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Synthesis of Functionalized Tetrahydrobenzofuran via Cascade Cycloaddition Involving Silyloxyallyl Cation Intermediate

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Abstract

An expedient synthesis of highly substituted tetrahydrobenzofuran via unsymmetrical silyloxyallyl cation is reported. Conveniently generated under catalytic Brønsted acid conditions, nucleophilic capture of this reactive intermediate with silylenolate, followed by cascade Paal-Knorr cyclization in the presence of tosic acid monohydrate effectively constructed the tetrahydrobenzofuran core in a single synthetic step operation.

Tetrahydrobenzofuran is a class of heterocycles that can be found in numerous natural products. As exemplified in Figure 1, this ring motif is a key structural feature in a family of furanoeremophilane natural products;[1] some of which display a range of unique biological activities. For instance, atractylon reportedly exhibited apoptotic and antiviral activities.[2] Despite the remarkably close structural resemblance, tubipofuran is known as an ichthyotoxin toward the killifish *Oryzias latipes*.[1b] Other examples can be found in cafestol and isolinderalactone. Isolated from coffee beans, cafestol is a tetrahydrobenzofuran-containing diterpenoid that has been described to play a role in cholesterol homeostasis, along with other pharmacological effects.[3] In the case of isolinderalactone, recent pharmacology studies on this natural product revealed its antiproliferation and antimetastatic activities against several cancer cell lines.[4]

The relevance of tetrahydrobenzofuran in bioactive natural products has consequently rendered this heterocycle a valuable target for new synthetic reaction developments. A particularly effective platform to construct tetrahydrobenzofuran can be realized in a bimolecular manner via the [4+2] cycloaddition methodology, which enables the 6-membered ring formation.[5] There are three possible retrosynthetic disconnections in this approach; each would require dienes in their respective form of vinyl furan, along with electron-deficient dienophiles as reaction partners. As exemplified in Scheme 1, Yamazaki reported type 1 [4+2] strategy that proceeded upon coupling of vinyl furan **1a** and ethenetricarboxylate **1b**, followed by *in situ* cyclization of intermediate **1c**, thereby incorporating the C4-C5 segment in tetrahydrobenzofuran **1d**.[5a] Melchiorre reported type 2

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Conflicts of interest

There are no conflicts to declare

cyclization, in which nucleophilic activation of 2-furyl-acrolein substrate **1e** with an amine catalyst produced highly conjugated diene **1f**.[5b] This intermediate then underwent [4+2] cycloaddition with dienophile **1g** to install the C5-C6 segment in tetrahydrobenzofuran **1h**. A complementary type 3 synthesis, which readily introduced the C6-C7 segment was reported by Chen.[5c] In this instance, amine activation of ketone **1i** generated furan conjugated diene **1j**. The ensuing [4+2] cyclization with dienophile **1k** furnished tetrahydrobenzofuran motif **1l**.

The utility of cycloaddition methodology in addressing the need for concise synthesis of tetrahydrobenzofuran inspired us to develop a novel reaction to target this heterocycle. As a complement to the previous strategy that focused on the 6-membered ring, our work would approach the assembly of the furan core,[6] highlighted by cascade [3+2] ring forming processes via silyloxyallyl cation chemistries (Scheme 2). To be precise, we envisioned the use of six-membered unsymmetrical silyloxyallyl cations **2b** that would be readily generated from α-hydroxy silylenolate **2a** in the presence of catalytic Brønsted acid.[7] The ensuing capture of this species with silylenolate **3** at the less substituted α-carbon should produce monosilylenol ether **2c**.[8] The cascade reaction would ensue with Brønsted acid-catalyzed protodesilylation to unmask 1,4-diketone **2d**, followed by Paal-Knorr cyclization to furnish tetrahydrobenzofuran core **2e**.[9] The novelty of our method also lies in its modularity that would expediently incorporate different substituents at the C2 and C3 positions. This synthetically non-trivial undertaking would be possible by simply varying the substituents of silylenolate **3**.

Table 1 depicts our preliminary studies. Using α-hydroxy silylenolate **4** and acetophenone-derived silylenolate **5** as model systems, our optimization began with an investigation on ionization conditions that employed 0.2 equiv of Py•TfOH in MeCN at room temperature to enable α,α-coupling of the two silylenolates. This was then followed by warming the mixture to reflux to allow for the intended protodesilylation and Paal-Knorr cyclization to occur. Interestingly, such pilot conditions did not produce tetrahydrobenzofuran **6** despite the prolonged reaction time, yielding only the 1,4-diketone construct, *viz.* **2d**. This result indicated that while Py•TfOH readily promoted the key carbon-carbon bond forming step and protodesilylation of the monosilylenolate adduct, *viz.* **2c**, the furan cyclization appeared to require stronger acidic conditions. To address this issue, we introduced a second Brønsted acid as an additive immediately after the completion of the α,α-coupling step, commencing with CSA. These conditions indeed furnished tetrahydrobenzofuran **6** albeit in small quantities. A significant improvement in product yields was observed when the reaction was warmed to reflux and performed in more concentrated solutions. We also examined other Brønsted acid additives and found that the use of TsOH•H_2O afforded tetrahydrobenzofuran **6** in 79% yield. We noted the decreasing amount of TsOH•H_2O led to the decreasing product yield. Basing upon screening results, our optimized reaction protocol was developed as follows: α-hydroxy silylenolate **4** and silylenolate **5** were treated with 0.2 equiv of Py•TfOH at room temperature in acetonitrile at 0.5 M concentration. Upon completion of the α,α-coupling step, 1.2 equiv of TsOH•H_2O was added, and the mixture reaction was subsequently warmed to reflux to produce the desired tetrahydrobenzofuran **6**. These conditions were applicable to scale up synthesis while maintaining its efficacy.

As shown in Table 2, we investigated the scope of this reaction, commencing with various silylenol ethers **7** that would introduce different substituents the C2 and C3 positions. For instance, a series of acetophenone-derived silylenol ethers bearing electronically diverse substituents, such as electron-rich and poor groups as well as halogen furnished products **8a**-**8c** were isolated in acceptable yields. We then examined cyclic silylenol ethers derived from cycloheptanone, 4-phenylcyclo-hexanone, and α-tetralone, which afforded their respective polycyclic adducts **8d**-**8f** in 51–70% yields. The utility of fully aliphatic silylenolate derived from 3-pentanone was evaluated. This nucleophile readily introduced alkyl substituents at C2 and C3 in tetrahydrobenzofuran **8g**. A similar strategy could be applied to selectively incorporate two aromatic substituents at these positions, *i.e.* product **8h**. We also attempted to subject silyldienolate. While the reaction indeed generated the target product **8i**, it was isolated in a low yield due to decomposition that readily occurred during the cyclization sequence.

We then explored substituent effects at the α-carbon using α-hydroxy silylenolate **9** (Scheme 3). The presence of α-substituent was necessary, without which decomposition was noted instead of tetrahydrobenzofuran **10a**. Substrates bearing aliphatic group motifs produced the corresponding adduct **10b**-**10d** in 66–79%, but the furan cyclization in these products was performed with 1.2 equiv of CSA instead of TsOH•H_2O due to the presence of minor unidentifiable byproducts that could not be separated by column chromatography. The effect of various aromatic groups at the α-carbon was also examined. These included a phenyl group along with the para-methyl and *para*-chloro variants, as well as naphthalene, to afford tetrahydrobenzofuran **10e**-**10h** in good yields.

During reaction optimization (Table 1), the generation of tetrahydrobenzofuran **6** was found to be more effective in the presence of stoichiometric amount of TsOH•H_2O. Interestingly, Bharatam and co-workers have hypothesized that water, in particular hydronium ion, plays a significant role in enhancing the Paal-Knorr cyclization.[10] More specifically, hydronium ion is believed to readily form a hydrogen bond network in facilitating two key steps: the hydration of 1,4-diketone, leading to 5-membered cyclization, *viz.* **11a**, and dehydrative elimination of hemiacetal to furnish the furan core, *viz.* **11b** (Scheme 4).

Inspired by this report,[10] we probed the role of water by qualitatively comparing the kinetic profile between our typical reaction conditions, *i.e.* TsOH•H_2O, and the anhydrous protocols (Scheme 5). In these experiments, the corresponding additives were introduced upon completion of α,α-coupling between silylenolates **4** and **5**, followed by mixing the reaction at room temperature for 15 min to allow protodesilylation prior to furan cyclization at reflux. Aliquots of the mixtures were subjected to GC-MS every 15 minutes to determine the relative composition of monosilylenolate **12**, 1,4-diketone **13**, and tetrahydrobenzo-furan **6**. There are several notable results: 1) A remarkable rate difference in the furan formation was indeed noted, in which TsOH•H_2O led a faster rate of reaction, thereby supporting the computational studies by Baratham.[10] 2) While undetectable by TLC, the reaction mixture contained residual 1,4-diketone **13** that persistently remained uncyclized under equilibrium. 3) The rapid disappearance of monosilylenolate **12** with both additives suggested that water had negligible effects in affecting the rate of protodesilylation of **12** within the time scale of our reaction.

Gratifyingly, the tetrahydrobenzofuran motifs produced via our method proved to be highly valuable as they could serve as a convenient substrate for a rapid assembly of polycyclic architecture. As demonstrated in Scheme 6, compound **6** could be readily subjected to [4+3] cycloaddition upon ionization of α-tosyl cyclohexanone with Et_3N to furnish complex product **14** in 44% yield.[11] The relative stereochemistry of this polycyclic compound was confirmed by X-ray.[12]

In conclusion, we have developed a novel protocol for the concise synthesis of highly substituted tetrahydrobenzofuran via cascade reactions that are facilitated by silyloxyallyl cations and Paal-Knorr cyclization. The significance of water in affecting the rate of furan cyclization and the synthetic utility of the tetrahydrobenzofuran adduct toward a rapid construction of polycyclic molecular architectures were also demonstrated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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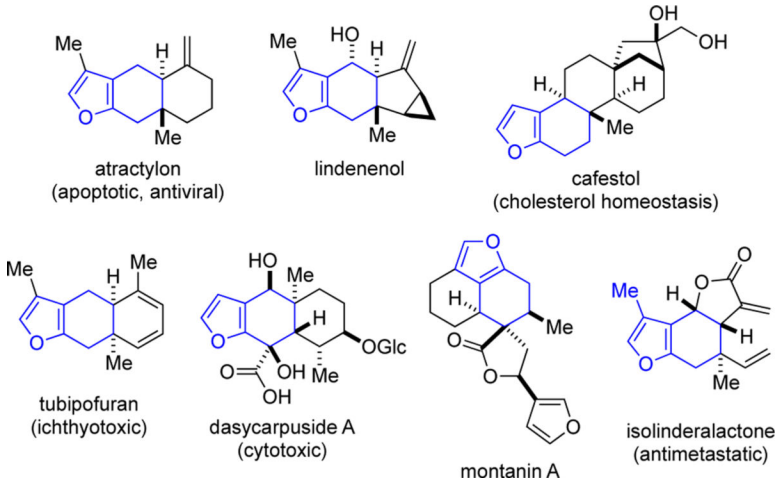
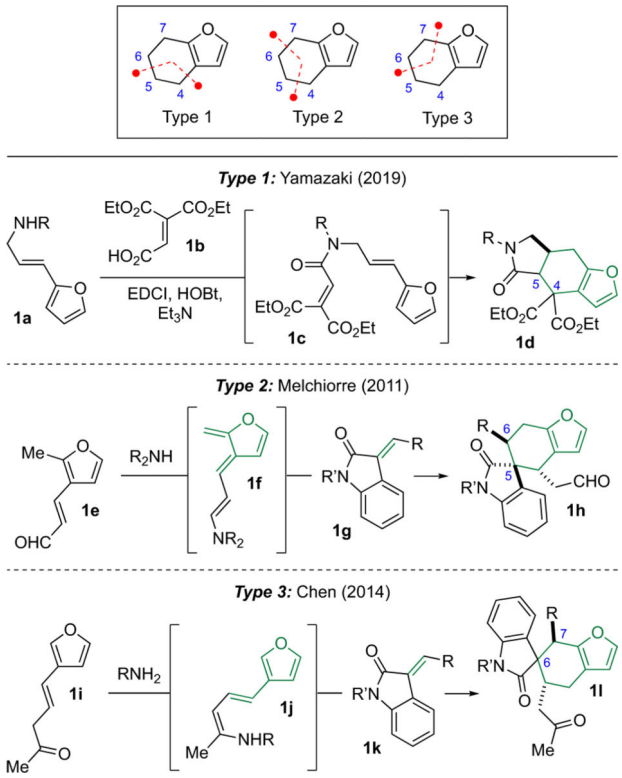
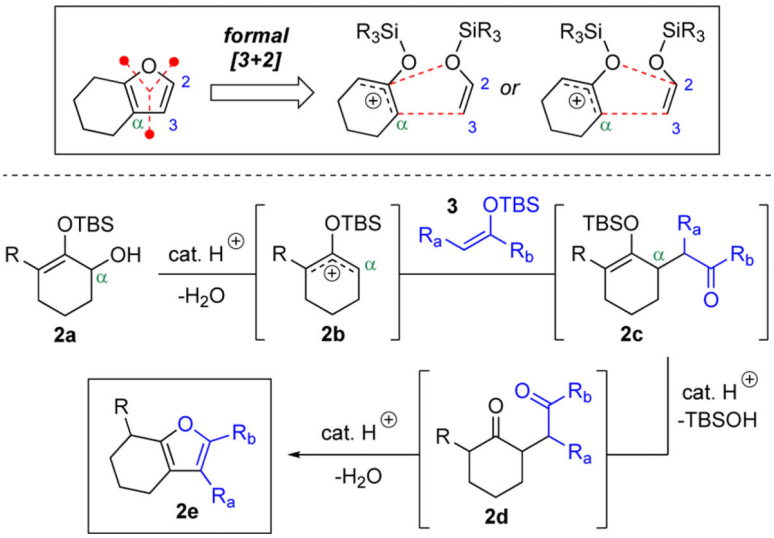


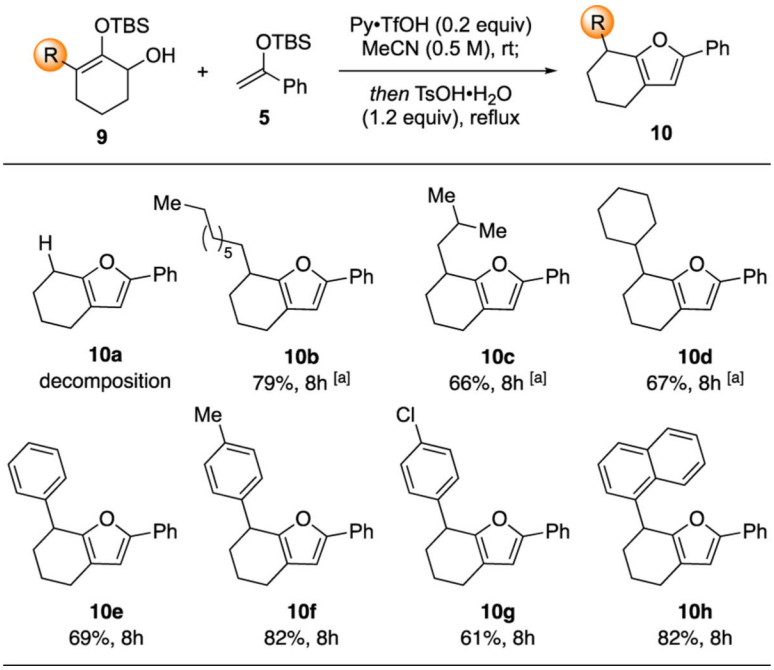
Figure 1.
Examples of Tetrahydrobenzofuran-Containing Natural Products.



Scheme 1.
[4+2] Cycloaddition Platforms

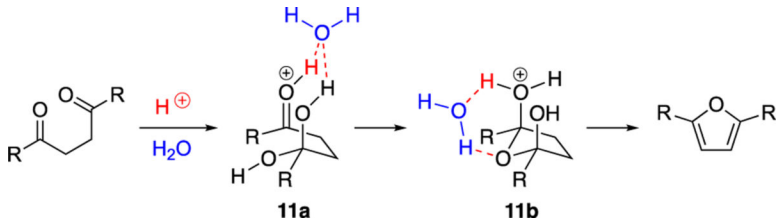


Scheme 2.
Proposed Formal [3+2] Cycloaddition

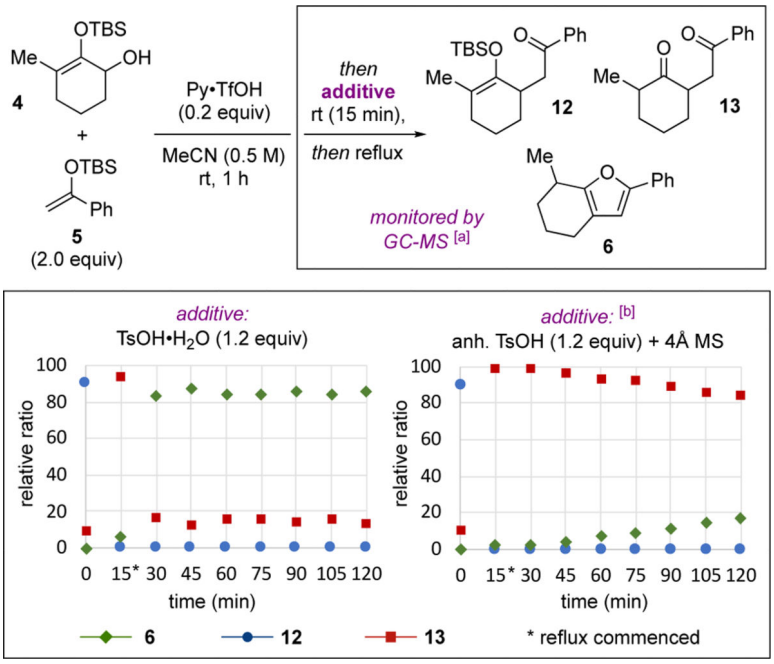


Scheme 3.

Scope of α-Hydroxy Silylenolate [a] 1.2 equiv of CSA was employed instead of $TsOH•H_2O$.



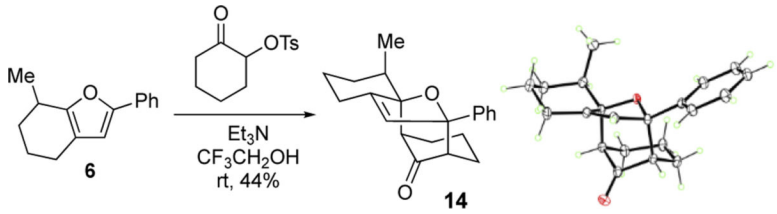
Scheme 4.
Putative Roles of Hydronium Ion



Scheme 5.

Comparative Rate of Furan Cyclization

[a] The relative ratio of products was determined by GC-MS analyses with an assumption that identical GC responses were elicited. [b] Anhydrous TsOH was prepared by subjecting TsOH•H_2O to reflux in toluene using the Dean-Stark apparatus.

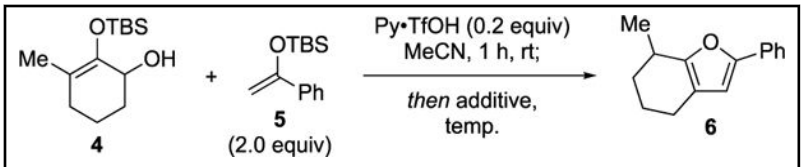


Scheme 6.

Diastereoselective Synthesis of Complex Polycyclic Architectures via [4+3] Cycloaddition.

Table 1.

Reaction Optimization



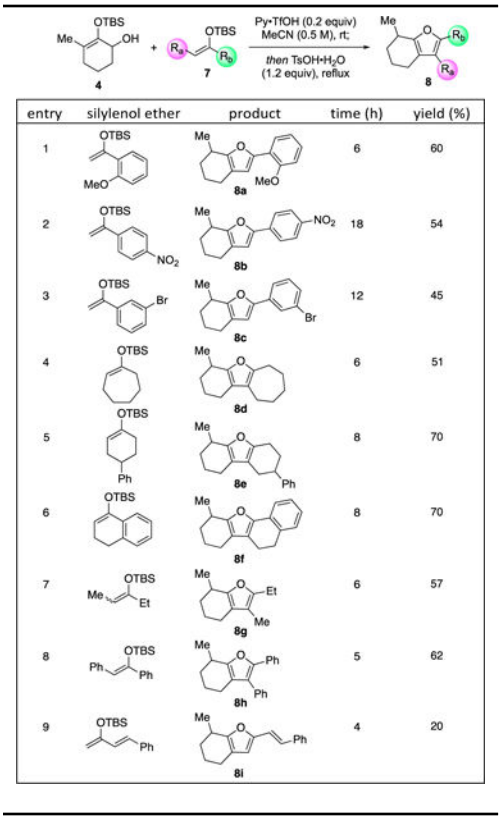
entry	additive	equiv	conc (M)	temp	time (h)	yield (%)
1	None	0	0.2	rt	55	0 [a]
2	CSA	0.5	0.2	rt	55	3
3	CSA	1.0	0.2	rt	52	12
4	CSA	1.2	0.2	rt	51	10
5	CSA	1.2	0.2	reflux	15	29
6	**CSA**	**1.2**	**0.5**	**reflux**	**9**	**66**
7	CSA	1.2	0.8	reflux	15	51
8	CSA	1.0	0.5	reflux	12	50
9	CSA	1.5	0.5	reflux	8	58
10	CSA	2.0	0.5	reflux	12	60
11	Py•TfOH	1.2	0.5	reflux	58	0 [a]
12	TFA	1.2	0.5	reflux	23	58
13	**TsOH•H_2O**	**1.2**	**0.5**	**reflux**	**7**	**79** [b]
14	TsOH•H_2O	0.2	0.5	reflux	23	40
15	TsOH•H_2O	0.5	0.5	reflux	7	64
16	TsOH•H_2O	1.0	0.5	reflux	7	74

*[a]*The reaction yielded only uncyclized 1,4-diketone adduct.

*[b]*One-gram synthesis with substrate **4** product **6** in 69% yield.

Table 2.

Scope of Nucleophiles



entry	silylenol ether	product	time (h)	yield (%)
1		8a	6	60
2		8b	18	54
3		8c	12	45
4		8d	6	51
5		8e	8	70
6		8f	8	70
7		8g	6	57
8		8h	5	62
9		8i	4	20