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Solution-Phase Synthesis of a Diverse Library of Benzisoxazoles Utilizing the [3 + 2] Cycloaddition of in Situ-Generated Nitrile Oxides and Arynes

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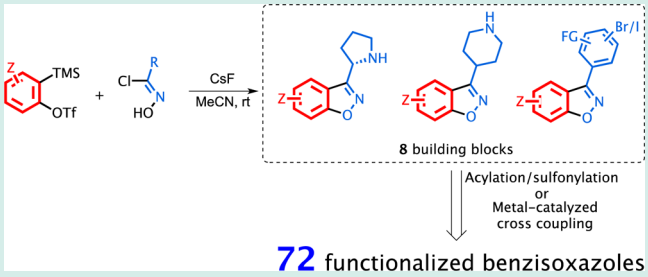
Supporting Information

ABSTRACT: A library of benzisoxazoles has been synthesized by the [3 + 2] cycloaddition of nitrile oxides with arynes and further diversified by acylation/sulfonylation and palladium-catalyzed coupling processes. The eight key intermediate benzisoxazoles have been prepared by the reaction of *o*-(trimethylsilyl)aryl triflates and chlorooximes in the presence of CsF in good to excellent yields under mild reaction conditions. These building blocks have been used as the key components of a diverse set of 3,5,6-trisubstituted benzisoxazoles.



KEYWORDS: *solution-phase synthesis, benzisoxazoles, [3 + 2] cycloaddition, palladium-catalyzed, library*

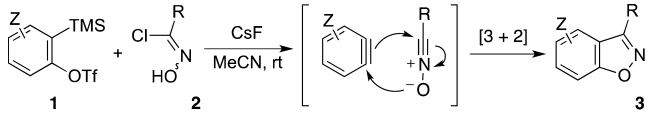
INTRODUCTION

Low molecular weight heterocycles are among the most highly recognized pharmacophores.[1] Among them, the benzisoxazole scaffold has evolved as a convenient cbioisosteric replacement for the benzoyl functionality of some biologically active molecules.[2] Benzisoxazoles, particularly their 3-alkyl and 3-aryl substituted derivatives, have displayed a broad range of biological activities, such as antipsychotic,[2a,3] antitumor,[4] anticonvulsant,[5] antimicrobial,[6] antibacterial,[7] diuretic,[8] antithrombotic,[2c] and acetylcholinesterase-inhibition[2b,9] (Alzheimer's disease treatment) activities (Figure 1).

Various routes to 3-alkyl/aryl benzisoxazoles have been reported. Most of the syntheses are 3 to 4 steps in length, usually involving formation of the carbon−oxygen bond (through S_NAr,[8b,10] or Pd-[11] or CuI[12]-catalyzed reactions) or the oxygen−nitrogen bond (through base-mediated cyclizations[13] or intramolecular Mitsunobu[14] reactions) via intermediate *o*-halo- or *o*-hydroxyaryl ketoximes during the final steps. The syntheses of the corresponding *o*-halo- or *o*-hydroxyaryl ketones often involve a strongly acidic Friedel−Craft's reaction and the use of one of the substrates as a solvent, or in other cases require the use of strongly basic organometallics.

Because of the extensive biological activity of benzisoxazoles, it is likely that libraries of low molecular weight benzisoxazoles will serve as valuable tools for drug discovery. However, the limitations of present convergent literature syntheses of these heterocycles have been an obstacle to expedient evaluation of diverse benzisoxazoles for biological activity. It should be noted that amino-containing benzisoxazoles have been produced and simple alkylation/acylation derivatization steps have been used to prepare and evaluate up to 36 members from a single scaffold in a divergent manner.[15]

Scheme 1. Aryne Methodology for the Synthesis of Benzisoxazoles



We have previously reported an efficient method leading to 3-alkyl- and 3-arylbenzisoxazoles by the [3 + 2] cycloaddition of nitrile oxides and arynes.[16] Both highly reactive components have been generated in situ by fluoride anion from commercially available aryne precursors and readily prepared chlorooximes (Scheme 1).

In an extension of our previous studies, we hereby report the synthesis of a solution-phase library using this methodology, which includes preparation of benzisoxazole-containing blocks **4**−**6**, followed by (a) their acylation/sulfonylation if the building block possesses an amino functionality, such as the piperidinyl-containing substrates **4** (their derivatives are prevalent in the literature)[17] or the L-proline-derived substrates **5**, and (b) elaboration using Pd-catalyzed coupling processes if

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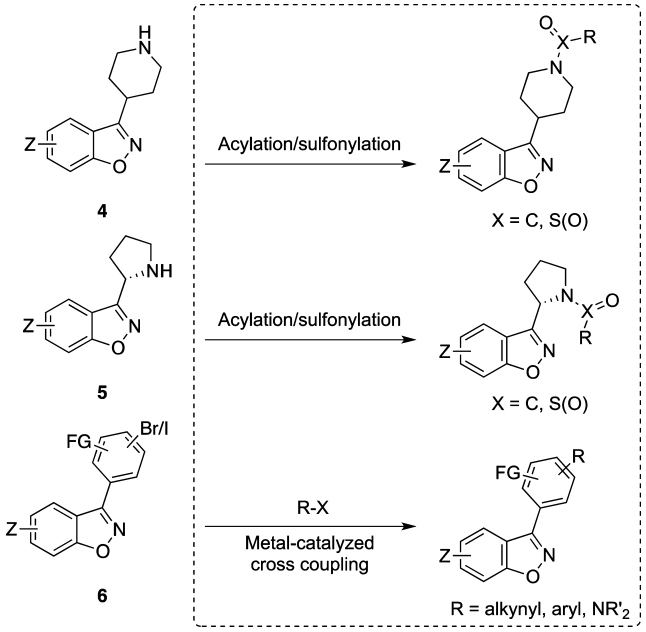
Scheme 2. Parent Benzisoxazole Scaffolds and Derivatization Methodology



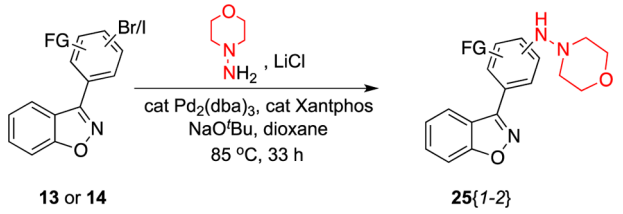
the building block possesses a Br/I handle, such as the 3-haloaryl-substituted benzisoxazoles **6** (Scheme 2).

As such, we set out to construct a diverse 72-membered library of benzisoxazoles to be screened for biological activity. This is the first example of the use of aryne chemistry for constructing a benzisoxazole library.

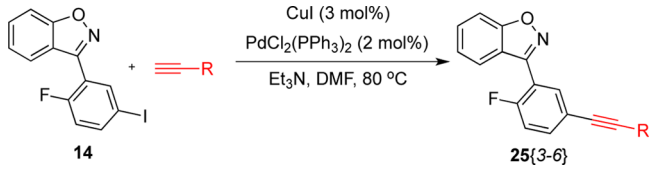
RESULTS AND DISCUSSION

To synthesize a library with greater chances for biological activity, the substituted derivatives **4**–**6** have been evaluated computationally for their drug-like properties using SYBYL,[18] plus Lipinski's "rule of five" and Veber's rule as additional guidelines for the prediction of oral bioavailability.[19] Lipinski calculations have been performed based on the commercial availability of the aryne precursors [the *o*-(trimethylsilyl)aryl triflates],[20] acylating/sulfonylating agents, boronic acids (for Suzuki–Miyaura coupling), amines and hydrazines (for Buchwald–Hartwig amination), and terminal alkynes (for Sonogashira coupling).[21] Four benzyne precursors, 52 acylating/sulfonylating agents, 21 boronic acids, 10 amines and hydrazines, and 10 terminal alkynes have been used to generate a 2440-membered virtual library. In silico analysis of this virtual set revealed 71 members

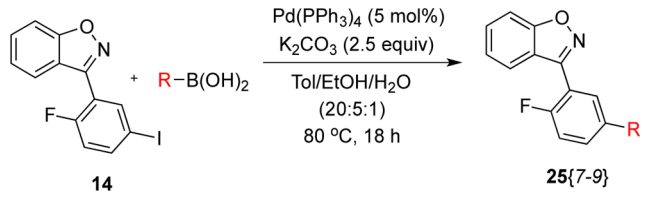
Scheme 3. Hartwig–Buchwald Amination of 13 and 14



Scheme 4. Sonogashira Coupling of 14



Scheme 5. Suzuki–Miyaura Coupling of 14



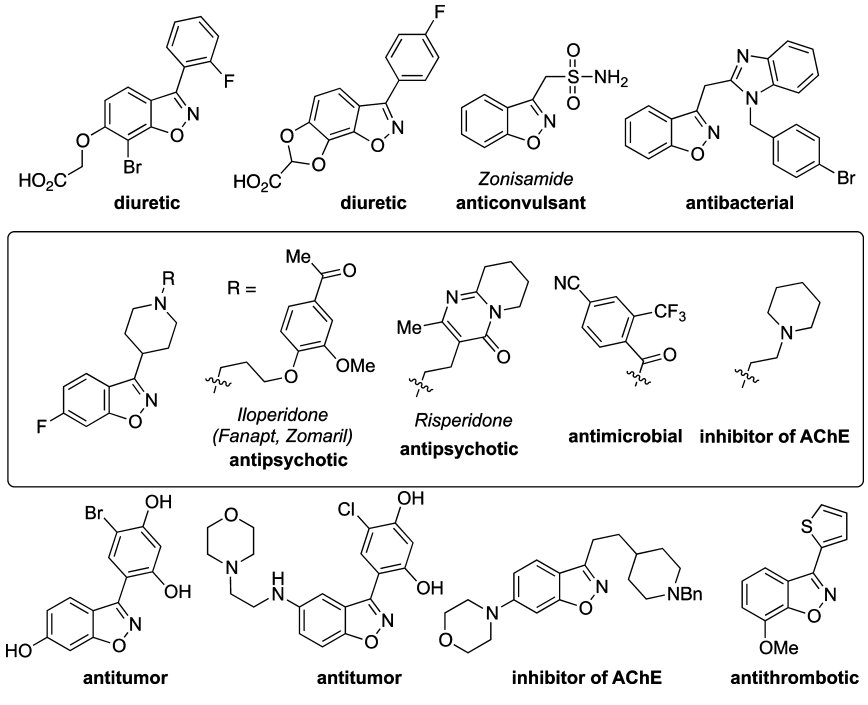


Figure 1. Examples of medicinally relevant benzisoxazoles.

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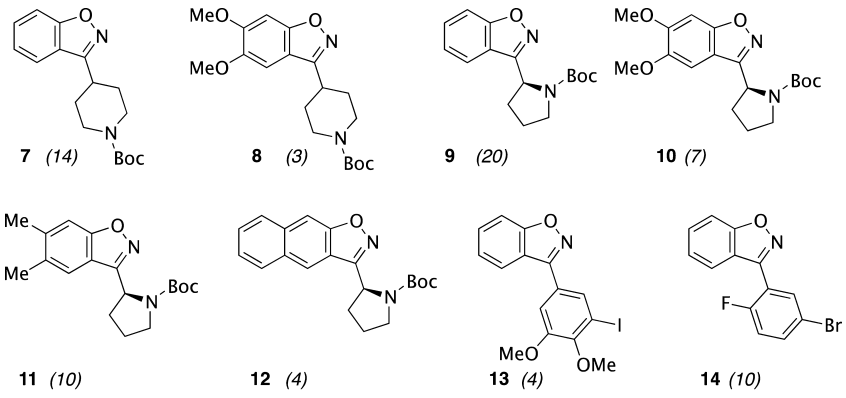

Figure 2. Desired benzisoxazole building blocks.

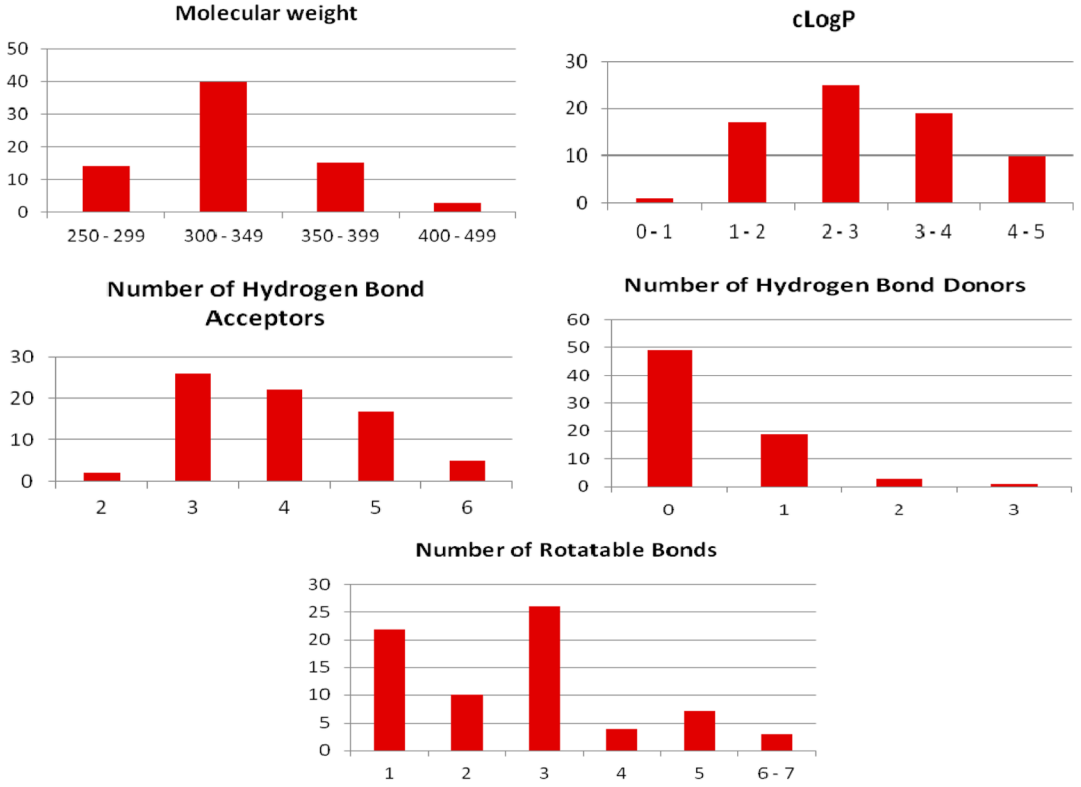

Figure 3. Distribution of the physicochemical and structural properties of our library entries.

with diversity scores[22] <1.0 along with one having a slightly higher score, allowing the synthesis of the target compounds from only eight building blocks (Figure 2). The distributions of the Lipinski and Veber parameters (molecular weight, cLogP, number of rotatable bonds, H-bond donors and acceptors) are shown in Figure 3. All compounds follow Lipinski's and Veber's rules with no violations.

Synthesis of the Building Blocks. For practical purposes, relatively stable benzisoxazole blocks were needed. Thus, we chose to synthesize amine-containing starting benzisoxazoles as their corresponding Boc-urethanes **7**−**12**. The amounts of the eight building blocks required were estimated assuming a 60% yield in the final diversification step and our goal of preparing 35 mg of each compound for screening.

Despite the scalability issues inherent in the heterogeneous CsF-promoted benzyne-mediated chemistry,[23] running the reactions in parallel at increased loadings (up to 4×) furnished starting materials **9**−**14** in sufficient amounts for further diversification (Table 1). Using our methodology, *N*-Boc-piperidine-derived chlorooxime **15** afforded the desired benzisoxazoles **7** and **8** in 88% and 59% yields, respectively, with different aryne precursors when performed on a 0.25 mmol scale (entries 1 and 3).

The coupling of the chiral proline-derived chlorooxime **16** with an array of symmetrical benzynes afforded the desired chiral benzisoxazoles **9**−**12** in 33−88% yields (entries 5−10). The substituted benzynes provided slightly lower yields than the parent system, with the dimethoxybenzyne being the best of

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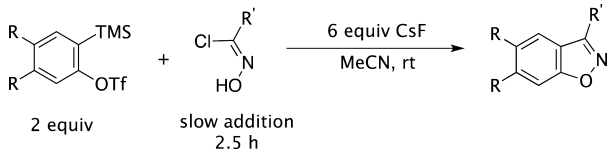
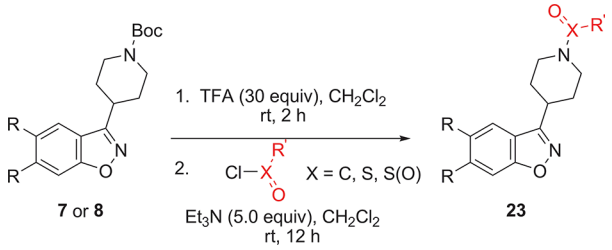
Table 1. Preparation of the Benzisoxazole Building Blocks 7−14



entry	chloro-oxime	R′	benzyne precursor	R	reaction scale (mmol)[a]	product	yield (%)[b]
1	**15**	4-(*N*-Boc-piperidinyl)	**19**	H	0.25	7	88
2	**15**	4-(*N*-Boc-piperidinyl)	**19**	H	0.50	7	78
3	**15**	4-(*N*-Boc-piperidinyl)	**20**	OMe	0.25	8	59
4	**15**	4-(*N*-Boc-piperidinyl)	**20**	OMe	0.75	8	40
5	**16**	(*S*)-2-(*N*-Boc-pyrrolidinyl)	**19**	H	0.25	9	85
6	**16**	(*S*)-2-(*N*-Boc-pyrrolidinyl)	**19**	H	0.50	9	88
7	**16**	(*S*)-2-(*N*-Boc-pyrrolidinyl)	**20**	OMe	0.50	10	73
8	**16**	(*S*)-2-(*N*-Boc-pyrrolidinyl)	**21**	Me	0.50	11	51
9	**16**	(*S*)-2-(*N*-Boc-pyrrolidinyl)	**21**	Me	1.00	11	33
10	**16**	(*S*)-2-(*N*-Boc-pyrrolidinyl)	**22**	C_4H_4	0.50	12	50
11	**17**	3-iodo-4,5-dimethoxyphenyl	**19**	H	0.25	13	76
12	**17**	3-iodo-4,5-dimethoxyphenyl	**19**	H	0.50	13	56
13	**18**	5-bromo-2-fluorophenyl	**19**	H	0.25	14	57
14	**18**	5-bromo-2-fluorophenyl	**19**	H	0.50	14	54

[a]The amount of chlorooxime used. [b]Isolated yields after normal phase column chromatography.

Table 2. Data for Library Compounds 23{*1−17*}[a]



product	R	HRMS (calcd)	HRMS (found)[b]	purity (%)[c]	yield (%)[d]
23{*1*}	H	298.0929	299.1051	99	24
23{*2*}	H	296.1161	297.1249	>99	35
23{*3*}	H	272.1525	273.1619	>99	52
23{*4*}	H	315.1583	316.1671	>99	31
23{*5*}	H	313.1790	314.1880	>99	36
23{*6*}	H	312.0932	313.1023	88	(3)
23{*7*}	H	306.1402	307.1512	95	21
23{*8*}	H	342.1038	343.1134	>99	32
23{*9*}	H	348.0602	349.0710	99	26
23{*10*}	H	346.1100	347.1189	>99	52
23{*11*}	H	347.0940	348.1025	97	48
23{*12*}	H	343.0991	344.1068	95	29
23{*13*}	H	497.9248	498.9355	96	62[e]
23{*14*}	H	366.1579	367.1654	99	95[e]
23{*15*}	OMe	358.1140	359.1227	88	(4)
23{*16*}	OMe	366.1613	367.1704	>99	33
23{*17*}	OMe	346.1892	347.1986	94	23

[a]Reactions were performed on a 0.25 mmol scale. TFA deprotection: 0.5 mL of TFA and 1 mL of DCM were used. Acylation: Et_3N (5 equiv), acyl/sulfonyl chloride (1.5 equiv) and anhydrous CH_2Cl_2 were used. [b]For $[M + H]^+$. [c]UV purity determined at 214 nm after preparative HPLC. [d]Isolated yields after MDF column chromatography. Yields in parentheses are considered failed entries (<90% purity and/or <5 mg quantity). [e]Purified by normal phase column chromatography.

the three (73% yield of the corresponding benzisoxazole **10**, entry 7). The dimethylbenzyne and the symmetrical naphthalyne provided the desired benzisoxazoles **11** and **12** in 51% and 50% yields, respectively, when allowed to react on a 0.50 mmol scale (entries 8 and 10). The electron-rich dimethoxyiodo-substituted chlorooxime **17** led to formation of the desired benzisoxazole **13** in a 76% yield on a standard 0.25 mmol scale (entry 11). The yield was significantly lower (56%) when the reaction was run on a 0.50 mmol scale. The more electron-deficient chlorooxime **18** afforded the benzisoxazole **14** in a lower 57% yield, when run on a 0.25 mmol scale (compared to 54% on a 0.50 mmol scale, entry 14). With the benzisoxazole building blocks **9**−**14** in hand, a 72-member library was designed. The library was constructed by diversification of the 3-substituted benzisoxazole core scaffold using acylation, sulfonylation and metal-catalyzed cross-coupling reactions as outlined in Scheme 2. This method permits the introduction of functional diversity to generate benzisoxazoles with potential biological activity using parallel synthesis.

Diversifications. *Acylation/Sulfonylation.* Our diversification sequence involved TFA-mediated Boc-deprotection of the cycloadducts **7**−**12** and subsequent *N*-acylation/sulfonylation with various acyl/sulfonyl chlorides. This deprotection−acylation procedure[24] was best carried out in one pot: TFA deprotection in DCM, addition of toluene, parallel concentration, addition of fresh DCM followed by basification using triethylamine (5.0 equiv), and finally the addition of an acyl/sulfonyl/sulfinyl chloride (1.5 equiv). The reactions were carried out in 1-dram vials using Mettler-Toledo Miniblocks in which the crude final reaction mixtures were concentrated and purified via automated mass-directed (MDF) LC/MS. Table 2 shows the chemset diversity inputs for the substituted 3-(4-piperidinyl)benzisoxazoles. Amide/sulfonamide products **23**{*1−17*} (Figure 4) derived from the starting blocks **7** and **8** were obtained in 3−95% yields and excellent purities (88 to >99%) after MDF purification.

A series of 3-(pyrrolidin-2-yl)-benzisoxazoles (Table 3) was prepared using the same procedure utilized for the synthesis of the 3-(4-piperidinyl)benzisoxazoles. The yields of *N*-acylated and *N*-sulfonylated benzisoxazoles **24**{*1−41*} (Figure 5) ranged from 1 to 57% with 60 to >99% purities obtained after MDF

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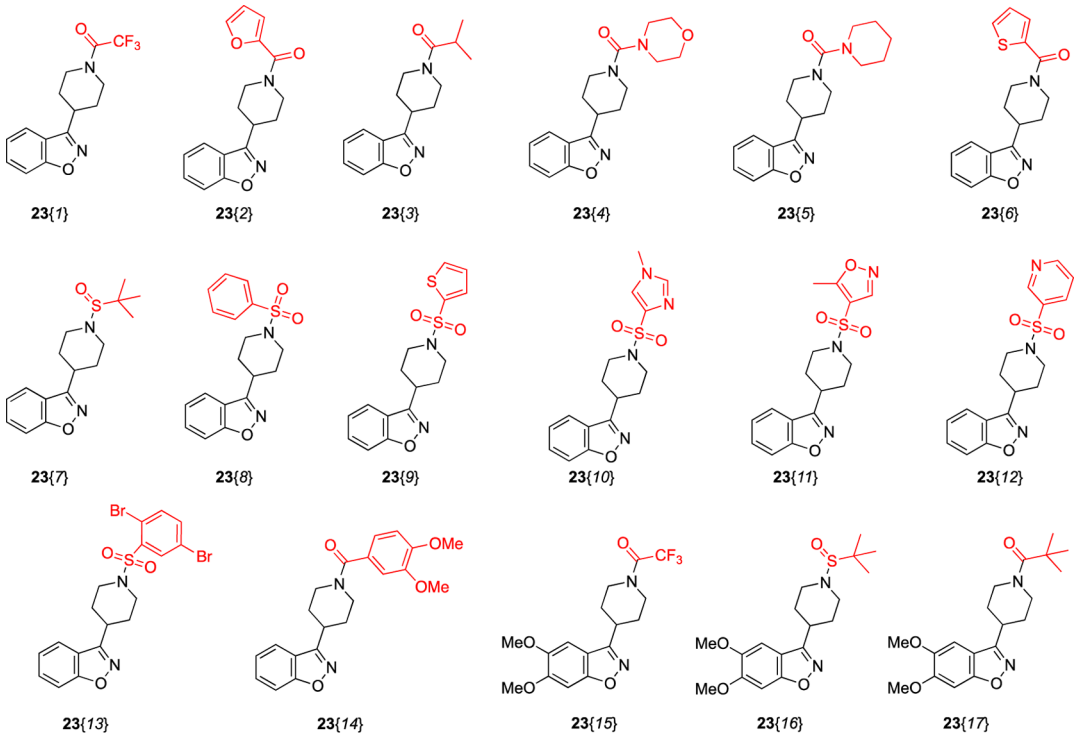
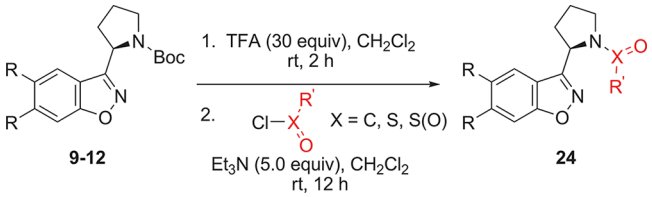


Figure 4. Derivatized 3-(4-piperidinyl)benzisoxazoles.

Table 3. Data for Library Compounds 24{*1*−*41*}[a]



product	R	HRMS (calcd)	HRMS (found)[b]	purity (%)[c]	yield (%)[d]
24{*1*}	H	337.1063	338.1152	96	27[e]
24{*2*}	H	284.0773	285.0860	>99	41
24{*3*}	H	282.1004	283.1085	>99	26
24{*4*}	H	317.1164	318.1272	>99	51
24{*5*}	H		not found		(nd)
24{*6*}	H	299.1634	300.1737	>99	38
24{*7*}	H	258.1368	259.1455	>99	52
24{*8*}	H	324.1274	325.1378	>99	41
24{*9*}	H	360.1086	361.1174	>99	56
24{*10*}	H	306.1368	307.1478	>99	28
24{*11*}	H	360.1086	361.1164	>99	33
24{*12*}	H	301.1426	302.1525	>99	43
24{*13*}	H	300.1222	301.1306	>99	44
24{*14*}	H	298.0776	299.0862	>99	24
24{*15*}	H	332.0943	333.1033	>99	45
24{*16*}	H	334.0446	335.0540	98	43
24{*17*}	H	328.0882	329.0983	>99	38
24{*18*}	H	346.0787	347.0879	>99	57
24{*19.1*}	H	292.1245	293.1357	96	37[f]
24{*19.2*}	H	292.1245	293.1335	94	37[f]
24{*20*}	H		not found		(nd)
24{*21*}	OMe	430.0528	431.0629	99	28
24{*22*}	OMe	332.1736	333.1831	>99	30
24{*23*}	OMe	344.0984	345.1090	>99	34
24{*24*}	OMe	388.1093	389.1180	>99	(5)
24{*25*}	OMe	432.0991	433.1060	99	(3)
24{*26*}	OMe	406.0999	407.1081	>99	34
24{*27.1*}	OMe	352.1457	353.1548	>99	28[f]
24{*27.2*}	OMe	352.1457	353.1553	>99	28[f]
24{*28*}	Me	312.1085	313.1180	>99	(3)
24{*29*}	Me	300.1837	301.1925	>99	40
24{*30*}	Me	327.1946	328.2033	>99	43
24{*31*}	Me	300.1837	301.1941	92	(7)
24{*32*}	Me	328.1535	329.1629	60	(1)
24{*33*}	Me	329.1739	330.1854	>99	32
24{*34*}	Me	362.0758	363.0855	94	27
24{*35.1*}	Me	320.1558	321.1657	>99	46[f]
24{*35.2*}	Me	320.1558	321.1650	95	46[f]
24{*36*}	Me	365.1375	366.1476	92	39
24{*37*}	Me	361.1096	362.1197	96	36
24{*38*}	C_4H_4	387.1219	388.1332	>99	29
24{*39*}	C_4H_4	334.0929	335.1029	>99	36
24{*40.1*}	C_4H_4	342.1402	343.1505	>99	37[f]
24{*40.2*}	C_4H_4	342.1402	343.1513	92	(37)[f]
24{*41*}	C_4H_4	350.1379	351.1490	>99	10

[a]Reactions were performed on a 0.25 mmol scale. TFA deprotection: 0.5 mL of TFA and 1 mL of DCM were used. Acylation: Et_3N (5 equiv), acyl/sulfonyl chloride (1.5 equiv) and anhydrous CH_2Cl_2 were used. [b]For $[M + H]^+$. [c]UV purity determined at 214 nm after preparative HPLC. [d]Isolated yields after MDF column chromatography. Yields in parentheses are considered failed entries (<90% purity and <5 mg quantity). [e]Purified by normal phase column chromatography. [f]Combined yield for the two diastereomers formed.

purification. In the case of sulfinylamides **24**{*19*, *27*, *35*, and *40*}, mixtures of diastereomers were obtained, which were separable by MDF separation. The relative stereochemical assignments of the diastereomers were not determined.

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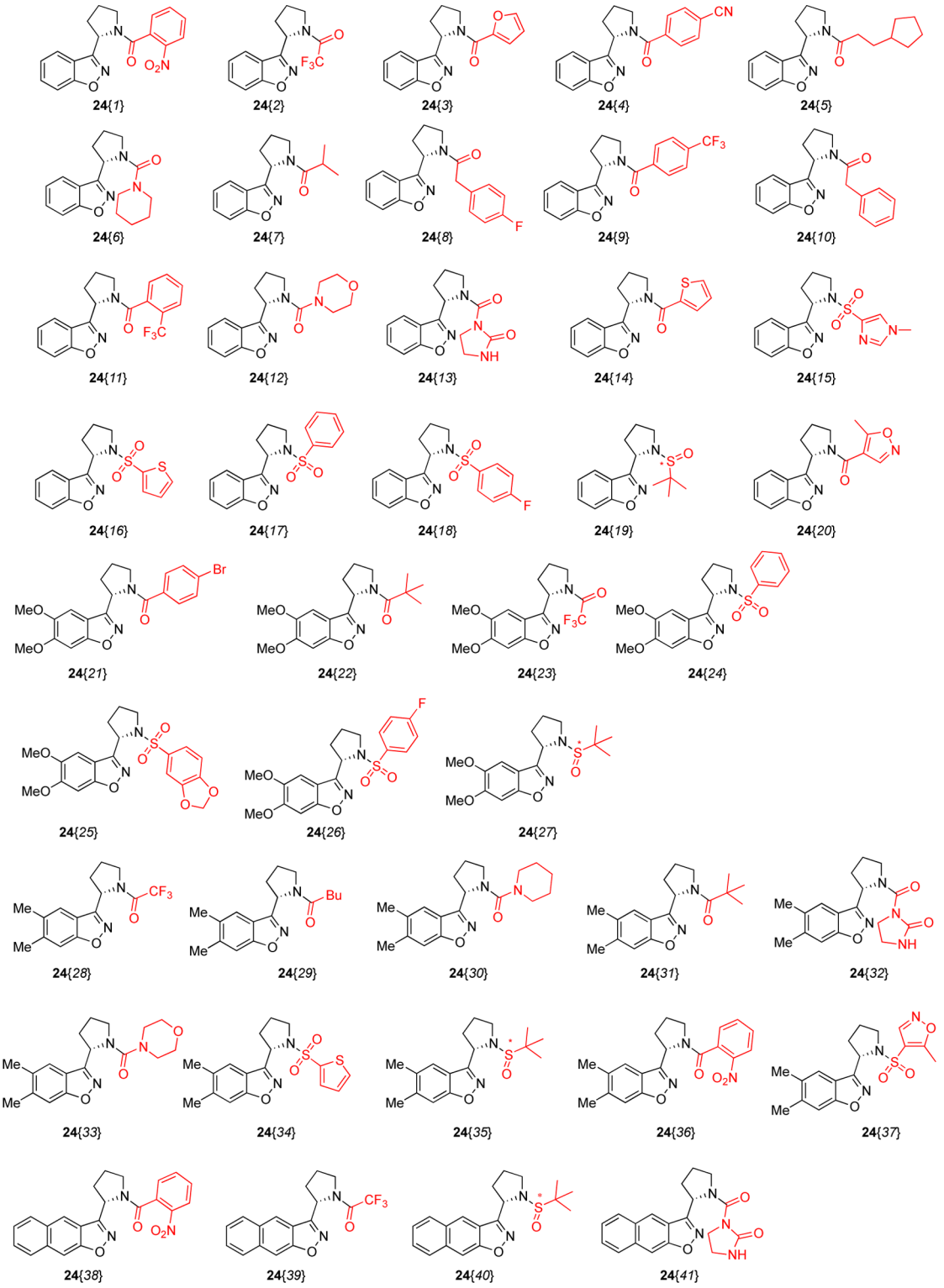

Figure 5. Derivatized 3-(2-pyrrolidinyl)benzisoxazoles.

Pd/Cu-Catalyzed Cross-Couplings. To prepare libraries derived from 3-(3-iodo-4,5-dimethoxyphenyl)benzisoxazole (**13**) and 3-(2-fluoro-5-iodophenyl)benzisoxazole (**14**), we utilized various Pd/Cu-catalyzed cross-coupling reaction sequences, such as Suzuki–Miyaura coupling with aryl boronic acids, Hartwig–Buchwald coupling with alkyl hydrazines, and Sonogashira coupling with terminal alkynes. The data for the compounds (Figure 6) obtained through these diversification procedures are combined in Table 4.

Hartwig–Buchwald coupling[25] of 3-(3-iodo-4,5-dimethoxyphenyl)benzisoxazole (**13**) with morpholin-4-amine afforded the desired product **25**{*1*} in a 41% yield (Scheme 3). With optimized conditions in hand, we employed this method for coupling of 3-(2-fluoro-5-iodophenyl)benzisoxazole (**14**) with appropriate alkyl hydrazines. While we were unable to isolate any

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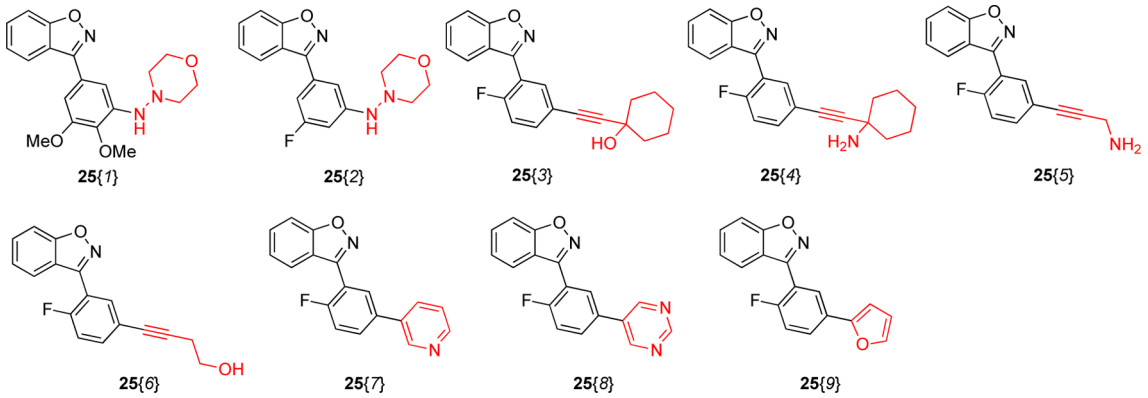

Figure 6. Benzisoxazoles derivatized through Pd/Cu-catalyzed coupling.

Table 4. Data for Library Compounds 25{*1*–*9*}[a]

product	reaction	HRMS (calcd)	HRMS (found)[b]	purity (%)[c]	yield (%)[c]
25{*1*}	amination[d]	355.1532	356.1635	>99	41
25{*2*}	amination[d]	313.1226	314.1322	97	14[e]
25{*3*}	Sonogashira[f]	335.1322	336.1407	98	39
25{*4*}	Sonogashira[f]	334.1481	335.1555	90	30
25{*5*}	Sonogashira[f]		not found		(nd)
25{*6*}	Sonogashira[f]	281.0852	282.0927	>99	16
25{*7*}	Suzuki–Miyaura[g]	290.0855	291.0941	>99	32
25{*8*}	Suzuki–Miyaura[g]	291.0808	292.0885	>99	25
25{*9*}	Suzuki–Miyaura[g]	279.0696	280.0992	>99	7

[a]Reactions were performed on a 0.25 mmol scale. [b]For $[M+H]^+$. [c]Yield/purities as in Table 1. Yields in parentheses are considered failed entries (<90% purity or <5 mg quantity). [d]For Hartwig–Buchwald coupling: alkyl hydrazine (2.0 equiv), LiCl (4.0 equiv), $Pd_2(dba)_3$ (2.5 mol %), xantphos (5 mol %), NaO^{t}Bu (2.0 equiv), dioxane, 85 °C, 33 h. [e]Purified by normal phase column chromatography. [f]For Sonogashira coupling: CuI (3 mol %), $PdCl_2(PPh_3)_2$ (2 mol %), terminal alkyne (1.5 equiv), Et_3N (1 mL), DMF, 80 °C. [g]For Suzuki–Miyaura coupling: aryl boronic acid (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), K_2CO_3 (2.5 equiv), Tol/EtOH/H_2O (20:5:1), 80 °C, 18 h.

of the desired compounds after MDF purification, we were able to obtain **25**{*2*} in a 14% yield after purification using normal phase chromatography.

Scheme 4 describes the synthesis of 4 analogues of 3-(2-fluoro-5-iodophenyl)benzisoxazole (**14**) using a Sonogashira coupling[26] with 16–39% yields for successful entries in 90 to >99% purities after MDF chromatography. The generation of 3 analogues based on Sonogashira couplings of 3-(3-iodo-4,5-dimethoxyphenyl)benzisoxazole (**13**) with terminal alkynes provided unfavorable results, and we were not able to isolate the desired products.

The Suzuki–Miyaura coupling[27] of 3-(2-fluoro-5-iodophenyl)-benzisoxazole (**14**) with aryl boronic acids afforded the desired products **25**{*7*–*9*} in 7–32% yields in excellent purities via preparative MDF purification (Scheme 5).

CONCLUSIONS

The aryne-mediated preparation and subsequent acylation/sulfonylation and palladium-catalyzed reactions of benzisoxazoles with various cross-coupling partners has enabled the construction of a 72-member library of diverse 3-substituted benzisoxazoles with potential biological activity. We anticipate that this methodology will be applicable in future diversity-oriented parallel synthesis for discovery purposes. The overall success rate for the library was 83% and the average purity after preparative MDF-HPLC was 99%.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization of a representative 20 library members, including full ^{1}H and ^{13}C NMR spectra and conditions for their high throughput liquid chromatography purification. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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