Studies on the Synthetic Compatibility of Aryloxime Linkers in the Solid-Phase Synthesis of 3-Aminobenzisoxazoles

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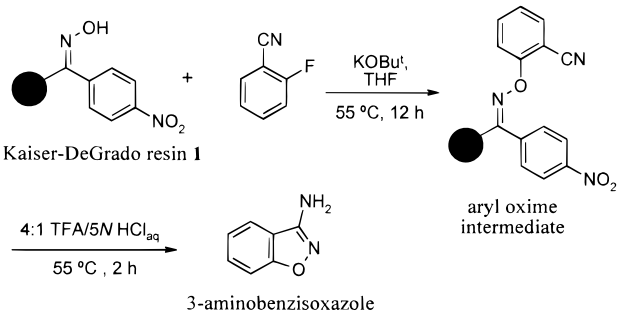
Further exploration of the scope of our solid-phase method for the synthesis of 3-aminobenzisoxazoles (using the Kaiser oxime resin **1**) is described. The effects of base, leaving group, and solvent on the nucleophilic aromatic substitution based resin-loading reaction are discussed. Representative aryloxime intermediates were subjected to a variety of acidic conditions commonly used in protecting group removal to establish the acid stability profile of this linker. Regioselectivity was evaluated with various di- and trifluorobenzonitriles, which gave single benzisoxazole products after loading and cyclorelease reactions. Substituent effects observed in the course of the acid stability and regioselectivity studies suggest that the nitrile plays a critical role in the oxime hydrolysis mechanism. Finally, to establish the compatibility of the aryloxime linker with a variety of useful on-resin synthetic transformations, functionalized substrates were loaded onto resin **1**, and carbon−nitrogen, carbon−oxygen, and carbon−carbon bond-forming reactions were successfully executed.

Introduction

In connection with our efforts to identify ligands for a variety of biological targets, we have been interested in the synthesis of 3-aminobenzisoxazoles.[1] To take advantage of parallel synthesis techniques,[2] we have recently developed a solid-phase adaptation of the Shutske method[3] for the synthesis of these interesting heterocycles.[4] In our initial disclosure, we reported that the potassium salt of the Kaiser−Degrado resin[5] **1** (Scheme 1) could react with 2-fluorobenzonitrile to give the nucleophilic aromatic substitution adduct. This aryl oxime intermediate was then treated with aqueous acidic conditions to effect a cyclitive[6] removal (or cyclorelease[7]) of the substrate giving 3-aminobenzisoxazole.

Although acylated derivatives of **1** have been widely utilized for the solid-phase synthesis of amides and related structures,[8] our method involves the first application of the Kaiser oxime resin to S_NAr reactions. Moreover, this linker strategy can be thought of as "traceless" since the desired heterocyclic product contains no residual functionality as a result of resin attachment.[9]

Scheme 1. Reaction of 2-Fluorobenzonitrile with Kaiser−DeGrado Resin 1 Followed by Cyclitive Removal



Finally, this approach to the synthesis of 3-aminobenzisoxazoles is particularly efficient since the cyclization reaction also serves as the cleavage step.

In this paper, we report further exploration of this methodology, including the effect of the base and the leaving group on the loading reaction, as well as studies on the stability of the aryl oxime linker under a variety of acidic conditions commonly used for protecting group removal. Finally, to establish the viability of this methodology for library generation, functionalized aryl oxime intermediates have been prepared and subjected to a variety of organic transformations that are widely used for the formation of C−N, C−O, and C−C bonds.

Results and Discussion

Loading Reaction. Nucleophilic aromatic substitution reactions have been extensively studied in solution.[10] However, the extent to which this precedent could be applied to predict the outcome of these heterogeneous reactions was not clear given the importance of resin-swelling properties, site accessibility, etc.[11] Therefore, we studied the effect of the solvent, leaving group, and

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(1) Suh has recently incorporated this heterocycle in the design of potent LTB_4 receptor antagonists. Suh, H.; Jeong, S.; Han, Y. N.; Lee, H.; Ryu, J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 389.

(2) Kaldor, S. W.; Siegel, M. G. *Curr. Opin. Chem. Biol.* **1997**, *1*, 101. Balkenhohl, F.: von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288.

(3) Shutske, G. M.; Kapples, K. J. *J. Heterocycl. Chem.* **1989**, *26*, 1293. For other examples of solution-phase intramolecular nucleophilic additions to nitrile by nitrogen, see: Kwok, R.; Pranc, P. *J. Org. Chem.* **1967**, *32*, 738. Blicke, F. F.; Zambito, A. J.; Stenseth, R. E. *J. Org. Chem.* **1961**, *26*, 1826.

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(10) Nudelman, N.; Mancini, P. M. E.; Martinez, R. D.; Vottero, L. R. *J. Chem. Soc., Perkin Trans. 2* **1987**, 951. Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: Amsterdam, 1968. Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147.

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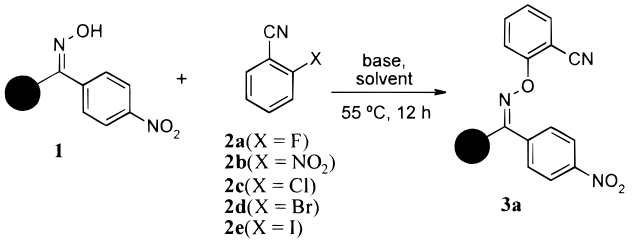
Table 1. Effect of Leaving Group, Solvent, and Counterion on Loading Reactions



entry	X	base	% loading yield of **3**[a] THF	MeCN	DMF	DMSO
1	F	KOBu^t	78	13	59	66
		KHMDS	62	14	60	63
		NaHMDS	42	20	63	65
		LiHMDS	<5	<5	46	67
2	NO_2	KOBu^t	72	28	41	54
3	Cl	KOBu^t	<5	<5	<5	15
4	Br	KOBu^t	<5			
5	I	KOBu^t	<5			

[a] Determined by resin weight difference (average of three experiments)

counterion on the solid-phase loading reaction (Table 1). In comparing THF, MeCN, DMF, and DMSO using potassium *tert*-butoxide (KOBu^t) to form the oxime anion, THF gave the best results, providing a 78% loading yield with 2-fluorobenzonitrile (**2a**) and 72% with 2-nitrobenzonitrile (**2b**).[12] A 10−30% decrease in the loading yield was observed for both **2a** and **2b** when DMF or DMSO was used as the solvent. Loading yields also decreased dramatically with the use of chloro- (**2c**), bromo- (**2d**), and iodobenzonitriles (**2e**).

The effect of the counterion on the loading reaction was evaluated with 2-fluorobenzonitrile as the substrate in several reaction solvents (Table 1, entry 1). In THF, the potassium salt of resin **1** gave the highest loading yields with KOBu^t giving slightly better results than potassium hexamethyldisilazide (KHMDS). Treatment of **1** with sodium hexamethyldisilazide (NaHMDS) gave a loading yield of 42%. Interestingly, with THF no loading was observed with lithium hexamethyldisilazide (LiHMDS) while in DMF and DMSO loading yields of 46% and 67% were observed. Other bases such as KOBu^t, KHMDS, and NaHMDS also gave reasonable loading yields in DMF and DMSO. In contrast, loading reactions performed in acetonitrile gave consistently poor results for each of the bases mentioned above.

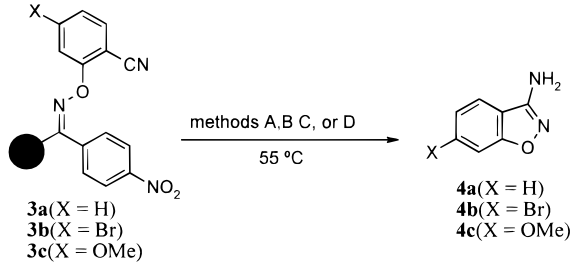
As described in our previous report, a variety of 2-fluorobenzonitriles can be loaded on the Kaiser resin.[4] Although the presence of an electron-withdrawing group facilitates loading at room temperature, substrates bearing either electron-withdrawing groups or electron-donating groups can be loaded in high yield in about 2 h at 55 °C. We also found that the loading reaction of 2-fluorobenzonitriles is not particularly sensitive to steric hindrance around the site of nucleophilic substitution.

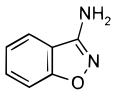
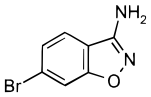
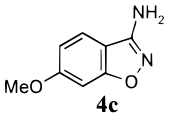
Studies on the Acid Stability of the Aryl Oxime Linker. As previously reported, the use of 4:1 TFA/aqueous 5 N HCl at 55 °C for 2 h (Table 2, method A) led to an efficient cyclorelease of a variety of substituted aminobenzisoxazoles. By contrast, we saw that the use

(11) Yan, B.; Fell J. B.; Gnanasambandam, K. *J. Org. Chem.* **1996**, *61*, 7467.

(12) Palermo, M. G. *Tetrahedron Lett.* **1996**, *37*, 2885.

Table 2. Acid Stability Profile of the Aryl Oxime Linker



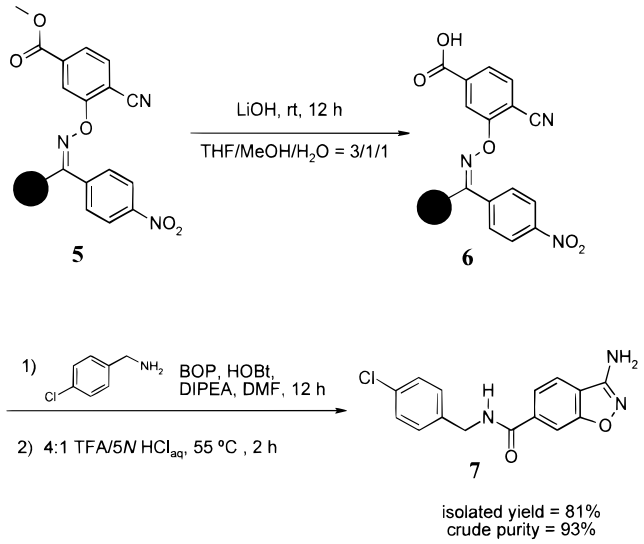
entry	X	product	method[a] (time)	yield[b] (% purity)
1	H	 **4a**	A (2 h) B (4 d)	78 (>96) 70 (65)
2	Br	 **4b**	A (2 h) B (4 d)	76 (>96) 53 (93)
3	MeO	 **4c**	A (2 h) B (2 h) C (2 h) D (2 h) E (12 h) F (12 h)	87 (>96) 85 (>96) <5 9 <5 <5

[a] Method A = 4:1 TFA/5 N HCl, 55 °C. Method B = 99:1 TFA/H_2O, 55 °C. Method C = 25% THF/CH_2Cl_2, rt. Method D = TFA, 55 °C. Method E = AcOH/THF/H_2O, 55 °C. Method F = TsOH/THF/H_2O, 55 °C. [b] Isolated yield after chromatography and based on loading. Crude purity based on HPLC analysis.

of 99:1 TFA/H_2O at 55 °C (Table 2, method B) with intermediates bearing either inductively neutral or electron-withdrawing substituents required significantly longer reaction times to reach completion. For example, hydrolysis of the resin bearing a bromo substituent para to the nitrile (Table 2, entry 2) using method B required 4 days to give the corresponding aminobenzisoxazole **4b** in 53% yield. On the other hand, treatment of the *p*-methoxybenzonitrile derivative **3c** (Table 2, entry 3), under the same conditions, gave the methoxy-substituted product **4c** in 85% isolated yield after only 2 h.

While the studies summarized above were important for identifying useful cyclorelease conditions, further experiments were performed in order to determine the acid stability profile of the linker under a variety of conditions commonly used for the removal of acid-sensitive protecting groups. The methoxy-substituted resin **3c** was selected for this study, since it is the most acid labile and therefore represents the worst case scenario. Upon treatment of the methoxy-substituted resin **3c** with 25% anhydrous TFA/CH_2Cl_2 at rt for 2 h (Table 2, entry 3, method C), conditions precedented for on-resin Boc removal,[4,5] <5% of the cyclization product **4c** was removed from the resin. Even under more forcing conditions, with 100% anhydrous TFA at 55 °C (Table 2, entry 3, method D) only 9% of the 3-aminobenzisoxazole product (>96% purity) was removed from the resin after 2 h. The aryl oxime linker was also stable to a number of milder aqueous acidic conditions that have been used for the removal of THP, silyl, and acetal protecting groups in solution. Thus, treatment of the resin **3c** with AcOH/

Scheme 2. On-Resin Hydrolysis and Amide Bond Formation

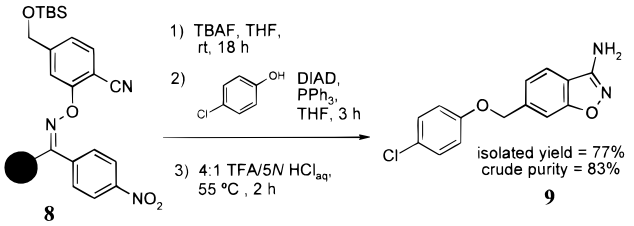


THF/H_2O (3/1/1) at 55 °C for 12 h[13] (Table 2, entry 3, method E) or with TsOH/THF/H_2O at 55 °C for 12 h[14] (Table 2, entry 3, method F) gave no detectable release of material from the resin.

Amide Bond Formation. Due to the importance of solid-phase peptide synthesis, amide bond forming reactions have been the most widely performed and most highly developed solid-phase reactions.[15] We have previously shown that amides can be formed in the presence of an aryl oxime linker by the reaction of an acid chloride or an acid anhydride with an aryl oxime-linked benzylamine.[4] In the present study, we set out to demonstrate that an aryl oxime-linked acid could be coupled to an amine under standard peptide coupling conditions. By proceeding through the intermediacy of methyl ester **5**, we also sought to demonstrate the compatibility of the aryl oxime linker with the aqueous basic conditions required for saponification (Scheme 2). Thus, the potassium anion of the Kaiser resin **1** was coupled with methyl 3-fluoro-4-cyanobenzoate to give resin **5** in a 69% loading yield. Treatment of resin **5** with LiOH in THF/MeOH/H_2O (3/1/1) at room temperature gave the corresponding acid (**6**) and no removal of the substrate from the resin was observed, demonstrating the stability of the aryl oxime linker under these conditions. Acid **6** was then coupled to 4-chlorobenzylamine to give the on-resin amide. Both the resin weight increase and chlorine analysis of the intermediate suggested that the coupling reaction went essentially to completion within 12 h. The resin was then treated with the standard cyclorelease conditions to give the desired amide **7** in a three step yield of 81% (93% crude purity).

Phenolic Mitsunobu Reaction. On-resin carbon−oxygen bond formation via the Mitsunobu reaction[16] has been identified as an important tool in combinatorial chemistry.[15] Application of this reaction to an aryl oxime-linked substrate is shown in Scheme 3. Resin **8** was

Scheme 3. On-Resin Mitsunobu Reaction



prepared by reacting the potassium anion of the Kaiser resin **1** with 2-fluoro-4-(*tert*-butyldimethylsilyloxymethyl)benzonitrile. The TBS protecting group was removed using TBAF in THF. The on-resin alcohol was then treated with *p*-chlorophenol, triphenylphosphine, and diisopropylazodicarboxylate (DIAD) in THF.[17] The best results were observed for reactions times of 3 h. Longer reaction times generally led to decreased purity in the crude cyclization product. Cyclitive removal using the standard conditions then gave aryl ether **9** in a 77% yield (three steps) and 83% crude purity.

On-Resin Nucleophilic Aromatic Substitution. Recently, examples of on-resin nucleophilic aromatic displacement reactions have appeared in the literature.[18] To evaluate the compatability of the aryl oxime linker with this reaction, a resin-attached fluorobenzonitrile (**10**) was prepared (Scheme 4). To avoid any regioselectivity issues in the loading reaction, the symmetrical 2,6-difluorobenzonitrile was chosen for this initial investigation. Resin **10** was then reacted with a variety of nucleophiles including an alkoxide,[19] amine,[20] and phenol[21] (Table 3). The potassium alkoxide of 4-chlorophenethanol (Table 3, entry 1) was prepared by treatment with 2 equiv of potassium *tert*-butoxide. This salt was then added to a THF suspension of resin **10** to give the corresponding product **11a** after cyclorelease in a two-step yield of 50%.

Addition of pyrrolidine to **10** proved more challenging (Table 3, entry 2). In our initial attempt (THF, 6 h, 55 °C), the desired product **11b** was produced in low isolated yield as a result of incomplete displacement. The major impurity in this reaction was 4-fluoro-3-aminobenzisoxazole, the cyclization product of the unreacted starting material (**10**). In an attempt to increase the rate of the S_NAr reaction in THF, variations in the reaction time, number of equivalents of nucleophile, and the temperature were evaluated. Unfortunately, none of these alternate protocols were found to improve the outcome of the reaction. However significant improvements were obtained with the use of alternate solvents. Although only a slight improvement was observed with acetonitrile,[22] both DMF and DMSO produced a significant increase in the reaction rate. After 6 h at 55 °C in DMSO, followed

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(14) Thomas, E. J.; Williams, A. C. *J. Chem. Soc., Chem. Commun.* **1987**, 992.

(15) Kaldor, S. W.; Siegel, M. G. *Comb. Chem. Mol. Diversity Drug Discovery* **1998**, 307−335; Gordon, E, M., Kerwin, J. F., Jr., Eds.; Wiley-Liss: New York, 1998.

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(17) Krchnák, V.; Flegelová, Z.; Weichsel, A. S.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6193. Rano, T. A.; Chapman, K. T. *Tetrahedron Lett.* **1995**, *36*, 3789.

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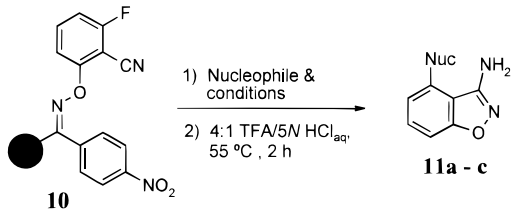
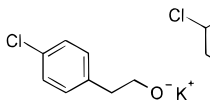
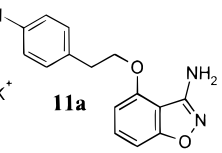
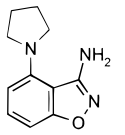
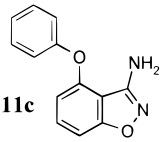
(19) Plenkiewicz, H.; Dmowski, W. *J. Fluorine Chem.* **1998**, *89*, 213.

(20) Morales, G. A.; Corbett, J. W.; DeGrado, W. F. *J. Org. Chem.* **1998**, *63*, 1172. Vojkovsky, T.; Weichsel, A.; Patek, M. *J. Org. Chem.* **1998**, *63*, 3162. Dankwardt, S. M.; Newman, S. R.; Krstenanski, J. L. *Tetrahedron Lett.* **1995**, *36*, 4923.

(21) Kiselyov, A. S.; Eisenberg, S.; Luo, Y. *Tetrahedron Lett.* **1999**, *40*, 2465. Burgess, K.; Lim, D.; Bois-Choussy, M.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 3345.

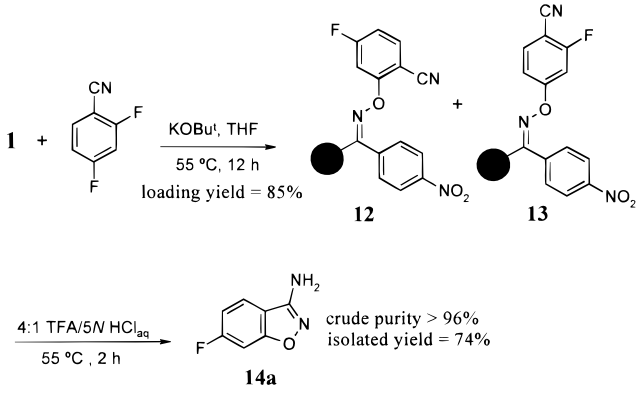
Table 3. On-Resin Nucleophilic Aromatic Substitution



entry	nucleophile & conditions	product	yield[a] (% purity)
1	 THF, 55 °C, 12 h	 **11a**	50 (95)
2	 55 °C, 8 h	THF CH_3CN DMF DMSO  **11b**	18 32 58 (69)[b] 80 (94)[b]
3	 DMF, 55 °C, 36 h, K_2CO_3	 **11c**	48 (93)[b]

[a] Isolated yield after chromatography and based on loading. Crude purity based on HPLC analysis. [b] Major impurity was the unreacted fluorine product (4-fluoro-3-aminobenzisoxazole).

Scheme 4. Regioselective Synthesis of 6-Fluoro-3-aminobenzisoxazole

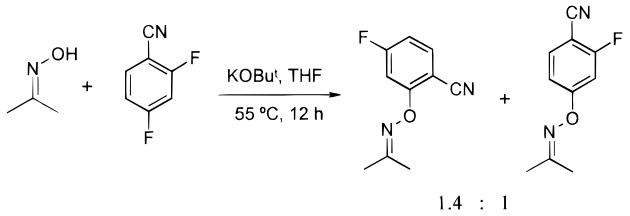


by the cyclorelease reaction, compound **11b** was obtained in 94% crude purity and subsequently isolated in 80% yield.

Similar to the pyrrolidine S_NAr reaction discussed above, the nucleophilic addition of phenol to resin **10** (Table 3, entry 3) proceeded at a faster rate in DMSO and DMF compared with THF. However, even in these solvents, the addition reaction required 36 h to bring about high conversion of the phenol adduct. Aryl ether **11c** was then obtained in 48% yield (two steps) and 93% crude purity after cyclitive removal.

To explore the question of regioselectivity, the loading reaction was next attempted with 2,4-difluorobenzonitrile. As illustrated in Scheme 4, this reaction could lead either to the desired aryloxime intermediate **12** through displacement of the 2-fluoro group or to an undesired isomer **13** through displacement of the 4-fluoro group. Treatment of the unsymmetrical nitrile with the potassium salt of resin **1** gave a 85% loading yield based on weight. Although the ratio of **12** to **13** was not determined, the presumed mixture was then hydrolyzed under the standard cyclization conditions to yield a *single* product **14a** (as determined by HPLC and NMR) in 74% isolated yield. The high selectivity observed for the formation of the desired product could arise from either of two pathways. On one hand, the resin loading reaction may be quite selective for the 2-position, giving primarily **12**, and then subsequently **14a** upon cyclorelease. Alternatively, mixtures of the two isomeric aryloxime adducts could be formed with the hydrolysis of intermediate **12** occurring much more rapidly than **13**. In order gain insight into the relative contributions of these two pathways, several experiments were performed. Scheme 5 depicts a solution-phase model study for the loading reaction of 2,4-difluorobenzonitrile. In this experiment, the potassium salt of acetone oxime was treated with 2,4-difluorobenzonitrile and showed only a slight preference for the addition to the 2-position (1.4:1).[23] Obviously such poor selectivity, if produced in the solid-phase loading reaction, could not account for the >96% purity of cyclorelease product **14a**.

Scheme 5. Solution-Phase Model of the Loading Reaction of 2,4-Difluorobenzonitrile



Scheme 6 illustrates a comparison of the relative rates of hydrolysis for analogous 2- vs 4-substituted aryloximes. Since the isolation of pure **12** and pure **13** was not practical, model resins **3a** and **15** were prepared from 2-fluorobenzonitrile and 4-fluorobenzonitrile, respectively. As described previously, when resin **3a** was treated with the standard cyclitive removal conditions, complete conversion to 3-aminobenzisoxazole was observed after 2 h.

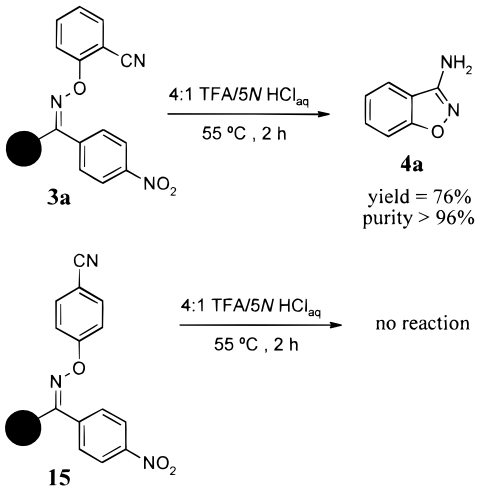
IR analysis of the recovered resin after hydrolysis showed complete disappearance of the nitrile peak, which had clearly been present in the starting material. Alternatively, upon exposure of the isomeric resin **15** to the same hydrolysis conditions, no organic material was released from the solid phase. In this experiment, IR analysis of the recovered resin confirmed that the nitrile remained intact, apparently unaffected by exposure to the aqueous acid.

These observations led us to reexamine the reaction shown in Scheme 4. This time, resin **12** and **13** were recovered after the cyclorelease reaction was complete and characterized by IR spectroscopy. The analysis

(22) Studies on the fluorine kinetic isotope effect in S_NAr reactions with aryl fluorides have shown that the use of acetonitrile as the reaction solvent leads to a different rate-limiting step in the overall mechanism when compared with THF. Persson, J.; Axelsson, S.; Matsson, O. *J. Am. Chem. Soc.* **1996**, *118*, 20.

(23) For related regioselectivity studies on solution-phase S_NAr reactions, see: (a) Wells, K. M.; Shi, Y. J.; Lynch, J. E.; Humphrey, G. R.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 6439. (b) Sasajima, K.; Ona, K.; Katsube, J.; Yamamoto, H. *Chem. Pharm. Bull.* **1978**, *26*, 2502.

Scheme 6. Comparison of the Relative Rates of Oxime Hydrolysis for 2- versus 4-Substituted Aryl Oximes



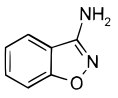
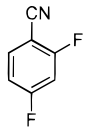
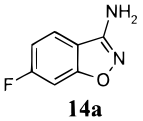
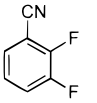
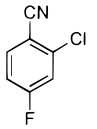
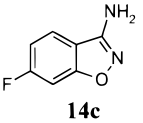
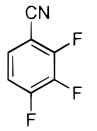
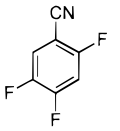
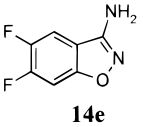
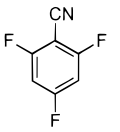
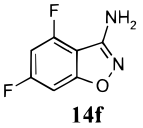
revealed that a nitrile peak was still present on the resin, although the intensity of the nitrile was diminished relative to that observed prior to hydrolysis. These data support the hypothesis that the difference in the hydrolysis rates of intermediate **12** vs **13** serves as the primary source of selectivity in this reaction.

Having successfully achieved the selective functionalization of 2,4-difluorobenzonitrile, a variety of additional unsymmetrical polyfluorobenzonitriles were carried through the same sequence. The results, presented in Table 4, demonstrate that the isolated yield of the desired product is significantly diminished in many cases, likely as a result of poor selectivity for the 2-position in the loading reaction. However, even with the significant decrease in isolated yield, HPLC analyses of the crude reaction mixtures illustrate that the desired product is selectively released from the solid phase.

Carbon−Carbon Bond-Forming Reactions. Compatibility with versatile methods for the formation of carbon−carbon bonds on-resin is an important measure of the suitability of any new linker.[24] Toward that goal, our initial efforts were focused on the application of catalytic palladium coupling chemistry such as the Suzuki and Sonogashira reactions. Thus, the aryl bromide resin **3b** was prepared[4] and reacted with phenylboronic acid under a variety of palladium-catalyzed coupling conditions and then hydrolyzed to give the biaryl product **16a** (Table 5). Initially, two sets of conditions that have previously been reported for on-resin Suzuki reactions were evaluated. Use of $Pd(PPh_3)_4$ with triethylamine/DMF for 12 h[25] (not shown) produced **16a**, but led to the formation of numerous byproducts. Alternatively, the use of $Pd(PPh_3)_4$, with Na_2CO_3 in 1:1 DME/H_2O at reflux for 12 h,[26] produced **16a** in 25% isolated yield, contaminated only by the cyclization product of the unreacted aryl bromide. Due to the superior purity observed with aqueous carbonate, optimization efforts were focused on these conditions. Numerous reaction parameters were carefully varied including cosolvent (DMF, DMSO, and THF) and the stoichiometry of the catalyst, boronic acid, and sodium carbonate. Although the crude purities were similar for the various solvents that were evaluated, in general, THF[27] was found to give the highest rate of product formation and, therefore, the highest isolated yields. Optimal results were obtained with 1.3 equiv of 2 N Na_2CO_3, at 55 °C, over 36 h. The reaction was found to be rather sensitive to deviation from these conditions, particularly with respect to the amount of added 2 N Na_2CO_3. However, in control experiments, resin **3b** was treated with varying amounts of 2 N Na_2CO_3 in THF at 55 °C over 36 h, and no removal of organic material from the resin was observed. As Table 5 indicates, the application of the optimized Suzuki conditions to several other substrates (Table 5, entries 2−4) provided similar yields and purities.

Application of the Sonogashira reaction to resin **3b** proved less difficult than the Suzuki coupling. We were able to couple phenethylacetylene to **3b** to give alkyne **17** in a 58% two-step yield using $Pd(PPh_3)_4$/CuI in THF (Scheme 7).[28] Again, as in the Suzuki chemistry, significantly better results were obtained with THF as the

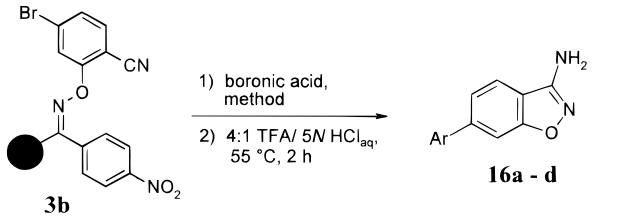
Table 4. Regioselective Synthesis of Fluoro-3-aminobenzisoxazoles

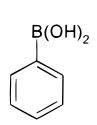
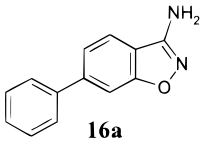
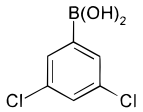
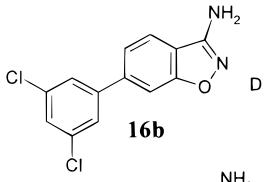
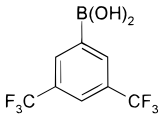
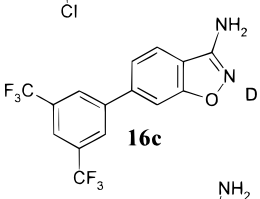
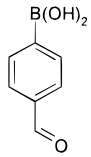
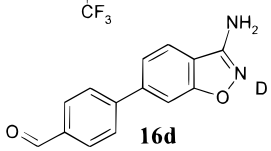
entry	electrophile	loading (%)	product	yield[a] (% purity)
1		64	 **4a**	76 (>96)
2		85	 **14a**	74 (>96)
3		66	 **14b**	56 (>96)
4		55	 **14c**	<5
5		66	 **14e**	27 (78)
6		53	 **14e**	<5
7		79	 **14f**	31 (>96)

[a] Isolated yield after chromatography and based on loading. Crude purity based on HPLC analysis.

(24) Hanessian, S.; Xie, F. *Tetrahedron Lett.* **1998**, *39*, 737.
(25) Han, Y.; Walker S. D.; Young, R. N. *Tetrahedron Lett.* **1996**, *37*, 2703. Ruhland, B.; Bombrun, A.; Gallop, M. A. *J. Org. Chem.* **1997**, *62*, 7820.
(26) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177.
(27) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171.

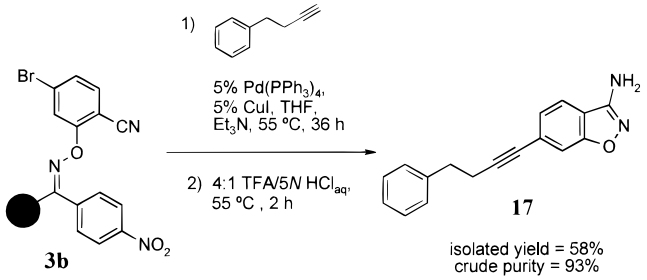
Table 5. On-Resin Suzuki Reaction



entry	boronic acid	product	method[a]	yield[b] (% purity)
1		 16a	A B C D	25 (50) 67 (60) 58 (91) 41 (>96)
2		 16b	D	54 (95)
3		 16c	D	46 (81)
4		 16d	D	43 (92)

[a] Methods A−D all use 4.0 equiv of boronic acid and 5% $Pd(PPh_3)_4$, 36 h. A = 2.5 equiv of 2 M Na_2CO_3, DME, reflux. B = 1.0 equiv of 2 M Na_2CO_3, THF, 55 °C. C = 1.3 equiv of 2 M Na_2CO_3, THF, 55 °C. D = 1.5 equiv of 2 M Na_2CO_3, THF, 55 °C. [b] Isolated yield after chromatography and based on loading. Crude purity based on HPLC analysis. Major impurity in all cases is 6-bromo-3-aminobenzisoxazole.

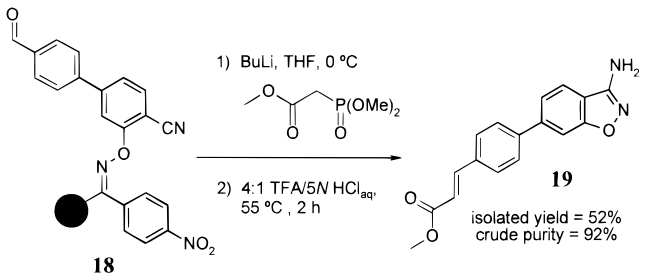
Scheme 7. On-Resin Sonogashira Coupling



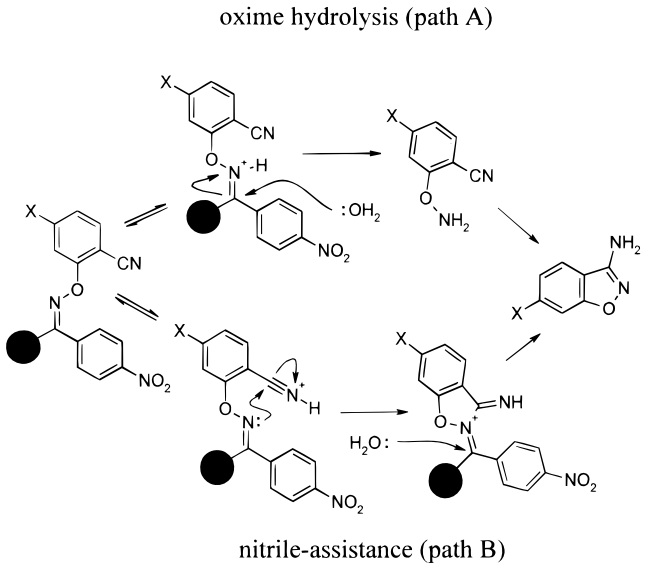
reaction solvent. The $Pd_2(dba)_3$/CuI/Et_3N conditions described by Moore[29] failed to give reasonable yields and purities.

The acquisition of aldehyde resin **18** (Scheme 8) from the Suzuki reaction with **3b** (Table 5, entry 4) provided an opportunity to evaluate the compatibility of the aryloxime linker with the Horner−Emmons olefination. Thus, treatment of **18** with the anion of trimethylphosphonoacetate in THF (preformed with *n*-BuLi at 0 °C) gave olefin **19** in 52% isolated yield (three steps, based on loading of resin **1**) and 92% purity.[30] The major impurity in this reaction is the cinnamic acid derivative that likely results from competing ester hydrolysis in the cyclitive removal step.

Scheme 8. On-Resin Horner−Emmons Olefination



Scheme 9. Possible Pathways for Heterocycle Formation



Mechanistic Implications. In the process of carrying out the studies described above, substituent effects were observed that have interesting implications regarding the mechanism of the cyclitive removal reaction. Although there may be numerous mechanistic nuances involved, two general pathways for cyclorelease are illustrated in Scheme 9. In path A, the first step involves direct protonation of the oxime nitrogen,[31] leading to the simple hydrolysis of the oxime from the resin to give a 2-aminooxybenzonitrile intermediate. This intermediate then cyclizes in a subsequent step to give the 3-aminobenzisoxazole product. Alternatively, in path B, protonation occurs initially on the nitrile. The oxime nitrogen then cyclizes onto the nitrilium ion, thus activating the imine toward hydrolysis. Both the effects of substituents para to the nitrile (illustrated in Table 2) and relative rates of hydrolysis observed for the aryloxime regioisomers (illustrated in Scheme 6) support the predominance of path B.

Comparing entries 2 and 3 in Table 2 (method B) reveals a significant difference in the hydrolysis rates for

(28) Kahn, S. I.; Grinstaff, M. W. *Tetrahedron lett.* **1998**, *39*, 8031.
(29) Nelson, J. C.; Young, J. K.; Moore, J. S. *J. Org. Chem.* **1996**, *61*, 8160.
(30) Chin, J.; Fell, B.; Shapiro, M. J.; Tomesch, J.; Wareing, J. R.; Bray, A. M. *J. Org. Chem.* **1997**, *62*, 538. Rotella, D. P. *J. Am. Chem. Soc.* **1996**, *118*, 12246.
(31) Egberink, H.; VanHeerden, C. *Anal. Chim. Acta* **1980**, *118*, 359.

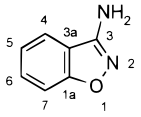
the bromo-substituted aryloxime relative to the methoxy-substituted analogue. Since these functional groups are not formally conjugated to the oxime, it seems unlikely that inductive effects would cause such a profound difference on the rate of hydrolysis six bonds away. On the other hand, these substituents are expected to have a significant effect on the basicity of the nitrile in the para position.[32] By increasing the basicity of the nitrile, the *p*-methoxy group[33] should facilitate nitrilium ion formation and, therefore, facilitate hydrolysis through path B.

The relative reactivity of the aryloxime regioisomers shown in Scheme 6 also illustrates the importance of nitrile assistance in the hydrolysis reaction (path B). Since the effect of the nitrile on the basicity of the oxime is expected to be similar in the ortho versus para position, clearly the dramatic difference in the hydrolysis rate of **3a** and **15** cannot be rationalized on the basis of path A. On the other hand, the results are completely consistent with the operation of path B.

Conclusion. The studies described above illustrate the broad utility of this approach to the synthesis of 3-aminobenzisoxazoles. While aqueous acidic conditions were found that efficiently mediate the cyclitive removal of a variety of substrates, stability studies demonstrated that the aryloxime linker is also stable to a range of acidic conditions widely used for protecting group manipulation. During the course of these studies, we observed substituent effects that suggest that the nitrile plays a critical role in facilitating the oxime hydrolysis reaction. Further, we have demonstrated that a variety of functionalized substrates can be loaded onto the Kaiser−DeGrado resin. These resin-bound intermediates can successfully undergo carbon−nitrogen, carbon−oxygen, and carbon−carbon bond-forming reactions without compromising the integrity of the aryloxime linker. These results clearly establish this method as a viable tool for library generation.

Experimental Section

General Methods. Reagents obtained from commercial sources were used without further purification. Kaiser oxime resin **1** was purchased from Novabiochem with a loading capacity of 1.07 mmol/g. All NMR spectra were recorded on a 400 MHz instrument. Mass spectra were obtained with either ESI or FAB as the ionization method. Infrared spectra of the functionalized resins were recorded on an FTIR spectrophotometer using the KBr pellet method. All purifications were carried out by radial chromatography (Chromatotron model 8924, Harrison Research) using 1 mm silica gel plates (Analtech). Crude purities were estimated from integrated peak areas of HPLC chromatographs with the UV detector monitoring at $\lambda = 215$ nm. Analytical HPLC setup: C_{18} Vydac column with solvent gradient A = acetonitrile (0.1% TFA) and B = water (0.1% TFA) at 1 mL/min flow rate. Unless otherwise noted, all HPLC retention times are given for an eluent gradient of 10% A to 60% A over 40 min. The nomenclature of 3-aminobenzisoxazole compounds is based on the heterocycle numbering system[3] shown below:



Synthesis of *O*-2-Benzonitrile-*p*-nitrobenzophenone Oxime Polystyrene (3a). To *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes microfilter funnel were added THF (7 mL) and potassium *tert*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After being shaken by hand for several minutes, the resin turned a deep purple color. To this suspension was added 2-fluorobenzonitrile (1.07 mmol, 116 μL). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h to give resin **3a** followed by cooling for 1 h. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven to a constant weight to give a Δwt = 42.1 mg (78% loading yield). An IR spectrum of this resin shows a nitrile absorption at 2227 cm^{-1}.

Synthesis of 6-[(*p*-Chlorophenyl)methylaminocarbonyl]-3-amino-1,2-benzisoxazole (7). To *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes microfilter funnel were added THF (7 mL) and potassium *tert*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After shaking by hand for several minutes, the resin turned a deep purple color. To this suspension was added 2-fluoro-4-(methoxycarbonyl)benzonitrile (1.07 mmol, 192 mg). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h to give resin **5** followed by cooling for 1 h. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 50.0 mg (58% loading yield). To effect ester hydrolysis, the resin was then suspended in THF (7 mL) followed by the addition of LiOH (39 mg, 1.61 mmol) dissolved in MeOH/H_2O (1:1, 2 mL) and rotated at rt for 12 h. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), MeOH (2 × 5 mL), and DMF (2 × 5 mL). The resin was then suspended in DMF (7 mL), and to this were added *p*-chlorobenzylamine (261 μL, 2.14 mmol), 1-hydroxybenzotriazole hydrate (HOBt) (289 mg, 2.14 mmol), benzotriazole-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) (947 mg, 2.14 mmol), and diisopropylethylamine (DIPEA) (467 μL, 2.68 mmol). The reaction was allowed to proceed for 12 h at rt. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 84 mg. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin, and the vessel was rotated for 2 h in a 55 °C Robbins oven. The TFA/HCl_{aq} was collected, and the resin was rinsed with CH_2Cl_2 (2 × 5 mL). These washings were combined and concentrated in vacuo to give the crude product **7** (93% purity by HPLC), which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/hexanes. Concentration of the product containing fractions gave pure 6-[(*p*-chlorophenyl)methylaminocarbonyl]-3-amino-1,2-benzisoxazole (**7**) (76 mg, three-step yield = 81% based on the ester loading yield): HPLC retention time (eluent gradient 10% A to 60% A over 45 min) = 24.9 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (t, J = 5.6 Hz, 1H), 7.84−7.91 (m, 2H), 7.72 (dd, J = 8.0, 1.2 Hz, 1H), 7.37−7.31 (m, 4H), 6.50 (bs, 2H), 4.45 (d, J = 6.0 Hz, 2H); MS (ESI) m/z 300 [^{35}Cl, $(M + H)^+$], 302 [^{37}Cl, $(M + H)^+$]; HRMS calcd for $C_{15}H_{13}ClN_3O_2$ 302.0689, found 302.0696.

Synthesis of 6-[(*p*-Chlorophenyl)oxymethyl]-3-amino-1,2-benzisoxazole (9). To *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes microfilter funnel were added THF (7 mL) and potassium *tert*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After being shaken by hand for several minutes, the resin turned a deep purple color. To this suspension was added 2-fluoro-4-(*tert*-butyldimethylsilyloxymethly)benzonitrile (1.07 mmol, 285 mg). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h to give resin **8** followed by cooling for 1 h. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 71.1 mg (54% loading yield). To effect TBS removal, the resin was then suspended in THF (6 mL) followed by the addition of TBAF (562 μL, 1 M in THF, 0.562 mmol) and rotated at rt

(32) Colominas, C.; Orozco, M.; Luque, F. J.; Borrell, J. I.; Teixido, J. *J. Org. Chem.* **1998**, *63*, 4947.

(33) Schaefer, F. C. In *The Chemistry of the Cyano Group*; Rappoport, Z., Ed.; Interscience Publishers (John Wiley & Sons): London, 1970; p 244.

for 12 h. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), MeOH (2 × 5 mL), and CH_2Cl_2 (2 × 5 mL). The resin was then suspended in CH_2Cl_2 (7 mL), and to this were added *p*-chlorophenol (690 mg, 5.35 mmol), triphenylphosphine (700 mg, 2.68 mmol), and diisopropylazodicarboxylate (DIAD) (530 μL, 2.68 mmol). The reaction was allowed to proceed for 1 h at rt. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 12 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin, and the vessel was rotated for 2 h in a 55 °C Robbins oven. The TFA/HCl_{aq} was collected, and the resin was rinsed with CH_2Cl_2 (2 × 5 mL). These washings were combined and concentrated in vacuo to give the crude product **7** (83% purity by HPLC), which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/hexanes. Concentration of the product containing fractions gave pure 6-[(*p*-chlorophenyl)oxymethyl]-3-amino-1,2-benzisoxazole (**9**) (61 mg, three-step yield = 77% based on loading yield): HPLC retention time (eluent gradient 10% A to 60% A over 45 min) = 37.5 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.0 Hz, 1H), 7.84−7.91 (m, 2H), 7.72 (dd, J = 8.0, 1.2 Hz, 1H), 7.44 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.25−7.21 (m, 2H), 6.99−6.95 (m, 2H), 5.17 (bs, 2H), 1.22 (d, J = 6.4 Hz, 2H); MS (ESI) m/z 274 [^{35}Cl, $(M + H)^+$], 276 [^{37}Cl, $(M + H)^+$]. Anal. Calcd for $C_{14}H_{11}ClN_2O_2$: C, 61.21; H, 4.04; N, 10.2; Cl, 12.91. Found: C, 61.08; H, 4.32; N, 10.19; Cl, 12.47.

Synthesis of Resin 10. To *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes microfilter funnel were added THF (7 mL) and potassium *tert*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After being shaken by hand for several minutes, the resin turned a deep purple color. To this suspension was added 2,6-difluorobenzonitrile (150 mg, 1.07 mmol). The reaction vessel was rotated at 55 °C in a Robbins oven for 8 h to give resin **10** followed by cooling for 1 h. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 40.1 mg (63% loading yield).

Synthesis of 4-[2-(*p*-Chlorophenyl)ethoxy]-3-amino-1,2-benzisoxazole (11a). In a separate vial, 2-(*p*-chlorophenyl)ethanol (128 μL, 1.07 mmol) was dissolved in 1 mL of THF followed by the addition of potassium *tert*-butoxide (1.07 mL, 1 M in THF, 1.07 mmol). This alkoxide solution was then added to a THF suspension (6 mL) of resin **10** (540.1 mg, assume 0.535 mmol). The reaction vessel was rotated for 12 h in a 55 °C Robbins oven. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin, and the vessel was rotated for 2 h in a 55 °C Robbins oven. The TFA/HCl_{aq} was collected, and the resin was rinsed with CH_2Cl_2 (2 × 5 mL). These washings were combined and concentrated in vacuo to give the crude product **11a** (95% purity by HPLC), which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/hexanes. Concentration of the product containing fractions gave pure 6-[(*p*-chlorophenyl)oxymethyl]-3-amino-1,2-benzisoxazole (**11a**) (66 mg, two-step yield = 50% based on loading yield): HPLC retention time (eluent gradient 10% A to 80% A over 45 min) = 31.8 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39−7.31 (m, 5H), 6.93 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.4, 1H), 5.72 (bs, 2H), 4.30 (t, J = 6.4 Hz, 2H), 3.12 (t, J = 6.4 Hz, 2H); MS (ESI) m/z 289 [^{35}Cl, $(M + H)^+$], 291 [^{37}Cl, $(M + H)^+$]. Anal. Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.41; H, 4.54; N, 9.70; Cl, 12.28. Found: C, 62.08; H, 4.61; N, 9.53; Cl, 12.41.

Synthesis of 4-Pyrrolidino-3-amino-1,2-benzisoxazole (11b). To a DMSO suspension (7 mL) of resin **10** (540.1 mg, assume 0.535 mmol) was added pyrrolidine (134 μL, 1.61 mmol). The reaction vessel was rotated for 8 h in a 55 °C Robbins oven. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin, and the vessel was rotated for 2 h in a 55 °C Robbins oven. The TFA/HCl_{aq} was collected, and the resin was rinsed with CH_2Cl_2 (2 × 5 mL). These washings were combined and concentrated in vacuo to give the crude product **11b** (94% purity by HPLC), which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/hexanes. Concentration of the product-containing fractions gave pure 4-pyrrolidino-3-amino-1,2-benzisoxazole (**11b**) (54 mg, two-step yield = 80% based on loading yield): HPLC retention time (eluent gradient 5% A to 40% A over 45 min) = 27.9 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (t, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 7.6, 1H), 5.62 (bs, 2H), 3.27−3.20 (m, 4H), 1.92−1.83 (m, 4H); MS (ESI) m/z 204 $(M + H)^+$. Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.46 H, 6.22; N, 20.11.

Synthesis of 4-Phenoxy-3-amino-1,2-benzisoxazole (11c). To a DMF suspension (7 mL) of resin **10** (540.1 mg, assume 0.535 mmol) were added phenol (503 mg, 5.35 mmol) and K_2CO_3 (738 mg, 5.35 mmol). The reaction vessel was rotated for 36 h in a 55 °C Robbins oven. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin, and the vessel was rotated for 2 h in a 55 °C Robbins oven. The TFA/HCl_{aq} was collected, and the resin was rinsed with CH_2Cl_2 (2 × 5 mL). These washings were combined and concentrated in vacuo to give the crude product **11c** (93% purity by HPLC), which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/hexanes. Concentration of the product-containing fractions gave pure 4-phenoxy-3-amino-1,2-benzisoxazole (**11c**) (38 mg, two-step yield = 48% based on loading yield): HPLC retention time (eluent gradient 10% A to 90% A over 45 min) = 23.7 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 9.6 Hz, 1H), 7.26−7.15 (m, 3H), 7.10 (d, J = 8.4 Hz, 1H), 6.36 (d, J = 7.6 Hz, 1H), 6.02 (bs, 2H); MS (ESI) m/z 227 $(M + H)^+$. Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.21 H, 4.06; N, 12.75.

General Procedure for the Synthesis of Fluoro-3-amino-1,2-benzisoxazoles 14a−f. To *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes microfilter funnel were added THF (7 mL) and potassium *tert*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After being shaken by hand for several minutes, the resin turned a deep purple color. To this suspension was added 2,4-difluorobenzonitrile (150 mg, 1.07 mmol). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h followed by cooling for 1 h. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 52.4 mg (90% loading yield). An IR analysis of the resin shows a nitrile stretching peak at 2230.3 cm^{-1}. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin, and the vessel was rotated for 2 h in a 55 °C Robbins oven. The TFA/HCl_{aq} was collected, and the resin was rinsed with CH_2Cl_2 (2 × 5 mL). An IR analysis of the resin after the cyclorelease reaction shows a diminished nitrile stretching peak. The CH_2Cl_2 washings were combined and concentrated in vacuo to give the crude product **14a** (>96% purity by HPLC), which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/hexanes. Concentration of the product containing fractions gave pure **6-fluoro-3-aminobenzisoxazole (14a)** (40 mg, two-step yield = 74% based on loading yield): HPLC retention time (eluent gradient 10% A to 60% A over 45 min) = 13.3 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (dd, J = 8.8, 5.2 Hz, 1H), 7.36 (dd, J = 9.6, 2.0 Hz, 1H), 7.11 (ddd, J = 11.2, 8.8, 2.4 1H), 6.44 (bs, 2H); MS (FD) m/z 152 M^+. Anal. Calcd for $C_7H_5FN_2O$: C, 55.27; H, 3.31; N, 18.41. Found: C, 55.21 H, 3.27; N, 18.20.

7-Fluoro-3-aminobenzisoxazole (14b) (30 mg, two-step yield = 56% based on loading yield): >96% crude purity; HPLC retention time (eluent gradient 5% A to 40% A over 45 min) = 20.1 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (dd, J = 8.4, 1.2 Hz, 1H), 7.40 (ddd, J = 11.6, 8.4, 0.8 Hz, 1H), 7.21 (dd, J = 8.0, 4.4 1H), 6.58 (bs, 2H); MS (FD) m/z 152 M^+. Anal.

Calcd for $C_7H_5FN_2O$: C, 55.27; H, 3.31; N, 18.41. Found: C, 55.19 H, 3.45; N, 18.36.

6,7-Difluoro-3-aminobenzisoxazole (14e) (23 mg, two-step yield = 27% based on loading yield): 78% crude purity; HPLC retention time (eluent gradient 5% A to 40% A over 45 min) = 27.6 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65−7.61 (m, 1H), 7.36−7.30 (m, 1H), 6.62 (bs, 2H); MS (FD) *m*/*z* 171 M^+; HRMS calcd for $C_7H_4F_2N_2O$ 171.0370, found 171.0368.

4,6-Difluoro-3-aminobenzisoxazole (14f) (22 mg, 2 step yield = 31% based on loading yield): >96% crude purity; HPLC retention time (eluent gradient 5% A to 40% A over 45 min) = 21.1 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (dd, J = 8.8, 1.2 Hz, 1H), 7.10 (dd, J = 10.0, 2.0 Hz, 1H), 6.34 (bs, 2H); MS (FD) *m*/*z* 171 M^+. Anal. Calcd for $C_7H_4F_2N_2O$: C, 49.42; H, 2.37; N, 16.47. Found: C, 49.36 H, 2.38; N, 16.39.

General Procedure for the Suzuki Coupling Reactions with Resin 3b. To *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes microfilter funnel were added THF (7 mL) and potassium *tert*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After being shaken by hand for several minutes, the resin turned a deep purple color. To this suspension was added 4-bromo-2-fluorobenzonitrile (214 mg, 1.07 mmol). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h to give resin **3b** followed by cooling for 1 h. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 64 mg (66% loading yield). The resin was then suspended in THF (7 mL), and to this were added phenylboronic acid (261 mg, 2.14 mmol), Na_2CO_3 (348 μL, 2 M in H_2O, 2.14 mmol), and $Pd(PPh_3)_4$. The vessel was then rotated for 36 h in a 55 °C Robbins oven followed by rinsing with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin, and the vessel was rotated for 2 h in a 55 °C Robbins oven. The TFA/HCl_{aq} was collected, and the resin was rinsed with CH_2Cl_2 (2 × 5 mL). These washings were combined and concentrated in vacuo to give the crude product **16a** (91% purity by HPLC), which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/hexanes. Concentration of the product-containing fractions gave pure **6-phenyl-3-amino-1,2-benzisoxazole (16a)** (46 mg, two-step yield = 58% based on loading yield): HPLC retention time (eluent gradient 10% A to 60% A over 45 min) = 13.3 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 8.4 Hz, 1H), 7.74−7.70 (m, 2H), 7.68 (s, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.48−7.43 (m, 2H), 7.40−7.35 (m, 1H), 6.42 (bs, 2H); MS (ESI) *m*/*z* 211 $(M + H)^+$. Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.59 H, 4.86; N, 13.36.

6-(3,5-Dichlorophenyl)-3-amino-1,2-benzisoxazole (16b) (two-step yield = 51% based on loading yield); 95% crude purity; HPLC retention time (eluent gradient 20% A to 80% A over 45 min) = 30.4 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 8.8 Hz, 1H), 7.82 (s, 1H), 7.81 (d, J = 1.6 Hz, 2H), 7.62−7.58 (m, 2H), 6.46 (bs, 2H); MS (FD) *m*/*z* 278 [^{35}Cl + ^{35}Cl, M^+], 280 [^{35}Cl + ^{37}Cl, $(M + H)^+$]. Anal. Calcd for $C_{13}H_8Cl_2N_2O$: C, 55.94; H, 2.89; N, 10.04. Found: C, 55.93 H, 2.60; N, 9.85.

6-(3,5-Ditrifluoromethylphenyl)-3-amino-1,2-benzisoxazole (16c) (two-step yield = 45% based on loading yield): 81% crude purity; HPLC retention time (eluent gradient 20% A to 80% A over 45 min) = 31.0 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 2H), 8.11 (s, 1H), 7.98 (s, 2H), 7.93 (d, J = 8.4 Hz, 1H), 7.76−7.71 (m, 2H), 6.49 (bs, 2H); MS (ESI) *m*/*z* 347 $(M + H)^+$. Anal. Calcd for $C_{15}H_8F_6N_2O$: C, 52.04; H, 2.33; N, 8.09. Found: C, 52.00 H, 2.06; N, 7.99.

6-(4-Formylphenyl)-3-amino-1,2-benzisoxazole (16d) (two-step yield = 43% based on loading yield): 92% crude purity; HPLC retention time (eluent gradient 5% A to 40% A over 45 min) = 37.6 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 7.98 (s, 4H), 7.90 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 7.63 (dd, J = 8.4, 1.6 Hz, 1H), 6.46 (bs, 2H); MS (ESI) *m*/*z* 239 $(M + H)^+$; HRMS calcd for $C_{14}H_{10}N_2O_2$ $(M + H)^+$ 239.0821, found 239.1816.

Sonogashira Coupling with Resin 3b. Resin **3b** was prepared in 66% loading yield from 0.535 mmol of Kaiser oxime **1** as detailed above. The resin was then suspended in THF (7 mL), and to this were added 4-phenylbutyne (280 mg, 2.14 mmol), Et_3N (500 μL), CuI (5.1 mg, 0.027 mmol), and $Pd(PPh_3)_4$ (31 mg, 0.027 mmol). The vessel was then rotated for 36 h in a 55 °C Robbins oven followed by rinsing with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin, and the vessel was rotated for 2 h in a 55 °C Robbins oven. The TFA/HCl_{aq} was collected, and the resin was rinsed with CH_2Cl_2 (2 × 5 mL). These washings were combined and concentrated in vacuo to give the crude product **17** (93% purity by HPLC), which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/hexanes. Concentration of the product containing fractions gave pure **6-(4-phenylbutynyl)-3-amino-1,2-benzisoxazole (17)** (58 mg, two-step yield = 58% based on loading yield): HPLC retention time (eluent gradient 20% A to 85% A over 45 min) = 26.2 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.0 Hz, 1H), 7.38 (s, 1H), 7.29−7.27 (m, 4H), 7.21−7.15 (m, 2H), 6.43 (bs, 2H), 2.84 (t, J = 7.6 Hz, 2H), 2.70 (t, J = 7.2 Hz, 2H); MS (ESI) *m*/*z* 263 $(M + H)^+$; HRMS calcd for $C_{13}H_{10}N_2O$ 263.1184, found 263.1172.

Horner−Emmons Olefination To Give 19. To *p*-nitrobenzophenone oxime polystyrene (Kaiser) resin (500 mg, 1.07 mmol/g, 0.54 mmol) in a tared 25 mL Kontes microfilter funnel were added THF (7 mL) and potassium *tert*-butoxide (640 μL, 1 M in THF, 0.642 mmol). After being shaken by hand for several minutes, the resin turned a deep purple color. To this suspension was added 4-bromo-2-fluorobenzonitrile (214 mg, 1.07 mmol). The reaction vessel was rotated at 55 °C in a Robbins oven for 12 h to give resin **3b** followed by cooling for 1 h. The resin was then rinsed with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was dried in a 35 °C vacuum oven for 12 h to give a Δwt = 64 mg (66% loading yield). The resin was then suspended in THF (7 mL), and to this were added 4-formylphenylboronic acid (482 mg, 3.21 mmol), Na_2CO_3 (348 μL, 2 M in H_2O, 0.696 mmol), and $Pd(PPh_3)_4$ (31 mg, 0.027 mmol). The vessel was then rotated for 36 h in a 55 °C Robbins oven followed by rinsing with CH_2Cl_2 (2 × 5 mL), MeCN (2 × 5 mL), H_2O (2 × 5 mL), and MeCN (4 × 5 mL) (care was taken to not rinse the resin with methanol in order to avoid methyl acetal formation). The resin was dried in a 35 °C vacuum oven for 3 h to give aldehyde resin **18**. In a separate vial, trimethylphosponoacetate (172 μL, 1.07 mmol) was dissolved in THF (4 mL) and cooled to 0 °C. To this vial was added BuLi (602 μL, 0.96 mmol, 1.6 M in hexanes) dropwise. This THF solution was then added dropwise by syringe to a suspension of resin **18** in THF (4 mL), and the vessel was rotated for 6 h at rt. This was followed by rinsing with CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), H_2O (2 × 5 mL), and MeOH (4 × 5 mL). The resin was then dried in a 35 °C vacuum oven for 3 h. TFA (4 mL) and 5 N HCl_{aq} (1 mL) were then added to the resin, and the vessel was rotated for 2 h in a 55 °C Robbins oven. The TFA/HCl_{aq} was collected, and the resin was rinsed with CH_2Cl_2 (2 × 5 mL). These washings were combined and concentrated in vacuo to give the crude product **19** (92% purity by HPLC), which was purified by radial chromatography on a 2 mm plate eluting with 50% EtOAc/hexanes. Concentration of the product con-taining fractions gave pure **6-[4-(methoxycarbonylethylenyl)phenyl]-3-amino-1,2-benzisoxazole (19)** (47 mg, three-step yield = 52% based on loading yield of resin **1**): HPLC retention time (eluent gradient 20% A to 85% A over 45 min) = 24.3 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 8.0 Hz, 1H), 7.80 (s, 4H), 7.76 (s, 1H), 7.69 (d, J = 16.4 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 16.4 Hz, 1H), 6.43 (bs, 2H), 3.71 (s, 3H); HRMS calcd for $C_{17}H_{15}N_2O_3$ 295.1082, found 295.1088.

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