

Furans and Benzofurans

Kap-Sun Yeung

Abstract This chapter reviews the significant developments in the metalation of furans and benzofurans and applications of the resulting metalated species in the past decade. New and interesting metalated furan and benzofuran derivatives and their novel reactions are featured. Topics encompass lithiation, magnesiation and zincation, the use of boronated and other metalated furans and benzofurans in cross-coupling reactions, as well as the use of metalated furans and benzofurans in addition reactions. Examples of regioselective metalation are highlighted, and metalation of related furo heterocycles is also summarized.

Keywords Addition reactions · Benzofurans · Cross-coupling · Furans · Metalation

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1 Introduction

Furan and benzofuran are common structural elements present in numerous bioactive natural products as well as pharmaceuticals, molecular electronic and functional polymers [1]. Recent noteworthy examples from natural sources, as shown in Fig. 1, include the cytotoxic diterpenoid salvileucalin B [2] and the selective phosphoinositide-3-kinase α inhibitor liphalgal [3]. The total syntheses of both of these unusual molecular structures have recently been accomplished [3, 4]. Due to their electron-rich character, furans also function as versatile precursors to a variety of functional moieties as well as carbocycles and heterocycles through the transformation of the furan nucleus, for example, by oxidation and cycloaddition reactions [5–7].

A broadly employed approach for the incorporation of furan and benzofuran rings is by utilizing their metalated species that participate primarily in metal-catalyzed cross-coupling reactions and as nucleophiles in addition reactions. Conventionally, direct deprotonation of furan and benzofuran takes place at the most acidic C2 position (or the C5 position in 2-substituted furans) by using alkyl lithiums with or without TMDEA, or using lithium amide bases. For example, as shown in Scheme 1, lithiation using *n*-BuLi presumably generated a 2,5-dianion,

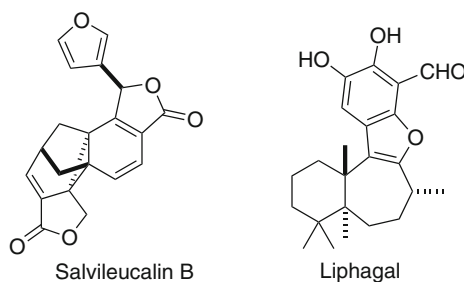
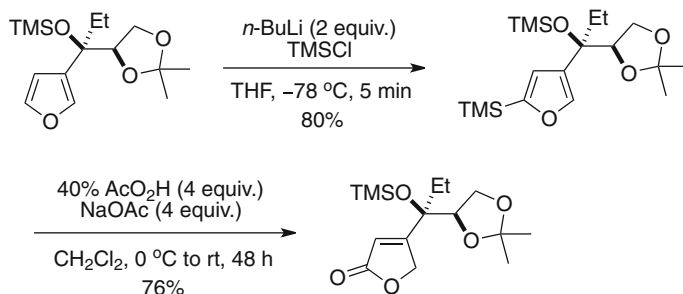


Fig. 1 Furan- and benzofuran-containing natural products



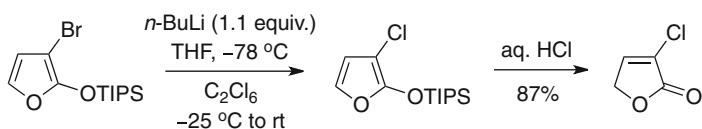
Scheme 1 Direct metalation of furan at C2 (C5) position

which was regioselectively silylated at the less hindered C5 position [8]. The incorporation of the TMS group directed the subsequent regioselective oxidation to the γ -butenolide.

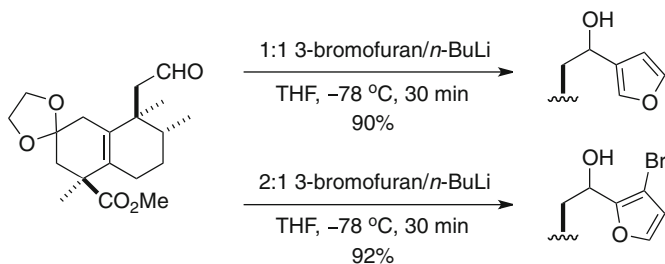
Metalation at the C3 position of furan generally requires lithium–halogen exchange using alkyl lithium bases. As exemplified in Scheme 2, Li–Br exchange of 3-bromo-2-triisopropylsilyloxyfuran occurred smoothly under standard conditions. The anion formed can be quenched with C, S, Se, Si, and halogen electrophiles to generate α -substituted γ -butenolides after acidic hydrolysis [9].

However, metalation outcomes were influenced by the stoichiometries of 3-bromofuran and *n*-BuLi used. For example, as demonstrated in a key addition reaction of furyllithium to an aldehyde during a synthesis of chettaphanin shown in Scheme 3 [10], mixing equimolar amounts of the two reactants generated 3-furyllithium as expected, while metalation occurred at the C2 position when half an equivalent of *n*-BuLi was used.

Lithiation followed by transmetalation of lithiofurans is commonly used to generate various metalated furan derivatives. Earlier developments in the metalation of furans and benzofurans and their applications have been reviewed extensively [6, 11, 12]. This chapter serves to capture the significant advances in these areas in the past decade, highlighting new and interesting metalated furan and benzofuran species and their novel transformations. Examples of regioselective metalation are described, and metalation of related furo heterocycles is also summarized.



Scheme 2 Lithium–bromide exchange of furan at C3 position



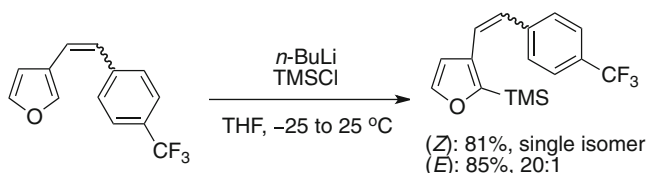
Scheme 3 Metalation of 3-bromofuran using different equivalent of *n*-BuLi

2 Lithiation of Furans and Benzofurans

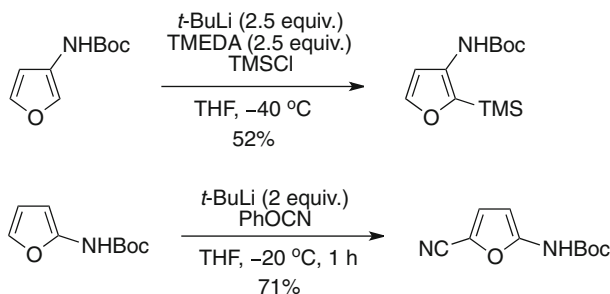
An interesting counter-steric regioselectivity was unexpectedly obtained in the lithiation of 3-phenyl as well as (*E*)- and (*Z*)-3-styrylfurans under conventional conditions using *n*-BuLi. The lithiation preferentially occurred at the more hindered C2-position, as illustrated in Scheme 4 [13]. The regioselectivity was increased by a phenyl ring bearing an electron-withdrawing group, attributed to the stabilization of the furyl anion in a late transition state.

The lithiation of 3-(*N*-*tert*-butoxycarbonyl)furan by using *t*-BuLi occurred regioselectively at the C2 position as assisted by the apparent *ortho*-directing effect of *N*-*tert*-butoxycarbonyl group to provide 2-substituted 3-(*N*-*tert*-butoxycarbonyl) furans after quenching with a range of electrophiles [14], as exemplified in Scheme 5. This is in contrast to an example of lithiation/cyanation of 2-(*N*-*tert*-butoxycarbonyl)furan, which took place at the C5 position [15].

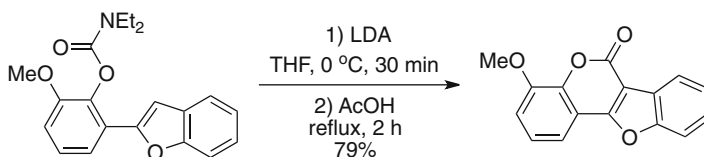
Directed *ortho* metalation could occur remotely at the C3 position of benzofuran as illustrated in a synthesis of a coumestan depicted in Scheme 6 [16].



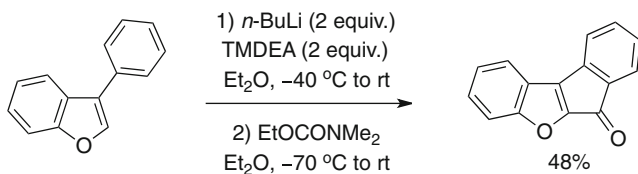
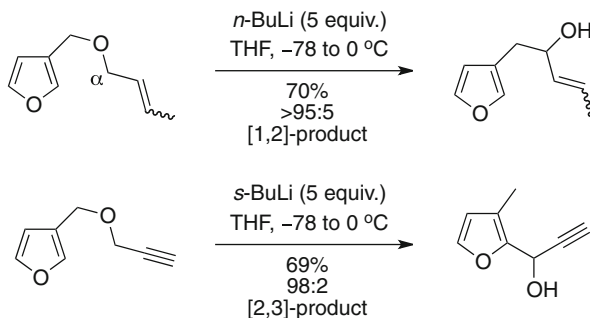
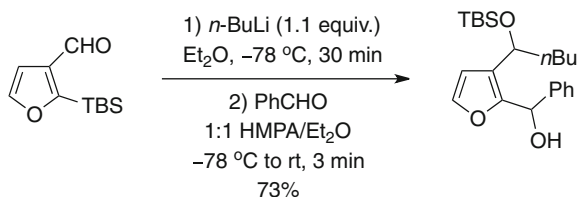
Scheme 4 Regioselective lithiation of (*E*)- and (*Z*)-3-styrylfurans



Scheme 5 Regioselective lithiation of 3- and 2-(*N*-*tert*-butoxycarbonyl)furans



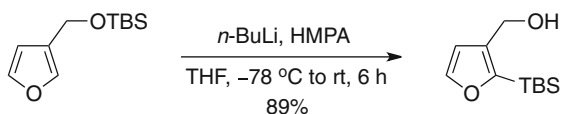
Scheme 6 Directed *ortho* remote metalation of benzofuran

**Scheme 7** Dilithiation of 3-phenylbenzofuran**Scheme 8** Deprotonation at the ethereal α position of 3-furylmethyl ethers**Scheme 9** Addition of organolithium reagent to 2-TBS-3-formylfuran

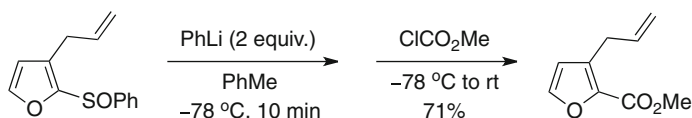
Dilithiation of 3-phenylbenzofuran also followed an *ortho* remote manner. As demonstrated in Scheme 7, this method was used for the synthesis of hetarenoindanones, which were reduced to provide hetarenoindenes [17].

Deprotonation at the ethereal α position of 3-furylmethyl ethers by alkyl lithiums (*n*-, *s*-, or *t*-BuLi) or LDA occurred more readily than deprotonation at the furan C2 position. As illustrated in Scheme 8, products arising from a formal [1,2]- and [2,3]-Wittig rearrangements were selectively obtained by using different bases [18].

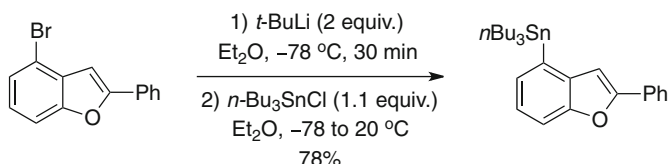
A furan C2 anion was regioselectively generated via the addition of organolithium reagents to 2-TBS-3-formylfuran and subsequent 1,4-Brook silyl migration of the intermediate lithium alkoxide [19]. Quenching the anion with aldehydes and ketones provided 2,3-disubstituted furans as exemplified in Scheme 9.



Scheme 10 retro-Brook rearrangement of a 2-lithiofuran



Scheme 11 Regioselective lithiation of furan via sulfoxide–lithium exchange



Scheme 12 Lithium–bromide exchange of 4-bromo-2-phenylbenzofuran using *t*-BuLi

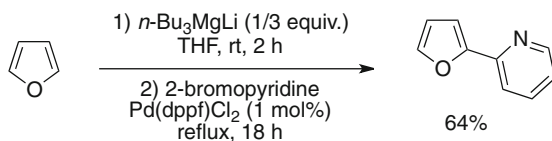
Interestingly, lithiation of the 3-furylmethyl TBS ether shown in Scheme 10 initiated a retro-Brook rearrangement of the corresponding 2-lithiofuran that conveniently installed a silyl blocking group regioselectively at the furan C2 position [20].

Another example of regioselective lithiation of furan resulted from a lithium–sulfoxide exchange that was carried out by using phenyllithium as a base [21], as shown in Scheme 11.

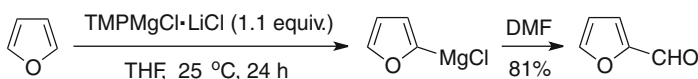
As depicted in Scheme 12, lithium–bromide exchange of 4-bromobenzofuran required the use of the strong base *t*-BuLi to generate 4-benzofuranyllithium, which was converted to the tin derivative [22].

3 Magnesium of Furans and Benzofurans, and Their Applications

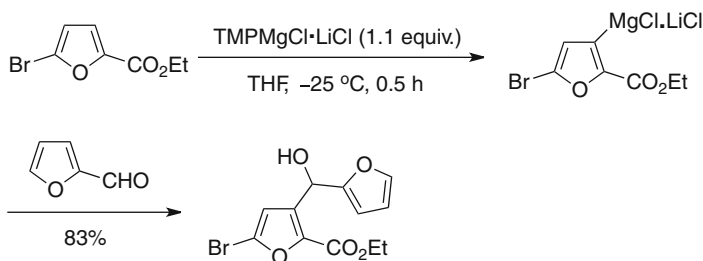
Metalation of furans and benzofurans can be performed at or near ambient temperature under new conditions that seek to avoid undesirable side reactions resulted from high reactivity and nucleophilicity of lithium bases. Deprotonation at the C2 position of unsubstituted furan and benzofuran at room temperature was achieved by using lithium magnesates Bu_3MgLi and Bu_4MgLi_2 [23], and the resulting lithium 2-furylmagnesate was stable and reactive toward Kumada-type cross-coupling, as exemplified in Scheme 13.



Scheme 13 Magnesylation of furan using Bu_3MgLi and the subsequent cross-coupling



Scheme 14 Magnesylation of furan using $\text{TMPMgCl}\cdot\text{LiCl}$



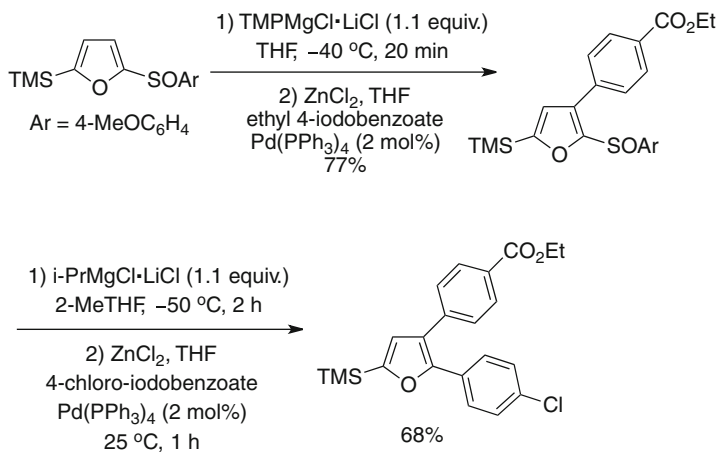
Scheme 15 Regioselective magnesylation of ethyl 5-bromofuran-2-carboxylate

As represented in Scheme 14, direct magnesylation of unsubstituted furan by using a mixed Mg/Li amide $\text{TMPMgCl}\cdot\text{LiCl}$ ($\text{TMP} = 2,2,6,6\text{-tetramethylpiperidine}$) also occurred at room temperature to generate 2-furylmagnesium chloride in situ, which was quenched with an electrophile [24].

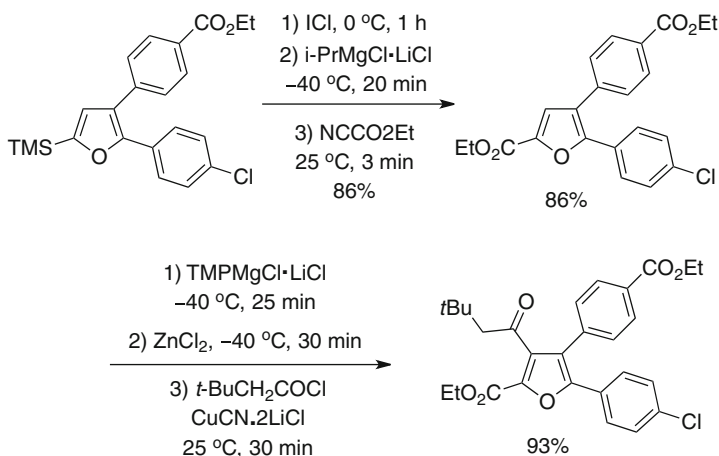
Interestingly, regioselective direct magnesylation at the C3 position of ethyl 5-bromofuran-2-carboxylate, presumably activated by the carboxylate group, has been demonstrated by employing $\text{TMPMgCl}\cdot\text{LiCl}$ at lower temperature as depicted in Scheme 15 [24].

2-(4-Methoxyphenyl)sulfinyl-substituted benzofuran and 5-trimethylsilylfuran were also magnesiated at the C3-position by using $\text{TMPMgCl}\cdot\text{LiCl}$ and then transmetalated to the corresponding zinc reagents for Negishi coupling [25, 26]. Subsequent sulfoxide–magnesium exchange was performed by using $i\text{-PrMgCl}\cdot\text{LiCl}$ for the formation of 2,3-disubstituted derivatives as illustrated in Scheme 16.

As represented in Scheme 17, further manipulation of the C4 and C5 positions of 2,3-disubstituted-5-trimethylsilylfurans again by consecutive application of these two different magnesium bases, i.e. iodide–magnesium exchange with $i\text{-PrMgCl}\cdot\text{LiCl}$ followed by magnesylation using $\text{TMPMgCl}\cdot\text{LiCl}$, led to tetrasubstituted furans.



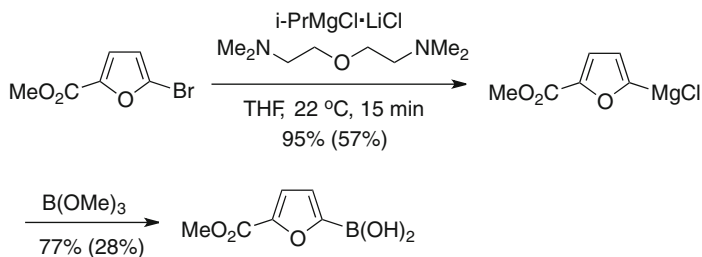
Scheme 16 Magnesonation of 2-(4-methoxyphenyl)sulfinyl-5-trimethylsilylfuran



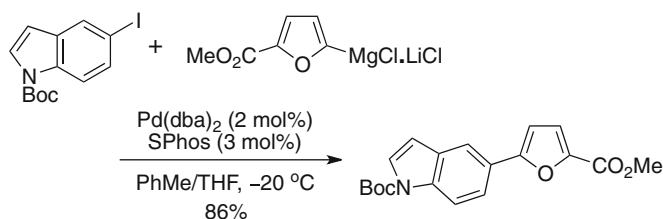
Scheme 17 Consecutive application of magnesium bases, *i*-PrMgCl·LiCl and TMPMgCl·LiCl, on a 2,3-disubstituted-5-trimethylsilylfuran

Efficient magnesium–bromide exchange of methyl 5-bromofuran-2-carboxylate could be performed at 22 °C by using *i*-PrMgBr in the presence of bis[2-(*N,N*-dimethylamino)ethyl] ether [27]. The resulting Grignard reagent was presumably stabilized by the formation of a tridentate complex with the diamine, leading to a 95% conversion as shown in Scheme 18. Addition of the complex to trimethylborate provided the corresponding boronic acid in high yield compared to the reaction without using the diamine.

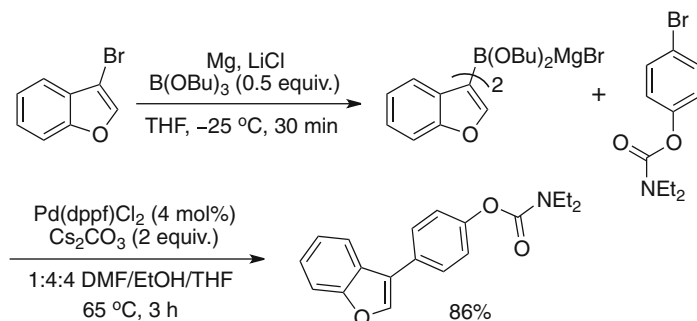
As shown in Scheme 19, a palladium-catalyzed Kumada coupling of the above Grignard reagent, generated via the usual Knochel's Mg/I exchange protocol, with an aryl iodide proceeded at lower temperature than is commonly used in the presence of SPhos as a ligand [28].



Scheme 18 Magnesonation of methyl 5-bromofuran-2-carboxylate in the presence of bis[2-(*N*, *N*-dimethylamino)ethyl] ether. The numbers in brackets correspond to the yields of the reactions in the absence of the diamine.



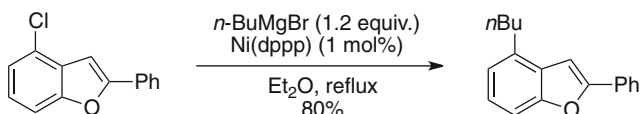
Scheme 19 Kumada coupling of (5-(methoxycarbonyl)2-furyl)magnesium chloride at low temperature



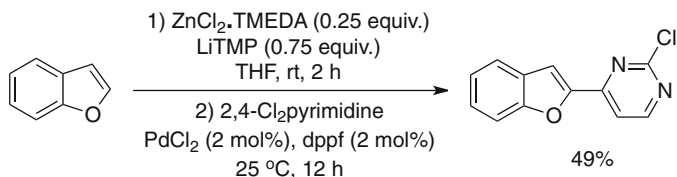
Scheme 20 Suzuki–Miyaura coupling of magnesium dibenzofuranylboronate

The interesting magnesium dibenzofuranylboronate depicted in Scheme 20 was prepared from 3-bromobenzofuran under Grignard-type conditions in the presence of 0.5 equivalents of B(OBu)_3 . This type of boronate was reactive toward Suzuki–Miyaura coupling, as illustrated [29].

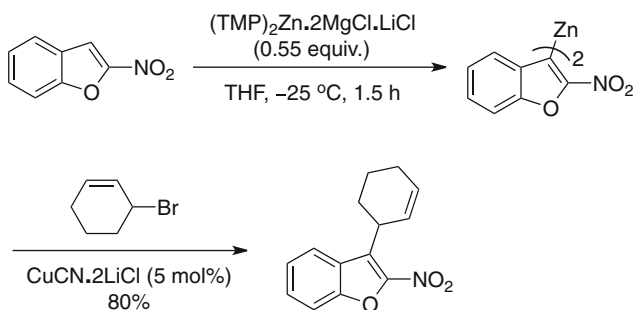
4-Chlorobenzofuran was sufficiently reactive toward a nickel-catalyzed $\text{sp}^3\text{--sp}^2$ Kumada coupling with an alkylmagnesium bromide, as depicted in Scheme 21 [22].



Scheme 21 Nickel-catalyzed Kumada coupling of 4-chloro-2-phenylbenzofuran



Scheme 22 Zincation of benzofuran using $\text{ZnCl}_2\cdot\text{TMEDA}/\text{LiTMP}$ and subsequent cross-coupling with aryl chloride

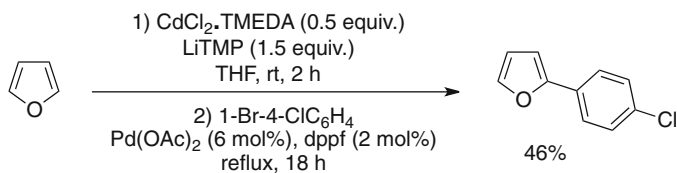


Scheme 23 Zincation of 2-nitrobenzofuran and subsequent Negishi coupling

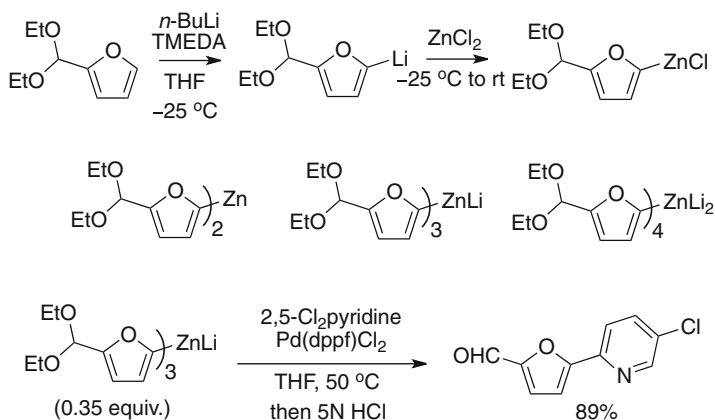
4 Zincation of Furans and Benzofurans, and Their Applications

Zincates at the C2 position of unsubstituted furan and benzofuran were prepared at room temperature by using a mixed base generated in situ from a 1:3 mixture of $\text{ZnCl}_2\cdot\text{TMEDA}/\text{LiTMP}$ [30, 31], and used for the addition to aldehydes or a palladium-catalyzed coupling with aryl and heteroaryl chlorides and bromides, as illustrated in Scheme 22.

Addition of 0.5 equivalent of ZnCl_2 to $\text{TMPMgCl}\cdot\text{LiCl}$ generated a complex mixed base $(\text{TMP})_2\text{Zn}\cdot 2\text{MgCl}\cdot 2\text{LiCl}$ [32]. This was used for zincation of arenes and heteroarenes bearing sensitive functional groups, e.g., aldehyde and nitro groups that are not compatible with lithium or magnesium bases, at or near ambient temperature. For example, as shown in Scheme 23, the zincate of 2-nitrobenzofuran



Scheme 24 Cross-coupling of 2-furyl cadmate with arylbromide



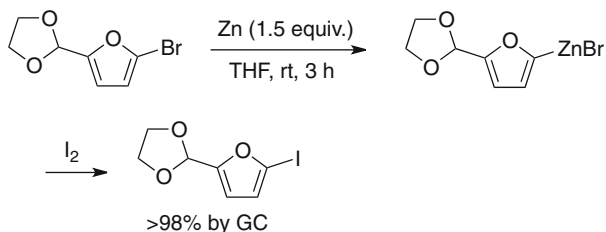
Scheme 25 Palladium-catalyzed cross-coupling of 2-furyl zincate

was formed smoothly at the C3 position using this base and then subjected to a copper-catalyzed Negishi coupling with 3-cyclohexenylbromide.

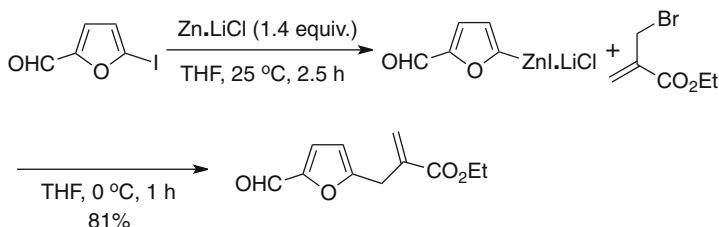
Similar to zincation, unsubstituted furan and benzofuran were also metalated at room temperature by using a cadmium–lithium mixed base generated in situ by mixing 0.5 equivalent of CdCl_2 -TMDEA with LiTMP [33]. The resulting 2-furyl cadmate directly participated in reaction with acid chlorides to form ketones and palladium-catalyzed cross-coupling with arylbromides, as demonstrated in Scheme 24. However, competing homocoupling and the toxicity associated with cadmium species may limit the application of this metalation method.

As shown in Scheme 25, a 2-furylzinc chloride as well as the corresponding di-, tri-, and higher order zincates were prepared from the 2-lithiofuran by transmetalation using the appropriate stoichiometries of ZnCl_2 [34]. These zincates were found to transfer all of the furyl groups during a palladium-catalyzed cross-coupling reaction, as exemplified in Scheme 25.

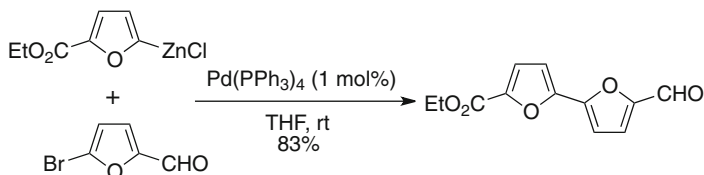
The related 5-(1,3-dioxolan-2-yl)-2-furylzinc was prepared by the direct insertion of Rieke's active zinc to the corresponding bromide at room temperature as shown in Scheme 26 [35]. However, furylzinc reagents could also be generated from unprotected 5-iodo-2-furaldehyde and ethyl 5-bromofuran-2-carboxylate by a LiCl-mediated direct insertion of zinc powder at room temperature, as demonstrated in Scheme 27 [36].



Scheme 26 Formation of 2-furylzinc by the direct insertion of active zinc to 2-bromofuran



Scheme 27 Formation of 5-formyl-2-furylzinc by LiCl-mediated direct insertion of zinc to 5-iodo-2-furaldehyde



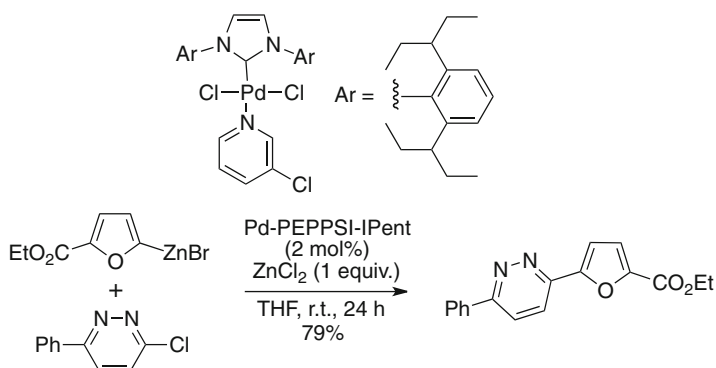
Scheme 28 Palladium-catalyzed cross-coupling of 5-bromo-2-furaldehyde

5-Aryl- and 5-heteroaryl-2-furaldehydes were also prepared from the cross-coupling of 5-bromo-2-furaldehyde with zinc reagents by employing 1 mol% of $(\text{Ph}_3\text{Ph})_4\text{Pd}$ as catalyst [36, 37], as shown by the interesting example summarized in Scheme 28.

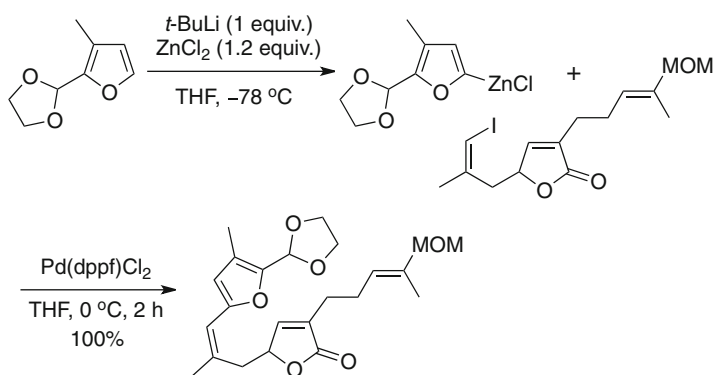
A new palladium-N-heterocyclic carbene (Pd-PEPPSI-IPent) complex was efficient for the Negishi coupling of a 2-furylzinc, enabling the reaction to proceed at room temperature, as depicted in Scheme 29 [38]. This catalyst was also useful for the Suzuki–Miyaura coupling of 3-furylboronic acid and 2-benzofuranylboronic acid [39]. A one-pot zincation of ethyl 5-bromofuran-2-carboxylate using Zn/LiCl followed by a Negishi coupling employing an *i*-Pr analog of Pd-PEPPSI-IPent as a catalyst was also reported [40].

The utility of zinc reagents of 2-furaldehyde derivatives as described above in Negishi coupling was further exemplified by a key step in a total synthesis of the marine natural product bipinnatin J, as shown in Scheme 30 [41].

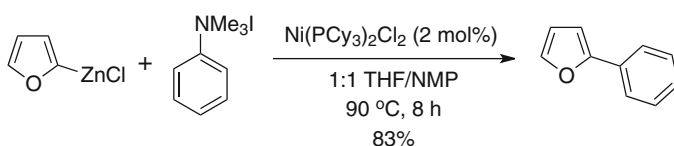
A Negishi coupling of 2-furylzinc with aryltrimethylammonium iodides was promoted by a nickel catalyst, as represented in Scheme 31 [42].



Scheme 29 Negishi coupling of 2-furylzinc using Pd-PEPPSI-IPent catalyst



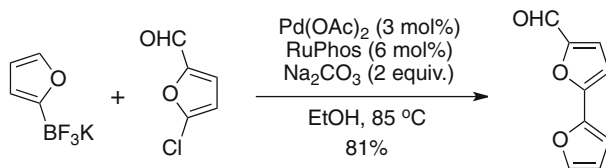
Scheme 30 A key Negishi coupling in a total synthesis of bipinnatin J



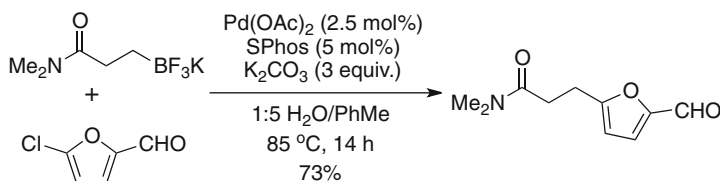
Scheme 31 Nickel-catalyzed cross-coupling of furylzinc with phenyltrimethylammonium iodide

5 Boronated Furans and Benzofurans in Cross-Coupling Reactions

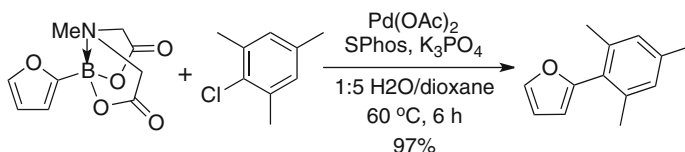
Potassium 2-furyl, 3-furyl, and 2-benzofuranyl trifluoroborates served as efficient nucleophilic coupling partners in equimolar amount in Suzuki–Miyaura cross-coupling reaction. By employing RuPhos as a ligand, the reaction proceeded even with less reactive aryl and heteroaryl chlorides [43]. An interesting example is depicted in Scheme 32. Potassium 2-furyl trifluoroborate, which was prepared by



Scheme 32 Suzuki–Miyaura cross-coupling of potassium 2-furyl trifluoroborate with 5-chloro-2-furaldehyde



Scheme 33 Suzuki–Miyaura cross-coupling of 5-chloro-2-furaldehyde with potassium β -trifluoroborato amide

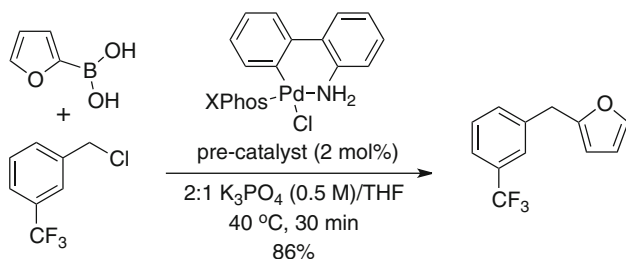


Scheme 34 Suzuki–Miyaura cross-coupling of 2-furyl MIDA boronate

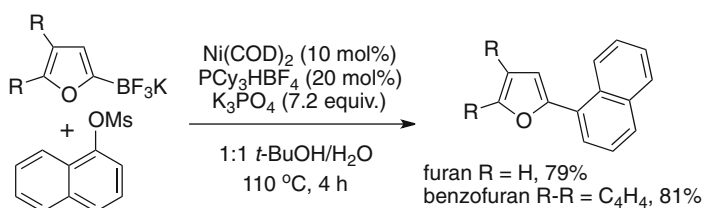
the addition of KHF_2 to 2-furylboronic acid, exhibited stability at ambient temperature for 3 months without sign of proto-deboronation.

Interestingly, 5-chloro-2-furaldehyde reacted with primary alkyl [44] and aminomethyl tetrafluoroborate [45] potassium salts, as well as potassium β -trifluoroborato amide [46], as shown in Scheme 33. Note that the reaction using SPhos as a ligand was sufficiently efficient to prevent undesirable β -hydride elimination.

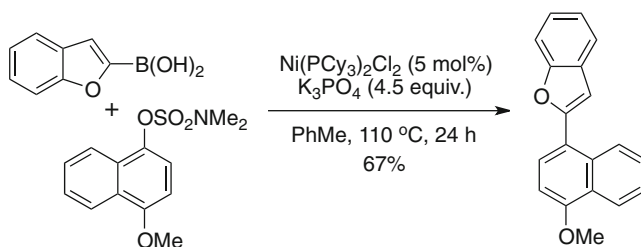
Cross-coupling methods were developed to circumvent the problem of instability of certain aryl and heteroaryl boronic acids, including 2-furyl and 2-benzofuranyl boronic acids, particularly during the reaction with unactivated substrates, e.g., aryl chlorides. 2-Furyl and 2-benzofuranyl *N*-methyliminoacetic acid (MIDA) boronates demonstrated bench-top stability compared to the corresponding boronic acids. Slow release of the boronic acid via in situ hydrolysis of the boronate using K_3PO_4 increased the reaction efficiency of Suzuki–Miyaura cross-coupling, as exemplified by the reaction with the hindered aryl chloride shown in Scheme 34 [47]. Another method employed a XPhosPd precatalyst [48], as illustrated by the benzylic $\text{sp}^3\text{--sp}^2$ coupling depicted in Scheme 35, to ensure a rapid formation of the catalytically active $\text{XPhosPd}(0)$ species for the transmetalation of the boronic acids.



Scheme 35 Suzuki-Miyaura cross-coupling of 2-furyl boronic acid using a XPhosPd precatalyst



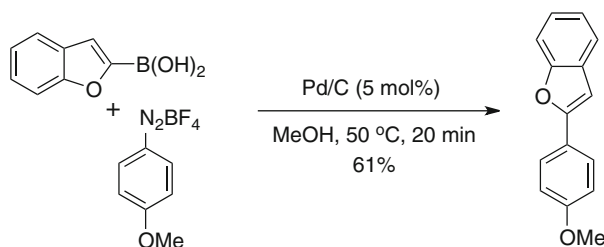
Scheme 36 Nickel-catalyzed cross-coupling of potassium 2-furyl and 2-benzofuranyl trifluoroborates with naphthalen-1-yl mesylate



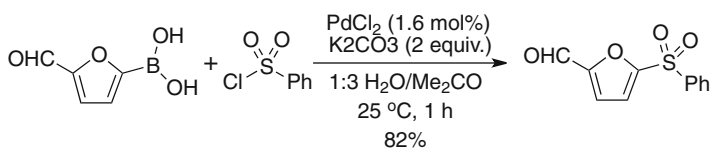
Scheme 37 Nickel-catalyzed cross-coupling of 2-benzofuranyl boronic acid with naphthalen-1-yl dimethylsulfamates

Cross-couplings of boronated furans and benzofurans were expanded to those with halide equivalents as electrophilic partners. For example, potassium 2-furyl, 3-furyl, and 2-benzofuranyl trifluoroborates reacted with various aryl and heteroaryl mesylates in a nickel-catalyzed reaction, providing cross-coupling products in good yields [49], as represented by the examples shown in Scheme 36.

Cross-coupling of 2-benzofuranyl boronic acid and 3-furyl boronic acid with naphthalen-1-yl dimethylsulfamates was accomplished by using NiCl₂(PCy₃)₂ as a catalyst [50], as represented in Scheme 37. An example of (BINAP)PdCl₂-catalyzed coupling of 3-furyl boronic acid with naphthalen-1-yl imidazolyl-sulfonate was also reported [51].



Scheme 38 Pd/C-catalyzed cross-coupling of 2-benzofuranyl boronic acid with arenediazonium salt



Scheme 39 Reaction of 2-furyl boronic acid with phenylsulfonyl chloride

2-Benzofuranyl boronic acid also underwent a fast cross-coupling reaction with an arenediazonium salt under ligand-free Pd/C-catalyzed conditions in methanol, as shown in Scheme 38 [52].

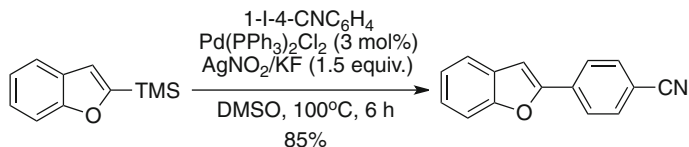
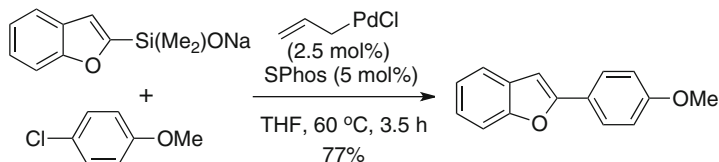
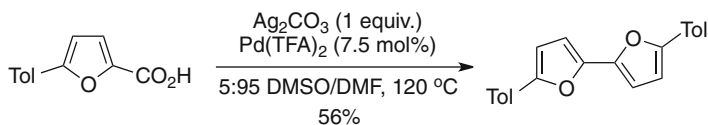
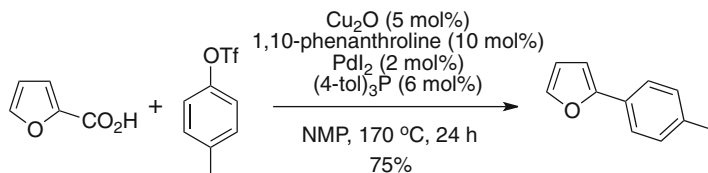
As shown in Scheme 39, a 2-furyl boronic acid also reacted with an arylsulfonyl chloride under palladium catalysis to give unsymmetrical diaryl sulfones at ambient temperature [53].

6 Other Metalated Furans and Benzofurans in Cross-Coupling Reactions

2-Trimethylsilylbenzofuran underwent a palladium-catalyzed Hiyama-type coupling with aryl iodides in the presence of AgNO_2/KF as an activator [54], as depicted in Scheme 40. Homocoupling to form 2,2'-bibenzofuran also occurred under these conditions.

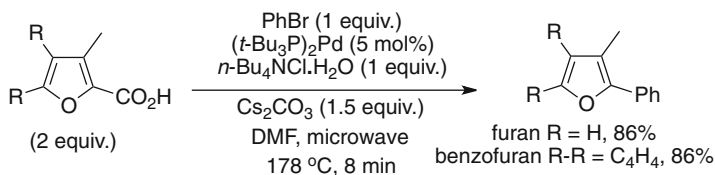
Sodium dimethyl(2-furyl)silanolate [55], and sodium dimethyl(2-benzofuryl)silanolate [56] participated in palladium-catalyzed cross-couplings with aryl iodides and bromides through a palladium silanolate complex, which underwent transmetalation at the furan (benzofuran) C2 position. Cross-coupling of the 2-benzofurylsilanolate with aryl chlorides was also made possible by using allylpalladium chloride as a palladium source and SPhos as a ligand, as represented in Scheme 41.

Various metalated furan species were postulated as intermediates in the decarboxylative coupling of furan-2-carboxylic acid. Decarboxylation of

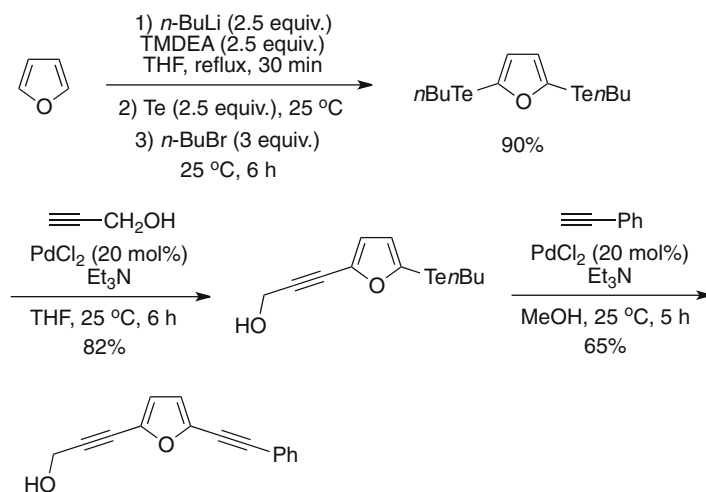
**Scheme 40** Hiyama-type cross-coupling of 2-trimethylsilylbenzofuran**Scheme 41** Palladium-catalyzed cross-couplings of sodium dimethyl(2-benzofuryl)silanolate with aryl chloride**Scheme 42** Decarboxylative homocoupling of 5-tolylfuran-2-carboxylic acid**Scheme 43** Decarboxylative hetero-coupling of furan-2-carboxylic acid

5-tolylfuran-2-carboxylic acid or 3-methylbenzofuran-2-carboxylic acid derivatives by silver carbonate generated a (benzo)furan-2-yl silver species that underwent a subsequent palladium-catalyzed homocoupling to give 2,2'-bi(benzo)furan products, as illustrated in Scheme 42 [57]. In the presence of AsPPh_3 , cross-coupling of 3-methylbenzofuran-2-carboxylic acid with 4-iodoanisole could be achieved [58]. However, the generality of this type of decarboxylative coupling of furan and benzofuran substrates has not been demonstrated.

Another example of decarboxylative hetero-coupling of furan-2-carboxylic acid with 4-tolyl triflate, as depicted in Scheme 43, involved a 2-furyl copper species in the catalytic cycle that underwent transmetalation with palladium [59, 60].



Scheme 44 Palladium-catalyzed decarboxylative coupling of furan- and benzofuran-2-carboxylic acids



Scheme 45 Palladium-catalyzed cross-coupling of 2,5-bis(butyltelluro)furan with acetylenes

A related palladium-catalyzed decarboxylative coupling only proceeded with furan- and benzofuran-2-carboxylic acids, but not with the corresponding 3-carboxylic acid, as represented in Scheme 44 [61]. A mechanism that involved an electrophilic palladation at the furan C3 position followed by C3–C2 palladium migration and decarboxylation was postulated.

2-Furyl zinc chloride reacted with vinyl tellurides in a Pd-catalyzed cross-coupling in the presence of CuI [62]. As demonstrated in Scheme 45, 2-(butyltelluro)furan [63] and 2,5-bis(butyltelluro)furan [64] were prepared via lithiofuran. Successive palladium-catalyzed coupling of 2,5-bis(butyltelluro)furan with different acetylenes was feasible, forming unsymmetrical 2,5-bis-alkynyl furans [64], as represented. 2-(Butyltelluro)furan is also reactive toward $(\text{Ph}_3\text{P})_4\text{Pd}$ -catalyzed Ag_2O -promoted cross-coupling with potassium phenyl tetrafluoroborate [65].

7 Regioselective Functionalization of Poly-halogenated Furans and Benzofurans

Earlier chemistry focused on the regioselective functionalization of 2,3-dibromofurans and 2,4-dibromofuran, as depicted in Fig. 2, through Suzuki–Miyaura, Stille and Sonogashira cross-couplings with reaction occurring initially at the C2 position has been demonstrated and recently reviewed [66].

A recent example in this area is the preparation of a template for the synthesis of a skeletally diverse small molecule library [67] through an sp^3 – sp^2 Suzuki–Miyaura coupling between a solid support-bound alkyl borane and 4,5-dibromo-2-furaldehyde, as shown in Scheme 46. Competitive β -hydride elimination was minimized by the use of $\text{Pd}(\text{dppf})\text{Cl}_2$ as a catalyst.

Interestingly, the Suzuki–Miyaura coupling of (Z)-2-(2-bromo-2-nitroethenyl)-5-bromofuran with one equivalent of a boronic acid also occurred regioselectively at the C2 position rather than at the exocyclic carbon–bromine bond, as illustrated in Scheme 47 [68].

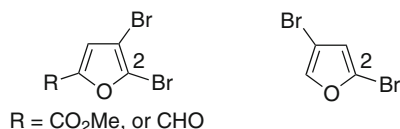
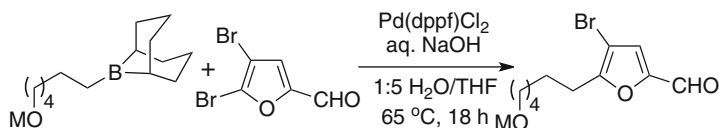
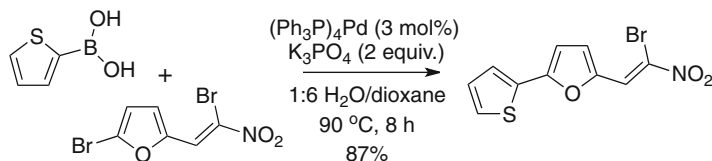


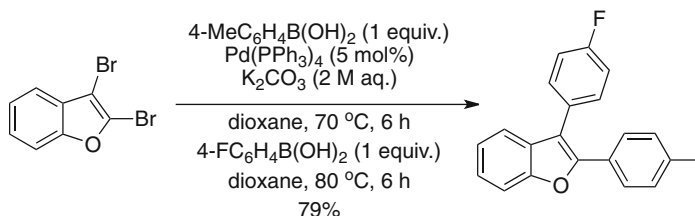
Fig. 2 2,3-Dibromofurans and 2,4-dibromofuran



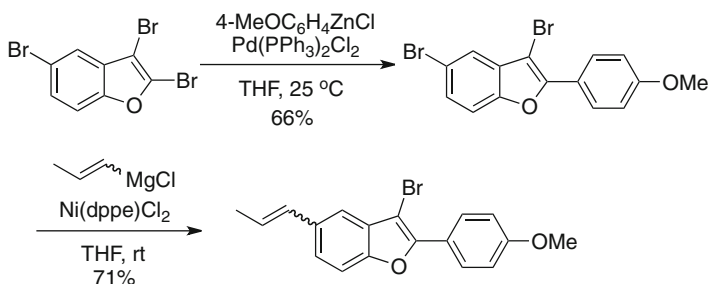
Scheme 46 Regioselective sp^3 – sp^2 Suzuki–Miyaura coupling of 4,5-dibromo-2-furaldehyde (M = macrobead)



Scheme 47 Suzuki–Miyaura coupling of (Z)-2-(2-bromo-2-nitroethenyl)-5-bromofuran with boronic acid



Scheme 48 Regioselective Suzuki–Miyaura coupling of 2,3-dibromobenzofuran



Scheme 49 Regioselective cross-coupling of 2,3,5-tribromobenzofuran

Regioselective cross-coupling of polybromobenzofuran is also feasible. The selectivity is based on the electronic nature of the substituted carbon atom, with the initial reaction occurs at the less electron-rich carbon atom. As illustrated in Scheme 48, 2,3-dibromobenzofuran could be sequentially functionalized at the C2 position and then the C3 position in a one-pot fashion in a $(\text{Ph}_3\text{Ph})_4\text{Pd}$ -catalyzed Suzuki–Miyaura coupling reaction using two different aryl boronic acids [69]. Benzofuran-3-yl triflates, prepared from benzofuran-3-ones, participated in palladium-catalyzed Stille, Heck, Suzuki–Miyaura and Sonogashira couplings [70]. A Stille coupling of 2-bromobenzofuran-3-yl triflate was observed to occur at the C3 position in a modest ~2:1 selectivity [71]. A related Stille coupling of 2,5-dibromo-7-methoxybenzofuran, however, took place predominantly at the C2 position [72].

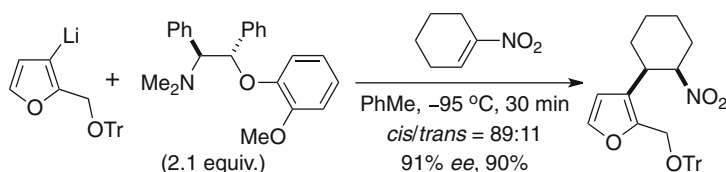
Negishi and Sonogashira couplings also occurred at the C2 position of 2,3,5-tribromobenzofuran first [73]. However, it was more challenging to differentiate the C3 and C5 positions by a palladium-catalyzed coupling. This was solved by a lithium–bromide exchange with *t*-BuLi that occurred selectively at the C3 position or by a nickel-catalyzed C5-selective Kumada coupling as shown in Scheme 49 [74]. The approach was applied to the synthesis of eupomatenoids [75].

8 Metalated Furans and Benzofurans in Addition Reactions

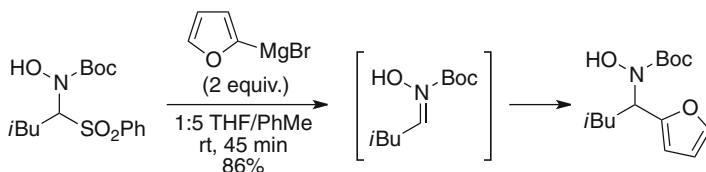
Metalated furans have been increasingly used in diastereoselective and enantioselective addition reactions. For example, reaction of 2-furyllithium with a chiral *tert*-butanesulfinyl imine provided the adduct with >12:1 diastereomeric ratio [76]. Addition of 2-furyllithium or 2-benzofuryllithium to chiral SMAP-hydrazone furnished the adduct in >95% diastereomeric excess [77]. A diastereoselective and enantioselective addition of a sterically bulky 3-(2-trityloxymethyl) furyllithium, prepared in situ from the corresponding 3-bromofuran and *n*-BuLi, to nitroalkene was realized by the use of a chiral amino ether ligand, as shown in Scheme 50 [78]. This method provided an access to interesting furo-fused piperidine ring.

2-Furylmagnesium bromide acted as a base and then a nucleophile in the reaction with a *tert*-butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamate to form the furyl-substituted hydroxylamine product through a *N*-Boc nitron intermediate, as depicted in Scheme 51 [79].

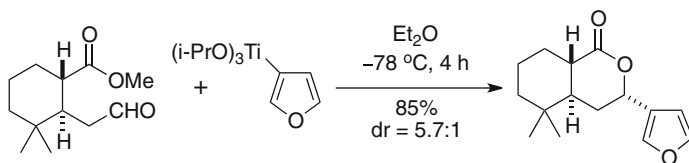
3-Furyltitanium, [(3-furyl)Ti(Oi-Pr)₃]₂, was prepared from the reaction of 3-furyllithium with Ti(Oi-Pr)₃Cl in THF at −78°C. Addition of this reagent to a range of acetophenone derivatives at 0°C in the presence of (*S*)-BINOL furnished tertiary 3-furanylcarbinols with *ee* up to 97% [80]. Similarly, the use of 2-furylaluminum (2-furyl)AlEt₂(THF) provided 2-furanylcarbinols with *ee* up to 93% [81]. 3-Furyltitanium also appeared to be more effective in addition to aliphatic aldehydes compared to the corresponding lithium, magnesium, and zinc reagents. As exemplified in a total synthesis of (+)-ricciocarpins A shown in Scheme 52, the



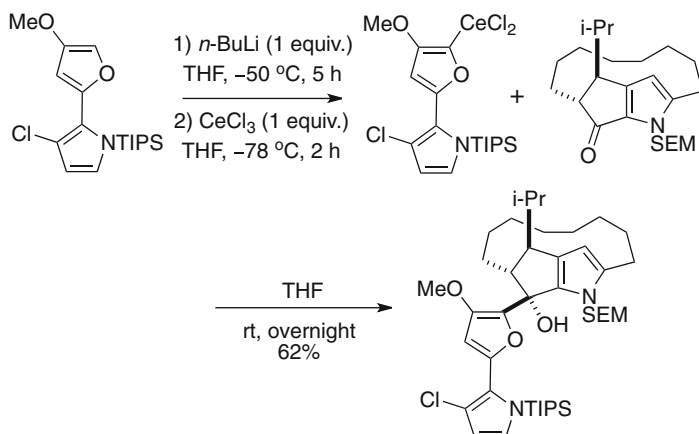
Scheme 50 Asymmetric addition of 3-(2-trityloxymethyl)furyllithium to nitroalkene



Scheme 51 Reaction of 2-furylmagnesium bromide with *tert*-butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamate



Scheme 52 Addition of 3-furyltitanium to an aliphatic aldehyde



Scheme 53 Addition of 2-furylcerium to a ketone

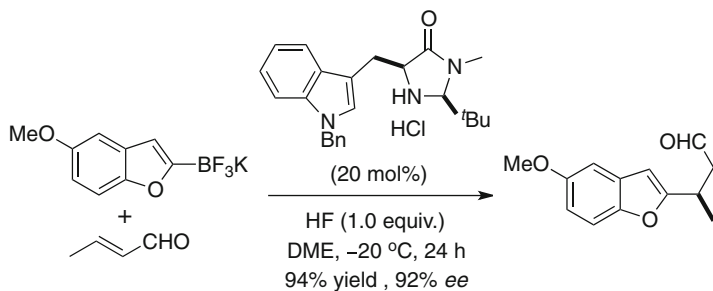
use of the titanium reagent provided the highest yield and diastereoselectivity in the reaction with the penultimate aldehyde bearing an acidic α -proton [82].

2-Furylcerium derivatives are less commonly used; however, they also appear to show high nucleophilicity to allow reactions with ketones and sterically demanding substrates. A remarkable example is the key penultimate reaction in a total synthesis of roseophilin, as shown in Scheme 53 [83]. Note that the furan C2 position was exclusively lithiated and transmetalated primarily due to the steric hindrance around the pyrrole C2 position that was imparted by the bulky TIPS group.

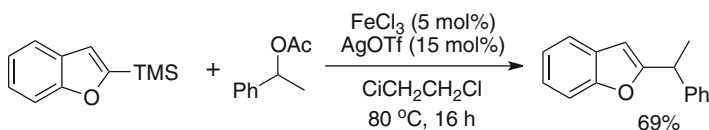
2-Benzofuranyl boronic acid and its potassium trifluoroborate salt reacted as nucleophiles in an enantioselective organocatalytic Friedel–Crafts alkylation with crotonaldehyde, as shown in Scheme 54. An example using potassium 2-furyl trifluoroborate was also reported [84]. This method was employed in a total synthesis of (+)-frondosin B [85].

A similar type of reaction involves the addition of 2-trimethylsilylbenzofuran to benzylic acetates in the presence of a catalytic amount of $\text{FeCl}_3/\text{AgOTf}$ to form 2-benzyl substituted benzofurans as shown in Scheme 55 [86].

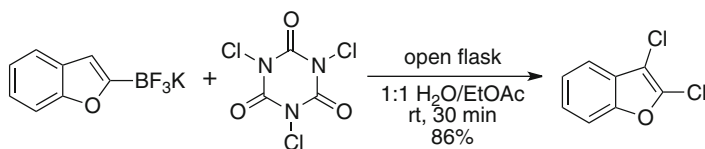
Potassium 2-benzofuranyl trifluoroborate reacted with trichloroisocyanuric acid to furnish 2,3-dichlorobenzofuran, as depicted in Scheme 56 [87]. Although it was shown that the dichloro product was not derived from an initial chlorodeboronation, the mechanism of this reaction remains uncertain.



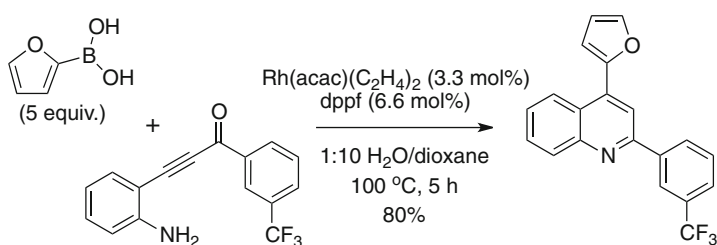
Scheme 54 Nucleophilic addition of potassium 2-benzofuranyl trifluoroborate to crotonaldehyde



Scheme 55 Iron-catalyzed addition of 2-trimethylsilylbenzofuran to benzylic acetate

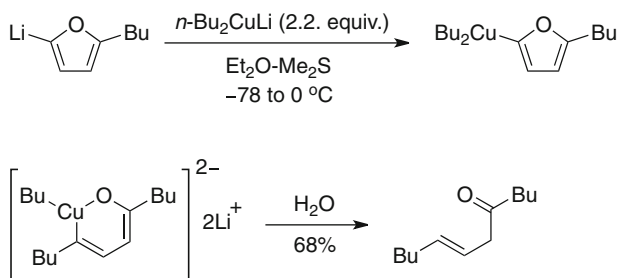


Scheme 56 Reaction of potassium 2-benzofuranyl trifluoroborate with trichloroisocyanuric acid

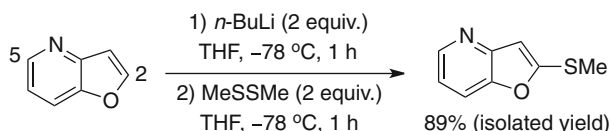


Scheme 57 Rhodium-catalyzed hydroarylation of a β-aminophenyl alkynone with 2-furyl-2-boronic acid

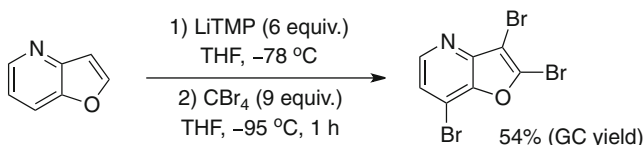
Hydroarylation of a β-aminophenyl alkynone to provide a quinolone derivative was achieved by using a rhodium catalyst, as illustrated in Scheme 57 [88].



Scheme 58 1,2-Metalate rearrangement of 2-furylcuprate



Scheme 59 Lithiation of 4-azabenzofuran (furo[3,2-*b*]pyridine) using *n*-BuLi



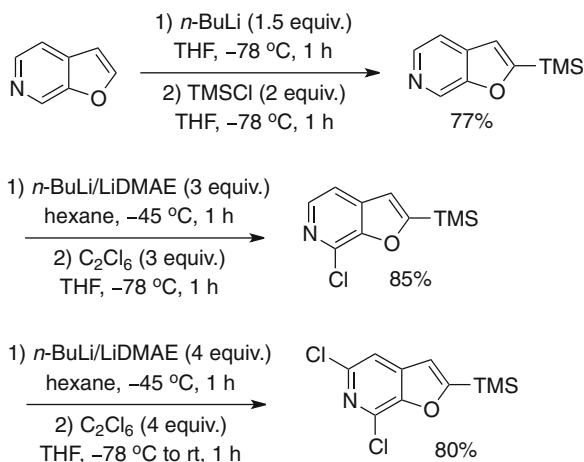
Scheme 60 Lithiation of 4-azabenzofuran (furo[3,2-*b*]pyridine) using LiTMP

The 2-furylcuprate shown in Scheme 58 underwent a 1,2-metalate rearrangement to provide the ring-opened product [89].

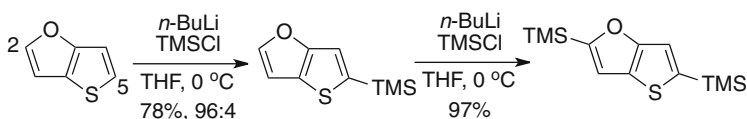
9 Lithiation of Related Furo Heterocycles

Lithiation of 4-azabenzofuran (furo[3,2-*b*]pyridine) using *n*-BuLi in THF occurred predominantly at the C2 position, which was quenched with various electrophiles (e.g., Br, Si, Sn, S, and B), as exemplified in Scheme 59 [90]. The use of an increased excess amount of LiTMP resulted in the di- and tri-lithiation at the C2, C3, and C7 positions as indicated by the 2,3-dibromo and 2,3,7-tribromo derivatives that were detected (Scheme 60). It was observed that the corresponding C3 mono-lithiated species was unstable and the lithiation at the C5 position had not occurred under these conditions.

The corresponding lithiation of 6-azabenzofuran (furo[2,3-*c*]pyridine) using *n*-BuLi in THF also occurred exclusively at the C2-position [91]. If the C2 position



Scheme 61 Sequential lithiation of 6-azabenzofuran (furo[2,3-*c*]pyridine)



Scheme 62 Lithiation of thieno[3,2-*b*]furan

was blocked by a TMS group, deprotonation occurred at the C7 position followed by at the C5 position using an *n*-BuLi/lithium dimethylaminoethoxide (LiDMAE) mixed base, as illustrated in Scheme 61.

However, deprotonation of thieno[3,2-*b*]furan, first isolated in 2009, using *n*-BuLi occurred predominantly at the C5 position [92]. Deprotonation at both the C2 and C5 was feasible by using two equivalents of the base, as shown in Scheme 62.

References

1. Keay BA, Hopkins JM, Dibble PW (2008) Chapter 3.08: Furans and their benzo derivatives: applications. In: Katritzky AR, Ramsden CA, Scriven EFV, Taylor RJK (eds) *Comprehensive heterocyclic chemistry III*. Elsevier, Oxford
2. Aoyagi Y, Yamazaki A, Nakatsugawa C, Fukaya H, Takeya K, Kawauchi S, Izumi H (2008) Selvileucalin B, a novel diterpenoid with an unprecedented rearranged neoclerodane skeleton from *Salvia ieucaantha* Cav. *Org Lett* 10:4429–4432
3. Marion F, Williams DE, Patrick BO, Hollander I, Mallon R, Kim SC, Roll DM, Feldberg L, Van Soest R, Anderson RJ (2006) Liphagal, a selective inhibitor of PI3 kinase α isolated from the sponge *Aka coralliphaga*: structure elucidation and biomimetic synthesis. *Org Lett* 8:321–324

4. Levin S, Nani RR, Reisman SE (2011) Enantioselective total synthesis of (+)-selvileucalin B. *J Am Chem Soc* 133:774–776
5. Wright DL (2005) Chapter 1: Furans as versatile synthons for target-oriented and diversity-oriented synthesis. In: Gribble GW, Joule JA (eds) *Progress in heterocyclic chemistry*, vol 17. Elsevier, Oxford
6. Wong HNC, Yeung K-S, Yang Z (2008) Chapter 3.06: Furans and their benzo derivatives: reactivity. In: Katritzky AR, Ramsden CA, Scriven EFV, Taylor RJK (eds) *Comprehensive heterocyclic chemistry III*. Elsevier, Oxford
7. Yeung K-S, Yang Z, Peng X-S, Hou X-L (2010) Chapter 5.3: Five-membered ring systems: furans and benzofuran. In: Gribble GW, Joule JA (eds) *Progress in heterocyclic chemistry*, vol 22. Elsevier, Oxford
8. Lee HK, Wong HNC (2002) An enantioselective synthetic pathway towards plakortones. *Chem Commun* 2114–2115
9. Boukouvalas J, Loach RP (2008) General, regiodefined access to α -substituted butenolides through metal-halogen exchange of 3-bromo-2-silyloxyfurans. Efficient synthesis of an anti-inflammatory gorgonian lipid. *J Org Chem* 73:8109–8112
10. Marcos IS, Hernández FA, Sexmero MJ, Basabe DDP, Pedrero AB, García N, Urones JG (2003) Synthesis and absolute configuration of (2)-chettaphanin I and (2)-chettaphanin II. *Tetrahedron* 59:685–694
11. Chinchilla R, Nájera C, Yus M (2004) Metalated heterocycles and their applications in synthetic organic chemistry. *Chem Rev* 104:2667–2722
12. Li JJ, Gribble GW (2000) Chapter 6: Furans and benzo[*b*]furans. In: *Palladium in heterocyclic chemistry. A guide for the synthetic chemist*. Pergamon, Oxford
13. Tofi M, Georgiou T, Montagnon T, Vassilikogiannakis G (2005) Regioselective *ortho* lithiation of 3-aryl and 3-styryl furans. *Org Lett* 7:3347–3350
14. Stanetty P, Kolodziejczyk K, Roiban G-D, Mihovilovic MD (2006) Establishing the NHBoc functionality as *ortho*-metallating group for furan. *Synlett* 789–791
15. Sato N, Yue Q (2003) An efficient synthesis of cyanoarenes and cyanoheteroarenes via lithiation followed by electrophilic cyanation. *Tetrahedron* 59:5831–5836
16. James CA, Coelho AL, Gevaert M, Forgione P, Snieckus V (2009) Combined directed *ortho* and remote metalation – Suzuki cross-coupling strategies. Efficient synthesis of heteroaryl-fused benzopyranones from biaryl *O*-carbamates. *J Org Chem* 74:4094–4103
17. Kashulin IA, Nifant'ev IE (2004) Efficient method for the synthesis of hetarenoindanones based on 3-arylheterarenes and their conversion into hetarenoindenes. *J Org Chem* 69:5476–5479
18. Tsubuki M, Okita H, Kaneko K, Shigihara A, Honda T (2009) Witting rearrangement of 3-furylmethyl ethers: facile synthesis of 3-methyl-2-furylmethanols and 3-furylmethanols. *Heterocycles* 77:433–444
19. Devarie NO, Kim W-S, Smith AB III, Xian M (2009) Multicomponent type II anion relay chemistry (ARC): one-pot synthesis of 2,3-disubstituted furans and thiophenes. *Org Lett* 11:1861–1864
20. Shanmugham MS, White JD (2004) A new route to furanoeremophilane sesquiterpenoids. Synthesis of (\pm)-6b-hydroxyeurypsins. *Chem Commun* 44–45
21. Akai S, Kawashita N, Satoh H, Wada Y, Kakiguchi K, Kuriwaki I, Kita Y (2004) Highly regioselective nucleophilic carbon-carbon bond formation on furans and thiophenes initiated by Pummerer-type reaction. *Org Lett* 6:3793–3796
22. Sanz R, Castroviejo MP, Fernández Y, Fañanás FJ (2005) A new and efficient synthesis of 4-functionalized benzo[*b*]furans from 2,3-dihalophenols. *J Org Chem* 70:6548–6551
23. Mongin F, Bucher A, Bazureau JP, Bayh O, Awad H, Trecourt F (2005) Deprotonation of furans using lithium magnesates. *Tetrahedron Lett* 46:7989–7992
24. Krasovsky A, Krasovskaya V, Knochel P (2006) Mixed Mg/Li amides of the type $R_2NMgCl \cdot LiCl$ as highly efficient bases for the regioselective generation of functionalized aryl and heteroaryl magnesium compounds. *Angew Chem Int Ed* 45:2958–2961

25. Melzig L, Rauhut CB, Knochel P (2009) 2,3-Functionalization of furans, benzofurans and thiophenes via magnesiation and sulfoxide–magnesium exchange. *Chem Commun* 3536–3538
26. Melzig L, Rauhut CB, Naredi-Rainer N, Knochel P (2011) Difunctionalisation of arenes and heteroarenes by directed metallation and sulfoxide–magnesium exchange. *Chem Eur J* 17:5362–5372
27. X-j W, Sun X, Zhang L, Xu Y, Krihnamurthy D, Senanayake CH (2006) Noncryogenic I/Br–Mg exchange of aromatic halides bearing sensitive functional groups using *i*-PrMgCl-bis[2-(*N,N*-dimethylamino)ethyl]ether complexes. *Org Lett* 8:305–307
28. Martin R, Buchwald SL (2007) Pd-catalyzed Kumada–Corriu cross-coupling reactions at low temperatures allow the use of Knochel-type Grignard reagents. *J Am Chem Soc* 129:3844–3845
29. Haag BA, Samann C, Jana A, Knochel P (2011) Practical one-pot preparation of magnesium di(hetero)aryl- and magnesium dialkenylboronates for Suzuki–Miyaura cross-coupling reactions. *Angew Chem Int Ed* 50:7290–7294
30. L’Helgoual’ch J-M, Seggio A, Chevallier F, Yonehara M, Jeanneau E, Uchiyama M, Mongin F (2008) Deprotonative metalation of five-membered aromatic heterocycles using mixed lithium–zinc species. *J Org Chem* 73:177–183
31. Snégaroff K, Komagawa S, Chevallier F, Gros PC, Golhen S, Roisnel T, Uchiyama M, Mongin F (2010) Deprotonative metalation of substituted benzenes and heteroaromatics using amino/alkyl mixed lithium–zinc combinations. *Chem Eur J* 16:8191–8201
32. Wunderlich SH, Knochel P (2007) (tmp)₂Zn·2MgCl₂·2LiCl: a chemoselective base for the directed zincation of sensitive arenes and heteroarenes. *Angew Chem Int Ed* 46:7685–7688
33. Snégaroff K, L’Helgoual’ch J-M, Bentabed-Ababsa G, Nguyen TT, Chevallier F, Yonehara M, Uchiyama M, Derdour A, Mongin F (2009) Deprotonative metalation of functionalized aromatics using mixed lithium–cadmium, lithium–indium, and lithium–zinc species. *Chem Eur J* 15:10280–10290
34. Gauthier DR Jr, Szumigala RH Jr, Dormer PG, Armstrong JD III, Volante RP, Reider PJ (2002) Synthesis of 5-pyridyl-2-furaldehydes via palladium-catalyzed cross-coupling with triorgano-zincates. *Org Lett* 4:375–378
35. Rieke RD, Kim S-H (2011) 5-(1,3-Dioxolan-2-yl)-2-furanylzinc bromide; direct preparation, and its application for the synthesis of 5-substituted furan derivatives. *Tetrahedron Lett* 52:1128–1131
36. Krasovskiy A, Malakhov V, Gavryushin A, Knochel P (2006) Efficient synthesis of functionalized organozinc compounds by the direct insertion of zinc into organic iodides and bromides. *Angew Chem Int Ed* 45:6040–6044
37. Kim S-H, Rieke RD (2010) A convenient synthesis of 5-aryl- and 5-heteroaryl-2-furaldehydes by the cross-coupling reaction of organozincs. *Tetrahedron Lett* 51:2657–2659
38. Valente C, Belowich ME, Hadei N, Organ MG (2010) Pd-PEPPSI complexes and the Negishi reaction. *Eur J Org Chem* 4343–4354
39. Organ MG, Calimsiz S, Sayah M, Hoi KH, Lough AJ (2009) Pd-PEPPSI-IPent: an active, sterically demanding cross-coupling catalyst and its application in the synthesis of tetra-*ortho*-substituted biaryls. *Angew Chem Int Ed* 48:2383–2387
40. Sase S, Jaric M, Metzger A, Malakhov V, Knochel P (2008) One-pot Negishi cross-coupling reactions of in situ generated zinc reagents with aryl chlorides, bromides, and triflates. *J Org Chem* 73:7380–7382
41. Huang Q, Rawal VH (2006) Total synthesis of (±)-bipinnatin J. *Org Lett* 8:543–545
42. Xie L-G, Wang Z-X (2011) Nickel-catalyzed cross-coupling of aryltrimethylammonium iodides with organozinc reagents. *Angew Chem Int Ed* 50:4901–4904
43. Molander GA, Canturk B, Kennedy LE (2009) Scope of the Suzuki–Miyaura cross-coupling reactions of potassium heteroaryltrifluoroborates. *J Org Chem* 74:973–980
44. Dreher SD, Lim S-E, Sandrock DL, Molander GA (2009) Suzuki–Miyaura cross-coupling reactions of primary alkyltrifluoroborates with aryl chlorides. *J Org Chem* 74:3626–3631

45. Molander GA, Gormisky PE, Sandrock DL (2008) Scope of aminomethylations via Suzuki-Miyaura cross-coupling of organotrifluoroborates. *J Org Chem* 73:2052–2057
46. Molander GA, Jean-Gérard L (2009) Use of potassium β -trifluoroborate amides in Suzuki-Miyaura cross-coupling reactions. *J Org Chem* 74:5446–5450
47. Knapp DM, Gillis EP, Burke MD (2009) A general solution for unstable boronic acids: slow-release cross-coupling from air-stable MIDA boronates. *J Am Chem Soc* 131:6961–6963
48. Kinzel T, Zhang Y, Buchwald SL (2010) A new palladium precatalyst allows for the fast Suzuki-Miyaura coupling reactions of unstable polyfluorophenyl and 2-heteroaryl boronic acids. *J Am Chem Soc* 132:14073–14075
49. Molander GA, Beaumard F (2010) Nickel-catalyzed C–O activation of phenol derivatives with potassium heteroaryltrifluoroborates. *Org Lett* 12:4022–4025
50. Quasdorf KW, Antoft-Finch A, Liu P, Silberstein AL, Komaromi A, Blackburn T, Ramgren SD, Houk KN, Snieckus V, Garg NK (2011) Suzuki-Miyaura cross-coupling of aryl carbamates and sulfamates: experimental and computational studies. *J Am Chem Soc* 133:6352–6363
51. Albaneze-Walker J, Raju R, Vance JA, Goodman AJ, Reeder MR, Liao J, Maust MT, Irish PA, Espino P, Andrews DR (2009) Imidazolylsulfonates: electrophilic partners in cross-coupling reactions. *Org Lett* 11:1463–1466
52. Taylor RH, Felpin F-X (2007) Suzuki-Miyaura reactions of arenediazonium salts catalyzed by Pd(0)/C. One-pot chemoselective double cross-coupling reactions. *Org Lett* 9:2911–2914
53. Bandgar BP, Bettigeri SV, Phopase J (2004) Unsymmetrical diaryl sulfones through palladium-catalyzed coupling of aryl boronic acids and arylsulfonyl chlorides. *Org Lett* 6:2105–2108
54. Matsuda S, Takahashi M, Monguchi D, Mori A (2009) C–H and C–Si functionalization of furan derivatives: palladium-catalyzed homocoupling and arylation reactions. *Synlett* 1941–1944
55. Denmark SE, Baird JD, Regens CS (2008) Palladium-catalyzed cross-coupling of five-membered heterocyclic silanolates. *J Org Chem* 73:1440–1455
56. Denmark SE, Smith RC, Chang W-TT, Muhuhi JM (2009) Cross-coupling reactions of aromatic and heteroaromatic silanolates with aromatic and heteroaromatic halides. *J Am Chem Soc* 131:3104–3118
57. Cornella J, Lahlali H, Larrosa I (2010) Decarboxylative homocoupling of (hetero)aromatic carboxylic acids. *Chem Commun* 46:8276–8278
58. Becht J-M, Catala C, Le Drian C, Wagner A (2007) Synthesis of biaryls via decarboxylative Pd-catalyzed cross-coupling reaction. *Org Lett* 9:1781–1783
59. Goossen LJ, Rodriguez N, Linder C (2008) Decarboxylative biaryl synthesis from aromatic carboxylates and aryl triflates. *J Am Chem Soc* 130:15248–15249
60. Goossen LJ, Rodriguez N, Linder C, Lange PP (2009) Biaryl and aryl ketone synthesis via Pd-catalyzed decarboxylative coupling of carboxylate salts with aryl triflates. *Chem Eur J* 15:9336–9349
61. Forgione P, Brochu M-C, St-Onge M, Thesen KH, Bailey MD, Bilodeau F (2006) Unexpected intermolecular Pd-catalyzed cross-coupling reaction employing heteroaromatic carboxylic acids as coupling partners. *J Am Chem Soc* 128:11350–11351
62. Zeni G, Alves D, Braga AL, Stefani HA, Nogueira CW (2004) Stereoselective sp^2 – sp^2 bond formation via Negishi cross-coupling of vinylic tellurides and 2-heteroarylzinc chlorides. *Tetrahedron Lett* 45:4823–4826
63. Zeni G, Lüdtké DS, Nogueira CW, Panatieri RB, Braga AL, Silveira CC, Stefani HA, Rocha JBT (2001) New acetylenic furan derivatives: synthesis and anti-inflammatory activity. *Tetrahedron Lett* 42:8927–8930
64. Zeni G, Nogueira CW, Silva DO, Menezes PH, Braga AL, Stefani HA, Rocha JBT (2003) Palladium(II) chloride catalyzes the cross-coupling reaction of 2,5-bis-(butyltelluro)-furan and 1-alkynes. *Tetrahedron Lett* 44:1387–1390

65. Cella R, Cunha RLOR, Reis AES, Pimenta DC, Klitzke CF, Stefani HA (2006) Suzuki-Miyaura cross-coupling reactions of aryl tellurides with potassium aryltrifluoroborate salts. *J Org Chem* 71:244–250
66. Schröter S, Stock C, Bach T (2005) Regioselective cross-coupling reactions of multiple halogenated nitrogen-, oxygen-, and sulfur-containing heterocycles. *Tetrahedron* 61:2245–2267
67. Burke MD, Berger EM, Schreiber SL (2004) A synthesis strategy yielding skeletally diverse small molecules combinatorially. *J Am Chem Soc* 126:14095–14104
68. Tuan DT, Tung DT, Langer P (2006) Synthesis of 2-(2-arylethenyl)-5-arylfurans by regioselective palladium(0)-catalyzed coupling reactions of 2-(2-bromo-2-nitroethenyl)-5-bromofuran. *Synlett* 2812–2814
69. Hung NT, Hussain M, Malik I, Villinger A, Langer P (2010) Site-selective Suzuki cross-coupling reactions of 2,3-dibromobenzofuran. *Tetrahedron Lett* 51:2420–2422
70. Morice C, Garrido F, Mann A, Suffert J (2002) Palladium assisted substitution of 3-benzo[*b*]furan triflates. *Synlett* 501–503
71. Masters K-S, Flynn BL (2010) An efficient synthesis of (±)-frondosin B using a Stille–Heck reaction sequence. *Org Biomol Chem* 8:1290–1292
72. Lin S-Y, Chen C-L, Lee Y-J (2003) Total synthesis of ailanthoidol and precursor XH14 by Stille coupling. *J Org Chem* 68:2968–2971
73. Bach T, Bartels M (2001) 2,3-Disubstituted and 2,3,5-trisubstituted benzofurans by regioselective Pd-catalyzed cross-coupling reactions; a short synthesis of eupomatenoid-15. *Synlett* 1284–1286
74. Bach T, Bartels M (2002) Synthesis of eupomatenoids by three consecutive transition metal-catalyzed cross-coupling reactions. *Tetrahedron Lett* 43:9125–9127
75. Bach T, Bartels M (2003) Regioselective C–C bond formation reactions on 2,3-dibromo- and 2,3,5-tribromobenzofuran as an access to multiply substituted benzofurans. Total syntheses of eupomatenoids 3, 4, 5, 6, and 15. *Synthesis* 925–939
76. Luo Y-C, Zhang H-H, Liu Y-Z, Cheng R-L, Xu P-F (2009) An asymmetric approach to 5-*O*-carbamoyl-2-*epi*-polyoxamic acid and the total synthesis of 2''-*epi*-polyoxin J. *Tetrahedron Asymmetry* 20:1174–1180
77. Enders D, Del Signore G (2004) Efficient asymmetric synthesis of α -(heteroaryl)alkylamines by 1,2-addition of lithiated hetarenes to aldehyde-SAMP-hydrazones. *Tetrahedron Asymmetry* 15:747–751
78. Yamashita M, Yamada K-i, Tomioka K (2004) Construction of arene-fused-piperidine motifs by asymmetric addition of 2-trityloxymethylarylolithiums to nitroalkenes: the asymmetric synthesis of a dopamine D1 full agonist, A-86929. *J Am Chem Soc* 126:1954–1955
79. Guinchard X, Denis J-N (2008) Reactions of in situ generated N-Boc nitrones with aromatic and heteroaromatic Grignard reagents: application to the synthesis of zileuton. *J Org Chem* 73:2028–2031
80. Zhou S, Chen C-R, Gau H-M (2010) Highly enantioselective 3-furylation of ketones using (3-furyl)titanium nucleophile. *Org Lett* 12:48–51
81. Wu K-H, Chuang D-W, Chen C-A, Gau H-M (2008) Chiral tertiary 2-furyl alcohols: diversified key intermediates to bioactive compounds. Their enantioselective synthesis via (2-furyl)aluminium addition to ketones catalyzed by a titanium catalyst of (S)-BINOL. *Chem Commun* 2343–2345
82. Sibi MP, He L (2004) Application of enantioselective radical reactions: synthesis of (+)-ricciocarpins a and b. *Org Lett* 6:1749–1752
83. Furstner A, Weintritt H (1998) Total synthesis of roseophilin. *J Am Chem Soc* 120:2817–2825
84. Lee S, MacMillan DWC (2007) Organocatalytic vinyl and Friedel-Crafts alkylations with trifluoroborate salts. *J Am Chem Soc* 129:15438–15439
85. Reiter M, Torssell S, Lee S, MacMillan DWC (2010) The organocatalytic three-step total synthesis of (+)-frondosin B. *Chem Sci* 1:37–42

86. Chan LY, Kim S, Chung WT, Long C, Kim S (2011) Fe(OTf)₃-catalyzed reaction of benzylic acetates with organosilicon compounds. *Synlett* 415–419
87. Molander GA, Cavalcanti LN (2011) Metal-free chlorodeboronation of organotrifluoroborates. *J Org Chem* 76:7195–7203
88. Abbiati G, Arcadi A, Marinelli F, Rossi E, Verdecchia M (2006) Rh-catalyzed sequential hydroarylation/hydrovinylation–heterocyclization of β -(2-aminophenyl)- α,β -ynones with organoboron derivatives: a new approach to functionalized quinolines. *Synlett* 3218–3224
89. Pommier A, Stepanenko V, Jarowicki K, Kocienski PJ (2003) Synthesis of (+)-manoalide via a copper(I)-mediated 1,2-metalate rearrangement. *J Org Chem* 68:4008–4013
90. Chartoire A, Comoy C, Fort Y (2008) Furo[3,2-*b*]pyridine: a convenient unit for the synthesis of polyheterocycles. *Tetrahedron* 64:10867–10873
91. Chartoire A, Comoy C, Fort Y (2010) Toolbox for regioselective lithiations of furo[2,3-*c*]pyridine. *J Org Chem* 75:2227–2235
92. Henssier JT, Matzgar AJ (2009) Facile and scalable synthesis of the fused-ring heterocycles thieno[3,2-*b*]-thiophene and thieno[3,2-*b*]furan. *Org Lett* 11:3144–3147

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Heterocycles

Gribble, G.W. (Ed.)

2012, XIV, 446 p., Hardcover

ISBN: 978-3-642-31790-3