Direct C-H-Sulfonylation of 6-Membered Nitrogen-Heteroaromatics

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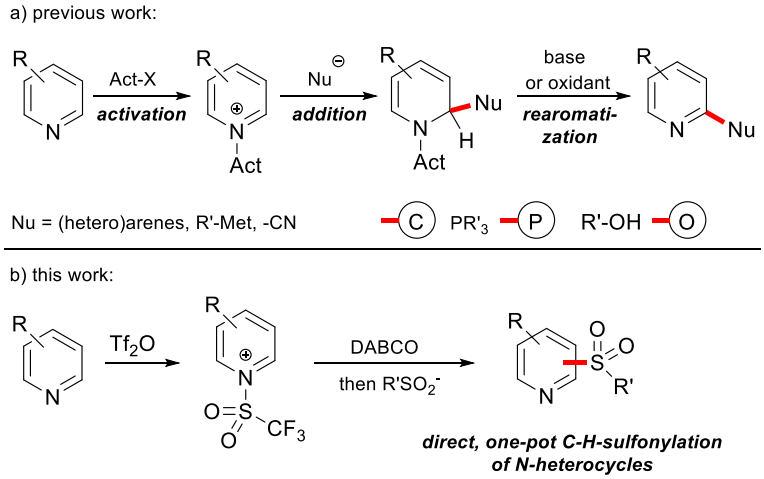
Abstract: Heterocyclic sulfones and sulfonamides represent important structural motives in medicinal chemistry and drug development. Therefore, efficient and reliable methods for their construction from simple building blocks are in high demand. Herein we report a novel approach for the direct C-H-sulfonylation of N-heteroaromatics via N-activation with triflic anhydride (Tf_2O), base-mediated addition of a sulfinate salt and subsequent rearomatization through trifluoromethanesulfinate elimination. This operationally simple one-pot protocol enables direct access to various sulfonylated 6-ring N-heterocycles. It is applicable to the late-stage functionalization of complex, drug-like molecules. The direct incorporation of sulfur dioxide with organometallic reagents as well as the utilization of a rongalite-based sulfonylation reagent provide opportunities for a highly modular synthesis of N-heterocyclic sulfones and sulfonamides from three different building blocks.

Introduction

Pyridines are omnipresent in synthetic organic chemistry and represent one of the most prevalent heterocycles in pharmaceuticals and natural products.[1] Most approaches for the synthesis of pyridine-containing target compounds employ prefunctionalized building blocks.[2] Alternatively, strategies for the direct functionalization of the pyridine scaffold can enable a more streamlined synthesis and offer ample opportunities for late-stage modification of the heterocyclic core.[3] The Minisci reaction represents a well-known and frequently used method for the direct alkylation, acylation or arylation of pyridines and other electron-deficient N-heterocycles.[4] Another approach for the direct functionalization of pyridines utilizes the corresponding *N*-oxides. After initial oxidation, activation of the oxygen renders the *N*-oxide reactive towards the addition of various nucleophiles.[5] Although this approach has been successfully exploited for the introduction of various functionalities, the corresponding *N*-oxides have to be synthesized and isolated in an additional step. As the oxidants required for the preparation of the *N*-oxides can also lead to the oxidation of various other functional groups, this approach is inherently limited. In addition, *N*-oxides are in general highly polar, hygroscopic and water-soluble, which renders the purification and handling of these compounds difficult.[6]



Scheme 1. Direct C-H-functionalization of activated pyridinium salts.

More recently, metal-catalyzed reactions for the direct functionalization of pyridines and related heterocycles via a metal-catalyzed C-H-activation have received increasing attention.[7] Usually, these types of transformations require an additional directing group and/or are limited to the formation of new C-C-bonds. The functionalization of pyridines via the corresponding *N*-pyridinium salts offers an attractive alternative for the direct installation of various new substituents (Scheme 1a).[5] After initial electrophilic activation of the N-atom with a suitable reagent, the heteroaromatic ring becomes more susceptible towards the addition of a nucleophilic species. Subsequent rearomatization, either via base-mediated elimination or oxidation, furnishes the modified heterocycle. This approach has been successfully exploited for the introduction of various carbon- and heteroatom functionalities.[8] Surprisingly, an analogous method for the direct installation of the important sulfonyl functionality into N-heteroaromatics has, to the best of our knowledge, not been reported so far.

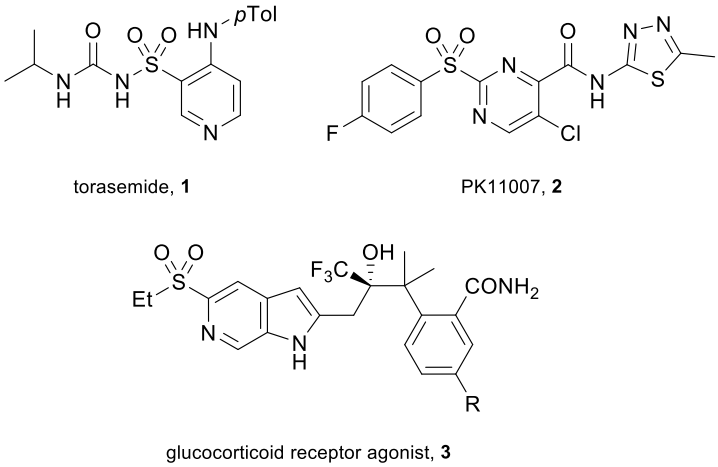


Figure 1. Bioactive, sulfonyl-containing N-heteroaromatics

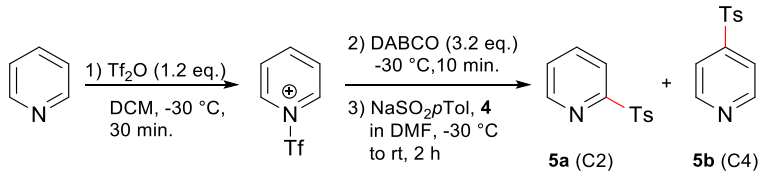
Sulfonyl-derived functional groups, such as sulfones or sulfonamides, are of particular importance for the synthesis of bioactive molecules.[9] As a result, both the sulfone and the sulfonamide moiety can be found in various biologically active N-heteroaromatics, such as the diuretic torasemide **1**[10], the anticancer agent PK 11007 **2**[11] or the nonsteroidal glucocorticoid receptor agonist **3**.[12] Therefore, a protocol for the direct installation of the sulfonyl functionality onto N-heteroaromatics would provide a highly versatile tool for medicinal chemistry with various potential applications in target synthesis and library generation. Herein, we report the development of a novel method for the direct sulfonylation of 6-membered N-heteroaromatics,

which is applicable to the late-stage diversification of complex, drug-like molecules (Scheme 1b).

Results and Discussion

We planned to exploit the previously reported activation of N-heterocycles with triflic anhydride for a mild and convenient late-stage sulfonylation procedure. After initial activation of the heterocycle, the sulfonyl functionality should be installed using a sulfinic acid salt[13] as nucleophile. Base-induced elimination of a trifluoromethanesulfinate anion should finally furnish the desired sulfonylated heteroaromatic product. Pyridine was chosen as model substrate to elucidate the feasibility of our envisioned one-pot approach (Table 1). A first survey of different reaction conditions, solvents and bases quickly revealed, that our initially envisioned three-stage process did not lead to the desired product at all. Activation of pyridine with Tf_2O in DCM followed by the addition of sodium *para*-toluenesulfinate **4** and subsequently an external base did not furnish the sulfonylated pyridine **5**.

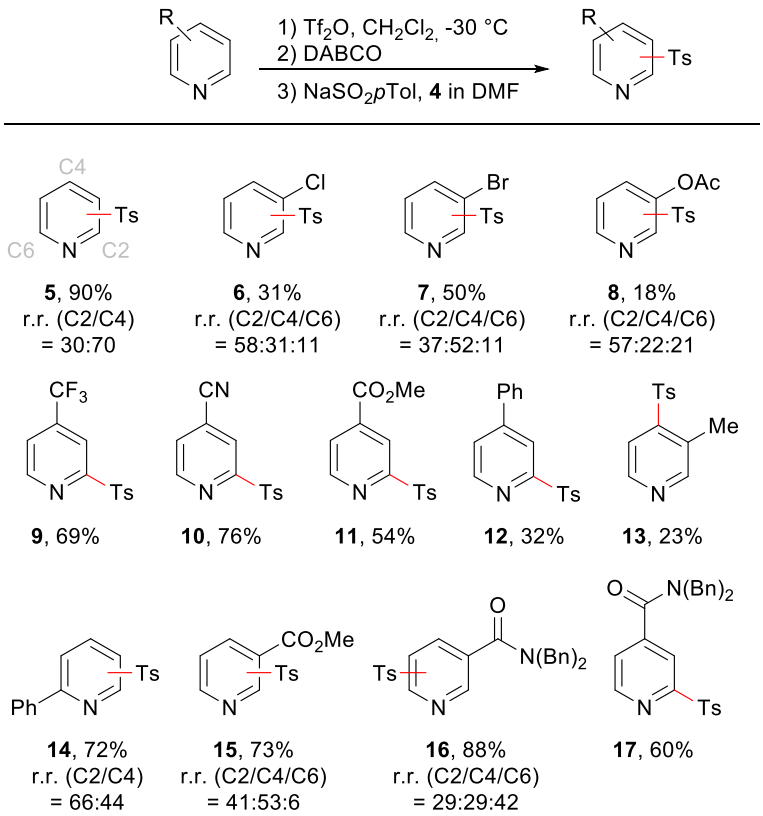
Table 1. Optimisation of reaction conditions



entry	deviating from standard conditions	Yield /[%][a]	Regioisomeric ratio (C2/C4)[b]
1	**none**	**87**	**30:70**
2	-78 °C instead of -30 °C[c]	90	31:69
3	0 °C instead of -30 °C	-[d]	n.d.
4	MeCN instead of DCM	-[d]	n.d.
5	$CHCl_3$ instead of DCM	83	22:78
6	Addition of $NaSO_2Tol$ before DABCO	-[d]	n.d.
7	DABCO and $NaSO_2Tol$ together	88[d]	26:74[d]
8	DMSO instead of DMF	25-65[d]	~ 23:77
9	NMP instead of DMF	55	48:52
10	2.0 equiv. DABCO instead of 3.2 equiv.	< 5[d]	37:63[d]
11	DIPEA or DBU instead of DABCO	< 5[d]	n.d.

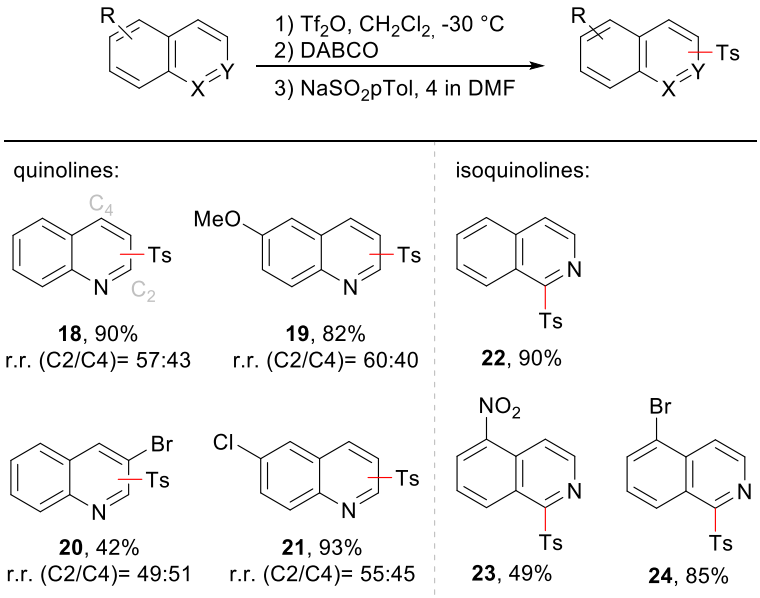
[a] isolated yields, [b] regioisomeric ratio determined by NMR of the crude mixture, [c] 1.5 h instead of 30 min., [d] yields and regioisomeric ratio determined by GC with dodecane as internal standard, DABCO = 1,4-diazabicyclo[2.2.2]octan, DIPEA = *N*,*N*-diisopropylethylamin, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Instead, addition of sulfinate **4** to the in situ generated pyridinium triflate promoted an instantaneous decomposition of the sulfinic acid salt. Furthermore, the low solubility of sodium sulfinate **4** in common organic solvents caused further complications. The use of polar, aprotic solvents, which can solubilize sulfinic acid salts is mandatory for a successful reaction. However, typical polar aprotic solvents, such as DMF or DMSO, led to additional side reactions, presumably by decomposition of the solvent with Tf_2O and/or the triflated pyridine.[14] After extensive experimentation, we realized, that the choice of base, as well as the order of addition, are decisive factors for obtaining the desired product **5**. The direct addition of 1,4-diazabicyclo[2.2.2]octane (DABCO) to the activated pyridinium species proved to be crucial for a successful transformation. Subsequent addition of a solution of the sulfinate salt **4** in DMF and warming of the mixture to room temperature afforded the desired sulfonylated pyridine **5** in 87% yield as a mixture of two regioisomers (entry 1). Cryogenic conditions are important during the first two steps in this procedure. Performing the reaction sequence in DCM at –78 °C or –30 °C afforded the desired product **5** in high yield and a comparable ratio of regioisomers (entries 1 and 2). Raising the temperatures to 0 °C in either the first or the second step led to no product formation at all (entry 3). DCM proved to be the solvent of choice for this transformation. No product was observed in various other solvents, including MeCN, which has been employed in similar transformations before (entry 4).[8a,b] However, similar yields and regioselectivties could be obtained using $CHCl_3$ as solvent (entry 5). If the sulfinic acid salt is added directly after the activation of pyridine, only decomposition products are observed (entry 6). Premixing of DABCO and the sulfinate in DMF and addition of this solution to the activated heterocycle provided the sulfonylated product **5** in similar yields as the stepwise procedure (entry 7). Further studies with other substrates reveled, that the stepwise protocol (DABCO and then the sulfinate) leads to more reliable results. Therefore, the stepwise approach was used throughout all subsequent studies. Addition of the sulfinic acid salt **4** dissolved in other polar aprotic solvents, e.g. DMSO or NMP, furnished the sulfonylated pyridine in lower yields (entries 8 and 9). The high melting points of DMSO (19 °C) and NMP (-24 °C) led to inhomogeneous mixtures, partially freezing of the solution and difficulties in stirring during the addition step. As a result, we encountered problems reproducing these reactions and inconsistent variations in the isolated yield, in particular in the case of DMSO. Therefore, DMF (melting point -61 C°) was chosen as polar aprotic cosolvent for all further studies. The addition of 3.2 equiv. of DABCO is crucial for an efficient transformation. Decreasing the amount to only 2.0 equiv. leads to a complete shutdown of the reaction (entry 10). In the presence of other bases, such as DIPEA or DBU, only traces of the desired product could be detected (entry 11).



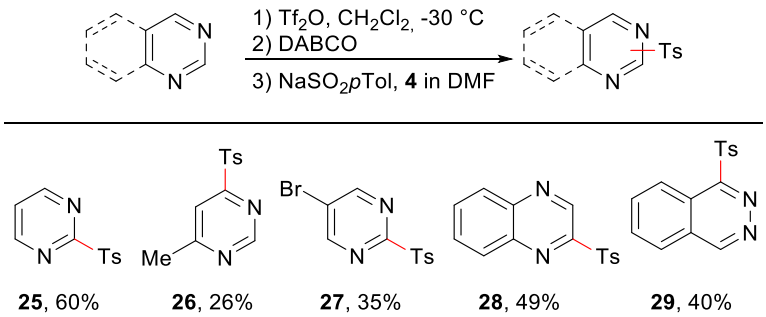
Scheme 2. Direct C-H-sulfonylation of pyridines

With the optimized procedure at hand, we investigated the substrate scope of this transformation. To our delight, this novel one-pot process proved efficient for the direct C-H-sulfonylation of a range of N-heteroaromatics. Pyridines bearing different substituents, including labile functionalities, such as ester, cyano or amide groups, were directly transformed into the corresponding sulfones **6-17** in 20-92% yield (Scheme 2). Whereas the sulfonylation of 4-substituted pyridines afforded only one regioisomer, reaction with 2- or 3-substituted pyridines usually led to a mixture of 2 or respectively 3 different regioisomers. Although the formation of more than one regioisomer can make the purification process more tedious, the isolation of these additional compounds could on the other hand provide highly valuable analogues for QSAR studies.



Scheme 3. Direct C-H-sulfonylation of quinolines and isoquinolines

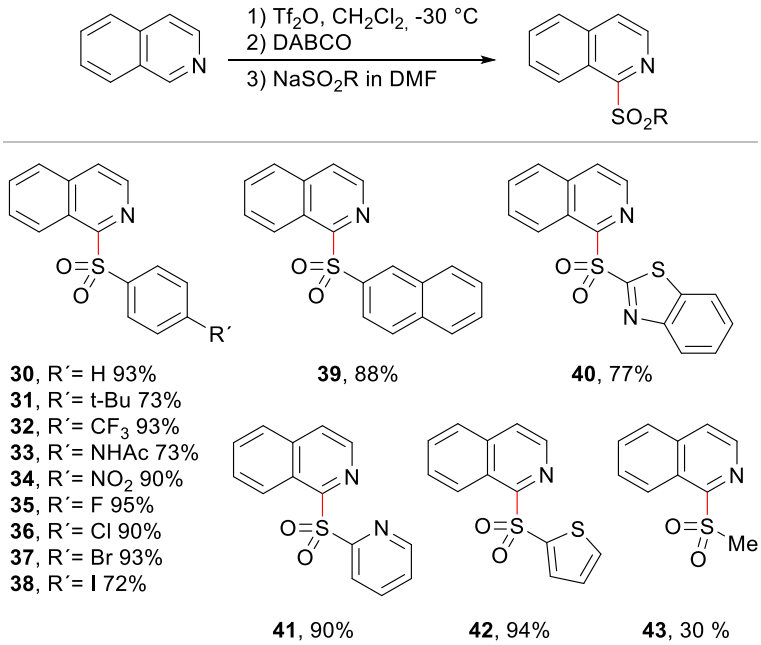
Quinolines and isoquinolines constitute important heterocyclic scaffolds in pharmaceutical chemistry and are therefore attractive substrates for our study. Pleasingly, the direct one-pot functionalization of quinolines proceeded smoothly, affording the sulfonylated products **18**-**21** in 42-93% yield (Scheme 3). In all cases an almost equimolar mixture of the C2- and the C4-regisomer was obtained. Due to the facile chromatographic separation of both regioisomers, our one-pot process can be utilized for the simultaneous synthesis of two compounds for extensive screening of structure-activity relationships. The direct functionalization of isoquinolines proceeded efficiently, furnishing selectively the C2-sulfonylated products **22**-**24** in 49-90% yield.



Scheme 4. Direct C-H-sulfonylation of diazines

In parallel, we investigated the direct sulfonylation of different diazines, another important scaffold in bioactive molecules (Scheme 4). To our delight, the sulfonylated pyrimidines **25**-**27** were isolated 26-60% yield with high regioselectivities (r.r. > 95/5) via the direct functionalization of the parent heterocycle. C-H-sulfonylation of quinoxaline and phthalazine furnished the desired sulfones **28** and **29** in 49 and 40% yield. Although the obtained yields for the sulfonylated diazines are only moderate, our one-pot procedure still can afford sufficient material for first biological studies.

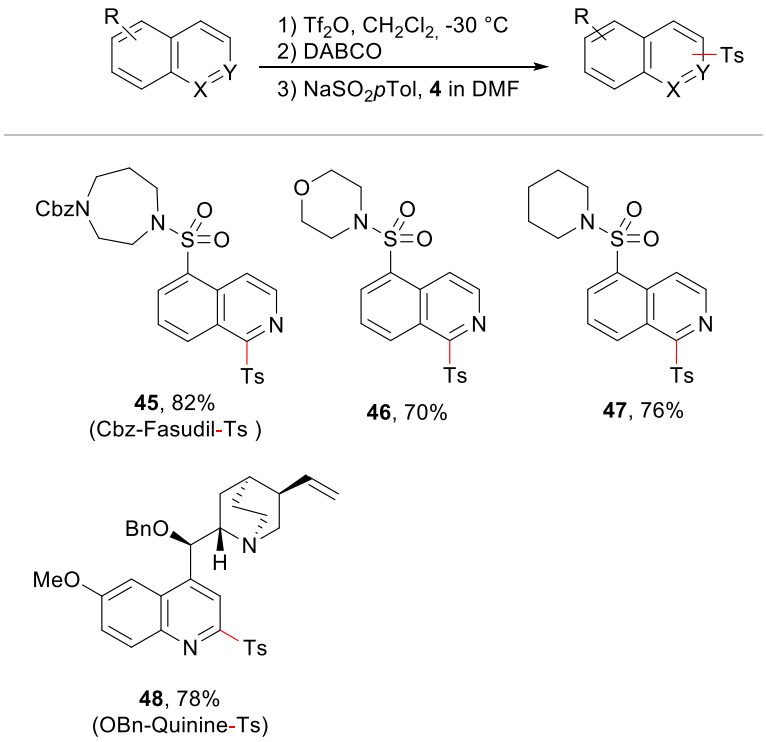
Next, we turned our attention towards the incorporation of different sulfonyl residues into N-heterocycles. Therefore, the direct functionalization of isoquinoline as simple model substrate with different sulfinic acid sodium salts was investigated (Scheme 5). In general, reactions with different aromatic sodium sulfinates proceeded efficiently, furnishing the desired sulfones **30-39** in 72-95% yield. Different functional groups, including halides, a nitro group or an amide, were well tolerated. This method could be extended to the direct installation of heterocyclic residues **40-42**. Only reactions with alkyl sulfinates, such as sodium methane sulfinate, proved to be problematic, affording the methyl sulfone **43** in a low yield of 30%. In the case of the corresponding trifluoromethane suflinic acid sodium salt, only traces of the desired product were observed.



Scheme 5. Direct C-H-sulfonylation of isoquinoline with various sulfinates

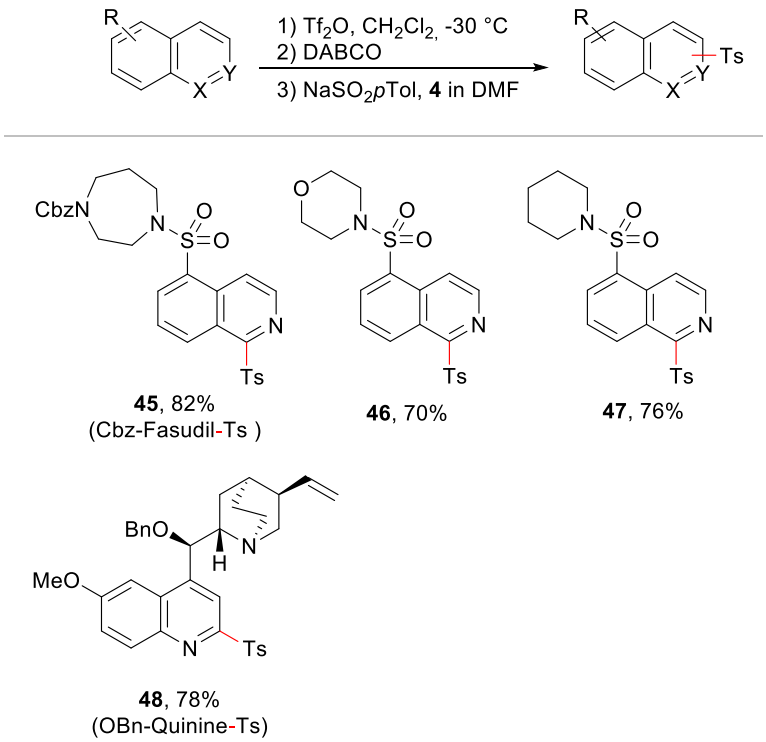
To further demonstrate the applicability of our method for medicinal chemistry, we examined the late-stage diversification of drug-like molecules and natural products. By using our standard protocol, we were able to directly introduce a sulfonyl residue into Cbz-protected Fasudil **44** (treatment of cerebral vasospasm and cognitive decline) and two of its close structural analogues, giving the desired sulfones **45-47** in high yields (Scheme 6). To our delight, the direct C-H-sulfonylation of OBn-Quinine afforded the desired sulfone **48** in 78% yield as a single regioisomer. These examples showcase the utility of our method for a controlled late-stage incorporation of the sulfonyl functionality into complex bioactive molecules.

In order to extend the scope of our method, we investigated different approaches for a modular installation of the sulfonyl functionality. In the last years, the synthesis of sulfones and sulfonamides using either sulfur dioxide or a suitable surrogate, has emerged as a versatile tool for the rapid construction of these functional groups.[15] In this regard the trapping of organometallic reagents with sulfur dioxide provides a convenient access to the corresponding sulfinic acid salts. To evaluate the possibility of a direct SO_2 incorporation, we prepared the benzene sulfinic acid salt **49** in quantitative yield from the reaction of phenyl lithium with SO_2 (Scheme 7). Gratifyingly, the obtained crude lithium sulfinate **49** could be used directly for the C-H-sulfonylation of both pyridine and isoquinoline heterocycles.



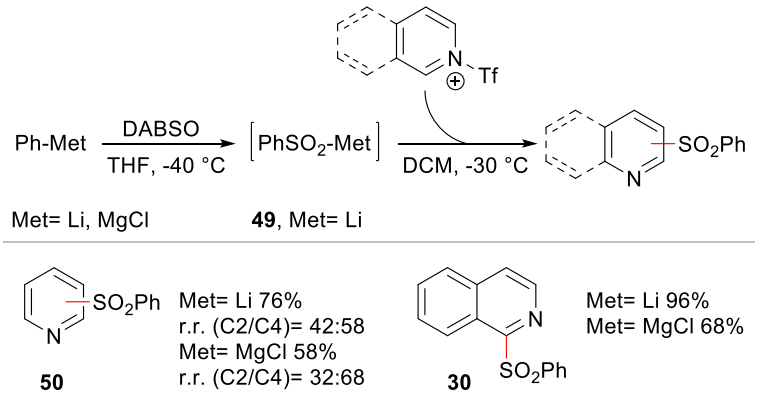
Scheme 6. Late-stage C-H-sulfonylation of drug-like molecules and natural products.

The desired products **30**, **50**-**52** were formed in yields and regioselectivities within the same as for the corresponding sodium sulfinates. Due to the decreased solubility of the lithium salt in DMF, a DMF/DMSO solvent mixture had to be used. To our delight, the crude phenyl sulfinate proved to be a versatile building block for the late-stage C-H-sulfonylation of more complex drug-like structures and natural products. The sulfonylated Fasudil analogues **53**-**55** and the quinine derivative **56** could be prepared in 67-97% yield from the phenyl sulfinic acid lithium salt **49**. These examples demonstrate, that our one-pot protocol can be extended to a modular installation of sulfonyl residues with SO_2 as key building block.



Scheme 7. C-H-sulfonylation based on a SO_2-derived lithium sulfinate

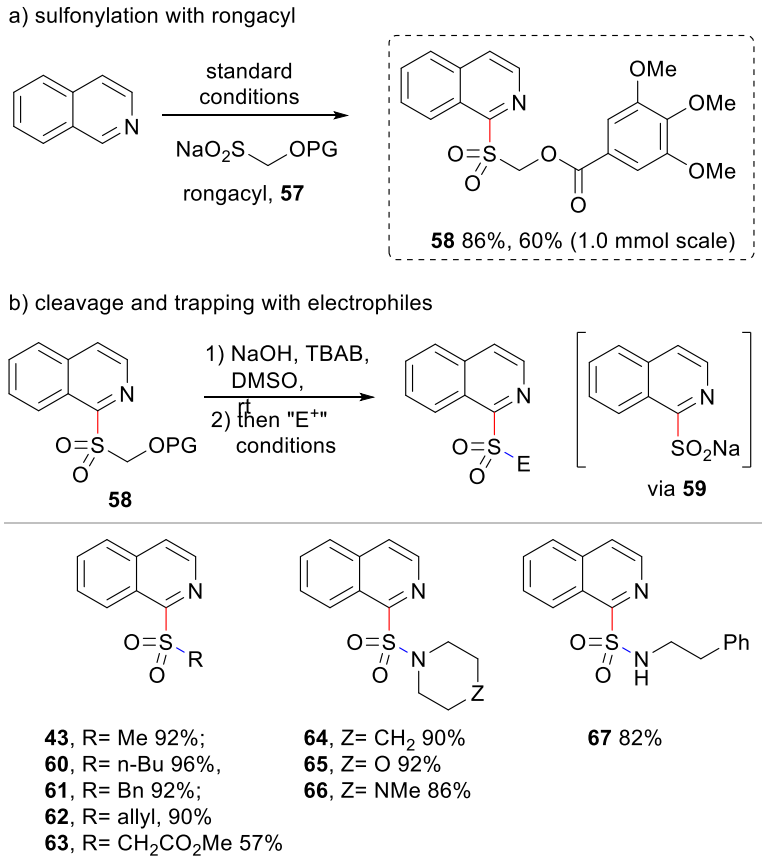
As SO_2 is a corrosive and toxic gas, safe handling in a typical laboratory setting, is usually considered problematic. The introduction of easy-to-handle, solid SO_2 surrogates, has been the single-most important driving force in advancing SO_2 insertion reactions in organic synthesis and medicinal chemistry. The DABCO-bis(sulfur dioxide) adduct DABSO, pioneered by Willis,[16] is arguably the most popular solid sulfur dioxide surrogate. As DABSO already contains one molecule of DABCO, the crucial base for our transformation, we envisioned, that this surrogate might be an ideal building block for our purposes. Therefore, we investigated a sequential, one-pot three-component version of our sulfonylation procedure. Towards this end, a solution of phenyl lithium sulfinate **49**, prepared from phenyllithium and DABSO, was added directly to a solution of the activated heterocycle (Scheme 8).



Scheme 8. One-pot approach using DABSO as building block

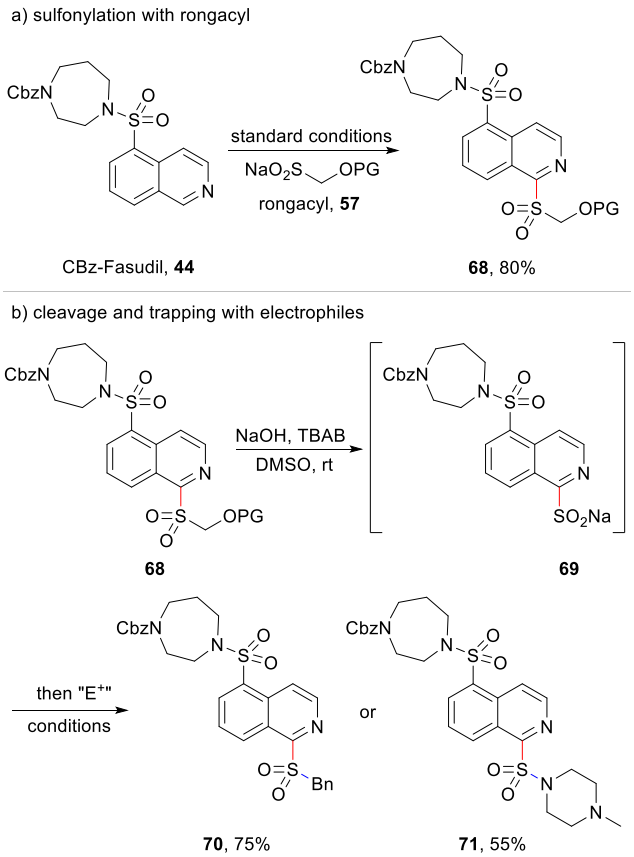
As expected, the reaction proceeded smoothly, and both the sulfonylated pyridine **50** and isoquinoline **30** could be isolated in high yields. In a similar manner, the sulfonylated heterocycles **30** and **50** could be prepared starting from phenyl magnesium chloride as organometallic reagent, albeit in slightly lower yields. These examples showcase the utility of

our method for a highly modular and operational simple direct functionalization of N-heteroaromatics.



Scheme 9. Modular assembly of sulfones and sulfonamides using rongacyl **57**. "E^+"= electrophil; PG= 3,4,5-trimethoxybenzoyl; TBAB= Tetrabutylammonium bromide; For sulfones: R-Hal, 50 °C, 3 h; For sulfonamides: NHR'R'', *N*-Bromo-succinimide, THF, 0 °C, 1 h.

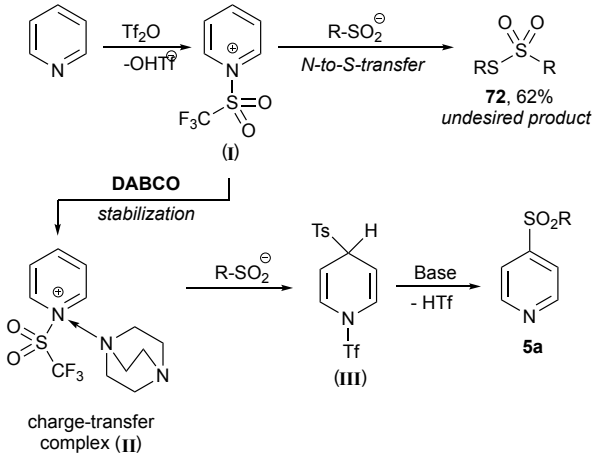
Another approach towards the modular synthesis of sulfones and sulfonamides is the utilization of synthetic equivalents of the SO_2^{2-} anion, such as SMOPS (3-morpholinopropanesulfonic acid)[17], BTS (sodium benzo[d]thiazole-2-sulfinate)[18] or rongalite[19]. Among these different reagents, the protected rongalite derivative (rongacyl) **57** offers a highly flexible access to various sulfonyl-functionalities.[20] Therefore, we investigated the incorporation of this masked sulfinate using our novel methodology. To our delight, the reaction of rongacyl **57** with isoquinoline using our standard conditions afforded the desired sulfone **58** in 86% yield on a 0.5 mmol scale (Scheme 9). Performing the reaction on a 1 mmol scale led to a slightly decreased yield of 60%. Next, we investigated the base-mediated cleavage of the sulfone **58** and trapping of the in situ formed sulfinate **59** with different alkyl halides. As seen in Scheme 9 various alkyl sulfones (**43**, **60**-**63**) could be prepared in 49-96% yield from **58** as the common intermediate. Reaction of the released sulfinate **59** with an amine and NBS afforded the sulfonamides **64**-**67** in 82-92% yield. These examples, demonstrate, that our direct C-H-sulfonylation with a masked sulfinate, such as rongacyl **57**, can serve as linchpin for the diversification of any given N-heterocycle into a diverse library of different sulfones and sulfonamides.



Scheme 10. Late-stage diversification of Cbz-protected Fasudil **44**. "E^+"= electrophil; PG= 3,4,5-trimethoxybenzoyl; TBAB= Tetrabutylammonium bromide; For sulfones: R-Hal, 50 °C, 3 h; For sulfonamides: NHR'R'', *N*-Bromo-succinimide, THF, 0 °C, 1 h.

Indeed, we could successfully apply this linchpin-approach to prepare two more Fasudil analogues (Scheme 10). The reaction of CBz-protected Fasudil **44** with the reagent **57** using our standard protocol furnished the key building block **68** in 80% yield. Base mediated cleavage and trapping of the formed sulfinate **69** afforded either the benzyl sulfone **70** or the sulfonamide **71** in 75 and 55% yield. The last two examples highlight the potential for our one-pot C-H-sulfonylation procedure for a highly modular late-stage diversification of complex, drug-like molecules. This process could provide a highly enabling tool for the synthesis of focused libraries from highly advanced intermediates or natural products.

Based on the reported mechanism for similar transformations [8], we initially envisioned a similar pathway for our sulfonylation process. Reaction of the N-heterocycle, exemplified by pyridine in scheme 11, affords the activated pyridinium salt (**I**). Usually, a direct addition of the nucleophilic species to the activate heterocycle leads of the formation of the new carbon-carbon or carbon-heteroatom bond. In our cases, direct addition of the sulfinate salt to the activated pyridinium salts does not furnish any desired product at all. Only decomposition of the sulfinate and formation of a thiosulfonate of type **72** were observed (see SI for experimental details). Presumably a direct N-to-S transfer of the CF_3SO_2-group takes place in the absence of DABCO. We assume, that addition of DABCO affords a charge transfer complex (**II**), which display a decreased reactivity on the sulfur atom. Reaction of the sulfinate salt with this complex leads to the desired addition of the sulfinate onto the activated heterocycle. As previously shown for other nucleophiles,[8] addition can either occur in the ortho- or the para-position, depending on the electronics and sterics of the corresponding N-heterocycle (for the sake of clarity only addition into the para-position is depicted in Scheme 11). Final base-mediated elimination of trifluoromethanesulfinic acid from intermediate (**III**) furnishes the rearomatized product **5a**.



Scheme 11. Proposed reaction pathway for the DABCO-mediated sulfonylation.

Conclusion

In conclusion, we have developed a straightforward method for the direct incorporation of the sulfonyl functionality into 6-ring N-heteroaromatics. This operationally facile procedure is based on the preactivation of the N-heterocycle with triflic anhydride followed by a DABCO-mediated addition of a nucleophilic sulfinate and a subsequent elimination-rearomatization. This method gives access to various sulfonylated N-heteroaromatics in good yields via a direct C-H-sulfonylation. We were able to extend our methodology towards the modular installation of sulfone or sulfonamide residues using either SO_2 or a masked SO_2^{2-} equivalent as key building blocks. Last but not least, we could demonstrate the utility of our method in the late-stage diversification of drug-like molecules and natural products. Altogether, this novel transformation can provide a highly enabling tool for the synthesis of biologically relevant sulfonylated N-heterocycles, an important scaffold for the development of new drugs.

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Author Contributions

Conceptualization: M. F., S. S. and G. M.; investigation and methodology: M. F., L. S., K. H., R. Z. and S. S.; Funding acquisition: N. M. and G. M.; supervision: N. M. and G. M.; writing, original draft: M. F. and G. M.; writing, reviewing & editing: M. F., S. S., N. M. and G. M.

Keywords: Sulfones, Sulfinate salts, N-Heteroaromatics, C-H-Functionalization,

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