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SO₂ Conversion to Sulfones: Development and Mechanistic Insights of a Sulfonylative Hiyama Cross-Coupling

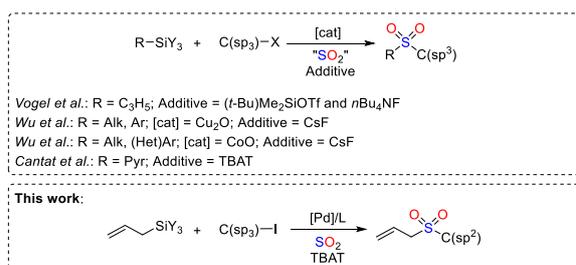
Aurélien Adenot,^a Joëlle Char,^a Niklas von Wolff,^a Guillaume Lefèvre,^a Lucile Anthore-Dalion,^a Thibault Cantat^{a*}

A sulfonylative Hiyama cross-coupling reaction using gaseous SO₂ is described, using Pd-catalysts. The use of silicon-based nucleophiles leads to the formation of allyl sulfones under mild conditions with a broad functional group tolerance. Control experiments coupled with DFT calculations shed light on the key steps of the reaction mechanism, revealing the crucial role of a transient sulfinate anion.

Present in many contemporary pharmaceuticals, agrochemicals and materials (e.g. the antibiotic Thiamphenicol or the herbicide Pyroxasulfone), sulfones are also used as key intermediates in organic synthesis^{1,2} (e.g. the Julia olefination³ or the Ramberg-Bäcklund reaction⁴). Given this combination of a prominent biological activity and an appealing synthetic utility, numerous methodologies have been developed for their preparation.¹ Because it has a high atom-efficiency, the insertion of a sulfur dioxide molecule upon coupling a nucleophile with an electrophile has recently emerged as a valuable route.⁵ Organomagnesium,⁶ organozinc⁷ and organoboron⁸ compounds were successively reported as nucleophiles; yet, they suffer from toxicity issues, functional group incompatibility, and/or air-sensitivity.⁹

Because they are readily available, air-stable and show an improved functional-group tolerance, organosilanes were recently considered to produce sulfones from SO₂ or SO₂ surrogates.¹⁰ However, up-to-date methods are still limited to sp³-hybridized electrophiles, which react through S-alkylation after the formation of an intermediate sulfinate anion (Scheme 1). Unlocking the utilization of sp²-hybridized electrophiles would require a change of mechanism; and, to tackle this issue, we report herein the first sulfonylative Hiyama cross-coupling affording sulfones from organosilanes, sulfur dioxide and aryl iodides, in a single-step reaction (Scheme 1). Mechanistic

control experiments, combined with DFT calculations performed on the key reaction steps, provide insight into the mechanism of the reaction.



Scheme 1. Representative state-of-the-art of sulfone synthesis from SO₂ and organometallic compounds.

Shortly after the discovery of the eponymous coupling, Hiyama *et al.* reported the carbonylative coupling of aryl iodides with organosilanes in the presence of a palladium catalyst (Figure 1a).¹¹ SO₂ is both more electrophilic and nucleophilic than CO,¹² and its frontier orbitals are centered on the sulfur atom as they are on the carbon atom of carbon monoxide (Figure 1c). Besides, the migratory insertion of SO₂ in a Pd–C bond has already been reported by Goddard and co-workers (Figure 1b).¹³ We hence hypothesized the feasibility of a sulfonylative Hiyama cross-coupling.

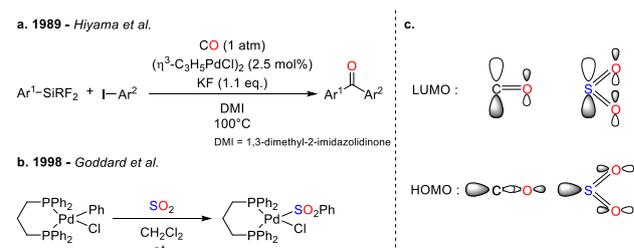
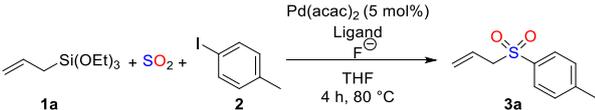


Figure 1. a) First example of a carbonylative Hiyama cross-coupling; b) Insertion of SO₂ in a Pd–C bond; c) Frontier orbitals of CO and SO₂.

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Table 1. Influence of the reaction conditions on the sulfonylative Hiyama cross-coupling of triethoxy(allyl)silane (**1a**) with 4-iodotoluene (**2**) (see Table S1 for a more exhaustive table).^a



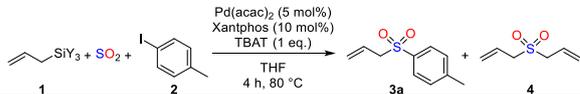
Entry	Fluoride source (eq.)	SO ₂ source (eq.)	Ligand (%)	Yield in 3a (%)
1	TBAF·3H ₂ O (1)	SO ₂ ^b (1)	-	12
2	TBAF·3H ₂ O (1)	DABSO (0.5)	-	0
3	TBAT (1)	SO ₂ ^b (1)	-	17
4	TBAT (1)	SO ₂ ^b (2)	-	26
5	TBAT (1)	SO ₂ ^b (4)	-	0
6	TBAT (1)	SO ₂ ^b (2)	XPhos (10)	41
7	TBAT (1)	SO ₂ ^b (2)	Xantphos (10)	78
8	TBAT (1)	SO ₂ ^b (2)	Xantphos (5)	65
9	TBAF (1M in THF) (1)	SO ₂ ^b (2)	Xantphos (10)	71

^aResults obtained in THF at 80 °C during 4 h on a 0.1 mmol scale. ^bSO₂ was generated by thermal decomposition of K₂S₂O₅, see Supporting Information. TBAF = tetrabutyl ammonium fluoride; TBAT = tetrabutylammonium difluorophenyl-silicate. Yields measured by ¹H NMR (internal standard: mesitylene).

We began our investigation by exploring the coupling of triethoxy(allyl)silane (**1a**), 4-iodotoluene (**2**), and gaseous sulfur dioxide, generated by thermal decomposition of K₂S₂O₅ in a two-chamber apparatus (see Supporting Information). In the presence of Pd(acac)₂ as a catalyst and TBAF·3H₂O as a fluoride source to activate the weakly polar C–Si bond, the desired sulfone **3a** was obtained in 12% yield (Table 1, entry 1). By contrast, the bench stable surrogate of SO₂, DABSO, popularized by Willis *et al.*,¹⁴ gave no desired product (Table 1, entry 2), presumably due to the coordination of the DABCO by-product to palladium. Changing the fluoride source to the anhydrous tetrabutylammonium difluorophenyl-silicate (TBAT) improved the reaction efficiency (17% yield, Table 1, entry 3). While two equivalents of SO₂ increased the yield up to 26% (Table 1, entry 4), an excess of SO₂ was detrimental to the reaction (Table 1, entry 5), possibly because of a poisoning of the catalyst. After screening a variety of palladium sources and phosphine ligands (Table 1, entries 5–7 and Table S1), a set of conditions (Pd(acac)₂ 5 mol%, Xantphos 10 mol%, TBAT 1 eq.) gave the best results in our hands, yielding the desired sulfone **3a** in 78% yield (Table 1, entry 7). No reaction took place without the catalyst, even after 24 h (Table S1).

During the screening process, the diallyl sulfone (**4**) was identified as a side-product. The relative proportion of **4** was found to depend directly on the nature of the substituents at the silicon atom (Table 2): the quantity of diallyl sulfone (**4**) increases with the fluoride-affinity of the organosilane (computed by the Gibbs free energy variation for the fluoride transfer from Me₃SiF₂[–] to the allylsilane). As a result, tri(ethoxy)allyl silanes were selected to explore this new reaction, as it provides the best balance between selectivity and productivity (see SI).

Table 2. Formation of the diallyl sulfone (**4**) as a side-product.

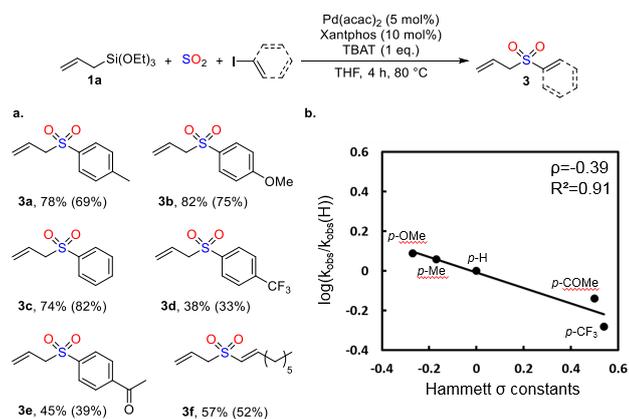


Y ₃	Yield 3a (%)	Yield 4 (%)	4/3a ratio	ΔG ^a (kcal.mol ⁻¹)
(OMe) ₃ (1b)	51	23	0.45	2.98
(OEt) ₃ (1a)	78	10	0.13	3.60
Me ₂ (OMe) (1c)	74	7	0.09	11.94
Me ₃ (1d)	54	0	0	15.60

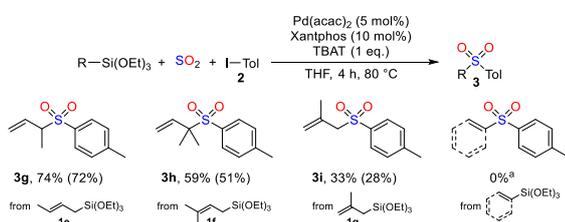
^aGibbs free energy variation for the fluoride transfer from Me₃SiF₂[–] to allylsilanes **1** (see SI for computational details). Yields measured by ¹H NMR (internal standard: mesitylene).

The chosen reaction conditions enabled the synthesis of allyl arylsulfones **3a–3e** from aryl iodides bearing electron-donating substituents as well as electron-withdrawing in 38–82% yield. The reaction tolerates well the presence of a ketone group and **3e** was formed in 45% yield. Interestingly, sulfones bearing electron-donating substituents **3a–3b** were obtained in better yields (78–82%) than the ones bearing electron-withdrawing substituents (**3d–3e**, 38–45%, Scheme 2a), as reflected by a Hammett correlation with a slope of ρ = -0.39 (Scheme 2b). Alkenyl sulfone **3f** was also prepared in 57% yield (Scheme 2a). Using aryl bromides, diallyl sulfone (**4**) was exclusively formed, presumably due to the more difficult activation of the C–Br bond by oxidative addition.

As regards the nucleophile, methyl-substituted allylsilanes **1e–1g** successfully provided the desired sulfones in 33–74% yields, with the selective formation of the α-substituted sulfones from the corresponding γ-substituted allylsilanes, while the classical Hiyama cross-coupling reaction using substituted allylsilanes usually faces regioselectivity issues.¹⁵ Disappointingly, triethoxy(phenyl)silane and triethoxy(vinyl)silane exhibited no reactivity (Scheme 3).



Scheme 2. a) Substrate scope in organiodides; b) Hammett plot of the reaction. Reaction conditions: electrophile (1 eq.), allylSi(OEt)₃ (**1a**, 1.1 eq.), electrophile (1 eq.), SO₂ (2 eq., generated by thermal decomposition of K₂S₂O₈, see SI), TBAT (1 eq.), Pd(acac)₂ (5 mol%), Xantphos (10 mol%), THF, 80 °C, 4 h. Yields measured by ¹H NMR (internal standard: mesitylene). Yields of isolated products from scaled-up experiments (1 mmol scale) are given within parentheses. †



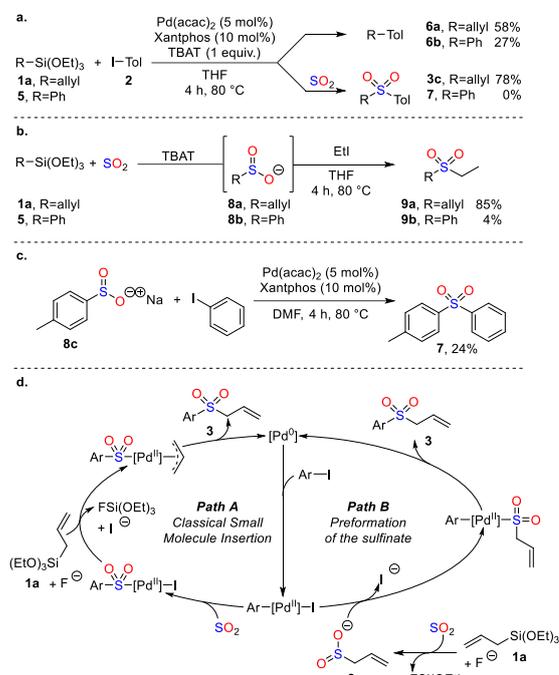
Scheme 3. Substrate scope in organosilanes. †In the case of aryl- and vinylsilane, the nucleophile were fully recovered. Reaction conditions: organosilane (1.1 eq.), 4-iodotoluene (**2**, 1 eq.), SO₂ (2 eq., generated by thermal decomposition of K₂S₂O₈, see SI), TBAT (1 eq.), Pd(acac)₂ (5 mol%), Xantphos (10 mol%), THF, 80 °C, 4 h. Yields measured by ¹H NMR (internal standard: mesitylene). Yields of isolated products from scaled-up experiments (1 mmol scale) are given within parentheses. ‡

These surprising results prompted us to conduct mechanistic control experiments. The catalytic system is an efficient catalyst in Hiyama couplings and, in the absence of SO₂, 1-allyl-4-methylbenzene (**6a**) and biphenyl (**6b**) were formed from triethoxy(allyl)silane (**1a**) and triethoxy(phenyl)silane (**5**), respectively (Scheme 4a). Nevertheless, in the presence of SO₂, sulfone **3a** was obtained in 78% yield, while the corresponding diarylsulfone **7** was not observed starting from phenylsilane **5**. These observations demonstrate that the successful formation of sulfones **3a–3i** cannot be explained by a direct transposition of the mechanism reported for carbonylative cross-couplings,¹⁶ where the insertion of the small molecule occurs after the oxidative addition (*path A*, Scheme 4d).

Careful ¹H NMR monitoring of the reaction revealed the formation of the allylsulfinate anion **8a** as an intermediate (Figure S3). Another pathway was hence devised, where **8a** is involved in a ligand exchange after an oxidative addition step (*path B* in Scheme 4d). The desired sulfone **3** would then be obtained through a reductive elimination step.

To probe the role of transient sulfinate anions, the organosilane nucleophiles **1a** and **5** were reacted with SO₂ and ethyl iodide, in the absence of the palladium catalyst. While sulfone **9a** was formed in 85% yield from the allylsilane, only 4% of the ethylphenylsulfone **9b** were observed, suggesting that the

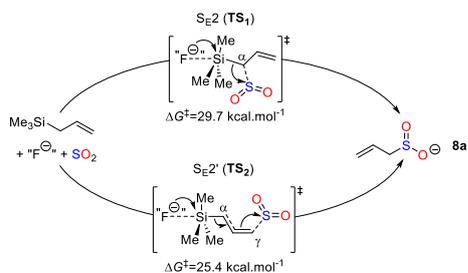
formation of phenylsulfinate from triethoxy(phenyl)silane (**5**) is blocked (Scheme 4b). This finding was confirmed when diarylsulfone **7** was obtained in 24% yield from the preformed arylsulfinate **8c** was exposed to phenyl iodide, in the presence of the palladium catalyst (Scheme 4c). All together, these data support path B in Scheme 4d, with the metal catalyst enabling the coupling between a transient sulfinate anion and the arylhalide electrophile.



Scheme 4. Mechanistic control experiments: a) Comparison between Hiyama cross-coupling and the sulfonylative version; b) in situ sulfinate formation; c) Direct cross-coupling of aryl sulfinate **7c** with phenyl iodide (DMF was used for solubility of **8c**, see SI for more details); d) Proposed pathways for the mechanism of the reaction. Yields measured by ¹H NMR (internal standard: mesitylene).

The regioselectivity observed with substituted allylsilanes (Scheme 3) readily derives from this mechanism. With an allylic nucleophile, the sulfinate formation can proceed through two different mechanisms: either a bimolecular electrophilic substitution at the α position of the silane (**TS₁**, Scheme 5), or the corresponding S_E2' mechanism with formation of the C–S bond at the γ position (**TS₂**, Scheme 5).⁵ DFT calculations revealed that the S_E2' path ($\Delta G^\ddagger(\text{TS}_2) = 25.4 \text{ kcal}\cdot\text{mol}^{-1}$) is favored over the corresponding *ipso* reaction ($\Delta G^\ddagger(\text{TS}_1) = 29.7 \text{ kcal}\cdot\text{mol}^{-1}$). Besides in the case of trimethyl(aryl)silane, for which only **TS₁** can be considered, the transition state lies 34.0 kcal·mol⁻¹ higher than the starting materials, which explains its lack of reactivity.

In classical Hiyama cross-coupling reactions, the rate-determining step (RDS) is usually the transmetalation.¹⁷ Here, the pre-formation of a sulfinate anion circumvents such a transmetalation and the Pd-catalyst instead mediates the formation of the second C–S bond, connecting the electrophile and the SO₂ fragment. According to the Hammett plot (Scheme 2b), the rate-determining step of the catalytic reaction is facilitated with electron-rich electrophiles ($\rho < 0$), suggesting that the rate-determining step is the reductive elimination,¹⁸ rather than the oxidative addition.¹⁹



Scheme 5. Computed reaction pathways for the formation of the sulfinate via S_E2 or S_E2' . Level of theory: B3LYP/G-D3/6-311+G(d) (C, H, O) and 6-311++G(d,p) (F, S, Si), PCM was used for THF solvation. Values given correspond to Gibbs free energies with respect to the starting materials ($G=0.0$ kcal.mol⁻¹). "F⁻" stands in fact for the anion FSO₂⁻.⁵⁵

In fact, the energy barrier computed for the reductive elimination of an allylsulfone from (allylSO₂)–Pd(PMe₃)₂–Ph is high, at 37.1 kcal.mol⁻¹ (compared to 23.2 kcal.mol⁻¹ for allyl–Pd(PMe₃)₂–Ph). Importantly, the DFT calculations also point to the positive influence of electron-donating groups on the kinetics of this step, in agreement with the slope of the experimental Hammett plot (Figure 2). Hartwig *et al.* have shown that the formation of C–S bonds by reductive elimination from Pd(II) thiolate complexes are, on the contrary, facilitated with electron-deficient aryl partners.²⁰ The inverse trends may be attributed to the lower nucleophilicity of the sulfinate anion compared to the thiolate anion, the lone pair of the sulfur atom being partly delocalized on the two oxygen atoms (Figure 2).

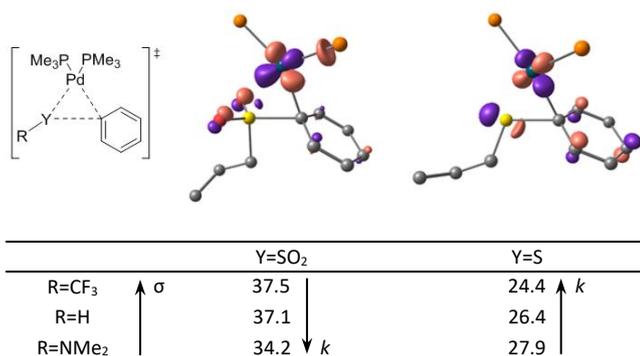


Figure 2. Representations of the HOMO in the transition states for the reductive elimination from (allylY)–Pd(PMe₃)₂–Ph (with Y=SO₂ or S, hydrogens and methyl groups from PMe₃ were omitted for clarity) and Gibbs free energy of the transition states ($\Delta G^\ddagger(\text{TS})$) with respect to the starting material ($G=0.0$ kcal.mol⁻¹). Level of theory: B3LYP/G-D3/6-311+G(d) (C, H, O, N, F), 6-311++G(d,p) (P, S) and SDD (Pd), PCM was used for THF solvation.

In conclusion, we have developed a practical palladium-catalyzed synthesis of allyl aryl sulfones from readily available organosilanes, aryl halides, and sulfur dioxide. This process represents the first approach that introduces a sp²-hybridized electrophile with an organosilane in a sulfonylative cross-coupling. Experimental and theoretical investigations have demonstrated the key role of transient sulfinate anions and their coupling with the aryl halides, mediated by palladium, and they highlight the challenges facing the synthesis of diaryl sulfones from organosilanes.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ As shown in Entry 9 of Table 1, TBAF (1M in THF) is a competent fluoride source and it was used for scaled-up experiments to avoid the formation of the allyl phenyl sulfone **3c** from TBAT.

§ As shown in the SI, the unimolecular pathway has to be discarded, the fluoride transfer from the fluoride source to the organosilane and subsequent C–Si bond scission of the hypervalent species being too energetically demanding.

§§ As already reported,^{10d} and experimentally evidenced (see SI), the fluoride anion is actually transferred to SO₂ to yield the stable anion FSO₂⁻ which acts as the fluoride source.

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