Taming Highly Unstable Radical Anions and 1,4-Organodilithiums by Flow Microreactors: Controlled Reductive Dimerization of Styrenes

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ABSTRACT: The reduction of styrenes with lithium arenide in a flow microreactor leads to the instantaneous generation of highly unstable radical anions that subsequently dimerize to yield the corresponding 1,4-organodilithiums. A flow reactor with fast mixing is essential for this reductive dimerization as the efficiency and selectivity are low under batch conditions. A series of styrenes undergo dimerization, and the resulting 1,4-organodilithiums are trapped with various electrophiles. Trapping with divalent electrophiles affords precursors for useful yet less accessible cyclic structures, for example, siloles from dichlorosilanes. Thus, we highlight the power of single-electron reduction of unsaturated compounds in flow microreactors for organic synthesis.

KEYWORDS: radical anion, reductive dimerization, dilithiation, flow microreactor, silole

1. INTRODUCTION

Organolithium reagents play an important role in organic synthesis, and their versatile reactivity has led to various applications.1−3 Accordingly, many methods have been developed for generating organolithium species, including lithiation at carbon−heteroatom bonds, deprotonation at acidic C−H bonds, and addition of lithium reagents across unsaturated bonds. In light of the paramount importance of organolithium species, organodilithium species that have two carbon−lithium bonds in a single molecule are a fascinating prospect, especially in the construction of cyclic frameworks.4−7 However, the generation of such dilithium species presents several problems (Figure 1): (A) doubly prefunctionalized precursors, most often dihalides, are not readily available; (B) as the second lithiation is more difficult than the first, unwanted intramolecular reductive C−C-bond formation can precede the desired second lithiation; (C) dilithiated species, which are inherently unstable and highly reactive, are generated under harsh conditions; therefore, the variety of useful dilithium species is currently limited.

A different way to generate dilithium species is the reductive dimerization of unsaturated compounds.8–13 This is a classical straightforward method for generating synthetically useful 1,4-dilithium species. However, this reductive dimerization lacks generality and is far from synthetically and practically useful. The impracticality originates from the difficulty in taming high-energy anionic intermediates. Styrene, for example, undergoes single-electron reduction from a strongly reducing alkali metal (Figure 2). The resulting radical anion of styrene could selectively homocouple to yield the corresponding benzylic 1,4-dilithium species; however, rapid reaction of the dilithium species with remaining styrene occurs. This is a well-known process for initiating anionic polymerization of styrene.14−17

Here, we disclose a method for efficiently generating 1,4-dilithium species via reductive dimerization of styrenes by
stirred for 12 h.

**Figure 2.** Reductive dimerization of styrene using lithium metal.

suppressing the unwanted polymerization with flow microreactors. The resulting high-energy dilithium species are indeed useful reagents for the synthesis of various cyclic skeletons such as siloles. Our findings will open a door to taming highly reactive radical anions and dianionic species for organic synthesis.

### 2. RESULTS AND DISCUSSION

First, we tried reductive dimerization of styrene (1a) in a batch reactor (Table 1). Styrene was added to a reductant in THF, followed by stirring for 12 h.

**Table 1.** Reductive Dimerization of Styrene Using a Batch Reactor

| entry | reductant   | x equiv | temp. (°C) | yield of 2a (%) | yield of 3 (%) |
|-------|-------------|---------|------------|----------------|---------------|
| 1     | Li powder   | 2       | 0          | 0              | 0             |
| 2     | LiNp        | 2       | 0          | 0              | 0             |
| 3     | LiNp        | 2       | 0          | 0              | 0             |
| 4     | LiNp        | 2       | 0          | 0              | 0             |
| 5     | LiNp        | 2       | 0          | 0              | 0             |
| 6     | LiNp        | 2       | 0          | 0              | 0             |
| 7     | LiNp        | 2       | 0          | 0              | 0             |
| 8     | LiDTBB      | 2       | 0          | 0              | 0             |

\(^{a}\)Yields were determined by GC analysis. \(^{b}\)With 0.4 mmol of 1a. Stirred for 12 h. \(^{c}\)Added over 5 min. \(^{d}\)Added in one stroke.

then the reaction was terminated with methanol to monitor the formation of 1,4-diphenylbutane (2a). When lithium powder (2 equiv monomolar amounts) was used as the reductant, styrene was completely consumed without formation of 2a (entry 1). We considered that electron transfer from the heterogeneous reductant to styrene was too slow causing anionic polymerization to outcompete dimerization. To favor dimerization, we used lithium naphthalenide (LiNp) as a homogeneous reductant to promote rapid reduction and consumption of styrene. Unfortunately, the polymerization still predominated to yield 2a in low yields along with trimeric byproduct 3 even at low temperatures (entries 2 and 3). Increasing the amount of LiNp for more rapid reduction resulted in only marginal improvement in the yield of 2a (entries 4 and 5). No significant changes were observed regardless of the duration of adding styrene (entries 6 and 7). The stronger reducing reagent lithium 4,4'-di-tert-butylibiphenylide (LiDTBB) did not improve the yield of 2a (entry 8). These unsuccessful results convinced us that the reductive dimerization to form the 1,4-dilithium species cannot predominate over polymerization in batch reactors.

We presumed that slow mixing in a batch reactor was a major factor in the failure. It generally takes a few seconds for a solution to become homogeneous when mixing two different components in a batch reactor.\(^{18}\) The results in Table 1 suggest that the time it takes to form a homogeneous solution is slower than the formation of the radical anion, the homocoupling, and the unwanted polymerization. To overcome the homogeneity problem, we decided to use flow microreactors that can control fast reactions by fast mixing\(^{19–44}\) and that realizes what selectivity should be without minding the mixing issue.\(^{35–50}\) We envisaged that fast mixing of styrene and a sufficiently powerful homogeneous reductant would allow quick radical anion generation/styrene consumption, thereby avoiding the undesired polymerization (Figure 3). As another advantage, the reaction time and temperature can be precisely controlled using flow microreactors in order to tame unstable dilithium species. To the best of our knowledge, reduction of unsaturated compounds by alkali metal arenesides using flow microreactors has not been developed, although lithiation of easy-to-reduce halides with lithium areneide has been reported.\(^{51–54}\)

We have designed a flow system with two micromixers (M1 and M2) and two microtubes (R1 and R2) for the reductive dimerization of styrene (Table 2). We designed the system in order to mix styrene and LiNp (0.40 M THF) with extreme efficiency to make a homogeneous solution in M1. As the mixture flows from M1 to M2 through R1, the instantaneous formation of the radical anion of styrene and subsequent dimerization should occur to give the 1,4-dilithium species. Finally, protonation with methanol in M2 and R2 yields the desired product 2a and a major byproduct 3a to monitor the selectivity of dimerization/polymerization. For the first attempt, we used a T-shaped mixer having a 500 μm internal diameter and a total flow rate of 6 mL/min at M1 (Table 2, entry 1), but the product 2a was obtained in only 49% yield. To our delight, the yields of 2a increased up to 77% as the flow rate increased, most likely due to more efficient mixing at M1 (entries 2–4).\(^{55}\) Moreover, when a smaller diameter mixer (φ = 250 μm) was used at M1 for more efficient mixing, the yield dramatically increased to 96% (entry 5). When sodium naphthalenide (NaNp) was used instead of LiNp as the reductant, a larger amount of byproduct 3 was formed (entry 6). This can be explained through the higher nucleophilicity of organosodium compounds in comparison to organolithiums, leading to a more efficient reaction of the sodium 1,4-dianion with styrene. In order to prevent the formation of 3 by smoother electron transfer to styrene, the
stronger reducing reagent LiDTBB was used (entry 7). With just 1.2 equiv of LiDTBB, only a trace amount of 3 was detected, and the yield of 2a was 96%. We thus decided to use LiDTBB as the reductant for further study.

With the success in using flow microreactors, we investigated the reductive dimerization of various styrenes (Table 3). Methyl and trimethylsilyl substituents did not hamper the reaction to yield the corresponding dimerization products 2b and 2c. Biphenyl-type substrate 1d reacted smoothly; however, the yield of 2d was moderate because of some side reactions including the formation of ethylbiphenyl. The reaction of p-methoxystyrene (1e) afforded dimer 2e in only 9% yield with concomitant formation of styrene via reductive demethoxylation (Table S5). In order to suppress the demethoxylation, the reaction temperature was lowered to −78 °C, using 2.0 equiv of LiDTBB for efficient reduction. Under these conditions, 2e was formed exclusively even with a 500 μm internal diameter mixer. The cryogenic conditions were also applicable to other methoxy-, dimethylamino-, and methylsulfanyl-substituted substrates to yield the desired products 2f–2i without loss of the functional groups. Moreover, under further modified conditions, the dimerization of halogenated styrenes 1j and 1k proceeded to yield 2j and 2k, respectively. These halogenated dimers could hardly be obtained in a batch reactor (Table S9). Unfortunately, 3-bromostyrene and 4-chlorostyrene underwent reduction of the halogen groups, and styrene was mainly obtained. Electron-deficient vinylpyridine (1l) also dimerized to form 2l in a moderate yield. Divinylbenzene (1m) was dimerized to give the product 2m, while the other vinyl group was left mostly untouched. The boryl group in 1n survived to afford 2n in 32% yield, although the boryl group can easily react with radical anions of styrenes. In addition to styrenes, vinylsilane 1o could be dimerized to form 2o in good yield because of the α effect of the silyl group.

We tried cross-dimerization of two different styrenes (Scheme 1). As the amount of styrene was increased, the yield increased (Table S8). When a mixture of p-methoxystyrene and 1d was used in a 1:1 ratio, the yield of 2d was increased to 72%.

### Table 2. Reductive Dimerization of Styrene Using Flow Microreactors

| entry | internal diameter of M1 (μm) | total flow rate at M1 (mL/min) | yield of 2a (%) | yield of 3 (%) |
|-------|-----------------------------|--------------------------------|----------------|---------------|
| 1     | 500                         | 6                              | 49             | 3             |
| 2     | 500                         | 8                              | 53             | 5             |
| 3     | 500                         | 10                             | 70             | 5             |
| 4     | 500                         | 12                             | 77             | 5             |
| 5     | 250                         | 12                             | 96             | 2             |
| 6     | 250                         | 12                             | 81             | 7             |

*Yields were determined by GC analysis. The internal diameter of M2 was 500 μm. *NaNp (0.40 M) was used instead of LiNp. *1.2 equiv of LiDTBB (0.40 M) was used instead of LiNp.

### Table 3. Reductive Dimerization of Various Styrenes Using Flow Microreactors

| 1   | R— | t (s) | T (°C) | 2   | Yield (%) |
|-----|-----|-------|--------|-----|------------|
| 1b  | MeO | 0.17  | 0      | 2b  | 96         |
| 1c  | MeS | 0.17  | 0      | 2c  | 90         |
| 1d  | Ph  | 7.9   | 0      | 2d  | 64         |
| 1e  | MeO | 7.9   | −78    | 2e  | 97         |
| 1f  | MeO | 7.9   | −78    | 2f  | 70         |
| 1g  | MeO | 7.9   | −78    | 2g  | 91         |
| 1h  | MeN | 7.9   | −78    | 2h  | 73         |
| 1i  | MeS | 7.9   | −78    | 2i  | 72         |
| 1j  | F   | 0.073 | −78    | 2j  | 55         |
| 1k  | Cl  | 0.073 | −78    | 2k  | 50         |
| 1l  | Cl  | 0.17  | 20     | 2l  | 59         |
| 1m  | Ph  | 0.19  | −40    | 2m  | 45         |
| 1n  | Ph  | 7.9   | 0      | 2n  | 32         |
| 1o  | Ph  | 7.9   | 0      | 2o  | 75         |

*Yields were determined by GC analysis unless noted. A T-shaped mixer with 250 μm internal diameter was used at M1. *2.0 equiv of LiDTBB was used. *A T-shaped mixer with 500 μm internal diameter was used at M1. *Isolated yield. *An anchor-shaped mixer with 250 μm internal diameter at M1 was used.
allylated, benzylated, and trimethylsilylated products 4a–4d were obtained in excellent yields. Trifluoroacetylation proceeded to give the product 4e in a moderate yield. The reaction with dichlorodimethylsilane provided a cyclic compound, silacyclopentane 4f, in 80% yield. The silacyclopentane skeleton is a potential precursor to siloles of optoelectronic interest; however, only one example of dehydrogenative oxidation of a silacyclopentane is known. As demonstrated in the synthesis of 4f, our reductive dimerization/silylative cyclization sequence provides access to 3,4-unsubstituted 2,5-diarylsiloles, which show an efficient conjugation over the rather coplanar skeleton because of the lack of substituents at the third and fourth positions. Despite many precedents for the synthesis and applications of nonplanar 2,3,4,5-tetraarylsiloles, there are few methods available for the synthesis of 3,4-unsubstituted 2,5-diarylsiloles. For the methods that are available, inconvenient starting materials or transition-metal catalysts are required.

To our delight, a variety of 2,5-diarylsiloles 5–18 were obtained by the reaction of the initially obtained silacyclopentanes with 2,3-dichloro-5,6-dicyano-1,4-benzochinone (DDQ) (Scheme 3). Several comments are worth noting: (1) methoxy, methylsulfanyl, trimethylsilyl, and methyl groups were compatible under oxidative conditions using strongly oxidizing DDQ to yield 5–8 and 10 in good yields. (2) Our initial attempts on the synthesis of dinaphthyl product 12 resulted in failure in the reductive dimerization stage because of clogging. We presumed that polymerization occurs because of the high reactivity of 2-vinylnaphthalene. When we used the less-reactive 1,2,3,4-tetrahydro-6-vinylnaphthalene instead of 2-vinylnaphthalene, clogging did not occur, and the corresponding silacyclopentane was afforded. Then, global oxidation by DDQ yielded silole 12. (3) In addition to dichlorodimethylsilane, other dichlorosilanes are available for use in this procedure, and siloles 11–16 were obtained in good yields. (4) Flow synthesis can be scaled up easily, and this is also the case for the gram-scale synthesis of silole 18. The productivity in the flow system was calculated to be 23 mmol/h. (5) The use of tetrachlorosilane as the electrophile provided spirobisilole 17, which is otherwise difficult to synthesize. (6) Germole 19 was obtained after trapping with dichlorophenyldigermene, which represents a rare example of the synthesis of germoles.

In addition, using our cross-dimerization method (Scheme 1), we could obtain more fascinating 2,5-unsymmetrical siloles 20–24 in moderate yields (Scheme 4).

Finally, we synthesized other cyclic compounds by treating the generated dilithium species with electrophiles other than silicon and germanium (Scheme 5). Trapping with dimethoxophosphine followed by oxidation yielded phospholane 25 that are known to be precursors for chiral phosphine ligands. Treatment of the dilithium species with elemental sulfur afforded a mixture of the corresponding tetrahydrothiophene 26 and 1,2-dithiane 26', which was convergently converted to 26 by treatment with P(NMe$_2$)$_2$. Cyclopentene 27 was formed by the reaction with an ester and the subsequent dehydration from the tertiary alcohol intermediate 27'. When carbamic chloride was used instead, cyclopentanone 28 was obtained in 89% yield.

3. CONCLUSIONS

In conclusion, the use of flow microreactors has realized a facile, rapid, and efficient generation of 1,4-dilithium species by reductive dimerization of styrenes. Fast mixing of styrenes and lithium arenides is crucial to achieve selective dimerization by suppressing unwanted polymerization. A series of styrenes are applicable to this dimerization, and the resulting 1,4-dilithium species reacted with various electrophiles. Trapping with difunctional electrophiles, such as dichlorosilanes, provides useful precursors for various cyclic compounds that are otherwise difficult to obtain, for example, siloles. Further exploration of single-electron reduction of unsaturated compounds in flow microreactors is ongoing in our laboratory.
4. METHODS

4.1. Typical Procedure for Reductive Dimerization of Styrenes

The dimerization of 1b is representative (Table 3). A flow microreactor system consisting of two T-shaped micromixers (M1...
and M2), two microtube reactors (R1 and R2), and three precleaning units [P1, P2, and P3 (inner diameter $\phi = 1000 \mu m$; length $L = 100 \text{ cm}$)] was used. The flow microreactor system was immersed in a cooling bath (0 °C). A solution of 1b (0.20 M THF; flow rate: 6 mL/min) and a solution of LiDTBB (0.40 M THF; flow rate: 3.6 mL/min) were introduced to M1 ($\phi = 250 \mu m$) using syringe pumps, and the mixed solution was passed through R1 ($\phi = 1000 \mu m$; $L = 3.5 \text{ cm}$). A solution of methanol (1.0 M THF; flow rate: 3.6 mL/min) was introduced to M2 ($\phi = 500 \mu m$) using a syringe pump, and the resulting solution was passed through R2 ($\phi = 1000 \mu m$; $L = 200 \text{ cm}$). After a steady state was reached, the product solution was collected for 20 s and was treated with aqueous HCl. The yield of 2b was determined to be 96% by GC analysis.

4.2. Typical Procedure for the Synthesis of Siloles

The synthesis of 10 is representative (Scheme 3). A flow microreactor system consisting of two T-shaped micromixers (M1 and M2), two microtube reactors (R1 and R2), and three precleaning units [P1, P2, and P3 (inner diameter $\phi = 1000 \mu m$; length $L = 100 \text{ cm}$)] was used. The flow microreactor system was immersed in a cooling bath (0 °C). A solution of 1b (0.20 M THF; flow rate: 6.0 mL/min) and a solution of LiDTBB (0.40 M THF; flow rate: 3.6 mL/min) were introduced to M1 ($\phi = 250 \mu m$) using syringe pumps, and the mixed solution was passed through R1 ($\phi = 1000 \mu m$; $L = 3.5 \text{ cm}$). A solution of Me2SiCl2 (0.20 M THF; flow rate: 3.6 mL/min) was introduced to M2 ($\phi = 500 \mu m$) using a syringe pump, and the resulting solution was passed through R2 ($\phi = 1000 \mu m$; $L = 200 \text{ cm}$). After a steady state was reached, the product solution was collected for 40 s (0.8 mmol scale) and stirred at room temperature. After 2 min, the mixture was treated with saturated aqueous NH4Cl, and the resulting biphasic solution was extracted three times with AcOEt. The combined organic layer was dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane) to give 10 (79.7 mg, 0.274 mmol, 69%) as a yellow solid.

Author Contributions

CRediT: Yiyuan Jiang data curation, formal analysis, investigation, methodology, writing-original draft, writing-review & editing; Hideki Yorimitsu conceptualization, funding acquisition, investigation, methodology, project administration, supervision, writing-review & editing.

Notes

The authors declare no competing financial interest.

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