Supporting Information

Regio- and diastereoselective 1,3-dipolar cycloadditions of 1,2,4-triazin-1-ium ylides: A straightforward synthetic route to polysubstituted pyrrolo[2,1-f][1,2,4]triazines

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General information

The chemicals were obtained from commercial suppliers and were used without further purification. Reactions with air- and moisture-sensitive reactants were performed in anhydrous solvents under nitrogen or argon atmosphere. Column chromatography was carried out on silica gel 60A (particle size: 40-60 μm) from Acros Organics. Mixtures of solvents are each stated as volume fractions. For flash column chromatography a CombiFlash® Rf+ from Teledyne ISCO was used. Thin-layer chromatography was performed on aluminum sheets from Merck (silica gel 60 F254, 20 × 20 cm).

1H- and 13C-NMR spectra were measured on a Bruker Avance III™ HD 400 MHz NMR system equipped with Prodigy cryo-probe. Chemical shifts δ are quoted in ppm in relation to the chemical shift of the residual non-deuterated solvent peak. The structures were assigned based on 2D NMR experiments (HSQC, HMBC). High-resolution mass spectra were recorded on an Agilent 5975C MSD Quadrupol or LTQ Orbitrap XL from Thermo Fisher Scientific. HPLC-MS measurements were performed on an LCMS-2020 system from Shimadzu equipped with a CORTECS C18 column (2.7 μm, 50 × 4.6 mm) or Luna C18 column (3 μm, 10 × 4.6 mm). Gradient of CH₃CN + 0.05% HCOOH in water + 0.05% HCOOH was used for the analysis. High-resolution mass spectra were recorded on an Agilent 5975C MSD Quadrupol, Q-Tof micro from Waters or LTQ Orbitrap XL from Thermo Fisher Scientific.

Synthesis of 1,2,4-triazines

Synthesis and characterization of the following 1,2,4-triazines was reported previously:

1e, 1f, 1g, 1h, 1j, 1k, 1l, 1m, 1n, 1o.

3-Phenyl-1,2,4-triazine (1a)

General procedure A: 3-(Methylthio)-1,2,4-triazine (2.00 g, 15.7 mmol, CAS 28735-21-9), phenylboronic acid (2.5 equiv., 4.79 g, 39.3 mmol), copper(I) thiophene-2-carboxylate (2.2 equiv., 6.60 g, 34.6 mmol) and Pd(PPh₃)₄ (10 mol%, 1.82 g, 1.57 mmol) were placed in an argon flushed flask and anhydrous 1,4-dioxane (100 mL) was added. The mixture was stirred under argon for 16 h at 95 °C. Then, the mixture was concentrated under reduced pressure and the product 1a was separated by column chromatography (1st: DCM/AcOEt 20:1; 2nd: Et₂O/PE 1:2) yielding 2.10 g (13.4 mmol, 85%) of a yellow solid. Characterization matched with reported values. The compound is also commercially available (CAS 18162-28-2).

3-(4-Methoxyphenyl)-1,2,4-triazine (1b)

General procedure A applied. Column chromatography (1st: AcOEt; 2nd: Et₂O/PE 1:2) afforded 2.38 g (12.7 mmol, 81%) of a yellow solid. Characterization matched with reported values.

Methyl 4-(1,2,4-triazin-3-yl)benzoate (1c)

General procedure A applied. Column chromatography (1st: AcOEt/PE 1:1; 2nd: Et₂O/PE 1:1) afforded 645 mg (3.00 mmol, 61%) of a yellow solid.

1H NMR (400 MHz, CDCl₃): δ 9.23 (s, 1H), 8.73 (s, 1H), 8.63 (d, J = 8.8, 2H), 8.21 (d, J = 8.8, 2H), 3.97 (s, 3H).

13C NMR (101 MHz, CDCl₃): δ 166.7, 149.0, 148.3, 138.8, 133.1, 130.2 (2×CH), 128.4 (2×CH), 52.5 (CH₃). Signal of one quart. carbon was not found.
3-(Methylthio)-5-(4-(piperidin-1-yl)phenyl)-1,2,4-triazine (1d)

4-Piperidinylphenylglyoxal (810 mg, 3.44 mmol, CAS 93290-93-8) was dissolved in EtOH (15 mL). Then, NaHCO₃ (3.0 equiv., 868 mg, 10.3 mmol) was dissolved in H₂O (15 mL) and added slowly to the ethanolic solution. The resulting mixture was stirred at room temperature for 10 min. Subsequently, S-methyl isothiosemicarbazide hydroiodide (1.1 equiv., 883 mg, 3.79 mmol) was added in one portion. The resulting mixture was stirred at 80 °C for 2 h. When finished, it was cooled to room temperature, diluted with H₂O (60 mL) and extracted with DCM (3×60 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was purified by column chromatography (AcOEt/DCM 1:9) yielding 700 mg (2.44 mmol, 71%) of an orange solid.

¹H NMR (400 MHz, CDCl₃): δ 9.21 (s, 1H), 8.06 – 8.00 (m, 2H), 6.95 – 6.88 (m, 2H), 8.63 (d, J = 8.8, 2H), 3.41 – 3.45 (m, 4H), 2.68 (s, 3H), 1.71 – 1.63 (m, 6H).
¹³C NMR (101 MHz, CDCl₃): δ 173.1, 154.4, 154.2, 141.4, 129.4, 121.0, 114.4 (2×CH), 48.7 (2×CH₂), 25.5 (2×CH₂), 24.5, 14.0.

HRMS (EI): m/z calcd. for C₁₅H₁₆N₄S [M]+ 286.1252, found 286.1251.

5-(3-Bromophenyl)-3-(methylthio)-1,2,4-triazine (1i)

3-Bromophenylglyoxal (1.16 g, 5.00 mmol, CAS 106134-16-1) was dissolved in EtOH (20 mL). Then, NaHCO₃ (3.0 equiv., 1.26 g, 15.0 mmol) was dissolved in H₂O (20 mL) and added slowly to the ethanolic solution. The resulting mixture was stirred at room temperature for 10 min. Subsequently, S-methyl isothiosemicarbazide hydroiodide (1.1 equiv., 1.28 g, 5.50 mmol) was added in one portion. The resulting mixture was stirred at 80°C for 2.5 h. When finished, it was cooled to room temperature and further to 0°C. Once precipitated, the mixture was concentrated under reduced pressure and the product was easily filtered off, washed with H₂O (2×20 mL) and dried under high vacuum yielding 1.41 g (5.00 mmol, 100%) of a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 9.33 (s, 1H), 8.33 – 8.27 (m, 1H), 8.03 (dd, J = 7.8, 1.7, 1.0, 1H), 7.70 (dd, J = 8.1, 2.0, 1.0, 1H), 7.41 (td, J = 7.8, 0.6, 1H), 2.72 (s, 3H).
¹³C NMR (101 MHz, CDCl₃): δ 174.0, 153.2, 141.8, 135.6, 135.3, 130.9, 130.7, 126.2, 123.7, 14.1.

HRMS (EI): m/z calcd. for C₁₀H₈N₃BrS [M]+ 280.9622, found 280.9616. m/z calcd. for C₁₀H₈N₃BrS [M]+ 282.9602, found 282.9596.

Alkylation of 1,2,4-triazines

**General procedure B:** Substituted triazine (2.00 mmol) was dissolved in anhydrous toluene (20 mL) under argon and this mixture was cooled to 0 °C. Then, methyl or ethyl triflate (1.2 equiv., 2.40 mmol) was added dropwise (≈ 5 min) and the cooling bath was removed. Progress of the reaction was followed by HPLC. When finished, usually the products precipitated from toluene and can be easily filtered off and washed with Et₂O. In some cases, we observed only partial precipitation or no precipitation at all. In such cases, we either added Et₂O directly to the mixture and cool it in an ice bath or we evaporated toluene and the residue was sonicated with Et₂O, which always produced fine powders. We used these products as such (always mixtures with minor N₂ alkylated isomer) but it can be separated on a reverse phase flash column chromatography, if wanted.

**Note:** we used anhydrous DCM as solvent in case of simple 3-aryl triazines (as shown in the maintext) but such derivatives are not productive during the cycloaddition step, and we omitted them from further study. Our theory is that the free position 5, which attracts nucleophiles, causes a ring opening and further chemical decomposition. The only evidence in our hands...
would be a simple TLC, which always showed just a huge brown/black spot at the start, and only traces of products were observed in all cases.

**Note 2:** in case of electron donating substituents (p-OMe, p-piperidyl) we also observed the minor formation of 6-substituted triazines (not 5-substituted). These can be easily separated from each other. However, such products were alkylated at position 3 and, since position 5 was free, we also tried these intermediates in cycloaddition with DMAD. However, only starting material was observed in the reaction, which was therefore not investigated further.

**Optimization of alkylation**

![Chemical structure](image)

**Table S1:** Conditions explored for optimization of the alkylation reaction

| Triazine | Alkylation agent | Solvent   | Temperature | Result           |
|----------|-----------------|-----------|-------------|------------------|
|          | BnBr            | DCM       | RT → 50 °C  | very slow        |
|          | MeI             | DCM       | RT          | no reaction      |
| Dimethyl sulfate |               | DCM       | RT          | slow reaction    |
|          | MeOBF₄·MeOH     | anh. DCM  | 0 °C → RT   | N1 product only  |
|          |                 | anh. PhMe |             | worse than DCM   |
|          |                 | anh. PhCl |             | worse than DCM   |
|          |                 | cyclohexan|             | worse than DCM   |
|          | TfOMe           | anh. DCM  |             | N1 product only  |
|          | TfOEt           | anh. DCM  |             | N1 product only  |
|          | BnBr            | anh. DCM  | RT          | N1: N2 70:30     |
|          | TfOMe           | anh. DCM  | 0 °C → RT   | N1: N2 85:15     |
|          |                 | anh. PhMe |             | N1: N2 75:25     |
|          |                 | anh. PhCl |             | N1: N2 75:25     |
|          |                 | anh. 1,2-DCE |           | N1: N2 80:20    |
|          |                 | anh. MeCN |             | decomp.         |
|          |                 | anh. THF  |             |                 |
|          | BnBr            | anh. DCM  | 0 °C → RT   | N1: N2 75:25     |
|          |                 | anh. PhMe |             | N1: N2 90:10     |
|          | BnBr            | anh. DCM  | RT          | slow reaction    |
|          |                 | anh. PhMe |             | slow reaction    |
1-Methyl-3-phenyl-1,2,4-triazin-1-ium trifluoromethanesulfonate (2a-Me)

Yield: 597 mg (1.86 mmol, 93%) of a colorless solid; only N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.76 (d, $J = 2.9$, 1H), 9.43 (d, $J = 2.9$, 1H), 8.48 – 8.44 (m, 2H), 7.81 – 7.76 (m, 1H), 7.71 – 7.66 (m, 2H), 4.65 (d, $J = 0.8$, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 168.9, 162.4 (CH), 142.9 (CH), 135.7 (CH), 132.0, 130.7 (2×CH), 130.0 (2×CH), 121.9 (q, $^1$J$_{C,F} = 321$, OTf), 63.4 (CH$_2$), 14.7.

HRMS (ESI): m/z calcd. for C$_{10}$H$_{10}$N$_3$ [M$^+$] 172.0869, found 172.0869.

1-Ethyl-3-phenyl-1,2,4-triazin-1-ium trifluoromethanesulfonate (2a-Et)

Yield: 644 mg (1.92 mmol, 96%) of a beige solid; only N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.75 (d, $J = 2.9$, 1H), 9.47 (dt, $J = 2.9$, 0.7, 1H), 8.51 – 8.45 (m, 2H), 7.82 – 7.75 (m, 1H), 7.72 – 7.65 (m, 2H), 4.90 (qd, $J = 7.3$, 0.7, 2H), 1.76 (t, $J = 7.3$, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 169.0, 162.4 (CH), 142.2 (CH), 135.7 (CH), 132.2, 130.7 (2×CH), 130.1 (2×CH), 121.9 (q, $^1$J$_{C,F} = 321$, OTf), 63.4 (CH$_2$), 14.7.

HRMS (ESI): m/z calcd. for C$_{11}$H$_{12}$N$_3$ [M$^+$] 168.1026, found 168.1025.

3-(4-Methoxyphenyl)-1-methyl-1,2,4-triazin-1-ium trifluoromethanesulfonate (2b-Me)

Yield: 674 mg (1.92 mmol, 96%) of a yellow solid; only N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.63 (d, $J = 2.9$, 1H), 9.27 (d, $J = 2.9$, 1H), 8.41 (d, $J = 9.1$, 2H), 7.18 (d, $J = 9.1$, 2H), 4.59 (d, $J = 0.8$, 3H), 3.93 (s, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 168.6, 166.2, 161.9, 141.6, 132.3 (2×CH), 124.1, 122.0 (q, $^1$J$_{C,F} = 321$, OTf), 116.2 (2×CH), 56.6, 54.1.

HRMS (ESI): m/z calcd. for C$_{11}$H$_{12}$N$_3$O [M$^+$] 202.0975, found 202.0976.

1-Ethyl-3-(4-methoxyphenyl)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2b-Et)

Triazine 1b (0.34 mmol) used. Yield: 101 mg (0.277 mmol, 89%) of an orange solid; only N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.62 (d, $J = 2.8$, 1H), 9.25 (dt, $J = 2.8$, 0.6, 1H), 8.44 (d, $J = 9.2$, 2H), 7.19 (d, $J = 9.2$, 2H), 4.82 (qd, $J = 7.3$, 0.7, 2H), 3.94 (s, 3H), 1.73 (t, $J = 7.3$, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 168.9, 166.3 (CH), 162.0 (CH), 140.8, 132.4 (2×CH), 124.3, 116.3 (2×CH), 121.9 (q, $J = 321$, OTf), 63.3 (OCH$_3$), 56.7 (CH$_2$), 14.7 (CH$_3$). OTf is not visible.

HRMS (ESI): m/z calcd. for C$_{12}$H$_{14}$N$_3$O [M$^+$] 216.1131, found 216.1133.
3-(4-(Methoxycarbonyl)phenyl)-1-methyl-1,2,4-triazin-1-ium trifluoromethanesulfonate (2c-Me)

Yield: 713 mg (1.88 mmol, 94%) of a beige solid; only N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.82 (d, $J = 2.9$, 1H), 9.48 (dt, $J = 2.9, 0.8$, 1H), 8.55 (d, $J = 8.8$, 2H), 8.25 (d, $J = 8.8$, 2H), 4.68 (d, $J = 0.8$, 3H), 3.94 (s, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 168.1, 166.7, 162.7 (CH), 143.5 (CH), 136.3, 135.8, 131.3 (2×CH), 130.2 (2×CH), 54.3, 53.2. OTf is not visible.

HRMS (ESI): m/z calcd. for C$_{12}$H$_{12}$NaO$_2$ [M$^+$] 230.0924, found 230.0925.

1-Ethyl-3-(4-(methoxycarbonyl)phenyl)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2c-Et)

Yield: 716 mg (1.82 mmol, 91%) of a beige solid; only N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.81 (d, $J = 2.9$, 1H), 9.53 (m, 1H), 8.57 (d, $J = 8.8$, 2H), 8.25 (d, $J = 8.8$, 2H), 4.93 (q, $J = 7.2$, 2H), 3.94 (s, 3H), 1.77 (t, $J = 7.2$, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 168.2, 166.7, 162.7 (CH), 142.8 (CH), 136.3, 136.0, 131.3 (2×CH), 130.2 (2×CH), 63.6 (CH$_2$), 53.2, 14.8. OTf is not visible.

HRMS (ESI): m/z calcd. for C$_{13}$H$_{14}$NaO$_2$ [M$^+$] 244.1081, found 244.1080.

1-Methyl-3-(methylthio)-5-(4-(piperidin-1-yl)phenyl)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2d-Me)

Yield: 847 mg (1.88 mmol, 94%) of a dark purple-black solid, of which 85% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.38 (bs, 1H), 8.20 – 8.07 (m, 2H), 7.20 – 7.00 (m, 2H), 4.32 (bs, 3H), 3.65 – 3.54 (m, 4H), 2.65 (s, 3H), 1.78 – 1.62 (m, 6H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 178.6, 161.7, 137.5, 132.6 (2×CH), 121.9 (q, $^1$J$_{C,F}$ = 321, OTf), 114.9 (2×CH), 52.9, 49.3, 26.0, 24.5, 14.3. Signals of two quart. carbons were not found.

HRMS (ESI): m/z calcd. for C$_{15}$H$_{21}$N$_4$S [M$^+$] 301.1481, found 301.1483.

1-Ethyl-3-(methylthio)-5-(4-(piperidin-1-yl)phenyl)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2d-Et)

Yield: 892 mg (1.92 mmol, 96%) of a dark purple-black solid, of which 85% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.34 (bs, 1H), 8.15 (d, $J = 9.3$, 2H), 7.11 – 7.02 (m, 2H), 4.55 (q, $J = 7.3$, 2H), 3.64 – 3.56 (m, 4H), 2.67 (s, 3H), 1.76 – 1.65 (m, 6H), 1.64 (t, $J = 7.3$, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 178.7, 168.0, 161.7, 136.7, 132.7 (2×CH), 122.0 (q, $^1$J$_{C,F}$ = 321, OTf), 114.9 (2×CH), 62.2 (CH$_2$), 49.2, 26.2, 24.7, 14.6, 14.3. Signal of one quart. carbon was not found.

HRMS (ESI): m/z calcd. for C$_{17}$H$_{23}$N$_4$S [M$^+$] 315.1638, found 315.1639.
5-(4-Methoxyphenyl)-1-methyl-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2e-Me)

Yield: 779 mg (1.96 mmol, 98%) of a bright yellow solid, of which 83% is major N1 isomer

1H NMR (400 MHz, CD3CN): δ 9.61 (bs, 1H), 8.32 (d, J = 9.1, 2H), 7.20 (d, J = 9.1, 2H), 4.45 (d, J = 0.8, 3H), 3.95 (s, 3H), 2.72 (s, 3H).

13C NMR (101 MHz, CD3CN): δ 179.6, 167.5, 164.3, 138.0, 132.6 (2×CH), 123.8, 122.0 (q, Jc,F = 321, OTf), 116.7 (2×CH), 56.9, 53.4, 14.6.

HRMS (ESI): m/z calcd. for C12H14N3OS [M⁺] 248.0852, found 248.0853.

1-Ethyl-5-(4-methoxyphenyl)-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2e-Et)

Yield: 757 mg (1.84 mmol, 92%) of a bright yellow solid, of which 86% is major N1 isomer

1H NMR (400 MHz, CD3CN): δ 9.60 (bs, 1H), 8.34 (d, J = 9.1, 2H), 7.21 (d, J = 9.1, 2H), 4.69 (q, J = 7.3, 2H), 3.96 (s, 3H), 2.73 (s, 3H), 1.69 (t, J = 7.3, 3H).

13C NMR (101 MHz, CD3CN): δ 179.8, 167.5, 164.4, 137.3, 132.6 (2×CH), 123.9, 122.0 (q, Jc,F = 321, OTf), 116.7 (2×CH), 63.0 (CH2), 56.9, 53.4, 14.62, 14.59.

HRMS (ESI): m/z calcd. for C13H16N3OS [M⁺] 262.1009, found 262.1009.

5-(4-Hydroxyphenyl)-1-methyl-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2f-Me)

Yield: 759 mg (1.98 mmol, 99%) of a light orange solid, of which 76% is major N1 isomer

1H NMR (400 MHz, CD3CN): δ 9.53 (q, J = 0.8, 1H), 8.73 (bs, 1H), 8.23 (d, J = 9.0, 2H), 7.09 (d, J = 9.0, 2H), 4.42 (d, J = 0.8, 3H), 2.71 (s, 3H).

13C NMR (101 MHz, CD3CN): δ 179.6, 165.9, 164.2, 137.8, 132.9 (2×CH), 123.0, 121.9 (q, Jc,F = 320, OTf), 118.1 (2×CH), 53.4, 14.5.

HRMS (ESI): m/z calcd. for C11H12N3OS [M⁺] 234.0696, found 234.0696.

1-Ethyl-5-(4-hydroxyphenyl)-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2f-Et)

Yield: 771 mg (1.94 mmol, 97%) of a light orange solid, of which 72% is major N1 isomer

1H NMR (400 MHz, CD3CN): δ 9.54 (bs, 1H), 8.25 (d, J = 9.0, 2H), 7.10 (d, J = 9.0, 2H), 4.67 (q, J = 7.3, 2H), 2.72 (s, 3H), 1.68 (t, J = 7.3, 3H).

13C NMR (101 MHz, CD3CN): δ 179.7, 165.8, 164.3, 137.1, 132.9 (2×CH), 123.1, 121.9 (q, Jc,F = 320, OTf), 118.1 (2×CH), 62.9 (CH2), 14.60, 14.56.

HRMS (ESI): m/z calcd. for C12H14N3OS [M⁺] 248.0852, found 248.0854.
1-Methyl-3-(methylthio)-5-phenyl-1,2,4-triazin-1-ium trifluoromethanesulfonate (2g-Me)

Yield: 698 mg (1.90 mmol, 95%) of a bright yellow solid, of which 87% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.76 (bs, 1H), 8.26 – 8.30 (m, 2H), 7.86 – 7.79 (m, 1H), 7.73 – 7.66 (m, 2H), 4.52 (bs, 3H), 2.75 (s, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 180.0, 165.6, 138.6, 136.9, 131.5, 131.0 (2×CH), 130.0 (2×CH), 121.9 (q, $^1$J$_{C,F}$ = 321, OTf), 53.6, 14.7.

HRMS (ESI): m/z calcd. for C$_{11}$H$_{12}$N$_3$S [M$^+$] 218.0746, found 218.0746.

1-Ethyl-3-(methylthio)-5-phenyl-1,2,4-triazin-1-ium trifluoromethanesulfonate (2g-Et)

Yield: 740 mg (1.94 mmol, 97%) of a bright yellow solid, of which 86% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.71 (bs, 1H), 8.36 – 8.32 (m, 2H), 7.87 – 7.81 (m, 1H), 7.74 – 7.68 (m, 2H), 4.76 (qd, $J$ = 7.3, 0.6, 2H), 2.76 (s, 3H), 1.71 (t, $J$ = 7.3, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 180.4, 165.8, 137.8, 136.9, 131.6, 131.0 (2×CH), 130.0 (2×CH), 122.0 (q, $^1$J$_{C,F}$ = 321, OTf), 63.3 (CH$_2$), 14.75, 14.68.

HRMS (ESI): m/z calcd. for C$_{12}$H$_{14}$N$_3$S [M$^+$] 232.0903, found 232.0905.

1-Methyl-3-(methylthio)-5-(naphthalen-2-yl)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2h-Me)

Yield: 818 mg (1.96 mmol, 98%) of an orange solid, of which 81% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.85 (q, $J$ = 0.9, 1H), 8.93 (d, $J$ = 1.9, 1H), 8.27 (dd, $J$ = 8.8, 1.9, 1H), 8.15 – 8.09 (m, 2H), 8.03 – 7.99 (m, 1H), 7.79 – 7.73 (m, 1H), 7.71 – 7.65 (m, 1H), 4.52 (d, $J$ = 0.9, 3H), 2.77 (s, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 180.1, 165.3, 138.6, 137.6, 133.7, 133.2, 131.5, 131.02, 130.96, 129.0, 128.92, 128.86, 124.0, 122.0 (q, $^1$J$_{C,F}$ = 321, OTf), 53.7, 14.7.

HRMS (ESI): m/z calcd. for C$_{15}$H$_{14}$N$_3$S [M$^+$] 268.0903, found 268.0903.

1-Ethyl-3-(methylthio)-5-(naphthalen-2-yl)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2h-Et)

Yield: 828 mg (1.92 mmol, 96%) of an orange solid, of which 83% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.89 (bs, 1H), 8.94 (d, $J$ = 1.9, 1H), 8.26 (dd, $J$ = 8.8, 1.9, 1H), 8.13 – 8.05 (m, 2H), 8.01 – 7.96 (m, 1H), 7.76 – 7.70 (m, 1H), 7.69 – 7.63 (m, 1H), 4.78 (q, $J$ = 7.3, 2H), 2.76 (s, 3H), 1.73 (t, $J$ = 7.3, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 180.2, 165.3, 137.9, 137.5, 133.6, 133.2, 131.4, 130.92, 130.90, 129.0, 128.9, 128.8, 124.0, 122.0 (q, $^1$J$_{C,F}$ = 321, OTf), 63.2 (CH$_2$), 14.74, 14.69.

HRMS (ESI): m/z calcd. for C$_{16}$H$_{16}$N$_3$S [M$^+$] 282.1059, found 282.1060.
5-(3-Bromophenyl)-1-methyl-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2i-Me)

Yield: 857 mg (1.93 mmol, 96%) of a bright yellow solid, of which 88% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.71 (q, $J = 0.8$, 1H), 8.47 (t, $J = 1.9$, 1H), 8.28 (ddd, $J = 8.0$, 1.9, 1.0, 1H), 7.97 (ddd, $J = 8.0$, 2.0, 0.9, 1H), 7.62 (t, $J = 8.0$, 1H), 4.52 (d, $J = 0.8$, 3H), 2.76 (s, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 180.3, 164.5, 139.4, 138.6, 133.6, 132.7, 132.4, 128.8, 124.4, 121.9 (q, $^1J_{C,F} = 321$, OTf), 53.8, 14.8.

HRMS (ESI): m/z calcd. for C$_{11}$H$_{11}$N$_3$BrS [M$^+$] 295.9852, found 295.9853. m/z calcd. for C$_{11}$H$_{11}$N$_3$BrS [M$^+$] 297.9832, found 297.9830.

5-(3-Bromophenyl)-1-ethyl-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2i-Et)

Yield: 727 mg (1.58 mmol, 79%) of a light-yellow solid, of which 94% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.70 (bs, 1H), 8.48 (t, $J = 1.9$, 1H), 8.32 – 8.27 (m, 1H), 8.00 – 7.95 (m, 1H), 7.62 (t, $J = 8.0$, 1H), 4.76 (q, $J = 7.3$, 2H), 2.77 (s, 3H), 1.71 (t, $J = 7.3$, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 180.5, 164.6, 139.3, 137.9, 133.7, 132.5, 128.9, 124.4, 122.0 (q, $^1J_{C,F} = 321$, OTf), 63.4 (CH$_2$), 14.8, 14.7.

HRMS (ESI): m/z calcd. for C$_{12}$H$_{13}$N$_3$BrS [M$^+$] 310.0008, found 310.0011. m/z calcd. for C$_{12}$H$_{13}$N$_3$BrS [M$^+$] 311.9988, found 311.9989.

5-(4-Bromophenyl)-1-methyl-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2j-Me)

Yield: 812 mg (1.82 mmol, 91%) of a bright yellow solid, of which 90% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.73 (bs, 1H), 8.21 (d, $J = 8.7$, 2H), 7.86 (d, $J = 8.7$, 2H), 4.51 (d, $J = 0.8$, 3H), 2.74 (s, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 180.2, 164.9, 138.4, 134.2 (2×CH), 131.9, 131.5 (2×CH), 130.7, 121.9 (q, $^1J_{C,F} = 321$, OTf), 53.7, 14.7.

HRMS (ESI): m/z calcd. for C$_{11}$H$_{11}$N$_3$BrS [M$^+$] 295.9852, found 295.9854. m/z calcd. for C$_{11}$H$_{11}$N$_3$BrS [M$^+$] 297.9832, found 297.9832.

5-(4-Bromophenyl)-1-ethyl-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2j-Et)

Yield: 838 mg (1.83 mmol, 91%) of a bright yellow solid, of which 89% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.72 (bs, 1H), 8.23 (d, $J = 8.8$, 2H), 7.88 (d, $J = 8.8$, 2H), 4.76 (q, $J = 7.3$, 2H), 2.76 (s, 3H), 1.71 (t, $J = 7.3$, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 180.4, 165.0, 137.7, 134.2 (2×CH), 131.8, 131.5 (2×CH), 130.8, 122.0 (q, $^1J_{C,F} = 321$, OTf), 63.3 (CH$_2$), 14.8, 14.7.

HRMS (ESI): m/z calcd. for C$_{12}$H$_{13}$N$_3$BrS [M$^+$] 310.0008, found 310.0011. m/z calcd. for C$_{12}$H$_{13}$N$_3$BrS [M$^+$] 311.9988, found 311.9990.
5-(4-Fluorophenyl)-1-methyl-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2k-Me)

Yield: 740 mg (1.92 mmol, 96%) of a bright yellow solid, of which 90% is major N1 isomer

H NMR (400 MHz, CD3CN): δ 9.70 (q, J = 0.9, 1H), 8.44 – 8.37 (m, 2H), 7.48 – 7.40 (m, 2H), 4.50 (d, J = 0.8, 3H), 2.75 (s, 3H).

13C NMR (101 MHz, CD3CN): δ 180.2, 168.4 (d, 1J_{C,F} = 258, C-F), 164.6, 138.4, 133.1 (d, 3J_{C,F} = 10.2, 2×CH), 128.1 (d, 4J_{C,F} = 2.9, C), 118.4 (d, 2J_{C,F} = 22.9, 2×CH), 53.8, 14.7. OTf is not visible.

HRMS (ESI): m/z calcd. for C11H11N3FS [M+1] 236.0652, found 236.0653.

1-Ethyl-5-(4-fluorophenyl)-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2k-Et)

Yield: 735 mg (1.84 mmol, 92%) of a bright yellow solid, of which 91% is major N1 isomer

H NMR (400 MHz, CD3CN): δ 9.72 (bs, 1H), 8.45 – 8.38 (m, 2H), 7.48 – 7.40 (m, 2H), 4.75 (q, J = 7.3, 2H), 2.76 (s, 3H), 1.71 (t, J = 7.3, 3H).

13C NMR (101 MHz, CD3CN): δ 180.2, 168.3 (d, 1J_{C,F} = 258, C-F), 164.6, 137.7, 133.1 (d, 3J_{C,F} = 10.1, 2×CH), 128.2 (d, 4J_{C,F} = 2.8, C), 122.0 (q, 1J_{C,F} = 321, OTf), 118.3 (d, 2J_{C,F} = 22.7, 2×CH), 63.3 (CH3), 14.7, 14.6.

HRMS (ESI): m/z calcd. for C12H13N3FS [M+1] 250.0809, found 250.0810.

1-Methyl-3-(methylthio)-5-(4-(trifluoromethyl)phenyl)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2l-Me)

Yield: 758 mg (1.74 mmol, 87%) of a bright yellow solid, of which 92% is major N1 isomer

H NMR (400 MHz, CD3CN): δ 9.70 (q, J = 0.8, 1H), 8.50 – 8.44 (m, 2H), 8.04 – 7.99 (m, 2H), 4.54 (d, J = 0.8, 3H), 2.78 (s, 3H).

13C NMR (101 MHz, CD3CN): δ 180.6, 164.8, 138.8, 136.5 (q, 2J_{C,F} = 32.9, C-CF3), 135.1, 130.7 (s, 2×CH), 127.8 (q, 3J_{C,F} = 3.9, 2×CH), 124.5 (q, 1J_{C,F} = 272, CF3), 121.9 (q, 1J_{C,F} = 321, OTf), 53.9, 14.8.

HRMS (ESI): m/z calcd. for C12H11N3FS [M+1] 286.0620, found 286.0620.

1-Ethyl-3-(methylthio)-5-(4-(trifluoromethyl)phenyl)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2l-Et)

Yield: 737 mg (1.64 mmol, 82%) of a light-yellow solid, of which 94% is major N1 isomer

H NMR (400 MHz, CD3CN): δ 9.80 (bs, 1H), 8.52 – 8.46 (m, 2H), 8.04 – 7.98 (m, 2H), 4.80 (q, J = 7.3, 2H), 2.78 (s, 3H), 1.73 (t, J = 7.3, 3H).

13C NMR (101 MHz, CD3CN): δ 180.7, 164.9, 138.2, 136.4 (q, 2J_{C,F} = 32.9, C-CF3), 135.2, 130.7 (s, 2×CH), 127.7 (q, 3J_{C,F} = 3.8, 2×CH), 124.5 (q, 1J_{C,F} = 272, CF3), 122.0 (q, 1J_{C,F} = 321, OTf), 63.5 (CH2), 14.8, 14.7.

HRMS (ESI): m/z calcd. for C13H13N3FS [M+1] 300.0777, found 300.0776.
1-Methyl-3-(methylthio)-5-(4-nitrophenyl)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2m-Me)

Yield: 783 mg (1.90 mmol, 95%) of a yellow solid, of which 85% is major N1 isomer

\[ ^1H \text{NMR (400 MHz, CD}_3\text{CN)}: \delta 9.81 \text{ (bs, 1H), 8.54 – 8.44 (m, 4H), 4.56 (bs, 3H), 2.78 (s, 3H).} \]

\[ ^13C \text{NMR (101 MHz, CD}_3\text{CN)}: \delta 163.6 \text{ (CH)} \]

HRMS (ESI): m/z calcd. for C\text{\textsubscript{11}}H\text{\textsubscript{13}}O\text{\textsubscript{2}}N\text{\textsubscript{4}}S [M\textsuperscript{+}] 263.0597, found 263.0595.

1-Ethyl-3-(methylthio)-5-(4-nitrophenyl)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2m-Et)

Yield: 750 mg (1.76 mmol, 88%) of a yellow solid, of which 90% is major N1 isomer

\[ ^1H \text{NMR (400 MHz, CD}_3\text{CN)}: \delta 9.83 \text{ (bs, 1H), 8.55 – 8.50 (m, 2H), 8.49 – 8.44 (m, 2H), 4.81 (q, J = 7.3, 2H), 2.79 (s, 3H), 1.73 (t, J = 7.3, 3H).} \]

\[ ^13C \text{NMR (101 MHz, CD}_3\text{CN)}: \delta 160.7 \text{ (CH)} \]

HRMS (ESI): m/z calcd. for C\text{\textsubscript{12}}H\text{\textsubscript{15}}O\text{\textsubscript{2}}N\text{\textsubscript{4}}S [M\textsuperscript{+}] 277.0754, found 277.0756.

1-Methyl-3,5-diphenyl-1,2,4-triazin-1-ium trifluoromethanesulfonate (2n-Me)

Yield: 779 mg (1.96 mmol, 98%) of an off-white solid, of which >99% is major N1 isomer

\[ ^1H \text{NMR (400 MHz, CD}_3\text{CN)}: \delta 9.97 \text{ (q, J = 0.8, 1H), 8.59 – 8.54 (m, 2H), 8.52 – 8.47 (m, 2H), 7.89 – 7.83 (m, 1H), 7.80 – 7.66 (m, 5H), 4.68 (d, J = 0.8, 3H).} \]

\[ ^13C \text{NMR (101 MHz, CD}_3\text{CN)}: \delta 168.2, 167.3, 140.8 \text{ (CH)}, 136.9 \text{ (CH)}, 135.5 \text{ (CH)}, 132.4, 132.0, 131.1 \text{ (2xCH)}, 130.6 \text{ (2xCH)}, 130.04 \text{ (2xCH)}, 130.01 \text{ (2xCH)}, 122.0 \text{ (q, J = 321, OTf)}, 54.0 \text{ (CH\textsubscript{3})}.} \]

HRMS (ESI): m/z calcd. for C\text{\textsubscript{16}}H\text{\textsubscript{18}}N\text{\textsubscript{2}} [M\textsuperscript{+}] 248.1182, found 248.1185.

1-Ethyl-3,5-diphenyl-1,2,4-triazin-1-ium trifluoromethanesulfonate (2n-Et)

Yield: 798 mg (1.94 mmol, 97%) of a colorless solid, of which >99% is major N1 isomer

\[ ^1H \text{NMR (400 MHz, CD}_3\text{CN + DMSO-d}_6: 5:1): \delta 10.52 \text{ (bs, 1H), 8.60 – 8.52 (m, 4H), 7.88 – 7.81 (m, 1H), 7.78 – 7.65 (m, 5H), 4.90 (q, J = 7.3, 2H), 1.76 (t, J = 7.3, 3H).} \]

\[ ^13C \text{NMR (101 MHz, CD}_3\text{CN + DMSO-d}_6: 5:1): \delta 167.5, 167.2, 141.0 \text{ (CH)}, 136.5 \text{ (CH)}, 135.1 \text{ (CH)}, 132.5, 132.2, 130.8 \text{ (2xCH)}, 130.4 \text{ (2xCH)}, 129.9 \text{ (2xCH)}, 129.7 \text{ (2xCH)}, 62.7 \text{ (CH\textsubscript{2})}, 14.9 \text{ (CH\textsubscript{3})}. \]

OTf is not visible.

HRMS (ESI): m/z calcd. for C\text{\textsubscript{17}}H\text{\textsubscript{16}}N\text{\textsubscript{2}} [M\textsuperscript{+}] 262.1339, found 262.1341.
**1-Methyl-3,5-bis(methylthio)-1,2,4-triazin-1-ium trfluoromethanesulfonate (2o-Me)**

Yield: 661 mg (1.96 mmol, 98%) of a light-yellow solid, of which 78% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.10 (bs, 1H), 4.28 (d, $J = 0.9$, 3H), 2.75 (s, 3H), 2.66 (s, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 178.5, 175.8, 140.0 (CH), 121.9 (q, $^1$J$_{C,F} = 321$, OTf), 52.8 (CH$_3$), 14.4 (SCH$_3$), 14.2 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_6$H$_{10}$N$_3$S$_2$ [M$^+$] 188.0311, found 188.0311.

**1-Ethyl-3,5-bis(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2o-Et)**

Yield: 661 mg (1.88 mmol, 94%) of a yellowish solid, of which 80% is major N1 isomer

$^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 9.13 (bs, 1H), 4.53 (qd, $J = 7.3$, 0.6, 2H), 2.74 (s, 3H), 2.67 (s, 3H), 1.76 (t, $J = 7.3$, 3H).

$^{13}$C NMR (101 MHz, CD$_3$CN): $\delta$ 178.6, 175.9, 139.3 (CH), 121.9 (q, $^1$J$_{C,F} = 321$, OTf), 62.2 (CH$_2$), 14.4 (CH$_3$), 14.2 (CH$_3$), 14.1 (CH$_3$).

HRMS (ESI): m/z calcd. for C$_7$H$_{12}$N$_3$S$_2$ [M$^+$] 202.0467, found 202.0468.

**Cycloadditions with DMAD**

**General procedure C:** Alkylated triazine 2d-2m (0.50 mmol) was dissolved in THF (10 mL) and DMAD (2.0 equiv.) was added. The mixture was cooled to 0 °C and DIPEA (1.5 equiv.) was added dropwise (= 5 min). Then, the cooling bath was removed and the mixture was stirred at room temperature for 5 h. We followed the reaction progress by HPLC and, usually, the oxidation was slower with ethylated derivatives. In such cases, we just opened the flask and stirred the mixture like that for the final 15 – 20 min. Then, the volatiles were evaporated under reduced pressure and the crude products were purified by column chromatography (the solvent mixtures are specified for each derivative separately). The yields are normalized for major N1 alkylated triazines.

**Dimethyl 2-(methylthio)-4-(4-(piperidin-1-yl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3d-H)**

Chromatography: DCM → DCM/AcOEt 50:1 → 25:1

Yield: 135 mg (0.307 mmol, 72%) of an orange-yellow solid
1H NMR (400 MHz, CDCl3): δ 8.06 (s, 1H), 7.66 (d, J = 8.9, 2H), 6.91 (d, J = 8.9, 2H), 3.86 (s, 3H), 3.57 (s, 3H), 3.35 – 3.29 (m, 4H), 2.56 (s, 3H), 1.70 – 1.61 (s, 6H).

13C NMR (101 MHz, CDCl3): δ 165.2, 163.4, 163.3, 161.1, 154.0, 130.3 (2×CH), 124.4, 121.2 (CH), 118.4, 116.5, 114.2 (2×CH), 113.3, 52.6 (OCH3), 52.1 (OCH3), 49.1 (2×CH2), 25.4 (2×CH2), 24.4 (CH3), 14.0 (SCH3).

HRMS (ESI): m/z calcd. for C22H25O4N4S [M+H]+ 441.1591, found 441.1587.

### Dimethyl 7-methyl-2-(methylthio)-4-(4-(piperidin-1-yl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3d-Me)

Chromatography: DCM → DCM/AcOEt 50:1 → 25:1

Yield: 147 mg (0.324 mmol, 76%) of an orange-yellow solid

1H NMR (400 MHz, CDCl3): δ 7.63 (d, J = 8.9, 2H), 6.90 (d, J = 8.9, 2H), 3.86 (s, 3H), 3.54 (s, 3H), 3.33 – 3.27 (m, 4H), 2.76 (s, 3H), 2.59 (s, 3H), 1.70 – 1.59 (s, 6H).

13C NMR (101 MHz, CDCl3): δ 165.8, 164.3, 162.6, 161.0, 153.8, 131.3, 130.2 (2×CH), 124.8, 117.4, 114.6, 114.3 (2×CH), 113.4, 52.4 (OCH3), 52.0 (OCH3), 49.2 (2×CH2), 25.4 (2×CH2), 24.4 (CH3), 14.0 (SCH3), 10.4 (CH3).

HRMS (ESI): m/z calcd. for C23H27O4N4S [M+H]+ 455.1748, found 455.1741.

### Dimethyl 4-(4-methoxyphenyl)-2-(methylthio)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3e-H)

Chromatography: DCM

Yield: 114 mg (0.295 mmol, 71%) of a yellow solid

1H NMR (400 MHz, CDCl3): δ 7.08 (s, 1H), 7.67 (d, J = 8.8, 2H), 6.97 (d, J = 8.8, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.53 (s, 3H), 2.55 (s, 3H).

13C NMR (101 MHz, CDCl3): δ 164.9, 163.6, 163.1, 162.4, 161.3, 130.3 (2×CH), 127.9, 121.3 (CH), 118.2, 116.7, 114.0 (2×CH), 113.5, 55.5 (OCH3), 52.5 (OCH3), 52.2 (OCH3), 14.0 (SCH3).

HRMS (ESI): m/z calcd. for C18H18O5N3S [M+H]+ 388.0961, found 388.0959.

### Dimethyl 4-(4-methoxyphenyl)-7-methyl-2-(methylthio)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3e-Me)

Chromatography: DCM

Yield: 133 mg (0.332 mmol, 77%) of a yellow solid

1H NMR (400 MHz, CDCl3): δ 7.67 (d, J = 8.8, 2H), 6.98 (d, J = 8.8, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.51 (s, 3H), 2.79 (s, 3H), 2.61 (s, 3H).

13C NMR (101 MHz, CDCl3): δ 165.6, 164.3, 162.9, 162.3, 161.1, 131.6, 130.4 (2×CH), 128.3, 117.4, 115.0, 114.0 (2×CH), 113.7, 55.6 (OCH3), 52.5 (OCH3), 52.1 (OCH3), 14.1 (SCH3), 10.5 (CH3).

HRMS (ESI): m/z calcd. for C19H20O5N3S [M+H]+ 402.1118, found 402.1118.
**Dimethyl 4-(4-hydroxyphenyl)-2-(methylthio)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3f-H)**

Chromatography: DCM/AcOEt 25:1 → 10:1

Yield: 112 mg (0.300 mmol, 79%) of an orange solid

$^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.27 (s, 1H), 8.39 (s, 1H), 7.53 (d, $J = 8.6$, 2H), 6.90 (d, $J = 8.6$, 2H), 3.80 (s, 3H), 3.51 (s, 3H), 2.56 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$): δ 164.1, 162.7, 162.6, 160.9, 160.8, 130.3 (2×CH), 125.7, 121.3 (CH), 117.5, 116.0, 115.3 (2×CH), 113.0, 52.3 (OCH$_3$), 52.1 (OCH$_3$), 13.4 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_{114}$H$_{113}$N$_{17}$O$_{9}$S [M+H]$^+$ 374.0805, found 374.0805.

**Dimethyl 4-(4-hydroxyphenyl)-7-methyl-2-(methylthio)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3f-Me)**

Chromatography: 1$^{st}$: DCM/AcOEt 20:1 → 10:1; 2$^{nd}$: DCM/AcOEt/PE 1:1:1

Yield: 98.0 mg (0.253 mmol, 70%) of a yellow solid

$^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.22 (s, 1H), 7.50 (d, $J = 8.7$, 2H), 6.89 (d, $J = 8.7$, 2H), 3.80 (s, 3H), 3.50 (s, 3H), 2.68 (s, 3H), 2.58 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$): δ 164.5, 163.4, 162.0, 160.7, 160.5, 130.6, 130.3 (2×CH), 125.9, 116.4, 115.2 (2×CH), 114.2, 113.1, 52.2 (OCH$_3$), 52.0 (OCH$_3$), 13.3 (SCH$_3$), 10.0 (CH$_3$).

HRMS (ESI): m/z calcd. for C$_{118}$H$_{118}$O$_{17}$N$_{17}$S [M+H]$^+$ 388.0961, found 388.0962.

**Dimethyl 2-(methylthio)-4-phenylpyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3g-H)**

Chromatography: DCM

Yield: 109 mg (0.305 mmol, 70%) of a light-yellow solid

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.13 (s, 1H), 7.69 – 7.66 (m, 2H), 7.55 – 7.46 (m, 3H), 3.87 (s, 3H), 3.41 (s, 3H), 2.58 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 164.6, 163.8, 163.1, 162.1, 135.5, 131.4 (CH), 128.6 (2×CH), 128.4 (2×CH), 121.4 (CH), 118.4, 116.9, 113.7, 52.4 (OCH$_3$), 52.3 (OCH$_3$), 14.1 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_{117}$H$_{116}$O$_{17}$N$_{17}$S [M+H]$^+$ 358.0856, found 358.0856.

**Dimethyl 7-methyl-2-(methylthio)-4-phenylpyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3g-Me)**

Chromatography: DCM

Yield: 133 mg (0.358 mmol, 83%) of a bright yellow solid

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.68 – 7.61 (m, 2H), 7.54 – 7.44 (m, 3H), 3.87 (s, 3H), 3.38 (s, 3H), 2.80 (s, 3H), 2.61 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 165.2, 164.1, 163.0, 161.7, 135.8, 131.7, 131.1 (CH), 128.5 (2×CH), 128.4 (2×CH), 117.4, 115.1, 113.8, 52.3 (OCH$_3$), 52.1 (OCH$_3$), 14.1 (SCH$_3$), 10.4 (CH$_3$).
HRMS (ESI): m/z calcd. for C_{18}H_{16}O_{6}N_{3}S [M+H]^+ 372.1012, found 372.1013.

**Dimethyl 2-(methylthio)-4-(naphthalen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3h-H)**

Chromatography: DCM

Yield: 119 mg (0.292 mmol, 72%) of a light-yellow solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.24 – 8.21 (m, 1H), 8.16 (s, 1H), 7.96 (d, $J$ = 8.4, 1H), 7.93 – 7.87 (m, 2H), 7.81 (dd, $J$ = 8.4, 1.8, 1H), 7.60 – 7.52 (m, 2H), 3.88 (s, 3H), 3.24 (s, 3H), 2.61 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 164.8, 163.8, 163.1, 162.0, 134.7, 132.8, 132.6, 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.0 (2×CH), 127.0 (CH), 125.0 (CH), 121.5 (CH), 118.5, 117.0, 113.8, 52.5 (OCH$_3$), 52.3 (OCH$_3$), 14.1 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_{21}$H$_{18}$O$_4$N$_3$S [M+H]$^+$ 408.1012, found 408.1013.

**Dimethyl 7-methyl-2-(methylthio)-4-(naphthalen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3h-Me)**

Chromatography: 1$^{\text{st}}$: DCM; 2$^{\text{nd}}$: DCM/hexanes 3:1

Yield: 147 mg (0.349 mmol, 84%) of a bright yellow solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.22 – 8.19 (m, 1H), 7.96 (d, $J$ = 8.5, 1H), 7.93 – 7.87 (m, 2H), 7.79 (dd, $J$ = 8.5, 1.8, 1H), 7.60 – 7.52 (m, 2H), 3.88 (s, 3H), 3.19 (s, 3H), 2.83 (s, 3H), 2.65 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 165.4, 164.1, 163.0, 161.6, 134.5, 133.0, 132.5, 131.8, 129.0 (CH), 128.9 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 126.9 (CH), 125.1 (CH), 117.5, 115.2, 113.9, 52.4 (OCH$_3$), 52.1 (OCH$_3$), 14.1 (SCH$_3$), 10.4 (CH$_3$).

HRMS (ESI): m/z calcd. for C$_{22}$H$_{20}$O$_4$N$_3$S [M+H]$^+$ 422.1169, found 422.1166.

**Dimethyl 4-(3-bromophenyl)-2-(methylthio)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3i-H)**

Chromatography: DCM

Yield: 119 mg (0.274 mmol, 62%) of a yellow solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.13 (s, 1H), 7.82 (t, $J$ = 1.8, 1H), 7.69 – 7.64 (m, 1H), 7.64 – 7.59 (m, 1H), 7.37 (t, $J$ = 7.9, 1H), 3.87 (s, 3H), 3.56 (s, 3H), 2.57 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 164.5, 163.7, 162.9, 160.3, 137.2, 134.4 (CH), 131.3 (CH), 130.2 (CH), 127.1 (CH), 122.6, 121.6 (CH), 117.9, 117.2, 113.6, 52.8 (OCH$_3$), 52.3 (OCH$_3$), 14.1 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_{17}$H$_{15}$O$_4$N$_3$S$^{79}$Br$^-$ [M+H]$^+$ 435.9961, found 435.9957. m/z calcd. for C$_{17}$H$_{15}$O$_4$N$_3$S$^{81}$Br$^-$ [M+H]$^+$ 437.9941, found 437.9934.
Dimethyl 4-(3-bromophenyl)-7-methyl-2-(methylthio)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3i-Me)

Chromatography: DCM

Yield: 163 mg (0.363 mmol, 77%) of a yellow solid

$^{1}$H NMR (400 MHz, CDCl$_3$): δ 7.80 (t, $J$ = 1.8, 1H), 7.68 – 7.62 (m, 1H), 7.62 – 7.57 (m, 1H), 7.35 (t, $J$ = 7.9, 1H), 3.87 (s, 3H), 3.53 (s, 3H), 2.79 (s, 3H), 2.61 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 165.1, 164.0, 162.9, 160.0, 137.5, 134.1 (CH), 132.0, 131.3 (CH), 130.1 (CH), 127.1 (CH), 122.5, 117.0, 115.4, 113.7, 52.7 (OCH$_3$), 52.2 (OCH$_3$), 14.0 (SCH$_3$), 10.4 (CH$_3$).

HRMS (ESI): m/z calcd. for C$_{18}$H$_{17}$O$_4$N$_3$SBr [M+H]$^+$ 450.0118, found 450.0116. m/z calcd. for C$_{18}$H$_{17}$O$_4$N$_3$BrS [M+H]$^+$ 452.0098, found 452.0093.

Dimethyl 4-(4-bromophenyl)-2-(methylthio)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3j-H)

Chromatography: DCM

Yield: 120 mg (0.276 mmol, 61%) of a bright yellow solid

$^{1}$H NMR (400 MHz, CDCl$_3$): δ 8.12 (s, 1H), 7.63 (d, $J$ = 8.5, 2H), 7.55 (d, $J$ = 8.5, 2H), 3.87 (s, 3H), 3.49 (s, 3H), 2.57 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 164.5, 163.7, 163.0, 160.8, 134.3, 131.9 (2×CH), 130.0 (2×CH), 126.2, 121.6 (CH), 118.0, 117.1, 113.5, 52.6 (OCH$_3$), 52.3 (OCH$_3$), 14.1 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_{17}$H$_{15}$O$_4$N$_3$SBr [M+H]$^+$ 435.9961, found 435.9958. m/z calcd. for C$_{17}$H$_{15}$O$_4$N$_3$SBr [M+H]$^+$ 437.9941, found 437.9935.

Dimethyl 4-(4-bromophenyl)-7-methyl-2-(methylthio)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3j-Me)

Chromatography: DCM

Yield: 156 mg (0.347 mmol, 78%) of a bright yellow solid

$^{1}$H NMR (400 MHz, CDCl$_3$): δ 7.59 (d, $J$ = 8.5, 2H), 7.51 (d, $J$ = 8.5, 2H), 3.85 (s, 3H), 3.45 (s, 3H), 2.77 (s, 3H), 2.58 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 165.0, 163.9, 162.9, 160.4, 134.5, 131.8, 131.7 (2×CH), 130.0 (2×CH), 125.7, 116.9, 115.2, 113.6, 52.4 (OCH$_3$), 52.1 (OCH$_3$), 14.0 (SCH$_3$), 10.3 (CH$_3$).

HRMS (ESI): m/z calcd. for C$_{18}$H$_{17}$O$_4$N$_3$SBr [M+H]$^+$ 450.0118, found 450.0115. m/z calcd. for C$_{18}$H$_{17}$O$_4$N$_3$SBr [M+H]$^+$ 452.0098, found 452.0092.

Dimethyl 4-(4-fluorophenyl)-2-(methylthio)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3k-H)

Chromatography: DCM

Yield: 117 mg (0.312 mmol, 69%) of a light-yellow solid

$^{1}$H NMR (400 MHz, CDCl$_3$): δ 8.12 (s, 1H), 7.73 – 7.67 (m, 2H), 7.21 – 7.14 (m, 2H), 3.87 (s, 3H), 3.51 (s, 3H), 2.57 (s, 3H).
13C NMR (101 MHz, CDCl3): δ 164.7 (d, 1J,C,F = 253, C-F), 164.6, 163.7, 163.0, 160.8, 131.7 (d, 4J,C,F = 3.3, C), 130.8 (d, 3J,C,F = 8.8, 2×CH), 121.5 (CH), 118.1, 117.0, 115.8 (d, 2J,C,F = 22.0, 2×CH), 113.6, 52.6 (OCH3), 52.3 (OCH3), 14.0 (SCH3).

HRMS (ESI): m/z calcd. for C17H15O4N3FS [M+H]+ 376.0762, found 376.0761.

**Dimethyl 4-(4-fluorophenyl)-7-methyl-2-(methylthio)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3k-Me)**

Chromatography: DCM

Yield: 145 mg (0.373 mmol, 82%) of a bright yellow solid

1H NMR (400 MHz, CDCl3): δ 7.70 – 7.64 (m, 2H), 7.19 – 7.13 (m, 2H), 3.87 (s, 3H), 3.48 (s, 3H), 2.79 (s, 3H), 2.60 (s, 3H).

13C NMR (101 MHz, CDCl3): δ 165.2, 164.5 (d, 1J,C,F = 252, C-F), 164.0, 162.9, 160.5, 131.9 (d, 4J,C,F = 3.4, C), 131.8, 130.7 (d, 3J,C,F = 8.8, 2×CH), 117.2, 115.7 (d, 2J,C,F = 21.9, 2×CH), 115.2, 113.7, 52.4 (OCH3), 52.1 (OCH3), 14.0 (SCH3), 10.4 (CH3).

HRMS (ESI): m/z calcd. for C18H17O4N5S [M+H]+ 390.0918, found 390.0917.

**Dimethyl 2-(methylthio)-4-(4-(trifluoromethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3l-H)**

Chromatography: DCM

Yield: 102 mg (0.240 mmol, 52%) of a light-yellow solid

1H NMR (400 MHz, CDCl3): δ 8.15 (s, 1H), 7.81 – 7.74 (m, 4H), 3.87 (s, 3H), 3.40 (s, 3H), 2.58 (s, 3H).

13C NMR (101 MHz, CDCl3): δ 164.3, 163.8, 162.9, 160.6, 138.8 (q, 5J,C,F = 1.4, C), 133.0 (q, 2J,C,F = 32.8, C), 128.9 (2×CH), 125.6 (q, 3J,C,F = 3.8, 2×CH), 123.7 (q, 1J,C,F = 273, CF3), 121.7 (CH), 118.0, 117.3, 113.6, 52.4 (OCH3), 52.3 (OCH3), 14.1 (SCH3).

HRMS (ESI): m/z calcd. for C18H15O4N3F3S [M+H]+ 426.0730, found 426.0729.

**Dimethyl 7-methyl-2-(methylthio)-4-(4-(trifluoromethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3l-Me)**

Chromatography: DCM

Yield: 151 mg (0.344 mmol, 73%) of a bright yellow solid

1H NMR (400 MHz, CDCl3): δ 7.79 – 7.73 (m, 4H), 3.87 (s, 3H), 3.37 (s, 3H), 2.80 (s, 3H), 2.62 (s, 3H).

13C NMR (101 MHz, CDCl3): δ 164.9, 163.9, 163.0, 160.2, 139.1 (q, 5J,C,F = 1.4, C), 132.8 (q, 2J,C,F = 32.7, C), 132.1, 128.9 (2×CH), 125.5 (q, 3J,C,F = 3.8, 2×CH), 123.8 (q, 1J,C,F = 273, CF3), 117.1, 115.5, 113.7, 52.3 (OCH3), 52.2 (OCH3), 14.0 (SCH3), 10.4 (CH3).

HRMS (ESI): m/z calcd. for C19H17O4N3F3S [M+H]+ 440.0886, found 440.0884.
Dimethyl 2-(methylthio)-4-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3m-H)

Chromatography: DCM

Yield: 63 mg (0.157 mmol, 37%) of a bright yellow solid

$^1$H NMR (400 MHz, CDCl₃): δ 8.34 (d, $J = 8.8$, 2H), 8.17 (s, 1H), 7.85 (d, $J = 8.8$, 2H), 3.88 (s, 3H), 3.49 (s, 3H), 2.59 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl₃): δ 164.3, 163.8, 162.8, 159.7, 149.4, 141.2, 129.7 (2×CH), 123.7 (2×CH), 121.9 (CH), 117.8, 117.6, 113.5, 52.7 (OCH₃), 52.4 (OCH₃), 14.1 (SCH₃).

HRMS (ESI): m/z calcd. for C₁₇H₁₆O₇N₄S [M+H]$^+$ 403.0707, found 403.0704.

Dimethyl 7-methyl-2-(methylthio)-4-(4-nitrophenyl)pyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (3m-Me)

Chromatography: DCM

Yield: 127 mg (0.305 mmol, 68%) of a yellow-orange solid

$^1$H NMR (400 MHz, CDCl₃): δ 8.32 (d, $J = 8.8$, 2H), 7.82 (d, $J = 8.8$, 2H), 3.87 (s, 3H), 3.46 (s, 3H), 2.80 (s, 3H), 2.62 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl₃): δ 164.8, 163.8, 163.0, 159.3, 149.3, 141.5, 132.3, 129.7 (2×CH), 123.6 (2×CH), 116.8, 115.8, 113.5, 52.6 (OCH₃), 52.3 (OCH₃), 14.1 (SCH₃), 10.4 (CH₃).

HRMS (ESI): m/z calcd. for C₁₈H₁₇O₆N₄S [M+H]$^+$ 417.0863, found 417.0863.

Cycloadditions with other dienophiles

Methyl 2-(methylthio)-4-phenylpyrrolo[2,1-f][1,2,4]triazine-5-carboxylate (4g-H)

General procedure C applied. Alkylated triazine 2g-Me (0.316 mmol) was used.

Chromatography: DCM

Optimization, yields are not normalized for 100% N1 isomer. Yellow solid

| Entry | Methyl propiolate | DIPEA | solvent | Isolated yield |
|-------|------------------|-------|---------|---------------|
| 1     | 2.0 equiv.       |       | THF     | 19%           |
| 2     | 2.0 equiv.       |       | anh. THF| 20%           |
| 3     | 5.0 equiv.       | 1.5 equiv. | THF     | 25%           |
| 4     | 15 equiv.        |       | THF     | 37%           |
| 5     | 30 equiv.        |       | THF     | 38%           |
| 6     | 2.5 mL          |       | 2.5 mL THF | 32%         |

$^1$H NMR (400 MHz, CDCl₃): δ 7.74 (d, $J = 2.8$, 1H), 7.69 – 7.65 (m, 2H), 7.55 – 7.45 (m, 3H), 7.30 (d, $J = 2.8$, 1H), 3.32 (s, 3H), 2.62 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl₃): δ 164.1, 162.3, 161.1, 137.6, 130.7, 128.7 (2×CH), 128.2 (2×CH), 119.5, 119.2, 116.7, 111.2, 51.5 (OCH₃), 14.1 (SCH₃).

HRMS (ESI): m/z calcd. for C₁₅H₁₄O₂N₃S [M+H]$^+$ 300.0801, found 300.0800.
**General procedure D:** Alkylated triazine 2g-Me (0.250 mmol) was dissolved in THF (3.5 mL) and dienophile (3.0 equiv.) was added. The mixture was cooled to 0 °C and DIPEA (1.5 equiv.) was added dropwise (= 5 min). Then, the cooling bath was removed, and the mixture was stirred at room temperature ON (18 h). We followed the reaction progress by HPLC. Then, the volatiles were evaporated under reduced pressure and the crude products were purified by column chromatography (the solvent mixtures are specified for each derivative separately). The yields are normalized for major N1 alkylated triazines.

(4aR,5R)-2-(Methylthio)-4-phenyl-4a,5,6,7-tetrahydropyrrrolo[2,1-f][1,2,4]triazine-5-carbonitrile (5g-H minor)

Chromatography: AcOEt/DCM 5:95 → 10:90

Yield: 10 mg (0.0370 mmol, 17%) of a brown solid

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.22 – 8.17 (m, 2H), 7.63 – 7.58 (m, 1H), 7.56 – 7.50 (m, 2H), 4.38 (d, $J = 9.3$, 1H), 4.04 (ddd, $J = 12.3$, 7.2, 2.4, 1H), 3.38 (ddd, $J = 12.2$, 10.0, 8.0, 1H), 2.29 (ddd, $J = 11.0$, 9.3, 5.8, 1H), 2.38 (s, 3H), 2.26 – 2.15 (m, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 165.6, 151.6, 133.8, 133.7, 129.2 (2×CH), 128.2 (2×CH), 121.0 (CN), 57.7, 57.2, 30.3, 13.6 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_{14}$H$_{15}$N$_4$S [M+H]$^+$ 271.1012, found 271.1012.

(4aR,5S)-2-(Methylthio)-4-phenyl-4a,5,6,7-tetrahydropyrrrolo[2,1-f][1,2,4]triazine-5-carbonitrile (5g-H major)

Chromatography: MeOH/AcOEt/DCM 1:10:90

Yield: 22 mg (0.081 mmol, 37%) of a brown solid, calculated from HPLC-MS. This isomer contained dealkylated triazine 1g, which eluted with the product during the column chromatography.

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.06 – 8.00 (m, 2H), 7.64 – 7.59 (m, 1H), 7.56 – 7.50 (m, 2H), 4.36 (d, $J = 8.3$, 1H), 4.13 (ddd, $J = 12.6$, 7.4, 1.6, 1H), 3.26 – 3.15 (m, 2H), 2.47 – 2.38 (m, 1H), 2.44 (s, 3H), 2.10 (dddd, $J = 12.6$, 11.0, 8.0, 6.2, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 164.4, 153.1, 134.4, 133.4, 129.2 (2×CH), 127.6 (2×CH), 119.5 (CN), 57.9, 56.2, 31.4, 30.7, 13.6 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_{14}$H$_{15}$N$_4$S [M+H]$^+$ 271.1012, found 271.1012.

(4aR,4bR,7aS)-6-Ethyl-2-(methylthio)-4-phenyl-4a,4b,7a,8-tetrahydro-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-f][1,2,4]triazine-5,7(6H)-dione (6g-H minor)

General procedure D applied. Alkylated triazine 2g-Me (0.131 mmol) was used.

Chromatography: DCM → AcOEt/DCM 1:1

Yield: 9 mg (0.026 mmol, 10%) of a yellow solid

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.19 – 8.13 (m, 2H), 7.62 – 7.55 (m, 1H), 7.53 – 7.47 (m, 2H), 4.34 (dd, $J = 13.0$, 8.0, 1H), 4.16 (d, $J = 8.0$, 1H), 3.58 (q, $J = 7.5$, 2H), 3.49 – 3.35 (m, 2H), 3.23 (dd, $J = 12.2$, 8.5, 1H), 2.39 (s, 3H), 1.19 (t, $J = 7.5$, 3H).
General procedure D applied. Alkylated triazine 2g-Me (0.131 mmol) was used.

Chromatography: DCM → AcOEt/DCM 1:1

Yield: 71 mg (0.208 mmol, 78%) of an orange solid

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.08 – 8.01 (m, 2H), 7.61 – 7.55 (m, 1H), 7.54 – 7.47 (m, 2H), 4.47 (d, J = 8.0, 1H), 4.43 (d, J = 13.0, 1H), 3.52 – 3.34 (m, 5H), 2.24 (s, 3H), 1.09 (t, J = 7.5, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 177.6, 175.0, 166.2, 152.5, 135.0, 133.2, 129.1 (2×CH), 127.6 (2×CH), 60.6, 56.7, 48.9, 45.7, 34.1, 13.4 (SCH$_3$), 12.7 (CH$_3$).

HRMS (ESI): m/z calcd. for C$_{17}$H$_{15}$O$_2$N$_4$S [M+H]$^+$ 343.1223, found 343.1220.

(4aR,4bS,7aR)-6-Ethyl-2-(methylthio)-4-phenyl-4a,4b,7a,8-tetrahydro-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-f][1,2,4]triazine-5,7(6H)-dione (6g-H major)

General procedure D applied. Alkylated triazine 2g-Me (0.250 mmol) was used.

Chromatography: AcOEt/DCM 0:100 → 16:84

Yield: 3 mg (0.009 mmol, 4%) of a yellow oil calculated from HPLC-MS. This isomer contained dealkylated triazine 1g, which eluted with the product during the column chromatography.

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.19 – 8.13 (m, 2H), 7.62 – 7.55 (m, 1H), 7.53 – 7.48 (m, 2H), 4.39 – 4.26 (m, 3H), 4.22 (d, J = 7.8, 1H), 3.53 – 3.41 (m, 2H), 3.29 (dd, J = 12.3, 8.2, 1H), 2.40 (s, 3H), 2.24 (t, J = 2.5, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 174.9, 174.5, 166.2, 153.0, 133.8, 133.5, 128.9 (2×CH), 128.8 (2×CH), 72.0, 67.5, 59.6, 55.6, 49.6, 46.6, 27.9, 13.6 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_{18}$H$_{17}$O$_2$N$_4$S [M+H]$^+$ 353.1067, found 353.1067.

(4aR,4bR,7aS)-2-(Methylthio)-4-phenyl-6-(prop-2-yn-1-yl)-4a,4b,7a,8-tetrahydro-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-f][1,2,4]triazine-5,7(6H)-dione (7g-H minor)

General procedure D applied. Alkylated triazine 2g-Me (0.250 mmol) was used.

Chromatography: AcOEt/DCM 0:100 → 16:84

Yield: 42 mg (0.119 mmol, 55%) of an orange solid

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.07 – 8.02 (m, 2H), 7.62 – 7.56 (m, 1H), 7.55 – 7.48 (m, 2H), 4.49 (d, J = 8.1, 1H), 4.49 – 4.42 (m, 1H), 4.21 – 4.09 (m, 2H), 3.59 – 3.50 (m, 1H), 3.50 – 3.42 (m, 2H), 2.25 (s, 3H), 2.13 (t, J = 2.5, 1H).
$^{13}$C NMR (101 MHz, CDCl$_3$): δ 176.4, 173.7, 166.3, 153.5, 134.9, 133.3, 129.2 (2×CH), 127.7 (2×CH), 76.3, 71.8, 60.6, 56.9, 48.7, 46.1, 28.0, 13.5 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_{18}$H$_{17}$O$_2$N$_4$S [M+H]$^+$ 353.1067, found 353.1067.

(4aR,4bR,7aS)-4-(4-Bromophenyl)-2-(methylthio)-6-(prop-2-yn-1-yl)-4a,4b,7a,8-tetrahydro-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-f][1,2,4]triazine-5,7(6H)-dione (7j-H minor)

General procedure D applied. Alkylated triazine 2j-Me (0.168 mmol) and THF (2.5 mL) were used.

Chromatography: AcOEt/DCM 2:98 → 12:88

Yield: 6 mg (0.014 mmol, 9%) of an orange solid

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.36 (t, $J = 1.8$, 1H), 8.06 (ddd, $J = 8.0$, 1.8, 1.0, 1H), 7.71 (ddd, $J = 8.0$, 2.0, 1.0, 1H), 7.39 (t, $J = 8.0$, 1H), 4.42 – 4.33 (m, 1H), 4.29 (d, $J = 2.5$, 2H), 4.14 (d, $J = 7.8$, 1H), 3.53 – 3.40 (m, 2H), 3.33 – 3.23 (m, 1H), 2.39 (s, 3H), 2.25 (t, $J = 2.5$, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 174.7, 174.4, 164.8, 152.6, 136.2, 135.9, 131.6, 130.3, 127.4, 123.3, 76.4, 72.1, 59.6, 55.5, 49.6, 46.5, 28.2, 13.6 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_{18}$H$_{16}$O$_2$N$_4$79BrS [M+H]$^+$ 431.0172, found 431.0171. m/z calcd. for C$_{18}$H$_{16}$O$_2$N$_4$81BrS [M+H]$^+$ 433.0152, found 433.0149.

(4aR,4bS,7aR)-4-(4-Bromophenyl)-2-(methylthio)-6-(prop-2-yn-1-yl)-4a,4b,7a,8-tetrahydro-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-f][1,2,4]triazine-5,7(6H)-dione (7j-H major)

General procedure D applied. Alkylated triazine 2j-Me (0.168 mmol) and THF (2.5 mL) were used.

Chromatography: AcOEt/DCM 2:98 → 12:88

Yield: 56 mg (0.130 mmol, 86%) of an orange solid

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.17 (t, $J = 1.8$, 1H), 7.96 (ddd, $J = 7.8$, 1.8, 1.0, 1H), 7.71 (ddd, $J = 7.8$, 1.8, 1.0, 1H), 7.39 (t, $J = 7.8$, 1H), 4.51 – 4.45 (m, 1H), 4.41 (d, $J = 7.8$, 1H), 4.20 – 4.09 (m, 2H), 3.57 – 3.51 (m, 1H), 3.51 – 3.44 (m, 2H), 2.25 (s, 3H), 2.14 (t, $J = 2.5$, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 176.2, 173.7, 165.0, 153.0, 136.9, 136.1, 130.6, 130.5, 126.2, 123.5, 76.2, 71.9, 60.6, 56.7, 48.7, 46.0, 28.0, 13.5 (SCH$_3$).

HRMS (ESI): m/z calcd. for C$_{18}$H$_{16}$O$_2$N$_4$79BrS [M+H]$^+$ 431.0172, found 431.0171. m/z calcd. for C$_{18}$H$_{16}$O$_2$N$_4$81BrS [M+H]$^+$ 433.0152, found 433.0149.
Modification of 3i-Me using cross-coupling reactions

**Dimethyl 4-(3-bromophenyl)-7-methyl-2-phenylpyrrolo[2,1-f][1,2,4]triazine-5,6-dicarboxylate (8i-Me intermediate)**

Cycloadduct 3i-Me (82.0 mg, 0.182 mmol), phenylboronic acid (2.5 equiv., 55.5 mg, 0.455 mmol), copper(I) thiophene-2-carboxylate (2.2 equiv., 76.4 mg, 0.401 mmol) and Pd(PPh₃)₄ (10 mol%, 21.0 mg, 0.018 mmol) were placed in an argon flushed flask and anhydrous 1,4-dioxane (2.0 mL) was added. The mixture was stirred under argon for 34 h at 95 °C. After cooling to RT, the mixture was diluted with CHCl₃ (100 mL) and washed subsequently with 2 M aq. NaOH (60 mL) and sat. NH₄Cl (60 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was purified by column chromatography (AcOEt/DCM 0:100 → DCM) yielding 47.0 mg (0.098 mmol, 54%) of a yellow solid.

1H NMR (400 MHz, CDCl₃): δ 8.49 – 8.43 (m, 2H), 7.94 (t, J = 1.7, 1H), 7.72 (dddd, J = 10.8, 8.0, 1.7, 1.0, 2H), 7.54 – 7.49 (m, 3H), 7.42 (t, J = 7.8, 1H), 3.91 (s, 3H), 3.59 (s, 3H), 2.93 (s, 3H).

13C NMR (101 MHz, CDCl₃): δ 165.3, 164.2, 161.0, 155.1, 138.5, 134.8, 134.1 (CH), 132.3, 131.6 (CH), 131.2 (CH), 130.2 (CH), 128.8 (2×CH), 128.0 (2×CH), 127.3 (CH), 122.6, 117.8, 116.7, 112.7, 52.8 (OCH₃), 52.3 (OCH₃), 10.6 (CH₃).

HRMS (ESI): m/z calcd. for C₂₃H₁₉O₄N₅⁷⁹Br [M+H]+ 480.0554, found 480.0551. m/z calcd. for C₂₃H₁₉O₄N₅⁸⁵Br [M+H]+ 482.0534, found 482.0530.

**8i-Me intermediate**

8i-Me intermediate (47.0 mg, 0.098 mmol), phenylboronic acid (2.0 equiv., 23.9 mg, 0.196 mmol), K₂CO₃ (2.0 equiv., 27.0 mg, 0.196 mmol) and PdCl₂(dppf)-DCM (10 mol%, 8.00 mg, 0.010 mmol) were placed in an argon flushed flask and suspended in 1,4-dioxane/H₂O mixture (1.2 + 0.5 mL) and stirred at 100 °C for 4 h. After cooling, the mixture was diluted with H₂O/brine (30 + 30 mL) and extracted with DCM (3×20 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was purified by column chromatography (AcOEt/DCM 0:100 → 2:98) yielding 42.0 mg (0.088 mmol, 90%) of a yellow solid.

1H NMR (400 MHz, CDCl₃): δ 8.52 – 8.46 (m, 2H), 7.97 (td, J = 1.8, 0.6, 1H), 7.81 (ddddd, J = 8.2, 7.5, 1.8, 1.2, 2H), 7.73 – 7.68 (m, 2H), 7.64 (td, J = 7.5, 0.6, 1H), 7.53 – 7.45 (m, 5H), 7.41 – 7.36 (m, 1H), 3.91 (s, 3H), 3.31 (s, 3H), 2.95 (s, 3H).

13C NMR (101 MHz, CDCl₃): δ 165.5, 164.3, 162.6, 155.2, 141.5, 140.2, 137.3, 135.0, 132.2, 131.1, 129.7, 129.4, 129.1 (2×CH), 128.7 (2×CH), 128.0 (2×CH), 127.9, 127.5, 127.3 (2×CH), 127.2, 118.3, 116.4, 112.8, 52.3 (OCH₃), 52.2 (OCH₃), 10.6 (CH₃).

HRMS (ESI): m/z calcd. for C₂₈H₂₄O₃N₅ [M+H]+ 478.1761, found 478.1754.
Calculations

Methods

The studied structures were subjected to geometry optimization at the DFT level using the B3LYP functional\textsuperscript{9, 10} with the standard 6-31+G(2d,p) basis set and the polarizable continuum model SMD used for implicit toluene solvation.\textsuperscript{11} Empirical dispersion correction GD3BJ was used in all calculations.\textsuperscript{12} The vibrational frequencies and free energies were calculated for all of the optimized structures, and the stationary-point character was thus confirmed (minimum – no negative frequency or transition state – one negative frequency). Zero-point energy, enthalpy and free energy corrections were also obtained at this level of theory, using a standard state of $p = 1$ atm and $T = 298$ K. The Gaussian16 program package was used throughout this study.\textsuperscript{13} The visualization of molecular structures and electrostatic potentials was done with GaussView 6.0.16.

Electrostatic potential

The electrostatic potential plots (Figure S1) of 3-methylthiotriazine and 3-phenyltriazine show that the most electronegative site in both triazines is nitrogen $N_1$ followed by $N_2$. However, the access to nitrogen $N_2$ is partially hindered by the presence of the substituent at position 3.

Figure S1. The electrostatic potential plots of two conformers of 3-methylthiotriazine (left and middle) and of 3-phenyltriazine (right).
Stability of 5-(4-Fluorophenyl)-1-methyl-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2k-Me)

Figure S2. $^1$H NMR spectrum (400 MHz, CD$_3$CN) of 5-(4-Fluorophenyl)-1-methyl-3-(methylthio)-1,2,4-triazin-1-ium trifluoromethanesulfonate (2k-Me) and the respective N2-alkylated regioisomer measured on the day of its preparation and three weeks later. The compound was stored in the NMR tube at room temperature (ca. 3% of the original compound decomposed).
Energies of the transition state for the reaction of 2g-Me with methyl propiolate

We found two different transition-state structures for this reaction (depicted in **Figure S3**). TS1 leading to the experimentally observed regioisomer 4g-H has lower calculated free energy by 5 kcal/mol. The DFT calculations thus rationalize the observation of a single product in the reaction.

![Diagram of reaction](image)

**Figure S3.** The transition-state structures for the reaction of 2g-Me with methyl propiolate. The free energy of the structure on the left-hand side is 5.0 kcal/mol lower.

Energies of the transition state for the reaction of 2g-Me with N-ethylmaleimide

The reaction of 2g-Me with N-ethylmaleimide provided two products, which differ in the configuration of the newly formed pyrrolidine ring. The structure of the two products was elucidated by a combination of 1D and 2D NMR experiments and by a comparison of experimental and calculated J-coupling constants (**Table S2**). We found transition-state structures leading to the two products (**Figure S4**). The TS structure leading to the major product has lower calculated energy by 0.9 kcal/mol.

![Diagram of reaction](image)
Table S2. Experimental and calculated $J$-coupling constants (Hz) in the major and minor products 6g-H.

| Coupling | major product | minor product |
|----------|---------------|---------------|
|          | Exp. | Calc. | Exp. | Calc. |
| 6–7      | 8.1  | 7.2   | 8.0  | 8.0   |
| 7–8      | 9.4  | 8.8   | 8.0  | 7.3   |
| 8–9a     | 8.5  | 6.8   | 0.9  | 0.5   |
| 8–9b     | 8.6  | 8.5   | 8.1  | 7.9   |

Figure S4. The transition-state structures for the reaction of 2g-Me with N-methylmaleimide. The free energy of the structure on the left-hand side is 0.9 kcal/mol lower. The N-ethyl group was substituted with N-methyl to simplify the calculations.
Tables of Cartesian coordinates

| Z   | x   | y   | z   | Z   | x   | y   | z   |
|-----|-----|-----|-----|-----|-----|-----|-----|
| 7   | 0.87947 | -1.38855 | -0.07181 | 7   | -1.52221 | 1.36000 | -0.07129 |
| 6   | -0.03076 | -0.62449 | -0.69410 | 6   | -1.45325 | 0.09426 | 0.30907 |
| 6   | 2.13992 | -0.92254 | -0.08332 | 6   | -0.40234 | 2.10414 | 0.12731 |
| 7   | 2.59814 | 0.19154 | -0.61534 | 7   | 0.72426 | 1.74726 | 0.68416 |
| 7   | 1.65829 | 0.95692 | -1.26048 | 7   | 0.77376 | 0.44349 | 1.13379 |
| 6   | 0.34491 | 0.56803 | -1.30977 | 6   | -0.24822 | -0.45529 | 0.82986 |
| 6   | 2.00919 | 2.21589 | -1.57567 | 6   | 1.95459 | -0.02788 | 1.50827 |
| 16  | 3.28670 | -1.98781 | 0.74190 | 16  | -0.57584 | 3.76306 | -0.45995 |
| 6   | 4.85996 | -1.08255 | 0.57220 | 6   | 1.05509 | 4.48192 | -0.08099 |
| 1   | -0.31211 | 1.20825 | -1.87373 | 1   | -0.26453 | 1.33846 | 1.45182 |
| 1   | 1.39922 | 2.71398 | -2.31768 | 1   | 1.97788 | -0.97563 | 2.02559 |
| 1   | 3.06663 | 2.43685 | -1.51480 | 1   | 2.77051 | 0.67697 | 1.58774 |
| 1   | 5.60880 | -1.70252 | 1.07254 | 1   | 1.01192 | 5.51333 | -0.44112 |
| 1   | 5.12408 | -0.96134 | -0.47993 | 1   | 1.24026 | 4.47271 | 0.99479 |
| 1   | 4.79842 | -0.10950 | 1.06302 | 1   | 1.84371 | 3.93900 | -0.60563 |
| 6   | 0.05678 | 2.74870 | 0.47280 | 6   | 0.79986 | -1.47262 | -0.75039 |
| 6   | 1.11422 | 3.24955 | 0.06966 | 6   | 2.01449 | -1.31538 | -0.53605 |
| 6   | -1.20995 | 2.22459 | 0.85754 | 6   | 3.43966 | -1.29461 | -0.65957 |
| 6   | -2.27657 | 2.58374 | 0.37827 | 8   | 4.06638 | -0.52610 | -1.36948 |
| 8   | -1.10869 | 1.30225 | 1.83997 | 8   | 4.02377 | -2.23052 | 0.12185 |
| 6   | -2.35382 | 0.73624 | 2.29773 | 6   | 5.46485 | -2.26948 | 0.08350 |
| 1   | -2.07200 | -0.04978 | 2.99878 | 1   | 5.75057 | -3.06848 | 0.76868 |
| 1   | -2.95405 | 1.49796 | 2.80429 | 1   | 5.81879 | -2.49243 | -0.92676 |
| 1   | -2.92034 | 0.31615 | 1.46463 | 1   | 5.88466 | -1.31619 | 0.41645 |
| 6   | -1.44345 | -1.06507 | -0.65587 | 6   | -2.63916 | -0.76486 | 0.11294 |
| 6   | -1.79848 | -2.16018 | 0.15013 | 6   | -3.87849 | -0.17868 | -0.19953 |
| 6   | -2.45256 | -0.39937 | -1.37153 | 6   | -2.56112 | -2.16437 | 0.22233 |
| 6   | -3.12419 | -2.57327 | 0.24143 | 6   | -5.00762 | -0.96928 | -0.38761 |
| 1   | -1.02794 | -2.67388 | 0.71169 | 1   | -3.94576 | 0.89929 | -0.28638 |
| 6   | -3.77838 | -0.81688 | -1.28080 | 6   | -3.69284 | -2.95362 | 0.02591 |
| 1   | -2.22042 | 0.45014 | -2.00182 | 1   | -1.61889 | -2.65095 | 0.44701 |
| 6   | -4.12024 | -1.90265 | -0.47281 | 6   | -4.91923 | -2.35989 | -0.27692 |
| 1   | -3.38126 | -3.41735 | 0.87368 | 1   | -5.95856 | -0.50080 | -0.62103 |
| 1   | -4.54492 | -0.28841 | -1.83837 | 1   | -3.61412 | -4.03302 | 0.10747 |
| 1   | -5.15482 | -2.22326 | -0.39958 | 1   | -5.80048 | -2.97581 | -0.42708 |
| 1   | 1.85535 | 4.02444 | 0.14869 | 1   | 0.00785 | -1.88691 | -1.34678 |

\[
E = -1293.509526 \\
G = -1293.285843
\]

\[
E = -1293.500678 \\
G = -1293.277857
\]
Table S4. Cartesian coordinates (Å) of the major and minor products 6g-H and their calculated electronic and free energies (hartree). The N-ethyl group was substituted with N-methyl to simplify the calculations.

| Z  | x      | y      | z      | Z  | x      | y      | z      |
|----|--------|--------|--------|----|--------|--------|--------|
| 7  | 0.71193| 1.46693| -0.29624| 7  | -1.89472| 1.08096| -0.02422|
| 6  | 1.27369| 0.32216| -0.50003| 6  | -1.31209| -0.03489| 0.26961|
| 6  | 0.45440| -0.82843| -1.04844| 6  | 0.15633| -0.02215| 0.64413|
| 7  | -0.62576| -0.29720| -1.89331| 7  | 0.46077| 1.23690| 1.34723|
| 6  | -0.64520| 1.56993| -0.59070| 6  | -1.14150| 2.24579| 0.07946|
| 6  | 2.70147| 0.13849| -0.19042| 6  | -2.08381| -1.28970| 0.22356|
| 6  | 3.49457| 1.24840| 0.15592| 6  | -3.45210| -1.25282| -0.11249|
| 6  | 4.84046| 1.08655| 0.46125| 6  | -4.20266| -2.42054| -0.15540|
| 6  | 5.41964| -0.18689| 0.43734| 6  | -3.60448| -3.65268| 0.13223|
| 6  | 4.64190| -1.29597| 0.10397| 6  | -2.25049| -3.70388| 0.46109|
| 6  | 3.29375| -1.13543| -0.21219| 6  | -1.49501| -2.53310| 0.50768|
| 6  | -0.24908| -1.79744| -0.02422| 6  | 1.18714| -0.06438| -0.54790|
| 6  | -1.55622| -2.18926| -0.74620| 6  | 2.36314| 0.79238| -0.03351|
| 6  | -1.51384| -1.44373| -2.10942| 6  | 1.92544| 1.28153| 1.38246|
| 16 | -1.38044| 2.98878| 0.17187| 16 | -1.93472| 3.61368| -0.72013|
| 6  | -3.13240| 2.75750| -0.26752| 6  | -0.72153| 4.94375| -0.44653|
| 6  | -0.70362| -1.13989| 1.26748| 6  | 1.79061| -1.43143| -0.80395|
| 7  | -2.08986| -1.10738| 1.28852| 7  | 3.12618| -1.40143| -0.42667|
| 6  | -2.66521| -1.67552| 0.16146| 6  | 3.54931| -0.14652| -0.00221|
| 6  | -2.84167| -0.47904| 2.36115| 6  | 3.98938| -2.56769| -0.51306|
| 8  | 0.00081| -0.70645| 2.15597| 1  | -3.91460| -0.29895| -0.33671|
| 8  | -3.85946| -1.74422| -0.04421| 1  | -5.25593| -2.37395| -0.41357|
| 1  | 1.07502| -1.45149| -1.69424| 1  | -1.77654| -4.65531| 0.68010|
| 1  | 3.04231| 2.23297| 0.18016| 1  | -0.44433| -2.60669| 0.75283|
| 1  | 5.44125| 1.95259| 0.72048| 1  | 2.26596| 2.28828| 1.61690|
| 1  | 5.08248| -2.28768| 0.08919| 1  | 0.24176| 4.68078| -0.88936|
| 1  | 2.70880| -2.01307| -0.46266| 1  | -0.60229| 5.14045| 0.62082|
| 1  | 0.40732| -2.63202| 0.22215| 1  | -1.12882| 5.82800| -0.94400|
| 1  | -1.68790| -3.26401| -0.88045| 1  | 4.96621| -2.29996| -0.10868|
| 1  | -2.49078| -1.10651| -2.45429| 1  | 3.56126| -3.39066| 0.06402|
| 1  | -1.06314| -2.08961| -2.86715| 1  | 4.09524| -2.88014| -1.55551|
| 1  | -3.67308| 3.57707| 0.21319| 1  | -4.19224| -4.56478| 0.09803|
| 1  | -3.49633| 1.80005| 0.11143| 7  | -0.03259| 2.38805| 0.71591|
| 1  | -3.26918| 2.80690| -1.34949| 8  | 4.68196| 0.11631| 0.34783|
| 1  | -3.90072| -0.52417| 2.10674| 8  | 1.23745| -2.41656| -1.24959|
| 1  | -2.66571| -1.00597| 3.30267| 1  | 0.38509| -0.82499| 1.34530|
| 1  | -2.52761| 0.56182| 2.47132| 1  | 0.73668| 0.31459| -1.46625|
| 1  | 6.47075| -0.31148| 0.67859| 1  | 2.58488| 1.64114| -0.68223|
| 7  | -1.33532| 0.77063| -1.32587| 1  | 2.27170| 0.59209| 2.15777|

\[ E = -1387.131407 \]  \[ E = -1387.127325 \]

\[ G = -1386.877016 \]  \[ G = -1386.871935 \]
Table S5. Cartesian coordinates (Å) of the two transition-state structures for the reaction of 2g-Me with maleimide and their calculated electronic and free energies (hartree). The N-ethyl group was substituted with N-methyl to simplify the calculations.

| Z  | x     | y     | z     | Z  | x     | y     | z     |
|----|-------|-------|-------|----|-------|-------|-------|
| 7  | 0.59817 | 1.53631 | -0.08343 | 7  | 2.30828 | -0.48142 | -0.07430 |
| 6  | 1.21175 | 0.46772 | -0.58637 | 6  | 1.39445 | 0.40799 | 0.31399 |
| 6  | 0.50800 | -0.45044 | -1.38616 | 6  | 0.14999 | -0.01161 | 0.81280 |
| 7  | -0.80062 | -1.88666 | -1.68653 | 7  | -0.08696 | -1.35307 | 0.92952 |
| 6  | -0.70794 | 1.68066 | -0.40630 | 6  | 1.94953 | -1.78048 | 0.02734 |
| 6  | 2.63977 | 0.26271 | -0.26794 | 6  | 1.72796 | 1.84345 | 0.21101 |
| 6  | 3.38145 | 1.13164 | 0.29683 | 6  | 3.07449 | 2.24289 | 0.23674 |
| 6  | 4.72888 | 1.14299 | 0.60095 | 6  | 3.40938 | 3.59124 | 0.14906 |
| 6  | 5.35561 | -0.08096 | 0.35383 | 6  | 2.40699 | 4.55643 | 0.01910 |
| 6  | 4.62532 | -1.13416 | -0.20073 | 6  | 1.06723 | 4.16513 | -0.02148 |
| 6  | 3.27833 | -0.96483 | -0.51064 | 6  | 0.72546 | 2.81788 | 0.07815 |
| 6  | -0.37329 | -2.51115 | 0.03050 | 6  | -1.68702 | -0.12597 | -1.16073 |
| 6  | -1.59246 | -2.56797 | -0.64055 | 6  | -2.22499 | -1.32075 | -0.68676 |
| 6  | -1.56690 | -1.16102 | 2.23313 | 6  | -1.34389 | -1.79665 | 1.16744 |
| 16 | -1.45108 | 3.10958 | 0.31894 | 16 | 3.20555 | -2.89334 | -0.52865 |
| 6  | -3.18354 | 2.95706 | -0.22526 | 6  | 2.43273 | -4.52161 | -0.24782 |
| 6  | -0.53903 | -1.69153 | 1.22933 | 6  | -2.57415 | 0.96708 | -0.77370 |
| 7  | -1.88831 | -1.26624 | 1.24398 | 7  | -3.66372 | 0.38529 | -0.08298 |
| 6  | -2.59855 | -1.83475 | 0.20477 | 6  | -3.57635 | -0.99415 | -0.11353 |
| 6  | -2.43952 | -0.37015 | 2.23777 | 6  | -4.80715 | 1.12163 | 0.41597 |
| 8  | 0.25593 | -1.40277 | 2.11120 | 1  | 3.85000 | 1.49207 | 0.33612 |
| 8  | -3.80049 | -1.73042 | 0.02444 | 1  | 4.45254 | 3.88949 | 0.18099 |
| 1  | 0.97440 | -1.24489 | -1.94364 | 1  | 0.28440 | 4.90747 | -0.14080 |
| 1  | 2.89371 | 2.26165 | 0.49009 | 1  | -0.31810 | 2.53284 | 0.00659 |
| 1  | 5.29037 | 1.96529 | 1.03291 | 1  | -1.44939 | -2.86892 | 1.26716 |
| 1  | 5.10263 | -2.09115 | -0.38583 | 1  | 1.52542 | -4.62684 | -0.84549 |
| 1  | 2.72632 | -1.80170 | -0.92228 | 1  | 2.20893 | -4.66363 | 0.81109 |
| 1  | 0.51504 | -3.09670 | -0.15138 | 1  | 3.17615 | -5.25505 | -0.57155 |
| 1  | -1.92390 | -3.37166 | -1.28570 | 1  | -4.50857 | 2.16005 | 0.56811 |
| 1  | -2.59581 | -0.88959 | -2.43004 | 1  | -5.63969 | 1.09002 | -0.29566 |
| 1  | -1.05853 | -1.82181 | -2.92320 | 1  | -5.13585 | 0.69113 | 1.36457 |
| 1  | -3.70530 | 3.81041 | 0.21607 | 1  | 2.66963 | 5.60720 | -0.05540 |
| 1  | -3.61782 | 2.02557 | 0.14260 | 7  | 0.81694 | -2.27755 | 0.47264 |
| 7  | -3.25240 | 3.00315 | -1.31352 | 8  | -4.43620 | -1.76384 | 0.27858 |
| 1  | -3.47855 | -0.16759 | 1.97429 | 8  | -2.47965 | 2.17020 | -0.97780 |
| 1  | -2.40163 | -0.82302 | 3.23309 | 1  | -0.55849 | 0.64621 | 1.29008 |
| 1  | -1.87657 | 0.56689 | 2.25421 | 1  | -0.85979 | 0.01031 | -1.83976 |
| 1  | 6.40559 | -0.21447 | 0.59518 | 1  | -2.04047 | -2.30050 | -1.10967 |
| 7  | -1.45081 | 0.89787 | -1.15292 | 1  | -1.94052 | -1.15710 | 1.80616 |

$E = -1387.072868$

$G = -1386.825107$
Copies of $^1$H and $^{13}$C NMR spectra

Figure S5. Compound 1c $^1$H NMR (400 MHz, CDCl$_3$)

Figure S6. Compound 1c $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S7. Compound 1d $^1$H NMR (400 MHz, CDCl$_3$)

Figure S8. Compound 1d $^{13}$C NMR (400 MHz, CDCl$_3$)
Figure S9. Compound 1i \(^1\)H NMR (400 MHz, CDCl\(_3\))

Figure S10. Compound 1i \(^{13}\)C NMR (400 MHz, CDCl\(_3\))
Figure S11. Compound 2a-Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S12. Compound 2a-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S13. Compound 2a-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S14. Compound 2a-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S15. Compound 2b-Me \(^1\)H NMR (400 MHz, CD\(_3\)CN)

Figure S16. Compound 2b-Me \(^{13}\)C NMR (101 MHz, CD\(_3\)CN)
Figure S17. Compound 2b-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S18. Compound 2b-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S19. Compound 2c-Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S20. Compound 2c-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S21. Compound 2c-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S22. Compound 2c-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S23. Compound 2d-Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S24. Compound 2d-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S25. Compound 2d-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S26. Compound 2d-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S27. Compound 2e-Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S28. Compound 2e-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S29. Compound 2e-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S30. Compound 2e-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S31. Compound 2f-Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S32. Compound 2f-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S33. Compound 2f-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S34. Compound 2f-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S35. Compound 2g-Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S36. Compound 2g-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S37. Compound 2g-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S38. Compound 2g-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S39. Compound 2h-Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S40. Compound 2h-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S41. Compound 2h-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S42. Compound 2h-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S43. Compound 2i-Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S44. Compound 2i-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S45. Compound 2i-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S46. Compound 2i-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S47. Compound 2j-Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S48. Compound 2j-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S49. Compound 2j-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S50. Compound 2j-Et $^1$H NMR (101 MHz, CD$_3$CN)
Figure S51. Compound 2k-\textsuperscript{1}H NMR (400 MHz, CD\textsubscript{3}CN)

![NMR Spectrum of Compound 2k-\textsuperscript{1}H]

Figure S52. Compound 2k-\textsuperscript{13}C NMR (101 MHz, CD\textsubscript{3}CN)

![NMR Spectrum of Compound 2k-\textsuperscript{13}C]
Figure S53. Compound 2k-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S54. Compound 2k-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S55. Compound 2l- Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S56. Compound 2l-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S57. Compound 2I-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S58. Compound 2I-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S59. Compound 2m-Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S60. Compound 2m-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S61. Compound 2m-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S62. Compound 2m-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S63. Compound 2n-Me \( ^1\)H NMR (400 MHz, CD\(_3\)CN)

Figure S64. Compound 2n-Me \( ^{13}\)C NMR (101 MHz, CD\(_3\)CN)
Figure S65. Compound 2n-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S66. Compound 2n-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S67. Compound 2o-Me $^1$H NMR (400 MHz, CD$_3$CN)

Figure S68. Compound 2o-Me $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S69. Compound 2o-Et $^1$H NMR (400 MHz, CD$_3$CN)

Figure S70. Compound 2o-Et $^{13}$C NMR (101 MHz, CD$_3$CN)
Figure S71. Compound 3d-\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})

Figure S72. Compound 3d-\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})
Figure S73. Compound 3d-Me $^1$H NMR (400 MHz, CDCl$_3$)

Figure S74. Compound 3d-Me $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S75. Compound 3e-H $^1$H NMR (400 MHz, CDCl$_3$)

Figure S76. Compound 3e-H $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S77. Compound 3e-Me $^1$H NMR (400 MHz, CDCl$_3$)

Figure S78. Compound 3e-Me $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S79. Compound 3f $^1$H NMR (400 MHz, DMSO-$d_6$)

Figure S80. Compound 3f $^{13}$C NMR (101 MHz, DMSO-$d_6$)
Figure S81. Compound 3f-\textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6)

Figure S82. Compound 3f-\textsuperscript{13}C NMR (101 MHz, DMSO-\textit{d}_6)
Figure S83. Compound 3g- $^1$H NMR (400 MHz, CDCl$_3$)

Figure S84. Compound 3g- $^{13}$C NMR (101 MHz, CDCl$_3$)
**Figure S85. Compound 3g-Me ¹H NMR (400 MHz, CDCl₃)**

![1H NMR spectrum of Compound 3g-Me]

**Figure S86. Compound 3g-Me ¹³C NMR (101 MHz, CDCl₃)**

![1³C NMR spectrum of Compound 3g-Me]
Figure S87. Compound 3h- H $^1$H NMR (400 MHz, CDCl$_3$)

Figure S88. Compound 3h- $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S89. Compound 3h-Me $^1$H NMR (400 MHz, CDCl$_3$)

Figure S90. Compound 3h-Me $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S91. Compound 3i-H $^1$H NMR (400 MHz, CDCl$_3$)

Figure S92. Compound 3i-H $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S93. Compound 3i-Me $^1$H NMR (400 MHz, CDCl$_3$)

Figure S94. Compound 3i-Me $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S95. Compound 3j-H $^1$H NMR (400 MHz, CDCl$_3$)

Figure S96. Compound 3j-H $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S97. Compound 3j-Me $^1$H NMR (400 MHz, CDCl$_3$)

Figure S98. Compound 3j-Me $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S99. Compound 3k-\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})

Figure S100. Compound 3k-\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})
Figure S101. Compound 3k-Me $^1$H NMR (400 MHz, CDCl$_3$)

Figure S102. Compound 3k-Me $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S103. Compound 3l-1H NMR (400 MHz, CDCl₃)

Figure S104. Compound 3l-13C NMR (101 MHz, CDCl₃)
Figure S105. Compound 3l-Me $^1$H NMR (400 MHz, CDCl$_3$)

Figure S106. Compound 3l-Me $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S107. Compound 3m- H NMR (400 MHz, CDCl₃)

Figure S108. Compound 3m- C NMR (101 MHz, CDCl₃)
Figure S109. Compound 3m-Me $^1$H NMR (400 MHz, CDCl$_3$)

Figure S110. Compound 3m-Me $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S111. Compound 4g- H NMR (400 MHz, CDCl₃)

Figure S112. Compound 4g- C NMR (101 MHz, CDCl₃)
Figure S113. Compound 5g-H minor $^1$H NMR (400 MHz, CDCl$_3$)

Figure S114. Compound 5g-H minor $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S115. Compound 5g-H major $^1$H NMR (400 MHz, CDCl$_3$)

Figure S116. Compound 5g-H major $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S117. Compound 6g-H minor $^1$H NMR (400 MHz, CDCl$_3$)

Figure S118. Compound 6g-H minor $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S119. Compound 6g-H major $^1$H NMR (400 MHz, CDCl$_3$)

Figure S120. Compound 6g-H major $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S121. Compound 7g-H minor $^1$H NMR (400 MHz, CDCl$_3$)

Figure S122. Compound 7g-H minor $^{13}$C NMR (400 MHz, CDCl$_3$)
Figure S123. Compound 7g-H major $^1$H NMR (400 MHz, CDCl$_3$)

Figure S124. Compound 7g-H major $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S127. Compound 7j-H major $^1$H NMR (400 MHz, CDCl$_3$)

![NMR spectrum of Compound 7j-H major $^1$H](image)

Figure S128. Compound 7j-H major $^{13}$C NMR (101 MHz, CDCl$_3$)

![NMR spectrum of Compound 7j-H major $^{13}$C](image)
Figure S129. Compound 8l-Me intermediate $^1$H NMR (400 MHz, CDCl$_3$)

Figure S130. Compound 8l-Me intermediate $^{13}$C NMR (101 MHz, CDCl$_3$)
Figure S131. Compound 8l-Me $^1$H NMR (400 MHz, CDCl$_3$)

Figure S132. Compound 8l-Me $^{13}$C NMR (101 MHz, CDCl$_3$)
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