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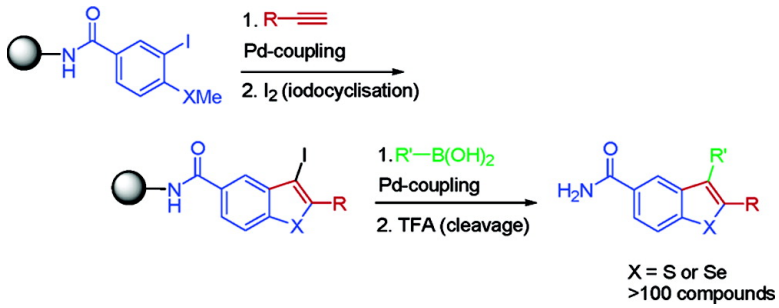

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Solid-Phase Synthesis of 2,3-Disubstituted Benzo[*b*]thiophenes and Benzo[*b*]selenophenes

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A concise and efficient solid-phase synthesis of benzo[*b*]thiophenes and benzo[*b*]selenophenes based on a combination of palladium-mediated coupling and iodocyclization protocols has been developed.

The benzo[*b*]thiophene ring system has long been recognized as an excellent scaffold for the development of bioactive compounds.[1] This scaffold may be used as an isosteric replacement for naturally occurring indoles and benzo[*b*]furans or used in its own right to develop novel pharmacophores.[1] Benzo[*b*]thiophene derivatives currently in pharmaceutical use or development include estrogen receptor antagonists,[2] antimitotic agents,[3] modulators of multidrug resistance,[4] angiogenesis inhibitors,[5] cognition enhancers,[6] and antifungal[7] and antiinflammatory[8] agents to name but a few. Indeed, benzo[*b*]thiophenes may be regarded as a "privileged class" of structure from which druglike bioactives can be reasonably readily developed.

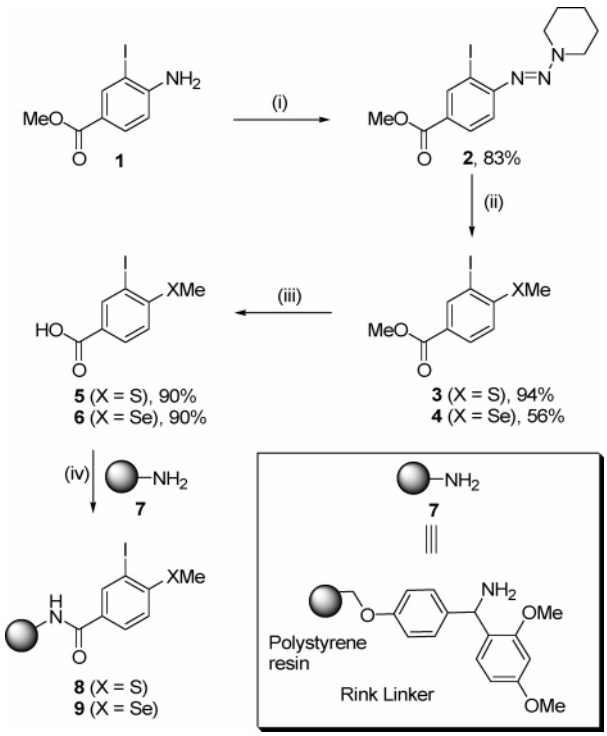
The benzo[*b*]selenophene ring system has been rarely utilized in drug discovery, but given its similarities to the benzo[*b*]thiophene ring system, it probably warrants greater attention than it has been given to date. Herein we report a solid-phase synthesis of both benzo[*b*]thiophenes and benzo[*b*]selenophenes that can be used to provide a high-throughput synthesis capability for drug discovery.

Recently, in connection with our ongoing efforts to develop a potent inhibitor of tubulin polymerization, we developed a concise access to benzo[*b*]thiophenes based on a combination of palladium-mediated coupling and iodocyclization protocols.[3a,9,10] We have now extended this to a solid-phase synthesis protocol for both benzo[*b*]thiophenes and benzo[*b*]selenophenes using identical chemistries in both cases. Resin-bound substrates **8** and **9** were conveniently prepared from commercially available methyl 3-iodo-4-aminobenzoate **1**. This involved initial formation of the triazene **2**, which could be converted to either the sulfide **3** or the selenide **4** in moderate to good yields (Scheme 1). After ester hydrolysis, the resultant acids **5** and **6** were linked to a polystyrene resin through a Rink linker to give the resin-bound amides **8** and **9**.

Resin-bound substrates **8** and **9** were coupled to a series of alkynes **10** (Figure 1) under Sonogashira conditions to give **11** and **12** (Scheme 2). Treatment of the resin-bound substrates **11** and **12** with elemental iodine in dichloromethane (DCM) gave the iodocyclized compounds **13** and **14**, which were coupled to a series of boronic acids **15** (Figure 1) under Suzuki coupling conditions to give **16** and **17**. Cleavage of **16** and **17** using TFA in DCM provided the 2,3-disubstituted benzo[*b*]thiophenes **18** and benzo[*b*]selenophenes **19** (110 compounds, see Tables 1 and 2). In both the Sonogashira and Suzuki couplings, the catalyst loading was quite high (20 and 40%, respectively). No studies were undertaken to verify if such high catalyst loading is absolutely necessary, and it may be that they can be reduced.

Compounds with less than 70% purity after initial cleavage (~40% of compounds) were subject to a simple purification procedure involving initial elution through a short pad of silica (2 cm long × 0.5 cm diameter) with 5% ethyl acetate

Scheme 1. Preparation of Resin-Bound *o*-Iodomethylphenyl Sulfide **8** and *o*-Iodomethylphenyl Selenide **9**[a]



[a] (i) 1 M HCl (aq), $NaNO_2$, piperidine; (ii) MeSNa (or MeSeNa generated from $NaBH_4$ and MeSe−SeMe), MeOH, then TFA; (iii) NaOH, H_2O/MeOH, then HCl (aq); (iv) **7**-Fmoc was deprotected with piperidine and free amine, **7**, coupled to **5** or **6** with HOBt, diisopropylcarbodiimide.

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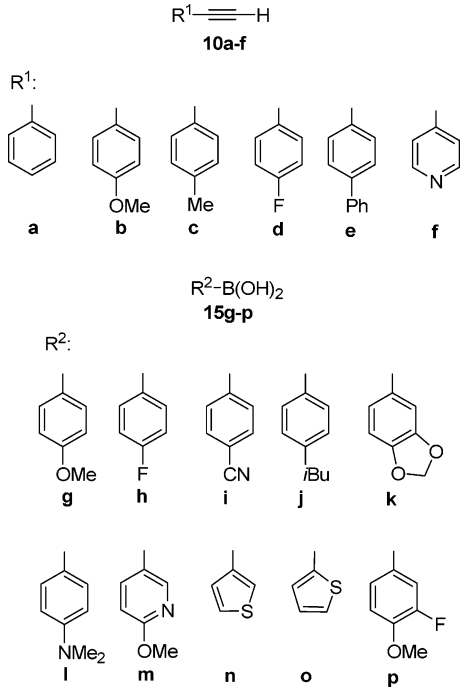
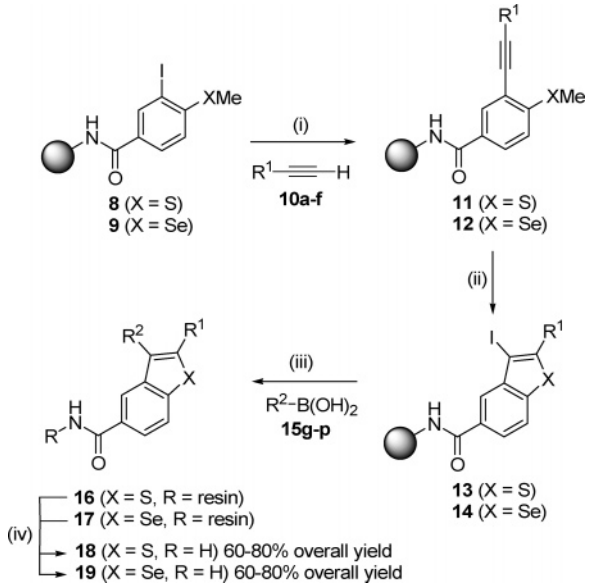


Figure 1. Alkynes **10a**−**f** and boronic acids **15g**−**p** used in library synthesis (see Scheme 2).

Scheme 2. Library Synthesis of Benzo[*b*]thiophenes **18** and Benzo[*b*]selenophenes **19** on Resin Solid Support[a]



[a] See Figure 1 for definitions of **10a**−**f** and **15g**−**p**. (i) **10** 8 equiv, $PdCl_2(PPh_3)_2$ 18 mol %, CuI 22 mol %, piperidine/THF (1:1), 65 °C, 16 h; (ii) I_2 2 equiv, DCM; (iii) **15** 5 equiv, $Pd(PPh_3)_4$ 40 mol %, TBAF, K_2CO_3, 65 °C, 16 h; (iv) 20% TFA in DCM.

in hexane, followed by a second elution with 60% ethyl acetate in hexane. The product was obtained by evaporation of the second elution. To establish that the first elution (5% ethyl acetate in hexane) did not contain significant quantities of product, we performed LC/MS traces on both fractions. The effect of this purification approach is exemplified for **18eh** (Figure 2). The product obtained directly from cleavage had a purity of 24% (LC/MS 1, Figure 2). The first fraction contained no observable product but significant impurity (LC/MS 2, Figure 2), and the second fraction contained all the product with a substantially improved purity of 85% (LC/MS 3, Figure 2).[11] In all cases where measurements were taken, the yield of the product was found to be between 60 and 80%.[12] Accordingly, this approach to compound library synthesis of benzo[*b*]thiophenes and benzo[*b*]selenophenes can provide products in good purity, in good yields, and in high throughput manner.

Table 1. Library Synthesis of Benzothiophene **18** (X = S)

	substituent				MS, M + H$^+$	
compd	R1	R2	LC: t_r, min	% purity[a]	expected	found
18ag	a	g	7.85	96	360.4	360.1
18ah	a	h	9.46	79	348.4	348.1
18ai	a	i	6.29	77	355.5	355.1
18aj	a	j	10.98	81	386.5	386.1
18ak	a	k	7.05	74	374.5	374.1
18al	a	l	10.36	83	373.5	373.1
18am	a	m	5.31	73	361.5	361.1
18an	a	n	7.14	71	336.5	336.1
18ao	a	o	7.04	75	336.4	336.1
18ap	a	p	8.26	70	378.4	378.1
18bg	b	g	6.85	71	390.5	390.1
18bh	b	h	7.21	77	378.4	378.1
18bi	b	i	5.3	69	385.4	385.1
18bj	b	j	8.38	87	416.5	416.2
18bk	b	k	5.92	72	404.4	404.1
18bl	b	l	8.65	81	403.5	403.2
18bm	b	m	4.61	71	391.4	391.1
18bn	b	n	5.96	78	366.4	366.1
18bo	b	o	5.99	79	366.4	366.1
18bp	b	p	6.41	80	408.5	408.1
18cg	c	g	9.82	66	374.5	374.1
18ch	c	h	11.05	70	362.4	362.1
18ci	c	i	8.29	76	369.4	369.1
18cj	c	j	42.79	72	400.5	400.2
18ck	c	k	9.19	70	388.4	388.1
18cl	c	l	13.42	80	387.5	387.2
18cm	c	m	6.95	78	375.4	375.1
18cn	c	n	8.99	76	350.4	350.1
18co	c	o	9.2	70	350.4	350.1
18cp	c	p	11.29	73	392.5	392.1
18dg	d	g	8.53	70	378.4	378.1
18dh	d	h	8.68	77	366.4	366.1
18di	d	i	6.32	73	373.4	373.1
18dj	d	j	36.32	73	404.5	404.2
18dk	d	k	7.76	71	392.4	392.1
18dl	d	l	11.15	84	391.5	391.1
18dm	d	m	5.75	69	379.4	379.1
18dn	d	n	7.71	75	354.4	354.1
18do	d	o	7.61	75	354.4	354.1
18dp	d	p	8.94	73[b]	396.4	396.1
18eg	e	g	17.46	76	436.5	436.2
18eh	e	h	20.94	85	424.5	424.1
18ei	e	i	14.48	71	431.5	431.1
18ek	e	k	15.47	58	450.5	450.1
18el	e	l	25.8	67[b]	449.5	449.1
18em	e	m	12.07	75	437.5	437.1
18en	e	n	16.55	71	412.5	412.1
18eo	e	o	15.69	83	412.5	412.1
18fg	f	g	3.32	70	361.4	361.1
18fh	f	h	3.31	77	349.4	349.1
18fi	f	i	2.09	81	356.4	356.1
18fl	f	l	4.31	81	374.4	374.1
18fo	f	o	3.01	88	337.4	337.1

[a] Purity measurements were made by integration of the LC/MS traces, based on UV absorption at 214 nm (similar integration patterns observed at 254 nm in most cases). [b] Based on integration after subtraction of solvent peak (ethyl acetate).

Table 2. Library Synthesis of Benzoselenophene **19** (X = Se)

	substituent				MS, M + H$^+$	
compd	R1	R2	LC: t_r, min	% purity	expected[a]	found
19ag	a	g	7.11	62	408.3	408.1
19ah	a	h	8.73	70	396.3	396.0
19ai	a	i	6.32	85	403.3	403.0
19aj	a	j	32.87	52[b]	434.4	434.1
19ak	a	k	7.06	80	422.3	422.0
19al	a	l	10.17	89	421.4	421.1
19am	a	m	4.98	74	409.3	409.0
19an	a	n	6.27	80	384.4	384.0
19ao	a	o	7.08	82	384.4	384.0
19ap	a	p	8.02	65	426.4	426.0
19bg	b	g	6.74	51[b]	438.4	438.1
19bh	b	h	7.73	84	426.3	426.0
19bi	b	i	5.19	68	433.3	433.1
19bj	b	j	25.86	75	464.4	464.1
19bk	b	k	6.21	67	452.3	452.0
19bl	b	l	8.53	65[b]	451.4	451.1
19bm	b	m	4.79	78	439.3	439.1
19bn	b	n	5.68	87	414.3	414.0
19bo	b	o	5.7	69[b]	414.3	414.0
19cg	c	g	10.87	67	422.4	422.1
19ch	c	h	12.25	64	410.3	410.0
19ci	c	i	7.86	81[b]	417.3	417.0
19cj	c	j	46.04	88	448.4	448.1
19ck	c	k	9.71	71	436.4	436.1
19cl	c	l	14.32	83	435.4	435.1
19cm	c	m	7.24	81	423.4	423.1
19cn	c	n	9.88	80	398.3	398.0
19co	c	o	9.67	65	398.4	398.0
19dg	d	g	8.67	69	426.3	426.0
19dh	d	h	9.42	77	414.3	414.0
19di	d	i	6.79	70	421.3	421.0
19dj	d	j	36.94	84	452.4	452.0
19dk	d	k	7.71	70	440.3	440.0
19dl	d	l	11.56	82	439.4	439.1
19dm	d	m	5.21	87	427.3	427.0
19dn	d	n	7.78	72	402.3	402.0
19do	d	o	7.79	66	402.3	402.0
19dp	d	p	8.68	81	444.3	444.0
19eg	e	g	19.27	60[b]	484.4	484.1
19eh	e	h	21.43	66	472.4	472.1
19ei	e	i	15.58	78[b]	479.4	479.1
19ek	e	k	15.16	69	498.4	498.1
19eo	e	o	15.85	57	460.4	460.1
19fg	f	g	3.03	92	409.3	409.0
19fh	f	h	3.12	98	397.3	397.0
19fi	f	i	2.41	89	404.3	404.0
19fo	f	o	2.87	90	385.3	385.0

[a] Purity measurements were made by integration of the LC/MS traces based on UV absorption at 214 nm (similar integration patterns observed at 254 nm in most cases). [b] Integration after subtraction of solvent (ethyl acetate). [c] Typical patterns of selenium isotopes were obtained in these mass spectra and the expected molecular weights of all compounds are based on the predominant isotope of selenium-80.

Experimental Section

Solvents and fine chemicals were purchased from Aldrich Chemical Company (Castle Hill, Australia) and used as supplied. Resins derivatized with Fmoc-protected Rink amide linker were purchased from Novabiochem (100−200 mesh; loading capacity: 0.47 mmol/g).

LC/MS Analysis. LC analysis was conducted with a Zorbax C8 (4.6 × 150 mm) column using isocratic mobile phase containing 49% acetonitrile, 50% water, and 1% of an ammonium formate solution (this solution was made up of 1 g of acetic acid and 315 mg of ammonium formate in 1 liter of 33% methanol in water). Detection was measured at 214 nm, and a flow rate was constant at 0.5 mL/min. MS analysis was conducted with an Agilent 1100 Series MSD system.

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded with a Bruker 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon. All spectra were recorded in $CDCl_3$ at 25 °C unless otherwise specified.

Solid-phase reactions were carried out in 10-mL or 1-mL screw-cap vials (Wheaton vials, Aldrich). The reaction vials were incubated in a heat block and gently shaken at specified temperatures. Purifications of resins were conducted with VacMaster-20 systems (Int. Sorbent Technology Ltd., UK).

Methyl 3-Iodo-4-[(*E*)-piperidin-1-yldiazenyl]benzoate (2). Sodium nitrite (0.7 g in 5 mL H_2O) was added to a magnetically stirred solution of methyl 4-amino-3-iodobenzoate (2.77 g. 10 mmol) in 1 M HCl (aq) (60 mL) at 5 °C. The resulting solution was allowed to stir at this temperature for 1 h and treated with piperidine in excess (10 mL). The reaction mixture was carefully decanted, and the precipitate (dark brown solid) was collected and redissolved in 5 mL of ethyl acetate. The crude product was subjected to flash chromatography (silica gel, 20% ethyl acetate in hexane elution) to afford the desired product **2** (3.1 g, 83% yield). LC: low chromophore-negative peak, t_r (retention time) = 28.2 min; MS: m/z = 374.0 [M + H]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 8.49 (s, 1H), 7.91 (d, J = 6.4 Hz, 1H), 7.38 (d, J = 6.4 Hz, 1H), 3.87 (s, 7H), 2.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.43, 153.17, 140.32, 129.75, 127.50, 116.33, 95.48, 52.84, 51.74, 44.04, 26.05, 23.83.

Methyl 3-Iodo-4-(methylsulfanyl)benzoate (3). Sodium thiomethoxide (1.2 g, 17 mmol) was carefully added to a magnetically stirred solution of compound **2** (3.73 g, 10 mmol) in methanol (20 mL) at room temperature for 30 min. The resulting solution was cooled to 5 °C (on ice); then treated with trifluoroacetic acid (20 mL); and finally, allowed to warm to room temperature and stirred for 1 h. The solvent was removed under reduced pressure, and the crude oil was subjected to chromatography (silica gel, 10% ethyl acetate in hexane) to afford the compound **3** (2.9 g, 94% yield). LC, t_r = 9.03 min; MS: m/z = 308.9 [M + H]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 8.38 (s, 1H), 7.97 (d, J = 7 Hz, 1H), 7.06 (d, J = 7 Hz, 1H), 3.88 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.14, 149.41, 139.66, 129.14, 126.87, 122.95, 95.05, 51.86, 16.42.

Methyl 3-Iodo-4-(methylselenyl)benzoate (4). $NaBH_4$ (1.81 g, 48 mmol) was added slowly (via spatula) into a solution of dimethyldiselenide (3.76 g, 20 mmol) in 100 mL of methanol over 1 h. The resulting reaction mixture was treated with **2** (3.73 g, 10 mmol) and allowed to stir at room temperature for 1 h. The reaction solution was then treated with trifluoroacetic acid (40 mL) at 70 °C for 1 h. The solvent was removed under reduced pressure, and the crude oil was subjected to flash chromatography (silica gel, 10% ethyl acetate in hexane elution) to afford the compound **4** (1.98 g, 56% yield). LC, t_r = 10.66 min; MS: m/z = 356.9 [M + H]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 8.31 (s, 1H), 7.88 (d, J = 7 Hz, 1H), 7.12 (d, J = 7 Hz, 1H), 3.88 (s, 3H), 2.34 (s,

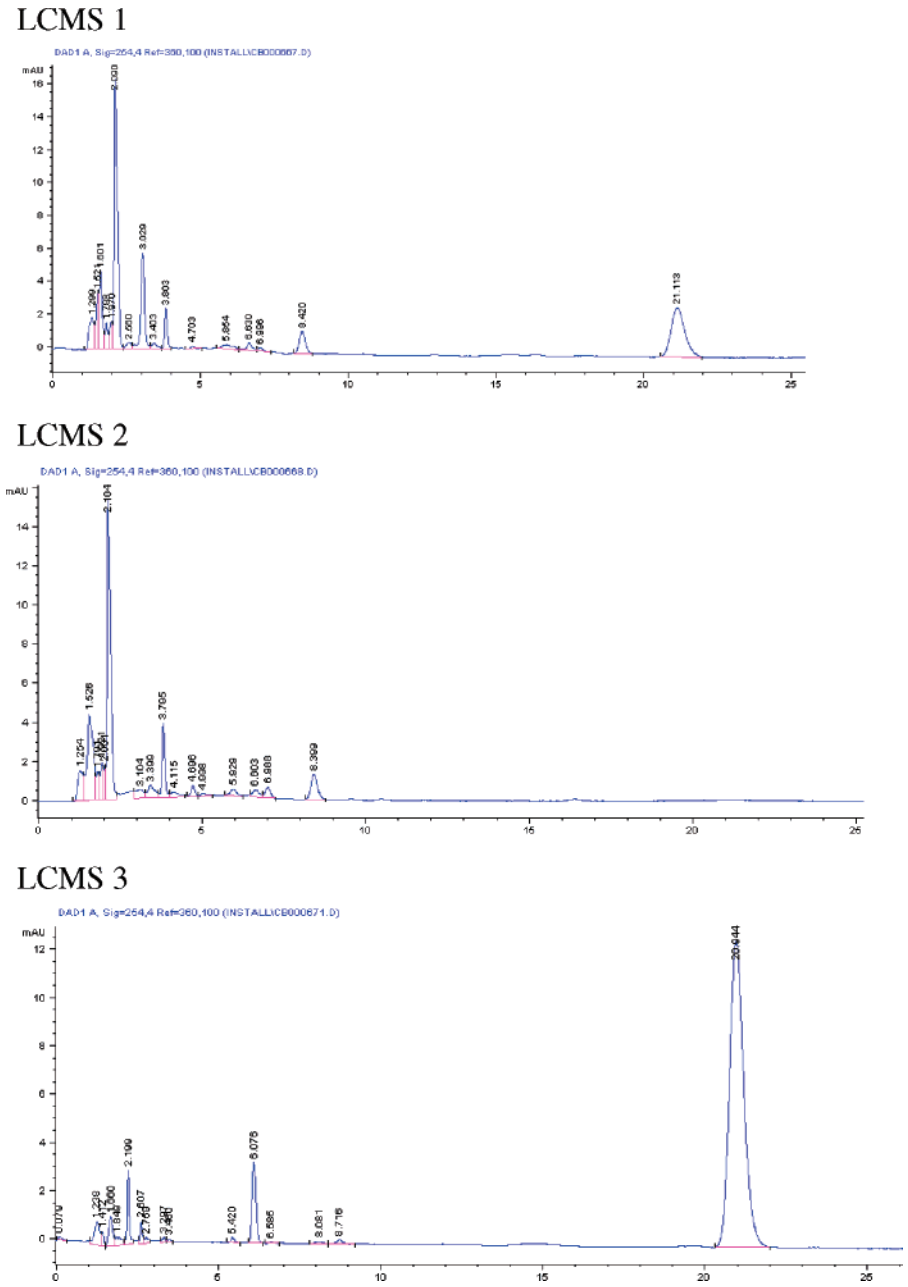


Figure 2. Partial purification of the compound **18eh**. LC/MS 1: crude product **18eh** (24% purity). LC/MS 2: impurities eluted with 5% EtOAc in hexane. LC/MS 3: compound **18eh** eluted with 60% EtOAc in hexane (85% purity).

3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.22, 146.64, 139.51, 128.94, 127.82, 126.43, 110.63, 51.90, 8.82.

3-Iodo-4-(methylsulfanyl)benzoic Acid (5). Methyl 3-iodo-4-(methylsulfanyl)benzoate (**3**) (2 g, 6.5 mmol) methanol (5 mL) was added dropwise to 2 M NaOH aqueous solution (50 mL). The resulting mixture was stirred at room temperature for 2 h; then acidified using 2 M HCl solution until the pH reached 2−3; and finally, extracted with ether (3 × 20 mL). The combined extract was dried ($MgSO_4$) and concentrated under reduced pressure to afford the compound **5** as a white powder (1.7 g, 90% yield). LC, t_r = 3.0 min; MS (molecular ion peak was not detected). ^{1}H NMR (300 MHz, DMSO-d_6): 8.21 (s, 1H), 7.89 (d, J = 7 Hz, 1H), 7.25 (d, J = 7 Hz), 2.47 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): 165.89, 149.27, 139.22, 129.49, 127.23, 124.22, 95.96, 16.10.

3-Iodo-4-(methylselenyl)benzoic Acid (6). Methyl 3-iodo-4-(methylselenyl)benzoate (**4**) (0.3 g, 0.85 mmol) in methanol (5 mL) was added dropwise to 2 M NaOH (aq) (10 mL). The resulting mixture was stirred at room temperature for 1 h; then acidified by addition 2 M HCl (aq) until the pH reached 2−3; and finally, extracted with ether (3 × 10 mL). The combined extract was dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound **6** (0.26 g, 90% yield). LC, t_r = 3.3 min; MS: m/z = 296.0 [M − COOH].$^+$ ^{1}H NMR (300 MHz, DMSO-d_6): 8.16 (s, 1H), 7.82 (d, J = 7 Hz, 1H), 7.27 (d, J = 7 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): 165.99, 146.43, 139.12, 129.32, 128.93, 127.45, 98.69, 8.80.

Preparation of Resin-Bound *o*-Iodomethylphenyl Sulfide 8 and Selenide 9. Rink amide resin (1 g, Novabiochem, 0.47 mmol/g) was suspended in 10 mL of 20% piperidine

in DMF for 30 min (Fmoc deprotection) and carefully washed with DMF (3 × 5 mL) and DCM (3 × 5 mL). The resulting resin **7** was gently mixed (on shaker) with a mixture of **5** (0.28 g, 0.95 mmol), HOBt (0.135 g, 1 mmol), and 1,3-diisopropylcarbodiimide (0.126 g, 1 mmol) in DCM/DMF (1:1, 10 mL) at 40 °C for 16 h. The resins were carefully washed with DCM/DMF (1:1, 3 × 5 mL) and DCM (3 × 5 mL) and dried under reduced pressure for 2−3 h to afford **8**. A similar procedure was applied for preparation of **9** from **6**.

Typical Procedure for Coupling Alkynes To Give 11 or 12. Resins **8**/**9** (0.5 g, 0.23 mmol) were incubated with a mixture of alkyne **10** (2 mmol), $PdCl_2(PPh_3)_2$ (30 mg, 0.042 mmol), and CuI (5 mg, 0.052 mmol) in piperidine/THF (1:1, 4 mL) at 65 °C for 16 h. The resulting resins were filtered and carefully washed with DMF (3 × 5 mL), methanol (5 mL), and DCM (3 × 5 mL) and dried under reduced pressure for 30 min to afford **11**/**12**.

Typical Reaction for Preparation of Resins 13/14. Resins **11**/**12** (0.6 g, 0.23 mmol) were incubated with iodine (0.1 g, 0.39 mmol) in dichloromethane (DCM) at 65 °C for 6 h. The resulting resins were filtered and carefully washed with DMF (3 × 5 mL), methanol (3 × 5 mL), and DCM (3 × 5 mL) and dried under reduced pressure for 30 min to afford **13**/**14.**

Typical Procedure for Suzuki Coupling of Boronic Acid 15 to Resin-bound Iodides 13/14 to Give 16/17. Resins **13**/**14** (0.06 g, 0.023 mmol) were incubated with a mixture of boronic acid **15** (1 mmol), $Pd(PPh_3)_4$ (10 mg, 0.009 mmol), TBAF (0.5 mL of 1 M solution in THF), and K_2CO_3 (25 mg, dissolved in 3 drops of water) in DMF (1 mL) at 65 °C for 16 h. The resulting resins were filtered and carefully washed with DMF (3 × 5 mL), methanol (5 mL), and DCM (3 × 5 mL) and dried under reduced pressure for 30 min to give the product **16**/**17**.

Typical Procedure for the Cleavage of Resin-bound Products 16/17 To Give 18/19. Resins **16**/**17** were incubated with 20% TFA in DCM for 1 h. The cleavage solution was separated and dried under a stream of N_2 gas (15 min). The resulting crude product was dissolved in ethyl acetate (1 mL) and eluted with ethyl acetate (1 mL) through a plug of silica (2 cm long × 0.5 cm diameter). The ethyl acetate was removed using a stream of N_2 (g) and the product, **18**/**19**, was redissolved in methanol and analyzed by LC/MS (see above for typical conditions, see also Supporting Information). For compounds of less than 70% purity, the product was subject to a second purification procedure. This involved taking the product up in 5% ethyl acetate in hexane (1 mL) and transferring it to a small plug of silica (2 cm long × 0.5 cm diameter) and eluting with 5% ethyl acetate in hexane (2 mL), followed by elution with 60% ethyl acetate in hexane (2 mL). The second elution was evaporated under a stream of N_2 (g) and redissolved in methanol, and an LC/MS profile was obtained (see above for typical conditions, see also Supporting Information).

Supporting Information Available. LC/MS profiles of all compounds in Table 1 and 2. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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(11) Structural validation and purity of cleaved reaction mixtures was determined using LC/MS; see also Supporting Information.

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