A General Approach to Selective Functionalization of 1,2,4-Triazines Using Organometallics in Palladium-Catalyzed Cross-Coupling and Addition Reactions

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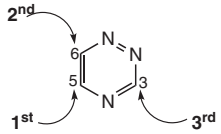
Abstract: A selective way to obtain disubstituted 1,2,4-triazines in good yields by combining addition reactions and palladium-catalyzed cross-coupling reactions of organometallics with 3-methylsulfanyl-1,2,4-triazine is described.

Key words: 1,2,4-triazines, palladium, cross-coupling, selective addition, organometallics, catalysis

1,2,4-Triazine derivatives, especially aryl 1,2,4-triazines, are well known in therapeutic chemistry as antifungal,[1] or antitumoral,[1] in agronomy as insecticides[2] and in selective complexation as metallic cations ligands.[3] Many of them were prepared by cyclization of the triazine ring. 4+2 Atom combination of 1,2-dicarbonyl compounds with amidrazones is the most frequently described synthesis of aryl or hetaryl substituted 1,2,4-triazines.[4] Unfortunately, both cyano and diketone precursors are sometimes difficult to synthesize. Furthermore, diketones have to be symmetrical to avoid mixture of isomeric triazines and to obtain better yields.[5]

Another way to prepare those substituted triazines is the direct functionalization of a triazine ring by carbon-carbon bond formation.[6] Indeed, Yamanaka et al.[7] have described the addition of phenylmagnesium bromide on 1,2,4-triazines to form 5-phenyl-, 5,6-diphenyl- and 3,5,6-triphenyl-1,2,4-triazines, subsequently. This study also showed that the relative reactivity of positions 3, 5 and 6 of the 1,2,4-triazine ring with Grignard reagents is controlled. Indeed, the most active position is position 5 and the least active is position 3 (Scheme 1).



Scheme 1 Reactivity of 1,2,4-triazine towards Grignard reagents

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At this stage, we thought it would be interesting to be able to supervise the functionalization order on the 1,2,4-triazine ring. Therefore, the reactivity of readily available 3-methylsulfanyl-1,2,4-triazine (**1**)[8] was investigated with different organometallics: organolithium reagents, Grignard reagents, boronic acids, organostannanes and organozinc reagents. This paper describes a suitable choice of organometallics for the selective introduction of a wide range of substituents at C-3, C-5 and C-6 positions. The best combination between addition and palladium-catalyzed cross-coupling to obtain 3,5-diaryl-1,2,4-triazines is also reported. We first tried the addition reactions of organolithium reagents on 3-methylsulfanyl-1,2,4-triazine (**1**). The results are summarized in Table 1.

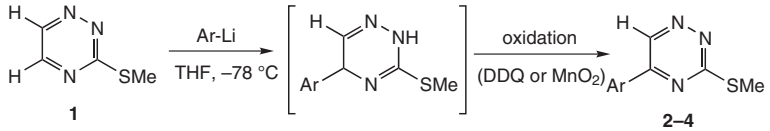
As expected, the addition of 1.25 equivalents of aryllithium to **1** led to 5-substituted compounds and a further oxidation step gave 5-aryl-1,2,4-triazines **2**–**4** in good yields (Table 1). Although the oxidation into furyl derivative **3** and pyridinyl derivative **4** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gave byproducts, the use of milder oxidant MnO_2 was successful.

According to the literature, Grignard reagents react with heteroaromatic thioethers in palladium or nickel-catalyzed cross-coupling reactions.[9,10] We attempted palladium catalyzed cross-coupling reaction conditions on 3-methylsulfanyl-1,2,4-triazine (**1**) (Table 2, entry 1). No coupled product **6** was observed and only the addition compound, 2,5-dihydro-5-(*p*-methoxyphenyl)-3-methylsulfanyl-1,2,4-triazine (**5**) was isolated. A further oxidation step with 1.25 equivalents of DDQ gave quantitatively the 5-(*p*-methoxyphenyl)-3-methylsulfanyl-1,2,4-triazine (**7**). A control experiment showed that the palladium catalyst is useless and triazine **5** was isolated in 85% yield without any transition metal (Table 2, entry 2).

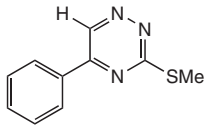
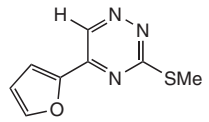
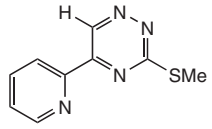
To summarize, regarding Grignard reagents, the C-5 position of the 1,2,4-triazine ring is more reactive towards addition reaction than the C-3 position towards transition metal catalyzed cross-coupling reaction.

We were then curious to evaluate the behavior of 3-methylsulfanyl-5-substituted-1,2,4-triazine towards palladium- or nickel-catalyzed cross-coupling reactions. When 5-(2-furyl)-3-methylsulfanyl-1,2,4-triazine (**3**) was treat-

Table 1 Addition Reactions of Aryllithium Reagents with 3-Methylsulfanyl-1,2,4-triazine (**1**)

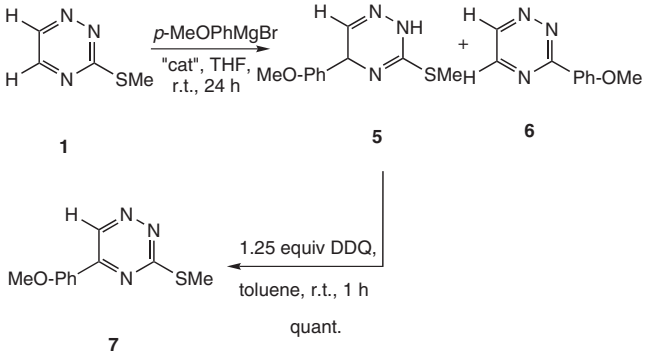


1 **2–4**

Entry	Time (h)	Oxidation conditions	Products	Yield (%)[a]
1	3	1.25 equiv DDQ, toluene, r.t., 24 h	 **2**	60
2	2[b]	10 equiv MnO_2, CH_2Cl_2, r.t., 24 h	 **3**	66
3	2	10 equiv MnO_2, CH_2Cl_2, r.t., 24 h	 **4**	70

[a] Yields after column chromatography.
[b] Reaction was performed in Et_2O instead of THF.

Table 2 Attempt to Palladium and Nickel-Catalyzed Cross-Coupling of *p*-Methoxyphenylmagnesium Bromide with **1**



1 **5** **6** **7**

Entry	Catalyst	**5** (%)[a]	**6** (%)
1	$PdCl_2$(dppf)	73	–
2	–	85	–

[a] Isolated after column chromatography.

ed with 1.2 equivalents of *p*-methoxyphenylmagnesium bromide in THF with 10 mol% $PdCl_2$(dppf) for 24 hours, we isolated a mixture of C-6 addition product **8** (7%) and C-3 coupled product **9** (20%) (Table 3, entry 1). With $NiCl_2$(dppe), a few traces of **8** were observed (Table 3, entry 2). Although, few palladium catalysts were tested [$Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd_2dba_3/AsPh_3$], none was selective towards cross-coupling reaction.

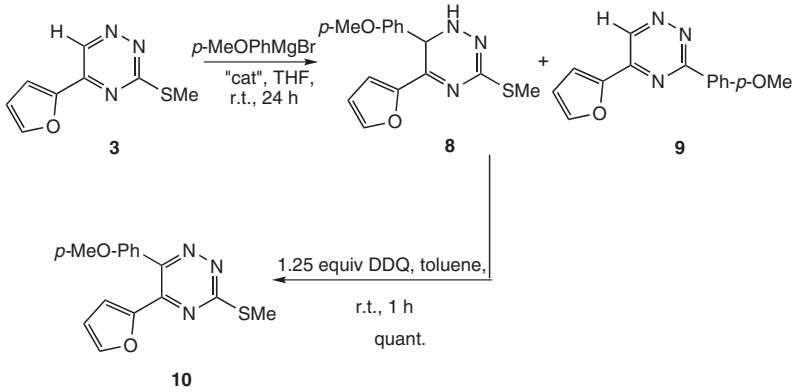
However, when 5-(2-furyl)-3-methylsulfanyl-1,2,4-triazine (**3**) was treated without catalyst with 2.4 equivalents of *p*-methoxyphenylmagnesium bromide in THF for 24 hours, only the addition product **8** was isolated in 45% yields (Table 3, entry 3). Treatment of non aromatic compound **8** with 1.25 equivalents of DDQ led quantitatively to 5-(2-furanyl)-6-(*p*-methoxyphenyl)-3-methylsulfanyl-1,2,4-triazine (**10**).

Considering the lack of selectivity of the transition metal catalyzed reaction, we thought it would be interesting to use non-nucleophilic organometallics.

Recently, Liebeskind and Srogl indicated[11,12] that heteroaromatic thioether-boronic acid cross-coupling mediated by copper (I) carboxylates would be feasible. Indeed, this method has been successfully reported for 3-methylsulfanyl-1,2,4-triazine (**1**).[13] Various 3-aryl-1,2,4-triazines were obtained in good yields using palladium-catalyzed cross-coupling reactions between boronic acids and 3-methylsulfanyl-1,2,4-triazine (**1**) in the presence of copper (I) methylsalicylate (CuMeSal) as cofactor (Scheme 2). The reactions were typically carried out at 55–60 °C in THF using 5–10 mol% of $Pd(PPh_3)_4$, 2.2 equivalents of boronic acid and 2.2 equivalents of CuMeSal. No addition product was observed.

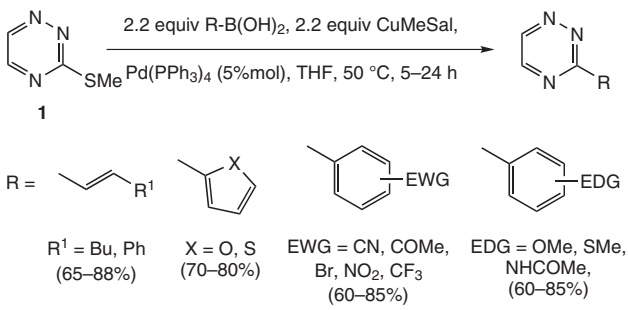
Considering the advantages of using trialkylorganotin species [they are readily available (especially alkenyl and heteroaromatic stannanes)],[14] we investigated this strategy on heteroaromatic stannanes.[15] Many vinyl and arylstannanes were coupled in excellent yields using 2.2

Table 3 Attempt to Palladium and Nickel-Catalyzed Cross-Coupling of *p*-Methoxyphenylmagnesium Bromide with **3**



Entry	Catalyst	**8** (%)[a]	**9** (%)[a]
1	$PdCl_2$(dppf)	7	20
2	$NiCl_2$(dppe)	Traces	–
3	–	45[b]	–

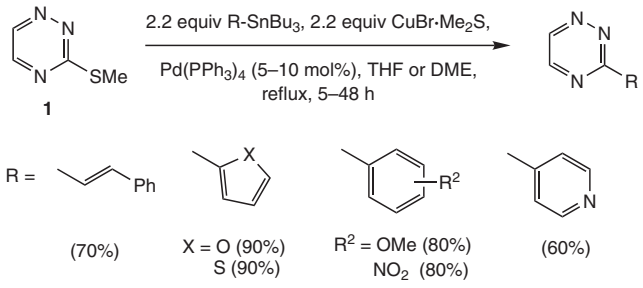
[a] Isolated after column chromatography.
[b] 2.4 Equiv of Grignard reagent were used instead of 1.2 equiv.



Scheme 2 Palladium and copper mediated cross-coupling of organoboron reagents with 3-methylsulfanyl-1,2,4-triazine (**1**)

equivalents of organostannanes, 2.2 equivalents of CuBr·Me_2S with 5–10 mol% of $Pd(PPh_3)_4$, in refluxing THF or DME (Scheme 3). No addition product was observed.

We were then interested in organozinc compounds. They are versatile reagents for metal catalyzed cross-coupling reactions and are compatible with many functional groups.[16] Furthermore, with the growing interest for the Negishi reaction (among others for the synthesis of bihetaryl compounds),[17] many organozinc derivatives are commercially available or their synthesis is described in the literature.[18]



Scheme 3 Palladium and copper mediated cross-coupling of organostannane reagents with 3-methylsulfanyl-1,2,4-triazine (**1**)

On the basis of recent results of Casalnuovo and Angiolelli[19] on palladium-catalyzed cross-coupling reactions of benzylzinc reagents with methylthio azaheterocycles, 3-methylsulfanyl-1,2,4-triazine (**1**) was treated with two equivalents of benzylzinc bromide in THF using 10 mol% of $Pd(PPh_3)_4$ (Table 4, entry 1). Surprisingly, we exclusively isolated the addition product **11** in 73% yields. The presence of the catalyst is not necessary since compound **11** was isolated in 60% yield when the reaction was conducted without palladium (Table 4, entry 2). The oxidation of the unstable dihydro compound **11** with ten equivalents of MnO_2 led to **13** in 28% yields (Scheme 4).

We also tested palladium-catalyzed cross-coupling reactions between phenylzinc bromide and 3-methylsulfanyl-1,2,4-triazine (**1**) under similar conditions. In this case 3-phenyl-1,2,4-triazine (**12**) was isolated in 30% yield (Table 4, entry 3) probably due to the lower nucleophilic phenylzinc reagent.

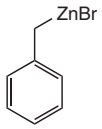
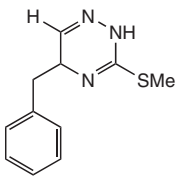
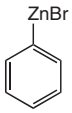
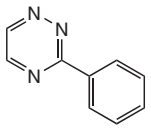
At this stage, we investigated whether the original functionalization order (C-5, C-6 and C-3) of the 1,2,4-triazine ring towards nucleophiles could be deliberately modified using different organometallics species.

We examined two pathways to obtain regioselectively 3,5-disubstituted-1,2,4-triazines starting from 3-methylsulfanyl-1,2,4-triazine (**1**):

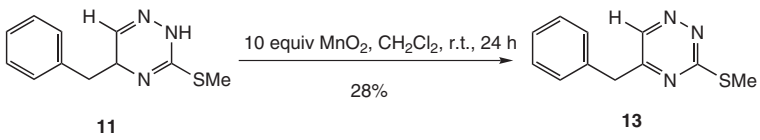
Pathway 1: addition reaction + cross-coupling reaction

Pathway 2: cross-coupling reaction + addition reaction

Table 4 Addition Reactions and Palladium-Catalyzed Cross-Coupling of 3-Methylsulfanyl-1,2,4-triazine (**1**) with Organozinc Reagents in THF for 48 h

Entry	Ar-ZnBr	Time(h)	Catalyst	Products	Yield (%)[a]
1		48	$Pd(PPh_3)_4$	 **11**	73
2		48	/	**11**	60
3		2	$Pd(PPh_3)_4$	 **12**	30[b]

[a] Isolated yields after column chromatography.
[b] Reaction was performed with 20 mol% of $Pd(PPh_3)_4$.



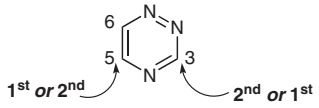
11 **13**

Scheme 4 Oxidation of 2,5-dihydro-5-benzyl-3-methylsulfanyl-1,2,4-triazine (**11**) with MnO_2

As summarized in Table 5, addition products **3**, **4** and **7** were coupled with *p*-methoxyphenyl boronic acid in the presence of palladium and CuMeSal,[13] to afford 3,5-disubstituted-1,2,4-triazines **9, 14** and **15**, respectively, in good yields (pathway 1). In the case of 3-(*p*-methoxyphenyl)-5-(pyridin-2-yl)-1,2,4-triazine (**14**), 3.2 equivalents of CuMeSal were necessary to observe complete cross-coupling reaction probably because of complexation of copper in the coordination site N-C-C-N of the starting material **4**.

The same 3,5-disubstituted-1,2,4-triazines **9**, **14** and **15** were also isolated when the coupled product **6**[13,15] was treated with selected aryllithiums and Grignard reagents (pathway 2).

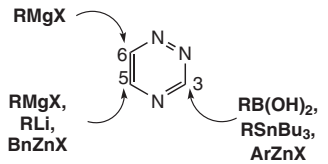
To sum up, the functionalization order of the 1,2,4-triazine ring can be easily modified (Scheme 5): position 3 can be first substituted followed by position 5 or position 5 can be first substituted followed by position 3, both of them leading to similar yields.



Scheme 5 Alternative functionalization orders of 1,2,4-triazine

In conclusion, we have extended addition reactions on 1,2,4-triazines to organolithiums and benzylzinc reagents. Furthermore, 3-methylsulfanyl-1,2,4-triazine (**1**) was successfully coupled with boronic acids and organostannanes in the presence of copper (I) and a catalytic amount of $Pd(PPh_3)_4$.

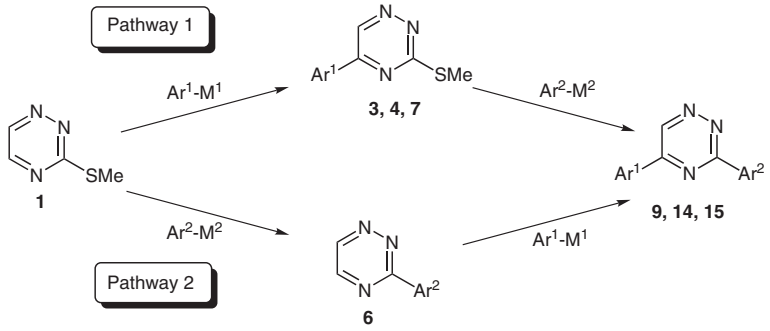
With all those new functionalization tools combined with Yamanaka's results,[7] one can regioselectively functionalize the 1,2,4-triazine ring to obtain 5-aryl-, 3-aryl-, 3,5-diaryl-, 5,6-diaryl- and 3,5,6-triaryl-1,2,4-triazines (Scheme 6).

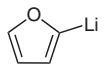
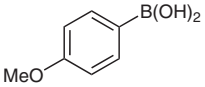
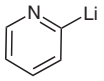
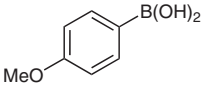
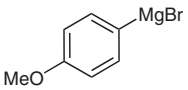
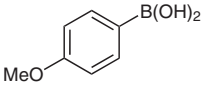


Scheme 6 New tools to functionalize the 1,2,4-triazine ring

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 250 MHz spectrometer. ^1H NMR spectra are reported as follows: chemical shifts in ppm (δ) downfield from TMS as an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broadened), integration and coupling constants spectra (Hz). ^{13}C NMR spectra reported in ppm (δ) relative to the central line of triplet for $CDCl_3$ at 77 ppm. IR spectra were recorded on a Perkin-Elmer FT PARAGON 1000PC spectrometer

Table 5 Different Combinations Between Addition Reaction and Cross-Coupling Reaction Starting with **1**



Entry	Ar_1-M_1	Ar_2-M_2	Products, Yields (pathway 1/pathway 2) (%)[a]
1			**9**, 44:17
2			**14**, 55:55
3			**15**, 55:47

[a] Isolated after column chromatography.

and absorption are reported in cm^{-1}. HRMS (CI) were acquired on a Thermofinnigan-MAT instrument 95 XL Analytical spectrometer. Melting points, uncorrected values, were measured on a Büchi 510 instrument. Microanalyses were taken on a ThermoFinnigan Flash EA1112 CHNS/O + MAS apparatus. Analytical TLC was performed on 0.2 mm precoated Kieselgel 60 F_{254} (Merck) plates.

THF and 1,2-dimethoxyethane (DME) were distilled over sodium and benzophenone before use. 3-Methylsulfanyl-1,2,4-triazine (**1**) was prepared according to the litterature.[8] Compounds **6** and **12** were described in previous papers.[13,15] All other compounds used were commercially available.

Addition of Organolithium Derivatives; Typical Procedure

To a solution of 3-methylsulfanyl-1,2,4-triazine (**1**) (100 mg, 0.79 mmol) in anhyd THF (3 mL) cooled to –78 °C under Ar was added dropwise phenyllithium (2 M, 500 μL, 1.25 equiv). The reaction mixture was kept at this temperature for 3 h and then was allowed to warm to r.t. over a period of 2 h. The reaction was quenched with a sat. solution of NH_4Cl and extracted twice with Et_2O. The crude product was dissolved in toluene (7 mL) under Ar and 2,3-dichloro-5,6-dicyanoquinone (188 mg, 1.25 equiv) was added by portion. After stirring for 1 h at r.t., the reaction mixture was filtrated on celite and the filtrate was diluted with a sat. solution of K_2CO_3 and extracted with CH_2Cl_2. Purification by flash chromatography (silica gel, petroleum ether–EtAOc, 90:10) afforded aromatic product **2** (96 mg, 60% yield) as a pale yellow solid.

3-Methylsulfanyl-5-phenyl-1,2,4-triazine (2)[6e,8]

Yields 60%; pale yellow solid; mp 97–99 °C (lit.[8] mp 99–100 °C).

IR (NaCl): 1597, 1538, 1501, 1237, 761, 663 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.37 (s, 1 H), 8,15 (dd, *J* = 1.6, 7.9 Hz, 2 H), 7.61-7.55 (m, 3 H), 2.73 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 173.9, 154.6, 142.0, 133.2, 132.8, 129.5 (2 × C), 127.8 (2 × C), 13.9.

5-(2-Furanyl)-3-methylsulfanyl-1,2,4-triazine (3)

Purified by flash chromatography (silica gel, petroleum ether–EtOAc, 70:30). Yield: 66%; yellow solid; mp 83–85 °C (lit.[20] mp 88–90 °C).

IR (KBr): 1490, 1253, 1107, 767 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.22 (s, 1 H), 7.71 (m, 1 H), 7.46 (d, *J* = 3.4 Hz, 1 H), 6.65 (dd, *J* = 2.3, 3.7 Hz, 1 H), 2.69 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 173.7, 149.1, 147.6, 146.1, 140.5, 116.9, 113.7, 14.2.

3-Methylsulfanyl-5-(pyridin-2-yl)-1,2,4-triazine (4)

Purified by flash chromatography (silica gel, petroleum ether–EtOAc–Et_3N, 90:10:01). Yield: 70%; yellow solid; mp 128–130 °C.

IR (KBr): 1533, 1507, 1469, 1311, 1301, 1234 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.95 (s, 1 H), 8.79–8.76 (m, 1 H), 8.51 (d, *J* = 7.9 Hz, 1 H), 7.89 (td, *J* = 1.8, 7.9 Hz, 1 H), 7.48 (ddd, *J* = 1.2, 4.9, 7.9 Hz, 1 H), 2.77 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 173.5, 153.2, 151.7, 150.1, 142.7, 137.4, 126.6, 123.0, 14.1.

HRMS (CI): *m/z* $[M + H]^+$ calcd for $C_9H_9N_4S$: 205.0548; found: 205.05420.

Addition of Organomagnesium Derivatives; Typical Procedure

To a solution of 3-methylsulfanyl-1,2,4-triazine (**1**) (200 mg, 1.57 mmol) in anhyd THF (5 mL) under Ar was added dropwise *p*-methoxyphenylmagnesium bromide (0.5 M, 3.8 mL, 1.2 equiv.) at r.t. The reaction mixture was stirred for 20 h, was then diluted with a sat. solution of NH_4Cl and extracted twice with CH_2Cl_2. Purification by flash chromatography (silica gel, petroleum ether–EtOAc, 70:30) afforded non-aromatic product **5** (314 mg, 85% yield) as a pale yellow oil. Oxidative step with 2,3-dichloro-5,6-dicyanoquinone was carried like in the case of organolithium. Purification by flash chromatography (silica gel, petroleum ether–EtAOc, 50:50)

afforded quantitatively aromatic product **7** (311 mg) as a yellow powder.

2,5-Dihydro-5-*p*-methoxyphenyl-3-methylsulfanyl-1,2,4-triazine (5)
Yield: 85%; yellow pale oil.

^{1}H NMR ($CDCl_3$): δ = 8.39 (br s, 1 H, NH), 7.29 (d, *J* = 8.4 Hz, 2 H), 6.90 (d, *J* = 8.4 Hz, 2 H), 6.75 (d, *J* = 2.2 Hz, 1 H), 6.68 (d, *J* = 2.2 Hz, 1 H), 3.79 (s, 3 H), 2.44 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 159.5, 154.7, 141.5, 133.1, 129.9 (2 × C), 114.5 (2 × C), 57.9, 55.7, 14.0.

5-*p*-Methoxyphenyl-3-methylsulfanyl-1,2,4-triazine (7)[20,21]
Quantitative yield; yellow powder; mp 108–110 °C (lit.[20] mp 106–107 °C).

IR (KBr): 3074, 3002, 2927, 2839, 1603, 1506, 1243, 1175 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.25 (s, 1 H), 8.07 (d, *J* = 9.1 Hz, 2 H), 6.98 (d, *J* = 9.1 Hz, 2 H), 3.86 (s, 3 H), 2.68 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 173.1, 163.3, 153.7, 141.2, 129.3 (2 × C), 124.9, 114.6 (2 × C), 55.4, 13.6.

1,6-Dihydro-5-(2-furanyl)-6-*p*-methoxyphenyl-3-methylsulfanyl-1,2,4-triazine (8)
Purified by flash chromatography (silica gel, petroleum ether–EtOAc: 70:30). Yield: 45%; red oil.

IR (NaCl): 3452, 2940, 2846, 1608, 1510, 1252, 1177, 1029, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.58 (d, *J* = 1.6 Hz, 1 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 7.02 (d, *J* = 3.1 Hz, 1 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 6.50 (dd, *J* = 1.6, 3.1 Hz, 1 H), 6.3 (br s, 1 H, NH), 5.13 (s, 1 H), 3.76 (s, 3 H), 2.34 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 159.9, 152.6, 150.2, 150.0, 146.7, 129.3, 128.4 (2 × C), 117.1, 114.3 (2 × C), 112.8, 55.3, 50.9, 13.6.

5-(2-Furanyl)-6-*p*-methoxyphenyl-3-methylsulfanyl-1,2,4-triazine (10)
Purified by flash chromatography (silica gel, petroleum ether–EtOAc, 50:50). Quantitative yield; red oil.

IR (NaCl): 3137, 3118, 2928, 2835, 1609, 1573, 1523, 1480, 1358, 1250, 1185, 1054, 832 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.57 (dd, *J* = 0.6, 1.9 Hz, 1 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 7.0 (d, *J* = 8.8 Hz, 2 H), 6.70 (dd, *J* = 0.6, 3.6 Hz, 1 H,), 6.43 (dd, *J* = 1.9, 3.6 Hz, 1 H,), 3.88 (s, 3 H), 2.74 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 170.7, 160.9, 151.4, 148.7, 146.8, 144.7, 130.5 (2 × C), 127.8, 118.7, 114.2 (2 × C), 112.6, 55.5, 14.0.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}N_3O_2S$: 300.0807; found: 300.08001.

Addition of Organozinc Derivatives; Typical Procedure
3-Methylsulfanyl-1,2,4-triazine (**1**) (200 mg, 1.57 mmol) was placed in a 25 mL Schlenk tube under Ar and a solution of benzylzinc bromide (0.5 M in THF, 6.3 mL, 2 equiv) was added dropwise at r.t. After stirring for 24 h, the reaction mixture was quenched with a sat. solution of $NaHCO_3$, filtrated on celite and extracted twice with EtOAc. Purification by flash chromatography (silica gel, petroleum ether–EtOAc, 95:5) afforded non-aromatic product **11** (206 mg, 60% yield) as an orange oil. To a solution of 2,5-dihydro-5-benzyl-3-methylsulfanyl-1,2,4-triazine (**11**) (136 mg, 0.66 mmol) in CH_2Cl_2 (10 mL) under Ar was added MnO_2 (1.1 g, 10 equiv) portiowise. After stirring for 24 h at r.t., the reaction mixture was filtrated on celite. Purification by flash chromatography (silica gel, petroleum ether–EtAOc: 95:5) afforded aromatic product **13** (80 mg, 28% yield) as a brown oil.

5-Benzyl-2,5-dihydro-3-methylsulfanyl-1,2,4-triazine (11)
Yield: 60%; orange oil.

IR (NaCl): 3019, 1215, 771 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.09 (br s, 1 H, NH), 7.34–7.21 (m, 5 H), 6.64 (d, *J* = 3.4 Hz, 1 H), 3.98 (ddd, *J* = 2.0, 6.5, 8.2 Hz, 1 H), 3.09–3.03 (dd, *J* = 6.4, 13.5 Hz, 1 H), 2.95–2.86 (dd, *J* = 6.4, 13.5 Hz, 1 H), 2.44 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 154.8, 141.3, 137.6, 129.6 (2 × C), 128.5 (2 × C), 126.6, 55.9, 38.9, 13.7.

5-Benzyl-3-methylsulfanyl-1,2,4-triazine (13)
Yield: 28%; brown oil.

IR (NaCl): 3241, 3160, 3056, 3003, 1725, 1677, 1530, 1142 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.21 (s, 1 H), 7.40–7.25 (m, 5 H), 4.29 (s, 2 H), 2.67 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 156.5, 149.0, 143.6, 134.7, 129.6 (2 × C), 129.2 (2 × C), 128.8, 39.6, 14.1.

Anal. Calcd for $C_{11}H_{11}N_3S$: C, 60.80; H, 5.10; N, 19.34; S, 14.76. Found: C, 60.52; H, 5.15; N, 19.26; S, 14.71.

Palladium-Catalyzed Cross-Coupling Reaction with Boronic Acids; Typical Procedure
To a mixture of 5-substituted-3-methylsulfanyl-1,2,4-triazine (0.393 mmol, 1.0 equiv), CuMeSal (0.867 mmol, 2.2 equiv), boronic acid (0.867 mmol, 2.2 equiv) in anhyd THF (3 mL) under Ar, was added $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 5% mol). The reaction was stirred for 5 h at 50 °C. The mixture was quenched with a Na_2CO_3 solution (2 N, 5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with a Na_2CO_3 solution (2 N, 15 mL) and water, dried over $MgSO_4$ and concentrated in vacuo. The products were purified by column chromatography on silica gel.

5-(2-Furanyl)-3-(*p*-methoxyphenyl)-1,2,4-triazine (9)
Purified by flash chromatography (silica gel, petroleum ether–EtOAc, 95:5). Yield: 70%; yellow solid; mp 144–146 °C.

IR (KBr): 2956, 2924, 2854, 1610, 1599, 1535, 1259 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.39 (s, 1 H), 8.54 (d, *J* = 9.1 Hz, 2 H), 7.73 (m, 1 H), 7.57 (d, *J* = 3.7 Hz, 1 H), 7.04 (d, *J* = 9.1 Hz, 2 H), 6.68 (dd, *J* = 1.8, 3.7 Hz, 1 H), 3.91 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 163.4, 163.0, 149.9, 147.2, 142.2, 130.5 (2 × C), 127.8, 126.3, 116.1, 114.5 (2 × C), 113.5, 55.8.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_4H_{12}N_3O$: 254.0930; found: 254.09325.

3-(*p*-Methoxyphenyl)-5-(pyridin-2-yl)-1,2,4-triazine (14)
Purified by flash chromatography (silica gel, petroleum ether–EtOAc: 80:20). Yield: 79%; yellow solid; mp 147–149 °C.

IR (KBr): 1609, 1537, 1257, 1027, 782 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 10.11 (s, 1 H), 8.71–8.69 (m, 1 H), 8.69 (d, *J* = 7.8 Hz, 1 H), 8.68–8.59 (m, 2 H), 7.98–7.91 (td, *J* = 2.0, 7.8 Hz, 1 H), 7.25–7.47 (ddd, *J* = 1.2, 4.6, 7.8 Hz, 1 H), 7.09–7.05 (m, 2 H), 3.92 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 163.0, 162.8, 153.6, 152.5, 149.9, 144.2, 137.4, 130.2 (2 × C), 127.6, 126.4, 122.8, 114.3 (2 × C), 55.5.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_4O$: 265.1089; found: 265.10885.

3,5-bis-(*p*-Methoxyphenyl)-1,2,4-triazine (15)
Purified by flash chromatography (silica gel, petroleum ether–EtOAc: 90:10). Yield: 80%; yellow solid; mp 139–141 °C.

IR (KBr): 1606, 1510, 1498, 1252, 1167 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.42 (s, 1 H), 8.57 (d, *J* = 9.0 Hz, 2 H), 8.20 (d, *J* = 9.0 Hz, 2 H), 7.04 (d, *J* = 9.0 Hz, 4 H), 3.88 (s, 3 H), 3.87 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 163.2, 162.9, 162.6, 154.4, 143.1, 130.1 (2 × C), 129.3 (2 × C), 127.8, 126.1, 114.8 (2 × C), 114.2 (2 × C), 55.6, 55.5.

HRMS (CI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{16}N_3O_2$: 294.1243; found: 294.12386.

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