

On-Demand Selection of the Reaction Path from Imino Diels–Alder to Ene-Type Cyclization: Synthesis of Epiminopyrimido[4,5-*b*]azepines

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Controlling the mode of reaction of a reactive intermediate such as an imine or iminium ion should enable the on-demand selection of the final products from the same starting materials. The successful execution of such a strategy will reduce the time required to prepare diverse scaffolds. The imines derived from 4-(allylamino)pyrimidine-5-carbaldehydes and anilines undergo Diels–Alder reactions to give pyrimido[4,5-*h*][1,6]naphthyridines in high yields. A complete switch from the intramolecular aza-Diels–Alder (IADA) path to an ene-type cyclization reaction was achieved by simply adjusting the reaction conditions (amount of acid catalyst, solvent, and temperature). This newly introduced ene-type cyclization reaction was used to prepare a series of epi-

minopyrimido[4,5-*b*]azepines. To gain insight into the mechanism of the two reaction pathways, a DFT study was carried out. Theoretical calculations showed that under acidic conditions an iminium intermediate favors the low-energy IADA pathway, which proceeds in a [4⁺ + 2] fashion. When acid is absent, the neutral imine intermediate favors the thermal ene-type cyclization reaction, which takes place by transfer of an allylic proton from the allylic amine to imine, followed by a barrierless nucleophilic addition process between the in-situ-generated anionic allylic amine and iminium ion. Amine addition to the alkene finally gives the epiminopyrimido[4,5-*b*]azepines.

Introduction

Efficient access to diverse scaffolds is highly desirable in organic and medicinal chemistry.^[1] Different scaffolds usually require different sets of starting materials, which must be prepared separately, leading to additional effort and cost. However, organic compounds very often contain multiple reactive sites that can potentially lead to multiple products by following different pathways. It is therefore desirable for different scaffolds to be prepared from the same set of starting materials by simply changing the reaction conditions. This has been an important area of research in synthetic organic chemistry.^[2]

The intramolecular inverse electron-demand aza-Diels–Alder (IADA) reaction (also known as the Povarov reaction^[3]) and the ene reaction^[4] are two powerful methods that can be used for the synthesis of nitrogen-containing

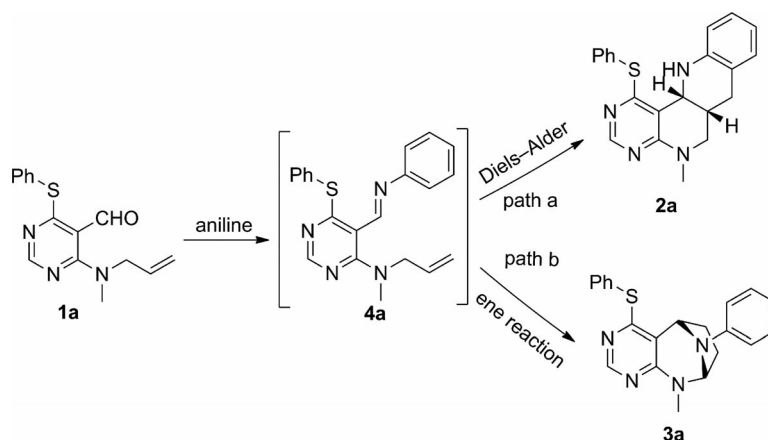
heterocycles such as alkaloids, and they also represent two alternative reaction pathways available to suitable imines. They share several features: both involve six electrons, and their mechanisms may be pericyclic or stepwise. Thus, they may exist as competing reactions. However, the activation energy of a simple alkene ene reaction is generally higher than that of the IADA reaction, so it usually requires higher temperatures, and this may limit its synthetic application.^[5] Recently, the discovery of Lewis-acid- and Brønsted-acid-catalyzed ene reactions of a variety of substrates has expanded their utility in organic synthesis.^[5b,6] We wondered whether these two reactions could be used to generate different scaffolds from the same starting materials at will by changing the reaction conditions. Noguchi's group has thoroughly investigated the intramolecular ene-like reactions of several heterocyclic substrates,^[7] and they reported that a competition exists between thermal ene reactions and IADA reactions in 2-[*N*-(alk-2-enyl)benzylamino]-3-vinylpyrido[1,2-*a*]pyrimidin-4(4*H*)-ones.^[7k] In addition, Nagarajan et al. have studied the switch from IADA to ene-type cyclization of aminoanthraquinones with citronellal or prenylated salicylaldehydes resulting from changes in the substituents.^[8] However, to date, a complete switch from an IADA to an ene-type reaction of an imine involving the same set of reactants has not been reported.

As part of our ongoing research into the synthesis of heterocyclic scaffolds,^[9] we previously prepared hexa-

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Scheme 1. The IADA and ene-type cyclization pathways of imine **4a**.

hydrobenzo[*b*]pyrimido[4,5-*h*][1,6]naphthyridines **2a** by the IADA reaction of imine intermediate **4a** under acidic conditions (for details, see the left part of Figure 1b and the corresponding discussions in the DFT calculation section; path a in Scheme 1).^[10] Subsequently, we recognized that imine **4a** might also undergo an ene-type cyclization to produce another fused heterocycle **3a** (for details, see the right part of Figure 1a and the corresponding discussions in the DFT calculation section), provided suitable reaction conditions could be identified. In this aspect, we have thoroughly investigated the transitions between IADA and ene-type cyclizations in this unique molecular system under various conditions, and we have obtained a complete switch from the IADA to the ene-type reaction product in nearly quantitative yield. In this paper, the details of this conditions-oriented synthesis are discussed.

Results and Discussion

Transition and Switch between the IADA and Ene-Type Reactions

Previously, we reported that treatment of (allylamino)-pyrimidinecarbaldehyde **1a** with aniline in the presence of trifluoroacetic acid (TFA) in acetonitrile/water at ambient temperature generated *cis*-configured tetracyclic IADA reaction product **2a** (path a, Scheme 1; Table 1, Entry 1).^[10] Subsequently, we recognized that imine intermediate **4a** had all the elements required for an intramolecular ene-type reaction, and that – if successfully executed – this ene-type cyclization could be developed into a useful method to prepare heterocycles such as compounds **3a** (path b, Scheme 1). To direct the imine reaction towards the ene cy-

Table 1. Investigation of IADA vs. ene-type reactions.^[a]

Entry	Solvent	Catalyst (equiv.)	Temp [°C]	Time [h]	Ratio ^[b] 2a/3a	Yield [%] ^[c]
1	MeCN/H ₂ O (1:1)	TFA (2.0)	25	11	2a	94
2	DMF	TsOH (1.0)	115	1	2a	71
3	DMSO	TsOH (1.0)	115	1	2a	86
4	<i>n</i> BuOH	TsOH (1.0)	115	1	2a	78
5	benzene	TsOH (1.0)	80 ^[d]	1	2a	94
6	toluene	TsOH (1.0)	111 ^[d]	0.5	2a	95
7	<i>n</i> BuOH	TsOH (0.05)	115	6	2.1:1	83
8	DMF	TsOH (0.05)	115	3	2.3:1	77
9	DMSO	TsOH (0.05)	115	1.5	2.1:1	70
10	benzene	TsOH (0.05)	80 ^[d]	16	3a ^[e]	93
11	toluene	TsOH (0.05)	111 ^[d]	3	3a ^[e]	97
12	toluene	TsOH (0.05)	111	3.5	3a ^[e]	95
13	MeCN	none	81	24	–	0 ^[f]
14	benzene	none	80 ^[d]	15	–	0 ^[f]
15	<i>n</i> BuOH	none	115	30	3a	46 ^[g]
16	DMF	none	115	48	3a ^[h]	51
17	DMSO	none	115	6.5	3a ^[e]	67
18	toluene	none	111	48	3a ^[h]	28 ^[i]
19	toluene	none	111 ^[d]	48	3a ^[h]	57 ^[j]

[a] Unless otherwise noted, reactions were carried out with **1a** (0.50 mmol) and aniline (0.525 mmol) in solvent (4 mL). [b] Determined from the ¹H NMR spectrum of the crude reaction mixture. [c] Isolated yield after flash column chromatography. [d] Using a Dean–Stark trap to remove water. [e] A trace of **2a** was detected, but it could not be isolated. [f] Starting material **1a** was recovered (98%). [g] Starting material **1a** was recovered (17%). [h] Contained carbonyl-ene reaction product. [i] Starting material **1a** was recovered (63%). [j] Starting material **1a** was recovered (29%).

clization pathway, we decided to investigate reaction conditions such as solvent, temperature, and acid catalyst, and to delineate their influences on the two competing reactions. This could guide us to select the best conditions for a desired reaction pathway. The results of this investigation are summarized in Table 1.

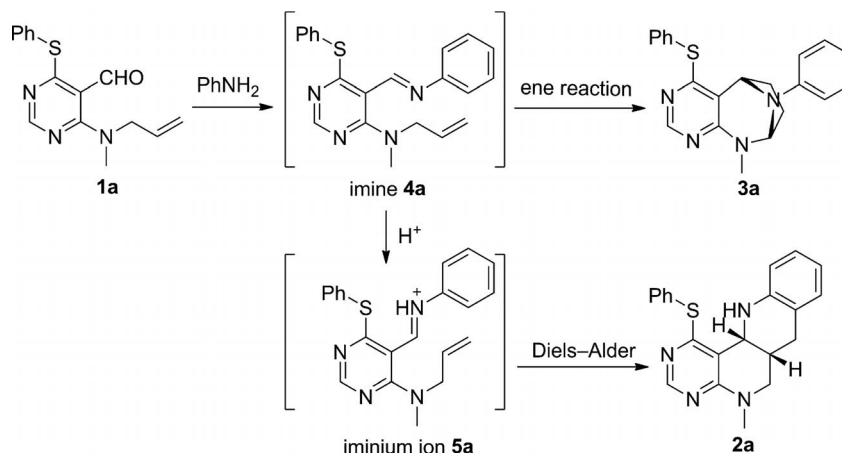
In our previous studies, we had found that TFA was an important component for the IADA reaction;^[10] so to steer the reaction away from the IADA pathway, we first investigated the effects of TFA on the two reaction pathways. Replacing TFA with *p*-toluenesulfonic acid (TsOH; 1 equiv.) and exploring solvents with various polarities led only to the IADA reaction product (i.e., **2a**; Table 1, Entries 2–6). Next the amount of TsOH was reduced from a full equivalent to a catalytic amount, and encouragingly, we began to see a mixture of IADA and ene-type reaction products. We noted that the IADA product (i.e., **2a**) was predominant when a polar solvent was used (Table 1, Entries 7–9), whereas only the ene product (i.e., **3a**) was obtained in high yield when the reaction was conducted in a non-polar solvent such as benzene or toluene (with water removal using a Dean–Stark trap; Table 1, Entries 10 and 11). To further investigate the acid issue, we decided to test the reaction in the absence of any acid (Table 1, Entries 13–19). When the reaction was carried out at 81 °C in the absence of acid, neither product was obtained, regardless of whether a polar (Table 1, Entry 13) or a non-polar (Table 1, Entry 14) solvent was used. When the reaction temperature was increased to 111 °C (Table 1, Entries 15–19) the ene-type reactions were facilitated, although they required longer reaction times and led to lower yields compared to Table 1, Entries 10–12. These results indicate that catalytic amounts of acid and less polar solvents favor the ene-type reaction, which is consistent with the envisioned reaction mechanisms.

Therefore, we were able to induce a complete switch from the previously reported IADA reaction^[10] to an ene-like reaction with the same set of starting materials in nearly quantitative yields by simply changing the reaction conditions. The ene-type reaction seems to have a high transition-

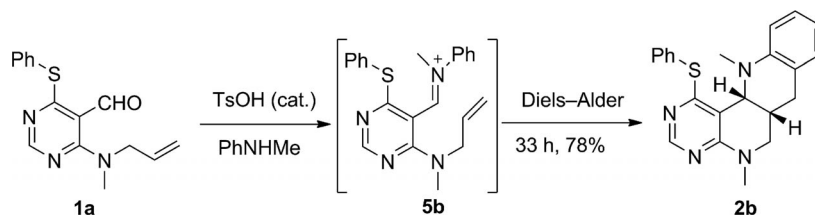
state energy barrier, since the reaction only occurred at higher temperatures. The IADA reaction proceeded at much lower temperatures.

Experimental Rationalization of the Transition from the IADA to the Ene-Type Reaction

The above results can readily be rationalized by the existence of two competing reaction processes, as shown in Scheme 2. The reaction of pyrimidinecarbaldehyde **1a** with aniline should initially form imine intermediate **4a**, which may undergo a thermal ene-type reaction (higher activation energy) directly to yield product **3a**,^[7] or proceed through an IADA reaction (lower activation energy) via iminium ion **5a** to generate product **2a**.^[10] The formation of the phenyliminium ion is required for the low-energy IADA reaction in which the phenyliminium ion acts as the azadiene. When the same reaction was carried out under thermal conditions in the absence of acid, only the ene-type cyclization product was formed. Therefore, a polar solvent, low temperature, and the presence of a proton source favor the IADA reaction pathway. This analysis is consistent with the experimental results shown in Table 1. A catalytic amount of acid promoted the formation of imine intermediate **4a**. This intermediate either continued on the ene-type pathway to give **3a** (Table 1, Entry 11), as was seen in the non-polar solvent toluene at high temperature, or, in a polar solvent, it resulted in a mixture of **2a** and **3a** (Table 1, Entries 7–9). This is seen, because in a non-polar solvent, the formation of an imine intermediate is favored over the iminium ion, whereas in the polar solvent, the iminium intermediate is favored. In the absence of an acid catalyst and at elevated temperature, pyrimidinecarbaldehyde **1a** could either react with aniline to form imine **4a**, which could undergo an ene-type reaction to give product **3a**, or it could overcome a higher energy barrier to give the carbonyl-ene product (Table 1, Entries 15, 16, 18, and 19). In refluxing acetonitrile or benzene, i.e., low-boiling solvents, in the absence of an acid catalyst (Table 1, Entries 13 and 14), no imine



Scheme 2. Two competing reaction processes.



Scheme 3. Verification of the iminium ion leading to the IADA product.

or iminium intermediate was formed, so no product was obtained from either reaction pathway.

To further verify the above proposed processes, pyrimidinecarbaldehyde **1a** and *N*-methylaniline were subjected to the optimized reaction conditions of the ene-like reaction [i.e., TsOH (0.05 equiv.), refluxing toluene with removal of water; Scheme 3].^[10] As expected, only the IADA product was obtained. This is, because only the IADA pathway iminium intermediate (i.e., **5b**) should be formed in this case. This experiment provided additional evidence that the IADA product was derived from an iminium intermediate. Following on from this, DFT calculations were used to gain further mechanistic insight.

DFT Study of the Mechanisms and Origins of Regioselectivity

To gain further insight into the mechanisms and the origins of the experimentally observed regioselectivity, theoretical calculations were carried out to investigate both the IADA and ene-type reaction pathways, using imine **4a** or iminium ion **5a** as the model reactants (Figure 1). All calculations were carried out with Gaussian 03 programs.^[11] Geometrical optimizations of all species were performed at the B3LYP/6-311+G(d,p) level.^[12] Solvent effects were computed using UAHF (united atom topological model for Hartree–Fock) radii and a CPCM (conductor polarized continuum model)^[13] solvent model in toluene. Unless otherwise specified, all the energies discussed in this paper are the Gibbs free energies in toluene at 298 K ($\Delta G_{\text{sol } 298}$). Gibbs free energies in the gas phase ($\Delta G_{\text{gas } 298}$) and gas phase enthalpies (ΔH) are also provided for reference.

DFT calculations found that imine **4a** can be converted into **IN2** via **TS2** with an activation Gibbs free energy in toluene of 24.1 kcal/mol in the ene-type pathway (Figure 1a). Transition state **TS2** is more favored than the competing IADA transition states, *endo*-**TS1** and *exo*-**TS1**, by 3.5 and 8.7 kcal/mol, respectively. These calculations suggested that the ene-type reaction is favored over the IADA reactions, which is consistent with the experimental observation that in the absence of a proton source, ene-type product **3a** was obtained exclusively. It is interesting to find that in the ene-type reaction transition state (i.e., **TS2**), the allylic proton, which is also adjacent to the nitrogen atom, is transferring to the enamine moiety, while the C–C4 bond formation is not taking place at all, with the distance between C-1 and C-4 being 3.36 Å (Figure 1c). IRC (intrinsic reaction coordinate)^[14] calculations and the potential

energy surface (PES) scan (see Supporting Information for details) found that **TS2** connects **4a** and **IN2**. The calculations did not find any intermediates between **TS2** and **IN2**, neither in the gas phase nor in toluene solution.^[15] This suggests that the ene-type reaction can be regarded as a proton transfer from the allylic moiety to the enamine, generating a zwitterionic intermediate, **IN3**, which has an iminium ion moiety and a carbanion moiety (see Figure 1a).^[16] Intermediate **IN3** does not represent an energy minimum, neither in the gas phase nor in solution, and it can easily collapse (in a barrierless process) to give **IN2** by nucleophilic addition. Due to the highly asynchronous character of **TS2**, it is better to describe this step as a [1,6]-proton shift, followed by a rapid nucleophilic addition. Intermediate **IN2** then can be converted into the final tertiary amine (i.e., **3a**) by addition of the secondary amine to the C=C double bond, which could be catalyzed by a trace amount of Brønsted acid.^[17]

However, for protonated species **5a** (Figure 1b), we could not locate an ene-like transition state (**HTS2**). This was attributed to the fact that the nitrogen atom in **5a** is an ammonium ion, which prevents any proton transfer (instead, there is a possible [1,5]-hydride shift process via transition state **HTS3**, but this is not favored either). In contrast, the IADA reaction of **5a**, which can be termed a [4⁺ + 2]^[18] reaction between the protonated phenylimine moiety and the terminal olefin moiety, can take place by either of two competing pathways, the *endo*- and the *exo*-IADA pathways. The *endo*-IADA transition state (i.e., *endo*-**HTS1**), which gives rise to intermediate *cis*-**HIN1**, is more favored than the *exo* transition state (i.e., *exo*-**HTS1**), which gives rise to intermediate *trans*-**HIN1**, by 4.9 kcal/mol.^[19] The IADA reactions are irreversible, since the reverse reactions are difficult with activation energies of >30 kcal/mol. After the IADA reaction, cycloadducts *cis*-**HIN1** and *trans*-**HIN1** can then be transformed into *cis*-**2a** and *trans*-**2a** by deprotonation, which is not expected to be the rate-limiting step. The results of these calculations suggest that the *cis* Diels–Alder product (i.e., *cis*-**2a**) should be obtained as the major product from **5a**, which matches the experimental results in Table 1.

The activation energy of the [4⁺ + 2] transition state (i.e., *endo*-**HTS1**; Figure 1b) is 16.0 kcal/mol, which is much lower than that of the [4 + 2] transition state (i.e., *endo*-**TS1**, 27.6 kcal/mol; Figure 1a). This observation can be rationalized using frontier molecular orbital (FMO) theory. Protonated **5a** has a significantly lower-energy LUMO, which is mainly composed of the diene (phenylimine moi-

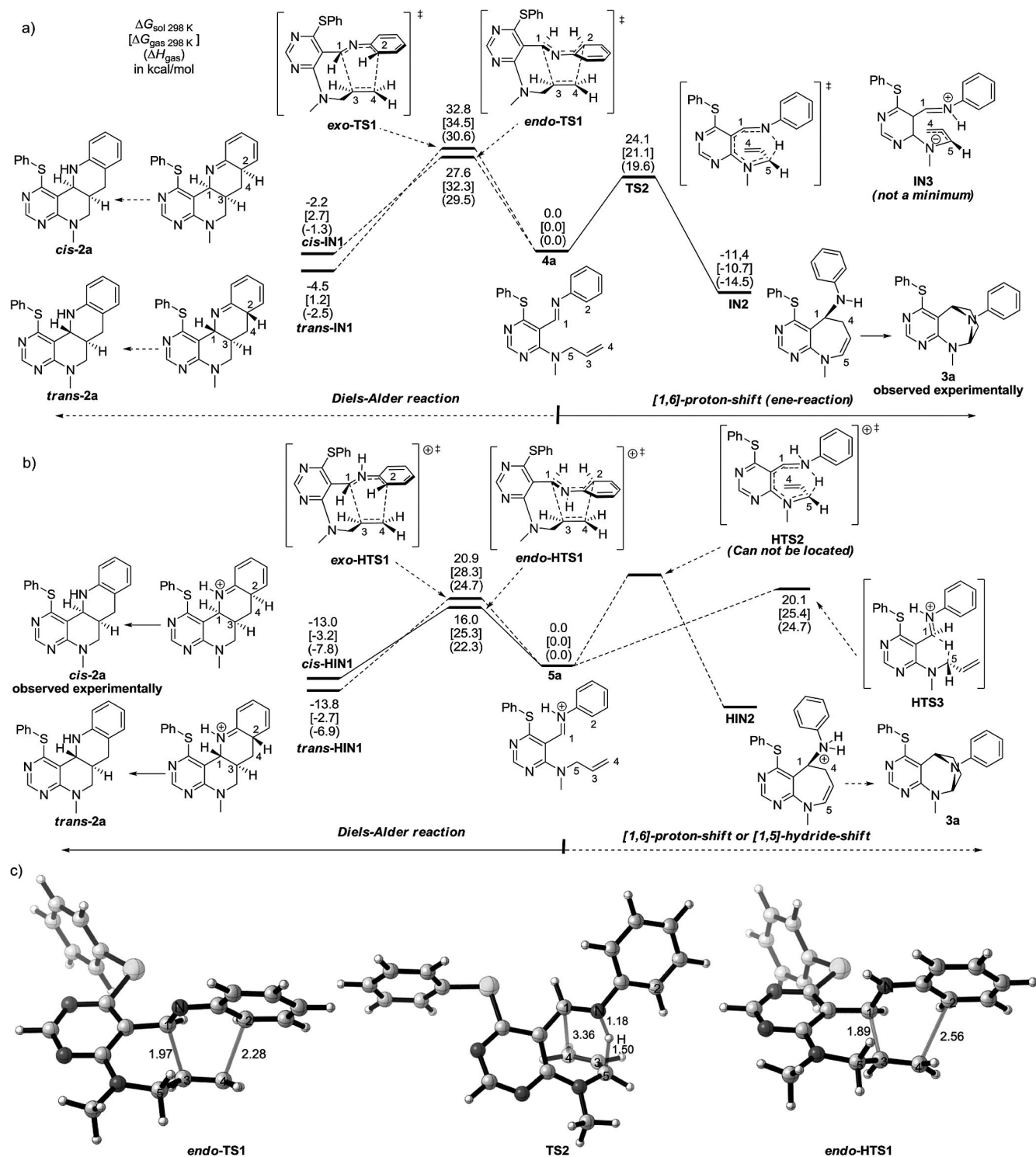


Figure 1. (a) Two calculated reaction pathways of **4a**. (b) Two calculated reaction pathways of **5a**. (c) Selected DFT calculated structures (distances in Å).

ety) π orbitals. The reacting π orbital of the dienophile is HOMO-6 (Figure 2). The energy gap between the LUMO and HOMO-6 is 7.5 eV. In contrast, for **4a**, the corresponding energy gap between the two reacting orbitals is 8.3 eV, which is 0.8 eV larger than that in **5a**. Therefore, the IADA reaction between the protonated phenylimine and the “electron-rich” olefin in **5a** become favored.

A comparison of the results of the calculations shown in Figure 1a and b reveals that in the presence of a full equivalent of acid, the phenylimine moiety of **5a** is protonated, which leads to a lower LUMO energy and favors the IADA reaction. In contrast, the ene-type reaction cannot occur, since the protonated amine moiety cannot accept a proton from the allylic moiety in **5a**. When an acid is absent, or

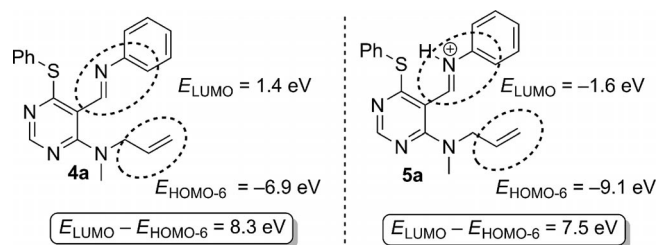


Figure 2. FMOs of **4a** and **5a**, orbital energies calculated at the HF/6-31G(d) level.

only a catalytic amount of acid is present, the IADA reaction under neutral conditions is difficult, due to its higher LUMO energy. On the other hand, an ene-type reaction can take place, due to the easier [1,6]-proton transfer and barrierless nucleophilic addition.

Synthesis of Epiminopyrimido[4,5-*b*]azepines

Having identified the optimal conditions for the ene-type reaction pathway, the scope of the reaction was explored for the preparation of epiminopyrimido[4,5-*b*]azepines. Thus, the reaction was tested with various pyrimidinecarbaldehydes and amines, using a catalytic amount of TsOH, refluxing toluene, and a Dean–Stark trap for the removal of water. The results are summarized in Table 2.

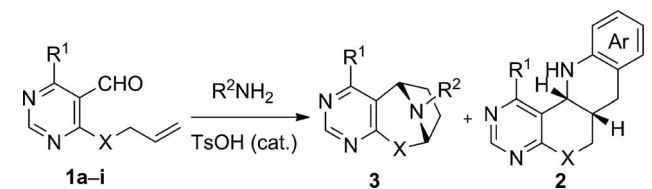
Generally, this ene-type reaction has a broad scope, and variations of the R^1 , R^2 , and X groups were tolerated to give epiminopyrimido[4,5-*b*]azepines in good yields. First, we explored the scope of the R^2 group with various amines (Table 2, entries 1–8). Both aryl and aliphatic R^2 groups led to productive ene-type products, with aryl groups giving higher yields than aliphatic groups. Aromatic amines with

various functional groups, such as nitro, ester, cyano, and halo groups, were tolerated, producing good to excellent yields of epiminopyrimido[4,5-*b*]azepines. However, when an *ortho*-nitro group was present (Table 2, Entry 4), a lower yield was observed, which may be due to a steric effect. Next, the scope of the R^1 group was investigated. Halo, alkoxy, phenoxy, and amino groups were found to be suitable substituents, and moderate to good yields were obtained (Table 2, Entries 10–13).

Conclusions

A complete switch from an imine Diels–Alder reaction to an ene-type cyclization reaction was achieved. The same set of starting materials could be used to prepare two distinct heterocyclic scaffolds simply by changing the reaction conditions, such as the amount of acid catalyst, the solvent, and the reaction temperature. This approach avoids the usual practice of using different sets of starting materials for the synthesis of different scaffolds, and therefore makes access of new scaffolds more efficient. These results could be rationalized by the existence of two competing processes: the low-activation-energy Diels–Alder cyclization with an iminium ion as the intermediate, and the thermal ene-type cyclization with an imine as the key intermediate. To gain insight into the mechanisms of the two reaction pathways, a DFT study was carried out. Theoretical calculations showed that under acidic conditions, an iminium intermediate favors the low-energy IADA pathway, while the neutral imine intermediate favors the thermal ene-type cyclization pathway as the low-energy process. The ene-type cyclization was further successfully applied to the preparation of a series of epiminopyrimido[4,5-*b*]azepines. These results could serve as an interesting example of efficiency in organic synthesis and green chemistry, and could encourage further studies in the generation of diverse scaffolds from the same sets of starting materials.

Table 2. Selected imine ene-type reactions.



Entry	1	R^1	X	R^2	Time [h]	Product	Yield [%]
1	1a	PhS	NMe	Ph	3.5	3a	97
2	1a	PhS	NMe	4-NCC ₆ H ₄	4.5	3b	93
3	1a	PhS	NMe	4-O ₂ NC ₆ H ₄	5	3c	95
4	1a	PhS	NMe	2-O ₂ NC ₆ H ₄	7	3d	66
5	1a	PhS	NMe	4-MeOC ₆ H ₄	2.5	3e	88 ^[a]
6	1a	PhS	NMe	EtO ₂ CCH ₂	6	3f	60
7	1a	PhS	NMe	<i>n</i> Bu	86	3g	61
8	1a	PhS	NMe	Bn	10	3h	84
9	1b	PhS	NAllyl	Ph	1.5	3i	95
10	1c	Cl	NMe	Ph	2	3j	80
11	1d	PhO	NMe	Ph	5.5	3k	67
12	1e	MeO	NMe	Ph	5	3l	70
13	1f	Et ₂ N	NMe	Ph	23	3m	44

[a] Diels–Alder product **2e** was isolated (6%).

Experimental Section

General Methods: Unless otherwise noted, reactions were carried out in air. Chemicals and solvents were purchased from commercial suppliers, and were either used as supplied or purified by standard procedures. Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator, and compounds were visualized by irradiation with UV light or by treatment with iodine. Flash column chromatography was performed with silica gel 200–300 mesh. Mass spectra and HPLC data were recorded with an LC–MS system with ELSD (evaporative light-scattering detection). ¹H and ¹³C NMR spectra were recorded at 300 and 75 MHz, respectively. The spectra were recorded in CDCl₃ at room temperature unless otherwise noted. ¹H and ¹³C NMR chemical shifts are reported in ppm relative to TMS, which was used as an internal standard. Multiplicities are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br., broad. Compounds **1a**, **1c**, **2a**, **2b**, **2e** are known compounds, and were prepared according to the previous report.^[10]

4-[Allyl(methyl)amino]-6-(phenylthio)pyrimidine-5-carbaldehyde (1a**):** Pale yellow solid (0.541 g, 95%). M.p. 57–58 °C. ¹H NMR

(300 MHz, CDCl_3): δ = 10.23 (s, 1 H, CHO), 8.24 (s, 1 H, pyrimidyl-H), 7.57–7.52 (m, 2 H, phenyl-H), 7.46–7.43 (m, 3 H, phenyl-H), 5.94–5.85 (m, 1 H, $\text{CH}=\text{C}$), 5.32–5.23 (m, 2 H, $\text{C}=\text{CH}_2$), 4.23 (d, J = 5.1 Hz, 2 H, CH_2), 3.10 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 186.7, 173.4, 163.0, 157.0, 135.4, 132.3, 129.3, 129.0, 128.9, 118.4, 109.4, 55.3, 39.6 ppm. MS (ESI): m/z = 285.9 $[\text{M} + \text{H}]^+$.

4-(Diallylamino)-6-(phenylthio)pyrimidine-5-carbaldehyde (1b): A mixture of Et_3N (1.220 mL, 8.8 mmol) and diallylamine (1.080 mL, 8.8 mmol) was slowly added to a solution of 4,6-dichloro-5-formylpyrimidine (1.408 g, 8.0 mmol) in anhydrous CHCl_3 (12 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 30 min, then the mixture was quenched with water (15 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4 , and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/EtOAc, 5:1, v/v) gave 4-chloro-6-(diallylamino)pyrimidine-5-carbaldehyde (1.855 g, 95%) as a white solid. M.p. 44–45 °C. Thiophenol (0.220 g, 2.0 mmol) was added to a solution of 4-chloro-6-(diallylamino)pyrimidine-5-carbaldehyde (0.475 g, 2.0 mmol) and Et_3N (0.270 mL, 2.0 mmol) in CHCl_3 (4 mL) at ambient temperature. The reaction mixture was stirred for 1.5 h, then it was diluted with water (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4 , and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/EtOAc, 5:1, v/v) gave **1b** (0.520 g, 84%) as a pale yellow oil. ^1H NMR (300 MHz, CDCl_3): δ = 10.13 (s, 1 H, CHO), 8.25 (s, 1 H, pyrimidyl-H), 7.54 (dd, J = 6.6, 3.0 Hz, 2 H, phenyl-H), 7.44 (m, 3 H, phenyl-H), 5.95–5.82 (m, 2 H, $\text{CH}=\text{C}$), 5.32 (d, J = 1.2 Hz, 1 H, $\text{C}=\text{CH}_2$), 5.28 (dd, J = 1.8, 1.2 Hz, 2 H, $\text{C}=\text{CH}_2$), 5.22 (d, J = 1.2 Hz, 1 H, $\text{C}=\text{CH}_2$), 4.16 (d, J = 5.4 Hz, 4 H, 2 CH_2) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 186.9, 172.9, 163.4, 157.0, 135.4, 132.5, 129.2, 129.1, 128.8, 118.6, 109.9, 52.9 ppm. MS (ESI): m/z = 311.9 $[\text{M} + \text{H}]^+$. HRMS (ESI-TOF): calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_3\text{OS}$ $[\text{M} + \text{H}]^+$ 312.1157; found 312.1165.

4-[Allyl(methyl)amino]-6-chloropyrimidine-5-carbaldehyde (1c): White solid (0.400 g, 96%). M.p. 53–54 °C. ^1H NMR (300 MHz, CDCl_3): δ = 10.38 (s, 1 H, CHO), 8.35 (s, 1 H, pyrimidyl-H), 5.86–5.79 (m, 1 H, $\text{CH}=\text{C}$), 5.25–5.19 (m, 2 H, $\text{C}=\text{CH}_2$), 4.31–4.29 (m, 2 H, CH_2), 2.89 (s, 3 H, CH_3) ppm. MS (ESI): m/z = 212.0 $[\text{M} + \text{H}]^+$.

4-[Allyl(methyl)amino]-6-phenoxy pyrimidine-5-carbaldehyde (1d): Sodium hydride (0.080 g, 2.0 mmol) was added in portions to a solution of phenol (0.094 g, 1.0 mmol) in THF (3 mL) in an ice/water bath under nitrogen. The mixture was stirred for 30 min, then a solution of compound **1c** (0.211 g, 1.0 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred in the ice/water bath for a further 2 h. Then the mixture was diluted with water (15 mL) and extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4 , and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/EtOAc, 1:1, v/v) gave **1d** (0.224 g, 83%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3): δ = 10.47 (s, 1 H, CHO), 8.22 (s, 1 H, pyrimidyl-H), 7.47–7.42 (m, 2 H, phenyl-H), 7.31–7.28 (m, 1 H, phenyl-H), 7.20–7.13 (m, 2 H, phenyl-H), 6.00–5.81 (m, 1 H, $\text{CH}=\text{C}$), 5.28–5.27 (m, 1 H, $\text{C}=\text{CH}_2$), 5.26–5.21 (m, 1 H, $\text{C}=\text{CH}_2$), 4.30 (dt, J = 5.7, 1.5 Hz, 2 H, CH_2), 2.98 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 186.5, 172.4, 162.1, 158.4, 152.5, 132.5, 129.6, 125.7, 121.7, 118.2, 99.9, 54.6, 40.0 ppm. MS (ESI): m/z = 270.4 $[\text{M} + \text{H}]^+$. $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$ (269.30): calcd. C 66.90, H 5.61, N 15.60; found C 66.69, H 5.36, N 15.65.

4-[Allyl(methyl)amino]-6-methoxypyrimidine-5-carbaldehyde (1e): Potassium carbonate (0.276 g, 2.0 mmol) was added to a solution of **1c** (0.211 g, 1.0 mmol) in MeOH (2 mL). The reaction mixture was heated at reflux for 4 h. The reaction solution was then diluted with water (10 mL) and extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4 , and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/EtOAc, 5:1, v/v) gave **1e** (0.151 g, 73%) as a pale yellow oil. ^1H NMR (300 MHz, CDCl_3): δ = 10.24 (s, 1 H, CHO), 8.27 (s, 1 H, pyrimidyl-H), 5.95–5.82 (m, 1 H, $\text{CH}=\text{C}$), 5.25–5.17 (m, 2 H, $\text{C}=\text{CH}_2$), 4.41–4.15 (m, 2 H, CH_2), 4.04 (s, 3 H, OCH_3), 2.92 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 186.4, 172.5, 161.7, 158.2, 132.6, 117.8, 99.3, 55.4, 54.3, 39.6 ppm. MS (ESI): m/z = 208.3 $[\text{M} + \text{H}]^+$. HRMS (ESI-TOF): calcd. for $\text{C}_{10}\text{H}_{14}\text{N}_3\text{O}_2$ $[\text{M} + \text{H}]^+$ 208.1078; found 208.1081.

4-[Allyl(methyl)amino]-6-(diethylamino)pyrimidine-5-carbaldehyde (1f): Diethylamine (0.146 g, 2.0 mmol) was added to a solution of **1c** (0.211 g, 1.0 mmol) and Et_3N (0.151 g, 1.5 mmol) in CHCl_3 (2 mL). The reaction mixture was heated at reflux for 2 h. The mixture was then diluted with water (10 mL) and extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4 , and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/EtOAc, 2:1, v/v) gave **1f** (0.161 g, 65%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3): δ = 9.37 (s, 1 H, CHO), 8.06 (s, 1 H, pyrimidyl-H), 5.96–5.85 (m, 1 H, $\text{CH}=\text{C}$), 5.29–5.26 (m, 1 H, $\text{C}=\text{CH}_2$), 5.23–5.22 (m, 1 H, $\text{C}=\text{CH}_2$), 4.27 (dt, J = 5.7, 1.5 Hz, 2 H, CH_2), 3.69 (q, J = 7.2 Hz, 4 H, 2 CH_2), 3.15 (s, 3 H, CH_3), 1.29 (t, J = 7.2 Hz, 6 H, 2 CH_3) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 181.5, 165.9, 164.9, 158.1, 133.0, 117.8, 96.0, 54.7, 44.6, 39.1, 13.3 ppm. MS (ESI): m/z = 249.4 $[\text{M} + \text{H}]^+$. HRMS (ESI-TOF): calcd. for $\text{C}_{13}\text{H}_{21}\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$ 249.1697; found 249.1710.

5-Methyl-1-(phenylthio)-5,6,6a,7,12,12a-hexahydrobenzo[b]pyrimido[4,5-*h*][1,6]naphthyridine (2a): White solid (0.169 g, 94%). M.p. 203–204 °C. ^1H NMR (300 MHz, CDCl_3): δ = 8.28 (s, 1 H, pyrimidyl-H), 7.56–7.52 (m, 2 H, phenyl-H), 7.43–7.39 (m, 3 H, phenyl-H), 7.06–7.00 (m, 2 H, phenyl-H), 6.68 (t, J = 7.2 Hz, 1 H, phenyl-H), 6.51 (d, J = 7.8 Hz, 1 H, phenyl-H), 4.75 (d, J = 2.4 Hz, 1 H, CH), 3.92 (s, 1 H, NH), 3.56 (t, J = 12.3 Hz, 1 H, CH_2), 3.30 (dd, J = 17.1, 6.3 Hz, 1 H, CH_2), 3.16 (s, 3 H, CH_3), 3.12 (dd, J = 12.6, 4.8 Hz, 1 H, CH_2), 2.62 (d, J = 17.1 Hz, 1 H, CH_2), 2.47 (m, 1 H, CH) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 162.9, 157.7, 157.3, 141.5, 134.8, 129.7, 129.4, 129.0, 127.6, 118.2, 118.1, 114.8, 111.3, 90.6, 49.7, 47.5, 36.3, 29.2, 28.8 ppm. MS (ESI): m/z = 361.1 $[\text{M} + \text{H}]^+$.

5,12-Dimethyl-1-(phenylthio)-5,6,6a,7,12,12a-hexahydrobenzo[b]pyrimido[4,5-*h*][1,6]naphthyridine (2b): White solid (0.134 g, 78%). M.p. 167–169 °C. ^1H NMR (300 MHz, CDCl_3): δ = 8.27 (s, 1 H, pyrimidyl-H), 7.54–7.52 (m, 2 H, phenyl-H), 7.40–7.39 (m, 3 H, phenyl-H), 7.17 (t, J = 7.2 Hz, 1 H, phenyl-H), 7.03 (d, J = 6.6 Hz, 1 H, phenyl-H), 6.76–6.73 (m, 2 H, phenyl-H), 4.60 (s, 1 H, CH), 3.57 (t, J = 12.6 Hz, 1 H, CH_2), 3.33 (dd, J = 17.1, 6.6 Hz, 1 H, CH_2), 3.14 (s, 3 H, CH_3), 3.14–3.09 (m, 1 H, CH_2), 2.84 (s, 3 H, CH_3), 2.66 (d, J = 17.1 Hz, 1 H, CH_2), 2.48 (br. s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 164.7, 157.0, 144.9, 134.9, 129.5, 129.0, 128.8, 127.6, 119.7, 117.4, 112.7, 109.4, 53.1, 49.5, 35.8, 34.0, 29.7, 29.2 ppm. MS (ESI): m/z = 375.2 $[\text{M} + \text{H}]^+$.

9-Methoxy-5-methyl-1-(phenylthio)-5,6,6a,7,12,12a-hexahydrobenzo[b]pyrimido[4,5-*h*][1,6]naphthyridine (2c): White solid (0.012 g, 6%). M.p. 201–202 °C. ^1H NMR (300 MHz, CDCl_3): δ = 8.28 (s, 1 H, pyrimidyl-H), 7.53–7.51 (m, 2 H, phenyl-H), 7.39–7.37 (m, 3

H, phenyl-H), 6.66 (d, J = 8.1 Hz, 1 H, phenyl-H), 6.60 (s, 1 H, phenyl-H), 6.48 (d, J = 8.1 Hz, 1 H, phenyl-H), 4.69 (s, 1 H, CH), 3.82 (s, 4 H, OCH₃, NH), 3.58 (t, J = 12.3 Hz, 1 H, CH₂), 3.30 (dd, J = 16.8, 5.7 Hz, 1 H, CH₂), 3.16 (s, 3 H, CH₃), 3.11 (dd, J = 12.3, 3.6 Hz, 1 H, CH₂), 2.59 (d, J = 17.7 Hz, 1 H, CH₂), 2.45 (br. s, 1 H, CH) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 162.5, 157.5, 157.1, 152.2, 135.2, 134.5, 129.4, 129.0, 128.6, 119.0, 115.6, 114.4, 113.4, 111.1, 55.6, 49.3, 47.4, 36.0, 29.1, 28.5 ppm. MS (ESI): m/z = 391.1 [M + H]⁺.

General Procedure for the Synthesis of Epiminopyrimido[4,5-*b*]azepines 3: TsOH (0.025 mmol) was added to a solution of *N*-allylpyrimidinylcarbaldehyde **1** (0.5 mmol) and aniline (0.525 mmol) in toluene. The resulting solution was stirred at reflux, and water was removed using a Dean–Stark trap until **1** had been consumed, as monitored by TLC. The reaction mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (petroleum ether/EtOAc, 2:1, v/v).

(5*R,8*R**)-9-Methyl-10-phenyl-4-(phenylthio)-6,7,8,9-tetrahydro-5*H*-5,8-epiminopyrimido[4,5-*b*]azepine (3a):** Pale yellow solid (0.175 g, 97%). M.p. 89–90 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.12 (s, 1 H, pyrimidyl-H), 7.51–7.48 (m, 2 H, phenyl-H), 7.41–7.35 (m, 3 H, phenyl-H), 7.24–7.19 (m, 2 H, phenyl-H), 6.90–6.82 (m, 3 H, phenyl-H), 5.19 (s, 1 H, CH), 5.18 (s, 1 H, CH), 3.14 (s, 3 H, CH₃), 2.43–2.27 (m, 3 H, CH₂), 2.14–2.08 (m, 1 H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.1, 156.8, 156.5, 144.9, 133.9, 130.3, 129.3, 129.1, 128.4, 120.4, 117.4, 115.7, 74.5, 55.9, 34.5, 33.6, 33.4 ppm. MS (ESI): m/z = 361.1 [M + H]⁺. C₂₁H₂₀N₄S (360.48): calcd. C 69.97, H 5.59, N 15.54, S 8.90; found C 70.13, H 5.26, N 15.74, S 8.72.

(5*R,8*R**)-10-(4-Cyanophenyl)-9-methyl-4-(phenylthio)-6,7,8,9-tetrahydro-5*H*-5,8-epiminopyrimido[4,5-*b*]azepine (3b):** White solid (0.164 g, 93%). M.p. 157–158 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.16 (s, 1 H, pyrimidyl-H), 7.56–7.48 (m, 4 H, phenyl-H), 7.44–7.39 (m, 3 H, phenyl-H), 6.92 (d, J = 8.7 Hz, 2 H, phenyl-H), 5.23 (s, 1 H, CH), 5.22 (s, 1 H, CH), 3.15 (s, 3 H, CH₃), 2.51–2.34 (m, 3 H, CH₂), 2.22–2.15 (m, 1 H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.6, 156.6, 148.7, 134.0, 133.5, 129.5, 129.1, 128.6, 119.2, 117.3, 114.7, 102.7, 74.0, 55.9, 34.2, 33.5, 33.3 ppm. MS (ESI): m/z = 386.3 [M + H]⁺. HRMS (ESI-TOF): calcd. for C₂₂H₂₀N₅S [M + H]⁺ 386.1426; found 386.1434.

(5*R,8*R**)-9-Methyl-10-(4-nitrophenyl)-4-(phenylthio)-6,7,8,9-tetrahydro-5*H*-5,8-epiminopyrimido[4,5-*b*]azepine (3c):** Pale yellow solid (0.192 g, 95%). M.p. 200–201 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.15 (s, 1 H, pyrimidyl-H), 8.13 (d, J = 9.0 Hz, 2 H, phenyl-H), 7.52–7.49 (m, 2 H, phenyl-H), 7.41–7.39 (m, 3 H, phenyl-H), 6.92 (d, J = 9.3 Hz, 2 H, phenyl-H), 5.28 (s, 1 H, CH), 5.26 (s, 1 H, CH), 3.16 (s, 3 H, CH₃), 2.53–2.38 (m, 3 H, CH₂), 2.24–2.17 (m, 1 H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.9, 156.8, 156.6, 150.7, 140.6, 134.2, 128.8, 125.73, 125.71, 116.6, 114.7, 90.5, 74.4, 56.3, 34.3, 33.7, 33.5 ppm. MS (ESI): m/z = 406.1 [M + H]⁺. C₂₁H₁₉N₅O₂S (405.47): calcd. C 62.21, H 4.72, N 17.27, S 7.91; found C 62.28, H 4.55, N 17.43, S 7.77.

(5*R,8*R**)-9-Methyl-10-(2-nitrophenyl)-4-(phenylthio)-6,7,8,9-tetrahydro-5*H*-5,8-epiminopyrimido[4,5-*b*]azepine (3d):** Yellow solid (0.134 g, 66%). M.p. 155–156 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.19 (s, 1 H, pyrimidyl-H), 7.76 (d, J = 1.5 Hz, 1 H, phenyl-H), 7.55–7.52 (m, 2 H, phenyl-H), 7.41–7.34 (m, 4 H, phenyl-H), 7.02 (t, J = 8.1 Hz, 1 H, phenyl-H), 6.90 (d, J = 8.4 Hz, 1 H, phenyl-H), 4.97 (d, J = 5.1 Hz, 1 H, CH), 4.85 (d, J = 4.2 Hz, 1 H, CH), 3.04 (s, 3 H, CH₃), 2.50–2.44 (m, 2 H, CH₂), 2.29–2.24 (m, 1 H, CH₂), 2.14–2.09 (m, 1 H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.6, 156.7, 156.6, 142.2, 138.3, 134.5, 133.6, 129.1, 129.1,

128.8, 126.0, 121.7, 121.5, 114.1, 75.7, 57.7, 34.5, 33.7, 33.0 ppm. MS (ESI): m/z = 406.1 [M + H]⁺. C₂₁H₁₉N₅O₂S (405.47): calcd. C 62.21, H 4.72, N 17.27, S 7.91; found C 62.00, H 4.63, N 17.33, S 7.80.

(5*R,8*R**)-10-(4-Methoxyphenyl)-9-methyl-4-(phenylthio)-6,7,8,9-tetrahydro-5*H*-5,8-epiminopyrimido[4,5-*b*]azepine (3e):** White solid (0.172 g, 88%). M.p. 190–192 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.13 (s, 1 H, pyrimidyl-H), 7.50–7.48 (m, 2 H, phenyl-H), 7.37–7.36 (m, 3 H, phenyl-H), 6.83–6.75 (m, 4 H, phenyl-H), 5.11–5.09 (m, 2 H, 2 CH), 3.73 (s, 3 H, OCH₃), 3.12 (s, 3 H, CH₃), 2.48–2.23 (m, 3 H, CH₂), 2.12–2.06 (m, 1 H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.1, 156.7, 156.4, 153.6, 138.5, 133.9, 130.3, 129.1, 128.4, 118.5, 115.6, 114.7, 75.1, 56.3, 55.4, 34.6, 33.6, 33.4 ppm. MS (ESI): m/z = 391.1 [M + H]⁺. C₂₂H₂₂N₄OS (390.50): calcd. C 67.67, H 5.68, N 14.35, S 8.21; found C 67.76, H 5.53, N 14.44, S 7.92.

Ethyl 2-[(5*R,8*R**)-9-Methyl-4-(phenylthio)-6,7,8,9-tetrahydro-5*H*-5,8-epiminopyrimido[4,5-*b*]azepin-10-yl]acetate (3f):** White solid (0.111 g, 60%). M.p. 62–63 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.25 (s, 1 H, pyrimidyl-H), 7.55–7.45 (m, 2 H, phenyl-H), 7.43–7.33 (m, 3 H, phenyl-H), 4.54 (d, J = 4.8 Hz, 1 H, CH), 4.43 (d, J = 6.0 Hz, 1 H, CH), 4.21 (q, J = 7.2 Hz, 2 H, CH₂), 3.37 (A of AB, J = 16.8 Hz, 1 H, CH₂), 3.30 (B of AB, J = 16.8 Hz, 1 H, CH₂), 3.07 (s, 3 H, CH₃), 2.41–2.30 (m, 2 H, CH₂), 2.20–2.05 (m, 1 H, CH₂), 1.98–1.89 (m, 1 H, CH₂), 1.28 (t, J = 7.2 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.1, 160.0, 156.42, 156.37, 134.2, 129.6, 128.8, 128.4, 112.6, 77.1, 60.7, 58.5, 48.0, 34.3, 33.6, 33.0, 14.0 ppm. MS (ESI): m/z = 371.5 [M + H]⁺. C₁₉H₂₂N₄O₂S (370.47): calcd. C 61.60, H 5.99, N 15.12, S 8.66; found C 61.53, H 6.02, N 14.87, S 8.40.

(5*R,8*R**)-10-Butyl-9-methyl-4-(phenylthio)-6,7,8,9-tetrahydro-5*H*-5,8-epiminopyrimido[4,5-*b*]azepine (3g):** Pale yellow oil (0.104 g, 61%). ¹H NMR (300 MHz, CDCl₃): δ = 8.23 (s, 1 H, pyrimidyl-H), 7.50–7.47 (m, 2 H, phenyl-H), 7.37–7.35 (m, 3 H, phenyl-H), 4.32 (d, J = 6.3 Hz, 1 H, CH), 4.29 (d, J = 4.2 Hz, 1 H, CH), 3.07 (s, 3 H, CH₃), 2.54–2.35 (m, 2 H, CH₂), 2.28–2.01 (m, 3 H, CH₂), 1.93–1.86 (m, 1 H, CH₂), 1.56–1.46 (m, 2 H, CH₂), 1.38–1.30 (m, 2 H, CH₂), 0.91 (t, J = 6.6 Hz, 3 H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.1, 156.8, 156.3, 133.9, 130.3, 128.9, 128.2, 113.7, 77.2, 57.1, 45.9, 34.3, 33.4, 33.1, 30.3, 20.5, 13.8 ppm. MS (ESI): m/z = 341.1 [M + H]⁺. C₁₉H₂₄N₄S (340.49): calcd. C 67.02, H 7.10, N 16.45, S 9.42; found C 67.27, H 6.82, N 16.40, S 9.32.

(5*R,8*R**)-10-Benzyl-9-methyl-4-(phenylthio)-6,7,8,9-tetrahydro-5*H*-5,8-epiminopyrimido[4,5-*b*]azepine (3h):** Pale yellow oil (0.157 g, 84%). ¹H NMR (300 MHz, CDCl₃): δ = 8.28 (s, 1 H, pyrimidyl-H), 7.51–7.48 (m, 2 H, phenyl-H), 7.41–7.35 (m, 3 H, phenyl-H), 7.34–7.26 (m, 5 H, phenyl-H), 4.26 (d, J = 5.7 Hz, 1 H, CH), 4.15 (d, J = 4.5 Hz, 1 H, CH), 3.64 (A of AB, J = 12.9 Hz, 1 H, CH₂), 3.59 (B of AB, J = 12.9 Hz, 1 H, CH₂), 3.04 (s, 3 H, CH₃), 2.31–2.20 (m, 1 H, CH₂), 2.18–2.12 (m, 1 H, CH₂), 2.10–2.01 (m, 1 H, CH₂), 1.95–1.88 (m, 1 H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.3, 156.5, 156.1, 137.6, 133.9, 129.9, 128.9, 128.6, 128.0, 126.9, 113.1, 76.1, 57.2, 50.5, 34.1, 33.4, 32.6 ppm. MS (ESI): m/z = 375.1 [M + H]⁺. HRMS (ESI-TOF): calcd. for C₂₂H₂₃N₄S [M + H]⁺ 375.1632; found 375.1638.

(5*R,8*R**)-9-Allyl-10-phenyl-4-(phenylthio)-6,7,8,9-tetrahydro-5*H*-5,8-epiminopyrimido[4,5-*b*]azepine (3i):** Pale yellow solid (0.183 g, 95%). M.p. 120–121 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.14 (s, 1 H, pyrimidyl-H), 7.53–7.51 (m, 2 H, phenyl-H), 7.41–7.36 (m, 3 H, phenyl-H), 7.24–7.18 (m, 2 H, phenyl-H), 6.90–6.82 (m, 3 H, phenyl-H), 5.78–5.73 (m, 1 H, CH=C), 5.26–5.16 (m, 4 H, 2 CH,

C=CH₂), 4.29 (ddt, *J* = 15.3, 6.0, 1.5 Hz, 1 H, CH₂), 4.08 (ddt, *J* = 15.6, 6.6, 1.2 Hz, 1 H, CH₂), 2.47–2.38 (m, 2 H, CH₂), 2.31–2.25 (m, 1 H, CH₂), 2.15–2.08 (m, 1 H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.6, 156.4, 156.3, 144.5, 133.9, 133.4, 130.2, 129.1, 129.0, 128.4, 120.3, 118.0, 117.5, 115.4, 72.3, 55.3, 48.5, 35.3, 33.3 ppm. MS (ESI): *m/z* = 386.9 [M + H]⁺. C₂₃H₂₂N₄S (386.51): calcd. C 71.47, H 5.74, N 14.50, S 8.30; found C 71.37, H 5.60, N 14.58, S 8.15.

(5R*,8R*)-4-Chloro-9-methyl-10-phenyl-6,7,8,9-tetrahydro-5H-5,8-epiminopyrimido[4,5-*b*]azepine (3j): White solid (0.116 g, 80%). M.p. 174–176 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.11 (s, 1 H, pyrimidyl-H), 7.22–7.19 (m, 2 H, phenyl-H), 6.88–6.83 (m, 3 H, phenyl-H), 5.21 (d, *J* = 5.1 Hz, 1 H, CH), 5.13 (d, *J* = 6.3 Hz, 1 H, CH), 3.16 (s, 3 H, CH₃), 2.51–2.39 (m, 2 H, CH₂), 2.32–2.29 (m, 1 H, CH₂), 2.20–2.21 (m, 1 H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 158.6, 156.4, 147.6, 144.4, 129.4, 120.7, 117.2, 114.9, 74.8, 56.3, 34.5, 33.7, 33.4 ppm. MS (ESI): *m/z* = 287.0 [M + H]⁺. C₁₅H₁₅ClN₄ (286.76): calcd. C 62.83, H 5.27, N 19.54; found C 62.98, H 5.30, N 19.50.

(5R*,8R*)-9-Methyl-4-phenoxy-10-phenyl-6,7,8,9-tetrahydro-5H-5,8-epiminopyrimido[4,5-*b*]azepine (3k): Yellow solid (0.115 g, 67%). M.p. 67–69 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.06 (s, 1 H, pyrimidyl-H), 7.43–7.38 (m, 2 H, phenyl-H), 7.24–7.19 (m, 3 H, phenyl-H), 7.11–7.08 (m, 2 H, phenyl-H), 6.94–6.84 (m, 3 H, phenyl-H), 5.25 (d, *J* = 6.0 Hz, 1 H, CH), 5.22 (d, *J* = 4.5 Hz, 1 H, CH), 3.21 (s, 3 H, CH₃), 2.53–2.33 (m, 3 H, CH₂), 2.28–2.22 (m, 1 H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 156.1, 153.7, 129.5, 129.3, 127.3, 124.9, 124.8, 123.2, 121.2, 121.0, 120.4, 117.4, 74.5, 53.4, 34.5, 34.3, 33.9 ppm. MS (ESI): *m/z* = 345.0 [M + H]⁺. HRMS (ESI-TOF): calcd. for C₂₁H₂₁N₄O [M + H]⁺ 345.1702; found 345.1710.

(5R*,8R*)-4-Methoxy-9-methyl-10-phenyl-6,7,8,9-tetrahydro-5H-5,8-epiminopyrimido[4,5-*b*]azepine (3l): Yellow solid (0.099 g, 70%). M.p. 119–120 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.09 (s, 1 H, pyrimidyl-H), 7.19–7.15 (m, 2 H, phenyl-H), 6.86–6.78 (m, 3 H, phenyl-H), 5.15 (d, *J* = 4.2 Hz, 1 H, CH), 5.02 (d, *J* = 5.4 Hz, 1 H, CH), 3.94 (s, 3 H, OCH₃), 3.13 (s, 3 H, CH₃), 2.42–2.22 (m, 3 H, CH₂), 2.15–2.08 (m, 1 H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 164.0, 158.5, 155.6, 145.3, 129.1, 120.0, 117.3, 100.1, 74.3, 53.4, 53.0, 34.6, 34.2, 33.6 ppm. MS (ESI): *m/z* = 283.0 [M + H]⁺. C₁₆H₁₈N₄O (282.34): calcd. C 68.06, H 6.43, N 19.84; found C 68.01, H 6.36, N 19.92.

(5R*,8R*)-N,N-Diethyl-9-methyl-10-phenyl-6,7,8,9-tetrahydro-5H-5,8-epiminopyrimido[4,5-*b*]azepin-4-amine (3m): Pale yellow solid (0.071 g, 44%). M.p. 74–75 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.09 (s, 1 H, pyrimidyl-H), 7.13–7.10 (m, 2 H, phenyl-H), 6.80–6.75 (m, 3 H, phenyl-H), 5.15 (d, *J* = 4.2 Hz, 1 H, CH), 4.88 (d, *J* = 6.6 Hz, 1 H, CH), 3.57–3.46 (m, 2 H, CH₂), 3.13–3.10 (m, 5 H, CH₃, CH₂), 2.58–2.50 (m, 1 H, CH₂), 2.39–2.32 (m, 2 H, CH₂), 2.26–2.18 (m, 1 H, CH₂), 1.18 (t, *J* = 6.9 Hz, 6 H, 2 CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 161.9, 158.0, 155.2, 145.1, 128.9, 124.4, 120.0, 117.4, 104.6, 74.5, 54.9, 45.3, 34.3, 34.0, 13.7 ppm. MS (ESI): *m/z* = 324.0 [M + H]⁺. C₁₉H₂₅N₅ (323.44): calcd. C 70.56, H 7.79, N 21.65; found C 70.80, H 7.76, N 21.88.

Supporting Information (see footnote on the first page of this article): Copies of LC-mass and NMR spectra for all products, and additional computational results and discussion.

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- [15] In a computational study of a similar ene-type reaction, an intermediate formed from the 1,6-H-shift (ene-type) reaction was located.^[7f]
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