Palladium-Catalyzed Suzuki Coupling with Terminal Alkynes – Application to the Synthesis of 2,3-Disubstituted Benzo[*b*]furans

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The Suzuki coupling reaction between alkynylboronic esters (generated in situ from acetylenic derivatives) and aryl bromides, pyridyl bromides or vinyl bromides is reported. 5-*endo*-*dig*-iodocyclisation of *o*-alkynylanisoles, generated by this palladium-catalyzed Suzuki coupling reaction, was performed with *N*-iodosuccinimide (NIS) in the presence of BCl_3. 2-Substituted 3-iodobenzo[*b*]furans were synthesized and transformed into 2,3-disubstituted benzo[*b*]furans by Suzuki coupling reactions in high yields.

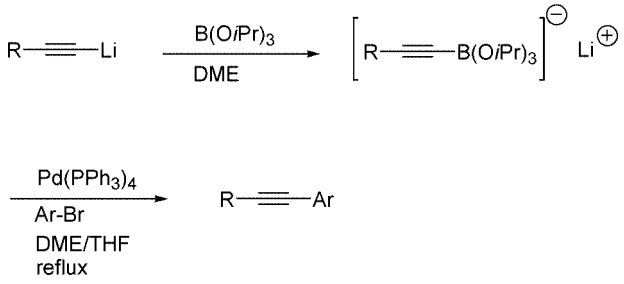
Introduction

The benzo[*b*]furan ring can be found as a key structural unit in many biologically active compounds which have applications not only as pharmaceuticals but also as flavoring and fragrance compounds.[1] Recently there has been a growing interest in developing general and versatile synthetic methods for the synthesis of benzofuran derivatives because of their activities as *anti*-tumor agents,[2] as ligands of the adenosine A1 receptor,[3] as inhibitors of 5-lipoxygenase, as antagonists of angiotensin II receptors[4] or as blood coagulation factor Xa inhibitors.[5] Some 2-arylbenzofuran derivatives are potent calcium blockers[6] while others show very good fungicidal activity in vitro and in vivo.[7]

Although various methods for the preparation of benzo[*b*]furans[8] are known, recent research has focused on the utilization of palladium-catalyzed systems. Most of these strategies employ suitably functionalized alkynes as starting materials.[9] The palladium-catalyzed coupling/cyclization of alkynes with *o*-hydroxy(*hetero*)aryl halides represents one of the most straightforward methods for the preparation of 2-substituted benzofurans.[10]

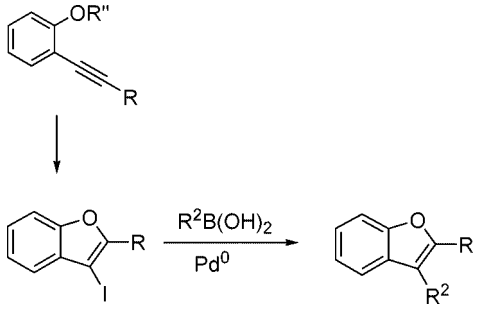
Recently, we reported on the palladium-catalyzed coupling reaction between aryl bromides and in situ generated acetylenic boronic esters[11] (Scheme 1).

As part of a program to develop direct synthesis of biologically active compounds, we report herein a full account of our results as well as a new synthetic application of this



Scheme 1. Suzuki coupling of acetylenic boronic esters.

sp-sp^2 Suzuki coupling reaction, giving access to functionalized benzofuran derivatives. *o*-Alkynylanisoles, generated by the palladium-catalyzed Suzuki coupling reaction, were submitted to 5-*endo*-*dig*-iodocyclisation using NIS in the presence of BCl_3. Further Suzuki coupling reactions afforded 2,3-disubstituted benzo[*b*]furans in high yields (Scheme 2).



Scheme 2. Synthesis of 2,3-disubstituted benzo[*b*]furans.

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Results and Discussion

Suzuki Coupling Reaction of Alkynes with Various Halogenobenzene Derivatives[11]

Treatment of alkynyllithium reagents (1.3 equiv.) with triisopropylborate (1.3 equiv.) in DME/THF (10:1) at –78 °C afforded the "lithiated boronate complex". The latter undergoes transmetallation with the Pd complexes obtained by insertion of palladium [0.03 equiv. $Pd(PPh_3)_4$] into the C–Br bond of aryl or vinylbromides (1 equiv.) followed by reductive elimination to give the coupling products **2a**–**g** (Table 1).

Excellent to good yields were obtained especially with *ortho*-substituted and unactivated arylbromides without homocoupling of terminal alkynes.

Uncharacterized decomposition products were observed for the Suzuki coupling between bromostyrene and 1-octyne (Table 1, entry 6).

The boronate complex can be in situ generated from the lithiated acetylenic substrate with triisopropylborate in THF/DME (THF is necessary to dissolve the "ate complex"). This Suzuki type methodology presents the ability to generate nucleophilic acetylides in situ, avoiding the necessity of preparing and storing large quantities of potentially unstable organometallic reagents.

Additionally, the coupling reaction was attempted with $B(OMe)_3$ instead of $B(OiPr)_3$. In this case, the addition of THF was not necessary to dissolve the "boronate complex" and yields were similar to those obtained with $B(OiPr)_3$.

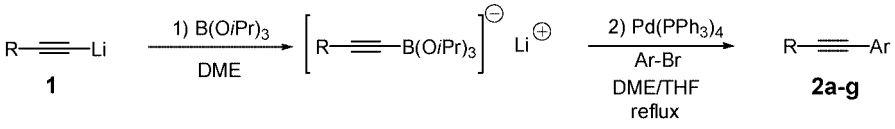
Thus we attempted to perform the sp-sp^2 Suzuki coupling reaction sub-stoichiometrically with respect to boron.

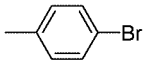
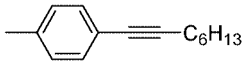
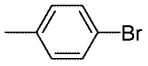
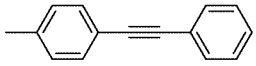
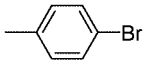
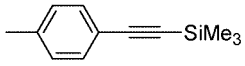
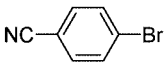
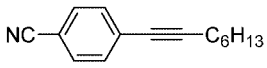
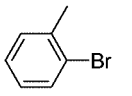
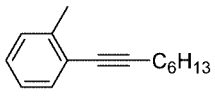
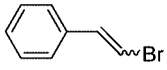
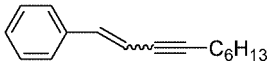
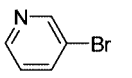
The coupling reaction between 1-octyne and *p*-bromotoluene in the presence of 0.25 equiv. of trimethylborate in THF was investigated. A clean reaction was observed, affording the coupling product in 70% yield.

Actually, trimethylborate generates in situ the alkynylboronate complex. The latter undergoes then the transmetallation step setting free again trimethylborate. This became obvious by studying the course of the reaction with ^{11}B NMR spectroscopy. The trimethylborate signal disappears first in favor of the corresponding alkynylboronate complex, then reappears and gains intensity as the reaction proceeds (Figure 1).

Therefore, we propose a catalytic cycle for this reaction, catalytic both in palladium and boron (Scheme 3).

Table 1. Palladium-catalyzed arylation or vinylation of alkynyllithium reagents mediated by $B(OiPr)_3$. [Reaction conditions: alkyne (1.3 equiv.), *n*BuLi (1.4 equiv.), $B(OiPr)_3$ (1.3 equiv.), bromide (1 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), DME/THF: 10:1, reflux.]



Entry	R	Ar–Br	Product	Yield [%]
1	C_6H_{13}			**2a**, 98
2	Ph			**2b**, 96[a]
3	$SiMe_3$			**2c**, 55[b]
4	C_6H_{13}			**2d**, 79
5	C_6H_{13}			**2e**, 75
6	C_6H_{13}			**2f**, 60[c]
7	C_6H_{13}			**2g**, 75

[a] DME/THF: 2.5:1. [b] Formation of ditolylacetylene (40%). [c] Uncharacterized decomposition products were observed.

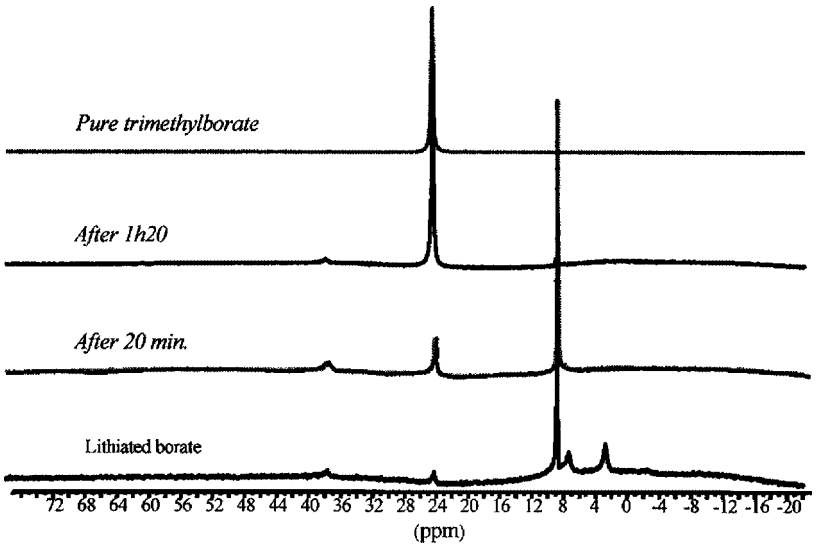
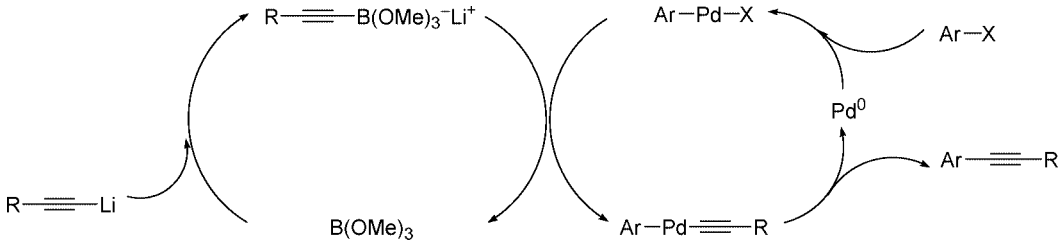


Figure 1. ^{11}B NMR signals during the Suzuki coupling of lithiated octynylboronate with *p*-bromotoluene.



Scheme 3. sp-sp^2 Suzuki coupling reaction sub-stoichiometric in $B(OMe)_3$.

Suzuki Coupling Reaction of Alkynes with Functionalized *o*-Hydroxyhalogenobenzenes

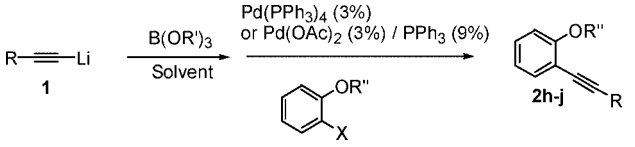
With the intention of preparing *o*-hydroxyalkynylbenzene derivatives as suitable precursors for benzo[*b*]furans, the Suzuki coupling reaction of alkynes with functionalized *o*-hydroxyhalogenobenzenes was next investigated. To determine the most suitable *o*-hydroxyhalogenobenzene derivative, the sp-sp^2 Suzuki coupling reaction was performed between 1-octyne or phenylacetylene and either *o*-iodophenol, *o*-(trimethylsilyloxy)iodobenzene, *o*-(*tert*-butyldimethylsilyloxy)iodobenzene, and *o*-bromo- and iodoanisole (Table 2).

No reaction occurred between nonprotected *o*-iodophenol and 1-octyne under the previously described[11] conditions (Table 2, entry 1).

The reaction of *o*-(trimethylsilyloxy)iodobenzene and 1-octyne gave the deprotected *o*-bromophenol and traces of 2-hexylbenzo[*b*]furan. Thus, the trimethylsilyl group was deprotected under our reaction conditions and deprotection of the coupling product and cyclization occurred at once (Table 2, entry 2).

Therefore, we tried the coupling reaction with the expected more stable *o*-(*tert*-butyldimethylsilyloxy)iodobenzene in DME. The coupling product **2h** was obtained in 74% yield (Table 2, entry 3).[12]

Table 2. Suzuki coupling of alkynyllithium reagents **1** with *o*-hydroxyhalogenobenzene derivatives [reaction conditions: alkyne (1.3 equiv.), *n*BuLi (1.4 equiv.), $B(OR')_3$ (1.3 equiv.), aryl bromide or aryl iodide (1 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.) or $Pd(OAc)_2$ (0.03 equiv.)/PPh_3 (0.09 equiv.), reflux.].



Entry	R	R′	R′′	X	Solvent	Yield [%]
1	C_6H_{13}	*i*Pr	H	I	DME/THF[a]	0
2	C_6H_{13}	*i*Pr	$SiMe_3$	I	DME/THF[a]	0[b]
3	C_6H_{13}	Me	TBDMS	I	DME	**2h**, 74
4	C_6H_{13}	*i*Pr	Me	Br	DME/THF[a]	**2i**, 75
5	C_6H_{13}	Me	Me	Br	DME	**2i**, 79
6	Ph	Me	Me	I	DME	**2j**, 89

[a] DME/THF: 10:1. [b] Traces of hexylbenzo[*b*]furan.

When the sp-sp^2 coupling reaction was performed with 2-bromo- or 2-iodoanisole, and either 1-octyne or phenyl-

acetylene, the coupling products were obtained in excellent yields (Table 2, entries 4, 5, 6).

Formation of 2-Substituted Benzo[*b*]furans and 2-Substituted 3-Iodobenzo[*b*]furans via Deprotection/(Iodo)-cyclization

The Suzuki coupling products **2h**–**j** were converted in a "one pot" deprotection/cyclization step into benzo[*b*]furans (Table 3).

Table 3. "One pot" deprotection/cyclization of **2h**–**j** [reaction conditions: alkyne **2** (1 equiv.)].

Entry	Starting products	R	R''	R^1	Reagents	Yield [%]
1	2h	C_6H_{13}	TBDMS	H	TBAF[a]	**3a**, 75
2	2j	Ph	Me	H	LiI[b]	**3b**, 35
3	2j	Ph	Me	H	BCl_3[c]	**3b**, 61
4	2i	C_6H_{13}	Me	H	BCl_3[c]	**3a**, 46
5	2j	Ph	Me	H	$BCl_3/AgNO_3$[d]	**3b**, 59
6	2j	Ph	Me	I	BCl_3/I_2[e]	**3c**, 63
7	2j	Ph	Me	I	BCl_3/NIS[f]	**3c**, 80
8	2i	C_6H_{13}	Me	I	BCl_3/NIS[f]	**3d**, 78

[a] TBAF (1.3 equiv.), THF, room temp. [b] LiI (2.4 equiv.), collidine, reflux. [c] BCl_3 1 M in heptane (1.6 equiv.), CH_2Cl_2, room temp. [d] BCl_3 1 M in heptane (1.6 equiv.), $AgNO_3$ (0.1 equiv.). [e] BCl_3 1 M in heptane (1.6 equiv.), I_2 (3.2 equiv.), CH_2Cl_2, room temp. [f] BCl_3 1 M in heptane (1.6 equiv.), NIS (2 equiv.), CH_2Cl_2, room temp.

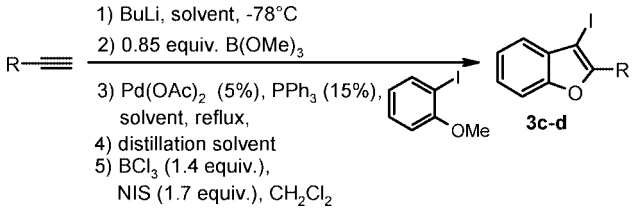
Deprotection of the *tert*-butyldimethylsilyloxy derivative **2h** in the presence of TBAF and molecular sieves afforded the cyclization product **3a** in 75% yield (Table 3, entry 1).

Furthermore, the deprotection/cyclization of the methoxy derivatives **2i** and **2j** was performed under different conditions (LiI, BCl_3, $BCl_3/AgNO_3$) as illustrated in Table 3 (entries 2–5). The best yield (61%) was obtained starting from the anisole **2j** in the presence of BCl_3 (entry 3). With these reaction conditions, we noticed that the deprotection of the methoxy with BCl_3 was complete. Therefore, in order to enhance the reactivity of the triple bond towards cyclization, $AgNO_3$ was added but the yield was not improved (Table 3, entry 5).

We next attempted a "one pot" deprotection/iodocyclization of anisole **2j** in the presence of iodine.[13] The concomitant treatment of **2j** with BCl_3 and I_2 gave rise to iodobenzofuran **3c** in 63% yield. Replacement of I_2 by NIS led to an improvement of the yield and compounds **3c** and **3d** were isolated respectively in 80% and 78% yield.

We next investigated the tandem sp-sp^2 Suzuki coupling/5-*endo*-*dig*-iodocyclization from *o*-iodoanisole and terminal alkynes. Addition of $B(OMe)_3$ (0.85 equiv.) to the lithiated alkyne at room temperature, followed by a solution of $Pd(OAc)_2$ (5%), PPh_3 (15%), and *o*-iodoanisole, resulted after gentle heating for 4 h in the formation of the corresponding coupling product. For the deprotection/iodocyclization step, it was necessary to distil off the coupling solvent (DME or CH_3CN) before the addition of BCl_3 (1.4 equiv.) and NIS (1.7 equiv.) in CH_2Cl_2. In this way, 2-substituted 3-iodobenzo[*b*]furans were obtained in moderate yields (Table 4).

Table 4. Tandem sp-sp^2 Suzuki coupling/5-*endo*-*dig*-iodocyclization starting from *o*-iodoanisole and terminal acetylenes.



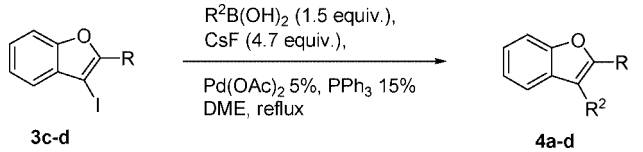
Entry	R	Solvent	Yield [%]
1	Ph	DME	**3c**, 52
2	Ph	CH_3CN	**3c**, 37
3	C_6H_{13}	DME	**3d**, 58

As side products, varying ratios (10 to 20%) of 2-substituted benzo[*b*]furans, as well as small amounts (about 7%) of diiodinated products with one iodine in position 3 and another iodine on the aromatic cycle, were obtained.

Formation of 2,3-Disubstituted Benzo[*b*]furans via Suzuki Coupling

The 2-substituted 3-iodobenzo[*b*]furans **3c**–**d** were then submitted to a further Suzuki coupling reaction, affording 2,3-disubstituted benzo[*b*]furans **4** (Table 5).

Table 5. Suzuki coupling reaction of 3c–d with various boronic acids [reaction conditions: benzofuran **3** (1 equiv.), $Pd(OAc)_2$ (5.2%), PPh_3 (14.6%), boronic acid (1.5 equiv.), CsF (4.7 equiv.), DME, 75 °C].



Entry	R	R^2	Yield [%]
1	C_6H_{13}	Ph	**4a**, 90
2	Ph	Naphthyl	**4b**, 91
3	Ph	*o*-MeO–Ph	**4c**, 91
4	Ph	*o*-Me–Ph	**4d**, 64

Good to excellent yields were obtained using cesium fluoride as base. The coupling reaction with sterically more hindered *ortho*-substituted boronic acids, as for example *o*-tolylboronic acid, gave the 2,3-disubstituted benzo[*b*]furan **4d** in lower yield (Table 5, entry 4).

Conclusions

We have shown that Suzuki aryl-alkynyl or vinyl-alkynyl coupling is very efficient in the synthetic chemistry of enyne derivatives. Suzuki coupling of acetylenic boronic esters with *o*-halogenoanisole or *o*-silyloxy-iodobenzene followed by deprotection/intramolecular cyclization afforded 2-substituted benzo[*b*]furans in good yield. Furthermore "one pot" deprotection/5-*endo*-*dig*-iodocyclisation of *o*-alkynylanisoles represents a good way to obtain 2-substituted 3-iodobenzo[*b*]furans. These compounds can be transformed into 2,3-disubstituted benzo[*b*]furans by further palladium-catalyzed Suzuki coupling reactions.

Experimental Section

General Remarks: All reactions were carried out under argon. NMR spectra were recorded with a Bruker AC-200. Chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. ^{1}H NMR spectra are relative to tetramethylsilane (δ = 0.00 ppm). ^{13}C NMR spectra are relative to $CDCl_3$ (δ = 77.0 ppm). IR spectra were recorded with a Perkin–Elmer Spectrum One. Melting points were obtained with a Büchi 535 apparatus and were not corrected. Flash Chromatography was carried out with silica gel 70–230 Mesh (Merck) using hexane as eluent. Thin layer chromatography was performed with silica gel 60 F_{254} (Merck). DME was dried with sodium/benzophenone and degassed prior to use. $B(OMe)_3$ and $B(OiPr)_3$ were freshly distilled over sodium.

Representative Procedure for the Preparation of Lithiated 1-Alkynyl-(triisopropyl)borates and Their Cross-Coupling with Aryl and Vinyl Bromides: A solution of *n*-butyllithium in hexanes (1.35 equiv.) was slowly added to a cooled solution (–78 °C) of 1-alkyne (1.85 mmol, 1.30 equiv.) in dimethoxyethane (10 mL). After 1 h at –78 °C, triisopropylborate (1.35 equiv.) was slowly added, and, 2 h later, the temperature was raised during 30 min to 20 °C. In parallel, tetrakis(triphenylphosphane)palladium(0) (0.03 equiv.) and the *o*-hydroxyhalogenobenzene derivative (1.00 equiv.) were dissolved in dimethoxyethane (10 mL) and stirred for 10 min at room temperature. To the lithiated alkynylborate were successively added anhydrous tetrahydrofuran (3 mL) and the solution of $Pd(PPh_3)_4$ and aryl halide via cannula. The cannula and the flask were rinsed with dimethoxyethane (2 × 5 mL). The reaction mixture was heated under reflux for 16 h (or until the complete disappearance of the aryl halide) and allowed to cool to room temperature. After addition of water and extraction with ethyl acetate, the combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography.

Representative Procedure for the Preparation of Lithiated 1-Alkynyl-(trimethyl)borates and Their Cross-Coupling with *o*-Hydroxyhalogenobenzenes: A solution of *n*-butyllithium in hexanes (1.35 equiv.) was slowly added to a cooled solution (–78 °C) of 1-alkyne (10.4 mmol, 1.30 equiv.) in dimethoxyethane (50 mL). After 1 h at –78 °C, trimethylborate (1.35 equiv.) was slowly added and, 2 h later, the temperature was raised during 30 min to 20 °C. In parallel, tetrakis(triphenylphosphane)palladium(0) (0.02 equiv.) and the *o*-hydroxyhalogenobenzene derivative (1.00 equiv.) were dissolved in dimethoxyethane (30 ml) and stirred for 10 min at room temperature. To the lithiated alkynylborate was added the solution of $Pd(PPh_3)_4$ and the aryl halide via cannula. The cannula and the flask were rinsed with dimethoxyethane (2 × 5 mL). The reaction mixture was heated under reflux for 16 h (or until the complete disappearance of the aryl halide) and allowed to cool to room temperature. After addition of water and extraction with ethyl acetate, the combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography.

1-Methyl-4-(oct-1-ynyl)benzene (2a): Yield 98%, colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, J = 6 Hz, 3 H), 1.27–1.61 (m, 8 H), 2.33 (s, 3 H), 2.40 (t, J = 7.0 Hz, 2 H), 7.19 (AB, J = 8.1 Hz, $\Delta\nu$ = 40.6 Hz, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 19.5, 21.5, 22.7, 28.7, 28.9, 31.5, 80.7, 89.7, 121.1, 129.0, 131.5, 137.5 ppm. IR (neat): $\tilde{\nu}$ = 2956 (m), 2930 (s), 2858 (m), 2199 (w), 1510 (m), 1456 (w), 1106 (w), 816 (m), 757 (w) cm^{-1}. This compound was previously described.[14]

1-Methyl-4-(phenylethynyl)benzene (2b): Yield 96%, White solid, m.p. 70 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 7.30 (AB, J = 8 Hz, $\Delta\nu$ = 53.9 Hz, 4 H), 7.31–7.36 (m, 3 H), 7.50–7.55 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6, 88.9, 89.7, 120.3, 123.6, 128.2, 128.4, 129.3, 131.6, 131.7, 138.5 ppm. IR (neat): $\tilde{\nu}$ = 3080 (w), 3051 (w), 2923 (m), 1655 (w), 1594 (w), 1510 (m), 1441 (s), 1110 (m), 1070 (m), 915 (m), 818 (s), 755 (s), 690 (s) cm^{-1}. This compound was previously described.[14]

Trimethyl(*p*-tolylethynyl)silane (2c): Yield 55%, pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.25 (s, 9 H), 2.35 (s, 3 H), 7.24 (AB, J = 8 Hz, $\Delta\nu$ = 51.9 Hz, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 0.1, 21.6, 93.3, 105.4, 120.1, 129.0, 132.0, 138.7 ppm. IR (neat): $\tilde{\nu}$ = 3015 cm^{-1} (w), 2961 (w), 2925 (w), 2156 (m), 1507 (w), 1251 (m), 1216 (m), 865 (m), 843 (m), 818 (w), 758 (s), 699 (w) cm^{-1}. This compound was previously described.[15]

4-(Oct-1-ynyl)benzonitrile (2d): Yield 79%, colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 6.7 Hz, 3 H), 1.26–1.65 (m, 8 H), 2.43 (t, ^3J = 7.0 Hz, 2 H), 7.51 (AB, J = 8.6 Hz, $\Delta\nu$ = 21.7 Hz, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 19.6, 22.6, 28.5, 28.7, 31.4, 79.5, 95.8, 110.8, 118.8, 129.2, 132.0, 132.2 ppm. IR (neat): $\tilde{\nu}$ = 3020 (w), 2956 (m), 2931 (s), 2227 (s), 1604 (m), 1500 (m), 1466 (m), 1406 (w), 1379 (w), 1330 (w), 1271 (w), 1216 (w), 1177 (w), 1105 (w), 840 (s), 758 (s), 668 (w), 555 (m) cm^{-1}. This compound was previously described.[16]

1-Methyl-2-(oct-1-ynyl)benzene (2e): Yield 75%, colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 6.5 Hz, 3 H), 1.30–1.70 (m, 8 H), 2.44 (s, 3 H), 2,47 (t, ^3J = 6.7 Hz, 2 H), 7.09–7.20 (m, 3 H), 7.39 (d, ^3J = 6.5 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 19.7, 20.8, 22.7, 28.7, 29.0, 31.5, 79.6, 94.5, 124.0, 125.5, 127.5, 129.4, 131.9, 140.0 ppm. IR (neat): $\tilde{\nu}$ = 3062 (m), 3022 (m), 2930 (s), 2858 (s), 2227 (w), 1600 (w), 1486 (m), 1457 (m), 1378 (m), 1330 (w), 1115 (w), 1044 (w), 755 (s), 716 (m) cm^{-1}. This compound was previously described.[14]

(Dec-1-en-3-ynyl)benzene (2f): Yield 60%, pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 6.7 Hz, 3 H), 1.26–1.62 (m, 8 H), 2.38 (td, ^3J = 6.8, ^4J = 2.2 Hz, 2 H), 6.16 (dt, ^3J = 16.2, ^5J = 2.2 Hz, 1 H), 6.87 (d, ^3J = 16.2 Hz, 1 H), 7,24–7,39 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 19.8, 22.7; 28.7, 31.5, 79.8, 93.2, 109.0, 126.1, 128.3, 128.7, 136.7, 140.1 ppm. IR (neat): $\tilde{\nu}$ = 3061 (w), 3028 (w), 2955 (m), 2930 (s), 2858 (m), 2210 (w), 1697 (br), 1635 (w), 1599 (w), 1492 (w), 1449 (m), 1271 (w), 952 (m), 748 (m), 692 (m) cm^{-1}. This compound was previously described.[17]

(3-Oct-1-ynyl)pyridine (2g): Yield 75%, pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 6.7 Hz, 3 H), 1.25–1.70 (m, 8 H), 2.42 (t, ^3J = 6.9 Hz, 2 H), 7.17–7.24 (m, 1 H); 7.66 (dt, ^3J = 7.9, ^4J = 1.9 Hz, 1 H), 8.47 (dd, ^3J = 4.8, ^4J = 1.6 Hz, 1 H), 8.62 (d, ^4J = 1.4 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1,

19.5, 22.6, 28.6, 28.7, 31.4, 77.4, 94.2, 121.3, 123.0; 138.5, 148.0, 152.5 ppm. IR (neat): $\tilde{\nu}$ = 3030 (w), 2931 (s), 2859 (m), 2230 (w), 1561 (w), 1476 (m), 1407 (m), 1186 (w), 1023 (w), 803 (m), 756 (s), 706 (m) cm^{-1}. $C_{13}H_{17}N$ (187.28): calcd. C 83.37, H 9.15, N 7.48; found C 83.56, H 8.82, N 7.64.

1-(*tert*-Butyldimethylsilyloxy)-2-(oct-1-ynyl)benzene (2h): Yield 74%, pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.24 (s, 6 H), 0.92 (t, ^3J = 6.6 Hz, 3 H), 1.05 (s, 9 H), 1.28–1.64 (m, 8 H), 2.43 (t, ^3J = 7.0 Hz, 2 H), 6.79–6.89 (m, 2 H), 7.15 (td, ^3J = 7.7, ^4J = 1.9 Hz, 1 H), 7.36 (dd, ^3J = 7.7, ^4J = 1.9 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.2, 14.2, 18.4, 19.9, 22.7, 25.8, 28.8, 28.9, 31.5, 94.1, 116.7, 119.8, 121.2, 128.6, 133.6, 156.4 ppm. IR (neat): $\tilde{\nu}$ = 3014 (w), 2957 (m), 2931 (m), 2858 (m), 1596 (w), 1568 (w), 1488 (m), 1444 (m), 1284 (m), 1256 (m), 1216 (m), 1108 (w), 907 (m), 840 (m), 807 (w), 758 (s), 668 (w) cm^{-1}.

1-Methoxy-2-(oct-1-ynyl)benzene (2i): Yield 75% and 79%, respectively, colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 6.2 Hz, 3 H), 1.24–1.70 (m, 8 H), 2.47 (t, ^3J = 6.85 Hz, 2 H), 3.88 (s, 3 H), 6.88 (m, 2 H), 7.24 (td, ^3J = 7.8, ^4J = 1.6 Hz, 1 H), 7.38 (dd, ^3J = 7.5, ^4J = 1.6 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.5, 20.2, 23.0, 29.0, 29.2, 31.8, 56.2, 77.0, 95.1, 110.9, 113.6, 120.8, 129.2, 134.0, 160.2. IR (neat): $\tilde{\nu}$ = 3012 (w), 2956 (m), 2930 (s), 2857 (m), 2198 (w), 1729 (w), 1664 (w), 1597 (w), 1493 (m), 1465 (m), 1434 (m), 1260 (m), 1217 (w), 1117 (w), 1048 (w), 1026 (w), 754 (s) cm^{-1}. This compound was previously described.[14]

1-Methoxy-2(phenylethynyl)benzene (2j): Yield 89%, colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 6.90–7.00 (m, 2 H), 7.28–7.37 (m, 4 H), 7.50–7.62 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.0, 85.9, 93.6, 110.8, 112.6, 120.6, 123.7, 128.2, 128.4, 129.9, 131.8, 133.7, 160.0 ppm. IR (neat): $\tilde{\nu}$ = 3063 (w), 3014 (w), 2941 (w), 2837 (w), 1594 (w), 1574 (w), 1498 (m), 1484 (m), 1462 (m), 1434 (m), 1276 (m), 1247 (m), 1217 (m), 1182 (w), 1162 (w), 1107 (m), 1047 (w), 1025 (m), 753 (s), 691 (m), 668 (w) cm^{-1}. This compound was previously described.[14]

Synthesis of 2-Hexylbenzo[*b*]furan (3a) via Deprotection/Cyclization of 2a in the Presence of TBAF: A mixture of tetrabutylammonium fluoride (TBAF, 1 M in THF, 10 mL) and molecular sieves (4 Å, 5 g) in tetrahydrofuran (17 mL) was stirred for 1 h at room temperature. 0.75 mL of this solution (0.28 mmol of TBAF, 1.3 equiv.) was then added to a solution of **2a** (70.0 mg, 0.221 mmol, 1.0 equiv.) in dry tetrahydrofuran (1.5 mL) and the reaction mixture was stirred at 55 °C. The evolution of the reaction was checked by TLC and, after the complete disappearance of **2a**, water was added. After extraction with ethyl acetate, the combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography afforded **3a** (33.5 mg, 75%). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 6.5 Hz, 3 H), 1.27–1.5 (m, 6 H), 1.67–1.8 (m, 2 H), 2.77 (t, ^3J = 7.5 Hz, 2 H), 6.38 (s, 1 H), 7.15–7.26 (m, 2 H), 7.40–7.53 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 22.7, 27.7, 28.5, 29.0, 31.7, 101.8, 110.8, 120.2, 122.4, 123.1, 129.1, 154.7, 159.9 ppm. IR (neat): $\tilde{\nu}$ = 3017 (w), 2930 (m), 2859 (w), 1602 (w), 1456 (m), 1254 (w), 1216 (m), 1104 (w), 948 (w), 759 (s), 669 (w) cm^{-1}. This compound was previously described.[16]

Synthesis of 2-Phenylbenzo[*b*]furan (3b) via Deprotection/Cyclization of 2b in the Presence of LiI: Lithium iodide (268 mg, 2.00 mmol, 2.4 equiv.) was added to a solution of **2b** (176 mg, 0.845 mmol, 1 equiv.) in collidine (5 mL) and the resulting suspension was heated at 150 °C for 18 h. The reaction mixture was cooled to room temperature before the addition of a 10% aqueous solution of hydrogen chloride. After extraction with diethyl ether, the combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. Flash column chromatography afforded **3b** as a white solid (57 mg, 35%), m.p. 120–123 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.04 (s, 1 H), 7.20–7.62 (m, 7 H), 7.86–7.91 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 101.4, 111.3, 121.0, 123.0, 124.4, 125.0, 128.7, 128.9, 129.3, 130.6, 155.0, 156.0 ppm. IR (neat): $\tilde{\nu}$ = 3068 (w), 2924 (w), 1614 (w), 1563 (w), 1471 (w), 1456 (m), 1272 (w), 1208 (w), 1074 (w), 1038 (m), 1021 (m), 919 (m), 807 (m), 763 (m), 746 (s), 690 (m) cm^{-1}. This compound was previously described.[15]

Representative Procedure for the Synthesis of 2-Substituted Benzo[*b*]furans via Deprotection/Cyclization of *o*-Alkynylanisoles in the Presence of BCl_3

Synthesis of 2-Phenylbenzo[*b*]furan (3b):[16] Under argon, boron trichloride (1 M *in* heptanes, 1.3 mL, 1.3 mmol, 1.6 equiv.) was added to a solution of **2b** (165.7 mg, 0.795 mmol, 1 equiv.) in dry dichloromethane (8 mL). The reaction mixture was stirred for 16 h at room temperature before water (8 mL) was added. The two phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography gave **3b** as a white solid (94 mg, 61%).

2-Hexylbenzo[*b*]furan (3a)[16] was obtained analogously. The analytical data are given above.

Synthesis of 3-Iodo-2-phenylbenzo[*b*]furan (3c) via Deprotection/5-*endo-dig*-Iodocyclization of 2c in the Presence of BCl_3/I_2: To a solution of **2c** (142 mg, 0.682 mmol, 1 equiv.) in dry CH_2Cl_2 iodine (550 mg, 2.167 mmol, 3.2 equiv.) and boron trichloride (1 M *in* heptanes, 1.1 mL, 1.1 mmol, 1.6 equiv.) were added. The reaction mixture was stirred for 16 h at room temperature, before being diluted with water/ethyl acetate. The organic phase was washed with a saturated aqueous solution of sodium sulfite, dried with magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography afforded **3c** as a pale yellow oil (137 mg, 63% yield). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.26–7.56 (m, 7 H), 8.16–8.21 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 61.2, 111.3, 121.9, 123.6, 125.8, 127.6, 128.6, 129.3, 130.1, 132.6, 153.2, 154.0 ppm. IR (neat): $\tilde{\nu}$ = 3059 (w), 2923 (w), 1590 (w), 1488 (m), 1452 (m), 1442 (m), 1341 (w), 1253 (m), 1202 (m), 1062 (m), 1029 (m), 1008 (w), 971 (m), 888 (w), 818 (w), 764 (m), 742 (s), 689 (m) cm^{-1}. This compound was previously described.[10c]

Representative Procedure for the Synthesis of 2-Substituted 3-Iodobenzo[*b*]furans by Using BCl_3 and NIS

Synthesis of 3-Iodo-2-phenylbenzo[*b*]furan (3c):[10c] To a solution of 1-methoxy-2-(2-phenylethynyl)benzene (**2c**: 156.0 mg, 0.749 mmol, 1.0 equiv.) in dry dichloromethane (20 mL) was added successively *N*-iodosuccinimide (335 mg, 1.49 mmol, 2.0 equiv.) and boron trichloride (1 M *in* heptanes, 1.1 mL, 1.1 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 2 h (monitored by TLC) before water was added. After extraction with dichloromethane, the combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography gave 3-iodo-2-phenylbenzo[*b*]furan (**3c**) as a pale yellow oil (192 mg, 80% yield). The analytical data are mentioned above.

2-Hexyl-3-iodobenzo[*b*]furan (3d): Was obtained analogously as a pale yellow oil (192 mg, 78% yield). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 6.7 Hz, 3 H), 1.27–1.46 (m, 6 H), 1.68–1.82 (m, 2 H), 2.86 (t, ^3J = 7.4 Hz, 2 H), 7.25–7.42 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 22.6, 27.9, 28.1, 28.8, 31.6, 62.6, 111.0, 120.8, 123.2, 124.5, 131.2, 154.3, 159.3 ppm. IR (neat): $\tilde{\nu}$ = 2955 (m), 2928 (m), 2858 (m), 1587 (w), 1450 (s), 1256 (w), 1216 (w),

1190 (w), 1170 (w), 1106 (w), 1010 (w), 983 (w), 759 (s), 744 (s) cm^{-1}. This compound was previously described.[18]

Representative Procedure for the Tandem sp-sp² Suzuki Coupling/5-*endo*-*dig*-Iodocyclization of *o*-Iodoanisole with Terminal Alkynes: A solution of *n*-butyllithium in hexanes (1.35 equiv.) was slowly added to a cooled solution (–78 °C) of 1-alkyne (10.4 mmol, 1.30 equiv.) in dimethoxyethane (10 mL). After 1 h at –78 °C, trimethylborate (0.85 equiv.) was slowly added and, 30 min later, the temperature was raised during 15 min. to 20 °C. In parallel, tetrakis(triphenylphosphane)palladium(0) (0.015 equiv.) and *o*-iodoanisole (1.00 equiv.) were dissolved in dimethoxyethane (10 ml) and stirred for 10 min at room temperature. To the lithiated alkynyl borate was added the solution of $Pd(PPh_3)_4$ and the aryl halide via cannula. The cannula and the flask were rinsed with dimethoxyethane (2 × 5 mL). The reaction mixture was heated under reflux for 4 h (or complete disappearance of the aryl halide) and allowed to cool to room temperature.

Evaporation of the DME was then performed before adding CH_2Cl_2 (30 mL), NIS (1.7 equiv.) and BCl_3 M in hexane (1.4 equiv.). After stirring overnight at room temperature, addition of water and extraction with CH_2Cl_2, the combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography. The analytical data of **3c** and **3d** are given above.

Representative Procedure for Suzuki Coupling Reaction of 2-Substituted 3-Iodobenzo[*b*]furans 3c–d with Various Boronic Acids

Synthesis of 2-Hexyl-3-phenylbenzo[*b*]furan (4a): To a solution of 2-hexyl-3-iodobenzo[*b*]furan (**3d**: 182.5 mg, 0.556 mmol, 1 equiv.) in dry dimethoxyethane (10 mL) were successively added palladium(II) acetate (6.5 mg, 0.029 mmol, 5.2%), triphenylphosphane (21.3 mg, 0.081 mmol, 14.6%), phenylboronic acid (108.4 mg, 0.89 mmol, 1.5 equiv.) and cesium fluoride (407 mg, 2.65 mmol, 4.7 equiv.). The reaction mixture was heated for 16 h at 75 °C and allowed to cool to room temperature, before water was added. The mixture was extracted with dichloromethane, the combined organic phases were dried with magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by flash column chromatography. (139 mg, 90%), colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 6.5 Hz, 3 H), 1.29–1.44 (m, 6 H), 1.68–1.86 (m, 2 H), 2.88 (t, ^3J = 7.6 Hz, 2 H), 7.20–7,68 (m, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 22.7, 26.9, 28.5, 29.1, 31.6, 110.9, 116.9, 119.5, 122.6, 123.6, 127.1, 128.8, 129.0, 129.2, 133.0, 154.1, 155.5 ppm. IR (neat): $\tilde{\nu}$ = 3058 (w), 3034 (w), 2955 (m), 2928 (s), 2858 (m), 1611 (m), 1597 (w), 1497 (w), 1455 (s), 1377 (w), 1245 (w), 1207 (w), 1175 (w), 1106 (w), 1074 (w), 1012 (w), 969 (m), 859 (w), 771 (m), 749 (s), 700 (s) cm^{-1}. $C_{20}H_{22}O$ (278.38): calcd. C 86.28, H 7.96; found C 86.00, H 8.001.

3-(1-Naphthyl)-2-phenylbenzo[*b*]furan (4b): Yield 162 mg, 91%, white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.17–7.81 (m, 14 H), 8.00 (d, ^3J = 6.22 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 111.2, 115.8, 120.6, 123, 124.8, 126, 126.1, 126.3, 126.5, 126.7, 127.9, 128, 128.3, 128.5, 128.6, 130.6, 131.6, 132.3, 134.2, 151.4, 154 ppm. $C_{24}H_{16}O$ (320.38): calcd. C 89.97, H 5.03, O 4.99; found C 89.52, H 5.05, O 4.68.

3-(*o*-Methoxyphenyl)-2-phenylbenzo[*b*]furan (4c):[19] Yield 152 mg, 91%, pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.66 (s, 3 H), 7.04–7.9 (m, 13 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.4, 111, 111.6, 113.9, 120.6, 121.1, 121.7, 122.7, 124.4, 126.5, 128.1, 128.3, 129.5, 130.7, 131.3, 131.9, 151, 154, 157.6 ppm. $C_{21}H_{16}O_2$ (300.35): calcd. C 83.98, H 5.37; found C 83.69, H 5.476.

3-(*o*-Methylphenyl)-2-phenylbenzo[*b*]furan (4d): Yield 97 mg, 64%, colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.17 (s, 3 H), 7.27–7.62 (m, 13 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.3, 111.4, 117.3, 120.6, 123.3, 125.1, 126.4, 126.8, 128.5, 128.6, 128.8, 128.9, 131, 131.2, 131.4, 132.7, 137.9, 150.7, 154.3 ppm. $C_{21}H_{16}O$ (284.35): calcd. C 88.7, H 5.67; found C 88.46, H 5.893.

[1] a) A. R. Katritzky, in *Advances in Heterocyclic Chemistry*, Academic Press, New York, **1982**; b) G. Vernin, in *The Chemistry of Heterocyclic Flavouring and Aroma Compounds*, Hellis Horwood, Chichester, **1982**; c) A. R. Katritzky, C. W. Rees, in *Comprehensive Heterocyclic Chemistry*, Pergamon, New York, **1984**; d) H. B. Lipshutz, *Chem. Rev.* **1986**, *86*, 795–819; e) C. C. Felder, K. E. Joyce, E. M. Briley, M. Glass, K. P. Mackie, K. J. Fahey, G. J. Cullinan, D. C. Hunden, D. W. Johnson, M. O. Chaney, G. A. Koppel, M. Brownstein, *J. Pharmacol. Exp. Ther.* **1998**, 291–297.

[2] A. Gangjee, R. Devraj, J. J. Mc Guire, R. L. Kisliuk, *J. Med. Chem.* **1995**, *38*, 3798–3805.

[3] Z. Yang, H. B. Liu, C. M. Lee, H. M. Chang, H. N. Wong, *J. Org. Chem.* **1992**, *57*, 7248–7257.

[4] K. A. Ohemeng, M. A. Appolina, V. N. Nguyen, C. F. Schwender, M. Singer, M. Steber, J. Ansell, D. Argentieri, W. Hageman, *J. Med. Chem.* **1994**, *37*, 3663–3667.

[5] T. Nagahara, Y. Yokoyama, K. Inamura, S. Katakura, S. Komoriya, H. Yamaguchi, T. Hara, M. Iwamoto, *J. Med. Chem.* **1994**, *37*, 1200–1207.

[6] A. P. Kozikowsky, D. Ma, L. Du, N. E. Lewin, P. M. Blumberg, *J. Am. Chem. Soc.* **1995**, *117*, 6666–6672.

[7] G. A. Carter, K. Chamberlain, R. L. Wain, *Ann. Appl. Biol.* **1978**, *88*, 57–64.

[8] a) A. Fürstner, D. N. Jumbam, *Tetrahedron* **1992**, *48*, 5991–6010; b) R. S. Givens, P. S. Athey, B. Matuszewski, L. W. Kuepper, J. Xue, T. Fister, *J. Am. Chem. Soc.* **1993**, *115*, 6001–6012; c) D. Hellwinkel, K. Göke, *Synthesis* **1995**, 1135–1141; d) X. Du, R. W. Armstrong, *J. Org. Chem.* **1997**, *62*, 5678–5679; e) Y. Ito, T. Aoyama, T. Shioiri, *Synlett* **1997**, 1163–1164; f) C. Fuganti, S. Serra, *Tetrahedron Lett.* **1998**, *39*, 5609–5610; g) D. D. Hennings, S. Iwasa, V. H. Rawal, *Tetrahedron Lett.* **1997**, *38*, 6379–6382.

[9] a) N. J. Kundo, M. Pal, J. S. Mahanty, M. J. De, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2815–2820; b) Y. Kondo, F. Shiga, N. Murata, T. Sakamoto, H. Yamanaka, *Tetrahedron* **1994**, *50*, 11803–11812; c) A. Arcadi, S. Cacchi, M. Del Rosario, G. Fabrizi, F. Marinelli, *J. Org. Chem.* **1996**, *61*, 9280–9288; d) N. Monteiro, G. Balme, *Synlett* **1998**, 746–747; e) N. Monteiro, A. Arnold, G. Balme, *Synlett* **1998**, 1111–1113.

[10] a) S. Cacchi, *J. Organomet. Chem.* **1999**, *576*, 42–64; b) A. Arcadi, S. Cacchi, F. Marinelli, *Synthesis* **1986**, 749–751; c) A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, L. Moro, *Synlett* **1999**, *9*, 1432–1434; d) R. C. Larock, E. K. Yum, M. J. Doty, K. K. C. Sham, *J. Org. Chem.* **1995**, *60*, 3270–3271; e) C. Amatore, E. Blart, J. P. Genêt, A. Jutand, S. Lemaire-Audoire, M. Savignac, *J. Org. Chem.* **1995**, *60*, 6829–6839.

[11] A.-S. Castanet, F. Colobert, T. Schlama, *Org. Lett.* **2000**, *2*, 3559–3561.

[12] Contrary, using *o*-(*tert*-butyldimethylsilyloxy)bromobenzene the reaction was unreproducible, affording 2-bromophenol, starting material, coupling product and 2-hexylbenzo[*b*]furan in varying ratios.

[13] For other examples of iodine-promoted electrophilic cyclization of alkynes to give heterocycles, see: a) A. Arcadi, S. Cacchi, S. Di Giuseppe, G. Fabrizi, F. Marinelli, *Org. Lett.* **2002**, *4*, 2409–2412; b) T. Yao, M. A. Campo, R. C. Larock, *Org. Lett.* **2004**, *6*, 2677–2680.

[14] Y. Ma, C. Song, W. Jiang, Q. Wu, Y. Wang, X. Liu, M. B. Andrus, *Org. Lett.* **2003**, *5*, 3317–3319.

[15] G. W. Kabalka, L. Wang, R. M. Pagni, *Tetrahedron* **2001**, *57*, 8017–8028.

[16] D. Gelman, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2003**, *42*, 5993–5996.

[17] H. Sashida, A. Kuroda, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1965–1969.
[18] D. R. Buckle, C. J. M. Rockell, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2443–2446.
[19] Y. Hu, K. J. Nawoschik, Y. Liao, J. Ma, R. Fathi, Z. Yang, *J. Org. Chem.* **2004**, *69*, 2235–2239.
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