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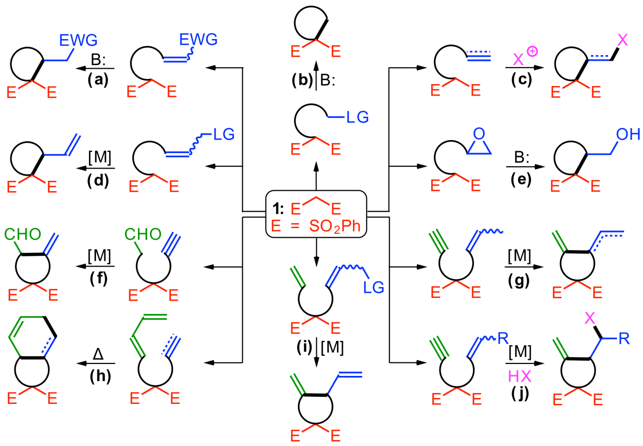
Sulfones as Synthetic Linchpins: Transition Metal-Free sp^3-sp^2 and sp^2-sp^2 Cross-Couplings Between Geminal bis(Sulfones) and Organolithium Compounds

Barry M. Trost* and Christopher A. Kalnmals[a]

Abstract: Herein, we report a valuable umpolung strategy that highlights the ambiphilic nature of the bis(phenylsulfonyl)methyl synthon and demonstrates its utility as a synthetic linchpin. While the bis(phenylsulfonyl)methyl group is typically introduced as an sp^3 carbon nucleophile, we demonstrate that it can also function as an effective sp^2 carbon electrophile in the presence of organolithium nucleophiles. Akyl- and aryllithiums couple with the central carbon of the bis(phenylsulfonyl)methyl unit to ultimately generate trisubstituted alkenes, comprising a formal sp^3-sp^2 and sp^2-sp^2 cross-coupling between organolithiums and bis(sulfones). This process occurs almost instantaneously at -78 °C in the absence of any transition metals. By developing this curious transformation, we demonstrate that bis(phenylsulfonyl)methane is a valuable synthetic linchpin that can undergo two C-C bond formations as an sp^3 nucleophile, followed by a third C-C bond forming reaction as an effective sp^2 electrophile. This discovery significantly enhances the utility of this ubiquitous – but underutilized – linker group.



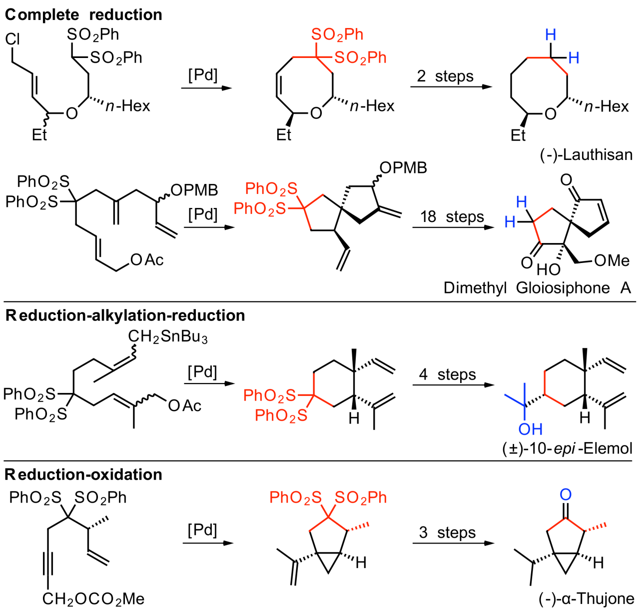
Scheme 1. Some cyclizations facilitated by bis(sulfones).

Introduction

For more than 30 years, bis(phenylsulfonyl)methane (**1**) has been employed as a linker unit in an impressive array of cyclization reactions (Scheme 1). In some cases, the bis(phenylsulfonyl) methyl unit is directly involved in the cyclization step; bis(sulfones) have been employed as nucleophiles in a variety of intramolecular annulations, including conjugate additions (Scheme 1, path a),[1] S_N2 and S_N2' displacements (path b),[2] allylic alkylations (path d),[3] and epoxide openings (path e).[4] Cyclizations can also proceed via the addition of a bis(sulfone) to a π-system – such as an alkene, alkyne, or allene – activated by either a transition metal[5] or an electrophilic halogen source (path c).[6]

More commonly, the bis(phenylsulfonyl) group is employed as a convenient carbon-based linker to facilitate the synthesis of substrates that are subsequently cyclized using other means. This strategy has been extensively employed to assemble precursors for transition metal-catalyzed cycloisomerizations (paths f, g, i, and j). A vast array of bis(sulfones) with assorted alkene, alkyne, and allene side chains have been cyclized using a variety of different metals, including Ag,[7] Au,[8] Ca,[9] Cu,[10] Fe,[11] Ga,[12] In,[13] Ir,[14] Mo,[15] Ni,[16] Pd,[7a-b],[16d],[17] Pt,[7a-b],[8b],[12],[18] Rh,[19] and Ru.[7a-b],[12],[20] bis(Sulfones) have also been used to prepare substrates for intramolecular Barbier[21] and Diels-Alder reactions (path h),[22] as well as a variety of other thermal cycloadditions.[23]

Regardless of whether it participates directly in the ring-closing step or simply facilitates substrate synthesis, the bis(phenylsulfonyl)methyl synthon has been employed in hundreds of cyclization reactions. Unfortunately, while bis(sulfones) are easy to introduce, they are not typically desired in the final products and have limited synthetic utility for future steps, as illustrated by several total syntheses that employ this ubiquitous functional group (Scheme 2). Often, bis(sulfones) are simply fully reduced to the corresponding alkanes, as is done in the syntheses of (-)-lauthisan[3b] and dimethyl gloiosiphone A.[7d]



Scheme 2. Further transformations of bis(sulfones).

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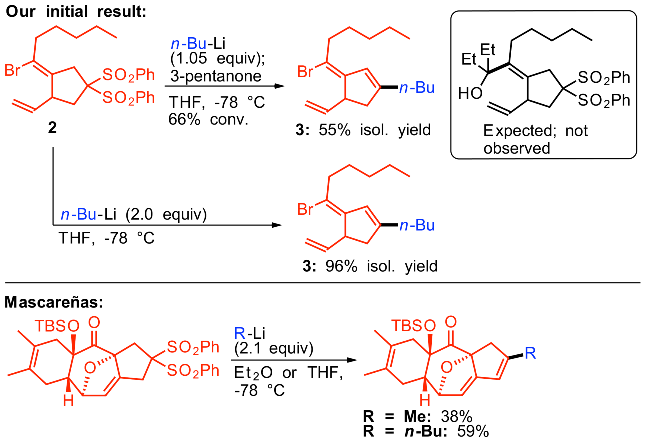
In their synthesis of (±)-10-*epi*-elemol, Echavarren and coworkers employ a three-step partial reduction-alkylation-reduction sequence to install a single new C-C bond.[17m] In a related process, partial reduction followed by oxidation of the sulfone enolate was used in the synthesis of (-)-α-thujone to transform the bis(sulfone) into a ketone.[17n] While this sequence involves both reduction and oxidation steps, the oxidation state of the central carbon of the bis(sulfone) is ultimately unchanged. Given the exemplary utility of bis(sulfonyl) groups in facilitating cyclization reactions, finding new ways to use this functionality for further structural elaboration becomes an important objective.

In the context of our recently published Ru-catalyzed halotropic cycloisomerization,[20g] we encountered an unusual transformation involving a bis(sulfone) and an alkyllithium reagent. When cycloisomerization adduct **2** was treated with 1.05 equivalents of *n*-butyllithium followed by excess 3-pentanone, we were surprised to find that none of the expected tertiary alcohol product had formed (Scheme 3). By crude ^{1}H NMR, only unreacted starting material **2** and triene **3** – which presumably arose via a coupling reaction between the bis(sulfone) and the butyllithium – were present in the reaction mixture. Intrigued by this curious result, we repeated the experiment using 2.0 equivalents of *n*-butyllithium and were delighted to find that triene **3** formed in excellent yield. Notably, the vinyl bromide was still intact, suggesting that the coupling pathway was faster than lithium-halogen exchange. Since lithium-halogen exchange is typically rapid – sometimes faster than even proton transfer – this result was quite striking.[24]



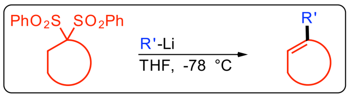
Scheme 3. Coupling of bis(sulfones) with alkyllithiums.

Organosulfones have been dubbed “chemical chameleons” due to their ability to act as both nucleophiles and electrophiles; in addition to stabilizing carbanions, sulfones can also act as leaving groups.[25] Although the mechanism for the formation **3** was not immediately obvious, it was clear that the sulfones performed several orthogonal tasks. After facilitating the synthesis of **2** – which was prepared from bis(phenylsulfonyl)methane **1** using sequential nucleophilic substitutions – one sulfone was displaced during C-C bond formation and the other acted as a leaving group for an elimination reaction. Thus, this eliminative coupling between a bis(sulfone) and an alkyllithium uses a single functional group to perform three distinct tasks.

Upon examining the literature, we found almost no precedence for this unexpected transformation. Apart from an isolated report from Mascareñas and coworkers, who observed a related reaction in their efforts towards the dolastane and spheroane diterpene scaffolds,[23a] couplings between bis(sulfones) and organolithiums are unknown. Given that reactions of this type have not been explored and since reactions that constructively utilize bis(sulfones) are scarce, we set out to further investigate this transition metal-free coupling process.

Results and Discussion

Taking advantage of Falck’s ring-closing Mitsunobu protocol,[2f] several cyclic bis(sulfones) were prepared from diols and bis(phenylsulfonyl)methane **1** and evaluated as coupling partners (Table 1). When bis(sulfone) **4** was treated with *n*-butyllithium, none of the desired eliminative coupling product formed and dihydropyran **5** – which presumably formed via elimination to the vinyl sulfone followed by olefin isomerization – was isolated instead. Compound **6** also failed to generate any of the desired product, leading us to suspect that the protons on the carbon adjacent to the bis(sulfone) needed to be activated in order for the eliminative coupling reaction to occur. To test this hypothesis, vinyl cyclopropane **7**[2a] was subjected to the reaction conditions, but only decomposition was observed. With cyclohexene **8**,[26] a different reaction pathway predominated and sulfone **9** was isolated instead of the expected trisubstituted alkene. To our delight, when tetrahydronaphthalene **10a** was treated with a slight excess of *n*-butyllithium, the expected eliminative coupling adduct **11aa** was formed in 84% yield.



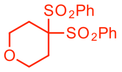
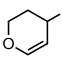
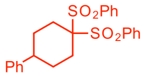
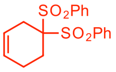
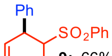
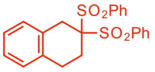
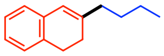
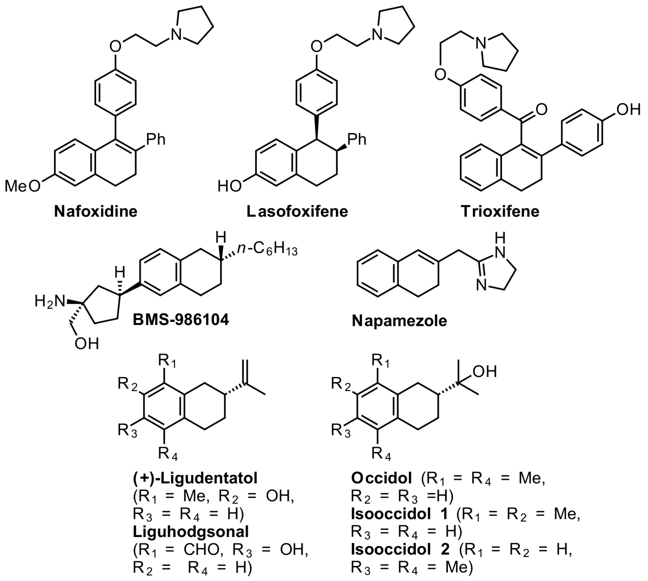
bis(Sulfone)		R'-Li	Result
4		*n*-BuLi (2.0 equiv)	 **5:** yield n.d. No desired prod.
6		*n*-BuLi (2.0 equiv)	Messy; No desired prod.
7		*n*-BuLi (2.1 equiv)	Decomposition; No desired prod.
8		PhLi (2.1 equiv)	 **9:** 66%, 2:1 dr; No desired prod.
10a		*n*-BuLi (2.5 equiv)	 **11aa:** 84%

Table 1. Searching for viable coupling partners.

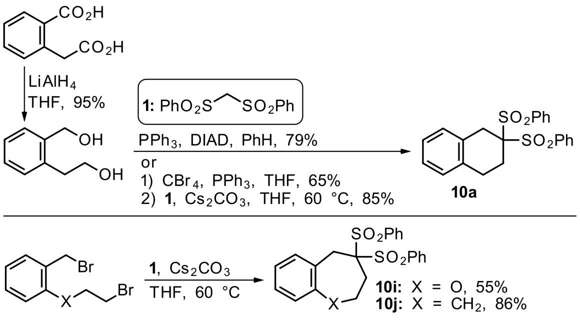
In spite of their high reactivity, there has been recent interest in developing processes that directly utilize organolithium reagents. Such compounds have successfully been used in "on-water" processes[27] and are also attractive nucleophiles in cross-coupling reactions, since they are easy and economical to synthesize via lithium-halogen exchange or direct metallation. In fact, since many common cross-coupling partners – such as organoboron, -zinc, and -tin compounds – are often synthesized from the corresponding lithium compounds, the direct use of the latter is particularly attractive. Along these lines, organolithiums have recently been employed in cross-coupling reactions catalyzed by Pd,[28] Fe,[29] and Ni.[30] Thus, the formation of **11aa** was particularly exciting because it suggested that we could not only use organolithium reagents directly in a cross-coupling reaction, but also do so without any transition metals.

Furthermore, **11aa** represents an important carbon scaffold, since 3-substituted di- and tetrahydronaphthalenes are present in a variety of pharmaceutical compounds and natural products (Scheme 4). Methods for preparing this important class of compounds – particularly when the 3-substituent is an alkyl group – typically rely on transition metal-catalyzed cross-couplings between a vinyl electrophile, such as a halide or triflate, and an organometallic partner, such as a Grignard or alkylzinc reagent. Since we were able to access **11aa** without the use of any transition metals, we quickly set out to explore the scope of this process knowing that if it was general, it would hold a distinct advantage over existing methods for synthesizing 3-substituted 1,2-dihydronapthalenes.

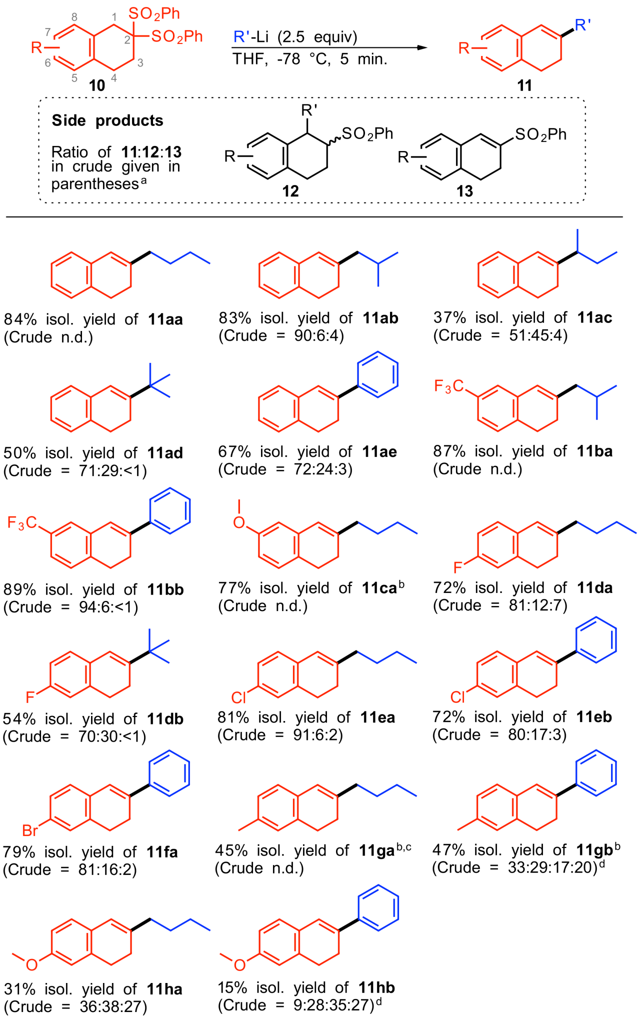


Scheme 4. Pharmaceuticals and natural products containing di- and tetrahydronaphthalenes.

The requisite bis(sulfone) substrates **10** were easily accessed from homophthalic acids[31] and bis(phenylsulfonyl) methane using Falck's Mitsunobu protocol,[2f] though purifications were tedious. As a result, we developed a double S_N2 route that was operationally simpler, easily scalable, and cleanly afforded bis(sulfones) **10** in high yields (Scheme 5). This process nicely highlights the ability of **1** to facilitate cyclizations, as even 7-membered rings **10i** and **10j** could be prepared using this double S_N2 approach.



Scheme 5. Convenient synthesis of bis(sulfone) substrates.



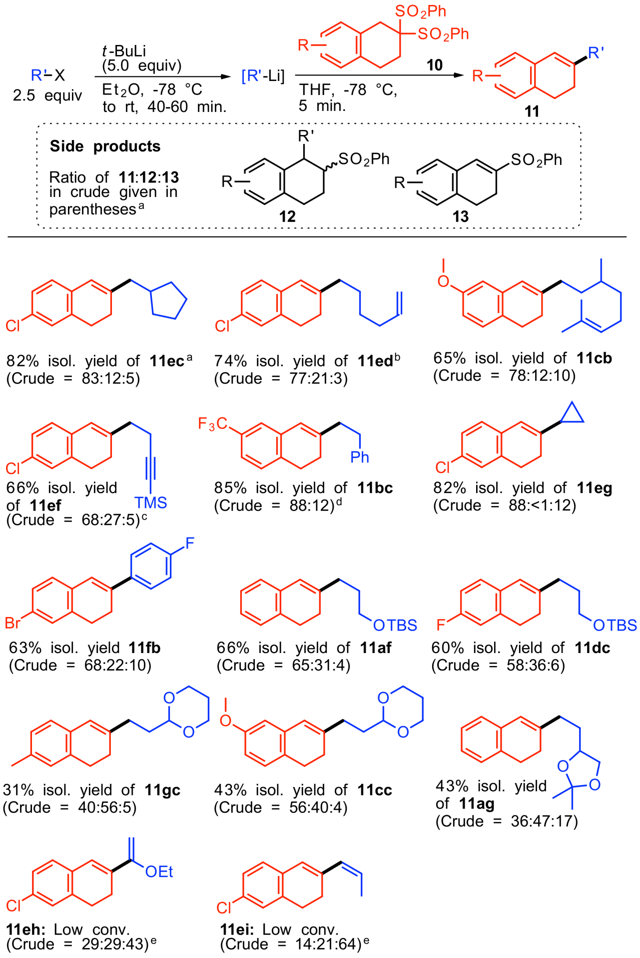
Scheme 6. Coupling reactions between bis(sulfones) and commercial organolithium reagents. For products **11**, the first letter corresponds to the bis(sulfone) **10** employed. All reactions performed on 0.20 mmol scale at 0.1 M unless otherwise noted. [a] Estimated by crude ^{1}H NMR. [b] 0.10 mmol scale. [c] 16% isolated yield of **13g**. [d] Ratio of **11**:**12**:**13**:**10**.

With several substrates in hand, we began exploring the scope of our transition metal-free cross-coupling using a variety of commercial organolithium compounds (Scheme 6). We quickly found that regardless of the partners employed, all reactions were nearly instantaneous, even at -78 ºC. In rare cases where low conversion was observed, increasing the temperature or reaction time had no effect. While most of the reactions examined were very clean, we consistently observed small amounts of **12** and **13**, which were quantified in most cases using crude ^{1}H NMR.

In regards to the bis(sulfone) partner, substrates with inductively electron-withdrawing substituents at the 6- and 7-positions worked best. Of all the bis(sulfones) examined, trifluoromethyl-substituted **10b** gave the best yields, and 7-methoxy **10c** was also a good performer. Halogens were well tolerated, with 6-fluoro- (**10d**), 6-chloro- (**10e**), and 6-bromo- (**10f**) substrates all giving similar results. Notably, lithium-halogen exchange was not a problem when **10f** was treated with phenyllithium. Electron-donating groups at the 6-position were problematic. With 6-methyl substrate **10g**, synthetically useful yields of **11** were still obtained but with a more donating 6-methoxy group (**10h**), products **12** and **13** predominated. Interestingly, ring-expanded **10i** and **10j** were unsuitable coupling substrates, and in both cases mixtures of various vinyl sulfones and other elimination products were observed. When **10i** was treated with isopropylmagnesium chloride, no reaction occurred at -78 °C or 4 °C and at room temperature, only slow decomposition was observed. Thus, Grignard reagents do not appear to participate in the eliminative coupling.

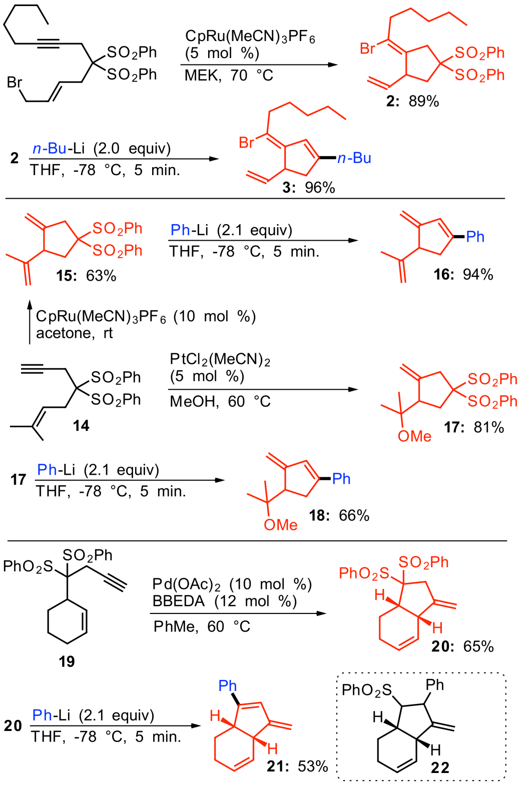
With parent substrate **10a**, primary alkyllithiums performed the best, with *n*-butyllithium (**10aa**) and *iso*-butyllithium (**10ab**) giving identical results. Substituted alkyllithiums also coupled, albeit with slightly reduced yields. With *sec*-butyllithium, the reaction was uncharacteristically messy and a large amount of **12** was observed, along with several other unidentified side products. When *tert*-butyllithium was used, the reaction was clean but the selectivity for **11** slightly decreased. Phenyllithium (**11ae**) was also a viable reaction partner, allowing us to access both sp^2-sp^2 and sp^3-sp^2 coupling products. The trends observed with **10a** were largely conserved with other bis(sulfones); primary alkyllithiums and phenyllithium consistently performed well, while *tert*-butyllithium was slightly less selective for **11**. Regardless of the bis(sulfone) employed, methyllithium cleanly afforded vinyl sulfone **13** with no trace of coupling products **11** or **12**. This is presumably due to the reluctance of methyllithium tetramer to deaggregate, which renders it less reactive than other organolithium reagents.[32]

Next, we shifted our focus from commercial lithium compounds to more functionalized organometallics (Scheme 7). A variety of hydrocarbon-derived nucleophiles gave good results, including alkyllithiums containing alkenes (**11ed**, **11cb**), alkynes (**11ef**), and phenyl groups (**11bc**). Using cyclopropyllithium, we were able to generate **11eg** in excellent yield—a noteworthy result, considering the utility of vinylcyclopropanes in thermal rearrangements and transition metal-catalyzed processes.[34] As previously observed, an aryllithium coupled with bromide **10f** without any competing lithium-halogen exchange. Oxygen-containing organolithium reagents were also suitable coupling partners. While a silyl ether was not problematic (**11af**, **11dc**), acetal- and ketal-containing alkyllithiums (**11gc**, **11cc**, **11ag**) were less selective for **11**. Interestingly, while aryllithiums were suitable coupling partners, non-aromatic sp^2 nucleophiles gave low conversion (**11eh**, **11ei**).



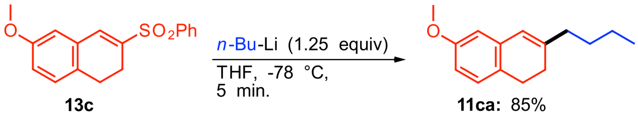
Scheme 7. Coupling reactions between bis(sulfones) and freshly prepared organolithium reagents. All reactions performed on 0.20 mmol scale at 0.1 M. Ratios of **11**:**12**:**13** are given in parentheses and were estimated by crude ^{1}H NMR. [a] Organolithium was prepared by thermal rearrangement of 5-hexenyllithium.[33] [b] Organolithium kept at -78 ºC to avoid rearrangement. [c] Ratio of **11**:**12**:**10**. [d] Ratio of **11**:**12**. [e] Ratio of **11**:**13**:**10**.

Given the ubiquity of bis(sulfones) in cycloisomerization substrates and in light of our initial success with **2**, we next set out to determine whether our eliminative coupling would apply to other cycloisomerization products and were pleased to find that the reaction was quite general (Scheme 8). Using CpRu(MeCN)$_3$PF$_6$, enyne **14** was isomerized into cyclopentadiene **15**,[20a] which cleanly underwent coupling with phenyllithium to afford triene **16** in excellent yield. By changing the catalyst system to PtCl$_2$(MeCN)$_2$ in methanol,[18b] **14** was transformed into tertiary ether **17**, which was also a viable substrate for our transition metal-free coupling reaction. With 2.1 equivalents of phenyllithium, 91% conversion occurred and diene **18** was isolated in 66% yield. Bicyclic sulfone **20**, which was prepared via Pd-catalyzed isomerization of enyne **19**,[35] gave rise to coupled triene **21** in 53% yield. In this case, an appreciable amount of **22** was isolated, presumably due to increased steric demands adjacent to the bis(sulfone) center.



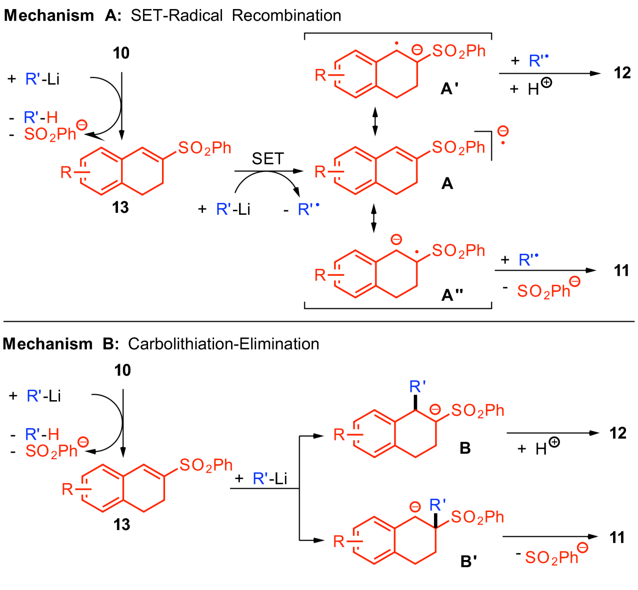
Scheme 8. Coupling reactions between cycloisomerization products and organolithium reagents.

While the mechanism for our eliminative coupling was not immediately obvious, we suspected that vinyl sulfone **13** acted as an intermediate in the reaction. This proposal seemed reasonable, since the base-promoted elimination of sulfinate anion from geminal sulfones is facile[36] and since we observed small amounts of **13** in nearly every coupling reaction we studied. To test this hypothesis, an isolated sample of **13c** was subjected to the reaction conditions (Scheme 9). Upon treatment with 1.25 equivalents of *n*-butyllithium, **13c** was cleanly and rapidly transformed into **11ca**, suggesting that **13** was indeed involved in the coupling pathway.



Scheme 9. Testing a vinyl sulfone as an intermediate.

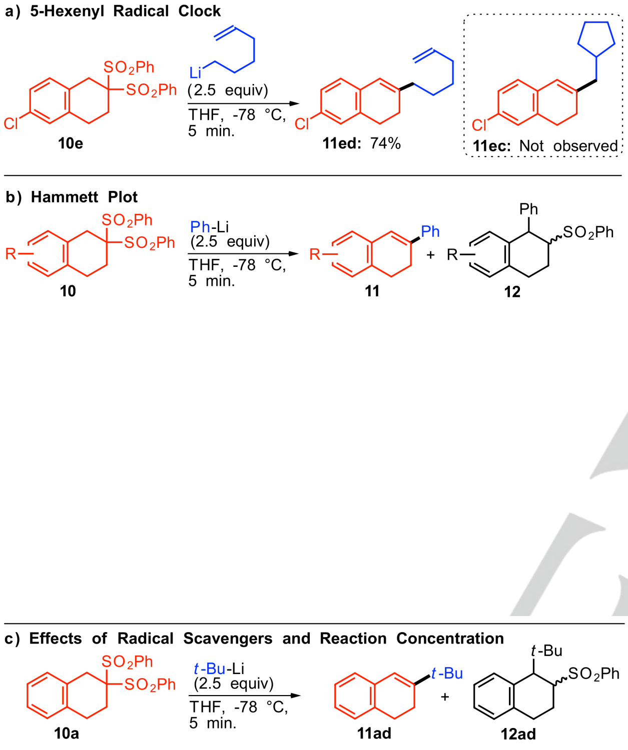
Having identified **13** as a likely intermediate, we envisioned two possible mechanisms to account for the formation of **11** and **12** (Scheme 10). The first pathway (Mechanism A) involves single electron transfer (SET) from the organolithium to vinyl sulfone **13**, giving rise to radical anion **A**.[37] Radical recombination with resonance form **A'** would give rise to **12**, whereas recombination with **A"** would, after E1cB elimination, generate **11**. Mechanism B involves direct carbolithiation of the vinyl sulfone. Attack at the benzylic position of the olefin would produce **12** via **B**, whereas addition to the sulfone carbon would lead to **11** via **B'**.



Scheme 10. Proposed mechanisms.

To probe the mechanism, we first employed 5-hexenyllithium as a potential radical clock (Scheme 11a). The 5-hexenyl radical irreversibly and rapidly cyclizes to the cyclopentylmethyl radical, so if an SET mechanism was operative, a mixture of coupling products could potentially result. When **10e** was treated with 5- hexenyllithium, only the open chain product **11ed** formed; none of the cyclized product **11ec** (which was prepared independently for comparison) was observed by crude ^{1}H NMR. While the absence of **11ec** is consistent with an anionic mechanism, it could also be attributed to a radical intermediate with a lifetime shorter than the radical clock. Although the 5-hexenyl radical cyclizes quickly at room temperature ($k = 1 \times 10^5$), the rate at -78 °C is significantly slower ($k = 130$).[38]

Fortunately, Hammett data provided some useful mechanistic insights (Scheme 11b). A series of bis(sulfones) **10** was treated with phenyllithium under the optimized reaction conditions, then the ratio of desired product **11** to conjugate addition product **12** was assessed by crude ^{1}H NMR. Qualitatively, substituents with positive σ values (relative to the benzylic position on the olefin) promoted the formation of **11**, whereas electron-donating substituents favored the formation of **12**. When the ratio of **11**:**12** was plotted against standard σ values, a good linear fit was obtained (R^2 = 0.87) with ρ = 1.89. Using σ^- values[39] – which account for discrete negative charges better than standard σ values – gave a slightly better fit (R^2 = 0.94) with ρ = 1.96. In contrast, poor fits were obtained when the ratio of **11**:**12** was plotted against a variety of radical-based substituent parameters, including $\sigma_J^\cdot$ (R^2 = 0.33),[40] $\sigma_\alpha^\cdot$ (R^2 = 0.33),[41] $\sigma_C^\cdot$ (R^2 = 0.34),[42] $\sigma_F^\cdot$ (R^2 = 0.67),[43] and $\sigma_{JJ}^\cdot$ (R^2 = 0.10).[44] The lack of any correlation to a variety of $\sigma^\cdot$ constants argues against an SET mechanism; if radical anion **A** was an intermediate, groups with $\sigma^\cdot > 0$ would be expected to favor the formation of **12**.



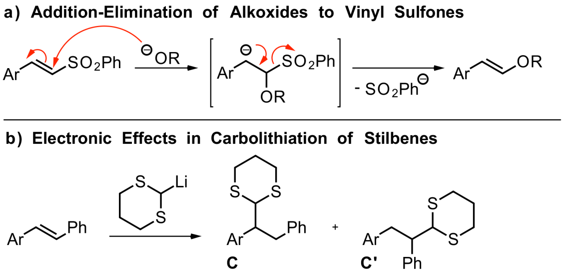
Conditions	11ad	12ad
Standard (0.1M, no additives)	71	29
0.3 M, no additives	71	29
0.1 M w/ 1 eq. α-methylstyrene	77	23
0.1 M w/ 1 eq. 1,4-dinitrobenzene	76	24

Scheme 11. Mechanistic experiments.

Radical trapping experiments (Scheme 11c) lent further support to anionic Mechanism B. In evaluating the addition of *t*-butyllithium to cinnamic acids, Mestres and coworkers successfully used α-methylstyrene and 1,4-dinitrobenzene as radical traps.[45] In our hands, neither compound had any appreciable impact on the selectivity of the coupling process. α-Methylstyrene had no effect on the coupling of **10a** with *t*-butyllithium and while low conversion was observed with 1,4-dinitrobenzene, the ratio of **11ad**:**12ad** was again unaffected. In both cases, the reactions were very clean and no products incorporating either of the radical traps were observed. Increasing the concentration threefold – which should increase the probability of crossover products if radical intermediates are involved – also had no effect on the course of the reaction or on the ratio of **11ad**:**12ad**.

Another piece of evidence in favor of an anionic mechanism is the lack of rearrangement products. Reactions that proceed via benzylic radical anions – such as the alkylation of benzophenone ketyls[46] and anils;[47] the addition of organolithiums to aromatic imines;[48] and the oxidative coupling of dilithiated carboxylic acids[49] – typically generate aromatic substitution products resulting from migration of the radical into the benzene ring. In all of the reactions we examined, we never observed any evidence of such rearrangements. Finally, the similarities in reactivity and selectivity observed with *t*-butyllithium and phenyllithium are not consistent with a radical pathway. While *t*-butyllithium readily undergoes single-electron transfer, phenyllithium is reluctant to do so.[50] If radical intermediates were involved, these two organometallics should behave differently, which is not the case here.

While differentiating between radical and polar mechanisms is difficult when dealing with organolithium additions,[51] we feel that our experimental evidence is most consistent with Mechanism B, especially since organolithium reagents are known to readily carbolithiate olefins – especially styrenes – at cryogenic temperatures.[52] Since vinyl sulfones are often employed as Michael acceptors,[53] a process that invokes preferential attack at the α-carbon may at first seem dubious. In fact, such *contra*-Michael additions have been reported with a variety of traditional Michael acceptors.[54] More specifically, a *contra*-Michael addition-elimination pathway nearly identical to Mechanism B has been invoked on multiple occasions to explain the formation of vinyl ethers when styryl sulfones are treated with alkoxides (Scheme 12a).[55]



Ar	C	C'
p-MeOC$_6$H$_4$	98	2
p-MeC$_6$H$_4$	96	4
p-ClC$_6$H$_4$	5	95

Scheme 12. Related processes.

In their studies on 1,3-dipolar cycloadditions with nitrile oxides, Caramella *et. al.* calculated the LUMO of (*E*)-methyl styryl sulfone and found that the orbital coefficients of the carbons α- and β- to the sulfone had nearly identical magnitude (-0.442 and +0.436, respectively).[56] Taken together with the work of She and coworkers, who demonstrated that carbolithiations of stilbenes are extremely sensitive to subtle electronic effects (Scheme 12b),[57] this could explain the trends in selectivity we observe. An electron-deficient aromatic ring may skew the polarization of vinyl sulfone **13** such that the α-position is marginally more electrophilic than the β-position, favoring *contra*-Michael addition to generate **11**. With electron-rich aromatic rings, "standard" polarization predominates and 1,4-addition is preferred. The larger amounts of **12** formed with non-primary organolithiums (e.g. *t*-BuLi, *s*-BuLi, ArLi) is likely due to steric interactions between the nucleophile and the sulfone, which has a cyclohexane *A*-value of 2.5 (identical to a trimethylsilyl group) and is thus reasonably large.[58]

Conclusions

We report a transition metal-free coupling process whereby bis(sulfones) combine with organolithium reagents to generate trisubstituted alkenes, likely via a carbolithiation-elimination mechanism. This process, which occurs cleanly and instantaneously at -78 °C, exhibits remarkable functional group compatibility in spite of the extreme reactivity of the nucleophiles involved; aryl and vinyl bromides, alkenes, alkynes, ethers, and acetals are all tolerated. Notably, our method can be used to easily perform both sp^2-sp^2 and sp^3-sp^2 cross-couplings, the latter of which can be challenging when using transition metal catalysis. In addition to giving ready access to a diverse library of 3-substituted dihydronaphthalenes, which are important skeletons found in both natural products and pharmaceuticals, our method easily extends to a variety of cycloisomerization products. We demonstrate that the bis(phenylsulfonyl) group is not just a convenient linker, but rather a valuable synthetic linchpin that can be introduced as an sp^3 nucleophile and transformed into an effective sp^2 electrophile. This umpolung strategy greatly increases the utility of the ubiquitous-but-underutilized bis(phenylsulfonyl) moiety and nicely highlights the ability of sulfones to act as chemical chameleons.

Experimental Section

Representative procedure for cross-coupling of a commercial organolithium with a bis(sulfone)

A flame-dried 3-dram vial was charged with bis(sulfone) **10a** (82.5 mg, 0.200 mmol, 1.00 equiv), sealed with a septum, and evacuated and backfilled with N_2 three times. Freshly distilled THF (2.0 mL) was added, and the resulting solution was cooled to -78 °C. A solution of *n*-butyllithium (2.73 M in hexanes; 0.18 mL, 0.50 mmol, 2.5 equiv) was added dropwise. After 5 minutes at -78 °C , the reaction was quenched with water (2 mL) at -78 °C. After warming to room temperature, the reaction was extracted with Et_2O (3 × 2 mL) and the combined organic layers were passed through a plug of $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography (800 mg silica, petroleum ether) to afford **11aa** as a clear colorless oil. (31.2 mg, 84%)

Representative procedure for cross-coupling of a freshly prepared organolithium with a bis(sulfone)

A flame-dried 2-dram vial was charged with phenethyl iodide (116 mg, 0.50 mmol, 2.5 equiv), sealed with a septum, and evacuated and backfilled with N_2 three times. Anhydrous Et_2O (1.0 mL) was added, the resulting solution was cooled to -78 °C, and *t*-butyllithium (1.63 M in pentane; 0.61 mL, 1.0 mmol, 5.0 equiv) was added dropwise. The reaction was stirred for 20 minutes at -78 °C, then the cooling bath was removed and the reaction was stirred for an additional 25 minutes. Meanwhile, a flame-dried 3-dram vial was charged with bis(sulfone) **10b** (96.1 mg, 0.200 mmol, 1.00 equiv), sealed with a septum, and evacuated and backfilled with N_2 three times. Freshly distilled THF (1.0 mL) was added, and the resulting solution was cooled to -78 °C at which point the room temperature organolithium solution was added dropwise via syringe. Five minutes after the addition, the reaction was quenched with water (2 mL) at -78 °C. After warming to room temperature, the reaction was extracted with Et_2O (3 × 2 mL) and the combined organic layers were passed through a plug of $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography (1.2 g silica, 15:1 petroleum ether/CH_2Cl_2) to afford **11bc** as a clear colorless oil. (51.1 mg, 85%)

Experimental procedures and characterization for all compounds (including starting materials); $^1H/^{13}C$ NMR spectra for compounds **2**, **3**, **10**, **11**, **13c**, **16**, **18**, **20**, and **21**; and raw data for Hammett plots are included in the supporting information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: sulfone • organolithium • umpolung • transition metal-free • cross-coupling

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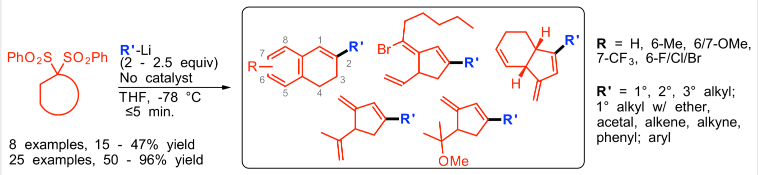

Shape-Shifting Sulfones: The bis(phenylsulfonyl)methyl synthon is widely employed as a nucleophilic sp^3 linker unit, but has limited utility for future steps. We demonstrate that this ubiquitous group can act as an effective sp^2 electrophile in the presence of organolithium reagents.This valuable umpolung approach greatly enhances the synthetic utility of this common linker group and highlights the ability of sulfones to act as chemical chameleons.

Prof. Dr. Barry M. Trost and Christopher A. Kalnmals*

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Sulfones as Synthetic Linchpins: Transition Metal-Free sp^3-sp^2 and sp^2-sp^2 Cross-Couplings Between Geminal bis(Sulfones) and Organolithium Compounds