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RESEARCH ARTICLE

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Design of a New SO_2-Surrogate and Its Applications in Palladium-Catalyzed Direct Aminosulfonylations between Aryl Iodides and Amines

Xiuwen Jia,[a] Søren Kramer,[b] Troels Skrydstrup[c] and Zhong Lian*[a]

[a] X. Jia, Prof. Dr. Z. Lian
Department of Dermatology, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital
Sichuan University
Chengdu 610041 (China)
E-mail: lianzhong@scu.edu.cn

[b] Prof. Dr. S. Kramer
Department of Chemistry
Technical University of Denmark
2800 Kgs. Lyngby, Denmark

[c] Prof. Dr. T. Skrydstrup
Carbon Dioxide Activation Center, Interdisciplinary Nanoscience Center (iNANO) and Department of Chemistry
Aarhus University
Gustav Wieds Vej 14, 8000 Aarhus C, Denmark

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***Abstract**: A new SO_2-surrogate is reported which is cheap, bench-stable, and can be accessed in just two steps from bulk chemicals. Essentially complete SO_2-release is achieved in 5 minutes. Eight established sulfonylation reactions proceeded smoothly by ex-situ formation of SO_2 utilizing a two-chamber system in combination with the SO_2-surrogate. Furthermore, we report the first direct aminosulfonylation between aryl iodides and amines. Broad functional group tolerance is demonstrated, and the method is applicable to pharmaceutically relevant substrates, including heterocyclic substrates.*

Introduction

The sulfonamide moiety is found in a wide range of pharmaceutical compounds (Figure 1a).[1] Accordingly, the development of convenient and efficient methods for installing this functional group has been a long-term interest of chemists. The classical method for sulfonamide synthesis is the condensation between sulfonyl chlorides and amines.[2] Due to their limited commercial availability and sensitivity toward moisture and basic conditions, the need for sulfonyl chlorides restricts the applications of this classical method. In the past decade, strategies for transition-metal-catalyzed synthesis of sulfonamides have been developed.[3] In the presence of a palladium or copper catalyst, aryl halides or pseudohalides can react with SO_2 to generate aryl sulfinates, which subsequently can be oxidized by NaOCl, forming aryl sulfonyl chlorides. Finally, these aryl sulfonyl chlorides can react with amines, forming S–N bond (Figure 1b). The complexity and handling of this multi-step process have limited its practical applications. Recently, sulfonylative cross-coupling reactions have received increasing attention due to diversity and availability of starting materials, straightforward reaction procedures, and potential applications in the synthesis of sulfonamides.[4] However, the existing methods for transition-metal-catalyzed aminosulfonylation of aryl halides are limited to the use of hydrazines as nucleophiles (Figure 1c).[5] Simple amine coupling partners can not be used in the aminosulfonylation except for the only intramolecular process reported by Manable in 2017.[6a] In 2018, Willis and coworkers disclosed a copper-catalyzed three-component oxidative cross-coupling reaction between aryl boronic acids, amines, and DABSO (a SO_2 surrogate reagent) for the synthesis of sulfonamides (Figure 1d).[6b] Nonetheless, complementary cross-coupling reactions with aryl electrophiles would represent a valuable alternative to the nucleophilic aryl boronic acids. In addition, the limited stability of organoboron compounds could complicate their use in the later stages of multi-step syntheses of complex molecules.

Due to the toxic nature and difficulties with storage and use of gaseous SO_2 especially in academic laboratories, the use of SO_2-surrogates is generally preferred. The most common SO_2 surrogate reagents include Na_2SO_3,[5d] $Na_2S_2O_5$ (or $K_2S_2O_5$),[7] $HOCH_2SO_2Na{\cdot}2H_2O$,[8] DABSO[9] and others.[10] $Na_2S_2O_3$ reacts with *conc.* H_2SO_4 to release gaseous SO_2 instantaneously. However, this method of SO_2 generation occurs via an exothermic reaction, which in combination with the use of *conc.* H_2SO_4 has limited the usage of this procedure. The application of other inorganic sulfur dioxide surrogates such as $Na_2S_2O_5$ and $K_2S_2O_5$ usually requires addition of phase transfer catalysts to promote exchange between two solvent phases. In addition, $HOCH_2SO_2Na{\cdot}2H_2O$ suffers from strong hygroscopicity, and it easily forms decomposition products such as sodium sulfite, sodium thiosulfate, and sodium sulfide. DABSO is a mild SO_2 surrogate reagent and was first employed in sulfonylation reactions by Willis.[5a] DABSO is moderately sensitive to temperature and moisture, and during SO_2-release a basic byproduct (DABCO) is generated directly in the reaction mixture. This can potentially lead to incompatibility with highly electrophilic and/or base-sensitive groups. Overall, there is a need for a general method for controllable *ex-situ* SO_2-release (Figure 1e).

Herein, we report the development of a SO_2-surrogate, which can release SO_2 in a highly controlled and predictable fashion. This SO_2-surrogate is a cheap, solid, and bench-stable reagent, easily accessible in two steps from bulk chemicals. The SO_2-surrogate is used in combination with the two-chamber system developed by Skrydstrup.[11] Using this technique, we demonstrate the compatibility with previously reported

sulfonylation reactions, which normally use *in-situ* SO_2-generation. Furthermore, we report the first direct aminosulfonylation reaction between aryl halides and amines (Figure 1f). The method displays broad functional group tolerance including heterocycles, and it can be applied to pharmaceutically relevant molecules.

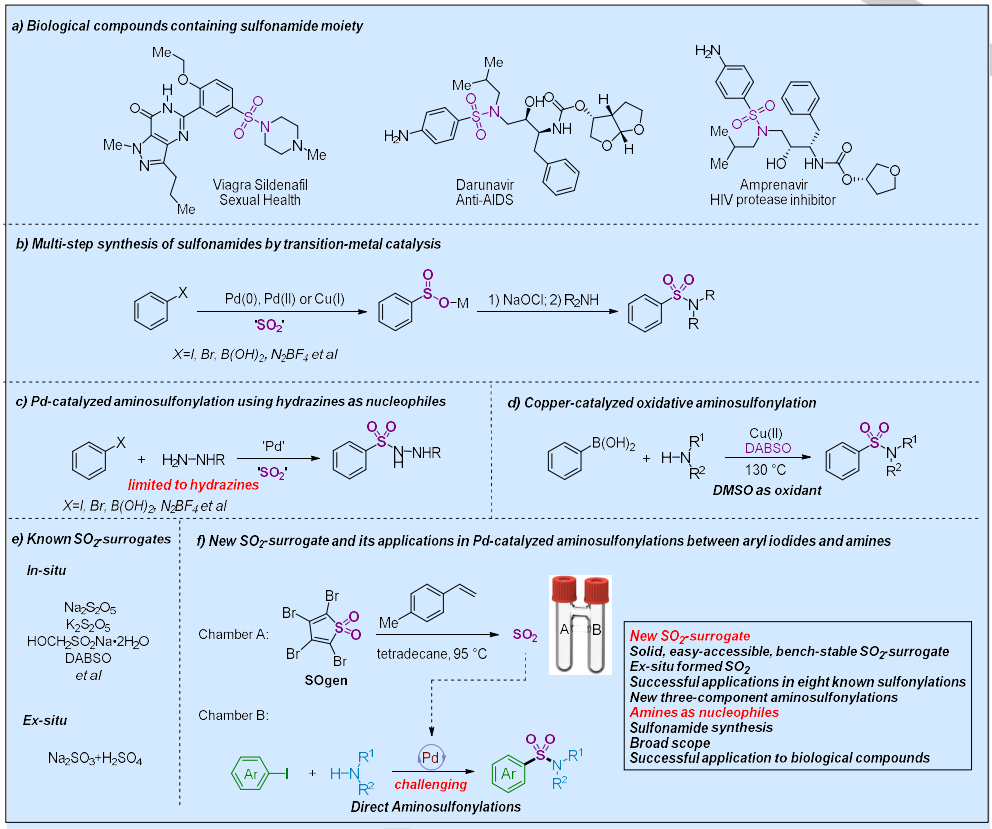
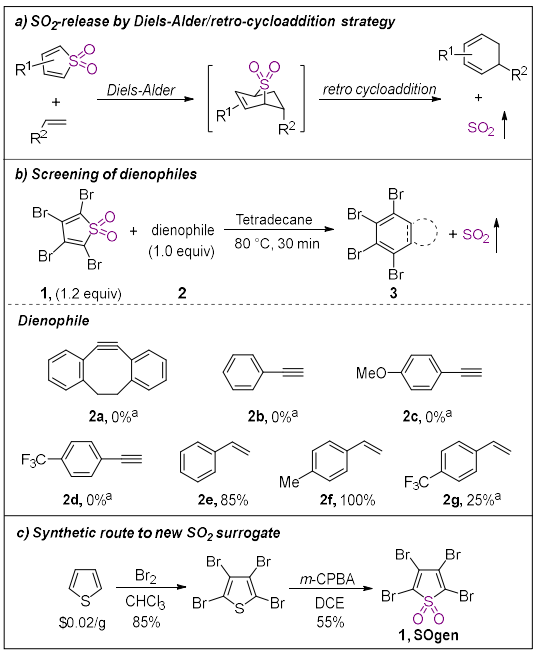


Figure 1. Outline of the importance of sulfonamides for pharmaceuticals and different strategies for their synthesis.

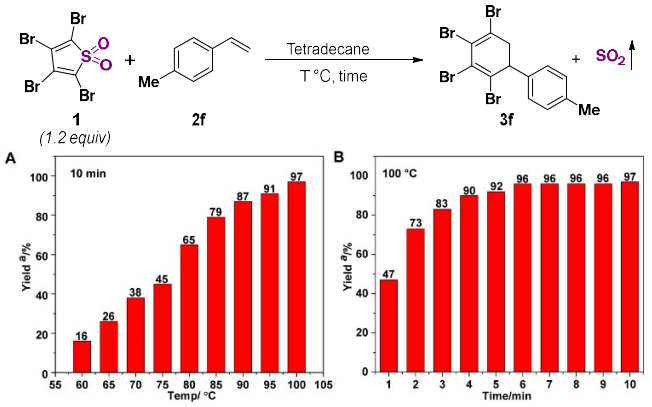
Results and Discussion

Inspired by a literature method,[12] we set out to explore the potential of SO_2-release by a Diels-Alder/*retro*-cycloaddition strategy (Scheme 1a). The study was initiated by the synthesis of tetrabromothiophene *S*,*S*-dioxide (**1**, SOgen), derived from the bromination of commercially available thiophene (0.02$/g) followed by oxidation by *m*-CPBA.[13] Using SOgen (**1**) as an electron-deficient diene, we screened various dienophiles, such as dibenzo-fused cyclooctyne (**2a**), phenylacetylenes (**2b–2d**), and styrenes (**2e** and **2f**). Tetradecane was used as the solvent because of SO_2's poor solubility. The results are summarized in Scheme 1b. In terms of rapid SO_2-release, it quickly became apparent that 4- methyl styrene (**2f**) is the best choice as dienophile reacting with SOgen (**1**) at 80 °C and providing complete SO_2-release in just 30 min.

In order to explore the temperature-dependence on SO_2-release, we monitored the yield of byproduct **3f** after 10 min at temperatures between 60 and 100 °C in 5 °C increments (Scheme 2). A clear correlation was observed, and, at 100 °C, the yield reached 97%. Subsequently, we monitored the yield at 100 °C from 1 to 10 min. Encouragingly, the yield of **3f** reached 90% within just 4 min and nearly 100% in 6 min. Overall, these results indicate that complete SO_2-release can be achieved rapidly by the Diels-Alder/*retro*-cycloaddition strategy.

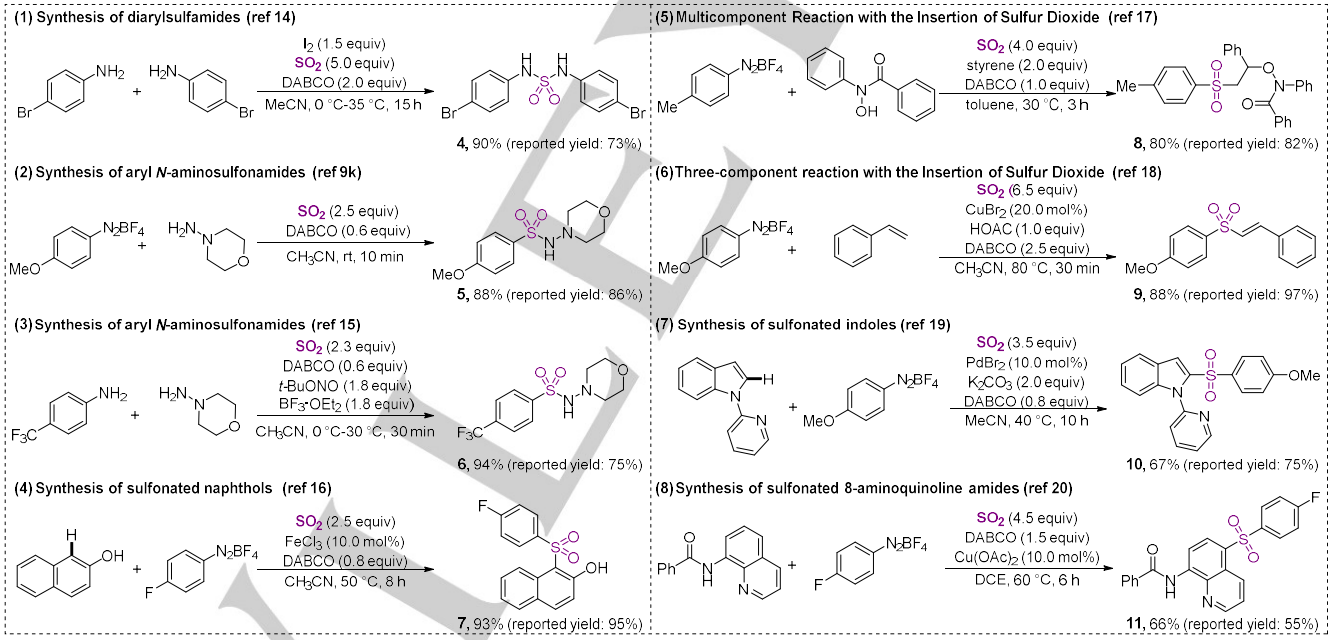


Scheme 1. Design of tetrabromothiophene *S*,*S*-dioxide (**1**) as new SO_2-surrogate. [a]The majority of the corresponding dienophile was recovered.



Scheme 2. A: Yields of **3f** in 10 minutes at different temperatures. B: Yields of 3f in 1 to 10 minutes at 100 °C. Reactions in this scheme were performed under an air atmosphere at 0.1 mmol scale. Yields were determined by GC using dodecane as internal standard.

With the optimal conditions for SO_2-release in hand, we turned to investigating the compatibility of our new SO_2-surrogate with previously reported sulfonylation reactions. *Ex-situ* SO_2-release was achieved by employing a two-chamber system: SO_2 was generated in Chamber A and consumed in the sulfonylation reaction in Chamber B. Eight different sulfonylation reactions were performed (Scheme 3). In the first example, 4-bromoaniline reacted smoothly furnishing the desired homo-coupling product, diarylsulfamide **4**, in 90% yield using 5.5 equiv SO_2 (Scheme 3-1).[14] Gaseous SO_2 could also be applied to aminosulfonylation reactions by coupling aryldiazonium or anilines with hydrazines under metal-free conditions. The corresponding products **5** and **6** were obtained in excellent yields (Scheme 3-2 and 3-3).[9k,15] The radical reaction between naphthols and arydiazonium tetrafluoroborates catalyzed by $FeCl_3$ was also compatible with gaseous SO_2 leading to the sulfonated naphthol **7** in 93% yield (Scheme 3-4).[16] Our SO_2 precursor could furthermore successfully be utilized in the four-component reaction between aryldiazonium tetrafluoroborates, sulfur dioxide, hydroxylamines, and alkenes, generating the desired compound **8** in 80% yield (Scheme 3-5).[17] In addition, *ex-situ* generated gaseous SO_2 could be applied as the source of the sulfonyl group in the synthesis of (*E*)-alkenyl sulfone **9** starting from aryldiazonium tetrafluoroborates and alkenes catalyzed by $CuBr_2$ (Scheme 3-6).[18] Lastly, the two-chamber methodology with our new SO_2-surrogate proved compatible with small heterocyclic molecules such as indole and 8-aminoquinoline for producing the corresponding 2-sulfonated indole **10**[19] and 5-sulfonyl-8-aminoquinoline amide (**11**)[20], respectively, through metal-catalyzed direct C–H functionalization (Scheme 3-7 and 3-8).

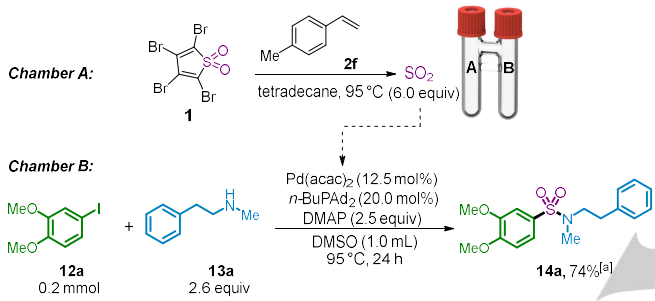


Scheme 3. Compatibility of *ex-situ* SO_2 generation (two chamber) from our new SO_2-surrogate with previously reported sulfonylations.

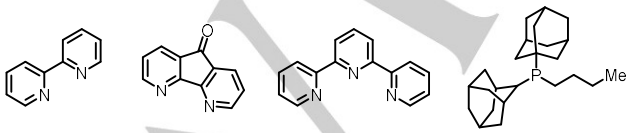
After having demonstrated the compatibility of the new SO_2-surrogate with various sulfonylations in the two-chamber system, we set out to investigate the potential of this method to address a yet unsolved challenge in sulfonylation chemistry. Specifically, we were interested in transition-metal-catalyzed aminosulfonylation between aryl halides and amines. Although hydrazines have been utilized for aminosulfonylation, the use of amines would constitute an important advancement providing directly arylsulfonamides, which are ubiquitous in medicinal chemistry. To initiate the investigation, we chose to study the cross-coupling of 4-iodo-1,2-dimethoxybenzene (**12a**), *N*-methylphenethylamine (**13a**), and sulfur dioxide as a model reaction. It was found when employing $Pd(acac)_2$ (12.5 mol%) and *n*-$BuPAd_2$ (20 mol%) as the catalyst system, DMAP (2.5

equiv) as base, and DMSO as the solvent, the desired sulfonamide **14a** could be formed in a satisfying 74% yield.[21] Specific deviations from the optimized conditions and the corresponding effect on reaction efficiency are also shown in Table 1. Solvent effects were very pronounced for this reaction as DMSO proved to be the only solvent compatible for this transformation (Entry 1). Both nitrogen and phosphine ligands could be utilized for the aminosulfonylation, however, *n*-BuPAd$_2$ (**L7**) turned out to be the most effective ligand (Entry 2). Other bases than DMAP were tested for the aminosulfonylation. In general, they decreased the product yield compared to DMAP, while switching to NaO*t*Bu completely inhibited the reaction (Entries 3-7). Lastly, the amount of sulfur dioxide had an impact on the reaction outcome. An increase in yield was observed with up to 6.0 equiv SO_2. The addition of more than 6.0 equiv SO_2 led to reduced yields probably due to poisoning of the palladium catalyst by excess SO_2 (Entry 8). Using DMAP•SO_2[10b] and DABSO as SO_2 surrogate both had a negative influence on the yield of product (Entries 9 and 10). *Ex-situ* formed SO_2 using Na_2SO_3 and *conc.* H_2SO_4[5d] only gave the desired product in 29% yield, since the mositure in the reaction system probably disturbed the transformation (Entry 11).

Table 1. The optimization of palladium-catalyzed aminosulfonylations.



Entry	Variation from standard conditions	Yield [b]
1[c]	other solvents instead of DMSO	0%
2[d]	Ligand **1**-**6** instead of Ligand **7**	33-63%
3	NaO*t*Bu instead of DMAP	0%
4	KF instead of DMAP	19%
5	K_3PO_4 instead of DMAP	29%
6	Cs_2CO_3 instead of DMAP	19%
7	DABCO instead of DMAP	38%
8	3.0, 4.0, 5.0,7.0 equiv SO_2 in place of 6.0	44-61%
9[e]	DMAP•SO_2 as SO_2 surrogate	46%
10[e]	DABSO as SO_2 surrogate	35%
11[f]	Na_2SO_3 and *conc.* H_2SO_4 as SO_2 surrogate	29%



L1, 33% **L2**, 62% **L3**, 52% **L7**, 74%

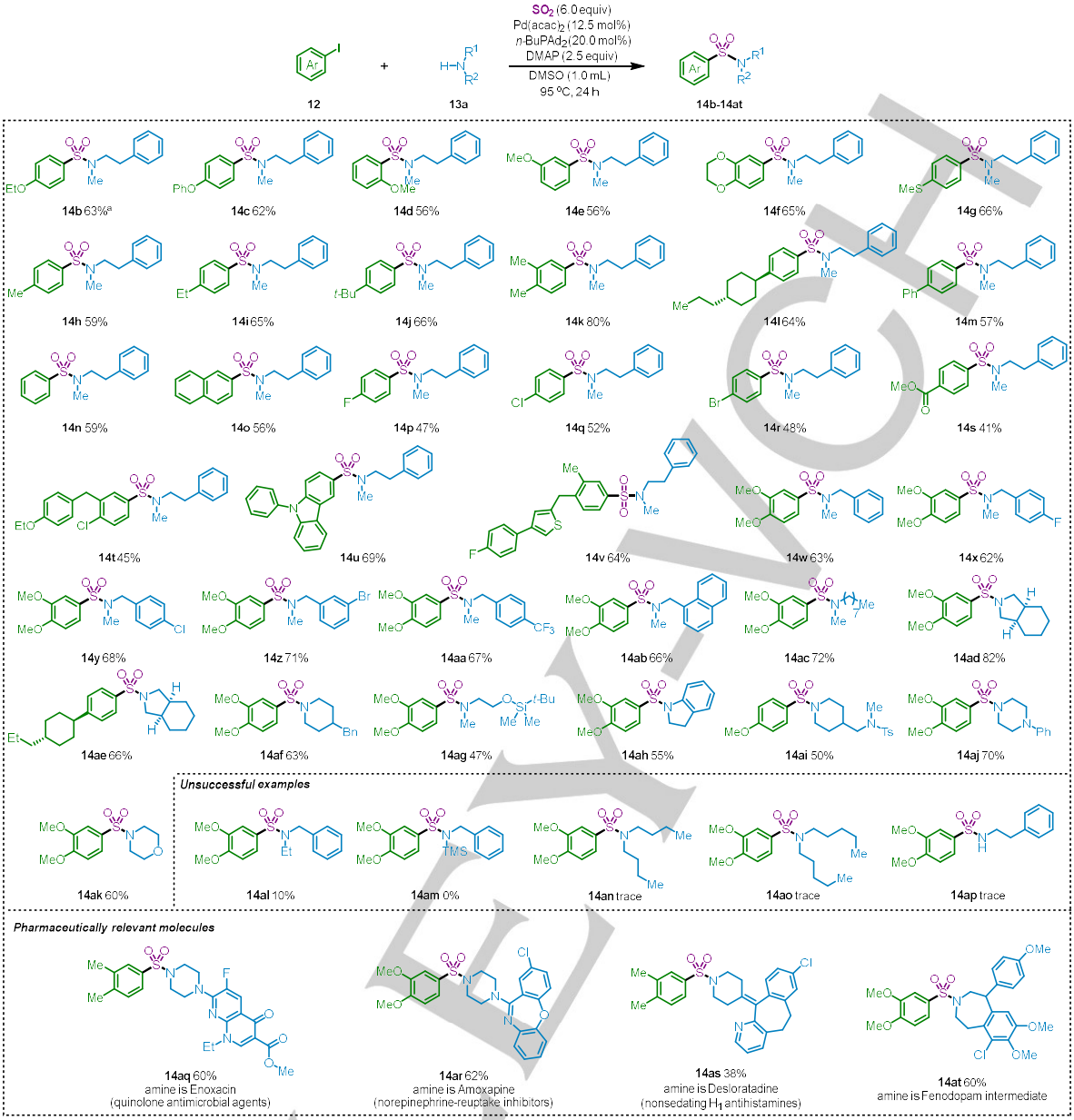
L4 PPh_3, 62% **L5** PCy_3, 63%; **L6** XantPhos, 54%.

[a] Isolated Yield. [b] Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c] Other solvents include *n*Butyl ether, DMF, NMP, xylenes and anisole. [d] Ligand **1**-**3**, **6** (10.0 mol%), Ligand **4**, **5** (20.0 mol%). [e] SO_2 surrogate (2.5 equiv) and reactions were carried out in a 4.0 mL vial. [f] in chamber A: Na_2SO_3 (1.2 mmol, 152 mg) was dissolved in water (1.0 mL), and *conc.* H_2SO_4 (1.5 mmol, 80 µL) was added dropwisely in two minutes at room temperature.

Having established the feasibility of palladium-catalyzed sulfonamide synthesis in a two-chamber system, we next investigated the scope of this transformation with respect to both aryl iodides and amines. First, a variety of aryl iodides were examined employing *N*-methyl-2-phenylethan-1-amine (**13a**) as the amine coupling partner. In general, the aminosulfonylation tolerated various substituted aryl iodides providing the desired products in moderate to good yields (**14a**–**14v**). More specifically, electron-donating substituents (e.g., 4-ethoxy, 4-phenoxy, 2- and 3-methoxyl, and 3,4-ethylenedioxy) on the phenyl ring were compatible with the transformation (**14b**–**14f**). Notably, a potentially catalyst-poisoning thioether was compatible with the transformation, producing the corresponding product **14g** in a good 66% yield. A series of alkyl-substituted (Me, Et, *t*-Bu) and cyclic alkyl-substituted iodobenzenes afforded the corresponding sulfonamides in 56–80% yields (**14h**–**14l**). Electron-neutral aryl iodides underwent the aminosulfonylation affording arylsulfonamides **14m**–**14o**. The high reactivity of the aryl iodides allowed for the synthesis of sulfonamides bearing fluoro, chloro, and bromo substituents (**14p**–**14r**). A strong electron-withdrawing group represented by a carboxylate ester was tolerated, but the product **14s** was isolated in a moderate yield. Aryl iodides in more complex structures reacted well under optimal reaction conditions, and the corresponding products were obtained in moderate to good yields (**14t**–**14v**).

Next, various amine fragments were evaluated in combination with different aryl iodide coupling partners. A series of *N*-methyl phenylmethanamines performed well, providing the corresponding sulfonamides (**14w**–**14aa**) in 62–71% yields. Notably, electronic properties of the substituents on the *N*-methyl phenylmethanamines had little influence on the catalytic efficiency. Acyclic aliphatic amines were compatible with the protocol leading to 66–72% yields of the desired products (**14ab** and **14ac**). Octahydro-isoindole could couple with different aryl iodides producing sulfonamides in an efficient manner (**14ad** and **14ae**). Furthermore, the aminosulfonylation protocol worked well for other cyclic amines, such as indoline, piperidine, and piperazine derivatives as well as an aliphatic amine containing a silyl ether, thus allowing the synthesis of **14af**–**14aj** in 47–70% yields. Morpholine proved to be a suitable amine substrate for this coupling reaction, affording the desired products in 60% yield (**14ak**). Unfortunately, more steric secondary amines (**14al**–**14ao**) and primary amine (**14ap**) failed to proceed this aminosulfonylation.

To highlight the compatibility of the aminosulfonylation with pharmaceutically relevant molecules, we explored four different amines that are either active pharmaceutical ingredients (APIs) or closely related derivatives. Direct aminosulfonylation with these substrates that bear different nitrogen-containing heterocyclic motifs and functional groups, proceeded well, allowing the incorporation of amine fragments from enoxacin, amoxapine, desloratadine, and fenodopam in moderate to good yields (**14aq–14at**).



Scheme 4. Scope of the palladium-catalyzed aminosulfonylations. Reaction conditions: aryl iodides (0.2 mmol), amine (2.6 equiv), SO_2 (6.0 equiv), $Pd(acac)_2$ (12.5 mol%), *n*-$BuPAd_2$ (20.0 mol%), DMAP (2.5 equiv), DMSO, 95 °C, 24 h. Isolated yields. [a]Using aryl bromide instead of iodide failed to give the corresponding product.

Conclusion

In summary, we have designed a new SO_2-surrogate (SOgen) which is cheap, easily accessible, and bench-stable. This gas-surrogate releases SO_2 in just few minutes, when heated in the presence of a styrene. Subsequently, the compatibility of this gas releasing protocol with eight previously reported sulfonylation reactions was demonstrated in a two-chamber system. Finally, we developed the first method, which allows use of amines in aminosulfonylations with aryl halides and SO_2. Broad functional group tolerance was demonstrated, and the method can be applied to the preparation of pharmaceutically relevant substrates bearing a sulfonamide, including heterocycle-containing substrates. This new SO_2-surrogate has the limitation of generating 6.0 equiv of an organic by-product when used in the aminosulfonylations, and efforts are underway to reduce the amount of SO_2-surrogate used. Overall, this new SO_2-surrogate is complementary to the existing SO_2-surrogates.

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Conflict of interest

The authors declare the following competing financial interest(s): T.S. is co-owner of SyTracks A/S, which commercializes COware (the two chamber technology).

Keywords: SO_2 surrogate • Aminosulfonylation • Sulfonamide • Aryl Halides• Cross-couplings

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[21] For the proposed mechanism, please see Supporting Information.

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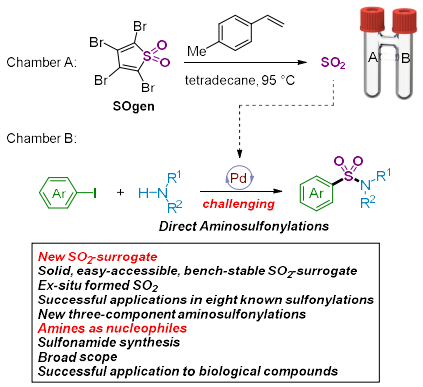

A new SO_2-surrogate (SOgen) is reported which is cheap, bench-stable, and can be accessed in just two steps from bulk chemicals. This gas-surrogate releases SO_2 in just few minutes, when heated in the presence of a styrene. The compatibility of this gas releasing protocol with eight previously reported sulfonylations was demonstrated in a two-chamber system. Lastly, we report the first direct aminosulfonylation between aryl iodides and amines.