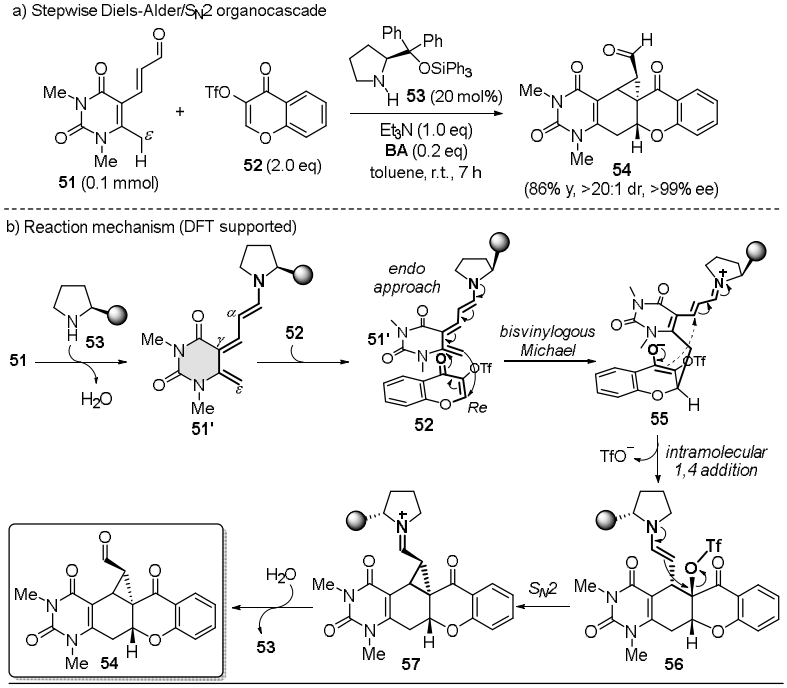
Interestingly, this target was obtained by starting from 6-methyluracil carbaldehyde **51**, which features an extended ε-enolizable dienal moiety; it was readily prepared from 1,3,6-trimethyluracil carbaldehyde **2a** *via* Wittig olefination (not shown). Under the optimized reaction conditions shown in Scheme 17a, **51** reacted with 3-OTf-4*H*-chromen-4-one **52** in the presence of catalytic amounts of bulky diarylprolinol silyl ether **53** (20 mol%), triethylamine and catalytic benzoic acid (20 mol%) as an additive, to afford the enantiopure ring system **54** in a 86% isolated yield as a sole isomer (>20:1 dr, >99% ee). A stepwise mechanism was envisaged for this transformation, which was corroborated by robust DFT calculations, as reported in Scheme 17b. In this case, the covalent activation of dienal **51** with chiral prolinol **53** generated a vinylogous trienamine *o*QDM **51'** which derives from the Cε-H vinylogous dearomative enolization of the parent iminium ion precursor. Chiral trienamine **51'** thus performed a formal [4+2]-Diels-Alder cycloaddition with dienophile **52**, *via* sequential bis-vinylogous Michael addition on the *β*-carbon of **52** to afford adduct **55**, followed by an intramolecular Michael-type ring closure that generates tetracycle **56**. Compound **56** features a 5,6-*trans*-6,7-*cis*-disposed pattern, which proved essential to enable the subsequent S_N2 displacement. The corresponding fused bicycle[4.1.0]heptane **57** was thus obtained, which finally consigned the targeted tetracycle **54** upon iminium ion hydrolysis and catalyst release.

3.2. NHC-catalyzed [4+2]-transformations

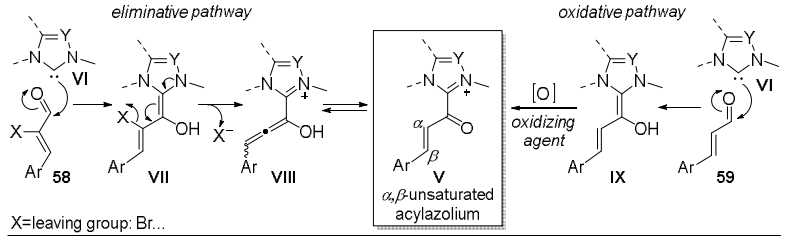
In the past two decades, enantioselective organocatalytic strategies based on the covalent activation of carbonyl moieties by chiral *N*-Heterocyclic Carbenes (NHC) organocatalysts have found enormous success, and many procedures and synthetic applications have been implemented to forge highly complex chiral molecules.[35] In this context, *α,β*-unsaturated acylazonium derivatives **V** have been widely investigated (Scheme 18), due to their ability in promoting useful stereoselective transformations, in particular behaving as electron-poor dienophiles in a plethora of stereoselective cycloaddition processes.[36] Indeed, these useful Michael acceptors, featuring an "*azolium*" auxiliary bonded to an *α,β*-unsaturated carbonyl system, are forged

in situ by the reaction of suitable enals such as **58** or **59** with the active NHC catalyst **VI**, readily available *via* base-catalyzed deprotonation of the parent pre-catalyst.

Two main pathways are known to generate unsaturated acylazolium electrophiles **V**, namely *i.* the "*eliminative pathway*" on *α*-halo-enals **58**, and *ii.* the most common "*oxidative pathway*" which foresees the use of an oxidizing agent. In the first path, the interaction of NHC **VI** with the carbonyl group of *α*-halo-enal **58** generates the known Breslow intermediate **VII**, which is transformed *via* conjugate elimination of the leaving group to a key allene intermediate **VIII**, that finally tautomerizes to the stable acylazolium carbonyl **V**. The absence of a suitable leaving group within enal **58**, as in *α,β*-unsaturated aldehydes **59**, makes the eliminative path quite unfeasible; in this instance, acylazolium **V** can be accessed directly by oxidation of the corresponding Breslow intermediate **IX** by suitable oxidizing agents. Very recently, the chemistry of *α,β*-unsaturated acylazonium derivatives has been exploited to access enantiopure 7,8-dihydroquinazoline-2,4-dione scaffolds.

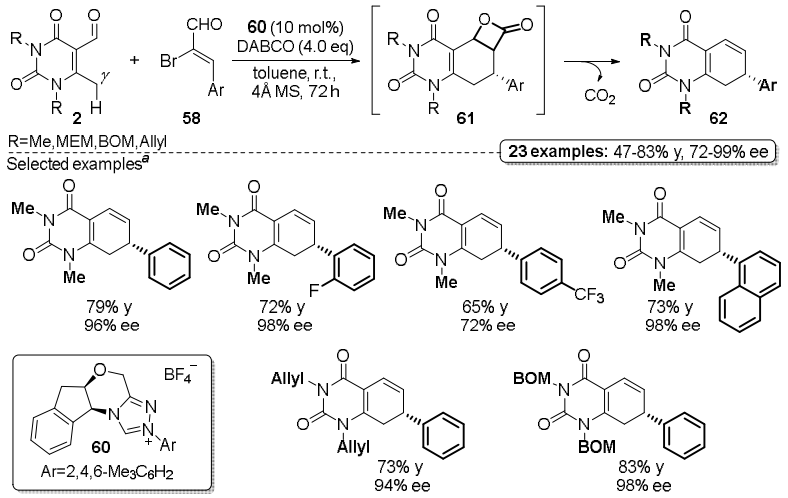


Scheme 17. Jørgensen's asymmetric, formal Diels-Alder/S_N2 organocascade, exploiting extended uracil **51** and 4*H*-chromen-4-one **52**.



Scheme 18. Common pathways to access *α,β*-unsaturated acylazolium electrophiles **V** starting from aromatic enals **58** and **59**.

Thus, as reported in Scheme 19, in 2022 Zhu, Du and co-workers reported the development of a stepwise, enantioselective [4+2]-cycloaddition reaction between 6-methyluracil-5-carbaldehydes **2** and a large set (23 examples) of aromatic 2-bromoenals **58** catalyzed by the chiral NHC from triazolium precursor **60**.[37] Under optimized reaction conditions, treatment of **2** with bromoenal acceptor **58** (2.5 equiv), excess DABCO and pre-catalyst **60** (10 mol%) in toluene at room temperature for 24 h, afforded the corresponding 7,8-dihydroquinazoline derivatives **62** in modest-to-good isolated yields (47-83%), and high enantioselectivities (72-99% ee). The reaction proved viable, irrespective of the nature and position of substituents, with two notable exceptions: the reaction with 3-(4-trifluoromethylphenyl)-2-bromoenal afforded the corresponding cycloadduct in a good yield (65%) but with a significant drop in the enantioselection (72% ee), while aliphatic bromoenals proved completely unreactive under the optimized reaction conditions (not shown).



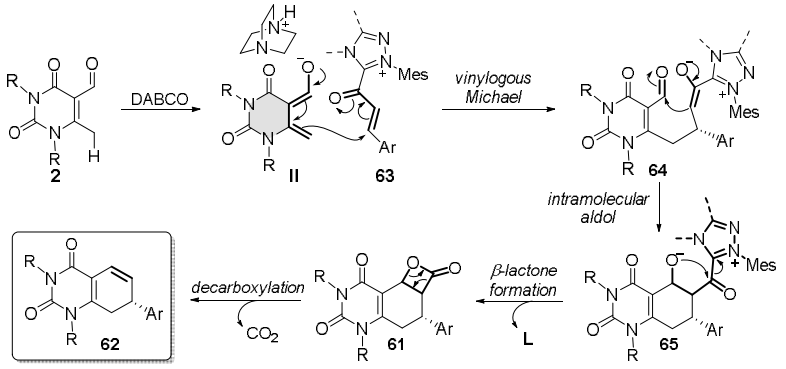
[a] All reactions were carried out using: **2** (0.1 mmol), **58** (2.5 eq), **60** (10 mol%), DABCO (4.0 eq) in toluene, at 23 °C for 24 h. Yields refer to isolated products; ee% were determined by chiral HPLC.

Scheme 19. Zhu's approach for the NHC-catalyzed formal [4+2]-cycloaddition between 6-methyluracil pronucleophiles **2** and 2-bromoenals **58**.

A likely catalytic cycle was proposed for this transformation, as depicted in Scheme 20. Thus, the reaction of the active form of the NHC catalyst (generated from precatalyst **60** by DABCO deprotonation) with 2-bromoenal **58** leads to the formation of the key *α,β*-unsaturated acylazonium intermediate **63**, which subsequently undergoes a stereoselective, vinylogous Michael-type addition by the ammonium dienolate *o*QDM **II**, in turn generated by base-catalyzed vinylogous dearomative enolization of the parent uracil **2**. Intermediate **64** is formed, embedding the newly created C7–C8 bond of the final product. Then, the reaction proceeds through an intramolecular aldol addition, followed by nucleophilic acyl substitution, where the carbinol oxyanion within **65** ousts the NHC catalyst, producing the *β*-lactone intermediate **61**, which finally provides the quinazoline product **64** *via* decarboxylation.

A similar approach was devised in same period by Biju and co-workers, who reported the formal [4+2]-benzannulation reaction between 1,3-disubstituted 6-methyluracils **2**, bearing an aryl ketone moiety at C5, and *α,β*-unsaturated acylazolium acceptors, in turn obtained from a series of aromatic enals of type **65** by oxidative NHC catalysis (Scheme 21a).[38] Upon activation of achiral NHC pre-catalyst **66** by DBU, the reaction of aryl ketones **2** with aromatic enals **65**, in the presence of bis-quinone **68** as the oxidant, provided a panel of achiral, structurally diversified scaffolds **70** in moderate-to-good isolated yields (35-83% yields, Scheme 21b). Interestingly, when the reaction was promoted by the chiral NHC catalyst derived from **67** (by treatment with Cs_2CO_3), the [4+2]-cycloaddition between an *ortho*-bromo-substituted ketone congener of **2** (R=Me,

Ar^1=2-BrC_6H_4) and a small panel of substituted cinnamaldehydes gave the corresponding enantioenriched, axially chiral products **70** in moderate isolated yields (50-52%) and with modest enantiocontrol (40-42% ees, Scheme 21c). Despite the poor enantioselectivity of the latter process, this represents the first example of an atroposelective [4+2]-cycloaddition reaction involving uracil-centered pronucleophiles; in this instance, a pathway similar to that shown in Scheme 20 is envisaged, featuring a point-to-axial chirality transfer during the decarboxylation of the key lactone intermediate **69** (Scheme 21a).



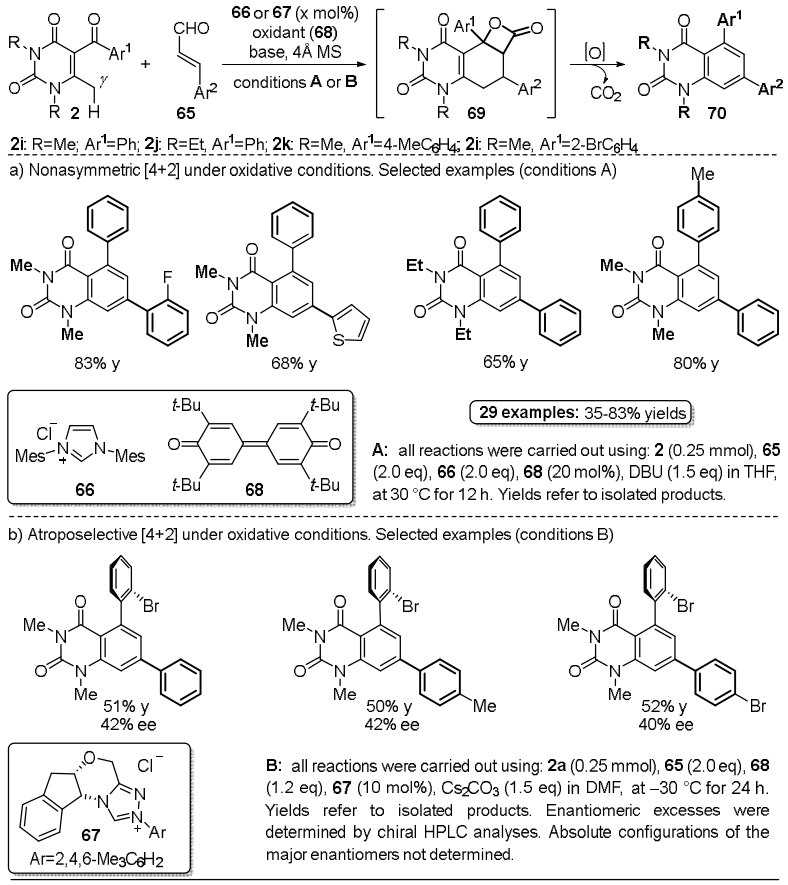
Scheme 20. Proposed reaction mechanism for the NHC-catalyzed organocascade leading to chiral 7,8-dihydroquinazolin-2,4-dione products **62**.

3.3. Noncovalent bifunctional organocatalytic strategies

The remarkable strategies described above, which enable access to chiral hydrogenated quinazoline-2,4-dione scaffolds in an asymmetric fashion, were based on the ability of chiral, secondary amines such as prolinols **36**, **48**, and **53** to covalently bind to the pronucleophile of type **2**, thus leading to the HOMO-raising activation of the enolizable π-system of the uracil carbaldehyde scaffold. On the other hand, chiral imidazolium and triazolium NHC organocatalysts **60**, **66**, and **67** promoted the activation of the α,β-unsaturated aldehyde partners *via* covalent, LUMO-lowering activation enabled by the formation of the corresponding chiral, acyl-azolium dienophiles. In this context, the domain of noncovalent activation of such systems resulted much less explored,[39] and only one report exists in which chiral, bifunctional amine/H–bond donor catalysts are employed to trigger the asymmetric formation of chiral quinazoline-2,4-dione scaffolds.[40]

The activation of substrates by hydrogen bonding and/or other noncovalent interactions has triggered the development of an enormous variety of organocatalyzed reactions in recent years, with the consequent production of chiral substances for several applications. Unfortunately, the implementation of such strategy for the formation of reactive *o*QDM intermediates is quite challenging, as it entails the direct, dearomative vinylogous enolization of unactivated aromatic carbonyl systems, and the control of the chirality transfer from the catalyst to the transition state of the reaction by way of weak noncovalent interactions.

A remarkable example of this activation mode was introduced in 2021 by Curti and co-workers,[40] who reported a novel [4+2]-cycloaddition of substituted uracil carbaldehydes **2** and a series of aromatic and aliphatic nitroalkenes **71** triggered by the chiral, tertiary amine-thiourea bifunctional organocatalyst **72** (Takemoto's catalyst, Scheme 22).[41] The reaction between uracils **2** and aromatic nitroalkenes **71** (R^2=Ar), bearing both electron-rich and electron-poor substituents, was carried out using catalyst **72** (10 mol%) in xylene at room temperature for 72 h, and provided a series of functionalized, enantioenriched 5,6,7,8-tetrahydroquinazoline-2,4-diones **73** bearing three contiguous stereocenters, in moderate to good yields (35-90%), with generally good levels of enantioselectivity (up to 90% ee), and complete diastereocontrol (>20:1 dr). The reaction proved viable also with (usually less reactive) aliphatic substrates such as cyclohexyl- and phenylethyl-containing nitroalkenes, which gave, under slightly modified reaction conditions (60 °C), the corresponding cycloadducts in modest 38-40% isolated yields and moderate enantioselectivity (ca. 80% ee). Of note, the ability to provide enantiopure products **73** (>99% ee) was demonstrated by simple one-cycle recrystallization/resolution from hexane/CH_2Cl_2 or EtOH at reflux.

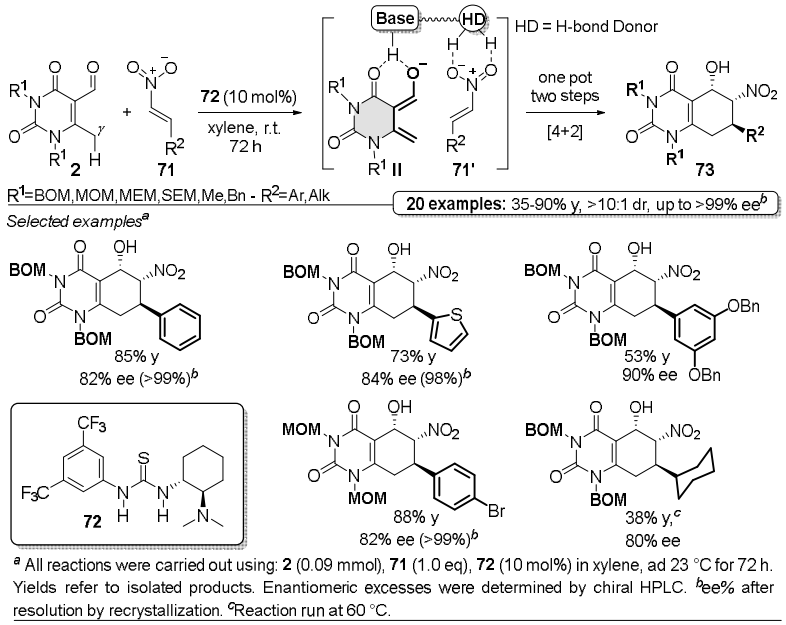


Scheme 21. [4+2]-Benzannulation strategy *via* oxidative NHC catalysis. Conditions A) non-asymmetric conditions using imidazolium precatalyst **66**; and conditions B) atroposelective attempts using chiral triazolium precatalyst **67**.

A plausible mechanistic scenario for this noncovalently activated [4+2]-cycloaddition was proposed, as depicted in Scheme 23. Starting from uracil carbaldehyde **2**, featuring a low-aromaticity profile, bifunctional organocatalyst **72** enabled the *in situ* vinylogous enolization to give the corresponding *o*QDM-type ammonium dienolate **II**, which was intercepted by nitroolefins **71**, in turn activated to complex **71'** *via* H-bonding with the thiourea group of the catalyst. This boosted a stepwise, asymmetric [4+2]-cyclization *via* an organocascade, which included a first stereoselective, vinylogous Michael addition reaction of the *γ*-carbon of dienolate **II** to the *Re* face of the *β*-carbon of **71** giving the corresponding adduct **74** (embedding the C7–C8 bond of the product with its C7 stereocenter), followed by nitro-aldol ring closure installing the remaining C5 and C6 stereocenters with complete diastereoselectivity, and finally consigning the product **73** after dissociation and recycle of the catalyst.

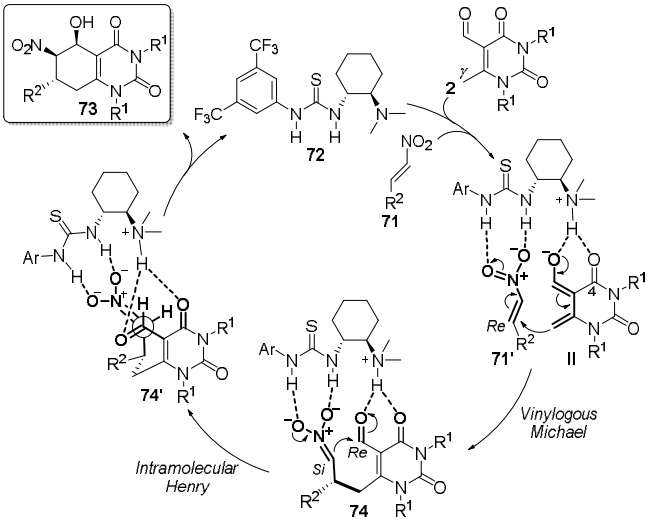
To prove the synthetic utility of the synthesized chiral derivatives **73**, several further transformations were performed (Scheme 24). Reduction of the nitro functionality within compounds **73a** and **73b** proved quite challenging, and only the use of zinc, ammonium formate and paraformaldehyde in refluxing methanol enabled the formation of the corresponding tricyclic oxazolidine derivatives **75** and **78** in 68% and 72% isolated yields, respectively. In the absence of paraformaldehyde as amino alcohol trapping agent, the reaction procedure proved still viable, albeit much less efficient, as exemplified by the reduction of MOM-protected

fused-uracil **73b**, which afforded amino alcohol **77** in a modest 42% yield (Scheme 24b). Furthermore, selective removal of the BOM group from **75** with BBr_3 gave access to the corresponding N1,N3–H uracil derivative **76** in a 78% isolated yield (Scheme 24a).

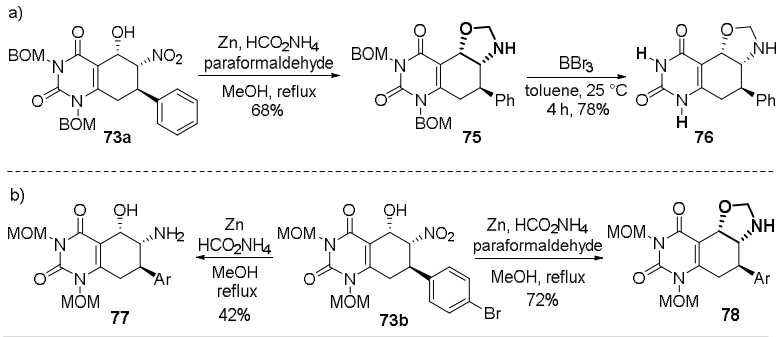


[a] All reactions were carried out using: **2** (0.09 mmol), **71** (1.0 eq), **72** (10 mol%) in xylene, ad 23 °C for 72 h. Yields refer to isolated products. Enantiomeric excesses were determined by chiral HPLC. [b]ee% after resolution by recrystallization. [c]Reaction run at 60 °C.

Scheme 22. Curti's catalytic, asymmetric [4+2]-cycloaddition of **2** with a series of aromatic and aliphatic nitroalkenes **71**, promoted by Takemoto's bifunctional tertiary amine-thiourea organocatalyst **72**.



Scheme 23. Proposed catalytic cycle for the stepwise, asymmetric [4+2]-cycloaddition between **2** and a series of aromatic and aliphatic nitroalkenes **71**, promoted by Takemoto's catalyst **72**.



Scheme 24. Functionalization of enantioenriched carbocycle-fused-uracil derivatives **73a** and **73b**.

Finally, despite the targeted tetrahydroquinazolines resulted stable to air oxidation at room temperature, it was reported that upon treatment with Et_3N in CH_2Cl_2 at reflux for 24 h, BOM-protected uracil **73a** underwent an oxidative aromatization to the corresponding aromatic quinazoline system.

Conclusions

The versatility of remotely enolizable 6-methyluracil-5-carbaldehydes as useful vinylogous pro-dienes in direct [4+2]-cycloadditions with suitable electron poor dienophiles proved to be the most investigated and useful strategy to access chiral 5,6-fused uracil derivatives, such as dihydro- and tetrahydroquinazoline-2,4-dione systems. These heterocyclic ring systems have attracted appreciable attention in the field of medicinal chemistry owing to their peculiar structure and promising pharmacological activities. These cycloadditions, be they concerted or stepwise reactions, grounded on the formation of elusive *o*QDM diene species, whose formation is crucial for the success of the reaction, albeit challenging, as it implies the temporary loss of the aromatic character of the uracil ring. To address this issue, clever solutions were found, as described in this account, where different strategies have been described to forge chiral, partially saturated quinazoline-2,4-diones emblazoned with *in-cycle* stereogenic units. Since the first, pioneering racemic attempts dating back almost 40 years ago, up to the last catalytic and enantioselective methodologies based on covalent and noncovalent organocatalytic systems, the reported achievements unlocked the access to this intriguing class of structures, paving the way to their further exploitation in both pharmaceutical and chemical sciences.

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