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1,2-Arylsulfonylation of Vinyl Ethers and Esters Enabled by Dual Ni Catalysis

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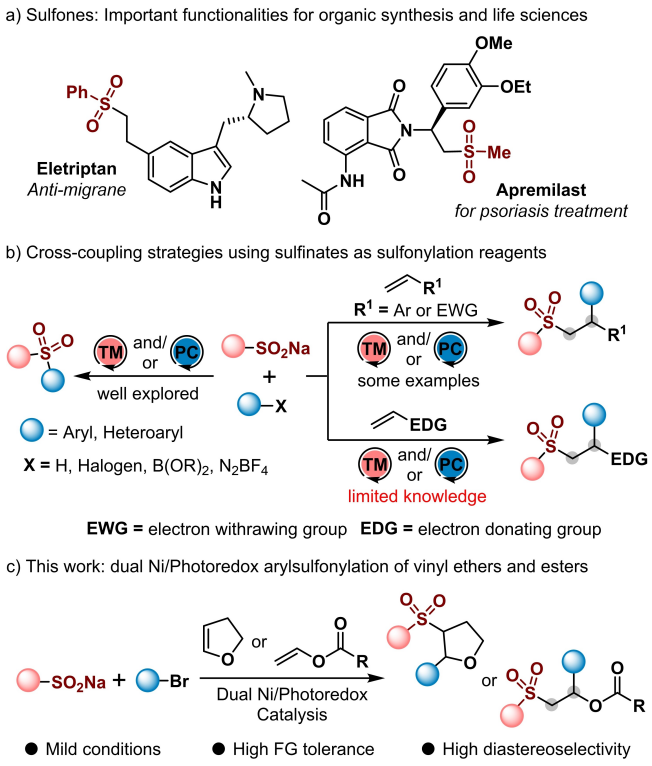
A dual photocatalytic sulfonylation-arylation of electron-rich alkenes is described. By combining sulfinate salts, (hetero)-aryl-bromides and 2,3-dihydrofuran under Ru and Ni dual catalysis, over 35 examples of aryl-sulfonylated scaffolds could be obtained in good to excellent yields, under mild reaction conditions and high diastereoselectivity.

Introduction

Over the last decade, transition-metal catalysis and its combination with visible-light photoredox catalysis has been established as a powerful approach for the synthesis of 1,2-difunctionalized alkenes.[1] Such multicomponent strategies enable a significant increase in molecular complexity from readily available unsaturated chemical feedstocks by incorporating C–C and/or C–X linkages in a simultaneous manner. In addition, these processes are atom-economical, reducing the need for lengthy synthetic sequences while simplifying the reaction setup.[1]

Driven by the prevalence of sulfones in pharmaceuticals and agrochemicals (Scheme 1a),[2] and their versatility as synthons in classical organic synthetic endeavors and photocatalytic events,[3,4] chemists have recently been encouraged to design new catalytic, yet atom-economical, sulfonylation protocols.[5] While significant advances have been made by Nevado and Rueping on Ni-catalyzed sulfonylation protocols,[6c,f] the utilization of electron-rich alkenes remains an unexplored endeavor (Scheme 1b).[6] Therefore, at the outset of our investigations, we questioned whether a site-selective catalytic 1,2-sulfonylation/arylation could be implemented with electron-rich alkenes under Ni/photoredox dual catalysis. If successful, this protocol would provide a rapid and reliable approach to exploring currently inaccessible chemical space en route to β-arylsulfonylated architectures. As part of our investigations of Ni-catalyzed reactions,[7] we report herein the successful development of such approach, culminating in a broadly applicable protocol that leverages the propensity of dual catalysis to generate radical intermediates prior to an arylation event enabled by a Ni-catalyzed endeavor (Scheme 1c).



Scheme 1. Cross-coupling strategies for the preparation of sulfonylated compounds

Results and Discussion

We began our studies investigating the multicomponent reaction of sodium benzenesulfinate (**1a**), *p*-trifluoromethyl bromobenzene (**2a**) and 2,3-dihydrofuran (**3a**) (Table 1). A

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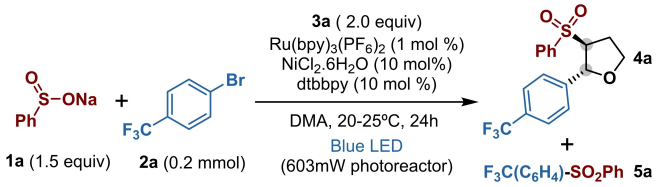
Table 1. Optimization of the reaction conditions.



Entry	Deviation from optimal condition	4a[a](%)
1	none	97 (95[b])
2	$NiBr_2$.diglyme, $NiBr_2$.glyme instead of $NiBr_2.6H_2O$	85/33
4	$Ni(OH_2)_4(dtbbpy)Cl_2$ instead of $NiBr_2.6H_2O$	85
5	No temperature control	28
6	DMF, MeCN or DMSO instead of DMA	85/–/82
7	No $NiCl_2.6H_2O$, PC or light	traces

[a][19] F NMR NMR yield. [b] Isolated yield.

thorough evaluation of the reaction parameters revealed that a combination of $Ru(bpy)_3(PF_6)_2$ (1 mol%), $NiCl_2.6H_2O$ (10 mol%) and dtbbpy (10 mol%) in DMA (0.2 M) with 603 mW blue LED photoreactor for 24 h at 20–25 °C afforded the best result, giving rise to **4a** in 95% isolated yield and excellent diastereoselectivity (entry1). Crystallographic analysis of **4a** allowed the unequivocal determination of the *trans*-stereochemistry. The preferential formation of the latter likely arises by the steric clash of the sulfonyl group and the adjacent alkyl-Ni center prior to reductive elimination. As shown in entries 2 and 3, the utilization of $NiBr_2$.diglyme or $[Ni(OH_2)_6(dtbbpy)]Cl_2$ as precatalysts resulted in lower yields of the desired product. A careful control of the temperature of the reaction turned out to be particularly important. Indeed, a significant erosion in yield was found in the absence of a fan by using a higher power light source (entry 4). Equally important was the nature of the solvent. Thus, reactions performed in DMF and DMSO led to slightly lower yields. Interestingly, the utilization of MeCN resulted in significant amounts of **5a**. As expected, control experiments indicated that trace amounts of **4a** were obtained in the absence of photocatalyst, nickel precatalyst or light (entry 6).

With optimized conditions in hand, we evaluated the scope of our 1,2-arylsulfonylation of unactivated olefins. As shown in Scheme 2, our protocol showed to be widely applicable across a wide range of aryl bromides. Aryl bromides bearing strong electron withdrawing substituents at the para-position resulted in moderate yields (**4b** and **4c**), whereas derivatives containing weak electron withdrawing or electron donating groups afforded the corresponding products in good to excellent yields (**4d–h**). The tolerance in the presence of aryl chlorides or pivalates is noteworthy, leaving ample room for further derivatizations via transition-metal catalyzed cross-coupling reactions.[8] While the reaction of *p*-bromoanisole afforded **4i** in 72% yield, the presence of an additional electron-withdrawing group at the meta position had a beneficial effect, resulting in the corresponding product **4j** in 89% yield. Unfortunately, ortho-substituted aryl-bromides were not tolerated in this protocol. Equally interesting was the compatibility with amides (**4l**) and the ability to extend this reaction to heteroaryl bromides with the pyridyl, quinoline, indole, furan or thiophene core with similar ease (**4m–r**). Interestingly, our protocol could be applied to advanced synthetic intermediates such as pregnenolone, phenylalanine or protected glycosides (**4s–4u**) as well as pharmaceutical ingredients such as Etodolac or memantine (**4** and **4w**), thus showing the prospective impact that this technique might have to access advanced sulfonylated building blocks from simple precursors.

Next, we turned our attention to evaluating the influence of the sulfinate counterpart in our multicomponent protocol (Scheme 3). As shown, arylsulfinates bearing electron-donating or electron withdrawing substituents reacted smoothly to afford the corresponding products **6a–6g** in good to excellent yields. The ability to access **6g** is particularly noteworthy given its potential applicability in the context of Julia-type olefinations.[3a] Pyridine-3-sulfinate and thiophene-2-sulfinate were also tolerated, affording **6h** and **6i** in 91% and 63% yield, respectively. Gratifyingly, sodium methylsufinate could also be employed as counterpart, furnishing **6j** in 71% yield. To showcase the structural diversity that can be accessed by our protocol we also prepared the arylsulfonylated tetrahydrofurans **6k–6n**, which could be obtained in yields ranging from 61%–93% yield.

Scheme 4 further illustrates the applicability of our reaction beyond 2,3-dihydrofuran. It is worth noting that the optimized reaction conditions shown in Table 1 (entry 1) were not suited for the coupling of acyclic vinyl ethers. Careful evaluation of the reaction parameters, however, revealed that a subtle change of the precatalyst to $NiBr_2$·diglyme was critical for success, leading to the targeted products **7a–7c** in good yields. The robustness of our protocol was further illustrated by the successful implementation of a scale-up process, affording **4f** in 74% yield (Scheme 5).

At present, we believe that our reaction can be interpreted on the basis of an initial single-electron transfer from the sodium sulfinate **1** ($PhSO_2^{\bullet}/PhSO_2Na$, $E_{1/2}red = +0.5$ V vs. SCE in MeCN, Scheme 6) to the photoexcited $Ru(bpy)_3(PF_6)_2$ Ru(II)* ($E = +0{,}77$ V vs. SCE in MeCN), affording a Ru(I) complex and an arylsulfonyl radical **I**. The latter can be intercepted by **3**, leading to an alkyl radical **II** stabilized by the adjacent oxygen atom.

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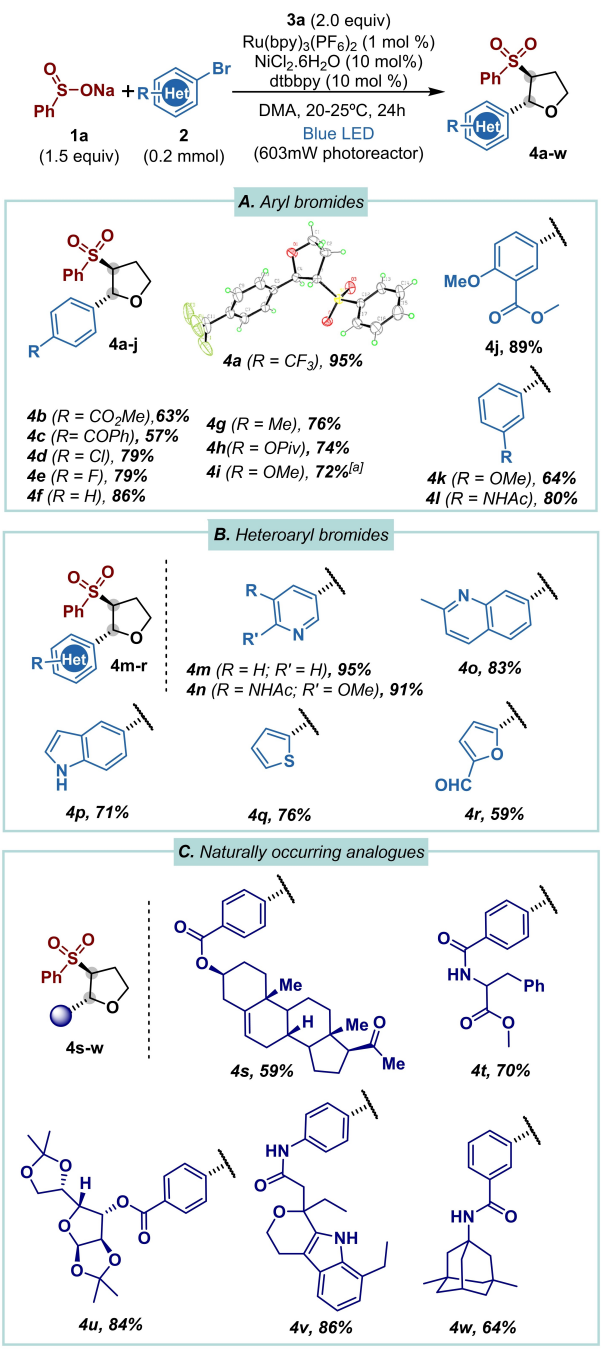
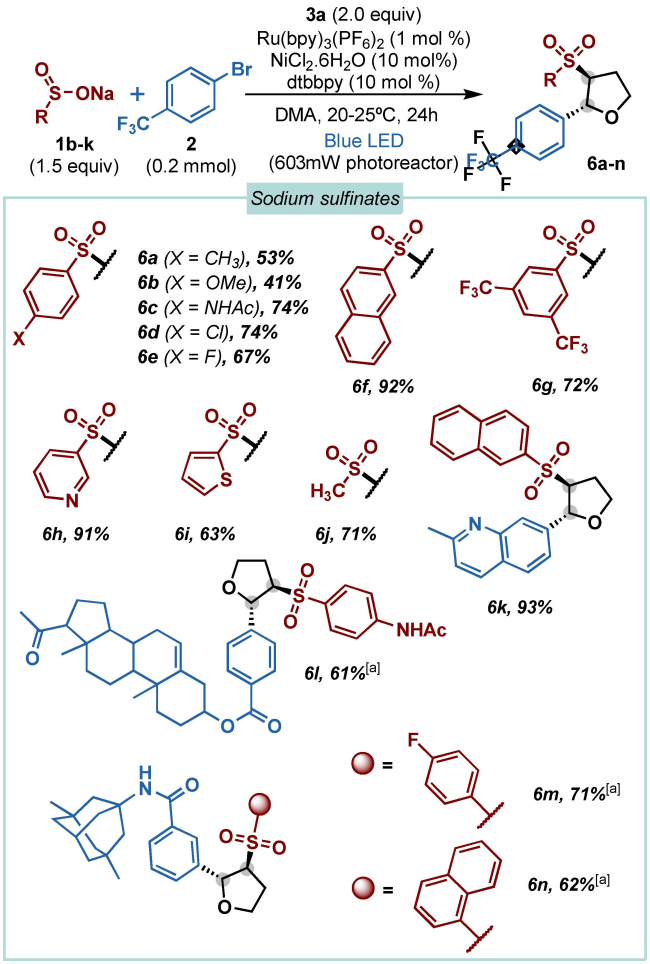
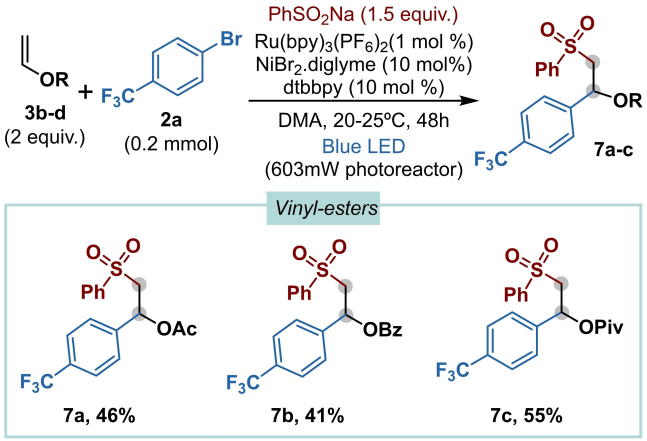


Scheme 2. Scope of (hetero)-aryl-halides. [a] Reaction time: 48 h.

Such an open-shell species can be interfaced by an oxidative addition complex **IV** arising from the reaction of an aryl bromide with Ni(0)L_n **III**, resulting in a Ni(III) complex **V**. Final reductive elimination leads to the targeted product and a Ni(I) complex that is intercepted by a final SET from Ru(I), thus recovering back the propagating catalytic species.



Scheme 3. Scope of sulfinates. [a] Reaction time: 48 h.



Scheme 4. Scope of vinyl-esters.

Conclusion

In summary, we have described the development of a dual catalytic manifold that enables the 1,2-arylsulfonylation of electron-rich alkenes. Our method showed good functional

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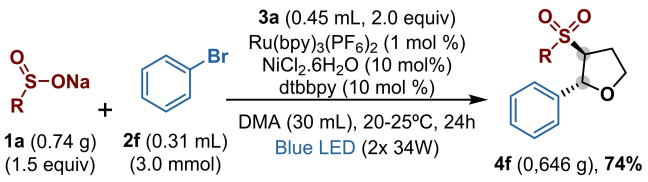
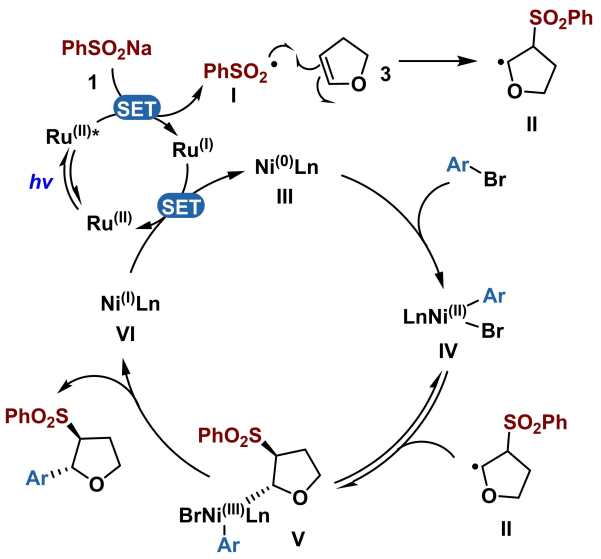


Scheme 5. Scale up experiment.



Scheme 6. Mechanistic proposal.

group tolerance, high diastereoselectivities and a wide scope, even with challenging substrate combinations. Indeed, the method is applicable to (hetero)aryl backbones and to advanced synthetic intermediates with equal ease, thus allowing to access densely functionalized sulfinylated building blocks from simple precursors. Further extensions of this chemistry and related endeavors are currently underway in our laboratories.

Experimental Section

General procedure for the sulfonyl-arylation of 2,3-dihydrofuran: a dried Schlenk tube of borosilicate glass equipped with a stir bar was charged with sodium sulfinate **1** (0.3 mmol, 1.5 equiv.), Ru-(bpy)$_3$(PF$_6$)$_2$ (1 mol %), NiCl$_2$.6H$_2$O (10 mol %), dtbbpy (10 mol %). The Schlenk tube was then caped, and the atmosphere was exchanged by N$_2$ (three cycles of evacuation and refilling). Next, keeping a positive N$_2$ atmosphere, the Schlenk was charged with the aryl bromide **2** (1.0 equiv.), 2,3-dihydrofuran **3a** (2.0 equiv.), and DMA (1 mL). The system was sealed and transferred to a photoreactor, where it was irradiated with blue LED (451 nm, 603 mW) for 24 h under a controlled temperature (20–25 °C). Upon completion, the reaction mixture was diluted with distilled water and extracted with AcOEt (3×10 mL). The joined organic layers were washed with water to remove residual DMA, dried with anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/AcOEt as mobile phase to afford the desired product.

General procedure for the sulfonyl-arylation of vinyl esters: a dried Schlenk tube of borosilicate glass equipped with a stir bar was charged with sodium sulfinate **1** (0.3 mmol, 1.5 equiv.), Ru-(bpy)$_3$(PF$_6$)$_2$ (1 mol %), NiBr$_2$.diglyme (10 mol %), dtbbpy (10 mol %). The Schlenk tube was then caped, and the atmosphere was exchanged by N$_2$ (three cycles of evacuation and refilling). Next, keeping a positive N$_2$ atmosphere, the Schlenk was charged with the aryl bromide **2** (1.0 equiv.), the vinyl ester **3** (2.0 equiv.), and DMA (1 mL). The system was sealed and transferred to a photoreactor, where it was irradiated with blue LED (451 nm, 603 mW) for 48 h under a controlled temperature (20–25 °C). Upon completion, the reaction mixture was diluted with distilled water and extracted with AcOEt (3×10 mL). The joined organic layers were washed with water to remove residual DMA, dried with anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/AcOEt as mobile phase to afford the desired product.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: sulfonyl-arylation · diastereoselective · dual catalysis · difunctionalization · photoredox

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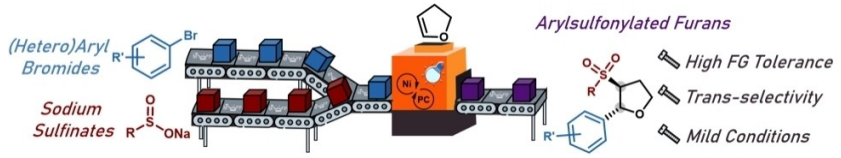

A dual photocatalytic sulfonylation-arylation of electron-rich alkenes is described. This protocol proceeds under mild reaction conditions and high functional group tolerance, streamlining the access to densely functionalized sulfonylated architectures from simple precursors and in high diastereoselectivities.

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