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Stille Coupling Reactions in the Synthesis of Hypoxia-Selective 3-Alkyl-1,2,4-Benzotriazine 1,4-Dioxide Anticancer Agents

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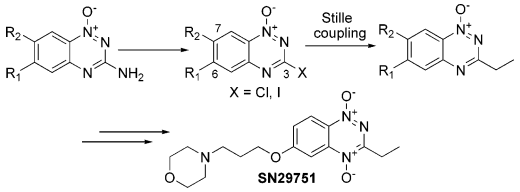
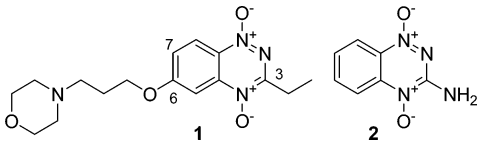


The introduction of a 3-alkyl substituent is a key step in the synthesis of 1,2,4-benzotriazine 1,4-dioxide hypoxia-selective anticancer agents, such as SN29751. The Stille reaction of 3-chloro-1,2,4-benzotriazine 1-oxides (BTOs) **5** was inhibited by the presence of electron donating substituents on the benzo ring, thus limiting the range of compounds available for SAR studies. The use of 3-iodo-BTOs **8** did not provide a significant improvement in the yields of 3-ethyl-BTOs **6**. Microwave-assisted Stille coupling of chlorides **5** gave dramatically improved yields, which were consistently superior to those from the corresponding iodides **8**. The application of microwave-assisted synthesis extended the range of substituted BTOs available for SAR studies and provided an efficient, scalable synthesis of the investigational anticancer agent, SN29751 (**1**).

Introduction

As part of a program to develop bioreductive hypoxia-selective anticancer agents[1,2] based on the 1,2,4-benzotriazine 1,4-dioxide template we recently described[3,4] a series of 3-alkyl 1,2,4-benzotriazine 1,4-dioxide derivatives with in vivo antitumor activity in combination with radiation. One of these analogues, SN29751 (**1**), in combination with radiation, has superior in vivo activity compared to tirapazamine (**2**), which is currently in Phase III clinical trial in combination with chemoradiation.[5−7]



A key step in the synthesis of **1** and related compounds is the introduction of the 3-alkyl substituent. Previous workers have used the Bamberger synthesis[8] to install 3-alkyl substituents as part of the 1,2,4-benzotriazine ring formation. This unwieldy approach, requiring the synthesis of the appropriately substituted formazan, cyclization to the 1,2,4-benzotriazine and *N*-oxidation, gave low[9] or unreported[10] yields of 3-alkyl-1,2,4-benzotriazine 1-oxides (BTOs). In a recent letter,[11] we reported a more

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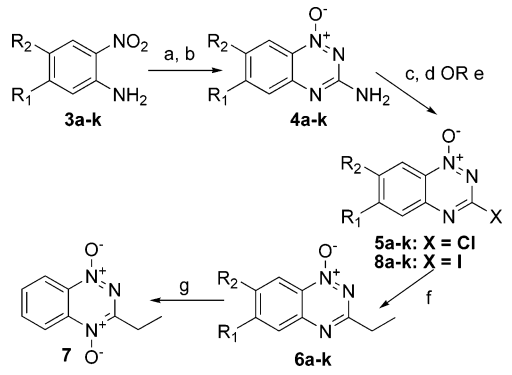
SCHEME 1[a]



[a] Reagents: (a) NH_2CN, concd HCl; (b) aq NaOH; (c) $NaNO_2$, CF_3CO_2H; (d) $POCl_3$, DMF; (e) *tert*-$BuNO_2$, I_2, CuI, THF; (f) Et_4Sn, $Pd(PPh_3)_4$, DME; (g) CF_3CO_3H, DCM.

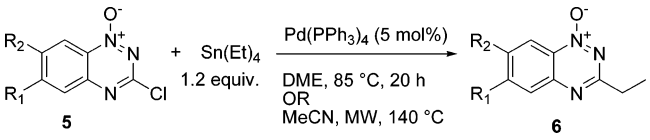
versatile approach using Stille coupling[12] of a 3-chloro-BTO **5a** with Et_4Sn to give the corresponding 3-ethyl-BTO **6a** ($R_1 = R_2 = H$; Scheme 1) in good yield, which could then be oxidized to the 1,4-dioxide **7**.

We wished to include alkyl and alkoxy moieties at the 6- and 7-position of these 3-alkyl-BTOs in order to modulate the reduction potentials and, consequently, the potency of the compounds[2] and also to link amine side chains in order to increase aqueous solubility. In this report we describe our efforts to extend the scope and utility of the Stille reaction in the 1,2,4-benzotriazine 1-oxide system. We have applied the Stille reaction to a variety of alkyl- and alkoxy-substituted BTOs, which were required for SAR studies, and have explored the application of microwave-assisted synthesis to this transformation. We also report the use of these results in the development of an efficient, scalable synthesis of **1**.

Results and Discussion

Stille Coupling of Chlorides 5a−k and Iodides 8a−k under Conventional Heating. A variety of alkyl- and alkoxy-substituted BTOs were required for SAR studies[13] (Table 1), and the use of the previously defined Stille methodology was considered to be most appropriate to provide these compounds. Thus, nitroanilines **3a−i** were converted to BTO-3-amines **4a−i** using the Mason and Tennant modification[14] of the method of Arndt (Scheme 1).[15] Subsequent diazotization, and chlorination of the intermediate phenols, gave the 3-chlorides **5a−i** in moderate to good yields (49−95%). The Stille reaction of BTO **5a** with Et_4Sn using $Pd(PPh_3)_4$[16] as the catalyst in refluxing DME for 20 h gave good yields (Table 1), although the reaction stalled after 6 h and required the addition of another batch of catalyst.[17] However, with the introduction of electron donating alkyl and methoxy substituents (compounds **5b−i**) into the 6- and 7-positions, incomplete reactions and low product yields (14−37%) were observed, irrespective of further catalyst addition (Table 1).

TABLE 1. Stille Coupling of 3-Cl−BTOs 5a−k under Thermal and Microwave-Assisted Conditions[a]



			thermal reaction of **5** (%)[b]		microwave-assisted reaction of **5** (%)[b]		
entry	R_1	R_2	**5**[c]	**6**	time (min)	**5**[c]	**6**
a	H	H	0	86[d]	40	0	78
b	Me	H	56	37[d]	60	0	84
c	H	Me	75	14	60	0	78
d	Me	Me	54	30	40	0	75
e	$-CH_2CH_2CH_2-$		38	12[d]	40	0	82
f	MeO	H	34	28[d]	40	0	54
g	H	MeO	70	16	40	0	74
h	MeO	Me	75	14	60	0	67
i	Me	MeO	76	14	20	0	86
j	F	H	0	75[d]	20	0	88
k	H	F	0	60[d]	40	0	86

[a] All reactions were carried out on a 0.4 mmol scale under N_2 with the same batch of catalyst. [b] Isolated yields. [c] Recovered starting material. [d] Addition of extra portion of $Pd(PPh_3)_4$ after 6 h.

Our first approach to remedy this shortcoming was to consider more active catalysts. The reaction of **5e** and **5f** with $Pd_2(dba)_3$/$PtBu_3$/CsF in dioxane[18] or $Pd(dba)_3$/P(2-furyl)$_3$/LiCl in DME[19] gave only traces of products **6e** and **6f**, respectively. The reaction of **5e** with $Pd(dppf)Cl_2$/DME gave only poor yields of the corresponding **6e**. Activation of the 3-chloride **5a** by oxidation to the corresponding 1,4-dioxide was attempted, but the product was insufficiently stable to isolate. Our next strategy was to modify the halogen atom since it is known that oxidative addition of Pd^0 to the strong carbon-chloride bond is disfavored because of the higher bond dissociation energy (Ph-Cl is 96 kcal mol^{-1} compared with 81 kcal mol^{-1} for Ph-Br and 65 kcal mol^{-1} for PhI).[20] Attempts to form the 3-bromo derivatives by diazotization of the 3-amine **4e** with $NaNO_2$ in a mixture of 48% HBr and DMF gave a very low yield of the corresponding bromide.[21] In contrast, reaction of BTO-3-amines **4a−i** and *tert*-butyl nitrite with a mixture of I_2 and CuI in THF at reflux temperature gave better yields (52−82%) of the 3-iodides **8a−i** (Scheme 1).

However, reaction of iodides **8a−i** under identical conditions described for chlorides **5a−i** gave mostly reduced yields or modest increases (−42 to 17%) of **6a−i** (Figure 1).[22] Furthermore, the overall mass recovery of starting material and product was consistently lower for the iodides **8** (49−83% mass recovery) compared to the chlorides **5** (50−93% mass recovery). This observation, as well as the presence of a variety of additional, unidentified byproducts in the coupling reaction of the iodides **8** indicated that the 3-iodo-BTOs **8** are unstable under

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(16) During the course of the study we found considerable variation in the efficacy of the $Pd(PPh_3)_4$ among different batches from suppliers. There appeared to be no relationship between the activity of the catalyst and its physical appearance. The data in this article were generated using the same batch of catalyst.

(17) Thermal Stille reactions were carried out in a 12 port carousel reactor to ensure identical reaction conditions.

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(22) Full tables with yields of starting material and product are available in the Supporting Information.

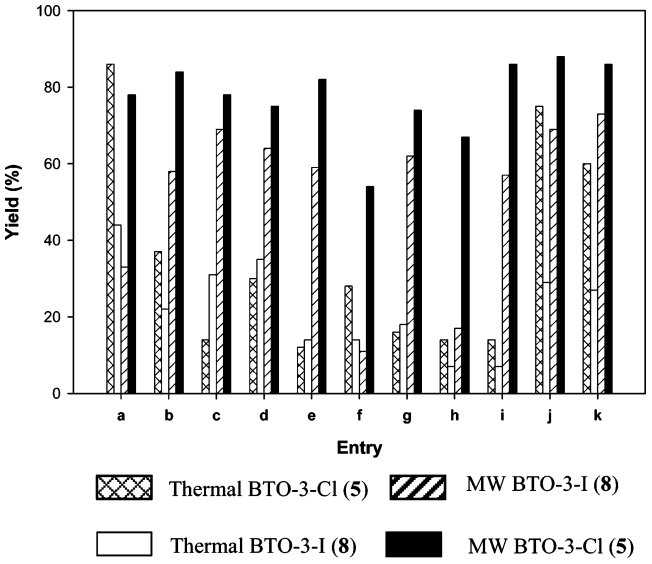
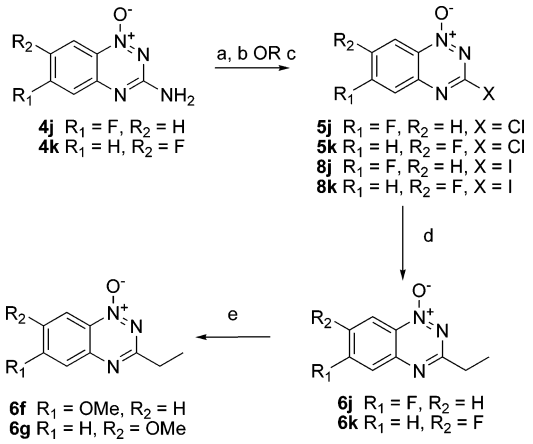


FIGURE 1. Stille coupling of chlorides **5a**−**k** and iodides **8a**−**k**.

SCHEME 2[a]



[a] Reagents: (a) $NaNO_2$, CF_3CO_2H; (b) $POCl_3$, DMF; (c) *tert*-$BuNO_2$, I_2, CuI, THF; (d) Et_4Sn, $Pd(PPh_3)_4$, DME; (e) NaOMe, MeOH.

the coupling conditions and undergo substantial decomposition. An alternative approach to access the methoxy derivatives **6f** and **6g** was considered (Scheme 2). The 6-fluoro-3-amine **4j** and the 7-isomer **4k** were converted to the 3-chlorides **5j** and **5k**, respectively, and also the corresponding 3-iodides **8j** and **8k**. The chlorides **5j** and **5k** underwent Stille coupling to give **6j** and **6k** in 75% and 60% yields, respectively (Table 1). In contrast, iodides **8j** and **8k** gave incomplete conversion and low yields (29 and 27%, respectively) of the corresponding compounds.[22] Displacement of the fluorides **6j** and **6k** with methoxide gave 3-ethyl-BTOs **6f** and **6g** in excellent yield, 95 and 91%, respectively (Scheme 2).

Microwave-Assisted Stille Coupling of Chlorides and Iodides. The use of microwave-assisted synthesis[23] with homogeneous catalysis has been well documented and has been used to overcome the disadvantages of thermal heating, such as low yields for electron-rich derivatives, formation of undesired byproducts, and long reaction times. Consequently, the use of microwave conditions with the Stille reaction of the 3-halo-BTOs and Et_4Sn was investigated. The 3-chloro-6-fluoro-BTO **5j** was used to optimize the reaction conditions (Table 2). Three solvents, DME, DMF, and MeCN, covering a range of polarity, were tested at 130, 140, and 150 °C. The highest yield of **6j** in DME was achieved at 140 °C, with lower temperatures giving incomplete conversion, even under prolonged reaction times, and higher temperatures showing significant formation of byproducts even with shorter reaction times. However, difficulty in maintaining the required temperature profile when using DME, because of its relatively low dielectric constant, resulted in poor reproducibility. The use of DMF as a solvent gave byproducts which could not be separated from the product by column chromatography. Reactions in MeCN needed longer reaction times compared to those carried out in DME and DMF, but MeCN proved to be the solvent of choice, providing clean and reproducible conversion to **6j** in 85% yield.

TABLE 2. Optimization of Microwave-Assisted Stille Coupling of 5j[a]

	solvent	*T* (°C)	time (min)	**6j** (%)[b]	comments
1	DME	130	60	47	incomplete reaction
2	DME	140	20	78	unstable temperature
3	DME	150	10	50	reaction incomplete, byproducts
4	DMF	140	20	<80	inseparable mixture
5	MeCN	130	60	43	incomplete reaction
6	MeCN	140	40	85	reproducible 0.1−1.0 g

[a] All reactions were carried out on a 0.5 mmol scale with the same batch of catalyst. [b] Isolated yields.

TABLE 3. Catalyst Selection for Microwave-Assisted Stille Coupling of 5j[a]

	catalyst[b]	time (min)	**6j** (%)[c]	comments
1	Pd/C	40	0	no reaction
2	$Pd(dppf)Cl_2$	40	0	no reaction
3	$Pd(CH_3CN)_2Cl_2$	40	0	no reaction
4	$Pd(OAc)_2$	60	trace	mainly unreacted sm
5	$Pd(PPh_3)_2Cl_2$	60	43	incomplete reaction
6	$Pd(PPh_3)_4$	40	85	time varied with batch

[a] All reactions were carried out in MeCN at 140 °C on a 0.5 mmol scale. [b] Catalyst loading of 5 mol %. [c] Isolated yields.

The variation in yields and conversion rates seen with different batches of $Pd(PPh_3)_4$ using thermal heating was less pronounced under microwave conditions (Table 3, entry 6), with some batches requiring longer reaction times but without lowering the yield. Nevertheless, this variation prompted us to examine several other catalysts with the aim to improve the reproducibility of the reaction. Again, 3-chloro-6-fluoro-BTO **5j** was used with a variety of Pd catalysts (Table 3). The use of Pd/C, $Pd(dppf)Cl_2$ and $Pd(CH_3CN)_2Cl_2$ catalysts did not give any conversion at all; $Pd(OAc)_2$ showed only a trace of **6j**; whereas $Pd(PPh_3)_2Cl_2$ gave incomplete conversion to yield 43% of **6j**, which was not improved by the addition of LiCl to the reaction.

The complete set of 3-chloro-BTOs **5** and 3-iodo-BTOs **8** were processed using $Pd(PPh_3)_4$ in MeCN at 140 °C. Reaction of the chlorides **5** proceeded smoothly to completion within 20−60 min, giving yields between 74 and 88%, with the exception of the 6-OMe substituted chlorides **5f** and **5h** where the yields were 54% and 67%, respectively (Table 1). The iodides **8** showed a similar pattern, but lower overall yields (57−73%)

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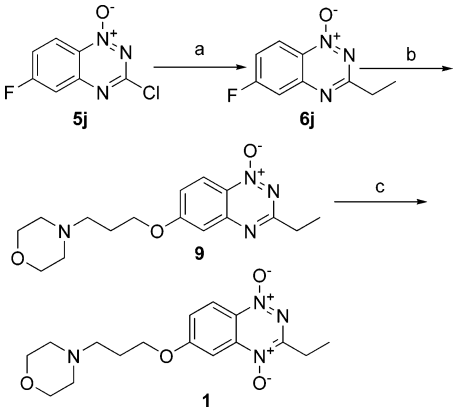
SCHEME 3[a]



[a] Reagents: (a) Et_4Sn, $Pd(PPh_3)_4$, DME; (b) $MORPHCH_2CH_2CH_2OH$, NaH, THF; (c) CF_3CO_3H, CF_3CO_2H, DCM.

were observed, with the exception of **8a** and the 6-MeO substituted iodides **8f** and **8h** where complete conversion could not be achieved after 60 min and low yields (33, 11, and 17%, respectively) were observed (Figure 1). The use of microwave-assisted reaction conditions allows Stille reactions to be carried out in good yields even on relatively electron-rich BTO chlorides **5**, allowing shorter reaction times, higher product yields, and cleaner reactions. Interestingly, the use of 3-iodides **8** in the Stille reaction did not provide any clear benefit in conjunction with either thermal or microwave heating, with the reactivity of the iodide under the reaction conditions leading to byproducts.

Evaluation of the data produced from the reaction array suggested that the most efficient approach to 6-alkoxy substituted BTO derivatives such as **1** would be via microwave-assisted Stille coupling of chloride **5j** followed by displacement of the fluoride **6j** with an alkoxide (Scheme 3). Thus, reaction of **5j** with Et_4Sn on a 9 × 1 g scale under microwave heating gave a combined yield of 84%. Alkylation of **6j** with the side chain alkoxide gave 1-oxide **9** in 76% yield. Selective aromatic *N*-oxidation at the 4-position was achieved in modest yield using an excess of trifluoroperacetic acid in the presence of trifluoracetic acid, which acts to protect the morpholine side chain from oxidation.

Although the 3-chloro-BTO system **5** is activated toward palladium-mediated coupling reactions, the presence of electron donating substituents on the benzo ring is sufficiently deactivating to limit their synthetic utility in the Stille reaction. The use of 3-iodo-BTOs **8** did not provide a significant improvement in yield of 3-ethyl-BTOs **6**. The use of microwave-assisted synthesis in the Stille coupling of chlorides **5** gave dramatically improved yields, which were consistently superior to those obtained with the iodides **8**. The application of microwave-assisted synthesis extends the utility and scope of palladium-mediated coupling reactions in this system and provides a more efficient synthesis of the investigational anticancer agent, SN29751 (**1**).

Experimental Section

Preparation of 3-Amino-1,2,4-benzotriazine 1-Oxides 4. General Method. A stirred mixture of nitroaniline **3** (20 mmol) and NH_2CN (80 mmol) were melted together at 100 °C, cooled to 50 °C. Concentrated HCl (10 mL) was added dropwise (CAUTION: exotherm), and the mixture was heated at 100 °C for 4 h. The mixture was cooled to 50 °C. A 7.5 M NaOH solution was added until the mixture was strongly basic, and the mixture was stirred at 100 °C for 3 h. The mixture was cooled, diluted with water (100 mL), filtered, washed with water (3 × 30 mL), washed with ether (2 × 5 mL), and dried. If necessary, the product was purified by chromatography, eluting with a gradient (0−10%) of MeOH/DCM, to give amine **4**. Compounds **4a**−**c**, **4f**, **4g**, **4j**, and **4k** were prepared as previously described.[2]

6,7-Dimethyl-1,2,4-benzotriazin-3-amine 1-Oxide (4d). Reaction of 4,5-dimethyl-2-nitroaniline (**3d**) gave amine **4d** (97%) as a yellow solid: mp 284−286 °C (lit.[14] mp 286 °C dec). ^{1}H NMR: δ 7.91 (s, 1H), 7.34 (s, 1H), 7.15 (br s, 2H), 2.36 (s, 3H), 2.33 (s, 3H).

Preparation of Chlorides (5a−k). General Method. Sodium nitrite (22 mmol) was added in small portions to a stirred solution of 1-oxide **4** (20 mmol) in TFA (40 mL) at 5 °C, and the solution stirred at 20 °C for 3 h. The solution was poured into ice/water (400 mL), stirred 30 min, filtered, washed with water (3 × 10 mL), and dried. The solid was suspended in $POCl_3$ (50 mL) and DMF (0.25 mL) and stirred at 100 °C for 1 h. The solution was cooled, poured into ice/water (500 mL), stirred for 30 min, filtered, washed with water (3 × 20 mL) and dried. The filtrate was extracted with EtOAc (3 × 70 mL) and dried, and the solvent was evaporated. The combined residues were purified by chromatography, eluting with 5% EtOAc/DCM to give chloride **5**.

3-Chloro-1,2,4-benzotriazine 1-Oxide (5a). Reaction of amine **4a** gave chloride **5a** (95%) as a pale yellow powder: mp (DCM) 119−119.5 °C; [lit.[24] (MeOH) 117−118 °C]. ^{1}H NMR [$(CD_3)_2$SO]: δ 8.38 (dd, J = 8.7, 1.0 Hz, 1H), 8.16 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H), 8.06 (dd, J = 8.2, 1.0 Hz, 1H), 7.90 (ddd, J = 8.7, 6.9, 1.3 Hz, 1H). ^{13}C NMR [$(CD_3)_2$SO]: δ 155.3 (C), 146.9 (C), 137.2 (CH), 133.9 (C), 131.5 (CH), 128.0 (CH), 119.9 (CH).

Stille Coupling of Chlorides 5a−k. General Method. $Pd(PPh_3)_4$ (0.025 mmol) was added to a N_2-purged, stirred solution of chloride **5** (0.50 mmol) and Et_4Sn (0.60 mmol) in DME (10 mL). The solution was degassed and stirred under N_2 at reflux temperature for 20 h. A second batch of $Pd(PPh_3)_4$ was added after 6 h if the reaction appeared to have stopped by TLC. The solvent was evaporated, and the residue was dissolved in DCM (10 mL) and stirred with saturated aqueous KF solution (10 mL) for 30 min. The mixture was filtered through Celite. The Celite was washed with DCM, and the combined organic filtrate was washed with water. The organic fraction was dried, and the solvent evaporated. The residue was purified by chromatography, eluting with DCM to give product, which was, if necessary, further purified by chromatography, eluting with 20% EtOAc/petroleum ether, to give 3-ethyl-1-oxide **6**.

3-Ethyl-1,2,4-benzotriazine 1-Oxide (6a). Reaction of chloride **5a** gave 1-oxide **6a** (86%) as a white solid: mp (EtOAc/petroleum ether) 78−80 °C. ^{1}H NMR: δ 8.45 (dd, J = 8.7, 1.1 Hz, 1H), 7.99 (dd, J = 8.5, 1.1 Hz, 1H), 7.93 (ddd, J = 8.5, 7.1, 1.3 Hz, 1H), 7.69 (ddd, J = 8.7, 7.1, 1.2 Hz, 1H), 3.06 (q, J = 7.6 Hz, 2H), 1.45 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 168.1 (C), 147.6 (C), 135.5 (C), 133.2 (C), 129.8 (CH), 128.7 (CH), 120.1 (CH), 30.7 (CH_2), 12.2 (CH_3). Anal. Calcd for $C_9H_9N_3O_3$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.33; H, 5.15; N, 23.72%.

3-Ethyl-6-methyl-1,2,4-benzotriazine 1-Oxide (6b). Reaction of chloride **5b** gave (i) starting material **5b** (56%) and (ii) 1-oxide **6b** (37%) as a white solid: mp (EtOAc/DCM) 68−70 °C. ^{1}H NMR: δ 8.33 (d, J = 8.8 Hz, 1H), 7.74 (br s, 1H), 7.49 (dd, J = 8.8, 1.7 Hz, 1H), 3.02 (q, J = 7.6 Hz, 2H), 2.59 (s, 3H), 1.44 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 168.2 (C), 147.8 (C), 147.1 (C), 132.0 (CH), 131.6 (C), 127.5 (CH), 119.8 (CH), 30.7 (CH_2), 22.1 (CH_3), 12.2 (CH_3). Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.46; H, 6.03; N, 22.31%.

3-Ethyl-7-methyl-1,2,4-benzotriazine 1-Oxide (6c). Reaction of chloride **5c** gave (i) starting material **5c** (75%) and (ii) 1-oxide **6c** (14%) as an off-white solid: mp (EtOAc/DCM) 128−131 °C.

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^{1}H NMR: δ 8.24 (br s, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.74 (dd, J = 8.6, 2.9 Hz, 1H), 3.04 (q, J = 7.6 Hz, 2H), 2.58 (s, 3H), 1.44 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 167.3 (C), 153.2 (C), 146.1 (C), 141.1 (C), 137.6 (CH), 128.3 (CH), 118.8 (CH), 30.6 (CH_2), 21.8 (CH_3), 12.3 (CH_3). Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.18; H, 5.74; N, 21.90%.

6,7-Dimethyl-3-ethyl-1,2,4-benzotriazine 1-Oxide (6d). Reaction of chloride **5d** gave (i) starting material **5d** (54%) and (ii) 1-oxide **6d** (30%) as a pale-yellow solid: mp (EtOAc/DCM) 61−63 °C. ^{1}H NMR: δ 8.20 (s, 1H), 7.72 (s, 1H), 3.02 (q, J = 7.6 Hz, 2H), 2.49 (s, 3H), 2.48 (s, 3H), 1.43 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 167.4 (C), 147.1 (C), 146.6 (C), 141.0 (C), 131.5 (C), 127.7 (CH), 119.0 (CH), 30.7 (CH_2), 20.6 (CH_3), 20.3 (CH_3), 12.3 (CH_3). Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.23; H, 6.27; N, 20.51%.

Ethyl-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (6e). Reaction of chloride **5e** gave (i) starting material **5e** (38%) and (ii) 1-oxide **6e** (12%) as a pale yellow solid: mp (MeOH) 80−81 °C. ^{1}H NMR: δ 8.26 (s, 1H), 7.26 (s, 1H), 3.11 (dt, J = 7.2 Hz, 4H), 3.02 (q, J = 7.6 Hz, 2H), 2.21 (p, J = 7.2 Hz, 2H), 1.43 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 167.0 (C), 154.6 (C), 148.7 (C), 147.6 (C), 132.3 (C), 122.7 (CH), 114.3 (CH), 33.2 (CH_2), 32.8 (CH_2), 30.6 (CH_2), 25.8 (CH_2), 12.4 (CH_3). Anal. Calcd for $C_{12}H_{13}N_3O\cdot{}^1/_4CH_3OH$: C, 65.90; H, 6.32; N, 18.82. Found: C, 66.06; H, 6.13; N, 18.51%.

3-Ethyl-6-methoxy-1,2,4-benzotriazine 1-Oxide (6f). Reaction of chloride **5f** gave (i) starting material **5f** (34%) and (ii) 1-oxide **6c** (28%) as a white solid: mp (EtOAc/petroleum ether) 109−111 °C; ^{1}H NMR: δ 8.32 (d, J = 9.5 Hz, 1H), 7.24 (dd, J = 9.5, 2.6 Hz, 1H), 7.19 (d, J = 2.6 Hz, 1H), 3.98 (s, 3H), 3.00 (q, J = 7.6 Hz, 2H), 1.43 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 168.8 (C), 165.3 (C), 150.3 (C), 128.5 (C), 122.9 (CH), 121.7 (CH), 105.8 (CH), 56.2 (CH_3), 30.7 (CH_2), 12.2 (CH_3). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.64; H, 5.37; N, 20.51%.

3-Ethyl-7-methoxy-1,2,4-benzotriazine 1-Oxide (6g). Reaction of chloride **5g** gave (i) starting material **5g** (70%) and (ii) 1-oxide **6g** (16%) as a bright yellow solid: mp (EtOAc/petroleum ether) 98−100 °C. ^{1}H NMR: δ 7.88 (d, J = 9.2 Hz, 1H), 7.72 (d, J = 2.8 Hz, 1H), 7.55 (dd, J = 9.2, 2.6 Hz, 1H), 3.99 (s, 3H), 3.04 (q, J = 7.6 Hz, 2H), 1.44 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 166.0 (C), 160.9 (C), 144.0 (C), 133.8 (C), 129.9 (CH), 128.9 (CH), 97.6 (CH), 56.4 (CH_3), 30.5 (CH_2), 12.4 (CH_3). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.43; H, 5.42; N, 20.70%.

3-Ethyl-6-methoxy-7-methyl-1,2,4-benzotriazine 1-Oxide (6h). Reaction of chloride **5h** gave (i) starting material **5h** (75%) and (ii) 1-oxide **6h** (14%) as an off-white solid: mp (EtOAc/petroleum ether) 111−113 °C. ^{1}H NMR: δ 8.20 (d, J = 0.9 Hz, 1H), 7.15 (s, 1H), 4.02 (s, 3H), 3.00 (q, J = 7.6 Hz, 2H), 2.40 (d, J = 0.9 Hz, 3H), 1.43 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 167.9 (C), 164.3 (C), 149.3 (C), 134.2 (C), 128.0 (C), 120.3 (CH), 104.4 (CH), 56.4 (CH_3), 30.6 (CH_2), 17.0 (CH_3), 12.3 (CH_3). Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.45; H, 5.85; N, 19.09%.

3-Ethyl-7-methoxy-6-methyl-1,2,4-benzotriazine 1-Oxide (6i). Reaction of chloride **5i** gave (i) starting material **5i** (76%) and (ii) 1-oxide **6i** (14%) as a yellow solid: mp (EtOAc/petroleum ether) 89−91 °C. ^{1}H NMR: δ 7.71 (d, J = 0.9 Hz, 1H), 7.66 (s, 1H), 4.01 (s, 3H), 3.02 (q, J = 7.6 Hz, 2H), 2.43 (d, J = 0.9 Hz, 3H), 1.43 (t, J = 7.6 Hz, 3H). ^{13}C NMR δ 166.0 (C), 159.9 (C), 143.9 (C), 140.4 (C), 132.4 (C), 128.8 (CH), 96.3 (CH), 56.4 (CH_3), 30.5 (CH_2), 17.3 (CH_3), 12.4 (CH_3). Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 59.96; H, 5.83; N, 19.10%.

3-Ethyl-6-fluoro-1,2,4-benzotriazine 1-Oxide (6j). Reaction of chloride **5j** gave 1-oxide **6j** (75%) as a white solid: mp (EtOAc/petroleum ether) 122−124 °C. ^{1}H NMR: δ 8.48 (dd, J = 9.5, 5.5 Hz, 1H), 7.60 (dd, J = 8.7, 2.6 Hz, 1H), 7.38−7.44 (m, 1H), 3.04 (q, J = 7.6 Hz, 2H), 1.43 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 168.6 (q, J = 175 Hz, C), 165.1 (C), 149.5 (d, J = 15 Hz, C), 130.5 (C), 123.2 (d, J = 11 Hz, CH), 120.0 (d, J = 26 Hz, CH), 112.7 (d, J = 22 Hz, CH), 30.7 (CH_2), 12.2 (CH_3). Anal. Calcd for $C_9H_8FN_3O$: C, 55.96; H, 4.17; N, 21.75. Found: C, 56.01; H, 4.20; N, 21.82%.

3-Ethyl-7-fluoro-1,2,4-benzotriazine 1-Oxide (6k). Reaction of chloride **5k** gave 1-oxide **6k** (60%) as a pale yellow solid: mp (EtOAc/petroleum ether) 91−92 °C. ^{1}H NMR: δ 8.10 (dd, J = 7.9, 2.8 Hz, 1H), 8.02 (q, J = 5.1 Hz, 1H), 7.67−7.72 (m, 1H), 3.06 (q, J = 7.6 Hz, 2H), 1.45 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 167.7 (d, J = 2 Hz, C), 163.4 (C), 160.8 (C), 144.8 (C), 131.3 (d, J = 9 Hz, CH), 125.8 (d, J = 26 Hz, CH), 105.0 (d, J = 27 Hz, CH), 30.6 (CH_2), 12.2 (CH_3). Anal. Calcd for $C_9H_8FN_3O$: C, 55.96; H, 4.17; N, 21.75. Found: C, 56.04; H, 4.21; N, 22.06%.

Preparation of Iodides 8a−k. General Method. *tert*-BuONO (18 mmol) was added to a stirred solution of amine **4** (6 mmol), I_2 (6 mmol), and CuI (0.6 mmol) in THF (100 mL), and the mixture was stirred at reflux temperature for 2 h. The mixture was cooled to 20 °C, and the mixture was filtered through a short plug of alumina and washed with THF (100 mL). The filtrate was evaporated. The residue was suspended in DCM (100 mL), washed with aqueous $Na_2S_2O_5$ solution (10%, 2 × 50 mL), water (50 mL), and brine (50 mL), and dried, and the solvent was evaporated. The residue was purified by chromatography, eluting with 5% EtOAc/DCM, to give iodide **8**.

3-Iodo-1,2,4-benzotriazine 1-Oxide (8a). Reaction of amine **4a** gave iodide **8a** (73%) as a pale yellow powder: mp (EtOAc/DCM) 207−210 °C. ^{1}H NMR: δ 8.37 (br d, J = 8.3 Hz, 1H), 7.93−8.00 (m, 2H), 7.77 (ddd, J = 8.5, 6.3, 2.3 Hz, 1H). ^{13}C NMR: δ 147.5 (C), 136.3 (CH), 134.4 (C), 131.1 (CH), 128.4 (CH), 123.1 (C), 120.3 (CH). Anal. Calcd for $C_7H_4IN_3O$: C, 30.79; H, 1.48; N, 15.39. Found: C, 31.09; H, 1.39; N, 15.52%.

Stille Coupling of Iodides 8a−k. General Method. $Pd(PPh_3)_4$ (0.020 mmol) was added to a N_2-purged, stirred solution of iodide **7** (0.40 mmol) and Et_4Sn (0.24 mmol) in DME (10 mL). The solution was degassed and stirred under N_2 at reflux temperature for 16 h. The solvent was evaporated, and the residue was dissolved in DCM (10 mL) and stirred with saturated aqueous KF solution (10 mL) for 30 min. The mixture was filtered through Celite. The Celite was washed with DCM, and the combined organic filtrate was washed with water. The organic fraction was dried, the solvent evaporated, and the residue purified by chromatography, eluting with DCM to give product, which was, if necessary, further purified by chromatography, eluting with 20% EtOAc/petroleum ether, to give 3-ethyl-1-oxide **6**. The yields of the 1-oxides **6** are given in Table 1.

Alternative Preparation of 3-Ethyl-6-methoxy-1,2,4-benzotriazine 1-Oxide (6f). Sodium (45 mg, 1.9 mmol) dissolved in MeOH (10 mL) was added to a stirred solution of fluoride (250 mg, 1.3 mmol) in MeOH (10 mL), and the solution was stirred at 20 °C for 2 h under N_2. The mixture was concentrated, and the precipitate was filtered off and washed with water to give 1-oxide **6f** (254 mg, 95%) as a white solid: mp (EtOAc/petroleum ether) 109−111 °C; spectroscopically identical to **6f** prepared above.

Alternative Preparation of 3-Ethyl-7-methoxy-1,2,4-benzotriazine 1-Oxide (6g). Sodium (18 mg, 0.8 mmol) dissolved in MeOH (5 mL) was added to a stirred solution of fluoride (100 mg, 0.5 mmol) in MeOH (5 mL), and the solution was stirred at 20 °C for 2 h under N_2. The mixture was concentrated, and the precipitate was filtered off and washed with water to give 1-oxide **6g** (96 mg, 91%) as a yellow solid: mp (EtOAc/petroleum ether) 98−100 °C; spectroscopically identical to **6g** prepared above.

Microwave-Assisted Stille Coupling of Chlorides 5a−k. General Method. $Pd(PPh_3)_4$ (0.025 mmol) was added to a N_2-purged, stirred solution of chloride **5** (0.50 mmol) and Et_4Sn (0.60 mmol) in MeCN (10 mL) in 100 mL sealed TFM rotors equipped with a pressure and temperature sensor, as well as a magnetic stirrer. The reaction tube was placed in a homogeneous microwave synthesis system, and the system was operated at 140 ± 5 °C, measured by an internal fiber-optic temperature sensor immersed in the reaction mixture, for 20 min with a 4 min ramp time. The

power input was controlled at an average power of 250 W by the internal temperature sensor. After completion of the reaction, the solvent was evaporated, and the residue was dissolved in DCM (10 mL) and stirred with saturated aqueous KF solution (10 mL) for 30 min. The mixture was filtered through Celite. The Celite was washed with DCM, and the combined organic filtrate was washed with water. The organic fraction was dried, the solvent evaporated, and the residue purified by chromatography, eluting with DCM to give crude product, which was, if necessary, further purified by chromatography, eluting with 20% EtOAc/petroleum ether, to give 3-ethyl-1-oxide **6**.

Microwave-Assisted Stille Coupling of Iodides 8a−k. General Method. $Pd(PPh_3)_4$ (0.020 mmol) was added to a N_2-purged, stirred solution of iodide **8** (0.40 mmol) and Et_4Sn (0.48 mmol) in MeCN (10 mL) in 100 mL sealed TFM rotors equipped with a pressure and temperature sensor, as well as a magnetic stirrer. Reactions were carried out as described above for chlorides **5**.

Preparation of SN29751 (1): 3-Ethyl-6-fluoro-1,2,4-benzotriazine 1-Oxide (6j). Nine portions of $Pd(PPh_3)_4$ (250 mg, 0.22 mmol) were added to nine N_2-purged, stirred solutions of chloride **5j** (1.0 g, 5.0 mmol) and Et_4Sn (1.2 mL, 6.0 mmol) in MeCN (40 mL) in nine 100 mL sealed TFM rotors. The reaction tubes were placed in a homogeneous microwave synthesis system, and the system was operated at 140 ± 5 °C, measured by an internal fiber-optic temperature sensor immersed in the reaction mixture, for 15 min with a 4 min ramp time. The power input was controlled at an average power of 220 W by the internal temperature sensor. After completion of the reaction, the nine reaction mixtures were combined, and the solvent was evaporated. The residue was dissolved in DCM (250 mL) and stirred with saturated aqueous KF solution (250 mL) for 30 min. The mixture was filtered through Celite. The Celite was washed with DCM, and the combined organic filtrate was washed with water. The organic fraction was dried, the solvent evaporated, and the residue purified by chromatography, eluting with DCM to give 1-oxide **6j** (7.30 g, 84%) as an off-white solid: mp (EtOAc/petroleum ether) 122−124 °C; spectroscopically identical to **6j** prepared above.

3-Ethyl-6-[3-(4-morpholinyl)propoxy]-1,2,4-benzotriazine 1-Oxide (9). A solution of 3-(4-morpholinyl)propanol[25] (22.53 g, 155 mmol) in dry THF (70 mL) was added dropwise to a stirred suspension of NaH (60% dispersion in oil, 6.21 g, 155 mmol) in dry THF (100 mL) at 20 °C, and the mixture was stirred for 30 min. A solution of fluoride **6j** (15.0 g, 77.7 mmol) was added, and the resulting solution was stirred for 2.5 h. The reaction was cooled to 0 °C, carefully quenched with water (30 mL), and the solution was extracted with DCM (4 × 100 mL). The combined organic fraction was dried, and the solvent was evaporated. The residue was purified by column chromatography, eluting with a gradient (0−5%) of MeOH/DCM to give 1-oxide **9** (18.82 g, 76%) as a pale yellow solid: mp 108−111 °C. ^{1}H NMR: δ 8.33 (d, J = 9.3 Hz, 1H), 7.21−7.26 (m, 2H), 4.22 (t, J = 6.4 Hz, 2H), 3.73 (t, J = 4.6 Hz, 4H), 3.00 (q, J = 7.6 Hz, 2H), 2.55 (t, J = 7.0 Hz, 2H), 2.48 (t, J = 4.6 Hz, 4H), 2.06 (m, 2H), 1.43 (t, J = 7.6 Hz, 3H). ^{13}C NMR: δ 168.7 (C), 164.6 (C), 150.3 (C), 128.4 (C), 123.1 (CH), 121.6 (CH), 106.3 (CH), 67.3 (CH_2), 66.9 (2 × CH_2), 55.1 (CH_2), 53.7 (2 × CH_2), 30.7 (CH_2), 26.0 (CH_2), 12.2 (CH_3). Anal. Calcd for $C_{16}H_{22}N_4O_3$: C, 60.36; H, 6.97; N, 17.60. Found: C, 60.42; H, 7.00; N, 17.40%.

3-Ethyl-6-[3-(4-morpholinyl)propoxy]-1,2,4-benzotriazine 1,4-Dioxide (1). Hydrogen peroxide (70%; 12.6 mL, ca. 251 mmol) was added dropwise to a stirred solution of TFAA (35.5 mL, 251 mmol) in DCM (100 mL) at 5 °C (CAUTION: exotherm). The solution was stirred at 20 °C for 5 min, then cooled to 5 °C, and added to a solution of 1-oxide **9** (8.0 g, 25.1 mmol) and TFA (9.7 mL, 126 mmol) in DCM (100 mL) at 5 °C. The solution was stirred at 20 °C for 3 h, cooled to 5 °C, and water (50 mL) was added. Concentrated NH_3 solution (60 mL) was added dropwise to the vigorously stirred mixture until the mixture was basic, and then the mixture was stirred for 30 min. The mixture was extracted with $CHCl_3$ (4 × 100 mL). The combined organic fraction was dried, and the solvent evaporated. The residue was purified by column chromatography, eluting with a gradient (0−5%) of MeOH/DCM to give (i) unreacted starting material **9** (3.63 g, 45%) and (ii) 1,4-dioxide **1** (1.98 g, 24%) as a yellow solid: mp 123−126 °C. ^{1}H NMR: δ 8.36 (d, J = 9.5 Hz, 1H), 7.77 (d, J = 2.6 Hz, 1H), 7.36 (dd, J = 9.5, 2.6 Hz, 1H), 4.29 (t, J = 6.4 Hz, 2H), 3.72 (t, J = 4.6 Hz, 4H), 3.21 (q, J = 7.5 Hz, 2H), 2.54 (t, J = 7.0 Hz, 2H), 2.47 (t, J = 4.6 Hz, 4H), 2.04−2.10 (m, 2H), 1.44 (t, J = 7.5 Hz, 3H). ^{13}C NMR: δ 165.1 (C), 157.1 (C), 141.5 (C), 129.6 (C), 124.4 (CH), 123.4 (CH), 98.0 (CH), 68.1 (CH_2), 66.9 (2 × CH_2), 55.0 (CH_2), 53.7 (2 × CH_2), 25.9 (CH_2), 24.1 (CH_2), 9.3 (CH_3). Anal. Calcd for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.17; H, 6.52; N, 16.54%.

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Supporting Information Available: General experimental details, data for all compounds, tables of reaction yields, and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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