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Synthesis of 1,2-Dihydropyrimidine-2-carboxylates via Regioselective Addition of Rhodium(II) Carbenoids to 2*H*-Azirine-2-carbaldimines

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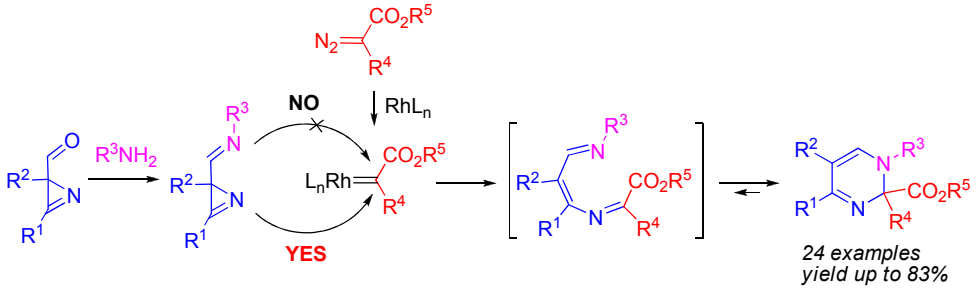
Graphical abstract



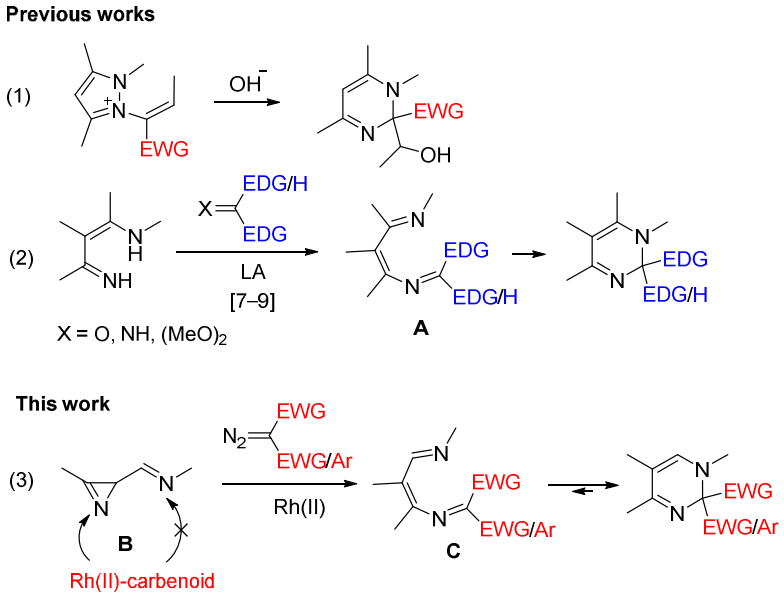
ABSTRACT: An efficient two-step procedure "imine formation/azirine–carbenoid coupling" has been developed for the preparation of 1,2-dihydropyrimidines from azirine-2-carbaldehydes, primary amines and diazo carbonyl compounds under Rh(II)-catalysis. The formation of 1,2-dihydropyrimidines involves 100% regioselective addition of the rhodium carbenoid to endocyclic nitrogen atom of the 2*H*-azirine-2-carbaldimine. According to the DFT calculations the reaction proceeds via dissociation of the metal-bound complex of the azirinium ylide to metal-free azirinium ylide, ring-opening of the latter to give a 1,5-diazahexa-1,3,5-triene, followed by 1,6-cyclization. The 1,2-dihydropyrimidines with two different electron-withdrawing substituents at the C^2 position can undergo in solution inversion of configuration of the stereogenic center at C^2 via "the N^1–C^2 bond cleavage/rotation around the N–C single bond/1,6-cyclization" sequence.

Introduction

The pyrimidine ring system has wide occurrence in natural, as well as in numerous synthetic molecules exhibiting a wide range of pharmacological activities.[1] Among the compounds containing the dihydropyrimidine moiety, there are derivatives with vasodilative and antihypertensive,[2] kinesin spindle protein inhibitory,[3] and anti-mycobacterial activity.[4] The 3,4-dihydropyrimidines, being more readily accessible, have been more studied. They are usually

synthesized by the condensation of α,β-unsaturated carbonyl compounds with amidines and related compounds.[2a,c,5] In contrast, the range of known 1,2-dihydropyrimidines are not so extensive due to the lack of general methods for their preparation. Synthetic applications and biological activity of these compounds have practically not been studied. De La Hoz and Pardo reported the synthesis of a 1,2-dihydropyrimidine derivative, containing an ester group at the C^2 atom, by ring expansion of an *N*-vinylpyrazolium salt (Scheme 1, reaction 1).[6] Another approach to 1,2-dihydropyrimidines involves the generation of the 1,5-diazahexatriene intermediate **A** and its subsequent 1,6-cyclization (Scheme 1, reaction 2). Diazatriene **A** could be prepared by the condensation of a 4-amino-substituted 1-azabuta-1,3-diene with a carbonyl compound[7] or by condensation of 2,2-dihydroperfluorocarbaldehydes with a carbonyl compound and ammonia.[8] The use of this method is limited, however, by the availability of 1,2-dihydropyrimidines with electron-donating substituents at the C2 position.[9] In this work we have developed a new approach to 1,5-diazahexatriene intermediates **C**, as precursors for C^2-functionalized 1,2-dihydropyrimidine derivatives, by means of a carbenoid-mediated ring-opening in azirine-2-carbaldimines **B** (Scheme 1, reaction 3). The use of acceptor-acceptor and donor-acceptor rhodium(II) carbenoids in this reaction, which could be generated from readily available diazo compounds, would allow the introduction of CO_2R, $CONR_2$, CN, CF_3 functional groups at the C^2 position of the pyrimidine system. The formation of the 2-azabuta-1,3-diene fragment from the azirine moiety in reactions of aryl, alkyl and halogeno-substituted azirines,[10] and azirine-2-carbaldehydes was previously reported.[11] These reactions were assumed to occur via the formation and ring-opening of azirinium ylides.[12] The problem that could arise here is a change of the reactive center in compound **B** from azirine nitrogen to the more nucleophilic imine nitrogen atom which can bound with the carbenoid to give azomethine ylide[13] and then undesirable products of its transformation. In particular, an electrophile such as diphenylketene reacts exclusively with the *exo*-imino group of 2*H*-azirine-2-carbaldimines to give 2*H*-azirin-2-ylazetidin-2-ones.[14] To our knowledge, the reactions of rhodium(II) carbenoids with substrates containing two and more sp^2 hybridized nitrogen atoms are unknown.

Scheme 1. Synthesis of 1,2-Dihydropyrimidines



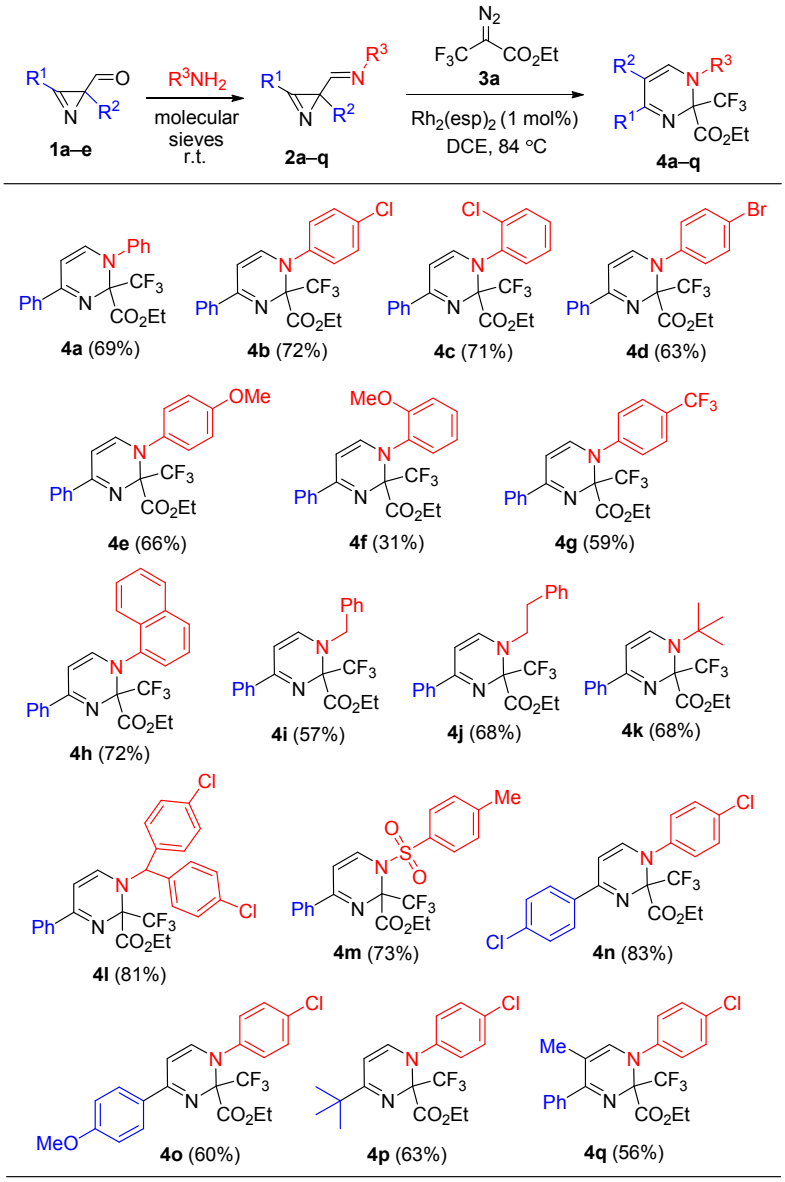
Herein, we report the reaction of azirine-2-carbaldimines with diazo carbonyl compounds under Rh(II)-catalysis as a synthetic route to novel 1,2-dihydropyrimidines. Theoretical and experimental evidence for "1,2-dihydropyrimidine – 1,5-diazahexa-1,3,5-triene" ring-chain tautomerism in 2,2-diacceptor-substituted 1,2-dihydropyrimidines and the ways for their formation from azirine-2-carbaldimines and rhodium(II) α-carbonyl carbenoids are presented in the second and third part of the work.

Results and Discussion

We initiated our studies by investigating the reaction of azirine-2-carbaldimines **2a–q** with diazo compound **3a** (Table 1) in the presence of catalytic amounts of Rh(II) carboxylates as the most commonly used catalysts for the decomposition of α-diazo esters to generate metal-stabilized carbenoids. Aldimines **2a–q** were prepared by the condensation of equimolar amounts of aldehydes **1a–e** and primary amines in the presence of molecular sieves in anhydrous benzene at room temperature. Aldimines **2a–q** are sensitive to hydrolysis and they were used without further purification. The completeness of the conversion of the aldehydes to aldimines was checked by ^{1}H and ^{13}C NMR spectra (Supporting Information). The reactions of azirines **2a–q** with 1.2–1.3 equiv of diazo compound **3a** were carried out in refluxing 1,2-dichloroethane (DCE) in the presence of $Rh_2(esp)_2$ (1 mol %) and gave pyrimidines **4a–q** (Table 1). The use of $Rh_2(OAc)_4$, $Rh_2(Oct)_4$, and $Rh_2(Piv)_4$ is also possible but leads to a slight decrease in yield of pyrimidines **4** (by 5–10%) and slight tarring of the reaction mixtures. The yields of compounds **4**

are generally good, with the exception of pyrimidines **4f**,**q**, which are derived from sterically hindered azirines **2f,q**. Aryl, alkyl and sulfonyl substituents at the imine nitrogen of compounds **2** tolerate the reaction conditions.

Table 1. Scope of Azirines 2[a]

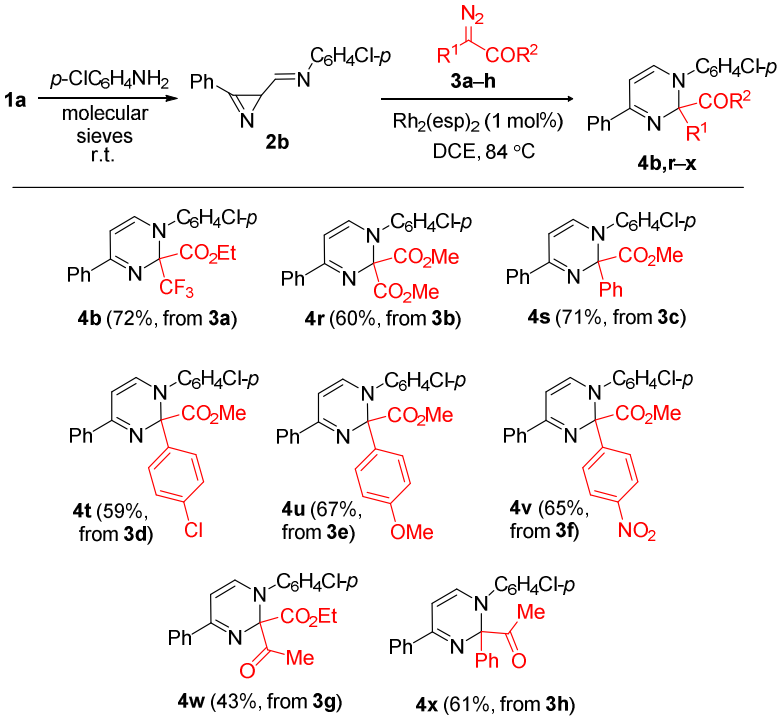


[a] Yields of **4** are calculated on azirinecarbaldehyde **1**.

Next, the substrate scope with respect to the diazo compound was evaluated (Table 2). The reactions of azirine **2b** with diazo esters **3b–f**, diazo keto ester **3g** and diazo ketone **3h** were performed, and the corresponding dihydropyrimidines **4r–x** were isolated in good yields. A slight decrease in product yield was observed in the reaction of diazo keto ester **3g**, in which 3

equiv of the diazo compound had to be used to achieve full conversion of the azirine. It is known that the Rh(II)-catalyzed reaction of α-diazo keto esters and α-diazo ketones with aryl- and alkyl-substituted 2*H*-azirines gives 2*H*-1,4-oxazines, the products of 1,6-cyclization of oxazapolyene intermediates.[10a,b] It was found, however, that the reactions of diazo compounds **3g** and **3h** with azirinecarbaldimine **2b** do not provide 2*H*-1,4-oxazine derivatives: 1,6-cyclization of oxadiazatetraene intermediates occurs exclusively across the C=N bond to give dihydropyrimidine derivatives. The structures of dihydropyrimidines **4a–x** were verified by ^{1}H, ^{13}C NMR and HRMS spectra, and the structure of pyrimidine **4r** was confirmed by X-ray analysis (Figure S-1, Supporting Information).[15]

Table 2. Scope of Diazo Compounds 3[a]

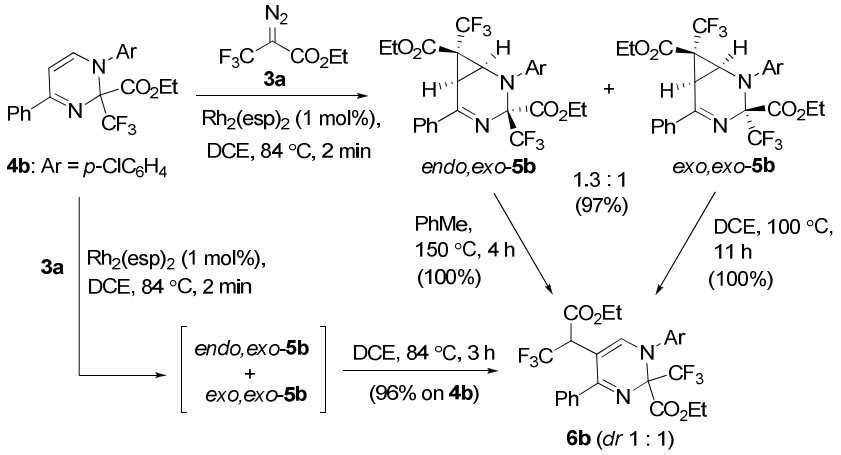


[a] Yields of **4** are calculated on azirinecarbaldehyde **1a**.

The decrease in yield of pyrimidine **4w** could be explained by its side reaction with the rhodium carbenoid derived from **3g**, but we failed to isolate products of these reactions from the reaction mixture. However, when pure pyrimidine **4b** was reacted under standard conditions with diazo compound **3a** in the presence of $Rh_2(esp)_2$ (1 mol%) a 1.3:1 mixture of cyclopropanes *endo,exo*-**5b** and *exo,exo*-**5b** was isolated in 97% yield (Scheme 2). The relative configurations of the stereogenic centers in both cyclopropapyrimidine isomers were established by X-ray diffraction analysis (Figures S-2, S-3, Supporting Information).[15] While studying the stability of

these compounds we found that heating of pure cyclopropane *exo,exo*-**5b** in DCE for 11 h gave pyrimidine **6b** as a 1:1 mixture of diastereomers *RS,RS*-**6b** and *RS,SR*-**6b** in quantitative yield. Under the same conditions the conversion of isomer *endo,exo*-**5b** to **6b** was only 40%, but the reaction was completed in toluene at 150 °C in 4 h. Interestingly, that when both cyclopropanes *endo,exo*-**5b** and *exo,exo*-**5b** were still in the reaction mixture after their synthesis and were not isolated, they isomerize to **6b** much faster. Thus, conversion of mixture **5b** to **6b** occurred completely in 3 h under reflux of the reaction mixture in DCE, the yield of pyrimidine **6b** after chromatographic purification being 96% (Scheme 2).

Scheme 2. $Rh_2(esp)_2$-Catalyzed Reaction of Pyrimidine 4b with Diazo Compound 3a

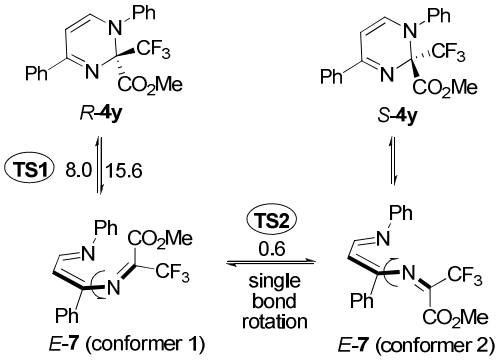


Compound **6b**, containing two chiral centers, was used to study ring-chain tautomerism of the 1,2-dihydropyrimidine system. Isomer *RS,RS*-**6b** was obtained in pure form from a diastereomeric mixture of **6b** by crystallization. The relative configuration of the chiral centers in this compound was established by X-ray diffraction analysis (Figure S-4, Supporting Information).[15] It was found that dihydropyrimidine *RS,RS*-**6b** undergoes epimerization in $CDCl_3$ solution to give an 1:1 mixture *RS,RS*-/*RS,SR*-**6b** in several minutes at room temperature. As the compounds containing a 2-aryl/hetaryl-3,3,3-trifluoropropanoate chiral fragment are known to be configurationally stable at room temperature[16] we assumed that the observed epimerization of *RS,RS*-**6b** involves the change of the configuration of the C^2 atom of the dihydropyrimidine ring and occurs via a "N^1–C^2 ring-opening to 1,5-diazahexatriene/rotation around the single C–N bond /cyclization" sequence (Scheme 3). To verify this hypothesis, we performed quantum-chemical calculations (DFT B3LYP/6-31+G(d,p), PCM for 1,2-dichloroethane) of the 1,2-dihydropyrimidine ring-opening using pyrimidine *R*-**4y** as a model structure (Scheme 3). According to the calculations the ring-opening of compound *R*-**4y** occurs non-torqueselectively:

the barriers for 'inward' and 'outward" rotation of the CF_3 group are practically equal ($\Delta\Delta G^{\neq}$ 0.4 kcal mol^{-1}). Calculated parameters for enantiomerization of *R*-**4y** through *E*-diazahexatriene *E*-**7** are presented in Scheme 3. The barrier for pyrimidine ring-opening of *R*-**4y** to diazahexatriene **7** (TS1) proved to be only 15.6 kcal mol^{-1}. The ring-opening is the rate-determining stage since the transition state energy for the rotation around the C^4–N^5 bond in diazahexatriene **7** (TS2) is lower than that for TS1 by 7.4 kcal mol^{-1}.

Thus, the experimental and calculation results reveal that 1,2-dihydropyrimidines having two electron-withdrawing substituents at the C^2 are configurationally labile systems in solution at room temperature, existing in equilibrium with stereoisomeric dihydropyrimidines and less stable open-chain 1,5-diazahexatriene forms. Such isomerization of 1,2-dihydropyrimidines was observed for the first time, while the 2*H*-1,3-oxazine ring-opening across the C^2–O bond into 1-oxa-5-aza-1,3,5-triene systems is a well-known process.[11a]

Scheme 3. Calculated Parameters for Enantiomerization of Model Dihydropyrimidine *R*-4y ($\Delta G^{\neq}$, kcal mol^{-1})



Possible pathways for the formation of 1,2-dihydropyrimidine **4z** in the model reaction of azirinecarbaldimine **2r** with methyl 2-diazo-3,3,3-trifluoropropanoate (**3i**) in the presence of dirhodium tetraformate are presented in Scheme 4. When analyzing the reaction mechanism, we tried to clarify two points: a) the reason for regioselective addition of the carbenoid to the azirine nitrogen atom of compound **2** and b) the structure of the precursor of diazatriene **12**, namely, whether **12** is formed directly from the metal-bound ylide **9** or an additional step, the formation of metal-free ylide **11**, should be included in the reaction sequence.

Scheme 4. Calculated Parameters for Possible Pathways of $Rh_2(form)_4$-catalyzed Reaction of Azirine 2r with Diazo Compound 3i ($\Delta G^{\neq}$, kcal mol^{-1})

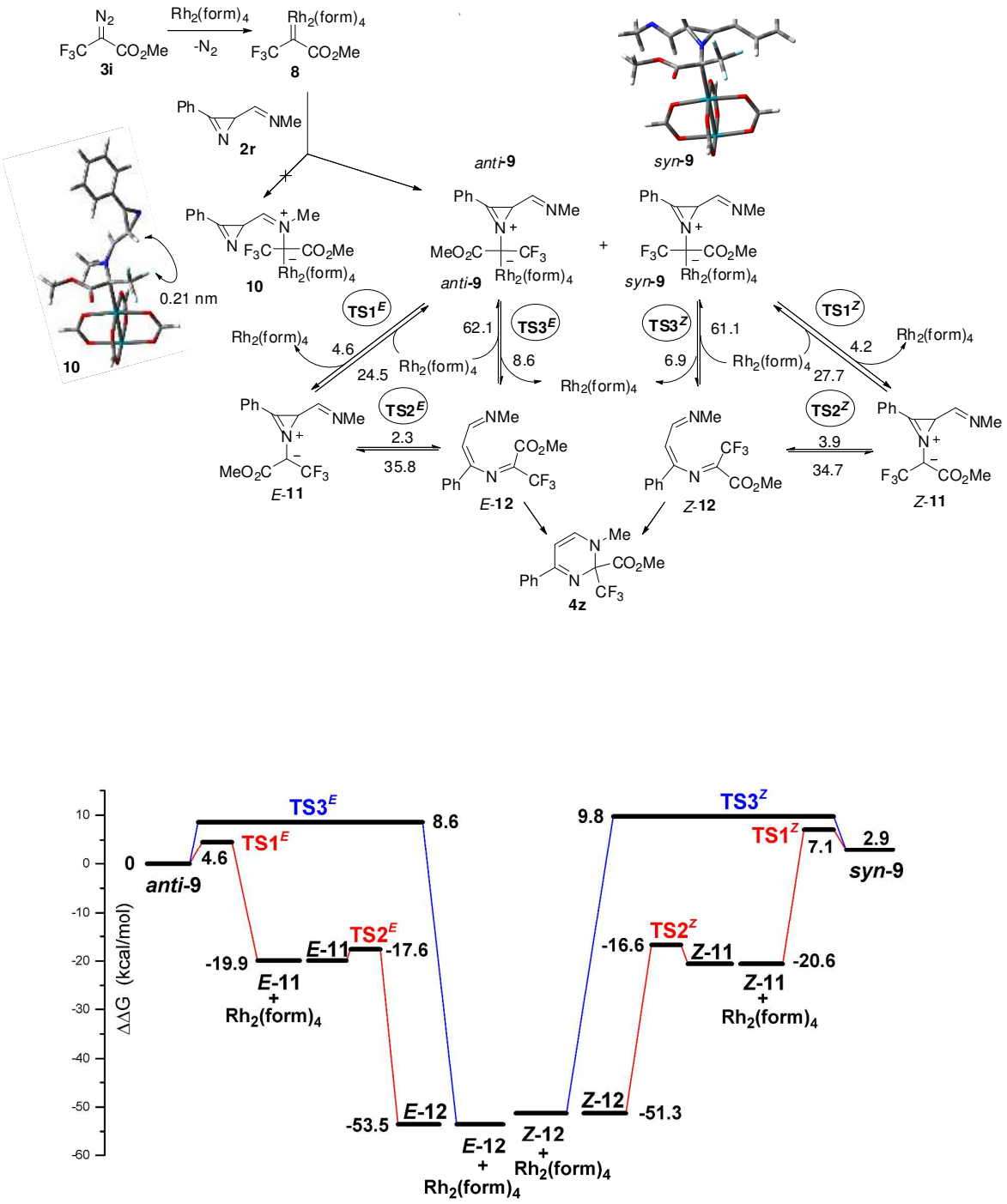


Figure 1. Energy Profiles (Gibbs Free Energies, B3LYP/6-31+G(d,p), kcal·mol^{-1}, 357K, 1,2-Dichloroethane) for Transformations of Metal-bound Azirinium Ylides *syn*-**9** and *anti*-**9** to Diazatrienes *Z*-**12**, *E*-**12**.

Scanning of potential energy surfaces (B3LYP/6-31+G(d,p)/Stuttgart RSC 1997 ECP) for the formation of metal-bound ylides **9** and **10** from azirine **2r** and carbenoid **8** along the forming

bonds C_{Rh}–$N_{azirine}$ or C_{Rh}–N_{imine} did not reveal any activation barriers. The calculations showed that each of diastereomeric azirinium ylides **9** and **9′** can adopt two stable conformations around the C_{Rh}–N bond: *syn*-**9**, *anti*-**9** (Scheme 4) and *syn*-**9′**, *anti*-**9′** (Table S-1, Supporting information). In contrast, each of diastereomeric iminium ylides, **10** (Scheme 4) and **10′** (Table S-1, Supporting information), can exist in a single conformation around the C_{Rh}–N bond. These compounds are less stable than the most favorable conformation of azirinium ylide (*anti*-**9**) by 9.9 and 9.0 kcal mol^{-1}, respectively. Spatial location of phenylazirinyl and methyl substituent at azomethine fragment of ylides **10** and **10′** does not enable rotation around the C_{Rh}–N bond. Thus, in contrast to azirinium ylides **9**, **9′**, the formation of iminium ylides **10**, **10′** from compound **2r** and carbenoid **8** could occur like a key slipping into a lock leading to the only possible conformation around the C_{Rh}–N bond. As the result, the increased entropy contribution to the activation Gibbs free energy for the formation of iminium ylides **10** and **10′** is likely the main reason for the absence of the products resulting from an attack of the cabenoid onto the nitrogen atom of azomethine group.

The structure of the intermediate species undergoing three-membered ring-opening in the reactions of azirines with rhodium carbenoids is still debatable. Often, in describing the mechanism, the authors confine themselves only to a mentioning of metal-bound azirinium ylide without specifying the sequence of the Rh–C and azirine N–C bond cleavage while forming the azapolyene.[12b,c,17] However, in some work the participation of metal-free ylides was also postulated.[18] A good agreement between the calculated torqueselectivity for the ring-opening of metal-free ylides and the experimental results on stereoselectivity of the 2-azabuta-1,3-dienes formation, [10a,c,19] as well as the fact of the formation of 1,5-electrocyclization products[10b] that is characteristic of metal-free 1,3-dipoles, gave reason for inclusion of metal-free azirinium ylides in some published mechanistic schemes. Using DFT calculations we tried to discover the most preferable transformation pathways from metal-bound ylide **9** to diazatriene **12** (Scheme 4). The calculations were performed for two complexes, *syn*-**9** and *anti*-**9**, which do not convert into each other and provide diazatrienes *Z*-**12** and *E*-**12** respectively. The calculation results are presented in Scheme 4 and Figure 1. The barriers for dissociation of the Rh–C bond in both *syn*-**9** and *anti*-**9** to give metal-free ylides *Z*-**11** and *E*-**11** ($TS1^Z$, $TS1^E$) are lower than those for ring-opening to diazatrienes *Z*-**12** and *E*-**12** ($TS3^Z$, $TS3^E$). Further ring-opening in metal-free azirinium ylides *Z*-**11** and *E*-**11** occurs with very low barriers in both cases ($\Delta G^{\neq}$ 3.9 and 2.3 kcal mol^{-1} respectively). Thus, the transformation of metal-bound ylides **9** to diazatrienes **12** occurs via sequential breaking of the Rh–C and the azirine N–C bond, i.e. via intermediate formation of metal-free azirinium ylides **11**.

In conclusion, we have developed an effective two-step method for the preparation of 1,2-dihydropyrimidines from azirine-2-carbaldehydes, primary amines and diazo carbonyl compounds. Azirine-2-carbaldimines, formed in the first step, react with rhodium carbenoids, generated from the diazo compounds under $Rh_2(esp)_2$ catalysis, by endocyclic nitrogen atom exclusively. The reaction involves dissociation of a metal-bound azirinium ylide complex to metal-free azirinium ylide, ring opening to 1,5-diazahexatriene followed by 1,6-cyclization. The formed 1,2-dihydropyrimidines with two different acceptor substituents on the C^2 atom undergo inversion of the C^2 stereogenic center via "the N^1–C^2 bond cleavage/ rotation around the N–C single bond /1,6-cyclization" sequence in solution at room temperature. 1,2-Dihydropyrimidines **4** are less active toward Rh(II)-carbenoids than azirines **2**, but can undergo cyclopropanation of the C^5=C^6 bond under standard conditions to give 2,4-diazabicyclo[4.1.0]hept-4-ene derivatives. The latter are isomerized to 5-substituted 1,2-dihydropyrimidines under heating.

EXPERIMENTAL SECTION

General Methods. Melting points were determined on a melting point apparatus. The ^{1}H NMR spectra were recorded at 400 MHz. The ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane in $CDCl_3$. High-resolution mass spectra were recorded on an HRMS-ESI-QTOF instrument, electrospray ionization, positive mode. Thin-layer chromatography (TLC) was conducted on aluminum sheets precoated with SiO_2 ALUGRAM SIL G/UV254. Column chromatography was performed on silica gel 60 M (0.04–0.063 mm). Benzene and toluene were distilled and stored over sodium metal. 1,2-Dichloroethane was washed with concentrated H_2SO_4 and water, distilled from P_2O_5, and stored over anhydrous K_2CO_3. The catalyst $Rh_2(esp)_2$,[20] 2*H*-azirine-2-carbaldehydes **1a**,**b**,**e**[21] and diazo compounds **3a**,[22] **3b**,[23] **3c**–**f**,[24] **3g**,[25] **3h**[26] were prepared by the reported procedures.

General procedure for the preparation of 2*H*-azirine-2-carbaldehydes 1c,d. The solution of 3-aryl-3-chloroacrylaldehyde (10 mmol) in DMSO (50 mL) was added dropwise at 10–15 ºC to the stirred suspension of NaN_3 (22.5 mmol) in DMSO (135 mL). After addition was completed, the reaction mixture was stirred for 15 min at room temperature. Then the reaction mixture was slowly poured into water (200 mL), maintaining the temperature of the mixture at 10–15 ºC. The product was extracted with benzene (3×150 mL), organic layer was washed with water (3×150 mL) and dried (Na_2SO_4). The solution obtained after filtration was heated for 2.5 h at 50–60 °C (oil bath temperature) and then the solvent was removed in vacuum. The residue was purified by flash column chromatography on silica gel (eluent hexane–EtOAc 5:1) to give azirinecarbaldehydes **1c**,**d**.

*3-(4-Methoxyphenyl)-2H-azirine-2-carbaldehyde (**1c**):* Obtained from 3-chloro-3-(4-methoxyphenyl)acrylaldehyde[27] according to the general procedure. Orange solid (670 mg, yield 38%). Mp: 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (d, J = 6.7 Hz, 1H), 3.93 (s, 3H), 7.05−7.15 (m, 2H), 7.80−7.91 (m, 2H), 8.93 (d, J = 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.0, 55.7, 114.9, 115.1, 132.7, 157.9, 164.5, 200.5; HRMS−ESI $[M + Na]^+$ calcd for $C_{10}H_9NNaO_2^+$ 198.0525; found 198.0532.

*3-tert-Butyl-2H-azirine-2-carbaldehyde (**1d**):* Obtained from 3-chloro-4,4-dimethylpent-2-enal[28] according to the general procedure. Pale yellow oil (300 mg, yield 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.62 (d, J = 6.4 Hz, 1H), 8.88 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 33.2, 39.7, 168.1, 199.8; HRMS−ESI $[M + Na]^+$ calcd for $C_7H_{11}NNaO^+$ 148.0733; found 148.0735.

General procedure for the preparation of 1,2-dihydropyrimidines 4a–x. Azirinecarbaldimine synthesis (stage 1).[29] Azirinecarbaldehyde **1a–e** (0.3 mmol, 1.0 equiv), amine (0.3 mmol, 1.0 equiv), molecular sieves 4Å (350 mg, dried at 150 °C in vacuum 0.1 Torr), and anhydrous benzene (2.0 mL) were placed into a round-bottom flask and stirred at room temperature for 1−7 days (control by ^{1}H NMR spectroscopy). The solid was decanted and washed thoroughly with benzene (3 × 1 mL). The mixture was filtered off through a pad of Celite and the solvent was removed in vacuum to give crude azirinecarbaldimine **2**.

1,2-Dihydropyrimidine synthesis (stage 2). The solution of diazo compound **3a–h** (1.1−3.0 equiv) in 1,2-dichloroethane (DCE) (0.7 mL) was added to the above residue. The solution was rapidly heated to reflux (oil bath temperature 115 °C) under stirring. Then $Rh_2(esp)_2$ (2.3 mg, 0.01 equiv) was added in one portion and refluxing was continued until nitrogen evolution had ceased (about 1−20 min). Full consumption of reagents was controlled by TLC (hexane−EtOAc). The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel (eluent hexane−EtOAc) unless otherwise stated to give 1,2-dihydropyrimidine **4a–x**.

*Ethyl 1,4-diphenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4a**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and aniline, 1 day. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 5 min, eluent for chromatography hexane−EtOAc 12:1. Pale yellow solid (77 mg, yield 69%). Mp: 89−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.1 Hz, 3H), 3.99–4.12 (m, 2H), 5.98 (d, J = 7.4 Hz, 1H), 6.90 (d, J = 7.4 Hz, 1H), 7.28–7.55 (m, 8H), 7.89–8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 62.3, 82.9 (q, J = 27.8 Hz), 96.0, 123.6 (q, J = 292 Hz), 126.2, 127.2, 127.3, 128.3, 129.1, 130.7, 136.7, 142.6, 143.3, 163.9, 165.0; HRMS−ESI $[M + H]^+$ calcd for $C_{20}H_{18}F_3N_2O_2^+$ 375.1315; found 375.1315.

*Ethyl 1-(4-chlorophenyl)-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4b**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 4-chloroaniline, 2 days. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 5 min, eluent for chromatography hexane–EtOAc 12:1. Pale yellow solid (88 mg, yield 72%). Mp: 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, J = 7.1 Hz, 3H), 4.10 (q, J = 7.1 Hz, 2H), 5.98 (d, J = 7.5 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 7.31–7.41 (m, 4H), 7.43–7.54 (m, 3H), 7.88–7.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 62.5, 82.8 (q, J = 27.8 Hz), 96.4, 123.4 (q, J = 291 Hz), 127.2, 127.8, 128.4, 129.2, 130.8, 133.0, 136.5, 141.8, 142.3, 163.8, 165.0; HRMS–ESI $[M + H]^+$ calcd for $C_{20}H_{17}{}^{35}ClF_3N_2O_2^+$ 409.0925; found 409.0924.

*Ethyl 1-(2-chlorophenyl)-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4c**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 2-chloroaniline, 2 days. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 5 min, eluent for chromatography hexane–EtOAc 12:1. Pale yellow solid (87 mg, yield 71%), mixture of two atropoisomers in 1 : 1.5 ratio. Mp: 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$, –40 °C) δ 0.83 (t, J = 6.9 Hz, 1.3H), 1.34 (t, J = 6.8 Hz, 2.1H), 3.87–4.03 (m, 0.8H), 4.28–4.49 (m, 1.3H), 6.08 (d, J = 7.2 Hz, 1H), 6.68–6.82 (m, 1H), 7.27–7.62 (m, 6.5H), 7.67–7.78 (m, 0.5H), 7.88–8.11 (m, 2.7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 13.9, 62.6, 63.2, 81.7 (q, J = 27.3 Hz), 82.3 (q, J = 28.3 Hz), 96.7, 97.1, 121.8 (q, J = 286 Hz), 123.6 (q, J = 295 Hz), 127.0, 127.28, 127.31, 127.4, 128.34, 128.38, 129.7, 130.08, 130.12, 130.58, 130.62, 130.8, 131.8 (2C), 134.8, 135.0, 136.4, 136.5, 138.1, 138.8, 143.3, 144.5, 163.73, 163.80, 164.6, 167.9; HRMS–ESI $[M + H]^+$ calcd for $C_{20}H_{17}{}^{35}ClF_3N_2O_2^+$ 409.0925; found 409.0943.

*Ethyl 1-(4-bromophenyl)-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4d**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 4-bromoaniline, 2 days. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 5 min, eluent for chromatography hexane–EtOAc 12:1. Pale yellow solid (86 mg, yield 63%). Mp: 104–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, J = 6.9 Hz, 3H), 4.10 (q, J = 6.9 Hz, 2H), 5.98 (d, J = 7.3 Hz, 1H), 6.83 (d, J = 7.3 Hz, 1H), 7.20–7.35 (m, 2H), 7.37–7.63 (m, 5H), 7.81–8.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 62.5, 82.8 (q, J = 28.0 Hz), 96.4, 120.9, 123.4 (q, J = 291 Hz), 127.2, 128.0, 128.4, 130.8, 132.2, 136.5, 142.2, 142.3, 163.8, 164.9; HRMS–ESI $[M + H]^+$ calcd for $C_{20}H_{17}{}^{79}BrF_3N_2O_2^+$ 453.0420; found 453.0428.

*Ethyl 1-(4-methoxyphenyl)-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4e**): O*btained according to the general procedure. Stage 1: from azirine **1a** and 4-methoxyaniline, 2 days. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 5 min, eluent for chromatography hexane–EtOAc 7:1. Pale yellow solid (80 mg, yield 66%). Mp: 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, J = 7.1 Hz, 3H), 3.83 (s, 3H), 4.11 (q, J = 7.1 Hz, 2H),

5.89 (d, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 1H), 6.84–6.94 (m, 2H), 7.32–7.40 (m, 2H), 7.42–7.53 (m, 3H), 7.89–7.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 55.4, 62.3, 83.1 (q, *J* = 27.6 Hz), 94.9, 114.1, 123.4 (q, *J* = 291 Hz), 127.3, 128.3, 128.9, 130.6, 135.9, 137.0, 143.7, 158.9, 163.8, 165.4; HRMS–ESI $[M + H]^+$ calcd for $C_{21}H_{20}F_3N_2O_3^+$ 405.1421; found 405.1421.

*Ethyl 1-(2-methoxyphenyl)-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4f**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 2-methoxyaniline, 9 days. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 5 min, eluent for chromatography hexane–EtOAc 7:1. Pale yellow solid (38 mg, yield 31%). Mp: 112–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.1 Hz, 3H), 3.81 (s, 3H), 4.19 (q, *J* = 7.1 Hz, 2H), 5.81 (d, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 1H), 6.92–7.00 (m, 2H), 7.30–7.37 (m, 1H), 7.41–7.57 (m, 4H), 7.91–7.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 55.8, 62.3, 82.9 (q, *J* = 27.6 Hz), 93.7, 112.1, 120.4, 123.1 (q, *J* = 291 Hz), 127.3, 128.3, 129.7, 129.9 (q, *J* = 2.3 Hz), 130.4, 131.2, 137.4, 145.5, 157.0, 163.8, 165.9; HRMS–ESI $[M + H]^+$ calcd for $C_{21}H_{20}F_3N_2O_3^+$ 405.1421; found 405.1421.

*Ethyl 4-phenyl-2-(trifluoromethyl)-1-[4-(trifluoromethyl)phenyl]-1,2-dihydropyrimidine-2-carboxylate (**4g**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 4-(trifluoromethyl)aniline, 2 days. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 5 min, eluent for chromatography hexane–EtOAc 12:1. Pale yellow solid (78 mg, yield 59%). Mp: 90–92 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.1 Hz, 3H), 4.01–4.14 (m, 2H), 6.07 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 7.43–7.55 (m, 5H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.90–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 62.6, 82.7 (q, *J* = 27.8 Hz), 97.6, 123.5 (q, *J* = 292 Hz), 123.8 (q, *J* = 272.0 Hz), 125.4 (q, *J* = 2.3 Hz), 126.4 (q, *J* = 3.7 Hz), 127.3, 128.5, 128.8 (q, *J* = 33.0 Hz), 131.0, 136.4, 141.3, 146.4 (q, *J* = 1.2 Hz), 163.8, 164.6; HRMS–ESI $[M + H]^+$ calcd for $C_{21}H_{17}F_6N_2O_2^+$ 443.1189; found 443.1193.

*Ethyl 1-(naphthalen-1-yl)-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4h**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 1-naphthylamine, 2 days. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 5 min, eluent for chromatography hexane–EtOAc 12:1. Pale yellow viscous oil (92 mg, yield 72%), mixture of two atropoisomers in 1 : 1.3 ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.36 (t, *J* = 7.1 Hz, 1.4H), 1.34 (t, *J* = 7.1 Hz, 1.8H), 3.52–3.72 (m, 0.9H), 4.32–4.45 (m, 1.2H), 6.05 (d, *J* = 7.3 Hz, 0.55H), 6.07 (d, *J* = 7.3 Hz, 0.45H), 6.78–6.89 (m, 1H), 7.44–7.60 (m, 6H), 7.75 (d, *J* = 8.0 Hz, 0.6H), 7.81 (d, *J* = 7.4 Hz, 0.5H), 7.85–7.97 (m, 2H), 8.00–8.08 (m, 2.5H), 8.10 (d, *J* = 7.4 Hz, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 13.9, 62.0, 62.8, 82.7 (q, *J* = 27.3 Hz), 83.3 (q, *J* = 28.4 Hz), 95.6, 95.9, 122.4 (q, *J* = 284.3 Hz), 123.1 (br s), 124.0, 124.1 (q, *J* = 292.8 Hz), 125.0, 125.1, 126.31, 126.35, 126.8, 127.1, 127.38, 127.41, 127.5, 127.8 (br s), 128.0, 128.1, 128.38,

128.41, 129.2, 129.3, 130.6, 130.7, 132.4, 132.7, 134.4, 134.5, 136.8, 137.0, 138.0, 138.4, 144.8, 146.0, 163.7, 164.3 (2C), 167.7; HRMS–ESI $[M + H]^+$ calcd for $C_{24}H_{20}F_3N_2O_2^+$ 425.1471; found 425.1488.

*Ethyl 1-benzyl-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4i**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and benzylamine, 2 h. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 5 min, eluent for chromatography hexane–EtOAc 16:1. Pale yellow solid (66 mg, yield 57%). Mp: 62–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H), 4.22–4.39 (m, 2H), 4.40–4.49 (m, 2H), 5.54 (d, J = 7.6 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 7.32–7.51 (m, 8H), 7.81–7.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 54.2 (q, J = 2.0 Hz), 62.7, 83.0 (q, J = 27.5 Hz), 91.7, 123.8 (q, J = 293 Hz), 127.1, 128.1, 128.3, 128.5, 128.9, 130.5, 135.7, 137.2, 144.0, 164.1, 165.9; HRMS–ESI $[M + H]^+$ calcd for $C_{21}H_{20}F_3N_2O_2^+$ 389.1471; found 389.1471.

*Ethyl 1-phenethyl-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4j**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and phenethylamine, 1 day. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 5 min, eluent for chromatography hexane–EtOAc–NEt_3 180:15:1. Yellow semisolid (82 mg, yield 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.1 Hz, 3H), 2.94–3.08 (m, 2H), 3.39–3.52 (m, 2H), 4.31–4.45 (m, 2H), 5.53 (d, J = 7.5 Hz, 1H), 6.67 (d, J = 7.5 Hz, 1H), 7.20–7.49 (m, 8H), 7.83–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 36.3, 52.8, 62.7, 82.9 (q, J = 27.8 Hz), 91.3, 123.5 (q, J = 292 Hz), 126.8, 127.1, 128.3, 128.75, 128.84, 130.5, 137.2, 137.8, 144.4, 164.0, 166.1; HRMS–ESI $[M + H]^+$ calcd for $C_{22}H_{22}F_3N_2O_2^+$ 403.1628; found 403.1638.

*Ethyl 1-tert-butyl-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4k**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and *tert*-butylamine, 3 days. Stage 2: from diazo compound **3a** (0.36 mmol, 1.2 equiv), 5 min, eluent for chromatography hexane–EtOAc 17:1. Pale yellow oil (81 mg, yield 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.2 Hz, 3H), 1.44 (s, 9H), 4.28–4.44 (m, 2H), 5.58 (d, J = 7.9 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 7.36–7.47 (m, 3H), 7.80–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 29.8, 59.8, 62.3, 81.2 (q, J = 27.0 Hz), 91.0, 124.0 (q, J = 295 Hz), 127.0, 128.2, 130.4, 137.0, 143.2, 162.7, 167.0. HRMS–ESI $[M + H]^+$ calcd for $C_{18}H_{22}F_3N_2O_2^+$ 355.1628; found 355.1618.

*Ethyl 1-[bis(4-chlorophenyl)methyl]-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4l**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and bis(4-chlorophenyl)methanamine, 3 days. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 4 min, eluent for chromatography hexane–EtOAc 17:1. Pale yellow solid (129 mg, yield 81%). Mp: 124–126 °C (hexane–Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, J = 7.1 Hz, 3H), 3.56 (dq, J = 10.8, 7.2 Hz, 1H), 4.05 (dq, J = 10.8, 7.2 Hz, 1H), 5.60 (d, J = 7.8 Hz, 1H), 5.99 (s,

1H), 6.67 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.31–7.52 (m, 7H), 7.82–7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 62.5, 64.5, 82.1 (q, *J* = 27.3 Hz), 91.8, 123.7 (q, *J* = 293 Hz), 127.0, 128.3, 128.8, 129.0, 129.5, 130.2, 130.7, 134.1, 134.4, 136.9, 137.5, 137.6, 141.5, 163.5, 165.3; HRMS–ESI $[M + H]^+$ calcd for $C_{27}H_{22}{}^{35}Cl_2F_3N_2O_2^+$ 533.1005; found 533.1022.

*Ethyl 1-(4-methylphenylsulfonyl)-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4m**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 4-methylbenzenesulfonamide, 7 days. Stage 2: from diazo compound **3a** (0.36 mmol, 1.2 equiv), 11 min, eluent for chromatography hexane–EtOAc 20:1. Pale yellow semisolid (99 mg, yield 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.1 Hz, 3H), 2.47 (s, 3H), 4.39–4.54 (m, 2H), 5.95 (d, *J* = 8.2 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 7.36–7.45 (m, 4H), 7.47–7.53 (m, 1H), 7.79–7.86 (m, 2H), 7.92 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 21.6, 63.3, 80.3 (q, *J* = 29.3 Hz), 98.3, 122.7 (q, *J* = 291 Hz), 127.2, 128.2, 128.5, 129.9, 131.6, 135.4, 135.5 (2C), 145.4, 161.8, 164.5; HRMS–ESI $[M + Na]^+$ calcd for $C_{21}H_{19}F_3N_2NaO_4S^+$ 475.0910; found 475.0924.

*Ethyl 1,4-bis(4-chlorophenyl)-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4n**):* Obtained according to the general procedure. Stage 1: from azirine **1b** and 4-chloroaniline, 3 days. Stage 2: from diazo compound **3a** (0.36 mmol, 1.2 equiv), 4 min, eluent for chromatography hexane–EtOAc 15:1. Pale yellow solid (100 mg, yield 75%). Mp: 107–109 °C ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, *J* = 7.1 Hz, 3H), 4.11 (q, *J* = 7.1 Hz, 2H), 5.91 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 7.31–7.39 (m, 4H), 7.40–7.46 (m, 2H), 7.81–7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 62.7, 82.8 (q, *J* = 27.7 Hz), 95.8, 123.3 (q, *J* = 291 Hz), 128.0 (q, *J* = 1.8 Hz), 128.6, 128.7, 129.3, 133.4, 135.0, 137.1, 141.6, 142.8, 162.8, 165.0; HRMS–ESI $[M + H]^+$ calcd for $C_{20}H_{16}{}^{35}Cl_2F_3N_2O_2^+$ 443.0535; found 443.0529.

*Ethyl 1-(4-chlorophenyl)-4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4o**):* Obtained according to the general procedure. Stage 1: from azirine **1c** and 4-chloroaniline, 2 days. Stage 2: from diazo compound **3a** (0.36 mmol, 1.2 equiv), 5 min, eluent for chromatography hexane–EtOAc 15:1. Pale yellow solid (79 mg, yield 60%). Mp: 94–95 °C (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.1 Hz, 3H), 3.88 (s, 3H), 4.03–4.14 (m, 2H), 5.95 (d, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.92–7.01 (m, 2H), 7.30–7.39 (m, 4H), 7.85–7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 55.4, 62.5, 82.8 (q, *J* = 27.7 Hz), 96.2, 113.7, 123.5 (q, *J* = 292 Hz), 127.7 (q, *J* = 2.1 Hz), 129.0, 129.1, 129.2, 132.9, 141.99, 142.01, 162.0, 162.8, 165.2; HRMS–ESI $[M + H]^+$ calcd for $C_{21}H_{19}{}^{35}ClF_3N_2O_3^+$ 439.1031; found 439.1025.

*Ethyl 4-tert-butyl-1-(4-chlorophenyl)-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4p**):* Obtained according to the general procedure. Stage 1: from azirine **1d** and 4-chloroaniline, 2 days. Stage 2: from diazo compound **3a** (0.45 mmol, 1.5 equiv), 5 min, eluent for chromatography hexane–EtOAc 20:1. Colorless solid (73 mg, yield 63%). Mp: 46–49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.1 Hz, 3H), 1.19 (s, 9H), 3.97–4.12 (m, 2H), 5.51 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 7.6 Hz, 1H), 7.20–7.27 (m, 2H), 7.29–7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 27.8, 37.7, 62.1, 82.5 (q, J = 27.2 Hz), 95.6, 123.4 (q, J = 291.4 Hz), 127.3 (q, J = 2.1 Hz), 129.1, 132.5, 140.8, 142.2, 165.0, 174.6; HRMS–ESI $[M + H]^+$ calcd for $C_{18}H_{21}{}^{35}ClF_3N_2O_2^+$ 389.1238; found 389.1243.

*Ethyl 1-(4-chlorophenyl)-5-methyl-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**4q**):* Obtained according to the general procedure. Stage 1: from azirine **1e** and 4-chloroaniline, 1 week. Stage 2: from diazo compound **3a** (0.39 mmol, 1.3 equiv), 5 min, eluent for chromatography hexane–EtOAc 15:1. Pale yellow solid (71 mg, yield 56%). Mp: 105–107 °C (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J = 7.1 Hz, 3H), 1.83 (d, J = 1.1 Hz, 3H), 4.00–4.13 (m, 2H), 6.55 (q, J = 1.1 Hz, 1H), 7.31–7.38 (m, 4H), 7.41–7.47 (m, 3H), 7.50–7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 16.0, 62.6, 82.6 (q, J = 27.6 Hz), 106.4, 123.3 (q, J = 292 Hz), 127.4 (q, J = 2.1 Hz), 128.2 (2C), 129.1, 129.3, 132.5, 137.8, 139.0, 141.8, 165.2, 169.1; HRMS–ESI $[M + H]^+$ calcd for $C_{21}H_{19}{}^{35}ClF_3N_2O_2^+$ 423.1082; found 423.1096.

*Dimethyl 1-(4-chlorophenyl)-4-phenylpyrimidine-2,2(1H)-dicarboxylate (**4r**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 4-chloroaniline, 2 days. Stage 2: from diazo compound **3b** (0.39 mmol, 1.3 equiv), 20 min, product was purified by washing with hexane–Et_2O (0.5 mL), filtration and drying instead of column chromatography. Pale yellow solid (69 mg, yield 60%). Mp: 171−174 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 6H), 6.02 (d, J = 7.3 Hz, 1H), 6.94 (d, J = 7.3 Hz, 1H), 7.30–7.37 (m, 4H), 7.40–7.50 (m, 3H), 7.88–7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.3, 84.4, 97.5, 125.8, 127.4, 128.3, 129.1, 130.5, 132.2, 136.7, 141.2, 141.7, 162.5, 169.1; HRMS–ESI $[M + H]^+$ calcd for $C_{20}H_{18}{}^{35}ClN_2O_4^+$ 385.0950; found 385.0964.

*Methyl 1-(4-chlorophenyl)-2,4-diphenyl-1,2-dihydropyrimidine-2-carboxylate (**4s**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 4-chloroaniline, 2 days. Stage 2: from diazo compound **3c** (0.33 mmol, 1.1 equiv), 1 min, eluent for chromatography hexane–EtOAc 20:1. Pale yellow foam (85 mg, yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 6.01 (d, J = 7.3 Hz, 1H), 7.01–7.06 (m, 2H), 7.08 (d, J = 7.3 Hz, 1H), 7.12–7.17 (m, 2H), 7.26–7.32 (m, 3H), 7.42–7.53 (m, 5H), 7.96–8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.7, 84.1, 96.7, 127.2, 127.7 (2C), 128.2, 128.4, 128.6 (2C), 130.1, 131.6,

137.4, 138.5, 142.2, 142.6, 162.0, 172.6; HRMS–ESI $[M + H]^+$ calcd for $C_{24}H_{20}{}^{35}ClN_2O_2^+$ 403.1208; found 403.1224.

*Methyl 1,2-bis(4-chlorophenyl)-4-phenyl-1,2-dihydropyrimidine-2-carboxylate (**4t**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 4-chloroaniline, 2 days. Stage 2: from diazo compound **3d** (0.33 mmol, 1.1 equiv), 1 min, eluent for chromatography hexane–EtOAc 20:1. Pale yellow solid (77 mg, yield 59%). Mp: 140–142 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 6.00 (d, J = 7.3 Hz, 1H), 6.98–7.06 (m, 2H), 7.07 (d, J = 7.3 Hz, 1H), 7.14–7.22 (m, 2H), 7.23–7.33 (m, 2H), 7.37–7.53 (m, 5H), 7.88–8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.9, 83.6, 97.0, 127.2, 127.4, 128.0, 128.3, 128.9, 130.0, 130.3, 132.0, 134.5, 137.1, 137.3, 142.1, 142.5, 162.0, 172.3; HRMS–ESI $[M + H]^+$ calcd for $C_{24}H_{19}{}^{35}Cl_2N_2O_2^+$ 437.0818; found 437.0811.

*Methyl 1-(4-chlorophenyl)-2-(4-methoxyphenyl)-4-phenyl-1,2-dihydropyrimidine-2-carboxylate (**4u**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 4-chloroaniline, 2 days. Stage 2: from diazo compound **3e** (0.33 mmol, 1.1 equiv), 1 min, eluent for chromatography hexane–EtOAc 10:1. Pale yellow oil (87 mg, yield 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.79 (s, 3H), 6.00 (d, J = 7.3 Hz, 1H), 6.74–6.87 (m, 2H), 6.96–7.06 (m, 2H), 7.07 (d, J = 7.3 Hz, 1H), 7.10–7.20 (m, 2H), 7.35–7.54 (m, 5H), 7.90–8.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.7, 55.2, 83.6, 96.6, 113.2, 127.2, 127.9, 128.2, 128.6, 129.9, 130.1, 130.7, 131.6, 137.5, 142.3, 142.8, 159.5, 162.0, 173.0; HRMS–ESI $[M + H]^+$ calcd for $C_{25}H_{22}{}^{35}ClN_2O_3^+$ 433.1313; found 433.1331.

*Methyl 1-(4-chlorophenyl)-2-(4-nitrophenyl)-4-phenyl-1,2-dihydropyrimidine-2-carboxylate (**4v**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 4-chloroaniline, 2 days. Stage 2: from diazo compound **3f** (0.33 mmol, 1.1 equiv), 1 min, eluent for chromatography hexane–EtOAc 6:1. Pale yellow oil (87 mg, yield 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 6.03 (d, J = 7.3 Hz, 1H), 7.02–7.07 (m, 2H), 7.11 (d, J = 7.3 Hz, 1H), 7.19–7.24 (m, 2H), 7.40–7.51 (m, 3H), 7.72–7.77 (m, 2H), 7.89–7.96 (m, 2H), 8.14–8.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.1, 83.7, 97.3, 122.8, 126.5, 127.1, 128.3, 129.1, 129.5, 130.4, 132.0, 136.8, 141.7, 141.9, 145.5, 147.6, 161.8, 171.2; HRMS–ESI $[M + H]^+$ calcd for $C_{24}H_{19}{}^{35}ClN_3O_4^+$ 448.1059; found 448.1071.

*Ethyl 2-acetyl-1-(4-chlorophenyl)-4-phenyl-1,2-dihydropyrimidine-2-carboxylate (**4w**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 4-chloroaniline, 2 days. Stage 2: from diazo compound **3g** (0.9 mmol, 3.0 equiv), 5 min, eluent for chromatography hexane–EtOAc 6:1. Pale yellow solid (49 mg, yield 43%). Mp: 82–84 °C (hexane–Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.1 Hz, 3H), 2.33 (s, 3H), 4.05–4.22 (m, 2H), 5.92 (d, J = 7.3 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.41–

7.53 (m, 3H), 7.87–7.98 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 26.3, 62.3, 87.8, 96.6, 125.3, 127.3, 128.4, 129.2, 130.6, 132.0, 136.8, 141.9, 142.0, 162.0, 168.7, 202.9. HRMS–ESI $[M + H]^+$ calcd for $C_{21}H_{20}{}^{35}ClN_2O_3^+$ 383.1157; found 383.1161.

*1-[1-(4-Chlorophenyl)-2,4-diphenyl-1,2-dihydropyrimidin-2-yl]ethanone (**4x**):* Obtained according to the general procedure. Stage 1: from azirine **1a** and 4-chloroaniline, 2 days. Stage 2: from diazo compound **3h** (0.36 mmol, 1.2 equiv), 2 min, product was purified by recrystallization from Et_2O (2 mL) and hexane–Et_2O mixture (1:1, 4 mL) instead of column chromatography. Orange solid (71 mg, yield 61%). Mp: 129–132 °C (hexane–Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 5.92 (d, J = 7.2 Hz, 1H), 6.99 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 8.5 Hz, 2H), 7.23–7.33 (m, 3H), 7.37–7.54 (m, 5H), 7.96–8.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 87.2, 95.3, 127.0, 127.8, 128.35, 128.41, 128.6, 129.05, 129.06, 130.2, 131.9, 137.57, 137.60, 142.4, 144.1, 162.3, 205.5. HRMS–ESI $[M + H]^+$ calcd for $C_{24}H_{20}{}^{35}ClN_2O^+$ 387.1259; found 387.1264.

*Diethyl rel-(1R,3R,6R,7R)-2-(4-chlorophenyl)-5-phenyl-3,7-bis(trifluoromethyl)-2,4-diazabicyclo[4.1.0]hept-4-ene-3,7-dicarboxylate (exo,exo-**5b**) and diethyl rel-(1R,3S,6R,7R)-2-(4-chlorophenyl)-5-phenyl-3,7-bis(trifluoromethyl)-2,4-diazabicyclo[4.1.0]hept-4-ene-3,7-dicarboxylate (endo,exo-**5b**):* Pyrimidine **4b** (88 mg, 0.215 mmol), diazo compound **3a** (98 mg, 0.54 mmol, 2.5 equiv) and 1,2-dichloroethane (1.0 mL) were placed to a round bottom flask and the solution was rapidly heated to reflux (oil bath temperature 115 °C) under stirring. Then $Rh_2(esp)_2$ (1.7 mg, 0.01 equiv) was added in one portion and refluxing was continued until the nitrogen evolution had stopped (about 2 min). The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel (eluent hexane–EtOAc 12:1) to give a 1.3:1 mixture of compounds *endo*,*exo*-**5b** and *exo*,*exo*-**5b** as a pale colorless solid (117 mg, yield 97%). Pure samples of each cyclopropane were obtained by column chromatography on silica gel (eluent hexane–Et_2O 10:1). **Compound *endo*,*exo*-5b** (major isomer). Mp: 105–107 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 2.92 (d, J = 8.6 Hz, 1H), 3.76 (d, J = 8.6 Hz, 1H), 4.00–4.20 (m, 2H), 4.32–4.45 (m, 2H), 7.21–7.27 (m, 2H), 7.33–7.40 (m, 2H), 7.47–7.60 (m, 3H), 8.02–8.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 14.0, 21.0 (q, J = 2.6 Hz), 44.0 (q, J = 3.1 Hz), 45.1 (q, J = 31.7 Hz), 62.5, 63.0, 81.0 (q, J = 27.4 Hz), 122.5 (q, J = 286 Hz), 122.7 (q, J = 277 Hz), 127.2, 128.5, 129.3 br, 129.7, 131.8, 133.3, 136.5, 143.9, 162.0 (q, J = 1.2 Hz), 163.4, 166.2. HRMS–ESI $[M + Na]^+$ calcd for $C_{25}H_{21}{}^{35}ClF_6N_2NaO_4^+$ 585.0986; found 585.1009. **Compound *exo*,*exo*-5b** (minor isomer). Mp: 112–114 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H), 3.05 (d, J = 7.1 Hz, 1H), 3.70 (d, J = 7.1 Hz, 1H), 3.89–3.99 (m, 1H), 4.01–4.11 (m, 1H), 4.14–4.28 (m, 2H), 7.15–7.22 (m, 2H), 7.26–7.31 (m, 2H), 7.48–7.60 (m, 3H), 8.01–8.07

(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 13.6, 21.6, 39.0, 42.8 (q, J = 30.9 Hz), 62.5, 62.9, 78.0 (q, J = 26.6 Hz), 118.3 (q, J = 2.2 Hz), 122.9 (q, J = 277 Hz), 123.9 (q, J = 293 Hz), 127.29, 127.31, 128.6, 128.7, 132.1, 135.9, 142.5, 161.0, 163.2, 164.8. HRMS–ESI $[M + Na]^+$ calcd for $C_{25}H_{21}{}^{35}ClF_6N_2NaO_4^+$ 585.0986; found 585.0995.

*Ethyl 1-(4-chlorophenyl)-5-(3-ethoxy-1,1,1-trifluoro-3-oxopropan-2-yl)-4-phenyl-2-(trifluoromethyl)-1,2-dihydropyrimidine-2-carboxylate (**6b**).* **Synthesis from pyrimidine 4b.** The above reaction mixture containing compounds *endo*,*exo*-**5b** and *exo*,*exo*-**5b** before chromatographic purification was refluxed for 3 h. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel (eluent hexane–EtOAc from 6:1 to 4:1) to give compound **6b** (116 mg, yield 96%) as a mixture of two diastereomers in 1 : 1 ratio.

Synthesis from cyclopropane *exo,exo*-5b. A solution of *exo*,*exo*-**5b** (10 mg, 0.018 mmol) in DCE (0.5 mL) was placed in a screw-cap ampule and heated at 100 °C (oil bath temperature) for 11 h. Evaporation of the solvent under reduced pressure affords compound **6b** quantitatively.

Synthesis from cyclopropane *endo,exo*-5b. A solution of *endo*,*exo*-**5b** (10 mg, 0.018 mmol) in toluene (0.5 mL) was placed in a screw-cap ampule and heated at 150 °C (oil bath temperature) for 4 h. Evaporation of the solvent under a vacuum affords compound **6b** quantitatively. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H), 3.93–4.37 (m, 10H), 7.22 (s, 1H), 7.28–7.33 (m, 3H), 7.37–7.43 (m, 4H), 7.46–7.51 (m, 10H), 7.52–7.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 13.6, 13.8, 14.0, 48.1 (q, J = 29.2 Hz), 48.2 (q, J = 29.7 Hz), 62.2, 62.3, 62.9, 63.2, 76.0 (q, J = 33.1 Hz), 82.0 (q, J = 27.7 Hz), 100.8 (2C), 122.2 (q, J = 287 Hz), 123.3 (q, J = 280 Hz), 123.6 (q, J = 279 Hz), 126.1 (d, J = 293 Hz), 126.9 (q, J = 2.3 Hz), 128.2, 128.5, 128.7 (2C), 129.4, 129.5, 129.8 (q, J = 1.4 Hz), 129.99, 130.03, 133.5, 134.7, 135.9, 136.0, 140.4, 141.2, 143.6, 145.3, 163.8, 166.0 (2C), 166.2 (q, J = 2.8 Hz), 167.1, 167.8. HRMS–ESI $[M + H]^+$ calcd for $C_{25}H_{22}{}^{35}ClF_6N_2O_4^+$ 563.1167; found 563.1191. Pure sample of *(RS,RS)*-isomer was obtained by crystallization from hexane. Mp: 129–132 °C (hexane).

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: …..

Tables S-1, S-2, S-3, ^{1}H and ^{13}C NMR spectra for all new compounds, X-ray crystallography data for compounds **4r**, *endo*,*exo*-**5b**, *exo*,*exo*-**5b**, and *RS*,*RS*-**6b**, computation details with energies of the reactants, transition states, their Cartesian coordinates, and tube representation of the calculated molecules (PDF)

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Notes

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