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Palladium-Catalyzed Direct α-Arylation of *p*-Methoxybenzyl-Protected *S*,*S*-Dimethylsulfoximine

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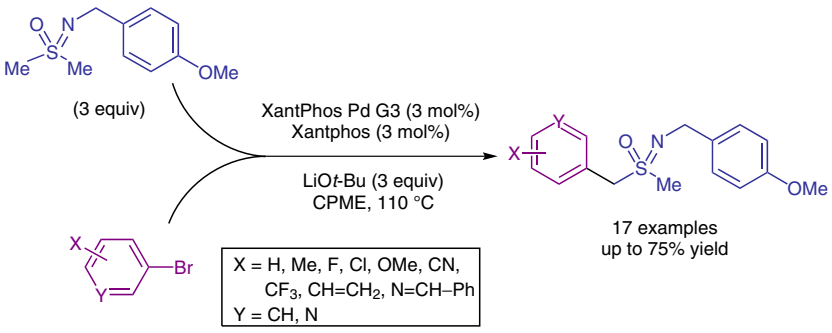

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Abstract Sulfoximines have recently gained considerable recognition as an important structural motif in the life sciences. This is especially true for (hetero)aryl-substituted *S*,*S*-dimethylsulfoximine derivatives, such as the marketed insecticide sulfoxaflor, as well as the clinical candidates PTEFb inhibitor BAY 1143572 and ATR inhibitor AZD 6738 for the treatment of cancer. Herein, the first palladium-catalyzed direct α-arylation of *p*-methoxybenzyl-protected *S*,*S*-dimethylsulfoximine using readily available (hetero)aryl bromides is reported. This new method provides a safe, short, and efficient approach to (hetero)aryl-substituted *S*,*S*-dimethylsulfoximine derivatives, an important class of bioactive compounds, demonstrated by application of this methodology to an improved synthesis of PTEFb inhibitor BAY 1143572.

Key words sulfoximines, palladium, cross-coupling, drug design, crop protecting agents

Since the late discovery of the sulfoximine group in 1949,[1] sulfoximine chemistry[2] has been rather a niche discipline. Applications have mainly focused on the use of sulfoximines as either chiral auxiliaries[3] or ligands in asymmetric catalysis.[4] Until very recently, the sulfoximine group has rarely seen use in life science applications, even though it offers a unique combination of interesting properties, namely high stability, favorable physicochemical properties, hydrogen-bond acceptor/donor functionalities, and structural diversity.[5] Possibly the very limited commercial availability and few available synthetic methods with associated safety concerns[6] have hampered the use of the sulfoximine group, especially in industry. Over the last decade, however, interest in sulfoximine chemistry has increased substantially, paving the way to new and safe synthetic methods.[7] Very recent developments include, for instance, the use of flow chemistry techniques, which mitigate the safety risks associated with the classical direct imination of sulfoxides to sulfoximines using azides,[8] and photochemical approaches to sulfoximines.[9] This progress in synthetic methodology goes hand in hand with the rapidly increasing interest in sulfoximines as pharmacophores in the life sciences.[10] In particular, (hetero)aryl-substituted *S*,*S*-dimethylsulfoximine derivatives such as the commercial insecticide sulfoxaflor[10a,11] and the clinical kinase inhibitors BAY 1143572[12] and AZD 6738[13] have drawn considerable attention recently (Figure 1).

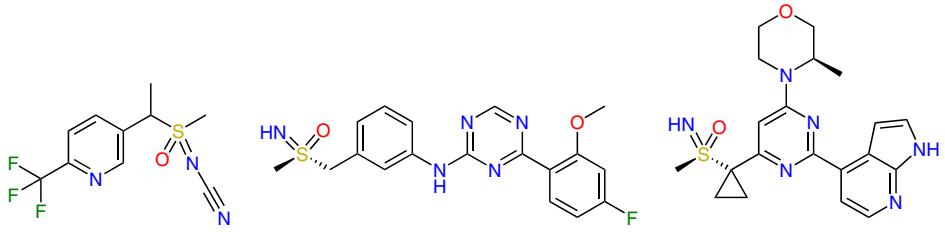
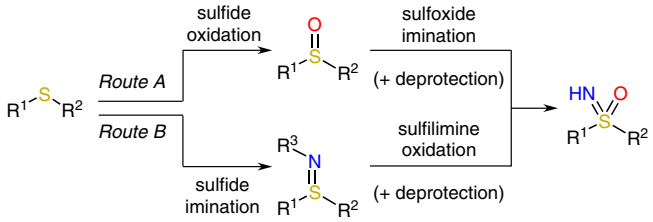


Figure 1 Structures of the commercial insecticide sulfoxaflor, and phase I kinase inhibitors BAY 1143572 and AZD 6738 for the treatment of cancer



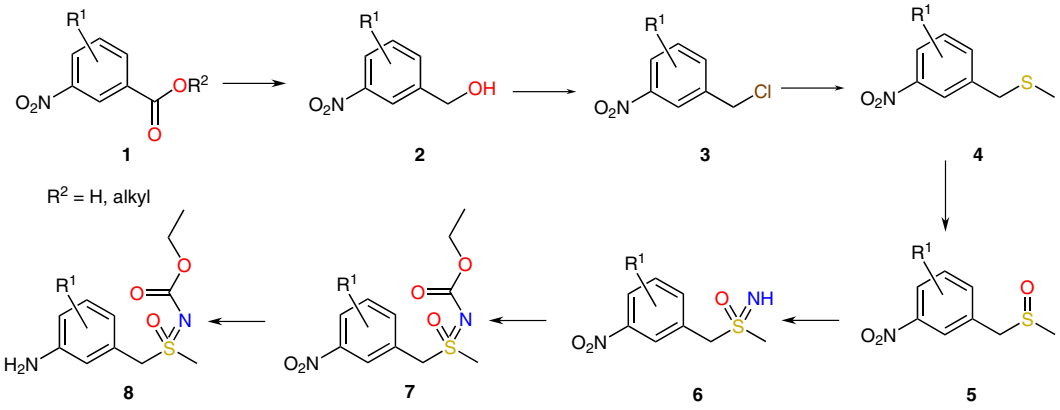
Scheme 1 Preparation of sulfoximines via oxidation/imination or imination/oxidation procedures (scheme adapted from Loso and co-workers[10a])

Whilst significant progress has been made, methods for sulfoximine synthesis remain rather limited. In general, most synthetic methods rely on sequential oxidation/imination (Route A) or imination/oxidation (Route B) procedures starting from thioethers (Scheme 1).

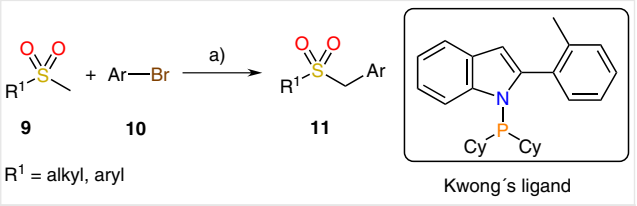
Our long-standing interest in sulfoximines as an underrepresented pharmacophore in drug discovery[14] has often been met with challenges in the syntheses of the desired sulfoximine targets. For instance, during the lead optimization program that led to the discovery of the potent and selective PTEFb inhibitor BAY 1143572 for the treatment of cancer, synthesis of the required sulfoximine building block **8** generally relied on the initial formation of a thioether **4**, for example, from a commercial acid or ester **1** via reduction and subsequent chlorination (Scheme 2). Thioether **4** was then converted into the unprotected sulfoximine building block **6** via sequential oxidation (**4** → **5**) and imination/deprotection (**5** → **6**) reactions.[15] Finally, introduction of a protecting group that is stable under both basic conditions and elevated temperatures, followed by reduction of the nitro group, gave the desired aniline building block **8**. In principle, however, this sequential approach has two major drawbacks: first of all, the syntheses are quite long, requiring seven steps to transform a commercial ester or acid **1** to the desired aniline building block **8** with a protected *S*-benzyl-*S*-methylsulfoximine group. Secondly, we often found that the sequential oxidation/imination or imination/oxidation procedures resulted in complex product mixtures in poor yields involving difficult purification procedures, or even that they failed completely, depending on the chemical structure of the starting thioether. This can be particularly problematic when attempting to construct the sulfoximine group via such sequential routes for more complex thioethers containing several heteroatoms.

We addressed this limitation by searching for methods that would allow the synthesis of (hetero)aryl-substituted *S*,*S*-dimethylsulfoximine derivatives via an intermolecular cross-coupling reaction utilizing a readily available, preformed sulfoximine building block.[16] Whilst the synthesis of functionalized benzylic sulfones using the palladium-catalyzed Negishi coupling reaction with various alkyl sulfones and aryl halides was reported by Zhou and co-workers in 2010,[17] in the present context two more recent publications on palladium-catalyzed α-arylations of sulfones were pivotal. In 2013, Walsh and co-workers reported the first deprotonative cross-coupling process for the direct α-arylation of aryl methyl and alkyl methyl sulfones **9** with aryl bromides **10** using Kwong's ligand (Scheme 3).[18] Even weakly acidic alkyl methyl sulfones **9** with pK_a values as high as 31 (in DMSO) were good substrates in this palladium-catalyzed cross-coupling process.

More recently, Nambo and Crudden utilized a related palladium-catalyzed C–H arylation of methyl phenyl sulfone (**9a**) to prepare complex triarylmethanes **12** via sequential α-arylations (Scheme 4).[19]



Scheme 2 General synthetic route to aniline building blocks **8** with a protected sulfoximine group in the lead optimization project that led to the identification of phase I PTEFb inhibitor BAY 1143572

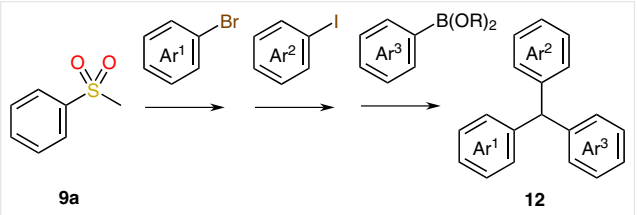


9 10 11

R^1 = alkyl, aryl

Kwong´s ligand

Scheme 3 Palladium-catalyzed direct α-arylation of methyl sulfones **9** with aryl bromides **10**. *Reagents and conditions*: a) $Pd(OAc)_2$ (10 mol%), Kwong's ligand (20 mol%), LiO*t*-Bu (3 equiv), toluene, 110 °C, 12 h; 18 examples, up to 90% yield.[18]



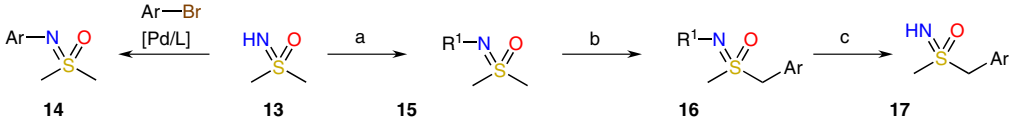
9a **12**

Scheme 4 Synthesis of triarylmethanes **12** via palladium-catalyzed sequential arylation reactions[19]

As sulfoximines are isoelectronic with sulfones, we envisaged developing a direct α-arylation of the structurally simplest sulfoximine, commercial *S*,*S*-dimethylsulfoximine (DMSI, **13**) (Scheme 5). However, in contrast to sulfones, sulfoximines offer an additional point for substitution, namely the weakly nucleophilic nitrogen atom. To avoid the well-established palladium-catalyzed N-arylation process which yields **14**,[20] the sulfoximine nitrogen would have to be protected (as **15**) for the desired C–H arylation reaction to obtain **16**. Moreover, simple and efficient deprotection of the cross-coupling products **16** should also be feasible, giving easy access to the free (hetero)aryl-substituted DMSI derivatives **17**. Assuming that the acidity of the *S*-methyl protons would be important for the intended α-arylation,[16b] we envisaged utilizing the mandatory N-protecting group to tune the reactivity of the protected DMSI derivatives **15**, since the substituent on the nitrogen atom significantly influences the acidity of the hydrogens at the α-position. Thus, pK_a values in the range of 23–32 (in DMSO) have been reported for various N-substituents.[2b,21] To obtain a first impression of the influence of the pK_a on cross-coupling reactivity, four N-protected DMSI compounds **15a–d** were prepared with protecting groups that differ significantly in their electron-donating/-withdrawing properties. Looking ahead, cleavage of the protecting groups used in **15b–d** to give the corresponding free sulfoximines has, in principle, been demonstrated previously.[22] While the *p*-methoxybenzyl (PMB) group (as in **15a**) is ubiquitous in organic synthesis, it has not been previously employed as a protecting group for sulfoximines.[23]

First, the protected DMSI compounds **15a–d** were subjected to reaction conditions adapted from the method of Walsh and co-workers (Scheme 5).[18] When $Pd(OAc)_2$ and Kwong's ligand with LiO*t*-Bu in toluene at 110 °C were used, all four cross-coupling reactions with bromobenzene failed to provide the desired product. However, when conditions modified from the method of Nambo and Crudden were utilized [$Pd(OAc)_2$, XPhos, LiO*t*-Bu, cyclopentyl methyl ether (CPME), 110 °C],[19] the corresponding cross-coupling product **16a** was formed in 25% yield, whereas the α-arylations with protected sulfoximines **15b–d** failed, with mostly starting material remaining. These results were rather surprising as electron-withdrawing substituents at the sulfoximine nitrogen that increase the C–H acidity at the α-position, such as in protected sulfoximines **15c** and **15d**, were expected to be beneficial for cross-coupling reactivity.[16b] Instead, sulfoximine **15a** with an electron-donating PMB group gave the best result. Since the PMB group should also enable easy deprotection under mild conditions, the palladium-catalyzed direct α-arylation of PMB-protected DMSI **15a** was further explored.

As our preliminary results had also indicated the importance of the ligand, a number of ligands structurally related to XPhos were initially evaluated under comparable reaction conditions (Table 1). *t*-BuXPhos did not efficiently



14 **13** **15** **16** **17**

15a: R^1 = PMB
15b: R^1 = TBDPS
15c: R^1 = Bz
15d: R^1 = Ts

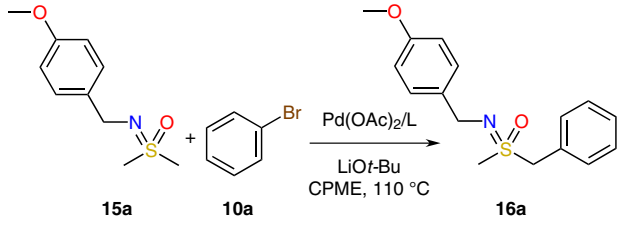
16a: R^1 = PMB; Ar = Ph

17a: Ar = Ph

Scheme 5 Approach for the palladium-catalyzed direct α-arylation of protected DMSI compounds **15** with (hetero)aryl bromides. *Reagents and conditions*: a) For **15a**: **13** (1 equiv), 4-methoxybenzaldehyde (1 equiv), $NaBH(OAc)_3$ (1.5 equiv), DCE, r.t., 16 h, 82%; For **15b**: **13** (1 equiv), TBDPSCl (1.2 equiv), imidazole (3 equiv), DMF, 60 °C, 2 h, 63%; For **15c**: **13** (1 equiv), BzCl (1.1 equiv), DMAP (0.1 equiv), Et_3N (1.2 equiv), CH_2Cl_2, r.t., 3 h, 97%; For **15d**: **13** (1 equiv), TsCl (1.05 equiv), pyridine, r.t., 12 h, 60%; b) Method A (based on that of Walsh and co-workers[18]): **15a–d** (2 equiv), PhBr (**10a**, 1 equiv), $Pd(OAc)_2$ (10 mol%), Kwong's ligand (20 mol%), LiO*t*-Bu (3 equiv), toluene, 110 °C, 16 h; Method B (based on that of Nambo and Crudden[19]): **15a–d** (2 equiv), PhBr (**10a**, 1 equiv), $Pd(OAc)_2$ (10 mol%), XPhos (20 mol%), LiO*t*-Bu (3 equiv), CPME, 110 °C, 16 h; c) **16a** (1 equiv), CAN (2 equiv), $MeCN/H_2O$ (3:1), r.t., 15 min, 80%.

promote the α-arylation of **15a**, whereas SPhos and DavePhos resulted in slightly improved yield of 30% and 33%, respectively (Table 1, entries 2–4). Next, a number of bidentate phosphine ligands were evaluated. With BINAP, a ligand that was successfully used by Bolm and co-workers in an early intramolecular α-arylation reaction of a methylsulfoximine compound,[16a] the desired cross-coupling reaction to **16a** failed (entry 5). The ferrocenyl ligand DTBPF gave little improvement over XPhos; however, with Xantphos the yield jumped to 74% (entries 6, 7). A decreased yield of 55% was obtained with the structurally related *N*-Xantphos, while *t*-BuXantphos failed to promote the desired cross-coupling (entries 8, 9).

Table 1 Optimization of the Ligand for the α-Arylation of PMB-Protected DMSI **15a** with Bromobenzene (**10a**)[a]

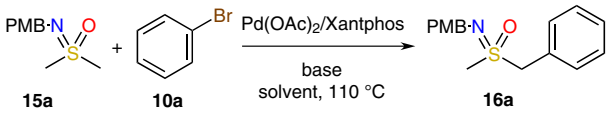


Entry	Ligand	Yield (%)[b]
1	XPhos	25
2	*t*-BuXPhos	<10
3	DavePhos	33
4	SPhos	30
5	*rac*-BINAP	–
6	DTBPF	29
7	Xantphos	74
8	*N*-Xantphos	55
9	*t*-BuXantphos	–

[a] Reaction conditions: **10a** (0.15 mmol, 1 equiv), **15a** (0.30 mmol, 2 equiv), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), LiO*t*-Bu (3 equiv), CPME (1 mL), 110 °C, 16 h, under argon.
[b] Reactions were performed in the presence of 4,4′-di-*tert*-butylbiphenyl (0.025 mmol, 0.167 equiv) as an internal standard. Yields were calculated from the ^{1}H NMR spectra of the reaction crude, by comparison of the methyl signal of product **16a** (δ = 2.71) and the *tert*-butyl signal of the internal standard (δ = 1.37).

Next, three alternative solvents were evaluated using Xantphos as the ligand and LiO*t*-Bu as the base, resulting in yield of 64% and 71% in toluene and 1,4-dioxane, respectively (Table 2, entries 1, 2). In DMF, the coupling product **16a** was obtained in a significantly lower 24% yield (entry 3). The reaction process was also sensitive to water, with the yield of **16a** sharply decreasing when a small quantity of water was added to CPME (Table 1, entry 7 vs Table 2, entry 4). In a screen of four alternative bases, a 51% yield of **16a** was obtained with NaO*t*-Bu, whereas the reaction with KO*t*-Bu failed to proceed (entries 5, 6). With LiHMDS only traces of product were observed, but the use of Cs_2CO_3[16a] resulted in a 44% yield (entries 7, 8). After establishing LiO*t*-Bu as the best base for this coupling, a reduced amount of base was also evaluated; however, 1 or 2 equivalents of LiO*t*-Bu resulted in a decreased yield of 28% and 63%, respectively (entries 9, 10).

Table 2 Optimization of the Solvent and Base for the α-Arylation of PMB-Protected DMSI **15a** with **10a**[a]

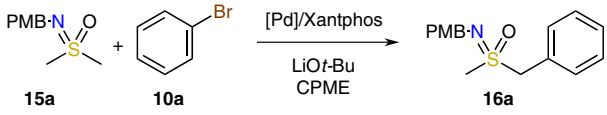


Entry	Solvent	Base	Base (equiv)	Yield (%)[b]
1	toluene	LiO*t*-Bu	3	64
2	1,4-dioxane	LiO*t*-Bu	3	71
3	DMF	LiO*t*-Bu	3	24
4	CPME + H_2O[c]	LiO*t*-Bu	3	<10
5	CPME	NaO*t*-Bu	3	51
6	CPME	KO*t*-Bu	3	–
7	CPME	LiHMDS	3	<10
8	CPME	Cs_2CO_3	3	44
9	CPME	LiO*t*-Bu	1	28
10	CPME	LiO*t*-Bu	2	63

[a] Reaction conditions: **10a** (0.15 mmol, 1 equiv), **15a** (0.30 mmol, 2 equiv), $Pd(OAc)_2$ (10 mol%), Xantphos (20 mol%), base (3 equiv), solvent (1 mL), 110 °C, 16 h, under argon.
[b] Reactions were performed in the presence of 4,4′-di-*tert*-butylbiphenyl (0.025 mmol, 0.167 equiv) as an internal standard. Yields were calculated from the ^{1}H NMR spectra of the reaction crude, by comparison of the methyl signal of product **16a** (δ = 2.71) and the *tert*-butyl signal of the internal standard (δ = 1.37).
[c] Addition of 0.02 mL of H_2O.

Employing an excess of PMB-protected DMSI **15a** is beneficial: when the reaction was conducted with a 3:1 ratio of **15a**/**10a** instead of 1:1, the yield of product **16a** increased from 50% to 80% (Table 3, entries 1, 2). An excess of **15a** probably minimizes the formation of diarylation products.[24] As PMB-protected DMSI **15a** is easily prepared in only one step from commercial DMSI (**13**), the subsequent cross-coupling reactions were performed with a 3:1 ratio of **15a**/**10a**. Altering the $Pd(OAc)_2$/Xantphos ratio from 1:2 to 1:1 resulted in a lower yield of **16a** (58%; entry 3). Use of a 1:2 ratio of $PdCl_2$/Xantphos provided a yield of 79%, whereas $Pd_2(dba)_3$/Xantphos (1:2) gave product **16a** in only 51% yield (entries 4, 5). $Pd(OAc)_2$/Xantphos (1:2) and a reduced 5 mol% palladium loading still resulted in 76% yield; however, upon further reduction to 2 mol% there was incomplete reaction and only a 43% yield of **16a** (entries 6, 7). Conducting the reaction with a 5 mol% palladium loading at only 90 °C was not beneficial, but a good yield of **16a** (78%)

Table 3 Optimization of the Reaction Stoichiometry, Catalyst Parameters, and Reaction Conditions for the α-Arylation of PMB-Protected DMSI **15a** with **10a**[a]



15a **10a** **16a**

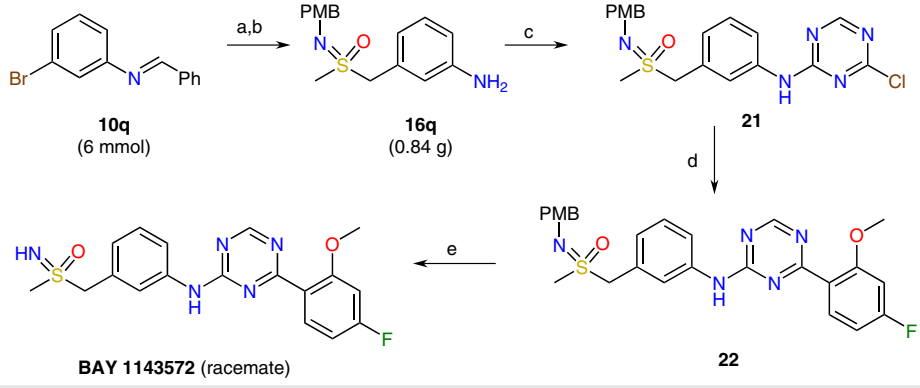
Entry	Ratio **15a**/**10a**	Ratio Pd/Xantphos	Pd source	Pd load (mol%)	Temp (°C)	[**10a**] (mmol/mL)	Yield (%)[b]
1	1:1	1:2	$Pd(OAc)_2$	10	110	0.15	50
2	3:1	1:2	$Pd(OAc)_2$	10	110	0.15	80
3	3:1	1:1	$Pd(OAc)_2$	10	110	0.15	58
4	3:1	1:2	$PdCl_2$	10	110	0.15	79
5	3:1	1:2	$Pd_2(dba)_3$	5	110	0.15	51
6	3:1	1:2	$Pd(OAc)_2$	5	110	0.15	76
7	3:1	1:2	$Pd(OAc)_2$	2	110	0.15	43
8	3:1	1:2	$Pd(OAc)_2$	5	90	0.15	31
9	3:1	1:2	$Pd(OAc)_2$	5	110	0.25	78

[a] Reaction conditions: **10a** (0.15 mmol), **15a**, Pd source, Xantphos, LiO*t*-Bu (3 equiv), CPME, temperature as given, 16 h, under argon.
[b] Reactions were performed in the presence of 4,4′-di-*tert*-butylbiphenyl (0.025 mmol, 0.167 equiv) as an internal standard. Yields were calculated from the ^{1}H NMR spectra of the reaction crude, by comparison of the methyl signal of product **16a** (δ = 2.71) and the *tert*-butyl signal of the internal standard (δ = 1.37).

was observed when employing 5 mol% of $Pd(OAc)_2$ and increasing the concentration of **10a** from 0.15 M to 0.25 M (entries 8, 9).

With the optimized conditions in hand, the scalability of the direct α-arylation of **15a** was evaluated by performing the cross-coupling reaction with bromobenzene (**10a**) on a 5.3 mmol scale (0.84 g). With 5 mol% $Pd(OAc)_2$, 10 mol% Xantphos, 3 equivalents of **15a**, and 3 equivalents of LiO*t*-Bu in a 0.25 M solution of **10a** in CPME at 110 °C for 7 hours, the desired α-arylation product **16a** was isolated in 76% yield (NMR yield: 75%). Furthermore, 8.1 mmol of **15a** was recovered with a purity of 97% and used in additional reactions.

Deprotection of the cross-coupling products **16** to yield the unprotected (hetero)aryl-substituted DMSI derivatives **17** (Scheme 5) was envisaged as being crucial for the applicability of this new α-arylation process. Gratifyingly, cleavage of the PMB group in **16a** using 2 equivalents of ammonium cerium(IV) nitrate (CAN) in acetonitrile and water (3:1) at room temperature gave the desired free sulfoximine product **17a** in 80% isolated yield. To our knowledge, the PMB group has not been previously utilized as a protecting group in sulfoximine chemistry, but our results clearly demonstrate its effectiveness: the PMB moiety can be easily introduced, has high stability under basic condi-



10q (6 mmol) **16q** (0.84 g) **21** **22** **BAY 1143572** (racemate)

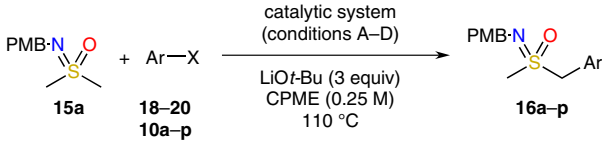
Scheme 6 Synthesis of PTEFb inhibitor BAY 1143572 in racemic form based on the direct α-arylation of PMB-protected DMSI **15a**. *Reagents and conditions*: a) **15a** (3 equiv), XantPhos Pd G3 (3 mol%), Xantphos (3 mol%), LiO*t*-Bu (3 equiv), CPME (0.25 M), 110 °C, 3 h; b) 0.5 M HCl, r.t., 45 min, 46% over two steps; c) 2,4-dichloro-1,3,5-triazine (1.1 equiv), DIPEA (2 equiv), THF/*i*-PrOH (1:1), 0 °C, 30 min, 97%; d) 4-fluoro-2-methoxyphenylboronic acid (1.5 equiv), $Pd(PPh_3)_4$ (5 mol%), aq 2 M K_2CO_3 (2 equiv), DME, 85 °C, MW, 5 h, 40%; e) CAN (2.5 equiv), $MeCN/H_2O$ (3:1), r.t., 1 h, 95%.

tions and elevated temperatures, and can be simply and efficiently removed.

After these successes with both scalability and deprotection, the scope of the (hetero)aryl substrates in the α-arylation of **15a** was explored (Table 4), employing the conditions from our scale-up experiment. With iodobenzene (**18**) and phenyl triflate (**19**), product **16a** was obtained in 59% and 23% yield, respectively, whereas the cross-coupling reaction with chlorobenzene (**20**) failed (Table 4, entries 1–3). Then, a broad range of (hetero)aryl bromides was evaluated, which disappointingly resulted in unsatisfactory yields for a number of substrates. Therefore, we opted to evaluate the use of XantPhos Pd G3 precatalyst instead of $Pd(OAc)_2$ to ensure efficient generation of the active catalyst species, which is often pivotal to the success of a cross-coupling reaction.[25] Although this switch to the precatalyst gave a comparable yield for our model reaction to product **16a** (entry 4), superior yields were indeed mostly obtained for other substrates. XantPhos Pd G3 precatalyst was therefore used to explore the scope of the α-arylation reaction, usually affording good to moderate yields of products **16a–p** (entries 4–19). The addition of an extra 3 mol% of Xantphos was necessary to obtain full conversion, although in a few cases it was not essential (entries 9, 11, 19). In general, electron-donating and electron-withdrawing substituents are compatible with the reaction, but *para*- and *meta*-substituted bromobenzenes resulted in better yields than the corresponding *ortho*-substrates (entries 4–16). The use of an increased palladium loading (10 mol%) was beneficial for formation of the *ortho*-fluoro derivative **16d**, but not for the more sterically hindered *ortho*-methyl compound **16g** (entries 7, 10). Interestingly, even a vinyl substituent is tolerated (entry 16). Moreover, 3-bromopyridine, 3-bromoquinoline, and 2-bromonaphthalene are compatible in this process, yielding the corresponding α-arylation products **16n–p** (entries 17–19). In some reactions, the formation of a side product in various amounts was observed, which was finally isolated and, to our surprise, identified as α-phenyl-substituted sulfoximine **16a**. After ruling out contamination, the only rational explanation for the formation of **16a** in these reactions is that a phenyl group from the phosphine ligand Xantphos is incorporated into the coupling product.[26]

Our new methodology was then successfully applied to an improved synthesis of PTEFb inhibitor BAY 1143572. Direct α-arylation of **15a** with 3-bromo-*N*-[(*E*)-phenylmethylidene]aniline (**10q**) on a 6 mmol scale, followed by hydrolysis of the imine moiety by addition of HCl to the crude coupling product, yielded the desired aniline **16q** in 46% isolated yield and only two steps, which compares favorably to the previous route (Scheme 2).[15] Aniline **16q** was then coupled with the commercial 2,4-dichloro-1,3,5-triazine to give chloride **21**, which was employed in a subsequent Suzuki reaction to yield **22** (Scheme 6). Finally, removal of the PMB group using CAN cleanly afforded the desired PTEFb inhibitor BAY 1143572 in racemic form.[27]

Table 4 Substrate Scope of the α-Arylation of **15a** with (Hetero)aryl Halides **10a–p**, **18**, **20**, and Triflate **19**[a]



Entry	ArX	Conditions[b]	Product	Time (h)	Yield (%)[c]
1	PhI (**18**)	A	**16a**	8	(59)
2	PhOTf (**19**)	A	**16a**	8	(23)
3	PhCl (**20**)	A	**16a**	8	n.r.
4	PhBr (**10a**)	A B	**16a** **16a**	16 6	78 75
5	4-FC_6H_4Br (**10b**)	B	**16b**	16	69
6	3-FC_6H_4Br (**10c**)	B	**16c**	4	62
7	2-FC_6H_4Br (**10d**)	B D	**16d** **16d**	24 24	9 34
8	4-MeC_6H_4Br (**10e**)	B	**16e**	4	54
9	3-MeC_6H_4Br (**10f**)	C	**16f**	3	67
10	2-MeC_6H_4Br (**10g**)	B D	**16g** **16g**	24 24	7 8
11	3,5-$Me_2C_6H_3Br$ (**10h**)	C	**16h**	5	73
12	3-$MeOC_6H_4Br$ (**10i**)	B	**16i**	5	49
13	3-ClC_6H_4Br (**10j**)	B	**16j**	10	62
14	3-NCC_6H_4Br (**10k**)	B	**16k**	24	38
15	4-$F_3CC_6H_4Br$ (**10l**)	B	**16l**	6	37
16	3-$(H_2C{=}CH)C_6H_4Br$ (**10m**)	B	**16m**	12	39
17	3-bromopyridine (**10n**)	B	**16n**	4	44
18	3-bromoquinoline (**10o**)	B	**16o**	5	48
19	2-bromonaphthalene (**10p**)	C	**16p**	6	54

[a] Reaction conditions: ArX (0.25 mmol, 1 equiv), **15a** (3 equiv), Pd source, ligand, LiO*t*-Bu (3 equiv), CPME (1.0 mL), 110 °C, under argon. Reactions were performed in the presence of 4,4′-di-*tert*-butylbiphenyl (0.042 mmol, 0.167 equiv) as an internal standard.
[b] Conditions A: $Pd(OAc)_2$ (5 mol%), Xantphos (10 mol%); Conditions B: XantPhos Pd G3 (3 mol%), Xantphos (3 mol%); Conditions C: XantPhos Pd G3 (3 mol%); Conditions D: XantPhos Pd G3 (10 mol%), Xantphos (10 mol%).
[c] Isolated yields. For entries 1 and 2, calculated yields in parentheses. n.r. = No reaction.

In summary, we have developed the first intermolecular direct α-arylation of PMB-protected DMSI **15a** with (hetero)aryl bromides. This palladium-catalyzed process provides a safe, short, and efficient approach to (hetero)aryl-substituted DMSI derivatives, which have recently drawn considerable attention in the life sciences due to their successful application as pharmacophores in biologically active molecules. With this new method, the often tedious, traditional sequential oxidation/imination or imi-

nation/oxidation procedures starting from thioethers can be avoided. A broad range of substrates and functional groups common in the life sciences were tolerated under the optimized conditions, which provided the target products in moderate to good yields. Very high selectivity for the desired monoarylation products was observed. Furthermore, the PMB group proved to be a versatile protecting group in sulfoximine chemistry that can be easily introduced, has high stability under basic conditions and elevated temperatures, and can be conveniently removed with CAN. We are currently investigating the regioselectivity of the palladium-catalyzed α-arylation of unsymmetrical *S*,*S*-dialkylsulfoximines as well as the stereoselectivity of this new process in the presence of chiral ligands or chiral benzyl protecting groups.

Commercially available reagents and anhyd solvents were purchased from Alfa Aesar, abcr, Acros Organics, Merck, and Sigma-Aldrich, and were used without further purification. Reactions were carried out under argon in microwave reaction vials (Biotage®) placed in a steel heating block. Reactions were monitored by UPLC analysis with a Waters Acquity UPLC MS Single Quad system; column: Acquity UPLC BEH C18 1.7 µm, 50 × 2.1 mm; eluent A: H_2O + 0.2 vol% aq NH_3 (32%), eluent B: MeCN; gradient: 0–1.6 min 1–99% B, 1.6–2.0 min 99% B; flow: 0.8 mL/min; temperature: 60 °C; DAD scan: 210–400 nm. Flash chromatography was carried out using a Biotage® Isolera™ One system with 200–400 nm variable detector, using Biotage® SNAP KP-Sil cartridges. Preparative HPLC was carried out with a Waters AutoPurification MS Single Quad system; column: Waters XBridge C18 5 µm, 100 × 30 mm; eluent A: H_2O + 0.2 vol% aq NH_3 (32%), eluent B: MeCN; gradient: 0–5.5 min 5–100% B; flow: 70 mL/min; temperature: 25 °C; DAD scan: 210–400 nm. Analytical TLC was carried out on aluminum-backed plates coated with Merck Kieselgel 60 F_{254}, with visualization under UV light at 254 nm. All NMR spectra were recorded on Bruker Avance III HD spectrometers. ^{1}H NMR spectra were obtained at 400 MHz and referenced to the residual solvent signal (7.26 ppm for $CDCl_3$). ^{13}C NMR spectra were obtained at 101 MHz and also referenced to the residual solvent signal (77.16 ppm for $CDCl_3$). All spectra were obtained at ambient temperature (22 ± 1 °C). Data are reported as follows: chemical shift (δ) in ppm, multiplicity (standard abbreviations), coupling constant(s) (Hz), and integration. Mass spectra were recorded on LC-MS instruments: (i) Waters Acquity UPLC MS Single Quad system; column: Kinetex 2.6 µm, 50 × 2.1 mm, or (ii) Agilent 1290 UPLC MS 6230 TOF system; column: BEH C18 1.7 µm, 50 × 2.1 mm; eluent A: H_2O + 0.05% formic acid (99%), eluent B: MeCN + 0.05% formic acid (99%). Fragment ions are reported as *m*/*z* values with relative intensities (%) in parentheses. High-resolution mass spectra were recorded on a Xevo® G2-XS QTof (Waters) instrument. Melting points were determined with a Büchi B-540 melting point apparatus.

N-(4-Methoxybenzyl)-*S*,*S*-dimethylsulfoximine (15a)

A solution containing *S*,*S*-dimethylsulfoximine (**13**; 2.79 g, 30 mmol) and 4-methoxybenzaldehyde (3.64 mL, 30 mmol) in DCE (20 mL) was stirred at r.t. for 2 h. Then, $NaBH(OAc)_3$ (9.54 g, 45 mmol) was added in one portion and the resulting suspension was stirred at r.t. for 16 h. The reaction mixture was hydrolyzed with sat. aq $NaHCO_3$ (60 mL) and extracted with EtOAc (2 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography (Cartridge: KP-Sil 100 g; eluent: EtOAc, then EtOH) to afford **15a** (5.27 g, 82%) as a white solid; mp 78–79 °C; R_f = 0.06 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.33 (m, 2 H), 6.81–6.90 (m, 2 H), 4.24 (s, 2 H), 3.79 (s, 3 H), 2.98 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.5, 133.4, 128.9, 113.9, 55.3, 46.5, 42.6.

MS (ES$^+$): *m*/*z* (%) = 214 (100, [M$^+$ + 1]), 121 (96), 215 (36), 216 (18), 122 (16).

HRMS (ES$^+$): *m*/*z* [M + H$^+$] calcd for $C_{10}H_{16}NO_2S$: 214.0902; found: 214.0899.

N-(*tert*-Butyldiphenylsilyl)-*S*,*S*-dimethylsulfoximine (15b)

To a solution of *S*,*S*-dimethylsulfoximine (**13**; 512 mg, 5.5 mmol) and imidazole (1.12 g, 16.5 mmol) in anhyd DMF (2.5 mL), cooled to 0 °C, was added TBDPSCl (1.71 mL, 6.6 mmol) dropwise. Then, the reaction mixture was stirred at 60 °C. After 2 h, the batch was cooled to r.t., hydrolyzed with brine (10 mL), and extracted with EtOAc (2 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography (Cartridge: KP-Sil 50 g; eluent: *n*-hexane/EtOAc, 60:40) to afford **15b** (1.14 g, 63%) as a white solid; mp 52–53 °C; R_f = 0.10 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.76 (m, 4 H), 7.33–7.42 (m, 6 H), 2.82 (s, 6 H), 1.06 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.4, 135.7, 129.3, 127.7, 47.2, 27.2, 19.3.

MS (ES$^+$): *m*/*z* (%) = 332 (100, [M$^+$ + 1]), 333 (29), 334 (12).

HRMS (ES$^+$): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{26}NOSSi$: 332.1504; found: 332.1506.

N-Benzoyl-*S*,*S*-dimethylsulfoximine (15c)[28]

A solution of *S*,*S*-dimethylsulfoximine (**13**; 240 mg, 2.6 mmol), benzoyl chloride (0.33 mL, 2.8 mmol), DMAP (31 mg, 0.26 mmol), and Et_3N (0.43 mL, 3.1 mmol) in CH_2Cl_2 (20 mL) was stirred at r.t. for 3 h. The reaction was hydrolyzed with H_2O (10 mL) and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic phases were combined, dried (Na_2SO_4), filtered, and concentrated at 1 mbar. The crude was obtained as a white crystalline solid and was used without further purification (492 mg, 97%); mp 99–102 °C (Lit.[28] mp 106–108 °C); R_f = 0.43 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.16 (m, 2 H), 7.47–7.54 (m, 1 H), 7.38–7.44 (m, 2 H), 3.39 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.3, 135.5, 132.3, 129.4, 128.2, 41.9.

MS (ES$^+$): *m*/*z* (%) = 198 (100, [M$^+$ + 1]), 199 (12).

HRMS (ES$^+$): *m*/*z* [M + H$^+$] calcd for $C_9H_{12}NO_2S$: 198.0589; found: 198.0590.

N-(*p*-Tolylsulfonyl)-*S*,*S*-dimethylsulfoximine (15d)

TsCl (859 mg, 4.5 mmol) was added to a solution of *S*,*S*-dimethylsulfoximine (**13**; 400 mg, 4.3 mmol) in pyridine (4 mL). The resulting suspension was stirred at r.t. for 12 h. Then, the mixture was poured into H_2O and extracted with $CHCl_3$ (3 × 15 mL). The combined organic phases were washed with H_2O, dried (Na_2SO_4), filtered, and concentrated under reduced pressure, affording **15d** (640 mg, 60%) as a white crystalline solid; mp 169–170 °C; R_f = 0.49 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.89 (m, 2 H), 7.27–7.31 (m, 2 H), 3.36 (s, 6 H), 2.41 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.1, 140.5, 129.5, 126.7, 44.3, 21.7.

MS (ES^+): *m*/*z* (%) = 248 (100, [M^+ + 1]), 249 (12), 407 (10).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_9H_{14}NO_3S_2$: 248.0415; found: 248.0419.

(Hetero)arylation of *N*-(4-Methoxybenzyl)-*S*,*S*-dimethylsulfoximine (15a); General Procedures for the Synthesis of Compounds 16

Conditions A: A stirred suspension containing *N*-(4-methoxybenzyl)-*S*,*S*-dimethylsulfoximine (**15a**; 160 mg, 0.75 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), Xantphos (14.5 mg, 0.025 mmol), LiO*t*-Bu (60 mg, 0.75 mmol), 4,4′-di-*tert*-butylbiphenyl as an internal standard (11.1 mg, 0.042 mmol), and the corresponding aryl bromide **10** (0.25 mmol) in anhyd cyclopentyl methyl ether (CPME, 1 mL) was heated under argon at 110 °C until reaction completion. Then, the reaction mixture was cooled to r.t., hydrolyzed with brine (5 mL), and extracted with EtOAc (2 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC using MeCN/H_2O mixtures as the mobile phase (see general information for details).

Conditions B: As for Conditions A, but $Pd(OAc)_2$ was replaced by XantPhos Pd G3 (7.8 mg, 0.008 mmol, 3 mol%), and Xantphos (4.3 mg, 0.008 mmol, 3 mol%) was used.

Conditions C: As for Conditions B, without the addition of Xantphos.

Conditions D: As for Conditions B, but XantPhos Pd G3 (25.8 mg, 0.025 mmol, 10 mol%) and Xantphos (14.4 mg, 0.025 mmol, 10 mol%) were used. For Conditions B–D, strict argon control is necessary.

{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}benzene (16a)

The general procedure was followed (Conditions B) using bromobenzene (**10a**, 26 µL); reaction time: 6 h; white solid (54 mg, 75%).

Gram-Scale Reaction: A stirred suspension containing *N*-(4-methoxybenzyl)-*S*,*S*-dimethylsulfoximine (**15a**; 3.41 g, 16.0 mmol), $Pd(OAc)_2$ (60 mg, 0.27 mmol), Xantphos (308 mg, 0.53 mmol), LiO*t*-Bu (1.28 g, 16.0 mmol), 4,4′-di-*tert*-butylbiphenyl as an internal standard (237 mg, 0.89 mmol), and bromobenzene (**10a**; 0.56 mL, 5.3 mmol) in anhyd CPME (21 mL) was heated at 110 °C for 7 h. Then, the reaction mixture was cooled to r.t., hydrolyzed with brine, and extracted with EtOAc (2 × 30 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography (Cartridge: KP-Sil 100 g; eluent: *n*-hexane/EtOAc, 12% → 100% EtOAc) to afford **16a** (1.18 g, 76%) as a white solid; mp 77–79 °C; R_f = 0.41 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.42 (m, 5 H), 7.28–7.33 (m, 2 H), 6.84–6.88 (m, 2 H), 4.23–4.32 (m, 4 H), 3.79 (s, 3 H), 2.71 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.5, 133.6, 130.7, 129.8, 129.0, 128.9, 128.8, 113.9, 61.1, 55.3, 46.5, 39.2.

MS (ES^+): *m*/*z* (%) = 290 (100, [M^+ + 1]), 291 (20).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{16}H_{20}NO_2S$: 290.1215; found: 290.1215.

1-Fluoro-4-{[*N*-(4-methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}benzene (16b)

The general procedure was followed (Conditions B) using 1-bromo-4-fluorobenzene (**10b**; 27 µL); reaction time: 16 h; white solid (53 mg, 69%); mp 74–76 °C; R_f = 0.40 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.38 (m, 2 H), 7.24–7.31 (m, 2 H), 7.03–7.11 (m, 2 H), 6.82–6.89 (m, 2 H), 4.19–4.30 (m, 4 H), 3.79 (s, 3 H), 2.71 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.1 (d, *J* = 248.8 Hz), 158.6, 133.5, 132.6 (d, *J* = 8.5 Hz), 129.0, 125.5 (d, *J* = 3.4 Hz), 116.1 (d, *J* = 21.6 Hz), 113.9, 60.5, 55.4, 46.5, 39.3.

MS (ES^+): *m*/*z* (%) = 308 (100, [M^+ + 1]), 309 (24), 121 (13).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{16}H_{19}FNO_2S$: 308.1121; found: 308.1126.

1-Fluoro-3-{[*N*-(4-methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}benzene (16c)

The general procedure was followed (Conditions B) using 1-bromo-3-fluorobenzene (**10c**; 27 µL); reaction time: 4 h; white solid (48 mg, 62%); mp 51–53 °C; R_f = 0.45 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (td, *J* = 7.8, 6.0 Hz, 1 H), 7.29 (d, *J* = 8.6 Hz, 2 H), 7.14 (d, *J* = 7.6 Hz, 1 H), 7.03–7.12 (m, 2 H), 6.84–6.88 (m, 2 H), 4.18–4.33 (m, 4 H), 3.79 (s, 3 H), 2.73 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.9 (d, *J* = 247.5 Hz), 158.6, 133.5, 132.2 (d, *J* = 7.6 Hz), 130.6 (d, *J* = 8.5 Hz), 129.0, 126.5 (d, *J* = 3.4 Hz), 117.8 (d, *J* = 22.0 Hz), 115.9 (d, *J* = 21.2 Hz), 114.0, 60.8 (d, *J* = 1.7 Hz), 55.4, 46.5, 39.6.

MS (ES^+): *m*/*z* (%) = 308 (100, [M^+ + 1]), 309 (27), 121 (22).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{16}H_{19}FNO_2S$: 308.1121; found: 308.1123.

1-Fluoro-2-{[*N*-(4-methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}benzene (16d)

The general procedure was followed (Conditions D) using 1-bromo-2-fluorobenzene (**10d**; 27 µL); reaction time: 24 h; colorless oil (26 mg, 34%); R_f = 0.53 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.42 (m, 2 H), 7.27–7.32 (m, 2 H), 7.15–7.21 (m, 1 H), 7.08–7.14 (m, 1 H), 6.83–6.89 (m, 2 H), 4.24–4.39 (m, 4 H), 3.79 (s, 3 H), 2.79 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.0 (d, *J* = 248.0 Hz), 158.6, 133.6, 133.1 (d, *J* = 3.0 Hz), 130.9 (d, *J* = 8.5 Hz), 129.0, 124.9 (d, *J* = 3.8 Hz), 117.6 (d, *J* = 14.8 Hz), 115.8 (d, *J* = 21.6 Hz), 113.9, 55.4, 53.9 (d, *J* = 3.0 Hz), 46.5, 39.6 (d, *J* = 3.0 Hz).

MS (ES^+): *m*/*z* (%) = 308 (100, [M^+ + 1]), 309 (20).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{16}H_{19}FNO_2S$: 308.1121; found: 308.1119.

1-{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}-4-methylbenzene (16e)

The general procedure was followed (Conditions B) using 4-bromotoluene (**10e**; 43 mg); reaction time: 4 h; white solid (41 mg, 54%); mp 81–83 °C; R_f = 0.45 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.9 Hz, 2 H), 7.22–7.27 (m, 2 H), 7.16–7.21 (m, 2 H), 6.83–6.88 (m, 2 H), 4.21–4.32 (m, 4 H), 3.79 (s, 3 H), 2.69 (s, 3 H), 2.36 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 138.9, 133.8, 130.7, 129.8, 129.0, 126.8, 113.9, 61.0, 55.4, 46.6, 39.1, 21.4.

MS (ES^+): *m*/*z* (%) = 304 (100, [M^+ + 1]), 121 (52), 305 (45), 306 (17).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{17}H_{22}NO_2S$: 304.1371; found: 304.1373.

1-{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}-3-methylbenzene (16f)

The general procedure was followed (Conditions C) using 3-bromotoluene (**10f**; 30 µL); reaction time: 3 h; white solid (51 mg, 67%); mp 63–65 °C; R_f = 0.45 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.33 (m, 3 H), 7.13–7.20 (m, 3 H), 6.83–6.89 (m, 2 H), 4.23–4.32 (m, 4 H), 3.79 (s, 3 H), 2.71 (s, 3 H), 2.35 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 138.9, 133.8, 131.5, 129.8, 129.6, 129.0, 128.9, 127.8, 113.9, 61.2, 55.4, 46.6, 39.3, 21.5.

MS (ES^+): *m*/*z* (%) = 304 (100, [M^+ + 1]), 305 (36), 306 (11).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{17}H_{22}NO_2S$: 304.1371; found: 304.1371.

1-{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}-2-methylbenzene (16g)

The general procedure was followed (Conditions D) using 2-bromotoluene (**10g**; 30 µL); reaction time: 24 h; white solid (6 mg, 8%); mp 70–73 °C; R_f = 0.42 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.38 (m, 6 H), 6.84–6.88 (m, 2 H), 4.41 (d, *J* = 13.9 Hz, 1 H), 4.23–4.32 (m, 3 H), 3.79 (s, 3 H), 2.75 (s, 3 H), 2.45 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 138.2, 133.9, 131.8, 131.2, 129.1, 128.9, 128.2, 126.5, 113.9, 59.0, 55.4, 46.6, 39.5, 20.2.

MS (ES^+): *m*/*z* (%) = 304 (100, [M^+ + 1]), 305 (26), 121 (9).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{17}H_{22}NO_2S$: 304.1371; found: 304.1371.

1-{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}-3,5-dimethylbenzene (16h)

The general procedure was followed (Conditions C) using 5-bromo-*m*-xylene (**10h**; 34 µL); reaction time: 5 h; colorless oil (58 mg, 73%); R_f = 0.48 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.6 Hz, 2 H), 6.92–7.02 (m, 3 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 4.16–4.34 (m, 4 H), 3.79 (s, 3 H), 2.71 (s, 3 H), 2.30 (s, 2 × 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.5, 138.6, 133.8, 130.5, 129.6, 128.9, 128.5, 113.9, 61.0, 55.4, 46.5, 39.2, 21.3.

MS (ES^+): *m*/*z* (%) = 318 (100, [M^+ + 1]), 320 (29), 294 (23), 293 (20).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{18}H_{24}NO_2S$: 318.1522; found: 318.1527.

1-Methoxy-3-{[*N*-(4-methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}benzene (16i)

The general procedure was followed (Conditions B) using 3-bromoanisole (**10i**; 32 µL); reaction time: 5 h; colorless oil (39 mg, 49%); R_f = 0.45 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.33 (m, 3 H), 6.88–6.96 (m, 3 H), 6.83–6.88 (m, 2 H), 4.21–4.35 (m, 4 H), 3.79 (s, 2 × 3 H), 2.72 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0, 158.6, 133.7, 131.3, 130.0, 129.0, 123.0, 116.2, 114.5, 113.9, 61.2, 55.4 (2 ×), 46.6, 39.3.

MS (ES^+): *m*/*z* (%) = 320 (100, [M^+ + 1]), 321 (46), 322 (16).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{17}H_{22}NO_3S$: 320.1320; found: 320.1317.

1-Chloro-3-{[*N*-(4-methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}benzene (16j)

The general procedure was followed (Conditions B) using 1-bromo-3-chlorobenzene (**10j**; 29 µL); reaction time: 10 h; white solid (50 mg, 62%); mp 68–70 °C; R_f = 0.43 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.38 (m, 6 H), 6.83–6.89 (m, 2 H), 4.24–4.31 (m, 2 H), 4.17–4.24 (m, 2 H), 3.79 (s, 3 H), 2.74 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 134.9, 133.5, 131.8, 130.8, 130.3, 129.1, 129.0, 128.9, 114.0, 60.7, 55.4, 46.6, 39.6.

MS (ES^+): *m*/*z* (%) = 324 (100, [M^+ + 1]), 326 (49), 325 (25), 121 (21).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{16}H_{19}ClNO_2S$: 324.0825; found: 324.0821.

3-{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}benzonitrile (16k)

The general procedure was followed (Conditions B) using 3-bromobenzonitrile (**10k**; 46 mg); reaction time: 24 h; white solid (30 mg, 38%); mp 104–106 °C; R_f = 0.33 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.68 (m, 1 H), 7.57–7.63 (m, 2 H), 7.46–7.53 (m, 1 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 6.82–6.90 (m, 2 H), 4.18–4.33 (m, 4 H), 3.79 (s, 3 H), 2.75 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.7, 135.1, 134.2, 133.3, 132.4, 131.5, 129.8, 128.9, 118.2, 114.0, 113.3, 60.6, 55.4, 46.5, 39.9.

MS (ES^+): *m*/*z* (%) = 315 (100, [M^+ + 1]), 121 (93), 316 (42), 317 (16), 290 (14), 122 (11).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{17}H_{19}N_2O_2S$: 315.1167; found: 315.1163.

1-{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}-4-(trifluoromethyl)benzene (16l)

The general procedure was followed (Conditions B) using 4-bromobenzotrifluoride (**10l**; 35 µL); reaction time: 6 h; white solid (33 mg, 37%); mp 83–85 °C; R_f = 0.44 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.1 Hz, 2 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 7.24–7.32 (m, 2 H), 6.82–6.89 (m, 2 H), 4.21–4.37 (m, 4 H), 3.79 (s, 3 H), 2.74 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.7, 133.9 (d, *J* = 1.3 Hz), 133.4, 131.1, 131.1 (q, *J* = 32.6 Hz), 128.9, 125.9 (q, *J* = 3.5 Hz), 124.0 (q, *J* = 272.1 Hz), 113.9, 60.8, 55.4, 46.5, 39.7.

MS (ES^+): *m*/*z* (%) = 358 (100, [M^+ + 1]), 121 (23), 359 (23).

HRMS (ES^+): *m*/*z* [M + H^+] calcd for $C_{17}H_{19}F_3NO_2S$: 358.1089; found: 358.1084.

1-{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}-3-vinylbenzene (16m)

The general procedure was followed (Conditions B) using 3-bromostyrene (**10m**; 33 µL); reaction time: 12 h; white solid (31 mg, 39%); mp 56–58 °C; R_f = 0.41 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.44 (m, 2 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 7.28–7.32 (m, 2 H), 7.23–7.28 (m, 1 H), 6.83–6.88 (m, 2 H), 6.69 (dd, *J* = 17.7, 10.9 Hz, 1 H), 5.76 (d, *J* = 17.7 Hz, 1 H), 5.29 (d, *J* = 10.9 Hz, 1 H), 4.23–4.33 (m, 4 H), 3.79 (s, 3 H), 2.72 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 138.4, 136.2, 133.7, 130.2, 130.0, 129.2, 128.9, 128.7, 126.6, 115.0, 113.9, 61.1, 55.4, 46.5, 39.3.

MS (ES^+): *m*/*z* (%) = 316 (100, [M^+ + 1]), 317 (24).

HRMS (ES$^+$): m/z [M + H$^+$] calcd for $C_{18}H_{22}NO_2S$: 316.1371; found: 316.1368.

3-{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}pyridine (16n)

The general procedure was followed (Conditions B) using 3-bromopyridine (**10n**; 24 µL); reaction time: 4 h; colorless oil (32 mg, 44%); R_f = 0.50 (CH_2Cl_2/MeOH, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (dd, J = 4.8, 1.3 Hz, 1 H), 8.57 (d, J = 1.5 Hz, 1 H), 7.74 (d, J = 7.9 Hz, 1 H), 7.32 (dd, J = 7.9, 4.8 Hz, 1 H), 7.24–7.29 (m, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 4.19–4.31 (m, 4 H), 3.78 (s, 3 H), 2.74 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 151.3, 150.1, 138.2, 133.4, 128.9, 126.1, 123.8, 114.0, 58.5, 55.4, 46.5, 39.6.

MS (ES$^+$): m/z (%) = 291 (100, [M$^+$ + 1]), 121 (60), 171 (42), 292 (33), 293 (12).

HRMS (ES$^+$): m/z [M + H$^+$] calcd for $C_{15}H_{19}N_2O_2S$: 291.1167; found: 291.1168.

3-{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}quinoline (16o)

The general procedure was followed (Conditions B) using 3-bromoquinoline (**10o**; 34 µL), reaction time: 5 h; yellow oil (41 mg, 48%); R_f = 0.31 (CH_2Cl_2/MeOH, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (d, J = 2.3 Hz, 1 H), 8.08–8.17 (m, 2 H), 7.79 (d, J = 8.1 Hz, 1 H), 7.75 (ddd, J = 8.4, 7.0, 1.5 Hz, 1 H), 7.55–7.62 (m, 1 H), 7.24–7.32 (m, 2 H), 6.80–6.88 (m, 2 H), 4.46 (d, J = 13.7 Hz, 1 H), 4.40 (d, J = 13.9 Hz, 1 H), 4.28 (s, 2 H), 3.78 (s, 3 H), 2.73–2.81 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 151.7, 148.0, 138.1, 133.4, 130.4, 129.4, 128.9, 128.0, 127.7, 127.4, 123.0, 114.0, 58.7, 55.4, 46.6, 39.8.

MS (ES$^+$): m/z (%) = 341 (100, [M$^+$ + 1]), 221 (31), 121 (25), 342 (23), 158 (22).

HRMS (ES$^+$): m/z [M + H$^+$] calcd for $C_{19}H_{21}N_2O_2S$: 341.1318; found: 341.1290.

2-{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}naphthalene (16p)

The general procedure was followed (Conditions C) using 2-bromonaphthalene (**10p**; 52 mg); reaction time: 6 h; white solid (34 mg, 54%); mp 94–96 °C; R_f = 0.40 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.89 (m, 4 H), 7.47–7.55 (m, 3 H), 7.32 (d, J = 8.6 Hz, 2 H), 6.82–6.90 (m, 2 H), 4.41–4.48 (m, 2 H), 4.28–4.36 (m, 2 H), 3.79 (s, 3 H), 2.73 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 133.7, 133.3, 133.2, 130.3, 129.0, 128.8, 128.0, 127.9, 127.9, 127.3, 126.8, 126.7, 113.9, 61.4, 55.4, 46.6, 39.3.

MS (ES$^+$): m/z (%) = 340 (100, [M$^+$ + 1]), 121 (76), 341 (61), 141 (33), 342 (27), 680 (22), 276 (13).

HRMS (ES$^+$): m/z [M + H$^+$] calcd for $C_{20}H_{22}NO_2S$: 340.1371; found: 340.1371.

[(*S*-Methylsulfonimidoyl)methyl]benzene (17a);[29] Typical Procedure for the Deprotection of *N*-(4-Methoxybenzyl)-Protected Sulfoximines 16

CAN (1.1 g, 2 mmol) was added to a solution of **16a** (289 mg, 1 mmol) in MeCN/H_2O (3:1, 4 mL). The resulting yellow solution was stirred at r.t. for 15 min. Then, sat. aq $NaHCO_3$ (5 mL) was added and the mixture was extracted with EtOAc (4 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography (Cartridge: KP-Sil 10 g; eluent: EtOAc/EtOH, 0 → 100% EtOH) to afford **17a** (135 mg, 80%) as a white solid; mp 80–84 °C; R_f = 0.10 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.46 (m, 5 H), 4.39 (d, J = 12.9 Hz, 1 H), 4.25 (d, J = 13.7 Hz, 1 H), 2.92 (s, 3 H), 2.60 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 130.9, 129.2, 129.1, 128.6, 64.1, 41.5.

MS (ES$^+$): m/z (%) = 170 (100, [M$^+$ + 1]), 106 (13), 171 (10).

HRMS (ES$^+$): m/z [M + H$^+$] calcd for $C_8H_{12}NOS$: 170.0640; found: 170.0638.

Synthesis of BAY 1143572

3-{[*N*-(4-Methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}aniline (16q)

A stirred suspension containing *N*-(4-methoxybenzyl)-*S*,*S*-dimethylsulfoximine (**15a**; 3.84 g, 18 mmol), XantPhos Pd G3 (186 mg, 0.18 mmol), Xantphos (104 mg, 0.18 mmol), LiO*t*-Bu (1.44 g, 18 mmol), 4,4′-di-*tert*-butylbiphenyl as an internal standard (267 mg, 1.0 mmol), and 3-bromo-*N*-[(*E*)-phenylmethylidene]aniline (**10q**; 1.56 g, 6 mmol) in anhyd CPME (24 mL) was heated at 110 °C for 3 h in a 100 mL round-bottom flask equipped with a reflux condenser. Then, the reaction mixture was cooled to r.t., hydrolyzed with brine (30 mL), and extracted with EtOAc (2 × 60 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude was dissolved in EtOAc (30 mL), HCl (0.5 M, 24 mL) was added, and the biphasic mixture was vigorously stirred for 45 min. The aqueous phase was separated, basified with sat. aq $NaHCO_3$, and then extracted with EtOAc (2 × 20 mL). These new organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude by column chromatography (Cartridge: KP-NH 55 g; eluent: EtOAc) afforded **16q** (840 mg, 46%) as a colorless oil; R_f = 0.19 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.32 (m, 2 H), 7.10–7.14 (m, 1 H), 6.83–6.87 (m, 2 H), 6.71 (d, J = 7.4 Hz, 1 H), 6.63–6.69 (m, 2 H), 4.30 (d, J = 13.9 Hz, 1 H), 4.26 (d, J = 13.9 Hz, 1 H), 4.17 (s, 2 H), 3.77 (s, 3 H), 3.67 (br s, 2 H), 2.70 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.4, 147.1, 133.7, 130.7, 129.8, 128.9, 120.5, 117.0, 115.3, 113.8, 61.0, 55.3, 46.4, 39.1.

MS (ES$^+$): m/z (%) = 305 (100, [M$^+$ + 1]), 306 (28), 121 (11), 307 (10).

HRMS (ES$^+$): m/z [M + H$^+$] calcd for $C_{16}H_{21}N_2O_2S$: 305.1324; found: 305.1326.

4-Chloro-*N*-(3-{[*N*-(4-methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}phenyl)-1,3,5-triazin-2-amine (21)

2,4-Dichloro-1,3,5-triazine (69 mg, 0.46 mmol) was dissolved in THF/*i*-PrOH (1:1, 2 mL) and the solution was cooled to 0 °C. Then, DIPEA (0.14 mL, 0.84 mmol) and a solution containing **16q** (128 mg, 0.42 mmol) in THF/*i*-PrOH (1:1, 2 mL) were added sequentially. The resulting solution was stirred at 0 °C for 30 min. Volatiles were re-

moved under reduced pressure and the crude was purified by column chromatography (EtOAc) to give **21** (170 mg, 97%) as a colorless oil; R_f = 0.27 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1 H), 8.15 (br d, *J* = 22.8 Hz, 1 H), 7.58 (br d, *J* = 8.1 Hz, 1 H), 7.56 (s, 1 H), 7.30–7.40 (m, 1 H), 7.27 (d, *J* = 8.6 Hz, 2 H), 7.14 (d, *J* = 7.6 Hz, 1 H), 6.79–6.86 (m, 2 H), 4.25–4.36 (m, 4 H), 3.77 (s, 3 H), 2.85 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 167.3, 163.9, 158.6, 137.3, 133.5, 130.8, 129.6, 128.9, 127.1, 123.4, 121.3, 113.9, 60.9, 55.4, 46.5, 39.5.

MS (ES^+): *m*/*z* (%) = 418 (100, $[M^+ + 1]$), 420 (72).

HRMS (ES^+): *m*/*z* $[M + H^+]$ calcd for $C_{19}H_{21}ClN_5O_2S$: 418.1104; found: 418.1101.

4-(4-Fluoro-2-methoxyphenyl)-*N*-(3-{[*N*-(4-methoxybenzyl)-*S*-methylsulfonimidoyl]methyl}phenyl)-1,3,5-triazin-2-amine (22)

A mixture containing chloride **21** (167 mg, 0.40 mmol), 4-fluoro-2-methoxyphenylboronic acid (102 mg, 0.6 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), and aq 2 M K_2CO_3 (0.4 mL) in DME (2 mL) was heated under microwave irradiation (Biotage® Initiator Classic, 60 W, 85 °C) for 5 h. The resulting solution was poured into sat. aq $NaHCO_3$ (10 mL) and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude was purified by column chromatography (Cartridge: KP-Sil 10 g; eluent: CH_2Cl_2/MeOH, 95:5) to afford **22** (82 mg, 40%) as a colorless oil; R_f = 0.31 (CH_2Cl_2/MeOH, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (s, 1 H), 7.93 (br s, 1 H), 7.65 (br s, 1 H), 7.60 (s, 1 H), 7.37 (t, *J* = 7.9 Hz, 1 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 7.11 (d, *J* = 7.4 Hz, 1 H), 6.81–6.88 (m, 2 H), 6.70–6.80 (m, 2 H), 4.23–4.33 (m, 4 H), 3.92 (s, 3 H), 3.77 (s, 3 H), 2.75 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.1, 166.4, 165.7 (d, *J* = 252.2 Hz), 163.6, 160.4, 158.6, 138.5, 133.6, 130.8, 129.7, 128.9, 126.2, 122.6, 122.1 (d, *J* = 3.4 Hz), 120.7, 113.9, 107.7 (d, *J* = 21.6 Hz), 100.3 (d, *J* = 25.9 Hz), 61.1, 56.4, 55.4, 46.6, 39.5.

MS (ES^+): *m*/*z* (%) = 508 (16, $[M^+ + 1]$), 388 (100), 121 (38), 389 (24).

HRMS (ES^+): *m*/*z* $[M + H^+]$ calcd for $C_{26}H_{27}FN_5O_3S$: 508.1819; found: 508.1823.

4-(4-Fluoro-2-methoxyphenyl)-*N*-{3-[(*S*-methylsulfonimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine (BAY 1143572)[15]

CAN (206 mg, 0.375 mmol) was added to a solution of **22** (76 mg, 0.15 mmol) in MeCN/H_2O (3:1, 4 mL) and the mixture was stirred at r.t. for 1 h. Then, sat. aq $NaHCO_3$ (5 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude was purified by column chromatography (Cartridge: KP-Sil 10 g; eluent: CH_2Cl_2/MeOH, 95:5) to afford BAY 1143572 (55 mg, 95%) as a white solid; mp 166–168 °C; R_f = 0.27 (CH_2Cl_2/MeOH, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (br s, 1 H), 7.51–8.19 (m, 4 H), 7.38 (t, *J* = 7.9 Hz, 1 H), 7.13 (br d, *J* = 7.5 Hz, 1 H), 6.67–6.79 (m, 2 H), 4.39 (br d, *J* = 12.8 Hz, 1 H), 4.25 (br d, *J* = 13.2 Hz, 1 H), 3.91 (br s, 3 H), 2.97 (s, 3 H), 2.82 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.1, 166.4, 165.7 (d, *J* = 251.1 Hz), 163.7, 160.4, 138.6, 133.9, 129.7, 129.4, 126.3, 122.7, 122.1 (d, *J* = 3.2 Hz), 121.1, 107.7 (d, *J* = 21.6 Hz), 100.3 (d, *J* = 26.1 Hz), 64.1, 56.4, 41.7.

MS (ES^+): *m*/*z* (%) = 388 (10, $[M^+ + 1]$), 195 (100).

HRMS (ES^+): *m*/*z* $[M + H^+]$ calcd for $C_{18}H_{19}FN_5O_2S$: 388.1243; found: 388.1240.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588894.

Primary Data

Primary data for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084 and can be cited using the following DOI: 10.4125/pd0084th.

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