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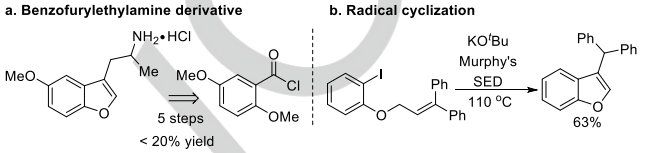
Synthesis of Benzofuran Derivatives via Cascade Radical Cyclization/Intermolecular Coupling of 2-Azaallyls

Guogang Deng,[+] Minyan Li,[+] Kaili Yu, Chunxiang Liu, Zhengfen Liu, Shengzu Duan, Wen Chen, Xiaodong Yang, Hongbin Zhang,* and Patrick J. Walsh**

Abstract: *Benzofurans are among the most popular structural units in bioactive natural products, however, the synthesis of such structures by radical cyclization cascade reactions is rare. Herein we report a mild and broadly applicable method for the construction of complex benzofurylethylamine derivatives through a unique radical cyclization cascade mechanism. Single-electron-transfer (SET) from 2-azaallyl anions to 2-iodo aryl allenyl ethers initiates a radical cyclization that is followed by intermolecular radical–radical coupling. This expedient approach enables the synthesis of a range of polycyclic benzofurans that would otherwise be difficult to prepare.*

Benzofurans are common structural units in bioactive compounds,[1] and are bioisosteres of indoles.[1a] They have attracted tremendous attention due to their profound physiological and chemotherapeutic properties.[2] In 2015, 34 clinically approved drugs were benzofuran derivatives, including Darifenacin, Vilazodone, and Ramelteon.[3] A subclass of these, benzofurylethylamines, have gained interest because they are precursors in the synthesis of α_2-adrenoceptor antagonists[4] and are known to exhibit high affinities for the serotonin 5-HT_2 and 5-HT_{1A} receptors. Their reported synthesis, however, is lengthy, low yielding and employed dangerous reagents (diazomethane, lithium aluminum hydride, and hydrazine, Scheme 1a).[5]

One potentially powerful pathway to benzofurans enabled by Murphy's "super electron donors" (SEDs) is through radical cyclization reactions, as exemplified in Scheme 1b.[6] Building on this strategy, a more sophisticated approach would involve capture of the cyclized radical intermediate to form an additional C–C bond, ideally with a functionalized coupling partner. The high functional group tolerance and gentle conditions of radical cyclization cascade reactions make them very attractive.[7] However, the interception of radical intermediates via intermolecular radical-radical coupling is challenging and, therefore, rare.[7b] This is largely attributed to the highly reactive and fleeting nature of radical species.[7b] To succeed in such couplings, the chemoselective radical hetero-coupling (vs. homo-coupling) must be controlled and side-reactions, such as hydrogen atom transfer (HAT) must be suppressed.



Scheme 1. **a**. Bioactive benzofurylethylamine derivative (prepared in 5 steps, 20% yield). **b.** Intramolecular radical cyclization to form benzofurans.

Recently, we introduced a unique radical generation strategy[8] for the transition metal-free C(sp^3)–C(sp^3) and C(sp^3)–C(sp^2) coupling reactions between 2-azaallyl radicals[9] and alkyl or aryl radicals (Scheme 2a).[10] Specifically, the single-electron-transfer (SET) process between 2-azaallyl anions[8] and aryl iodides or alkyl iodides or bromides led to the generation of the 2-azaallyl radical and aryl or alkyl radicals. The radical generation relies on the "super-electron-donor" (SED) feature of 2-azaallyl anions, which initiates the reaction. We hypothesized that the high chemoselectivity in the radical-radical coupling is due to the relative stability of the 2-azaallyl radical, which behaves as a persistent radical.[11]

We desired to explore the potential of this coupling strategy to build complexity through scalable and practical tandem reactions. Thus, in the present work we envisioned the use of 2-iodo aryl-allenyl ethers (Scheme 2b) as radical precursors. We hypothesized that SET from the 2-azaallyl anion to the aryl iodide would lead to an aryl radical that would undergo addition to the allene to generate a benzofuran methyl radical. This radical might then couple with the 2-azaallyl radical to form a second C–C bond and provide the desired benzofurylethylamines. Herein, we report the first radical cascade cyclization/intermolecular coupling between 2-azaallyl anions and aryl allenyl ethers. A diverse series of benzofurylethylamine derivatives were prepared in good to excellent yields in three steps from 2-iodophenols.

We selected 2-iodophenyl propadienyl ether **2a** as the model substrate,[10a] which was easily synthesized using the method of Grigg[12] by reaction of 2-iodo phenol with propargyl bromide (82% yield, see Supporting Information). We initiated our studies with the allenyl ether **2a** and ketimine **1a** with NaN($SiMe_3$)$_2$ in DME (dimethoxyethane) at room temperature for 12 h. To our delight, the tandem radical cyclization/coupling product **3aa** was obtained in 63% assay yield (AY, as determined by ^{1}H NMR integration against an internal standard, Table 1, entry 1). Replacing NaN($SiMe_3$)$_2$ with LiN($SiMe_3$)$_2$ gave increased AY [76%, Table 1, entry 2. Switching to other bases, such as KN($SiMe_3$)$_2$, LiO^{t}Bu, NaO^{t}Bu and KO^{t}Bu, however, led to lower

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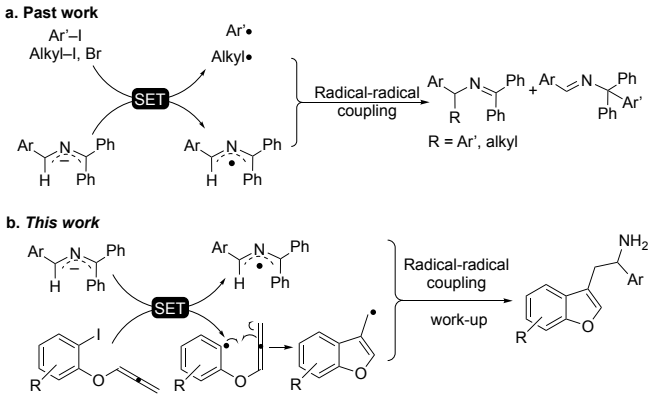
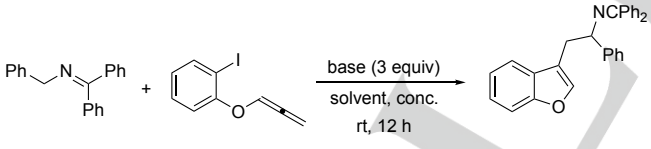
AY or no reaction (entries 3–6). We next studied the effect of solvent [CPME (cyclopentyl methyl ether), MTBE (methyl *tert*-butyl ether), toluene, THF, and dioxane].



Scheme 2. **a.** Transition-metal-free arylation and alkylation of 2-azaallyl radicals. **b.** Radical cyclization cascade of aryl-allenyl ethers enabled by 2-azaallyl anions as SED and sequential radical-radical coupling.

The reaction performed best in DME (entries 7–11).[13] Concentration can also play an important role in radical-radical coupling reactions. Reducing the concentration from 0.2 M to 0.1 M resulted in a slight increase to 78% AY, with 75% isolated yield (entry 12). In contrast, conducting the reaction at 0.05 M afforded only 50% AY (entry 13). The reaction proved to be relatively insensitive to temperature, as judged by heating to 60 (76% AY, entry 14) or 80 °C (73% AY, entry 15). Based on this optimization, the standard conditions for the tandem cyclization/coupling reaction that will be used for the remainder of the study are those in entry 12 of Table 1.

Table 1: Optimization of radical cyclization/coupling of ketimine **1a** and allenyl ether **2a**[a,b]



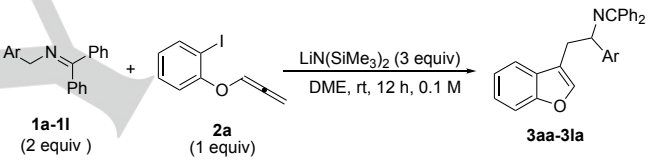
1a (2 equiv) **2a** (1 equiv) **3aa**

Entry	Base	Solvent	Conc.	Assay yield (%)
1	$NaN(SiMe_3)_2$	DME	0.2 M	63
2	$LiN(SiMe_3)_2$	DME	0.2 M	76
3	$KN(SiMe_3)_2$	DME	0.2 M	23
4	LiO^tBu	DME	0.2 M	0
5	NaO^tBu	DME	0.2 M	0
6	KO^tBu	DME	0.2 M	0
7	$LiN(SiMe_3)_2$	CPME	0.2 M	44
8	$LiN(SiMe_3)_2$	MTBE	0.2 M	42
9	$LiN(SiMe_3)_2$	Toluene	0.2 M	16
10	$LiN(SiMe_3)_2$	THF	0.2 M	67
11	$LiN(SiMe_3)_2$	Dioxane	0.2 M	0
12	$LiN(SiMe_3)_2$	DME	0.1 M	78(75)[c]
13	$LiN(SiMe_3)_2$	DME	0.05 M	50
14[d]	$LiN(SiMe_3)_2$	DME	0.1 M	76
15[e]	$LiN(SiMe_3)_2$	DME	0.1 M	73

[a] Reactions conditions: **1a** (0.2 mmol, 2.0 equiv), **2a** (0.1 mmol, 1.0 equiv), base (3.0 equiv), rt, 12 h. [b] Assay yields determined by ^{1}H NMR spectroscopy of the crude reaction mixtures using CH_2Br_2 as an internal standard. [c] Isolated yield after chromatographic purification. [d] 60 °C. [e] 80 °C.

Encouraged by the potential synthetic utility of this tandem SET/radical–radical coupling, and with an interest in determining its dependence on the SED properties of the 2-azaallyl anion, we initiated investigation of the scope of ketimines. As shown in Table 2, in general, *N*-benzyl groups bearing neutral, electron-rich and electron-deficient Ar groups provided good to excellent yields under the optimized conditions (Table 1, entry 12). Like the parent ketimine (**1a**) *N*-benzyl groups containing electron-rich arenes (**1b**, 4-OMe and **1c**, dioxol) afforded products **3ba** and **3ca** in 60% and 70% yield, respectively. *N*-Benzyl groups possessing electron-withdrawing substituents, such as 3-CF_3, 4-F, 4-Cl, 2-Br and 3,5-di-F, were also suitable coupling partners, leading to the corresponding products **3da**, **3ea**, **3fa**, **3ga** and **3ha** in 84, 68, 82, 74 and 82% yields, respectively. The sterically hindered 1-naphthyl derivative (**1i**) reacted with **2a** to generate the product **3ia** in 58% yield. Interestingly, heterocyclic ketimines possessing 4-pyridyl (**1j**), 3-pyridyl (**1k**) and 2-thiophenyl (**1l**) were also competent coupling partners, affording benzofurans **3ja**, **3ka** and **3la** in 75–77% yields.

Table 2: Scope of using ketimines as SED precursors and radical coupling partners[a,b]



1a-1l (2 equiv) **2a** (1 equiv) **3aa-3la**

Ar	Product	Yield (%)[b]	Ar	Product	Yield (%)[b]
Ph	**3aa**	75	2--C_6H_4-Br	**3ga**	74
4-C_6H_4-OMe	**3ba**	60	3,5--C_6H_3-F_2	**3ha**	82
Ph[*d*]1,3-dioxol	**3ca**	70	1-naphthyl	**3ia**	58
3--C_6H_4-CF_3	**3da**	84	4-pyridyl	**3ja**	77
4--C_6H_4-F	**3ea**	68	3-pyridyl	**3ka**	75
4--C_6H_4-Cl	**3fa**	82	2-thiophenyl	**3la**	75

[a] Reactions were conducted on a 0.4 mmol scale using 2 equiv ketimine, 1 equiv allenyl ether **2a** and 3 equiv $LiN(SiMe_3)_2$ at 0.1 M. [b] Isolated yields after chromatographic purification.

We next evaluated the ability of the tandem reaction to accommodate various substituents on the aryl ring of the aryl allenyl ether. As noted, allenyl ethers were easily synthesized from the corresponding aryl propargylic ethers (76–87%).[12, 14] Coupling of the parent ketimine **1a** with 4-^{t}Bu substituted aryl allenyl ether **2b** furnished product **3ab** bearing 5-(*tert*-butyl)benzofuran in 81% yield (Table 3). Electron-donating 5-methoxy substituents will make SET more difficult. Nonetheless, **2c** underwent the radical cyclization/coupling reaction to provide 6-methoxybenzofuran derivative (**3ac**) in 76% yield. Aryl allenyl ether **2c** bearing acetal and methoxy groups furnished the 5-(dimethoxymethyl)-7-methoxybenzofuran) **3ad** in 76% yield. Coupling **1a** with allenyl ethers bearing electron-withdrawing functional groups were also compatible under the standard reaction conditions, affording products **3ae** (5-(trifluoromethyl)benzofuran), **3af** (5-fluorobenzofuran), **3ag** (5-

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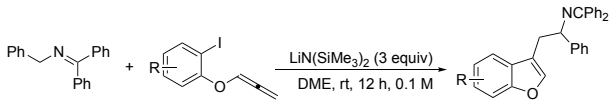
chlorobenzofuran) and **3ah** (6-bromobenzofuran) in 62, 69, 67 and 50% yields, respectively. The reaction with **2h**, where in the iodide undergoes selective reduction over the bromide, suggests that good chemoselectivity in the SET is achieved. Reaction with biphenyl derived allenyl ether **2i** led to **3ai** in 77%, offering a unique disconnection for benzofuro bi-aryl compounds.

Table 3: Scope of benzofuran from aryl allenyl ethers precursors and the parent ketimine **1a**[a]

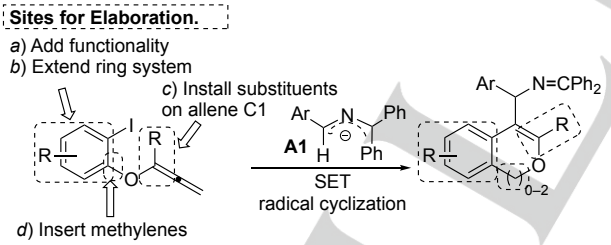


1a (2 equiv) **2b-2i** (1 equiv) **3ab-3ai**

R of **2b-2i**	Product	Yield (%)[b]	R of **2b-2i**	Product	Yield (%)[b]
4-^{t}Bu (**2b**)	**3ab**	81	4-F (**2f**)	**3af**	69
5-OMe (**2c**)	**3ac**	76	4-Cl (**2g**)	**3ag**	67
4-CH(OMe)$_2$-6-OMe (**2d**)	**3ad**	76	5-Br (**2h**)	**3ah**	50
4-CF$_3$ (**2e**)	**3ae**	62	4-Ph (**2i**)	**3ai**	77

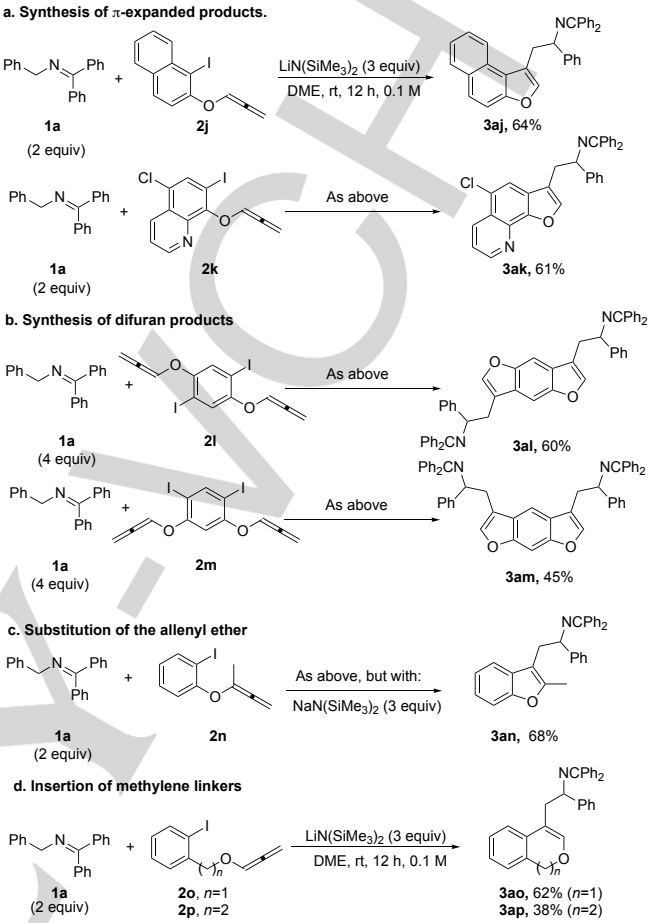
[a] Reactions were conducted on a 0.4 mmol scale using 2 equiv ketimine, 1 equiv allenyl ether and 3 equiv base at 0.1 M. [b] Isolated yields after chromatographic purification. NaN(SiMe$_3$)$_2$ was used as base for **3ae**, **3af** and **3ag**. R groups refers to substituents on the arenes of **2b-2i**.

The lack of sensitivity of the reaction to the substrate structures outlined in Tables 2 and 3 inspired us to set our sights on the synthesis of more elaborate aryl allenyl ethers with the aim of preparing novel fused heterocyclic ring systems. As outlined in Scheme 3, several potential avenues for elaboration of the benzofuran moiety could be realized by (**a**) functionalization of the aryl group; (**b**) extending the aryl system; (**c**) installation of functional groups at C1 of the allene motif and (**d**) adding carbon linkers between the aryl group and ether oxygen.



Scheme 3. Potential of modifications of the aryl allenyl ether coupling partner to more elaborate heterocyciic structures

To explore the versatility of the tandem cyclization/coupling reaction, we examined the modifications in Scheme 3. Modification **b** (Scheme 4) involved extension of the aryl allenyl ether system to naphthyl allenyl ether (**2j**). Subjecting **2j** to the standard coupling conditions enabled the assembly of the naphthol[2,1-*b*]furan framework found in **3aj** in 64% yield (Scheme 4a). Combining modifications **a** and **b** (Scheme 3) by replacing the naphthyl backbone with a chloro substituted quinoline led us to synthesize the 5-chloro quinoline allenyl ether **2k**. Reaction of **2k** with **1a** under the standard conditions afforded product **3ak** in 61% yield (Scheme 4a).



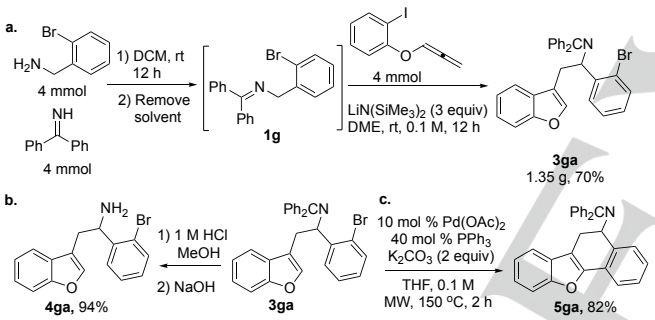
Scheme 4. Synthesis of novel poly-heterocyclic amine derivatives by modification of allenyl ethers.

We next examined the possibility of fused heterocyclic ring[15] synthesis from double-intramolecular radical cyclization followed by coupling with two 2-azaallyl radicals (Scheme 4b). The 1,4-di-allenyl diether **2l** was prepared and coupled with 4 equiv of ketimine **1a** leading to product **3al** in 60% yield. When isomeric 1,3-di-allenyl diether **2m** was employed, product **3am** was obtained in 45% yield. Both products are ~1:1 mixtures of diastereomers (see Supporting Information).

We explored the suitability of the cyclization/coupling reaction to functionalize the 2-position of the benzofuran ring (modification **c**, Scheme 3). Under the standard conditions, coupling of ketimine **1a** with methyl allenyl ether **2n** furnished the 2-methyl benzofuran product **3an** in 68% yield (Scheme 4c). Many radical cyclization reactions perform well in the formation of 5-membered rings, but are not suitable for the synthesis of larger analogues.[7b] To put our cyclization to the test, we examined modification **d** (Scheme 3). As shown in Scheme 4d, substrates **2o** and **2p** were tested. In the case of the one carbon homologated substrate **2o**, the 6-member-ring isochromene **3ao** was obtained with a yield similar to those in Tables 2–3 (62%).

The 7-member-ring benzooxepine **3ap** was isolated in 38% yield. Taken together, the results in Scheme 4 indicate that the tandem cyclization/radical-radical coupling reaction proceeds with diverse substrates and enables the synthesis of an array of heterocyclic products.

For a method to be practical, it must be straightforward and scalable. The scalability of our method was evaluated through the telescoped gram-scale synthesis starting with 2-bromobenzylamine. Thus, treatment of 2-bromobenzylamine with the benzophenone imine in dichloromethane at rt for 12 h was followed by solvent removal under reduced pressure (Scheme 5a). The unpurified imine **1g** was combined with the parent allenyl ether **2a** and 3 equiv $LiN(SiMe_3)_2$ in DME following the standard procedure. After 12 h at rt, workup and purification on silica gel 1.35 g of **3ga** was isolated (70% yield, Scheme 5a). Hydrolysis of benzofurylethylamine **3ga** afforded the corresponding benzofurylethylamine **4ga** in 94% yield (Scheme 5b). Compound **4ga** was characterized by X-ray crystallography, confirming its structure. The synthetic value was further demonstrated by an intramolecular Heck-type cyclization reaction. Thus, using $Pd(OAc)_2$ (10 mol %), PPh_3 (40 mol %) at 150 °C under microwave heating successfully converted benzofurylethylamine **4ga** to tetracyclic product **5ga** in 82% yield (Scheme 5c).[16]



Scheme 5. **a.** Gram-scale sequential one-pot synthesis. **b.** Product hydrolysis. **c.** Synthesis of tetracyclic product **5ga** via intramolecular Heck-type cyclization.

In summary, we have developed a unique strategy of constructing polycyclic architectures in a single synthetic operation that provides functionalized benzofuran derivatives of biologically active compounds. In this reaction, simple, readily synthesized 2-iodo aryl allenyl ethers and ketimines were coupled to afford a wide variety of benzofurylethylamines. This transformation was accomplished via a tandem SET/radical cyclization/intermolecular radical–radical coupling process in which the 2-azaallyl anion plays the roles of "super-electron-donor" (SEDs) and the precursor to the 2-azaallyl radical coupling partner. In particular, the 2-iodo aryl allenyl ethers can be diversified with 4 classes of modifications, including functionalization of the aryl group, expansion of the aryl-system, substitution of the C1 position of the allenyl group, and extension of the oxygen linker. Furthermore, the *N*-benzyl group of the ketimine can be easily decorated with substituents or with heterocycles. Thus, this method enables the synthesis of a diverse array of benzofurylethylamine derivatives. It is noteworthy that this method does not require addition of transition metals, avoiding challenges of sustainability, expense, and separation of trace transition metal-containing impurities, which is crucial and often very expensive in the pharmaceutical industry.[17]

Acknowledgements

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Keywords: radical cyclization • cascade reactions • radical coupling • benzofurylethylamine • azaallyl anions

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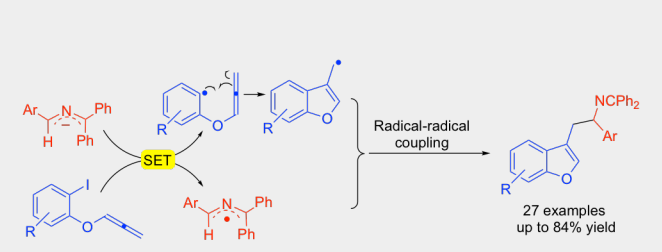

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Synthesis of Benzofuran Derivatives via Cascade Radical Cyclization/Intermolecular Coupling of 2-Azaallyls

Well behaved radicals: a mild and broadly applicable method for the construction of complex benzofurylethylamine derivatives through a unique radical cyclization cascade mechanism is presented. SET from 2-azaallyl anions to 2-iodo aryl allenyl ethers initiates a radical cyclization that is followed by intermolecular radical–radical coupling.