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# Palladium-catalyzed asymmetric allylic alkylation (AAA) with alkyl sulfones as nucleophiles†

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An efficient palladium-catalyzed AAA reaction with a simple α-sulfonyl carbon anion as nucleophiles is presented for the first time. Allyl fluorides are used as superior precursors for the generation of π-allyl complexes that upon ionization liberate fluoride anions for activation of silylated nucleophiles. With the unique bidentate diamidophosphite ligand ligated palladium as catalyst, the *in situ* generated α-sulfonyl carbon anion was quickly captured by the allylic intermediates, affording a series of chiral homo-allylic sulfones with high efficiency and selectivity. This work provides a mild *in situ* desilylation strategy to reveal nucleophilic carbon centers that could be used to overcome the p$K_a$ limitation of "hard" nucleophiles in enantioselective transformations.

## Introduction

Transition-metal-catalyzed *asymmetric allylic alkylation* (AAA) is a powerful tool for the enantioselective construction of stereogenic centers, enabling the elaboration of complex organic molecules and synthesis of pharmaceutical intermediates and bioactive natural products.[1] A variety of "soft" carbon nucleophiles (Nu-H with p$K_a$ <25) and heteroatoms have been used in AAA reactions, generating the corresponding stereogenic centers with good to excellent selectivity.[2] However, transition-metal-catalyzed allylic substitution reactions with "hard" nucleophiles (Nu-H with p$K_a$ > 25) is mainly limited to non-enantioselective transformations.[3] During the past decades, our group and many other research groups have made tremendous efforts to engage "unstable" nucleophiles, such as ketones, acyclic amides and nitrogen-contained heteroarenes, *etc.* in the palladium-catalyzed AAA reactions.[4,5] Despite these achievements, a great number of "hard" carbon nucleophiles are still not compatible in palladium-catalyzed AAA reactions. One important example of such unexplored carbon based nucleophiles for AAA reactions is α-sulfonyl carbon anion (p$K_a$ = 29 for (methylsulfonyl)benzene, Fig. 1a).[6]

Sulfone represents an important moiety that is widely spread in many biologically active compounds and pharmaceutical intermediates.[7] Moreover; sulfones can be converted into a wide range of other groups at the α position *via* traceless transformations.[8] Efficient utilization of α-sulfonyl carbon anion in the palladium-catalyzed AAA reaction would lead to chiral homo-allylic sulfones, which would provide promising opportunities for the exploration of chiral sulfone containing compounds (Fig. 1c). Previous exploration to build chiral homo-allylic sulfones *via* AAA reactions were limited to special sulfone reagents, an additional electron-withdrawing group was usually needed to enhance the acidity of α proton (Fig. 1a).[9] For example, the use of the ester group allowed removal after the reaction of Krapcho demethoxycarbonylation;[10] however,

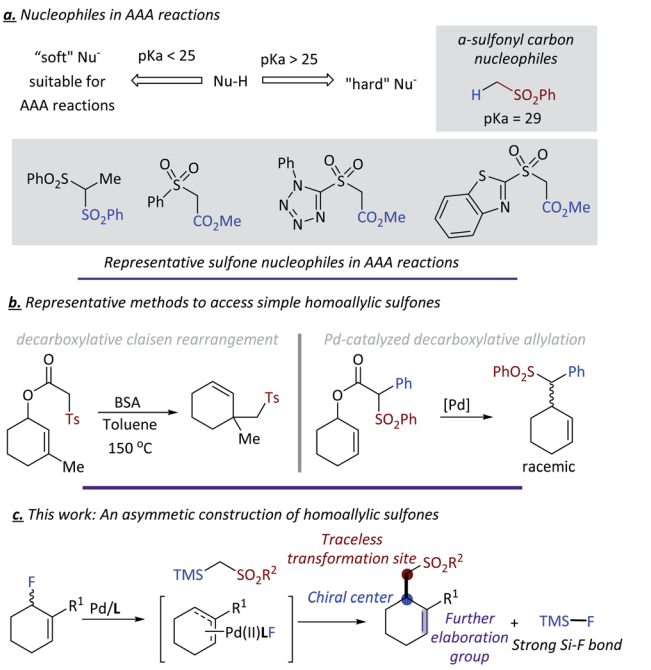


Fig. 1 Representative methods for homo-allylic sulfones.

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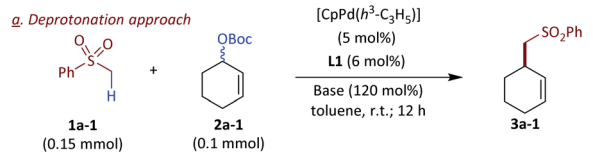
besides the moderate yield (60–80%), the harsh reaction conditions for demethoxycarbonylation would rule out many useful functional groups. Therefore, exploration of efficient method to realize the direct asymmetric allylic reaction of simple alkyl sulfones under mild reaction conditions is highly in needed.

To date, two elegant non-enantioselective reports on direct allylic alkylation of sulfones employed decarboxylation as the driving force. A thermodynamic decarboxylative Claisen-rearrangement reaction reported by Craig *et al.*[11] under harsh reaction conditions (150 °C) would restrict the diversity of functional groups (Fig. 1b). Another example is a palladium-catalyzed intramolecular decarboxylative allylation of sulfonyl acetic esters with *rac*-BINAP as the ligated ligand (Fig. 1b).[12] Notably, the conditions developed by Tunge *et al.* still needed high reaction temperature or microwave conditions to get acceptable results. In most cases, the key nucleophiles were stabilized by both sulfonyl and phenyl or heteroatoms ($pK_a$ = 23.4 for (benzylsulfonyl)benzene).[6] Herein, we report our endeavor and initial results on the palladium-catalyzed AAA reaction with simple α-sulfonyl carbon anion as the nucleophile ($pK_a$ > 25, Fig. 1c).

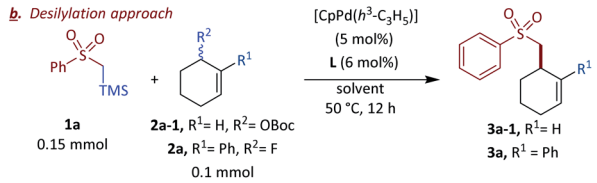
## Optimization of conditions

Recently, our and other groups have found that phosphoramidite and diamidophosphite ligands could facilitate transition-metal catalyzed transformations *via in situ* deprotonation of pro-nucleophiles.[4l,13] Notably, the Sawamura group found that the chiral phosphoramidite ligated palladium catalyst can facilitate the asymmetric allylic alkylation at the "hard"α position of 2-alkyl pyridines without additives.[4l] The above achievements inspired us to utilize these unique ligands and exploit α-sulfonyl nucleophiles in AAA reactions. We started our research with commercial compound **1a-1** as a donor, and *tert*-butyl cyclohex-2-en-1-yl carbonate **2a-1** as the model counterpart (Fig. 2a). Ligand **L1** (Fig. 2c) which has proven to be a suitable ligand for palladium-catalyzed transformations involving a deprotonation mechanism was selected as the ligated ligand to test different conditions.[14,15] We soon realized that in the absence of additional base, the reaction gave no desired results. The *tert*-butoxide presumably generated *in situ* from Pd-mediated ionization of **2a-1** is incompetent to efficiently deprotonate the sulfone **1a-1** or perhaps the carboxylate leaving group never lost $CO_2$ to form *tert*-butoxide. We surmised that addition of an external base could lead to deprotonation. Addition of LiHMDS, KHMDS and NaO-*tert*-Bu to facilitate the desired deprotonation failed to give acceptable results. Perhaps, these strong bases interfered with the ionization event of **2a-1** and the moisture sensitive nature of these strong bases makes the reaction hard to handle. We turned our attention to find mild conditions to generate the corresponding α-sulfonyl carbanion in a catalytic manner without additional stoichiometric base.

Recently, our group and the Hartwig group found that allylic fluoride can be used as an excellent electrophilic




| Entry | Base | Product 3a-1 |
|---|---|---|
| 1 | no base | no product |
| 2 | LiHMDS | < 10% yield |
| 3 | KHMDS | no product |
| 4 | NaO$^t$Bu | < 10% yield |
| 5 | NaO$^t$Bu, 50 °C | complex mixture |




| Entry | Allylic reagent | Solvent | Ligand | Product |
|---|---|---|---|---|
| 1 | **2a-1** | 1,4-dioxane | **L1** | **3a-1**, < 10% yield |
| 2[a] | **2a-1** | 1,4-dioxane | **L1** | **3a-1**, < 10% yield |
| 3 | **2a** | 1,4-dioxane | **L1** | **3a**, 83% yield, 91% *ee* |
| 4 | **2a** | $^t$BuOMe | **L1** | **3a**, 74% yield, 94% *ee* |
| 5 | **2a** | $^t$BuOMe | **L2** | **3a**, 51% yield, 84% *ee* |
| 6 | **2a** | $^t$BuOMe | **L3** | **3a**, 35% yield, 72% *ee* |
| 7 | **2a** | $^t$BuOMe | **L4** | **3a**, <10% yield |
| 8 | **2a** | $^t$BuOMe | **L5** | *no reaction* |
| 9 | **2a** | $^t$BuOMe | **L6** | **3a**, 61% yield, — |
| 10 | **2a** | toluene | **L1** | **3a**, <10% yield, — |
| 11 | **2a** | CPME | **L1** | **3a**, 67% yield, 92% *ee* |
| 12 | **2a** | $^t$BuOMe | *no ligand* | *no reaction* |
| 13[b] | **2a** | $^t$BuOMe | **L1** | **3a**, <10% yield, — |

[a] 0.15 mmol TBAF was added; [b] $Pd(bda)_2$ was used as palladium source

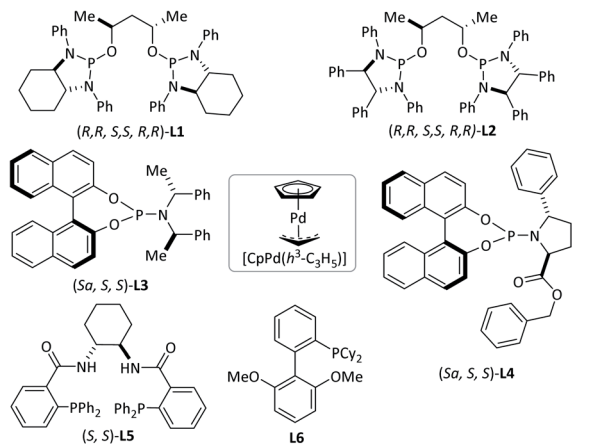



Fig. 2 Optimization of conditions.

precursor in transition metal-catalyzed asymmetric allylic alkylation, generating the nucleophile anion by *in situ* fluoride induced desilylation, respectively.[16] The strategy invoked a synergistic interplay of the fluoride leaving group to facilitate the generation of the electrophilic metal-allyl complex and delivery of a *catalytically activated* nucleophilic anion by

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desilylation. We sought to utilize this approach to engage α-sulfonyl **1a** in palladium-catalyzed asymmetric allylic alkylation with allyl fluoride **2a** (Fig. 2b). Encouragingly, using **L1** gave the desired product **3a** with good yield (83%) and excellent enantioselectivity (91% ee). When *t*-BuOMe was used as the solvent, the product **3a** was obtained in lower 74% yield but better 94% ee. When **L2** was used as the supporting ligand, the product **3a** was obtained in 51% yield and 83% ee. Some other phosphoramidite ligands were also tested. **L3** afforded the product in a moderate 72% ee with a poor 35% yield. On the other hand, **L4** [17] and **L5**, which were successful ligands in our previous palladium-catalyzed transformations, did not afford the desired results. Nevertheless, Sphos **L6** afforded **3a** in moderate 61% yield, thus this ligand was selected as the supporting ligand for the non-enantioselective transformations. The solvent effect was very important for this transformation and only ethereal solvents gave the desired sulfone **3a** with acceptable results. Other solvents such as toluene and DCE gave trace amounts of the desired product. *t*-BuOMe was proved to be the optimal solvent for the enantioselective transformations. Active CpPd($\eta^3$-$C_3H_5$) was another key factor for this reaction; other palladium sources such as commonly used $Pd(dba)_2$ gave poor results.

## Results and discussion

To generate more elaborate chiral homo-allylic sulfones, we first tested the scope of different sulfone donors with allyl fluoride **2a** as the reaction counterpart (Fig. 3). Aryl sulfones bearing an electron-donating (**3b**) or an electron-withdrawing (**3c**) group were suitable in our system, giving good to excellent results. The substrates bearing halogen atoms, such as fluoro and chloro afforded corresponding products with good results (**3e** and **3f**). Sterically hindered 2-naphthyl sulfone (**3f**) and bioactive 7-coumarinyl sulfone (**3g**) also gave rise to the desired products in good to excellent enantioselectivity. Additionally, different heteroaryl sulfones,[18] such as 2-pyridyl sulfone (**3h**), 4-pyridyl sulfone (**3i**), 1,3-pyrimidinyl sulfone (**3j**) and benzothiazolyl sulfone (**3k**) all gave the desired products with excellent results (>94% ee). Besides the above aryl sulfones, simple alkyl sulfones were also tested with the optimized conditions, and the corresponding chiral products could be obtained with slightly diminished enantioselectivity compared to aryl sulfones (**3l**, **3m**). Notably, sulfonamide which is a privileged functionality in modern drug discovery also could produce the corresponding homoallylic chiral sulfonamides with good results (**3n**, **3o**).[19] An interesting anion shift was observed for the reaction with benzyl sulfone, which gave the expected product **3p** in a good 63% yield and excellent 92% ee with a unseparated minor regioisomer **3p′**. A similar shift is not exhibited in Tunge's decarboxylative allylations of benzyl alkyl sulfone.[12] Regrettably, vinyl and alkynyl sulfones did not give the desired products. The absolute configuration of **3h** was determined by X-ray crystallography; the stereochemical outcome for all other homo-allylic sulfones was assigned by analogy.

Next we turned our attention to the substrate scope of allylic fluorides. To make the detection and separation of product easier, 2-pyridyl sulfone **1h** was selected as the standard

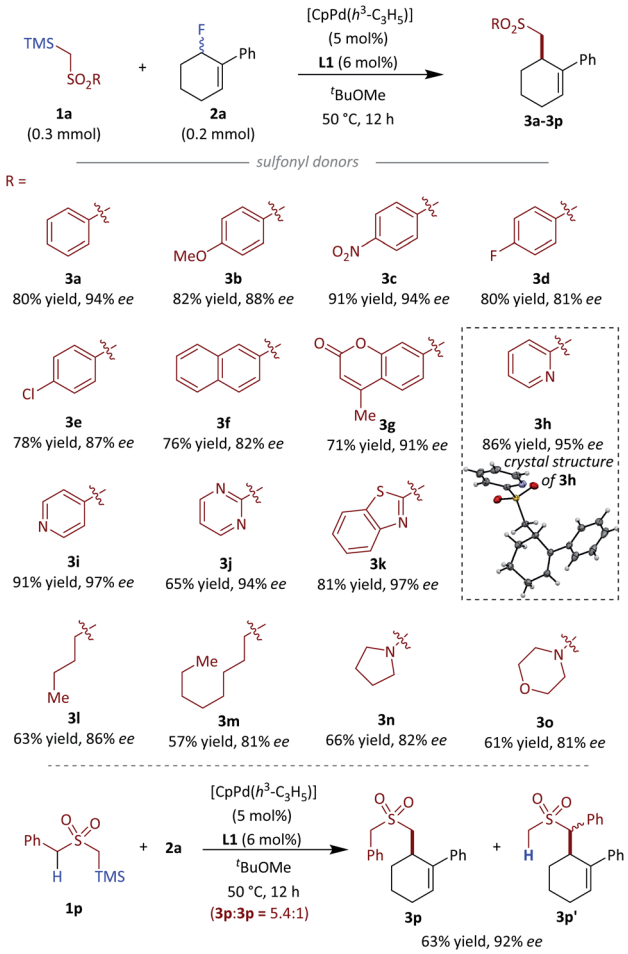


Fig. 3 Substrate scope of different sulfone donors.

nucleophile for most substrates (Fig. 4). Allylic fluorides bearing 2-naphthyl (**4a**), more sterically hindered 1-naphthyl (**4b**), electron-rich aryl (**4c**) and electron-deficient aryl (**4d**, **4e**) all gave a range of chiral homo allylic sulfones with good yields and good to excellent ee values. Substrate bearing a chlorine atom, which is a good handle for further functionalization, was compatible with the reaction conditions (**4f**). Heteroarenes are also good choices for the reaction. Electron-rich indolyl (**4g**), thiophenyl (**4h**), and electron-deficient quinolinyl (**4i**) were all successfully employed to give the desired products with excellent results (>89% ee). Besides the different aryls, alkenyl and alkyl substituted allylic fluorides were also subjected to the optimized conditions. Alkenyl substituted acceptors gave the desired homo-allylic sulfones in good yield with slightly lower ee values compared to aryl substituted acceptors (**4j**, **4k**). Simple benzyl substituted acceptor gave 57% yield but a poor 47% ee (**4l**). Added flexibility of the benzyl substituent could account for the compromised selectivity. A nitrogen-containing heterocyclic acceptor was also tested and delivered the desired product **4m** in 66% yield and an excellent 91% ee. Besides the six membered all carbon cyclic acceptors, medium-sized rings such as seven-membered cyclic acceptors also proved to be good substrates for this reaction, giving the desired products with excellent ee


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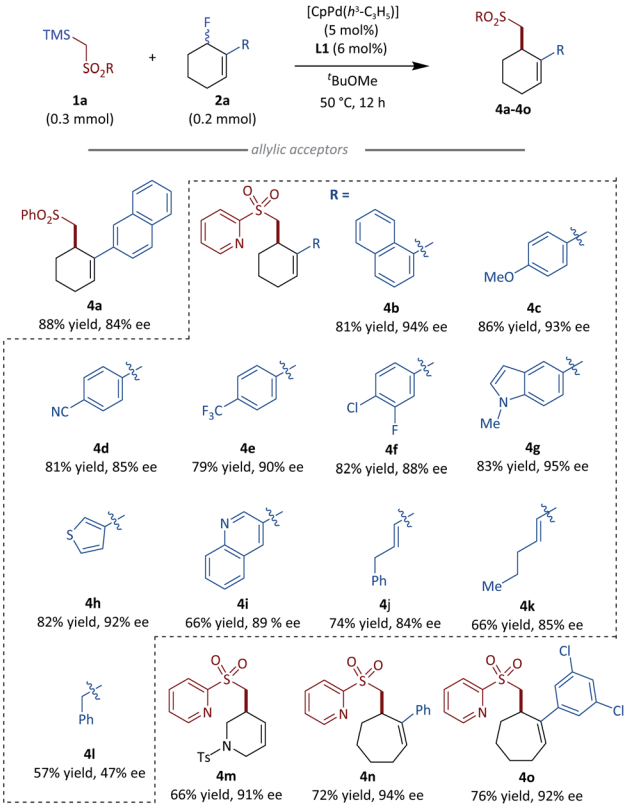


Fig. 4 Substrates scope of different allylic acceptors.

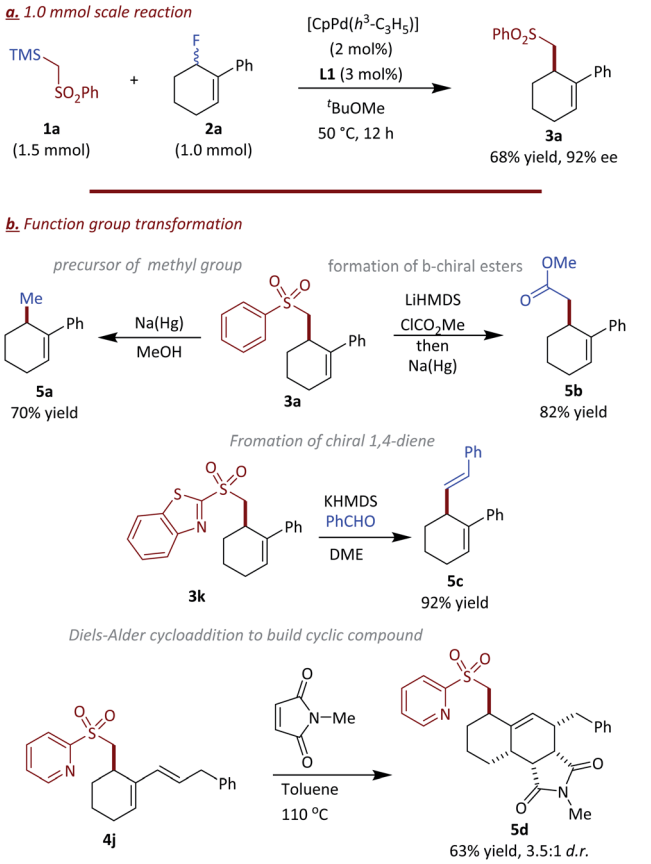


Fig. 5 Derivatization of the products.

values (**4n**, **4o**). Unfortunately, five-membered acceptors are not suitable for our current conditions, as the active allylic fluoride preferentially eliminated HF thereby forming cyclopentadiene spontaneously.[20]

To demonstrate the synthetic application of this transformation, the scale of the reaction was increased to 1.0 mmol (Fig. 5a). The palladium loading could be reduced to 2 mol% with 3 mol% of ligand **L1** whereby the product **3a** was obtained in 68% yield with 92% ee. Furthermore, the sulfone group in the products provides an enabling handle for further transformations (Fig. 5b). For example the sulfone group in **3a** could be reductively cleaved with Na(Hg) to access chiral allylic methyl compound **5a** in 70% yield. Notably, access to compound **5a** is difficult by other methods. Here the sulfone donor acts as a formal methylation reagent.[21] Additionally, the sulfone group could be replaced by an ester group *via* a two-steps synthetic sequence in 82% yield (**5b**). Furthermore, the heteroaryl sulfonyl group in **3k** could be used as a precursor for Julia–Kocienski olefination whereby upon reaction with benzaldehyde the skipped diene **5c** forms in excellent yield and *geometric* selectivity (**5c**) for the *E* isomer.[22] The 1,3-diene unit in **4j** is a good counterpart for an intermolecular Diels–Alder reaction, which afforded fused cyclic compound **5d** in 63% yield (dr = 3.5 : 1) upon reaction with *N*-methyl maleimide.[23]

## Conclusions

In conclusion, we realized the first palladium-catalyzed AAA reaction with "hard" α-sulfonyl carbanions as the nucleophiles. This transformation provides a rapid entry to chiral homo-allylic sulfones that otherwise are challenging to obtain. The presence of a sulfone motif provides a powerful handle for subsequent structural elaborations. The "outer sphere" reaction pathway is presumed to be involved in this transformation,[24] however, another possible reaction pathway involved anionic Si–F species couldn't be ruled out.[25] Detailed mechanistic studies and application of this novel AAA reaction in the synthesis of biologically active compounds and analogy of natural products are ongoing.

## Author contributions

Z. Jiao and H. Gholami performed the synthetic experiments. B. M. Trost supervised the research. B. M. Trost, Z. Jiao and H. Gholami wrote the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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