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Multicomponent Synthesis of Dihydropyrimidines and Thiazines

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Abstract: A broad range of differently substituted dihydropyrimidines and thiazines can be efficiently prepared by using a four-component reaction between phosphonates, nitriles, aldehydes, and iso(thio)cyanates. The scope and limitations of this multicomponent reaction are fully described. Variation of all four components has been investigated. The nitrile and aldehyde inputs can be varied extensively, but variation of the phosphonate input remains limited. An interesting rearrangement leading to phosphoramidates has been observed. Furthermore, the multicomponent reaction seems to be restricted to the use of isocyanates with strongly electron-withdrawing substituents, but an interesting additional exchange reaction under microwave conditions leads to dihydropyrimidines with less electron-withdrawing substituents at N3. In addition, a diastereoselective formation of dihydropyrimidines has been observed when using a chiral aldehyde as the input. Finally, by changing the isocyanate component to an isothiocyanate, thiazines are efficiently formed instead of the corresponding thio-dihydropyrimidines.

Keywords: heterocycles · hetero-Diels–Alder reaction · Horner–Wadsworth–Emmons reaction · microwave-assisted synthesis · multicomponent reactions

Introduction

Structurally diverse libraries of small molecules are conveniently generated by combinatorial assembly of different types of building blocks onto a common scaffold. Most approaches rely on a stepwise protocol, but for more complicated skeletons such sequential re-iteration of individual reactions becomes a limiting factor. A more convergent approach is desired that ideally provides the suitably decorated scaffold in a single synthetic operation. Procedures that yield complex molecules by performing multiple reaction steps in which several bonds are formed without isolation of intermediates are commonly referred to as tandem reactions.[1] An important subclass of tandem reactions are the multicomponent reactions (MCRs), which are defined as one-pot processes in which at least three easily accessible components are combined to form a single product.[2] In this regard, MCRs are receiving ever-increasing attention as useful tools for parallel syntheses of arrays of structurally diverse products of considerable complexity.[3–5]

Many small synthetic organic molecules with high medicinal potential contain heterocyclic rings. Also, the most potent ligand systems in (transition) metal-mediated (asymmetric) catalysis are often based on heterocyclic cores. The range of easily accessible and suitably functionalised heterocyclic building blocks is, however, surprisingly limited and the construction of even a small array of, for example, 500 relevant heterocyclic compounds is far from trivial. Heterocyclic chemistry therefore continues to attract the attention of medicinal and synthetic chemists,[6] and the development of novel methodologies allowing efficient access to heterocycles is still highly appreciated. Traditionally, methods based on MCRs have proved quite efficient for the construction of many different types of heterocycles.[5] For example, the Hantzsch four-component pyridine synthesis, the Bucherer–Bergs three-component thiazole synthesis, and the Biginelli three-component reaction for the preparation of dihydropyrimidinones are all well-known MCRs for the construction of heterocyclic species.[5] Recently, we have also contributed with several examples in this area.[7,8a]

Most relevant to the present work is a multicomponent approach for generating dihydropyrimidines (DHPMs).[8a] In this four-component reaction, phosphonates **1**, nitriles **2**, and aldehydes **3** are combined to produce 1-azadienes **4** by a

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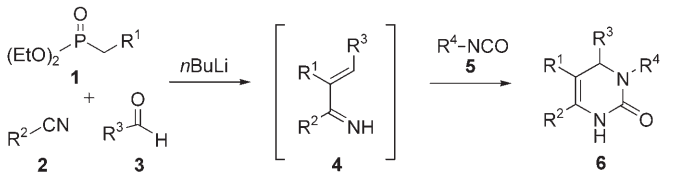
Horner–Wadsworth–Emmons (HWE) reaction.[8b] Subsequent in situ aza-Diels–Alder (aza-DA) cycloaddition with isocyanates **5** gives DHPMs of type **6** (Scheme 1).



1a R^1= H
1b R^1= Me
1c R^1= Ph
1d R^1= CH=CH_2
1e R^1= PO(OEt)$_2$
1f R^1= COOMe

2a R^2= Ph
2b R^2= *i*Pr
2c R^2= 2-Furyl
2d R^2= CH(Me)(Et)
2e R^2= *t*Bu
2f R^2= *n*Pr

3a R^3= 4-MeOPh
3b R^3= 4-ClPh
3c R^3= Ph
3d R^3= 4-NMe_2Ph
3e R^3= 3-NO_2Ph
3f R^3= 4-NO_2Ph
3g R^3= *i*Pr
3h R^3= $PhOCH_2OCH_2$
3i R^3= Me
3j myrtenal

5a R^4= Ts
5b R^4= 4-NO_2Ph
5c R^4= Ph
5d R^4= COPh
5e R^4= CO_2Me
5f R^4= CH(Me)Ph

Scheme 1. Inputs in Horner–Wadsworth–Emmons/aza-Diels–Alder four-component reaction (HWE/aza-DA 4CR).

DHPMs are versatile heterocyclic six-membered-ring scaffolds with remarkable pharmacological activities.[9] They are widely used in medicinal chemistry. For example, antiviral, antitumour, antibacterial, and anti-inflammatory activities have been reported, and DHPMs are also used as calcium channel modulators, α1 a-adrenoceptor-selective antagonists, and anti-hypertensive agents.[10,11] The methods hitherto used for the preparation of biologically active DHPMs have all involved multistep processes.[12–15] An interesting approach was reported by Elliott and co-workers during their work on the synthesis of batzelladine A,[16a,b] for which they developed an aza-DA reaction between a dihydro-oxazole and isocyanates that led to oxazolopyrimidines.[16c,d] Other well-known approaches to DHPMs use the classical Biginelli three-component reaction.[9a] In the past decade, a series of procedures has been developed to overcome the relatively harsh conditions (EtOH, HCl, Δ) of the original reaction.[17] A serious drawback of these protocols is that only the pharmacologically less important *N*1-substituted and *N*3-unsubstituted DHPM derivatives can be obtained. Additional synthetic manipulations are needed to obtain the biologically active *N*3-substituted DHPMs.[9a,18]

The four-component reaction (4CR) depicted in Scheme 1 offers an alternative, which largely overcomes these problems and produces the desired *N*3-substituted DHPMs **6** in a single step. The reaction seems quite flexible with respect to the nitriles **2** and aldehydes **3** that may be used, but only a limited number of combinations have been tested to date.[8a] Further studies employing more functionalised nitrile and aldehyde inputs are presented herein. In addition, an extensive scope study is reported that addresses the influence of the phosphonate (**1**) and the isocyanate (**5**) components on the HWE/aza-DA four-component assembly of DHPMs **6**. Steric and electronic factors that direct this MCR are discussed in detail to fully define its exploratory power, E_N. Also, the use of optically active inputs has been explored with a view to obtaining the desired DHPMs **6** diastereoselectively.

Abstract in Dutch: *Een breed spectrum van verschillend gesubstitueerde dihydropyrimidines en thiazines kan gesynthetiseerd worden via een vier-componenten reactie van fosfonaten, nitrillen, aldehydes en iso(thio)cyanaten. In dit artikel worden de mogelijkheden en de beperkingen van deze multicomponent reactie uitgebreid beschreven, waarbij variatie van alle vier de componenten onderzocht is. De variatiemogelijkheid in nitril en aldehyde is zeer uitgebreid, terwijl variatie in fosfonaat beperkt is. Hierbij is een interessante omlegging waargenomen die leidt tot fosforamidaten. Verder leidt alleen het gebruik van isocyanaten met sterk electronen-zuigende groepen tot de efficiente vorming van dihydropyrimidines. Dihydropyrimidines met zwak electronen-zuigende groepen kunnen echter gesynthetiseerd worden door uitwisseling van het isocyanaat onder magnetron condities. In dit artikel wordt ook de diastereoselectieve vorming van dihydropyrimidines beschreven waarbij een chiraal aldehyde gebruikt wordt. Tenslotte, als het isocyanaat vervangen wordt door een isothiocyanaat, wordt een thiazine in plaats van het thio-dihydropyrimidine gevormd.*

Results and Discussion

The HWE/aza-DA 4CR for the synthesis of **6** proceeds via 1-azadiene intermediates **4**. These species are conveniently generated by mixing a phosphonate (**1**) with a base (e.g., *n*BuLi) at −78 °C, followed by addition of a nitrile (**2**) and an aldehyde (**3**).[8] The mixture is then allowed to warm to room temperature, whereupon addition of an isocyanate (**5**) induces a formal Diels–Alder cycloaddition to give **6** (Scheme 1). Thus, reaction of diethyl methylphosphonate (**1a**) and tosyl isocyanate (**5a**) with aromatic nitriles **2** and aromatic aldehydes **3** proceeds smoothly and efficiently affords the corresponding DHPMs **6a–f** (entries 1–6; Table 1).

Aliphatic nitriles **2** in combination with aromatic aldehydes **3**, **1a**, and **5a** gave modest to good yields of the corresponding DHPMs **6g–o** (entries 7–15; Table 1). When secondary nitriles **2b** and **2d** were used (entries 7–13; Table 1) the yields of the corresponding DHPMs **6g–m** were still satisfying. However, when the sterically more demanding pivalonitrile (**2e**) was used as input (entry 14; Table 1) the yield of **6n** was rather poor. Also, use of the primary nitrile **2f** resulted in only a trace amount of the desired DHPM **6o** (entry 15; Table 1). In a related study directed towards the synthesis of α,β-unsaturated ketones via in situ generated 1-azadienes, it was reported that primary nitriles are quite prone to dimerisation and polymerisation,[19] which may account for the diminished yield of DHPM **6o**.

Table 1. HWE/aza-DA 4CR of phosphonate **1a** and isocyanate **5a** with nitriles **2** and aromatic aldehydes **3**.

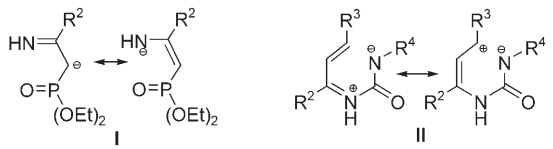
Entry	Nitrile	R^2	Aldehyde	R^3	Yield [%]	DHPM
1	**2a**	Ph	**3a**	4-$MeOC_6H_4$	65	**6a**
2	**2a**	Ph	**3b**	4-ClC_6H_4	80	**6b**
3	**2a**	Ph	**3c**	Ph	71	**6c**
4	**2a**	Ph	**3d**	4-$Me_2NC_6H_4$	54	**6d**
5	**2a**	Ph	**3e**	3-$NO_2C_6H_4$	38	**6e**
6	**2c**	2-furyl	**3a**	4-$MeOC_6H_4$	61	**6f**
7	**2b**	*i*Pr	**3a**	4-$MeOC_6H_4$	73	**6g**
8	**2b**	*i*Pr	**3b**	4-ClC_6H_4	65	**6h**
9	**2b**	*i*Pr	**3c**	Ph	55	**6i**
10	**2b**	*i*Pr	**3d**	4-$Me_2NC_6H_4$	49	**6j**
11	**2b**	*i*Pr	**3e**	3-$NO_2C_6H_4$	60	**6k**
12	**2b**	*i*Pr	**3f**	4-$NO_2C_6H_4$	55	**6l**
13	**2d**	CH(Me)Et	**3a**	4-$MeOC_6H_4$	49	**6m**
14	**2e**	*t*Bu	**3a**	4-$MeOC_6H_4$	15	**6n**
15	**2f**	*n*Pr	**3b**	4-ClC_6H_4	< 5	**6o**

Besides aromatic aldehydes, aliphatic aldehydes were also used as inputs in the MCR. When these aliphatic aldehydes (**3g**, **3h**, and **3i**) were allowed to react with nitriles **2a–c**, **1a**, and **5a**, only moderate yields of the corresponding DHPMs **6p–t** could be isolated (Table 2).

Table 2. HWE/aza-DA 4CR of phosphonate **1a** and isocyanate **5a** with nitriles **2** and aliphatic aldehydes **3**.

Entry	Nitrile	R^2	Aldehyde	R^3	Yield (%)	DHPM
1	**2a**	Ph	**3g**	*i*Pr	35	**6p**
2	**2a**	Ph	**3i**	Me	15	**6q**
3	**2c**	2-furyl	**3g**	*i*Pr	36	**6r**
4	**2b**	*i*Pr	**3g**	*i*Pr	40	**6s**
5	**2b**	*i*Pr	**3h**	$PhCH_2OCH_2$	21	**6t**

As became clear in the course of our earlier studies, generation of the initial intermediate **I** (Scheme 2) is crucial. Therefore, the use of aromatic nitriles or nitriles with poorly accessible α-H atoms is favourable (R^2). Furthermore, HWE reaction of the aldehyde component (R^3) with **I** produces 1-azadiene intermediates **4**, which undergo final cyclocondensation with the isocyanate (R^4) to form the corresponding DHPMs **6**. This most likely proceeds through stabilised dipolar intermediates **II** (Scheme 2). Compared to aliphatic R^3 substituents, aromatic R^3 substituents (Table 1 versus Table 2) are more efficient at stabilising the intermediate carbocation in **II**, which ultimately results in more efficient cyclocondensation. The electronic nature of R^2 is less important than that of R^3 for the stabilisation of the carbocationic species **II**, which is reflected in a less dramatic effect on the final cyclocondensation step.



Scheme 2. Intermediates **I** and **II**.

Another point of diversity in the DHPM scaffold (**6**) is R^1, which is introduced through the phosphonate input **1**. Therefore, we decided to investigate the application of different phosphonates in the HWE/aza-DA 4CR. Phosphonates **1** were prepared by way of the Michaelis–Arbuzov reaction.[20] Thus, reaction of triethyl phosphite with appropriate halides under controlled microwave heating in a monomode reactor afforded phosphonates **1a–d** in very good yields.[21]

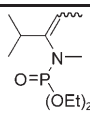
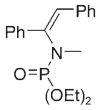
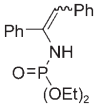
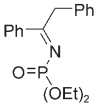
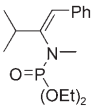
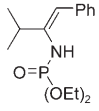
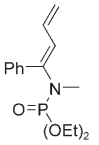
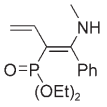
Phosphonates **1a–d** were used in combination with a small set of nitriles (**2a–c**), anisaldehyde (**3a**), and tosyl isocyanate (**5a**). The results are summarised in Table 3 and Table 4. The use of phosphonate **1b** instead of **1a** in combination with aromatic nitriles **2a**/**2c**, **3a**, and **5a** was found to result in moderate to good yields of the corresponding DHPMs **6u** and **6v** (entries 4 and 5, Table 3), although the yield of **6u** was considerably lower than that of **6v**. Moreover, when the aliphatic nitrile **2b** was reacted with **1b, 3a**, and **5a**, no DHPM could be detected (entry 6; Table 3). The other two synthesised phosphonates, **1c** and **1d**, also failed to give DHPMs in the HWE/aza-DA 4CR.

Table 3. HWE/aza-DA 4CR of phosphonates **1a** and **1b**, nitriles **2a–c**, aldehyde **3a**, and isocyanate **5a**.

Entry	Phosphonate	R^1	Nitrile	R^2	Yield [%]	DHPM
1	**1a**	H	**2a**	Ph	65	**6a**
2	**1a**	H	**2c**	2-furyl	61	**6f**
3	**1a**	H	**2b**	*i*Pr	73	**6h**
4	**1b**	Me	**2a**	Ph	35	**6u**
5	**1b**	Me	**2c**	2-furyl	90	**6v**
6	**1b**	Me	**2b**	*i*Pr	–	–

To clarify the course of the reaction, the consumption of phosphonates **1b**, **1c**, and **1d** by either **2a** or **2b** was studied in more detail by ^{31}P NMR spectroscopy. For the reaction involving **1b**, this revealed that although initial deprotonation with *n*BuLi proceeds smoothly, the resulting anion reacts rather slowly with **2b**. Even after stirring the reaction mixture at room temperature overnight, considerable amounts of unreacted **1b** were still detected. Nevertheless, formation of the corresponding intermediate of type **I** (Scheme 2) most likely took place. When the reaction mixture was quenched with MeI (no products could be identified with H_2O), the intermediate was indeed trapped. A mixture of products was formed; the main products were identified as the phosphoramidates (*E*)- and (*Z*)-**7a** (37%, entry 1; Table 4). Also, when phosphonate **1c** was used in combination with **2a**, **3a**, and **5a** in the 4CR, no corresponding DHPM was formed at all. However, if after initial deprotonation and addition of **2a** the reaction was quenched using MeI, the sole identifiable product was phosphoramidate (*Z*)-**7b** (quant., entry 2; Table 4). On the other hand, when the same reaction mixture was quenched with water instead of MeI (entry 3; Table 4), the phosphoramidates (*E*)- and (*Z*)-**8a** (58%) together with the imine **9** (42%)

Table 4. Reaction of phosphonates **1b–d** with nitriles **2a** and **2b**.[a]

Entry	Phosphonate	Nitrile	Quench method	Products	Recovery of **1** [%]
1	**1b**	**2b**	MeI	 **7a** (37%) *E*:*Z* = 1:6	56[b]
2	**1c**	**2a**	MeI	 (*Z*)-**7b** (100%)	–
3	**1c**	**2a**	H_2O	 **8a** (58%) *E*:*Z* = 1:1.5	
				 **9** (42%)	–
4	**1c**	**2b**	MeI	 (*Z*)-**7c** (20%)	7[c]
5	**1c**	**2b**	H_2O	 (*Z*)-**8b** (25%)[d]	7[c]
6	**1d**	**2a**	MeI	 (*E*)-**7d** (37%)	
				 (*E*)-**10** (63%)	–

[a] After reaction with nitrile was complete (entries 2, 3, and 6) or after stirring at room temperature overnight (entries 1, 4, and 5), the reactions were quenched with either MeI or H_2O and the product composition was analysed by ^1H and ^{31}P NMR; see Experimental Section for more details. [b] A third phosphoramidate (6%) was identified as well, see ref. [22]. [c] Another phosphonate (10–20%) was identified besides residual **1c**; see ref. [23]. [d] Phosphoramidate (*Z*)-**8b** rapidly decomposes.

were found, as concluded on the basis of the NMR data. Next, the reaction of **1c** with isobutyronitrile (**2b**) was investigated (entries 4 and 5; Table 4). Although initial deprotonation seemed to proceed smoothly, the resulting anion reacted only relatively slowly with **2b**. After stirring at room temperature overnight, 7% of unreacted **1c** remained. Additionally, some 20–25% of the corresponding phosphoramidates (*Z*)-**7c** and (*Z*)-**8b** were identified when MeI and water, respectively, were used to quench the reaction. Finally, when diethylallyl phosphonate (**1d**) was deprotonated in a similar fashion as above with *n*BuLi, the resulting anion was indeed found to react with benzonitrile (**2a**). After quenching with MeI, two main products, (*E*)-**7d** and **10**, were identified in a 1:2 ratio (entry 6; Table 4).

The process depicted in Scheme 3 can rationalise the formation of phosphoramidates **7** and **8** as well as the formation of imine **9**. After initial deprotonation of the phosphonates **1b–d**, the resulting anions **A** react with nitriles **2a** or **2b** to form the corresponding stabilised intermediates **B**. Then, **B** rearranges to **D**, which is also resonance-stabilised. Ultimately, the observed rearranged products are formed by reaction of **D** with MeI (**7**) or water (**8** and **9**). The rearrangement **B** → **D** may proceed via **C**, which is a four-membered N,P-containing ring analogous to the oxaphosphetane intermediates that play a role in the usual HWE reactions.[24]

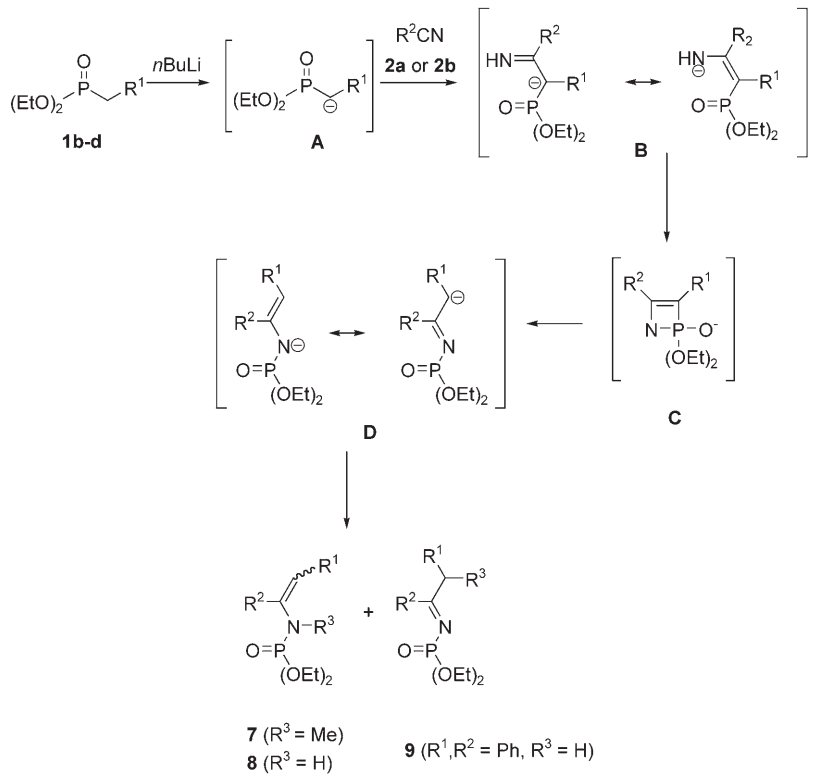
Intermediates **B** are similar to the previously postulated **I** (Scheme 2). Efficient formation of **B** depends on the stability of the initial anion **A** in combination with the accessibility of the α-proton of the nitrile input.[8] Furthermore, the intermediate **B** derived from **1b** is less stable than the corresponding anion derived from **1c** or **1d**.[25] Consequently, DHPMs **6** can still be formed upon reaction of the anion **A** of **1b** with aromatic nitriles **2** followed by a quick HWE/aza-DA process with **3a** and **5a** (entries 4 and 5; Table 3). On the other hand, after deprotonation of the phosphonates **1c** and **1d**, the anion reacts smoothly with the nitrile input to form **B**, but then fast rearrangement to **D** is preferred, which ultimately leads to products **7**, **8**, and **9**. Only one precedent for a similar rearrangement exists in the literature.[26]

Two commercially available phosphonates **1e** and **1f** were treated with *n*BuLi and a nitrile in a similar manner as described above. Deprotonation was successful in both cases, but resulted in a very stable anion that did not react with benzonitrile (**2a**) at all and no rearranged products were observed. Also, one-pot reaction of either **1e** or **1f** with **2a**, **3a**, and **5a** did not give the corresponding DHPM as a product. Addition of crown ethers or the use of HMPA as a co-solvent did not result in reaction of the anion. Also, the use of alternative bases, such as KO*t*Bu or LDA, did not result in any reaction of the anion of **1e** or **1f** with **2a**.

In order to further explore the scope of the HWE/aza-DA 4CR for the synthesis of DHPMs **6**, the isocyanate input **5** was also varied (Scheme 4). Isocyanates are versatile starting materials, which are also used in other MCRs.[27] Earlier, we showed that reaction of **5b** (instead of **5a**) with **1a**, **2a**, and **3a** in the presence of *n*BuLi afforded DHPM **6w** in a modest yield of 26%.[8a]

Strongly electron-withdrawing R^4 groups on the isocyanate favour aza-DA of the initially formed 1-azadiene **4** to form the corresponding DHPM **6**. Several pharmacological studies have shown that an ester or amide function at N3 or C5 in DHPMs such as **6** is required for biological activity.[9c] Therefore, the isocyanate **5e** was also considered as an input. In this way, pharmaceutically more relevant DHPMs **6x** and **6y** were prepared in 70% and 29% isolated yield, respectively. In addition, the use of benzoyl isocyanate (**5d**) in combination with **1a**, **2a**, and **3a** afforded DHPM **6z** in 70% yield.

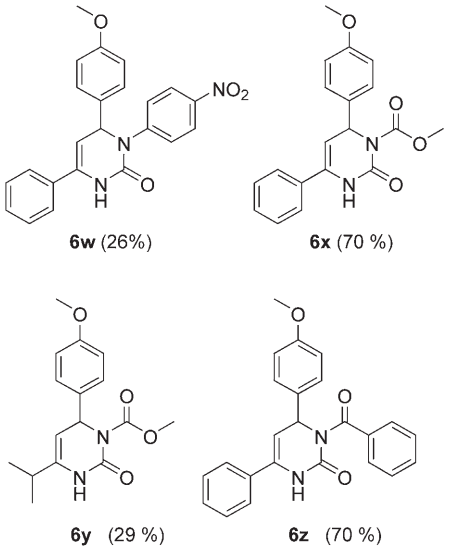
However, application of isocyanates **5** with less electron-withdrawing R^4 substituents did not give the desired DHPMs. For example, when **5c** (R^4 = Ph) was used in com-



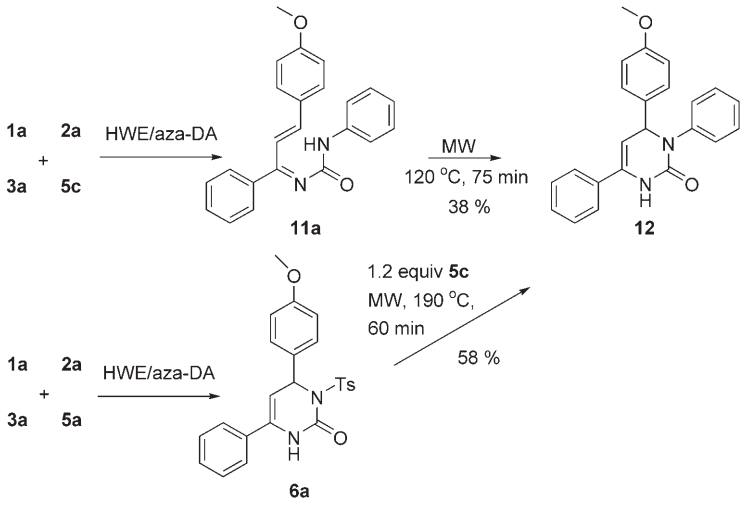
Scheme 3. Mechanism for the formation of phosphoramidates **7**–**9**.

tively strongly electron-withdrawing substituents R^4. However, the application of **5** with less electron-withdrawing R^4 can successfully lead to DHPMs under microwave (MW) conditions. To our satisfaction, **11a** could be cyclised under MW conditions at 120 °C in THF as the solvent and the desired DHPM **12** could be isolated in 38 % yield (Scheme 5). Moreover, we also observed an interesting exchange reaction under MW-irradiation. When DHPM **6a** (R^4 = Ts, yield 65 %) was heated together with isocyanate **5c** (R^4 = Ph) at 190 °C in dioxane for 1 h in a monomode MW oven, the DHPM **12** was formed in 58 % yield (Scheme 5).

The biological activity of DHPMs depends on the absolute configuration at the C4 centre, whereby the orientation of the substituent acts as a mo-



Scheme 4. DHPMs **6** formed with various isocyanates **5**.

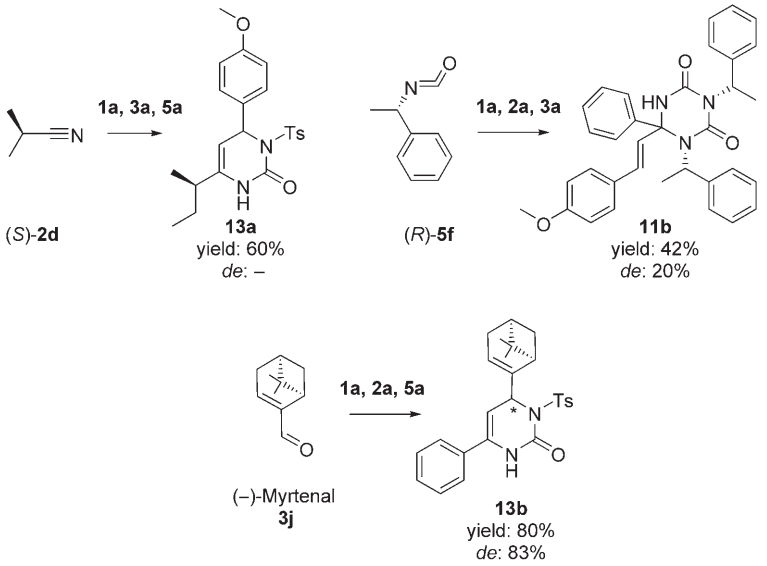


Scheme 5. Synthesis of DHPMs **12** with less electron-withdrawing R^4 substituents.

bination with **1a**, **2a**, and **3a**, the non-cyclised **11a** was formed, rather than the corresponding DHPM (Scheme 5). The isolation of the non-cyclised linear precursor **11a** strongly supports a stepwise cycloaddition of the corresponding 1-azadiene intermediate **4** with **5c**.[28] Thus, the HWE/aza-DA approach for the direct formation of DHPMs **6** seems to be confined to the use of isocyanates with relatively strongly electron-withdrawing substituents R^4. However, the application of **5** with less electron-withdrawing R^4 can successfully lead to DHPMs under microwave (MW) conditions. To our satisfaction, **11a** could be cyclised under MW conditions at 120 °C in THF as the solvent and the desired DHPM **12** could be isolated in 38 % yield (Scheme 5). Moreover, we also observed an interesting exchange reaction under MW-irradiation. When DHPM **6a** (R^4 = Ts, yield 65 %) was heated together with isocyanate **5c** (R^4 = Ph) at 190 °C in dioxane for 1 h in a monomode MW oven, the DHPM **12** was formed in 58 % yield (Scheme 5).

The biological activity of DHPMs depends on the absolute configuration at the C4 centre, whereby the orientation of the substituent acts as a molecular switch between agonist and antagonist activities.[10] A stereoselective synthesis of optically pure DHPMs is therefore of great relevance for medicinal applications of these compounds. Although not comparable to the HWE/aza-DA 4CR, stereoselective formation of DHPMs by way of the classical Biginelli 3CR has been reported. Dondoni and coworkers achieved good *de* values by using *C*-glycosylated

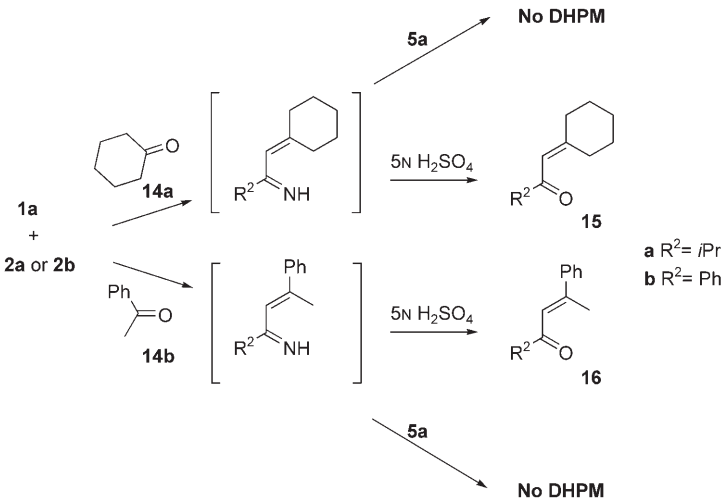
inputs,[29] and very recently an enantioselective Biginelli 3CR has been reported using a chiral ytterbium catalyst.[30] In order to induce chirality in our HWE/aza-DA 4CR, three reactions were performed with different optically pure inputs (Scheme 6). First, a reaction was performed with the commercially available optically pure nitrile (*S*)-(+)-**2d** in combination with **1a**, **3a**, and **5a**. This gave a 1:1 diastereomeric mixture of **13a** in 60% yield. When optically pure isocyanate (*R*)-**5f** was combined with **1a**, **2a**, and **3a**, the corresponding DHPM was not formed. Instead, triazinanedione **11b** was isolated in 42% yield as a 1:1.5 mixture of diastereomers. Formation of triazinanediones has been observed previously for less reactive isocyanate inputs.[8a] This interesting reaction will be the subject of a forthcoming paper. However, when the commercial (−)-myrtenal **3j** was used as the aldehyde input (with **1a**, **2a**, and **5a**), the corresponding DHPM **13b** was formed in 80% yield as an 11:1 diastereomeric mixture.



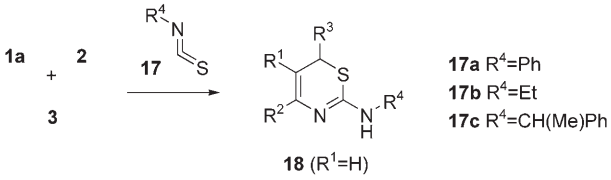
Scheme 6. Use of chiral inputs in the HWE/aza-DA 4CR.

To further explore the scope of the four-component HWE/aza-DA reaction, some ketones were also used as inputs instead of aldehydes. When cyclohexanone **14a** or benzophenone **14b** was combined with **1a**, **5a**, and either **2a** or **2b**, the corresponding DHPM was not formed (Scheme 7). However, when the reactions were quenched with sulfuric acid prior to addition of **5a**, the α,β-unsaturated ketones **15** and **16** were detected.[31] This indicates that the HWE process took place and that the corresponding 1-azadiene intermediate was indeed formed. Apparently, these are not reactive enough to undergo subsequent cycloaddition upon in situ treatment with **5a** to give the desired DHPM analogues.

Finally, application of isothiocyanates **17** instead of isocyanates **5** in the HWE/aza-DA 4CR was also explored (Scheme 8). Thus, in situ combination of **1a**, **2a**, and **3c** in the presence of *n*BuLi and subsequent addition of **17a** afforded the thiazine derivative **18a** in good yield (74%, entry 1; Table 5). This procedure proved to be quite general and a number of differently substituted thiazines **18** could be synthesised in reasonable to good yields by combining the appropriate inputs (Table 5). By simply changing the nature of the fourth component in our MCR from isocyanate to isothiocyanate, the course of the final cyclocondensation is altered. Thiazines are scarcely described in the literature and little is known about their biological activities.[12a,32] Our synthetic approach provides access to **18** and may facilitate further studies aimed at elucidating the biological relevance of these systems. In general, the thiazines **18** are rather stable compounds; they can be easily purified by column chromatography on silica gel, although in the case of **18b** (entry 2; Table 5) a rearrangement to the corresponding thio-DHPM was observed when a solution in $CDCl_3$ was left to stand at room temperature for a couple of hours. A more detailed study on this so-called Dimroth rearrangement[33,34] will be reported elsewhere.[35] Interestingly, not only electron-withdrawing but also alkyl R^4-substituents



Scheme 7. Use of ketones **14** in the HWE/aza-DA 4CR.



Scheme 8. Synthesis of thiazines **18**.

Table 5. Four-component reaction of phosphonate **1a** with nitriles **2**, aldehydes **3**, and isothiocyanates **17**.

Entry	Nitrile	Aldehyde	Isothiocyanate	Thiazine	Yield [%]
1	**2a**	**3c**	**17a**	**18a**	74
2	**2a**	**3a**	**17a**	**18b**	58
3	**2b**	**3c**	**17a**	**18c**	61
4	**2a**	**3a**	**17b**	**18d**	56
5	**2a**	**3a**	**17c**	**18e**	64

are tolerated in the formation of thiazines **18**, which is in contrast to the 4CR leading to DHPMs **6**.

Conclusion

A four-component HWE/aza-DA approach for the synthesis of a variety of DHPMs has been extensively explored. A broad range of different R^2 (nitrile) and R^3 (aldehyde) substituents can be introduced on the DHPM scaffold by way of this procedure. However, variation of R^1 (phosphonate) remains limited. Besides R^1 = H, R^1 = Me is tolerated depending on the type of nitrile applied, but with other R^1 groups in the phosphonate input a rearrangement reaction is observed that results in a phosphoramidate as the main product. The R^4 substituent can be varied, although direct formation of DHPMs is restricted to the use of isocyanates that bear a strongly electron-withdrawing R^4 substituent. However, less electron-withdrawing R^4 substituents can be easily introduced by heating the initially formed DHPM with appropriate isocyanates under microwave conditions. Furthermore, we have demonstrated that, in particular, the use of optically pure aldehydes as inputs results in diastereoselective formation of the corresponding DHPMs. Finally, when the fourth component in our MCR was changed from an isocyanate to an isothiocyanate, the final cyclocondensation could be directed towards the formation of thiazines instead of DHPMs. In summary, the HWE/aza-DA 4CR is a versatile reaction that can, in principle, be applied for the synthesis of a broad variety of *N*1-unsubstituted DHPMs. As such, this reaction represents a useful alternative to the Biginelli three-component approach.

Experimental Section

General: All reactions were carried out under dry nitrogen or argon. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC 200 (200.13 and 50.32 MHz, respectively), a Bruker Avance 250 MHz (250.13 and 62.90 MHz, respectively), or a Bruker MSL 400 MHz spectrometer (400.13 and 100.61 MHz, respectively); chemical shifts (δ) are given in ppm, internally referenced to residual solvent resonances (^{1}H: δ = 7.29 ppm, ^{13}C: δ = 77.0 ppm). ^{31}P NMR spectra were recorded on the Bruker Avance 250 MHz instrument at 101.25 MHz. Column chromatography was performed on Baker 7024–02 silica gel (40 μm, 60 Å) with petroleum ether (PE, boiling range 40–60 °C) and ethyl acetate (EA) as eluents. Thin-layer chromatography (TLC) was performed using silica plates from Merck (Kieselgel 60 F_{254} on aluminium with fluorescence indicator). Compounds on the TLC plates were visualised under UV light or by treatment with an anisaldehyde solution. High-resolution mass spectra (HRMS, EI) were recorded on a Finnigan MAT 900 spectrometer at 70 eV. IR spectra were recorded on a Mattson 6030 Galaxy spectrophotometer and are reported in cm^{-1}. Melting points were measured on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Diastereomeric excess (*de*) was determined on a Shimadzu Prominence, equipped with a DAD detector and a Shimadzu SIL-20 A auto-injector. Optical rotation was determined with an AA-10 automatic polarimeter from Optical Activity Ltd. Microwave reactions were performed in a monomode microwave (MW) reactor equipped with an autosampler (CEM Explorer). The temperature was controlled throughout the reaction and was assessed by measuring the surface temperature at the bottom of the reaction vessel by means of an infrared sensor. In all cases, capped vessels were used, allowing a pressure to build-up. The pressure was assessed by measuring the bulging of the septum, but never exceeded 20 bar. Tetrahydrofuran (THF) was dried and distilled from sodium benzophenone prior to use. PE was distilled prior to use. Benzonitrile (**2a**), isobutyronitrile (**2d**), and benzaldehyde (**3c**) were dried, distilled, and stored under a dry nitrogen atmosphere. Other commercially available chemicals were used as purchased.

Diethyl methylphosphonate (1a): Triethyl phosphite (3.0 mL, 17.5 mmol) and methyl iodide (1.95 mL, 31.3 mmol) were heated in a microwave oven (maximum power 50 W, ramp time 10 min, hold time 5 min at 130 °C). The ethyl iodide formed as a side product was distilled off at 40 °C and 10 mbar. Yield: 97 %; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.0 Hz, 6H; CH_3CH_2), 1.48 (d, J = 17.5 Hz, 3H; CH_3), 4.04–4.10 ppm (m, 4H; CH_2); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 10.4 (d, J = 144.2 Hz), 15.7 (d, J = 6.2 Hz), 60.6 ppm (d, J = 6.2 Hz); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 29.7 ppm.[21]

Diethyl ethylphosphonate (1b): Triethyl phosphite (1.0 mL, 5.83 mmol) and ethyl bromide (0.44 mL, 5.83 mmol) were heated in a microwave oven (maximum power 50 W, ramp time 10 min, hold time 15 min at 200 °C and 10 min at 180 °C). Ethyl bromide was distilled off from the resulting solution at 40 °C and 100 mbar. Yield: 100 %; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 0.83 (dt, J = 19.9 Hz, J = 7.7 Hz, 3H; CH_3CH_2P), 1.00 (t, J = 7.1 Hz, 6H; CH_3CH_2O), 1.32–1.49 (m, 2H; CH_2P), 3.70–3.83 ppm (m, 4H; CH_2O); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 6.3 (d, J = 6.8 Hz), 16.2 (d, J = 6.0 Hz), 18.5 (d, J = 142.6 Hz), 61.1 ppm (d, J = 6.5 Hz); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 34.4 ppm.[21]

Diethyl benzylphosphonate (1c): Triethyl phosphite (3.0 mL, 17.5 mmol) and benzyl bromide (2.71 mL, 22.75 mmol) were heated in a microwave oven (maximum power 200 W, ramp time 10 min, hold time 15 min at 140 °C). Ethyl bromide (40 °C/100 mbar) and diethyl ethylphosphonate (90 °C/20 mbar) were distilled off to leave the pure product. Yield: 98 %; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.0 Hz, 6H; CH_3), 3.18 (d, J = 21.7 Hz, 2H; CH_2Ph), 3.97–4.10 (m, 4H; CH_2), 7.25–7.34 ppm (m, 5H; Ph-H); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 16.1 (d, J = 6.0 Hz), 33.5 (d, J = 138.0 Hz), 61.9 (d, J = 6.8 Hz), 126.6 (d, J = 3.6 Hz), 128.3 (d, J = 3.1 Hz; 2C), 129.6 (d, J = 6.5 Hz, 2C), 131.4 ppm (d, J = 9.1 Hz); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 27.6 ppm.[21]

Diethyl allylphosphonate (1d): Triethyl phosphite (1.0 mL, 5.83 mmol) and allyl bromide (0.6 mL, 6.93 mmol) were heated in a microwave oven (maximum power 250 W, ramp time 10 min, hold time 5 min at 180 °C). Ethyl bromide was distilled off from the resulting solution at 40 °C and 100 mbar. Yield: 94 %; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 6H; CH_3), 2.64 (dd, J = 7.4 Hz, J = 21.9 Hz, 2H; PCH_2), 4.08–4.20 (m, 4H; CH_2CH_3), 5.22–5.29 (m, 2H; CH_2=CH), 5.77–5.88 ppm (m, 1H; CH); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 16.0 (d, J = 6.0 Hz), 31.4 (d, J = 139.3 Hz), 61.5 (d, J = 6.6 Hz), 119.5 (d, J = 14.4 Hz), 127.2 ppm (d, J = 11.2 Hz); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 27.9 ppm.[21]

General procedure for the synthesis of 6, 11, 13, 15, and 16 by the HWE/aza-DA reaction: *n*BuLi (1.6 M in hexane; 1.2 equiv) was added dropwise to a stirred solution of phosphonate **1** (0.2 M in dry THF) at −78 °C. The resulting solution was stirred for 1.5 h and then nitrile **2** (1.1 equiv) was added. The reaction mixture was allowed to warm to −5 °C over 1.5 h and then aldehyde **3** (1.1 equiv) was added. The mixture was stirred for a further 0.5 h at −5 °C and thereafter for 1.5 h at room temperature. Iso-

cyanate **5** (1.1 equiv) was then added dropwise over 10 min and the resulting solution was stirred overnight. The solvent was removed under reduced pressure and the crude product was purified by crystallisation, column chromatography (PE/EA, 4:1 → 1:1) or column chromatography and recrystallisation.

4-(4-Methoxyphenyl)-6-phenyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6a): The product was crystallised from THF. Yield: 65%; m.p. 179–182°C [THF]; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 2.32 (s, 3H; CH_3C$_6$H$_4$), 3.83 (s, 3H; CH_3O), 5.51 (d, J = 6.1 Hz, 1H; CHC), 6.15 (d, J = 6.1 Hz, 1H; CHN), 6.88 (d, J = 8.6 Hz, 2H; Ph-H), 6.99 (d, J = 8.3 Hz, 2H; Ph-H), 7.34–7.53 (m, 9H; Ph-H), 7.93 ppm (s, 1H; NH); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 21.4, 55.3, 59.1, 101.7, 114.2 (2C), 125.2 (2C), 125.3 (2C), 128.5 (2C), 128.7 (2C), 128.9 (2C), 129.3, 132.9 (2C), 134.0, 136.0, 143.9, 150.5, 159.6 ppm; IR (KBr): $\tilde{\nu}$ = 3243 (m), 3125 (m), 2932 (m), 1691 (s), 1356 (s), 1248 (s), 1168 cm^{-1} (s); HRMS (EI): m/z: 434.1285 $[M]^+$; calcd for $C_{24}H_{22}N_2O_4S$: 434.1300.

4-(4-Chlorophenyl)-6-phenyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6b): The product was crystallised from THF. Yield: 80%; m.p. 186–189°C [THF]; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 2.35 (s, 3H; CH_3C$_6$H$_4$), 5.39 (d, J = 6.1 Hz, 1H; CHC), 6.05 (d, J = 6.1 Hz, 1H; CHN), 7.00 (d, J = 8.5 Hz, 2H; Ph-H), 7.24–7.45 (m, 12H; Ph-H and NH); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 21.4, 58.8, 100.8, 125.2, 128.5 (2C), 128.7 (2C), 128.9 (6 C), 129.5 (2C), 132.6, 134.2, 134.6, 135.7, 139.2, 144.4, 150.3; IR (KBr): $\tilde{\nu}$ = 3239 (m), 3122 (m), 1693 (s), 1681 (s), 1360 (s), 1171 cm^{-1} (s); HRMS (EI): m/z: 438.0809 $[M]^+$; calcd for $C_{23}H_{19}ClN_2O_3S$: 438.0805.

4,6-Diphenyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6c): The product was purified by column chromatography and recrystallised from THF/pentane. Yield: 71%; m.p. 183–185°C [THF]; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.33 (s, 3H; CH_3C$_6$H$_4$), 5.52 (d, J = 6.1 Hz, 1H; CHC), 6.17 (d, J = 6.1 Hz, 1H; CHN), 7.00 (d, J = 8.2 Hz, 2H; Ph-H), 7.29–7.48 (m, 12H; Ph-H), 7.65 ppm (s, 1H; NH); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 21.4, 59.6, 101.4, 125.2 (2C), 127.2 (2C), 128.4, 128.5 (2C), 128.8 (2C), 128.9 (4C), 129.4, 132.8, 134.3, 135.8, 140.7, 144.0, 150.5 ppm; IR (KBr): $\tilde{\nu}$ = 3242 (m), 2986 (m), 1696 (s), 1683 (s), 1395 (s), 1361 (s), 1169 (s), 1086 cm^{-1} (s); HRMS (EI): m/z: 404.1193 $[M]^+$; calcd for $C_{23}H_{20}N_2O_3S$: 404.1195.

4-(4-(Dimethylamino)phenyl)-6-phenyl-3-tosyl-3,4-dihydropyrimidin-2-(1*H*)-one (6d): The product was purified by column chromatography. Yield: 54%; m.p. 187–189°C [EA]; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 2.28 (s, 3H; CH_3C$_6$H$_4$), 2.94 (s, 6H; $(CH_3)_2$N), 5.45 (d, J = 6.1 Hz, 1H; CHC), 6.03 (d, J = 6.1 Hz, 1H; CHN), 6.68 (d, J = 8.8 Hz, 2H; Ph-H), 7.00 (d, J = 8.2 Hz, 2H; Ph-H), 7.28–7.40 (m, 10H; Ph-H and NH); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 21.4, 40.6 (2C), 59.5, 102.3, 112.5 (2C), 125.3 (2C), 128.4, 128.6 (4C), 129.0 (2C), 129.1 (2C), 129.3, 133.3, 133.8, 136.5, 143.7, 150.6, 150.8; IR (KBr): $\tilde{\nu}$ = 3208 (m), 3108 (m), 2926 (m), 1674 (s), 1522 (s), 1350 (s), 1169 cm^{-1} (s); HRMS (EI): m/z: 447.1621 $[M]^+$; calcd for $C_{25}H_{25}N_3O_3S$: 447.1617.

4-(3-Nitrophenyl)-6-phenyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6e): The product was purified by column chromatography. Yield: 38%; m.p. 195–197°C [EA]; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 2.30 (s, 3H; CH_3C$_6$H$_4$), 5.47 (d, J = 6.1 Hz, 1H; CHC), 6.27 (d, J = 6.1 Hz, 1H; CHN), 7.07 (d, J = 8.4 Hz, 2H; *m*-C*H* (Ts)), 7.42–7.54 (m, 7H; Ph-H), 7.73 (d, J = 7.8 Hz, 1H; Ph-H), 8.00 (s, 1H, NH), 8.14–8.17 ppm (m, 2H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 21.6, 59.7, 99.9, 121.9, 123.3, 125.3 (2C), 129.0 (4C), 129.2 (2C), 130.0, 130.1, 132.5, 133.0, 135.7, 135.8, 142.9, 145.0, 148.6, 149.8 ppm; IR (KBr): $\tilde{\nu}$ = 3217 (m), 3106 (m), 1694 (s), 1676 (s), 1528 (s), 1348 (s), 1169 cm^{-1} (s); HRMS (EI): m/z: 449.1064 $[M]^+$; calcd for $C_{23}H_{19}N_3O_5S$: 449.1045.

6-(Furan-2-yl)-4-(4-methoxyphenyl)-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6f): The product was crystallised from Et_2O. Yield: 61%; m.p. 114°C (decomp) [Et_2O]; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.26 (s, 3H; CH_3C$_6$H$_4$), 3.74 (s, 3H; CH_3O), 5.56 (dd, J = 1.2 Hz, J = 6.1 Hz, 1H; CHC), 6.04 (d, J = 6.1 Hz, 1H; CHN), 6.38 (dd, J = 1.6 Hz, J = 3.2 Hz, 1H; CH (furan)), 6.58 (d, J = 3.2 Hz, 1H; CH (furan)), 6.77 (d, J = 8.6 Hz, 2H; *m*-CH (C_6H_4OMe)), 6.99 (d, J = 8.1 Hz, 2H; *m*-CH (Ts)), 7.25 (d, J = 8.6 Hz, 2H; *o*-CH (C_6H_4OMe)), 7.32–7.34 (m, 3H; CH (furan) and *o*-CH (Ts)), 7.71 ppm (s, 1H; NH); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 21.9, 55.8, 59.5, 100.0, 107.7, 112.1, 114.7 (2C), 126.1, 129.2 (2C), 129.3 (4C), 133.3, 136.7, 143.4, 144.6, 146.5, 150.8, 160.2 ppm; IR (KBr): $\tilde{\nu}$ = 3243 (w), 3121 (w), 1697 (s), 1684 (s), 1510 (m), 1169 cm^{-1} (s); HRMS: m/z: 424.1118 $[M]^+$; calcd for $C_{22}H_{20}N_2O_5S$: 424.1093.

6-Isopropyl-4-(4-methoxyphenyl)-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6g): The product was crystallised from THF. Yield: 73%; m.p. 178–179°C [THF]; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.9 Hz, 6H; $(CH_3)_2$CH), 2.15–2.26 (m, 1H; C$H(CH_3)_2$), 2.26 (s, 3H; CH_3C$_6$H$_4$), 3.76 (s, 3H; CH_3O), 4.84 (d, J = 5.7 Hz, 1H; CHC), 5.83 (d, J = 5.7 Hz, 1H; CHN), 6.82 (d, J = 8.7 Hz, 2H; Ph-H), 7.01 (d, J = 8.4 Hz, 2H; Ph-H), 7.22–7.30 (m, 4H; Ph-H), 7.61 ppm (s, 1H; NH); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 19.1, 19.2, 20.5, 29.9, 54.4, 58.1, 97.7, 113.1 (2C), 127.6 (2C), 127.8 (2C), 127.9 (2C), 132.8, 135.6, 138.9, 142.9, 149.8, 158.7 ppm; IR (KBr): $\tilde{\nu}$ = 3223 (m), 3111 (m), 2969 (m), 1676 (s), 1510 (s), 1343 (s), 1169 cm^{-1} (s); HRMS (EI): m/z: 400.1444 $[M]^+$; calcd for $C_{21}H_{24}N_2O_4S$: 400.1457.

4-(4-Chlorophenyl)-6-isopropyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6h): The product was crystallised from THF. Yield: 65%; m.p. 186–187°C [THF]; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.08 (d, J = 6.8 Hz, 6H; $(CH_3)_2$CH), 2.20–2.30 (m, 1H; C$H(CH_3)_2$), 2.33 (s, 3H; CH_3C$_6$H$_4$), 4.87 (d, J = 5.3 Hz, 1H; CHC), 5.9 (d, J = 5.3 Hz, 1H; CHN), 7.03–7.35 (m, 8H; Ph-H), 7.90 ppm (s, 1H; NH); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 20.1 (2C), 21.5, 30.6, 58.8, 97.9, 128.7 (4C), 128.9 (2C), 129.0 (2C), 134.1, 136.3, 140.2, 140.7, 144.3, 155.0 ppm; IR (KBr): $\tilde{\nu}$ = 3225 (m), 3117 (m), 2962 (m), 1705 (s), 1676 (s), 1344 (s), 1169 cm^{-1} (s); HRMS (EI): m/z: 404.0961 $[M]^+$; calcd for $C_{20}H_{21}ClN_2O_3S$: 404.0961.

6-Isopropyl-4-phenyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6i): The product was purified by column chromatography. Yield: 55%; m.p. 178–180°C [EA]; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 1.05 (d, J = 6.8 Hz, 6H; $(CH_3)_2$CH), 2.15–2.30 (m, 1H; C$H(CH_3)_2$), 2.29 (s, 3H; CH_3C$_6$H$_4$), 4.91 (d, J = 5.7 Hz, 1H; CHC), 5.91 (d, J = 5.7 Hz, 1H; CHN), 6.98 (d, J = 8.3 Hz, 2H; Ph-H), 7.21–7.30 (m, 8H; Ph-H), 7.97 ppm (s, 1H; NH); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 19.9, 20.0, 21.4, 30.8, 59.5, 98.2, 127.2 (2C), 128.2, 128.4 (2C), 128.7 (2C), 128.8 (2C), 136.2, 140.1, 141.5, 143.8, 151.1 ppm; IR (KBr): $\tilde{\nu}$ = 3219 (m), 3107 (m), 2962 (m), 1705 (s), 1678 (s), 1356 (s), 1169 cm^{-1} (s); HRMS (EI): m/z: 370.1358 $[M]^+$; calcd for $C_{20}H_{22}N_2O_3S$: 370.1351.

4-(4-(Dimethylamino)phenyl)-6-isopropyl-3-tosyl-3,4-dihydropyrimidin-2-(1*H*)-one (6j): The product was crystallised from THF. Yield: 49%; m.p. 178–180°C [THF]; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 1.05 (d, J = 6.8 Hz, 6H; $(CH_3)_2$CH), 2.20–2.29 (m, 1H; C$H(CH_3)_2$), 2.29 (s, 3H; CH_3C$_6$H$_4$), 2.94 (s, 6H; $(CH_3)_2$N), 4.88 (d, J = 5.7 Hz, 1H; CHC), 5.83 (d, J = 5.7 Hz, 1H; CHN), 6.62 (d, J = 8.8 Hz, 2H; Ph-H), 6.99 (d, J = 8.2 Hz, 2H; Ph-H), 7.15–7.29 (m, 4H; Ph-H), 7.40 ppm (s, 1H; NH); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 20.6 (2C), 21.9, 31.02, 41.0 (2C), 59.8, 99.3, 112.9 (2C), 128.9 (2C), 129.0 (2C), 129.3 (2C), 129.6, 137.2, 139.9, 143.9, 151.1, 151.3 ppm; IR (KBr): $\tilde{\nu}$ = 3230 (m), 2971 (m), 1676 (s), 1350 (s), 1169 cm^{-1} (s); HRMS (EI): m/z: 413.1755 $[M]^+$; calcd for $C_{22}H_{27}N_3O_3S$: 413.1773.

6-Isopropyl-4-(3-nitrophenyl)-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6k): The product was purified by column chromatography. Yield: 60%; m.p. 155–157°C [EA]; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.14 (d, J = 6.1 Hz, 6H; $(CH_3)_2$CH), 2.25–2.35 (m, 1H; C$H(CH_3)_2$), 2.33 (s, 3H; CH_3C$_6$H$_4$), 4.97 (d, J = 5.3 Hz, 1H; CHC), 6.11 (d, J = 5.3 Hz, 1H; CHN), 7.07 (d, J = 8.0 Hz, 2H; *m*-C*H* (Ts)), 7.49–7.57 (m, 4H; Ph-H), 7.67 (d, J = 7.7 Hz, 1H; CH (3-$NO_2C_6H_4$)), 8.14–8.18 ppm (m, 2H; Ph-H and NH); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 20.1 (2C), 21.5, 30.7, 58.5, 96.9, 122.0, 123.1, 128.8 (2C), 128.9 (2C), 130.0, 133.1, 136.0, 141.9, 143.6, 144.7, 148.5, 150.7 ppm; IR (KBr): $\tilde{\nu}$ = 3243 (m), 2967 (m), 1676 (s), 1535 (s), 1356 (s), 1169 (s), 689 (m), 573 cm^{-1} (m); HRMS (EI): m/z: 415.1223 $[M]^+$; calcd for $C_{20}H_{21}N_3O_5S$: 415.1202.

6-Isopropyl-4-(4-nitrophenyl)-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6l): The product was purified by column chromatography and recrystallised from THF/pentane. Yield: 55%; m.p. 170–171°C [THF]; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.07 (d, J = 6.5 Hz, 6H; $(CH_3)_2$CH), 2.11–2.28 (m, 1H; C$H(CH_3)_2$), 2.35 (s, 3H; CH_3C$_6$H$_4$), 4.91 (d, J = 5.4 Hz, 1H; CHC), 6.05 (d, J = 5.4 Hz, 1H; CHN), 6.91 (s, 1H; NH), 7.10 (d, J

= 8.2 Hz, 2H; *m*-CH (Ts)), 7.44–7.47 (m, 4H; *o*-CH (Ts) and *o*-C*H* (4-$NO_2C_6H_4$)), 8.16 ppm (d, J = 8.2 Hz, 2H; *m*-CH (4-$NO_2C_6H_4$)); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 20.0, 20.1, 21.6, 30.7, 58.7, 97.0, 124.2 (2C), 127.7 (2C), 128.9 (4C), 135.9, 141.4, 144.9, 147.7, 148.4, 150.2 ppm; IR (KBr): $\tilde{\nu}$ = 3211 (w), 3113 (w), 2963 (w), 1709 (m), 1680 (s), 1522 (s), 1346 (s), 1171 cm^{-1} (s); HRMS (EI): m/z: 415.1218 $[M]^+$; calcd for $C_{20}H_{21}N_3O_5S$: 415.1202.

6-*sec*-Butyl-4-(4-methoxyphenyl)-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6m): The product was crystallised from THF and was thereby obtained as a 1:1 mixture of diastereomers. Yield: 49%; m.p. 170–171°C [THF]; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 0.78 (t, J = 8.0 Hz, 6H; CH_3CH), 1.09 (d, J = 8.2 Hz, 6H; CH_3CH), 1.18–1.49 (m, 4H; CH_2CH), 2.01–2.17 (m, 2H; CHCH_3), 2.36 (s, 6H; CH_3C$_6$H$_4$), 3.73 (s, 6H; CH_3O), 4.90 (d, J = 5.8 Hz, 2H; CHC), 5.87 (dd, J = 5.8 Hz, J = 3.2 Hz, 2H; CHN), 6.53 (s, 2H; NH), 6.82 (d, J = 8.7 Hz, 4H; *o*-CH (C_6H_4OMe)), 7.09 (d, J = 8.4 Hz, 4H; *m*-CH (Ts)), 7.28–7.41 ppm (m, 8H; NH); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 10.8 (2C), 17.1, 17.4, 20.8 (2C), 26.1, 26.3, 36.8, 36.9, 54.7 (2C), 58.3, 58.4, 98.3, 98.6, 113.3 (4C), 127.9 (4C), 128.0 (4C), 128.2 (4C), 133.3, 133.4, 136.0 (2C), 138.6 (2C), 143.1 (2C), 149.6 (2C), 158.8 ppm (2C); IR (KBr): $\tilde{\nu}$ = 3239 (m), 2962 (m), 1681 (s), 1509 (m), 1345 (s), 1167 cm^{-1} (s); HRMS (EI): m/z: 414.1603 $[M]^+$; calcd for $C_{22}H_{26}N_2O_4S$: 414.1613.

6-*tert*-Butyl-4-(4-methoxyphenyl)-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6n): The product was purified by column chromatography. Yield: 16%; m.p. 197–202°C [EA]; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 1.10 (s, 9H; (CH_3)$_3$C), 2.31 (s, 3H; CH_3C$_6$H$_4$), 3.81 (s, 3H; CH_3O), 4.95 (d, J = 5.9 Hz, 1H; CHC), 5.89 (d, J = 5.9 Hz, 1H; CHN), 6.82 (d, J = 8.7 Hz, 2H; *o*-CH (C_6H_4OMe)), 7.03 (d, J = 8.2 Hz, 2H; *m*-CH (Ts)), 7.15–7.26 ppm (m, 5H; Ph-H and NH); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 21.5, 27.7 (3C), 33.2, 55.4, 58.9, 98.4, 114.1 (2C), 128.6 (2C), 128.8 (4C), 133.7, 136.5, 142.0, 143.8, 150.8, 159.7 ppm; IR (KBr): $\tilde{\nu}$ = 3435 (m), 3237 (w), 2961 (m), 1676 (s), 1350 (s), 1260 (s), 1163 cm^{-1} (s); HRMS (EI): m/z: 414.1613 $[M]^+$; calcd for $C_{22}H_{26}N_2O_4S$: 414.1613.

4-(4-Chlorophenyl)-6-propyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6o): The product was purified by column chromatography. Yield: < 5%; m.p. 144–147°C [EA]; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.3 Hz, 3H; CH_3CH$_2$), 1.43–1.57 (m, 2H; CH_2CH$_3$), 2.03 (t, J = 7.4 Hz, 2H; CH$_2$C), 2.34 (s, 3H; CH_3C$_6$H$_4$), 4.90 (d, J = 5.8 Hz, 1H; CHC), 5.90 (d, J = 5.8 Hz, 1H; CHN), 7.05–7.39 ppm (m, 9H; Ph-H and NH); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.3, 19.7, 21.5, 33.8, 59.0, 100.2, 127.8 (2C), 128.5 (2C), 128.7 (2C), 128.9 (2C), 134.1, 134.8, 136.2, 140.1, 144.4, 150.4 ppm; IR (KBr): $\tilde{\nu}$ = 3223 (m), 3113 (m), 2961 (m), 1709 (s), 1680 (s), 1356 (s), 1167 (s), 1088 cm^{-1} (s); HRMS (EI): m/z: 404.0940 $[M]^+$; calcd for $C_{20}H_{21}ClN_2O_3S$: 404.0961.

4-Isopropyl-6-phenyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6p): The product was purified by column chromatography. Yield: 35%; m.p. 170–171°C [THF]; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.8 Hz, 3H; CH_3CH), 0.96 (d, J = 6.8 Hz, 3H; CH_3CH), 2.18–2.31 (m, 1H; C*H*-(CH$_3$)$_2$), 2.34 (s, 3H; CH_3C$_6$H$_4$), 4.99–5.02 (m, 1H; CHC), 5.23 (dd, J = 6.1 Hz, J = 1.4 Hz, 1H; CHN), 6.68 (s, 1H; NH), 7.32 (s, 3H; Ph-H), 7.82–7.84 (m, 4H; Ph-H), 7.83 ppm (d, J = 8.2 Hz, 2H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.1, 18.7, 22.0, 35.7, 61.9, 98.2, 125.6 (2C), 129.3 (2C), 129.5 (2C), 129.6 (2C), 129.9, 133.7, 136.9, 137.0, 144.8, 151.2 ppm; IR (KBr): $\tilde{\nu}$ = 3238 (m), 2965 (m), 1693 (s), 1674 (s), 1344 (s), 1171 cm^{-1} (s); HRMS (EI): m/z: 369.1280 $[M]^+$; calcd for $C_{20}H_{22}N_2O_3S$: 369.1273.

4-Methyl-6-phenyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6q): The product was purified by column chromatography and recrystallised from THF/pentane. Yield: 15%; m.p. 177–179°C [THF]; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 1.45 (d, J = 6.5 Hz, 3H; CH_3CHN), 2.40 (s, 3H; CH_3C$_6$H$_4$), 5.21–5.35 (m, 1H; CHCH$_3$), 5.40 (dd, J = 6.2 Hz, J = 1.9 Hz, 1H; CHC), 6.89 (s, 1H; NH), 7.26 (d, J = 8.2 Hz, 2H; *o*-CH (Ts)), 7.38 (s, 5H; Ph-H), 7.93 ppm (d, J = 8.2 Hz, 2H; *m*-CH (Ts)); ^{13}C NMR (250.13 MHz, $CDCl_3$): δ = 22.0, 22.7, 52.6, 102.9, 125.5 (2C), 129.3 (2C), 129.4 (2C), 129.6 (2C), 129.9, 133.5, 135.7, 137.1, 144.9, 150.6 ppm; IR (KBr): $\tilde{\nu}$ = 3236 (m), 3116 (m), 1693 (s), 1678 (s), 1409 (s), 1345 (s), 1162 cm^{-1} (s); HRMS (EI): m/z: 342.1062 $[M]^+$; calcd for $C_{18}H_{18}N_2O_3S$: 342.1038.

6-(Furan-2-yl)-4-isopropyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6r): The product was purified by column chromatography. Yield: 36%; m.p. 90°C (decomp) [EA]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.8 Hz, 3H; CH_3CH), 1.01 (d, J = 6.9 Hz, 3H; CH_3CH), 2.24–2.29 (m, 1H; C*H*(CH$_3$)$_2$), 2.39 (s, 3H; CH_3C$_6$H$_4$), 5.05–5.09 (m, 1H; CHN), 5.47 (dd, J = 6.2 Hz, J = 1.9 Hz, 1H; CHC), 6.44 (dd, J = 1.6 Hz, J = 3.5 Hz, 1H; C*H*CHO (furan)), 6.51 (d, J = 3.5 Hz, 1H; CHC (furan)), 7.08 (s, 1H; NH), 7.26 (d, J = 8.1 Hz, 2H; *m*-CH (Ts)), 7.40 (d, J = 1.6 Hz, 1H; CHO (furan)), 7.88 ppm (d, J = 8.1 Hz, 2H; *o*-CH (Ts)); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.7, 18.2, 21.5, 35.3, 61.4, 95.6, 106.6, 111.6, 127.6, 128.7 (2C), 129.2 (2C), 136.5, 142.8, 144.4, 146.1, 150.5 ppm; IR: $\tilde{\nu}$ = 3243 (w), 2967 (w), 1696 (s), 1684 (s), 1177 cm^{-1} (s); HRMS: m/z: 360.1184 $[M]^+$; calcd for $C_{18}H_{20}N_2O_4S$: 360.1143.

4,6-Diisopropyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6s): The product was crystallised from THF. Yield: 40%; m.p. 177–181°C [THF]; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.82 (d, J = 6.9 Hz, 3H; CH_3CH), 0.91 (d, J = 6.9 Hz, 3H; CH_3CH), 1.04 (d, J = 6.8 Hz, 6H; CH_3CH), 2.08–2.25 (m, 2H; C*H*(CH$_3$)$_2$), 4.70 (d, J = 5.7 Hz, 1H; CHC), 4.87 (t, J = 5.7 Hz, 1H; CHN), 6.87 (s, 1H; NH), 7.24 (d, J = 8.1 Hz, 2H; *m*-CH (Ts)), 7.85 ppm (d, J = 8.1 Hz, 2H; *o*-CH (Ts)); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.7, 18.5, 20.7, 20.9, 22.0, 31.1, 35.3, 61.5, 94.0, 129.1 (2C), 129.5 (2C), 137.4, 142.8, 144.6, 151.8 ppm; IR (KBr): $\tilde{\nu}$ = 3455 (w), 2961 (w), 1676 (s), 1350 (m), 1163 cm^{-1} (m); HRMS (EI): m/z: 336.1516 $[M]^+$; calcd for $C_{17}H_{24}N_2O_3S$: 336.1508.

4-(Benzyloxymethyl)-6-isopropyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6t): The product was purified by column chromatography. Yield: 21%; m.p. 148–149°C [EA]; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.09 (d, J = 6.9 Hz, 6H; (CH_3)$_2$CH), 2.14–2.29 (m, 1H; C*H*(CH$_3$)$_2$), 2.42 (s, 3H; CH_3C$_6$H$_4$), 3.42–3.53 (m, 2H; CH_2CH), 4.51 (s, 2H; CH_2Ph), 4.87 (d, J = 5.2 Hz, 1H; CHC), 5.11–5.19 (m, 1H; CHN), 6.45 (s, 1H; NH), 7.22–7.98 ppm (m, 9H; Ph-H); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.2 (2C), 21.6, 30.6, 55.1, 72.0, 73.1, 95.1, 127.4 (2C), 127.6, 128.0 (2C), 128.9 (2C), 129.0 (2C), 136.9, 138.0, 143.1, 144.2, 150.8 ppm; IR (KBr): $\tilde{\nu}$ = 3221 (w), 3115 (w), 2963 (w), 1699 (s), 1670 (s), 1348 (s), 1167 cm^{-1} (s); HRMS (EI): m/z: 414.1612 $[M]^+$; calcd for $C_{22}H_{26}N_2O_4S$: 414.1613.

4-(4-Methoxyphenyl)-5-methyl-6-phenyl-3-tosyl-3,4-dihydropyrimidin-2-(1*H*)-one (6u): The product was crystallised from ethyl acetate. Yield: 35%; m.p. 194–195°C [EA]; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.65 (s, 3H; CH_3C), 2.32 (s, 3H; CH_3C$_6$H$_4$), 3.83 (s, 3H; CH_3O), 5.75 (s, 1H; CHN), 6.28 (s, 1H; NH), 6.85 (dd, J = 6.7 Hz, J = 2.0 Hz, 2H; *m*-CH (Ph)), 7.04 (d, J = 8.3 Hz, 2H; *m*-CH (Ts)), 7.28–7.40 ppm (m, 9H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.7, 21.5, 55.4, 63.9, 109.8, 114.2 (2C), 128.5 (2C), 128.7 (2C), 128.8, 128.9 (2C), 129.0 (2C), 129.1 (3C), 132.2, 133.8, 136.4, 144.0, 149.6, 159.9 ppm; IR (KBr): $\tilde{\nu}$ = 3208 (m), 3102 (m), 2932 (m), 1680 (s), 1511 (m), 1351 (m), 1167 cm^{-1} (s); HRMS (EI): m/z: 448.1465 $[M]^+$; calcd for $C_{25}H_{24}N_2O_4S$: 448.1457.

6-(Furan-2-yl)-4-(4-methoxyphenyl)-5-methyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (6v): The product was crystallised from ethyl acetate. Yield: 90%; m.p. 202–204°C (decomp) [EA]; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 1.89 (s, 3H; CH_3C), 2.32 (s, 3H; CH_3C$_6$H$_4$), 3.81 (s, 3H; CH_3O), 5.77 (s, 1H; CHN), 6.45–6.48 (m, 2H; CH (furan)), 6.78 (s, 1H; NH), 6.82 (d, J = 8.8 Hz, 2H; *m*-CH (C_6H_4OMe)), 7.06 (d, J = 8.2 Hz, 2H; *m*-CH (Ts)), 7.31 (d, J = 8.8 Hz, 2H; *o*-CH (C_6H_4OMe)), 7.39 (d, J = 8.2 Hz, 2H; *o*-CH (Ts)), 7.41–7.45 ppm (m, 1H; CHO (furan)); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 16.1, 21.4, 55.2, 64.0, 109.9, 110.0, 111.6, 114.0 (2C), 120.5, 128.6 (2C), 128.8 (2C), 129.0 (2C), 131.5, 136.1, 142.0, 144.0, 145.8, 149.5, 159.7 ppm; IR (KBr): $\tilde{\nu}$ = 3225 (m), 3116 (m), 2925 (w), 1688 (s), 1674 (s), 1510 (s), 1258 cm^{-1} (s); HRMS (EI): m/z: 438.1261 $[M]^+$; calcd for $C_{23}H_{22}N_2O_5S$: 438.1249.

4-(4-Methoxyphenyl)-3-(4-nitrophenyl)-6-phenyl-3,4-dihydropyrimidin-2-(1*H*)-one (6w): The product was crystallised from THF/pentane. Yield: 26%; m.p. 211–214°C [THF]; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 3.77 (s, 3H; CH_3O), 5.34 (d, J = 5.1 Hz, 1H; CHC), 5.45 (d, J = 5.1 Hz, 1H; CHN), 6.79–8.14 ppm (m, 14H; Ph-H and NH); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 55.3, 63.8, 100.1, 114.5 (2C), 124.2 (2C), 125.1 (2C), 127.4 (2C), 127.8 (2C), 129.0 (2C), 129.5, 133.1, 133.6, 134.7, 145.4, 147.1, 152.4, 159.6 ppm; IR (KBr): $\tilde{\nu}$ = 3225 (w), 3109 (w), 1667 (s), 1510 (s),

1345 cm^{-1} (s); HRMS (EI): *m/z*: 401.1387 $[M]^+$; calcd for $C_{23}H_{19}N_3O_4$: 401.1376.

Methyl 6-(4-methoxyphenyl)-2-oxo-4-phenyl-2,3-dihydropyrimidine-1-(6*H*)-carboxylate (6x): The product was purified by column chromatography. Yield: 70%; m.p. 147–150°C [EA]; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.68 (s, 3H; CH_3), 3.80 (s, 3H; CH_3), 5.49 (dd, J = 6.4 Hz, J = 1.5 Hz, 1H; CHC), 5.87 (d, J = 6.4 Hz, 1H; CHN), 6.80 (d, J = 8.6 Hz, 2H; Ph-H), 7.00 (s, 1H; NH), 7.29–7.41 ppm (m, 7H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 54.6, 55.7, 57.2, 102.2, 114.6 (2C), 125.6 (2C), 128.6 (2C), 129.5 (2C), 129.9, 132.6, 133.6, 135.6, 150.7, 155.0, 159.9 ppm; IR (KBr): $\tilde{\nu}$ = 3259 (m), 2910 (m), 1734 (s), 1694 (s), 1408 (s), 1268 cm^{-1} (s); HRMS: *m/z*: 338.1251 $[M]^+$; calcd for $C_{19}H_{18}N_2O_4$: 338.1267.

Methyl 4-isopropyl-6-(4-methoxyphenyl)-2-oxo-2,3-dihydropyrimidine-1-(6*H*)-carboxylate (6y): The product was purified by column chromatography and isolated as a light-yellow oil. Yield: 29%; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 1.06 (d, J = 6.9 Hz, 6H; $(CH_3)_2CH$), 2.20–2.36 (m, 1H; $CH(CH_3)_2$), 3.71 (s, 3H; CH_3), 3.76 (s, 3H; $COOCH_3$), 4.92 (d, J = 6.1 Hz, 1H; CHC), 5.65 (d, J = 6.1 Hz, 1H; CHN), 6.76 (d, J = 8.8 Hz, 2H; *m*-CH (C_6H_4OMe)), 7.22 (d, J = 8.8 Hz, 2H; *o*-CH (C_6H_4OMe)), 7.58 ppm (s, 1H; NH); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 20.4, 20.8, 20.9, 54.3, 55.6, 57.0, 99.0, 114.5 (2C), 128.5 (2C), 133.4, 141.7, 151.7, 155.1, 159.7 ppm; IR (KBr): $\tilde{\nu}$ = 3240 (w), 2962 (w), 1770 (s), 1714 (s), 1512 (m), 1255 cm^{-1} (s); HRMS: *m/z*: 304.1433 $[M]^+$; calcd for $C_{16}H_{20}N_2O_4$: 304.1423.

3-Benzoyl-4-(4-methoxyphenyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (6z): The product was crystallised from THF. Yield: 70%; m.p. 186–187°C (decomp) [THF]; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.78 (s, 3H; CH_3), 5.74 (d, J = 6.3 Hz, 1H; CHC), 6.01 (d, J = 6.3 Hz, 1H; CHN), 6.87 (d, J = 8.8 Hz, 2H; *o*-CH (C_6H_4OMe)), 7.35–7.46 (m, 10H; Ph-H), 7.57–7.59 ppm (m, 2H; *o*-CH (COPh)); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 55.3, 55.9, 102.9, 114.1 (2C), 125.1 (2C), 127.8 (2C), 128.0 (2C), 128.4 (2C), 129.1 (2C), 129.5, 131.2, 132.0, 133.0, 135.4, 136.3, 152.3, 159.4, 171.7 ppm; IR (KBr): $\tilde{\nu}$ = 3282 (s), 2968 (w), 2839 (w), 1702 (s), 1688 (s), 1509 (s), 1396 cm^{-1} (s); HRMS (EI): *m/z*: 384.1485 $[M]^+$; calcd for $C_{24}H_{20}N_2O_3$: 384.1474.

General procedure for the trapping experiments with MeI and H_2O: *n*BuLi (1.6 M in hexane; 1.2 equiv) was added dropwise to a stirred solution of phosphonate **1** (0.2 M in dry THF) at −78°C. The resulting solution was stirred for 1.5 h and then nitrile **2** (1.1 equiv) was added. The reaction mixture was allowed to warm to −5°C over 1.5 h. After completion or overnight stirring at room temperature, MeI or H_2O (1.1 equiv) was added. The solvent was then removed from the reaction mixture under reduced pressure at room temperature. The crude product was purified by column chromatography. The composition of the product was analysed by applying various NMR techniques (see below).

Trapping experiments with MeI

(*E,Z*)-Diethyl *N*-methyl-*N*-((*Z*)-(2-methylpent-3-en-3-yl)) phosphoramidate (7a): Application of the general procedure (see above) using **1b** and **2b** with overnight stirring gave **7a**. Yield: 37%; *E*:*Z* = 1:6; (*Z*)-**7a**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.02 (d, J = 6.8 Hz, 6H; $(CH_3)_2CH$), 1.25–1.29 (m, 6H; CH_3CH_2), 1.60–1.64 (m, 3H; =CHCH_3), 2.43–2.50 (m, 1H; $CH(CH_3)_2$), 2.76 (d, J = 9.0 Hz, 3H; NCH_3), 3.97–4.13 (m, 4H; OCH_2CH_3), 5.5 ppm (q, J = 6.8 Hz, 1H; =CH); ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 7.2; (*E*)-**7a**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.07 (d, J = 7.0 Hz, 6H; $(CH_3)_2CH$), 1.25–1.29 (m, 6H; CH_3CH_2), 1.60–1.64 (m, 3H; =CHCH_3), 2.74 (d, J = 9.9 Hz, 3H; NCH_3), 2.78–2.87 (m, 1H; $CH(CH_3)_2$), 3.97–4.13 (m, 4H; OCH_2CH_3), 5.46 ppm (dq, J = 2.7 Hz, J = 7.1 Hz, 1H; =CH); ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 7.8 ppm. Besides **7a**, 6% of another phosphoramidate was identified.[22]

(*Z*)-Diethyl-1,2-diphenylvinyl-(methyl)phosphoramidate (7b): Application of the general procedure (see above) using **1c** and **2a** with overnight stirring gave **7b**. Yield: 100%; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 6H; CH_3CH_2), 2.62 (d, J = 9.1 Hz, 3H; NCH_3), 4.06–4.18 (m, 4H; CH_2), 6.49 (s, 1H; =C*H*Ph), 6.82–7.25 ppm (m, 10H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.1 (d, J = 7.2 Hz), 35.5 (d, J = 5.7 Hz), 64.0 (d, J = 6.2 Hz), 123.0 (d, J = 3.2 Hz), 126.5 (s), 127.9 (s, 2C), 128.5 (s, 3C), 129.0 (s, 2C), 129.8 (s, 2C), 135.3 (d, J = 5.1 Hz), 136.0 (d, J = 1.2 Hz), 141.0 ppm (d, J = 3.3 Hz); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 6.0 ppm.

(*Z*)-Diethyl methyl(3-methyl-1-phenylbut-1-en-2-yl)phosphoramidate (7c): Application of the general procedure (see above) using **1c** and **2b** with overnight stirring gave **7c**. Yield: 20%; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.18 (d, J = 6.8 Hz, 6H; $(CH_3)_2CH$), 1.28 (td, J = 7.1 Hz, J = 0.7 Hz, 6H; CH_3CH_2O), 2.72 (d, J = 8.8 Hz, 3H; NCH_3), 2.73–2.81 (m, 1H; $CH(CH_3)_2$), 3.96–4.14 (m, 4H; CH_2O), 6.05 (s, 1H; =C*H*Ph), 7.16–7.31 ppm (m, 5H; Ph-H); ^{31}P NMR (101.25 MHz, THF): δ = 4.0 ppm. Besides **1c** and **7c**, 10–20% of another phosphonate was identified.[23]

(*E*)-Diethyl *N*-(methyl)-*N*-(1-phenylbuta-1,3-dienyl)phosphoramidate (7d): Application of the general procedure (see above) using **1d** and **2a** with overnight stirring gave **7d** and **10**.

7d: Yield: 37%; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.16–1.20 (m, 6H; CH_3CH_2O), 2.62 (d, J = 8.9 Hz, 3H; NCH_3), 3.94–4.04 (m, 4H; OCH_2), 4.86 (d, J = 9.4 Hz, 1H; =CH_2), 5.11 (d, J = 16.0 Hz, 1H; =CH_2), 6.10–6.38 ppm (m, 2H; =CHC*H*=), 7.16–7.53 ppm (m, 5H; Ph-H); ^{31}P NMR (101.25 MHz, THF): δ = 6.2 ppm.

(*E*)-Diethyl 1-(methylamino)-1-phenylbuta-1,3-dien-2-ylphosphonate (10): Yield: 63%; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.16–1.20 (m, 6H; CH_3CH_2O), 2.89 (d, J = 6.5 Hz, 3H; NCH_3), 3.73–4.04 (m, 4H; OCH_2), 5.35 (d, J = 6.8 Hz, 1H; =CH_2), 5.62–5.69 (m, 1H; =CH_2), 6.98–7.14 (m, 1H; C*H*=CH_2), 7.17–7.53 ppm (m, 5H; Ph-H); ^{31}P NMR (101.25 MHz, THF): δ = 22.1 ppm.

Trapping experiment with H_2O

Application of the general procedure (see above) using **1c** and **2a** with overnight stirring gave **8a** and **9**. Three products were identified, (*E*)- and (*Z*)-**8a** (yield: 58%; *E*:*Z* = 1:1.5) and **9** (yield: 42%).

(*Z*)-Diethyl *N*-(1,2-diphenylvinyl)phosphoramidate (8a): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.10 (dt, J = 0.9 Hz, J = 7.1 Hz, 6H; CH_3), 3.86–3.96 (m, 4H; CH_2), 5.91 (s, 1H; C*H*Ph), 7.16–7.57 ppm (m, 10H; Ph-H); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 3.7 ppm.

(*E*)-Diethyl *N*-(1,2-diphenylvinyl)phosphoramidate (8a): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.32 (dt, J = 0.7 Hz, J = 7.1 Hz, 6H; CH_3), 4.11–4.16 (m, 4H; CH_2), 6.32 (s, 1H; C*H*Ph), 6.82–7.01 (m, 5H; Ph-H), 7.16–7.57 ppm (m, 5H; Ph-H); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 10.4 ppm.

Diethyl *N*-(1,2-diphenylethylidene)phosphoramidate (9): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.24 (dt, J = 0.7 Hz, J = 7.1 Hz, 6H; CH_3), 3.98–4.04 (m, 4H; CH_2O), 4.20 (s, 2H; CH_2Ph), 7.16–7.57 (m, 8H; Ph-H), 7.93–7.95 ppm (m, 2H; Ph-H); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 2.2 ppm.

1-(3-(4-Methoxyphenyl)-1-phenylallylidene)-3-phenylurea (11a): The general HWE/aza-DA procedure was followed using **1a**, **2a**, **3a**, and **5c**. After purification by column chromatography, **11a** was isolated as a sticky oil. Yield: 40%; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 3.82 (s, 3H; CH_3O), 5.19 (s, 1H; NH), 6.81–7.72 ppm (m, 16H; Ph-H and CH); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 55.4, 114.1 (2C), 118.9, 119.0 (2C), 123.8, 127.2, 128.4 (2C), 129.0 (2C), 129.3 (2C), 129.9 (2C), 130.7, 137.3, 137.9, 145.5, 161.1 (2C), 172.3 ppm; IR (KBr): $\tilde{\nu}$ = 3380 (w), 3017 (w), 1580 (s), 1254 (m), 1173 cm^{-1} (m); HRMS (EI): *m/z*: 356.1523 $[M]^+$; calcd for $C_{23}H_{20}N_2O_2$: 356.1525.

6-(4-Methoxystyryl)-6-phenyl-1,3-bis((*S*)-1-phenylethyl)-1,3,5-triazinane-2,4-dione (11b): The general HWE/aza-DA procedure was followed using **1a**, **2a**, **3a**, and (*S*)-**5f**. The product was purified by column chromatography to afford **11b** in 42% yield with 20% *de*. Diastereomeric excess was determined by HPLC analysis (Pathfinder 100PS, 5.0 μm, methanol/0.02 M ammonium acetate buffer pH 4.5 70/30, 1 mL min^{-1}); t_r = 70.88 min (minor), t_r = 63.73 min (major); R = 2.22, α = 1.12; m.p. 66–69°C [EA]; $[\alpha]_D^{20}$ = −72.0 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.72 (d, J = 7.0 Hz, 3H; CH_3CH), 1.73 (d, J = 7.0 Hz, 3H; CH_3CH), 1.75 (d, J = 7.0 Hz, 3H; CH_3CH), 1.78 (d, J = 7.0 Hz, 3H; CH_3CH), 3.81 (s, 3H; CH_3O), 3.85 (s, 3H; CH_3O), 4.44 (q, J = 7.0 Hz, 1H; CH_3CH), 4.61 (br s, 1H; CH_3CH), 5.61–5.66 (m, 2H; CH_3CH), 6.15 (d, J = 15.9 Hz, 1H; CHCH), 6.29 (d, J = 15.6 Hz, 1H; CHCH), 6.30 (d, J = 15.9 Hz, 1H; CHCH), 6.63 (d, J = 15.6 Hz, 1H;

CHCH), 6.81 (d, J = 8.7 Hz, 2H; Ph-H), 6.91 (d, J = 8.7 Hz, 2H; Ph-H), 7.00–8.01 ppm (m, 34H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.5, 16.6, 19.9, 20.2, 51.1 (2C), 55.3, 55.4, 56.4, 57.5, 76.1, 76.6, 114.0 (2C), 114.2 (2C), 125.3, 125.5, 126.2, 126.3, 126.7, 126.9 (4C), 127.0 (2C), 127.1, 127.7 (6 C), 127.8 (6 C), 128.0 (2C), 128.2 (2C), 128.4 (4C), 128.6 (2C), 129.0 (2C), 129.4, 129.7, 132.3, 132.5, 140.3, 140.5, 141.2 (2C), 142.0, 142.3, 152.2, 152.5, 152.6, 153.1, 160.0, 160.2 ppm; IR (KBr): $\tilde{\nu}$ = 3027 (w), 1711 (s), 1698 (s), 1512 (s), 1446 (s), 1250 (s), 1028 cm^{-1} (s); HRMS (EI): m/z: 531.2522 $[M]^+$; calcd for $C_{34}H_{33}N_3O_3$: 531.2522.

4-(4-Methoxyphenyl)-3,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one (12): DHPM **12** was prepared under MW conditions from **6a** (procedure A) or from **11a** (procedure B).

Procedure A: DHPM **6a** (0.053 mmol, 23 mg) and phenyl isocyanate (1.2 equiv.) were dissolved in dry dioxane (1 mL) and heated in a microwave oven (maximum power 300 W, ramp time 30 min, hold time 60 min at 190 °C). The solvent was then evaporated and the crude product was purified by column chromatography using PE/EA (4:1) → EA. DHPM **12** was isolated in 58% yield.

Procedure B: Urea **11a** (0.13 mmol, 47 mg) was dissolved in toluene (2.5 mL) and heated in a microwave oven (maximum power 300 W, ramp time 20 min, hold time 75 min at 120 °C). The solvent was then evaporated and the crude product was purified by column chromatography using PE/EA (3:1) → EA. DHPM **12** was isolated in 38% yield.

m.p. 139–142 °C [EA]; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.81 (s, 3H; CH_3O), 5.28 (dd, J = 2.1 Hz, J = 4.9 Hz, 1H; CHC), 5.34 (d, J = 4.9 Hz, 1H; CHN), 6.80 (d, J = 8.7 Hz, 2H; *m*-C*H* (C_6H_4OMe)), 6.93 (s, 1H; NH), 7.07–7.51 ppm (m, 12H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 55.2, 64.6, 99.9, 114.0 (2C), 125.0 (2C), 127.0, 128.0 (2C), 128.5 (2C), 128.9 (4C), 129.1, 134.1, 134.2, 134.9, 141.0, 153.0, 159.4 ppm; IR (NaCl): $\tilde{\nu}$ = 2902 (w), 2839 (w), 1652 (s), 1507 (s), 1249 (m), 1174 cm^{-1} (m); HRMS (EI): m/z: 356.1516 $[M]^+$; calcd for $C_{23}H_{20}N_2O_2$ 356.1525.

(4*R*/S,6*R*)-6-*sec*-Butyl-4-(4-methoxyphenyl)-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (13a): The general HWE/aza-DA procedure was followed using **1a**, (*S*)-**2d**, **3a**, and **5a**. The product was purified by column chromatography to afford **13a** as a 1:1.01 mixture of diastereomers. Yield: 60%. Diastereomeric ratio was determined by HPLC analysis (LiChroCART 250–4 Whelk-O 1, *n*-hexane/2-propanol, 90:10, 1 mL min^{-1}); t_r = 9.33 min (minor), t_r = 10.88 min (major); R = 2.19, α = 1.26; m.p. 149–153 °C [EA]; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.3 Hz, 6H; CH_3CH$_2$), 1.10 (dd, J = 1.1 Hz, J = 5.8 Hz, 6H; CH_3CH), 1.41–1.52 (m, 4H; CH_2CH$_3$), 2.02–2.08 (m, 2H; CHCH$_3$), 2.35 (s, 6H; CH_3C$_6$H$_4$), 3.85 (s, 6H; CH_3O), 4.90 (d, J = 4.5 Hz, 2H; CHC), 5.82–5.90 (m, 2H; CHN), 6.86 (d, J = 8.2 Hz, 4H; *o*-C*H* (C_6H_4OMe)), 7.06 (d, J = 8.1 Hz, 4H; *m*-CH (Ts)), 7.24–7.29 ppm (m, 10H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 11.5, 11.6, 17.9, 18.0, 21.5, 21.5, 26.8, 26.9, 37.9, 38.1, 55.4, 55.4, 59.1, 59.2, 100.0, 100.1, 114.0 (2C), 114.1 (2C), 128.6 (4C), 128.8 (8C), 133.8, 133.9, 136.4 (2C), 138.2, 138.3, 143.9 (2C), 151.0 (2C), 159.6 ppm (2C); IR: (KBr): $\tilde{\nu}$ = 3239 (m), 2962 (m), 1681 (s), 1509 (m), 1345 (s), 1167 cm^{-1} (s); HRMS (EI): m/z: 414.1603 $[M]^+$; calcd for $C_{22}H_{26}N_2O_4S$: 414.1613.

(1*S*,4*R*/*S*,5*R*)-4-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)-6-phenyl-3-tosyl-3,4-dihydropyrimidin-2(1*H*)-one (13b): The general HWE/aza-DA procedure was followed using **1a**, **2a**, (−)-myrtenal (**3j**), and **5a**. The product was purified by column chromatography to afford **13b** as a 10.8:1 mixture of diastereomers (*de* = 83%). Yield: 80%. Diastereomeric excess was determined by HPLC analysis (LiChroCART 250–4 Whelk-O 1, *n*-hexane/2-propanol, 95:5, 1 mL min^{-1}); t_r = 13.39 min (minor), t_r = 16.12 min (major); R = 2.92, α = 1.25; m.p. 76–79 °C; $[\alpha]_D^{20}$ = +118 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400.13 MHz, $CDCl_3$): peaks of the major isomer are reported: δ = 0.76 (s, 3H; CH_3 myrtenal), 1.13 (s, 3H; CH_3 myrtenal), 1.96–2.27 (m, 6H; 2 × CH_2, 2 × CH (myrtenal)), 2.34 (s, 3H; CH_3C$_6$H$_4$), 5.15 (d, J = 6.2 Hz, 1H; CHC), 5.50–5.53 (m, 2H; CHN and CHCH$_2$), 6.69 (s, 1H; NH), 7.17–7.34 (m, 7H; Ph-H), 7.89 ppm (d, J = 8.1 Hz, 2H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$: δ = 21.6, 22.0, 26.5, 31.2, 31.6, 38.6, 40.9, 42.5, 60.1, 99.6, 121.3, 125.6 (2C), 129.4 (2C), 129.5 (2C), 129.7 (2C), 129.9, 133.8, 136.1, 137.0, 144.8, 145.4, 150.9 ppm; IR (KBr): $\tilde{\nu}$ = 3259 (m), 2912 (m), 1689 (s), 1669 (s), 1357 (s), 1171 (s), 1089 cm^{-1} (m); HRMS (EI): m/z: 448.1813 $[M]^+$; calcd for $C_{26}H_{28}N_2O_3S$: 448.1821.

α,β-Unsaturated ketones (15a,b and 16a,b): The general HWE/aza-DA procedure was followed, but instead of isocyanate **5**, 5N sulfuric acid (1 mL) was added and the reaction mixture was stirred for 1 h. The mixture was then extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (20 mL) and dried over Na_2SO_4. ^{1}H NMR analysis of the crude reaction mixture revealed that the α,β-unsaturated ketones **15** or **16** had been formed. The analytical data were in agreement with those reported previously.[30]

General procedure for the synthesis of thiazines 18a–f: *n*BuLi (1.6M in hexane; 1.2 equiv.) was added dropwise to a stirred solution of phosphonate **1** (0.2M in dry THF) at −78 °C. The resulting solution was stirred for 1.5 h and then nitrile **2** (1.1 equiv.) was added. The reaction mixture was allowed to warm to −5 °C over 1.5 h and then aldehyde **3** (1.1 equiv.) was added. The resulting mixture was stirred for a further 0.5 h at −5 °C and thereafter for 1.5 h at room temperature. Isothiocyanate **17** (1.1 equiv.) was then added dropwise over 10 min and the resulting solution was stirred overnight. The solvent was removed under reduced pressure and the crude product was isolated by column chromatography (PE/EA, 10:1 → 3:1).

***N*,4,6-Triphenyl-6*H*-1,3-thiazin-2-amine (18a)**: Yield: 74%; m.p. 128–129 °C [EA]; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 5.03 (d, J = 5.6 Hz, 1H; CHC), 5.76 (d, J = 5.6 Hz, 1H; CHS), 7.11 (t, J = 7.3 Hz, 1H; Ph-H), 7.29–7.57 (m, 12H; Ph-H), 7.79 ppm (d, J = 6.9 Hz, 2H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 44.5, 101.1, 120.9 (2C), 123.7, 125.9 (2C), 127.9 (2C), 128.1, 128.4, 128.5 (2C), 128.9 (4C), 138.2, 140.7, 141.5, 145.6, 150.0 ppm; IR (KBr): $\tilde{\nu}$ = 1574 (s), 1493 (w), 1292 (w), 1205 (w), 756 (m), 692 cm^{-1} (m); HRMS (EI): m/z: 342.1187 $[M]^+$; calcd for $C_{22}H_{18}N_2S$ 342.1191.

6-(4-Methoxyphenyl)-*N*,4-diphenyl-6*H*-1,3-thiazin-2-amine (18b): The product was isolated as a yellow-brown oil. Yield: 58%; ^{1}H NMR (400.13 MHz, DMSO): δ = 3.70 (s, 3H; CH_3), 5.11 (d, J = 6.5 Hz, 1H; CHC), 5.91 (d, J = 6.5 Hz, 1H; CHS), 6.88 (d, J = 8.6 Hz, 2H; *m*-CH (C_6H_4OMe)), 6.96–6.99 (m, 1H; *p*-CH (NHPh)), 7.25–7.40 (m, 7H; Ph-H), 7.78–7.81 (m, 4H; *o*-CH (NHPh and Ph)), 9.32 ppm (s, 1H; NH); ^{13}C NMR (100.61 MHz, DMSO): δ = 42.0, 55.1, 101.1, 114.0 (2C), 119.5 (2C), 122.3, 125.3 (2C), 127.7, 128.3 (2C), 128.5 (2C), 128.6 (2C), 133.6, 139.1, 140.5, 146.2, 148.4, 158.7 ppm; IR (NaCl): $\tilde{\nu}$ = 2961 (w), 1577 (s), 1509 (s), 1253 (s), 1030 cm^{-1} (s); HRMS (EI): m/z: 372.1230 $[M]^+$; calcd for $C_{23}H_{20}N_2OS$: 372.1296.

4-Isopropyl-*N*,6-diphenyl-6*H*-1,3-thiazin-2-amine (18c): Yield: 61%; m.p. 124–128 °C [EA]; ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 1.20 (d, J = 6.9 Hz, 6H; CH_3), 2.40–2.61 (m, 1H; CH(CH$_3$)$_2$), 4.77 (d, J = 4.9 Hz, 1H; CHC), 4.99 (d, J = 4.9 Hz, 1H; CHS), 7.01–7.29 ppm (m, 10H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 21.5, 21.6, 34.3, 44.3, 97.7, 121.6, 123.8, 128.2 (2C), 128.3 (2C), 129.1 (2C), 129.2 (2C), 139.3, 141.2, 149.9, 150.3 ppm; IR (KBr): $\tilde{\nu}$ = 3201 (w), 2962 (w), 1603 (s), 1581 (s), 1489 (m), 1309 (m), 1194 cm^{-1} (m); HRMS (EI): m/z: 308.1354 $[M]^+$; calcd for $C_{19}H_{20}N_2S$: 308.1347.

***N*-Ethyl-6-(4-methoxyphenyl)-4-phenyl-6*H*-1,3-thiazin-2-amine (18d)**: The product was isolated as a yellow oil. Yield: 56%; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.3 Hz, 3H; CH_3CH$_2$), 3.57–3.60 (m, 2H; CH_2), 3.78 (s, 3H; CH_3O), 4.88 (d, J = 5.8 Hz, 1H; CHS), 5.71 (d, J = 5.8 Hz, 1H; CHCHS), 6.84 (d, J = 8.7 Hz, 2H; Ph-H), 7.25–7.36 (m, 5H; Ph-H), 7.80 ppm (d, J = 7.4 Hz, 2H; Ph-H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 14.9, 37.3, 43.9, 55.3, 99.9, 114.2 (2C), 125.6 (2C), 127.8, 128.1 (2C), 128.9 (2C), 133.5, 139.4, 147.4, 152.4, 159.2 ppm; IR (NaCl): $\tilde{\nu}$ = 3400 (w), 2969 (w), 1567 (s), 1510 (s), 1249 cm^{-1} (s); HRMS (EI): m/z: 324.1310 $[M]^+$; calcd for $C_{19}H_{20}N_2OS$: 324.1296.

6-(4-Methoxyphenyl)-4-phenyl-*N*-(1-phenylethyl)-6*H*-1,3-thiazin-2-amine (18e): The product was isolated as a yellow oil as a 1:1 mixture of diastereomers. Yield: 64%; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.54 (d, J = 7.2 Hz, 3H; CH(CH_3)Ph), 1.56 (d, J = 7.5 Hz, 3H; CH(CH_3)Ph), 3.79 (s, 3H; OCH_3), 3.80 (s, 3H; OCH_3), 4.85 (d, J = 6.0 Hz, 1H; CHS), 4.88 (d, J = 5.6 Hz, 1H; CHS), 5.38–5.41 (m, 2 × 1H; CH(CH$_3$)Ph), 5.68 (d, J = 5.6 Hz, 1H; CHCHS), 5.71 (d, J = 6.0 Hz, 1H; CHCHS), 6.81–7.60 ppm (m, 28H; Ph-H); ^{13}C NMR (400.13 MHz, $CDCl_3$): δ = 22.7,

22.8, 43.8, 44.1, 51.9 (2C), 55.3, 55.4, 99.8, 100.3, 114.1 (2C), 114.2 (2C), 125.7 (4C), 126.0 (2C), 126.1 (2C), 127.0, 127.1, 127.8 (2C), 128.0 (4C), 128.5 (2C), 128.6 (2C), 128.9 (4C), 133.3, 133.4, 139.1 (2C), 144.0, 144.1, 150.3, 150.7, 159.2 (2C), 188.7 ppm (2C); IR (NaCl): $\tilde{\nu} = 3399$ (w), 2929 (w), 1567 (s), 1509 (s), 1250 cm^{-1} (s); HRMS (EI): m/z: 400.1612 $[M]^+$; calcd for $C_{25}H_{24}N_2OS$: 400.1609.

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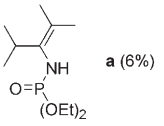
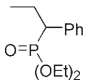
[22] Phosphoramidate **a**, bearing an additional Me group, was also identified.



a (6%)

[23] Besides the phosphoramidates, considerable amounts of the phosphonate **b** were also observed.



b (10-20%)

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