Strain-Enabled *S*-Arylation and *S*-Alkenylation of Sulfinamides

Xi Zou, # Boming Shen, # Gao-lin Li, Qian Liang, Yanhua Ouyang, Binghe Yang, Peiyuan Yu,* and Bing Gao*

Abstract: Converting commercially available and affordable chiral sulfinamides to pharmaceutically important chiral sulfoximines via S^{IV}-functionalization is synthetically appealing, however, remains little developed due to the competing *N*-functionalization pathway. To address this challenge, we disclose a strain-enabled stereospecific and chemoselective *S*-arylation and *S*-alkenylation of sulfinamides using arynes and cyclic alkynes. The origin of high S^{IV}-selectivity is elucidated by density functional theory (DFT) calculations, which reveals the potential involvement of a novel concerted mechanism. This method affords unprecedented chemical diversity on groups attached to the nitrogen center (*N*-R) that is valuable for diversity-oriented drug discovery.

Sulfoximines are isosteres of sulfones where one "=O" is substituted by an imino group "=NR" on sulfur(VI) (Figure 1A)[1] This modification is profound, because 1) chemical space on S^{VI} is expanded to three-dimensional ligations with a remarkable increase of molecular complexity, 2) the chemical, physical, and biological profiles become tunable and diversified that affords new functions,[2] and 3) the stereochemistry on and by the stereogenic S^{VI} center is enabled.[3] Therefore, sulfoximines are valuable targets in pharmaceuticals[4] and agrochemicals,[5] and useful reagents for organic synthesis.[6]

Conventional synthetic access to optically pure sulfoximines rely on kinetic resolution of racemic mixtures, affording one stereoisomer of interest in no more than 50% yield.[7] Alternatively, chiral sulfoxides or sulfimines are pre-installed, then converted to sulfoximines in a stereospecific manner.[8] Desymmetric modifications of the appendant groups of S^{VI} are also reported with specific substrates.[9] Despite being useful for the preparation of optically pure sulfoximines, these methods would not allow the direct creation of C–S^{VI} bond at the late stage of synthesis, thus restricting their potential utility in drug discovery.

Chiral sulfinamides are readily available through many synthetic processes, making them attractive substrates to prepare sulfoximines via S^{IV}-functionalization. Notably, the *tert*-butylsulfinamide is a commercial chemical in optically pure form at a low price.[10] However, one major challenge for this *S*-

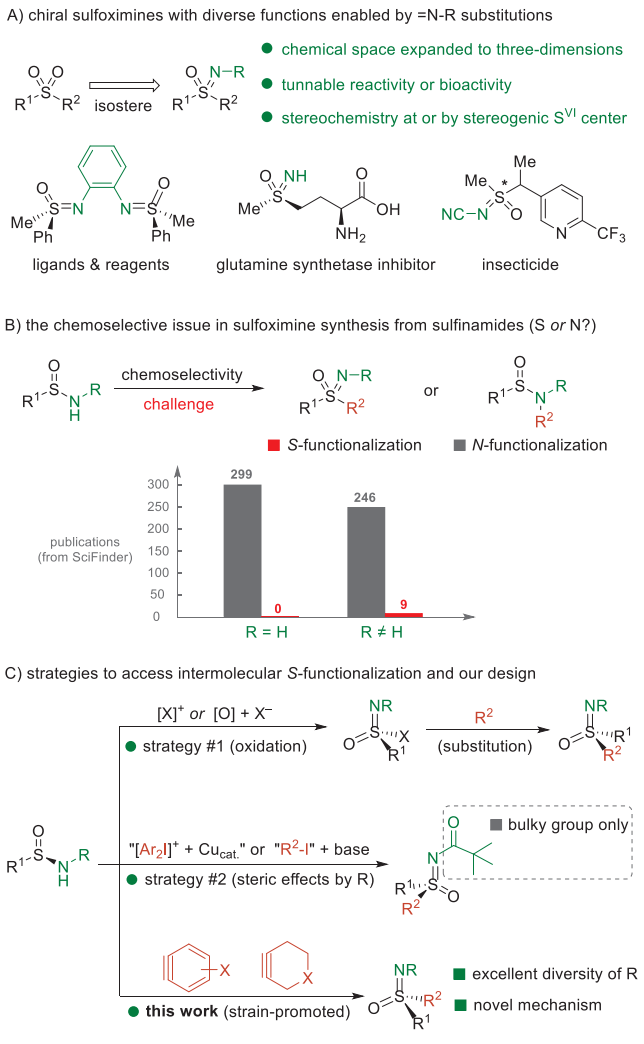


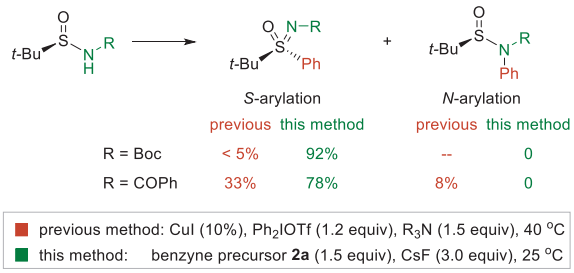
Figure 1, the challenge of *S*-functionalization and our design.

functionalization strategy is the undesired competing pathway of *N*-functionalization, which has actually dominated in previous studies (Figure 1B).[11] This is due to the fact that the nitrogen atom of sulfinamides, especially in its deprotonated form, is also a good nucleophile and less sterically congested than sulfur(IV) to be reacted with. One way to address this issue uses an oxidation-substitution stepwise protocol with halides as transient substituents (Figure 1C, strategy #1).[12, 13] A few ring-closing reactions might benefit *S*-functionalization but are limited in scope and applications.[14] Recently, Maruoka and Kano have established elegant *S*-alkylation and *S*-arylation of sulfinamides in reactions with alky halides and hypervalent iodine reagents (Figure 1C, strategy #2).[15, 16] By taking advantage of the steric hindrance of a bulky *N*-pivaloyl group, the *N*-substitutions are suppressed.

Disclosed herein is our development of a novel *S*-arylation and *S*-alkenylation of sulfinamides by harnessing the unique reactivity of strain-containing arynes and cyclic alkynes (Figure 1C, strategy 3#). The transformation is stereospecific and exclusively chemoselective on S^{IV} center, affording unprecedented functional group tolerance and structural diversity of the "–NR" vectors. The enriched chemical space of "=NR" on sulfoximines obtained thereof is valuable for drug development,[17, 18] which was restricted to specific protection groups due to the limitation of previous synthetic methods.

Results and discussion

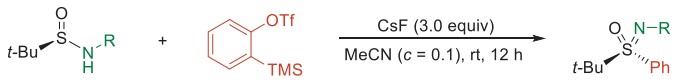
Strain-release as a strong driving force in arynes-based reactions that offers unique opportunities for organic synthesis[19] and has been widely appreciated since the pioneering work by Roberts,[20] Wittig,[21] and Huisgen.[22] With (*R*)-*N*-benzoyl *tert*-butylsulfinamide (**S3**) as the model substrate, the reaction with Kobayashi aryne precursor **2a**[23] in the presence of CsF at room temperature afforded sulfoximine (**3**) in high yield (Scheme 1, see supporting information 'SI' for reaction optimization). No *N*-arylation was detected that showed significant advantage to previous reaction systems. In a recent report,[16] the copper-catalyzed reaction of (*R*)-**S3** with diphenyl iodonium salt gave a mixture of *S*-arylation and *N*-arylation products, and only the use of a sterically more bulky pivaloyl group (Piv) could suppress the *N*-arylation.

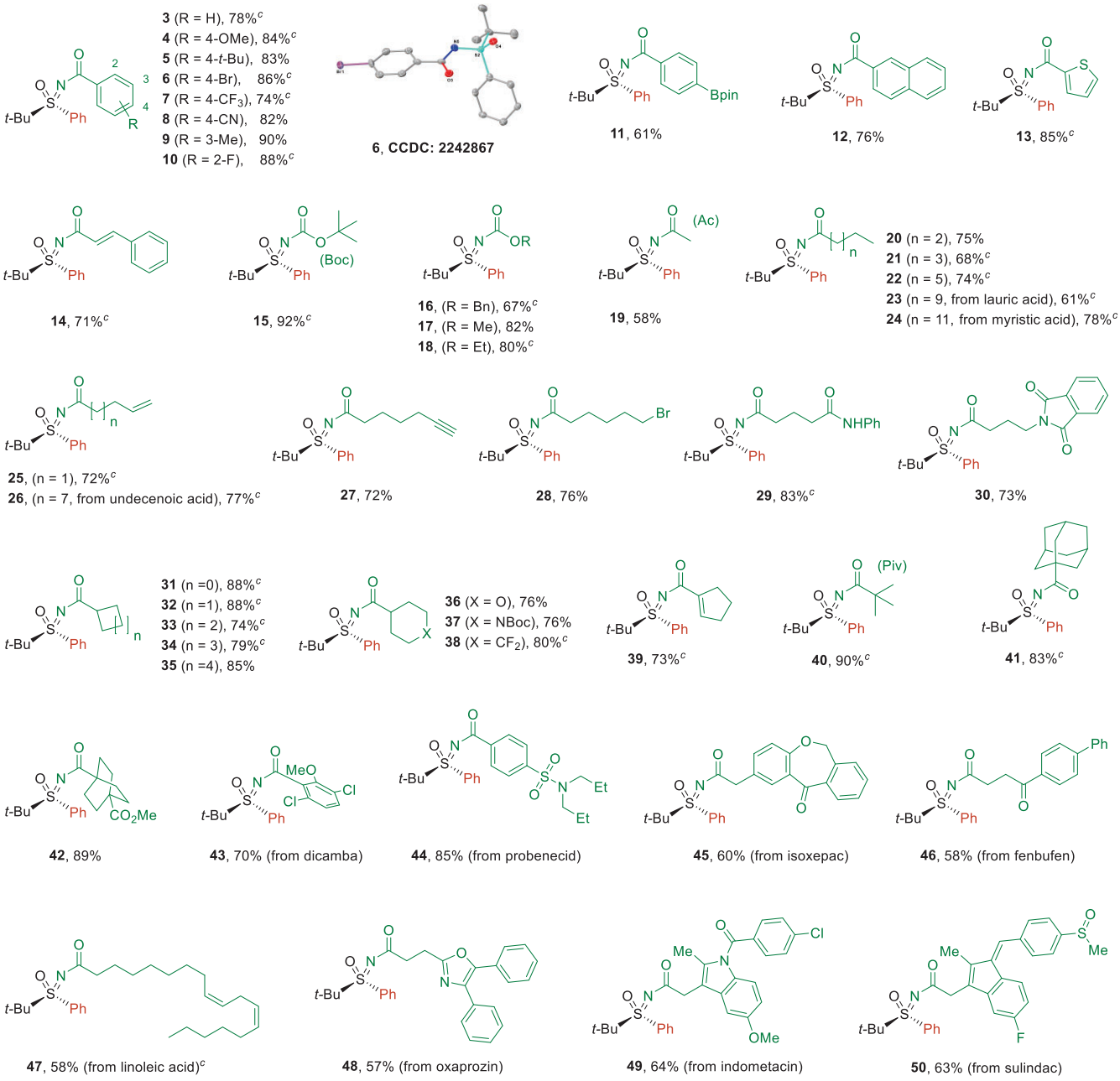


Scheme 1, the effect of *N*-substituents.

In Table 1, we demonstrated this *S*-arylation reaction was generally applicable to *tert*-butylsulfinamide bearing diverse –NR groups. When the benzoyl derivatives were used, the yields were excellent for substrates with either electron-donating or withdrawing motifs on the aromatic ring (**4**–**10**). Notably, a Bpin group was tolerated which would offer tremendous opportunity for late-stage functionalization (**11**). More examples included the heteroaryl motif (**13**) and an α,β-unsaturated amide motif (**14**). The alkyloxy carbonyl motifs, such as Boc and Cbz, were ubiquitous protection groups easy to install and remove. They were applicable in our reaction to afford exclusive *S*-arylation products (**15**–**18**). A broad spectrum of substrates containing alkyl carbonyl motifs of different lengths gave satisfactory yield of S-arylation products (**19**–**24**). Most importantly, functional groups including alkene (**25**, **26**), alkyne (**27**), alkyl bromide (**28**), amide (**29**, **30**), and ketone (**45**, **46**) were all well-tolerated. Some of these chemical handles could hardly survive in the previous *S*-arylation strategies where either harsh oxidation conditions[12] (alkene and terminal alkyne incompatible) or strong bases[15] (alkyl bromide incompatible) were applied. With our method, they could be left for diverse post-transformations. The cyclic side chains of various size turned out to be good as well, including the three- to seven-membered rings (**31**–**39**). Further increase of the steric hinderance of R group would not have negative impact on the related conversions (**40**–**42**). Finally, the mild reaction condition with excellent functional group tolerance, *S*-selectivity, and stereospecificity would allow us to do late-stage arylation of many sulfinamide-conjugated bioactive molecules and drugs. A few examples were highlighted accordingly in herein (**43**–**50**). In conventional approaches to these derivatives, free sulfoximines must be firstly prepared by multiple steps, including the protection and deprotection of the =NH motif, then were coupled with the other part by *N*-functionalization.

Table 1, the chemical diversity of –NR functional groups in the *S*-arylation of sulfinamides.[a,b]





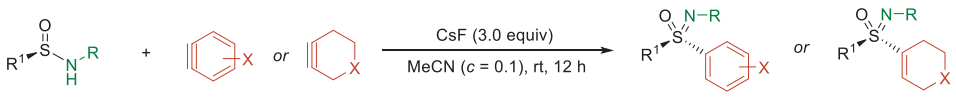
[a] Reaction conditions: sulfinamide **S3** (0.30 mmol), arynes (0.45 mmol), CsF (0.90 mmol), MeCN (3.0 mL), rt, 12 h. [b] Isolated yield. [c] No racemization was confirmed by chiral HPLC analysis.

Other chiral sulfinamides were available from a handful of synthetic processes and were used to investigate thescope of R^1 group (Table 2). We confirmed that the reaction was also not sensitive to the steric effects of the alkyl R^1 motifs, as compounds **51**–**54** were obtained in good yields. Again, alkyne and alkene were untouched under the current reaction conditions (**55**, **56**), as the reaction proceeded chemo-selectively on the S^{IV} center. Excellent compatibility to the electron effects of the aryl sulfinamides was observed. The yields maintained above 80% for either electron-deficient or electron-rich substrates (**58**–**63**).

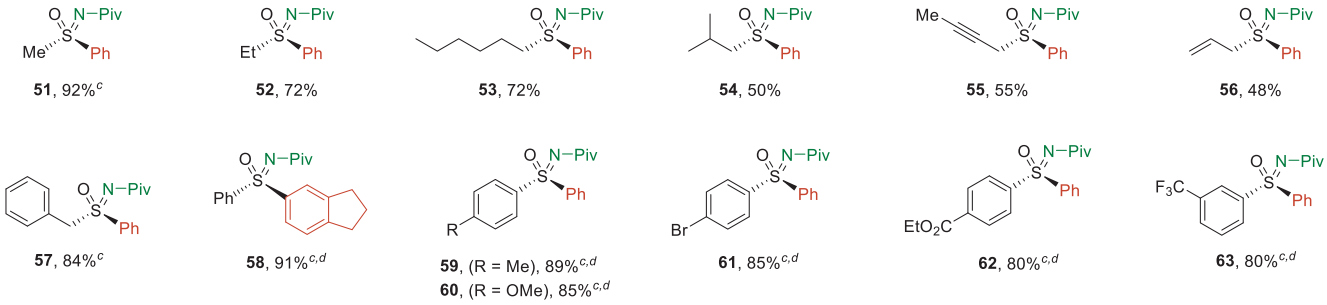
Arynes of different forms were also investigated under the standard reaction conditions with the commercially available (*R*)-*tert*-butylsulfinamide as the model substrate (Boc modified, Table 2). The unsymmetric arynes would give a mixture of *meta*

(*m*) and *para* (*p*) substituted arylation products (**64**, **65**). The *m*/*p* ratios were varied case-by-case.[24] On the other hand, the symmetric one gave a single product, and the yields were moderate to excellent as summerized therein (**66**–**71**).

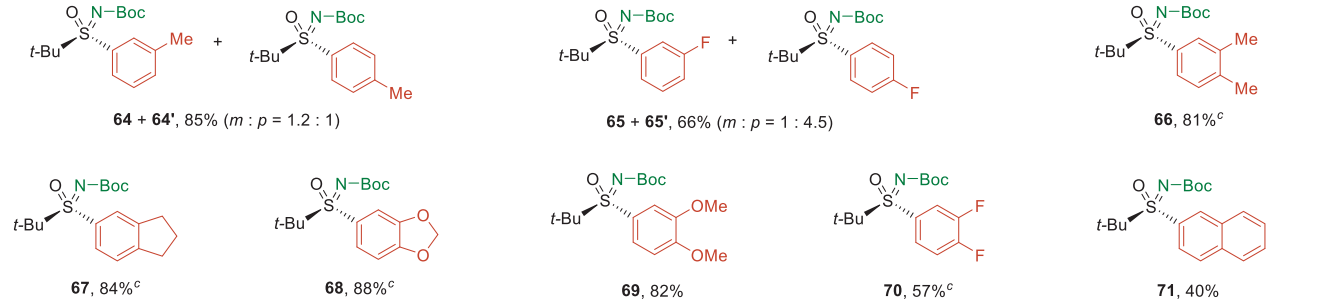
Table 2, the scope of sulfinamides, arynes, and strained cyclic alkynes in the *S*-arylation of sulfinamides. [a,b]



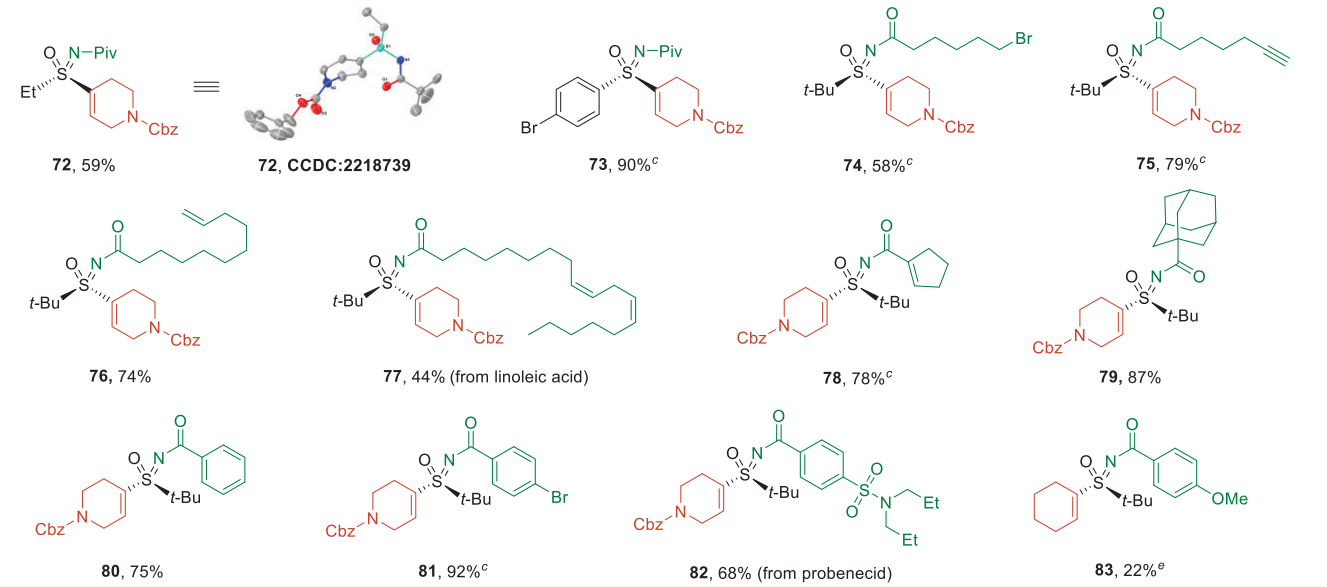
scope of sulfinamides



scope of arynes



strained cyclic alkyne-promoted sulfoximine synthesis



[a] Reaction conditions: sulfinamides (0.30 mmol), arynes (0.45 mmol) or 3,4-piperidyne (0.75 mmol), CsF (0.90 mmol), MeCN (3.0 mL), rt, 12 h. [b] Isolated yield. [c] No racemization was confirmed by chiral HPLC analysis. [d] Arynes (0.75 mmol). [e] 0.50 mmol scale.

Compared to arynes, the strained cyclic alkynes were less studied untile recently.[25] One of the most known modules was perhaps the cyclooctyne for copper-free click reaction and bioorthogonal conjugations that had gained enormous applications in chemical biology.[26] We envisioned that harnessing the strained intermediates for *S*-alkenylation might be a promising approach to the synthesis of alkenyl sulfoximines, which were otherwise difficult to access.[27] The

Cbz functionalized 3,4-piperidyne precursor was obtained in good yield through Garg's protocol.[28] To our delight, the standard reaction condition could be directly applied, giving the desired *S*-alkenylation product in 59% yield (**72,** Table 2). The regioselectivity was exclusively at the C4 terminus which was in good agreement with the reported theoretical prediction.[28] Both aryl and alkyl sulfinamides worked for this alkenylation reaction. Instead of giving a comprehensive scope of –NR motifs and functional group tolerance which had been demonstrated for arylation in table 1, here we only highlighted a few representative examples. The presence of bromide (**73**, **74**, **81**), alkyne (**75**), alkene (**76**, **77**), and α,β-unsaturated carbonyl group (**78**) were not affected. Substrates with either a bulky alkyl carbonyl group (**79**) or benzoyl groups (**80**, **81**, **82**) gave satisfactory yields. This method could also be extended to cyclohexyne (**83**), but the yield was slightly decreased due to the decomposition of the related alkynes.

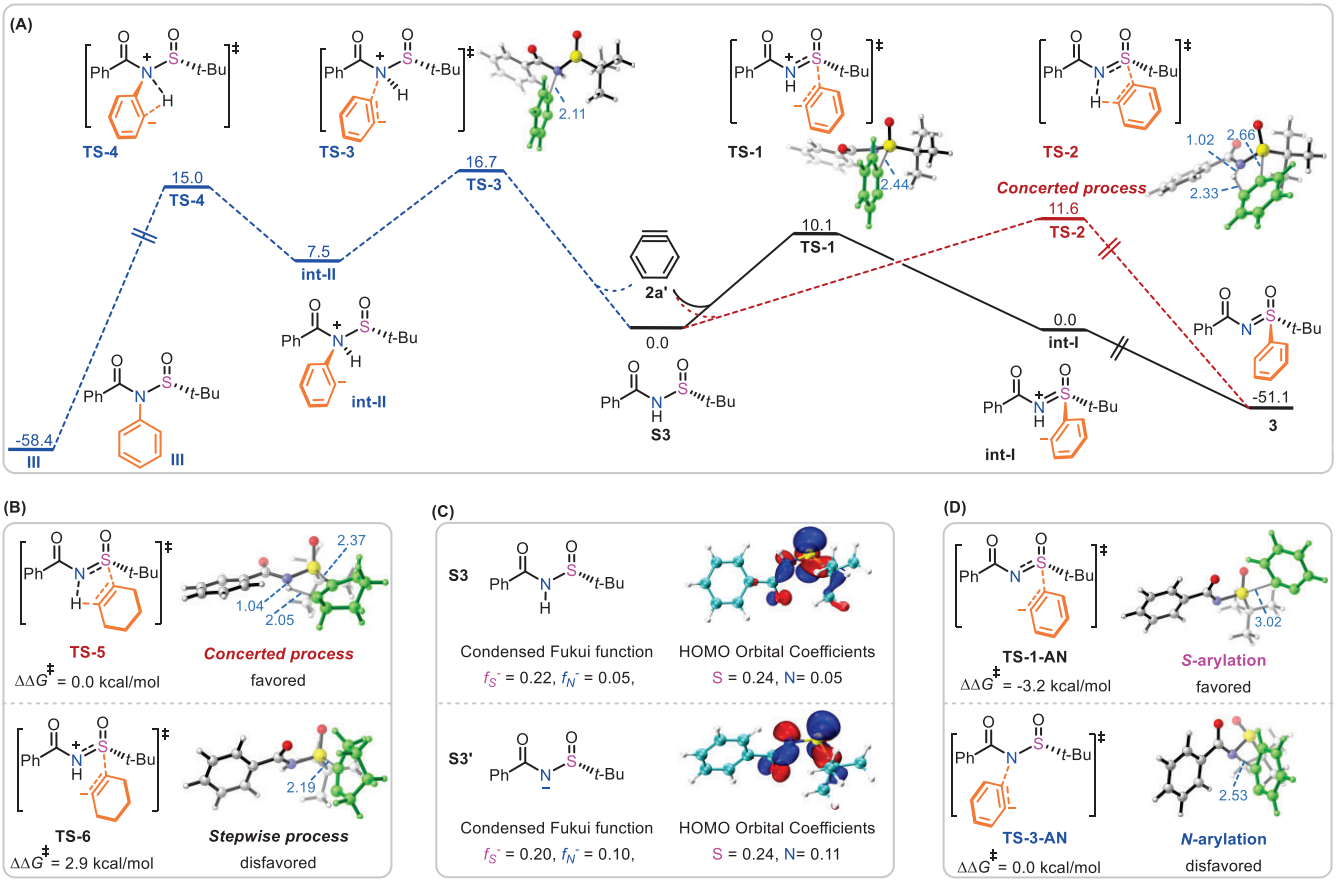
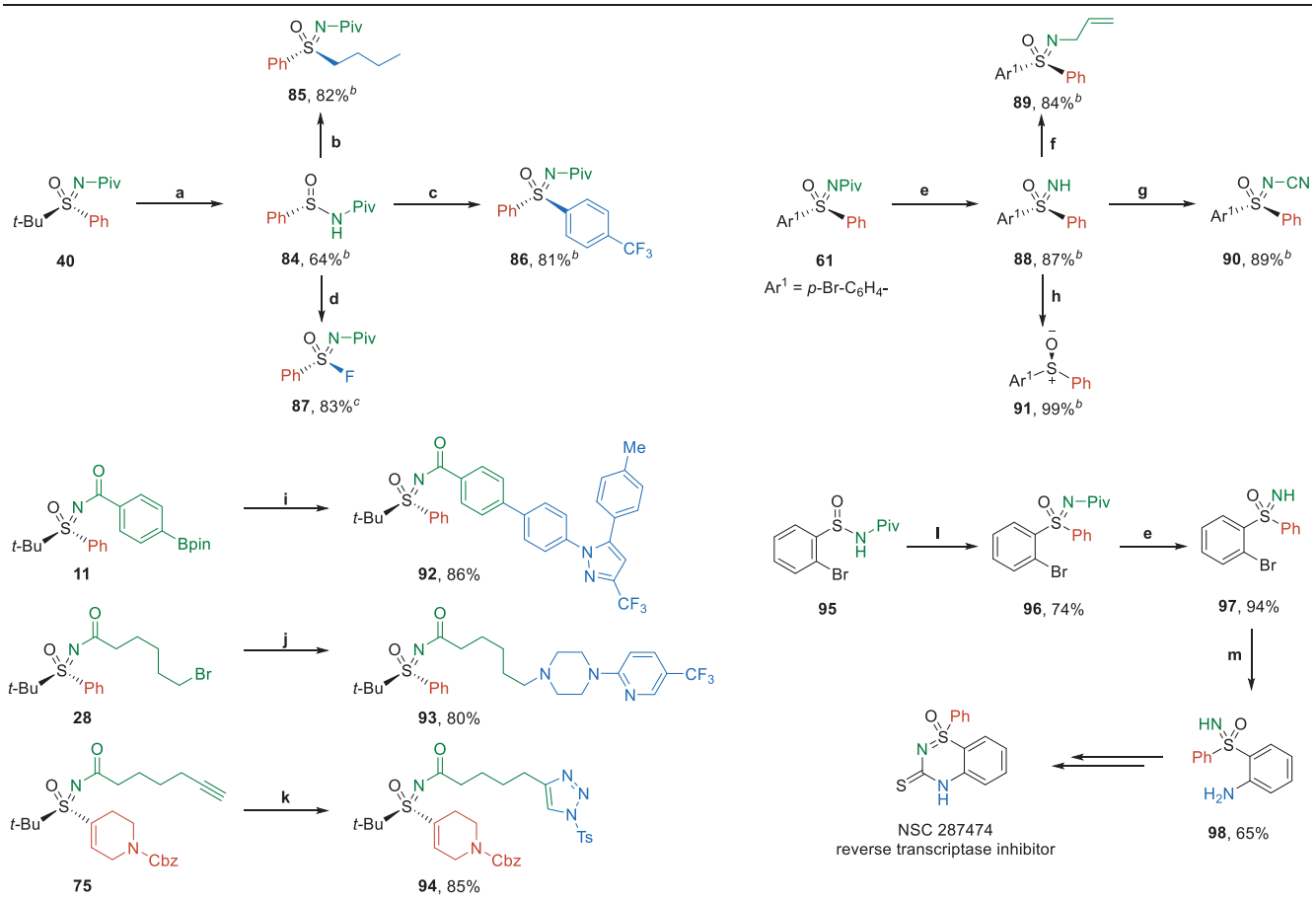


Figure 2, (A) Free energy profile of *S*-arylation and *N*-arylation between sulfinamide and aryne (calculated with the M06-2X method in acetonitrile). (B) DFT-computed transition state **TS-5** of concerted pathway and transition state **TS-6** of stepwise pathway between sulfinamide and cyclohexyne. (C) Condensed Fukui function and HOMO orbital coefficients for chiral N-benzoyl *tert*-butylsulfinamide **S3** and its anion **S3'**. (D) DFT-computed transition state **TS-1-AN** of *S*-arylation and transition state **TS-3-AN** of *N*-arylation between deprotonated sulfinamide and aryne. The values of the geometry information are given in Ångstrom. Energy differences are given in kcal/mol.

To further elucidate the reaction mechanism and the origin of exclusive chemoselectivity of *S*-arylation, we performed density functional theory (DFT) calculations on this reaction. Substrate **S3** and the in-situ generated benzyne intermediate **2a'** were used as model substrates for the computational studies (Figure 2). The calculated free energy barrier for nucleophilic addition of sulfur atom to aryne via transition state **TS-1** is 10.1 kcal/mol (Figure 2A). A zwitterionic intermediate **int-I** generated thereof quickly undergoes barrierless intramolecular 1,4-proton transfer to deliver the *S*-arylation product **3**. In contrast, a free energy barrier of 16.7 kcal/mol was found for the nucleophilic addition of nitrogen atom to aryne via transition state **TS-3**, followed by an intramolecular 1,3-proton transfer via a four-membered ring transition state **TS-4** that has a free energy barrier of 7.5 kcal/mol to afford the unobserved *N*-arylation product **III**. There was a 6.6 kcal/mol difference in the

free energy barriers (**TS-1** vs **TS-3**, $\Delta\Delta G^{\ddagger}$, Figure 2A) that favors the *S*-arylation over *N*-arylation, which is in good agreement with the exclusive chemoselectivity observed experimentally.

A concerted mechanism of *S*-arylation has also been studied. The free energy barrier of transition state **TS-2** ($\Delta G^{\ddagger}$ =11.6 kcal/mol) is slightly higher than that of transition state **TS-1** ($\Delta G^{\ddagger}$=10.1 kcal/mol). Therefore, this process was less likely to occur but could not be excluded in comparison with the stepwise pathway ($\Delta\Delta G^{\ddagger}$ =1.5 kcal/mol). Notably, the concerted *S*-arylation mechanism becomes more favorable than the corresponding stepwise mechanism for the reaction between **S3** and cyclohexyne according to our calculations (Figure 2B). The free energy barrier in transition states **TS-5** (concerted) is 2.9 kcal/mol lower than that of **TS-6** (stepwise). Therefore, a switch between the concerted and stepwise mechanisms for the *S*-arylation pathway may happen, and it is likely to be substrate-dependent.



[a] Reaction conditions: [a] CF_3CO_2H (3.0 equiv), DCM, rt, 6 h. [b] 1-iodobutane (4.0 equiv), NaH (1.2 equiv), 15-crown-5 (1.2 equiv), 1,4-dioxane, 40 °C, 72 h. [c] mesityl (4-(trifluoromethyl)phenyl)iodonium trifluoromethanesulfonate (1.5 equiv), $Cu(OTf)_2$ (10 mol%), *i*-Pr_2NEt (1.8 equiv), DMSO, 60 °C, 24 h. [d] NaH (2.1 equiv), THF, selectfluor (4.0 equiv), KOAc (4.0 equiv), EtOH, rt, 24 h. [e] 50% KOH (4.2 mL), THF/MeOH = 1:1, rt, 12 h. [f] allyl bromide (1.5 equiv), KOH (2.0 equiv), DMSO, rt, 8 h. [g] CuCN (2.0 equiv), $CuBr_2$ (20 mol%), Na_2SO_4 (2.0 equiv), TMEDA (2.0 equiv), CH_3CN, O_2, 50 °C, 12 h. [h] *t*-BuONO (1.5 equiv), CH_3CN, 35 °C. [i] 1-(4-bromophenyl)-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazole (1.2 equiv), $Pd(dba)_2$ (5 mol%), PPh_3 (20 mol%), K_3PO_4 (3.0 equiv), DMF, 80 °C, 24 h. [j] 1-(5-(trifluoromethyl)pyridin-2-yl)piperazine (1.2 equiv), K_2CO_3 (5.0 equiv), CH_3CN, 60 °C. [k] TsN_3 (1.1 equiv), CuTC (10 mol%), toluene, rt, 3 h. [l] 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (2.5 equiv), CsF (3.0 equiv), CH_3CN, rt, 12 h. [m] Cu_2O (10 mol%), $TMSN_3$ (2.0 equiv), TBAI (10 mol%), H_2O (1.0 mL), 90 °C, air. [b] No racemization was confirmed by chiral HPLC analysis. [c] Enantiomeric ratio (99:1) was confirmed by chiral HPLC analysis.

Figure 3, the downstream derivations and applications.

Depicted in Figure 2C, the HOMO coefficient and condensed Fukui function of sulfur in substrate **S3** are 0.24 and 0.22, respectively, whereas the corresponding values of nitrogen are both 0.05. These results imply that the nucleophilic ability of sulfur is higher than that of nitrogen, which might be responsible for the large energy difference in the corresponding transition states of *S*-arylation and *N*-arylation. In comparison, the nucleophilicity of nitrogen and the related *N*-arylation were enhanced if substrate **S3** was deprotonated. The HOMO orbital coefficient and condensed Fukui function of nitrogen in **S3'** increased to 0.11 and 0.10, respectively. Correspondingly, the free energy barrier difference of *S*-arylation and *N*-arylation in the stepwise nucleophilic addition to aryne got closer ($\Delta\Delta G^{\ddagger}$ = 3.2 kcal/mol for **TS-1-AN** and **TS-3-AN**, Figure 2D). Although *S*-arylation is still favored over *N*-arylation in this reaction, different electrophiles other than arynes or cyclic alkynes may

further deteriorate the chemoselectivity. This result might explain why *N*-substitution products could hardly be avoided in previous reactions of sulfinamide with other nucleophiles promoted by strong base. The assistance of steric effects by a bulky group (*N*-CO^{t}Bu instead of *N*-COPh) in suppressing *N*-substitution was essential in those systems. In our reaction, an anionic sulfinamide species was unlikely involved due to the mild reaction conditions.[29] This was further supported by the experimental result that the sodium salt of **S3** was unable to afford *S*-arylation product when treated with **2a** under our standard conditions (SI, Page S155). Therefore, we envisioned the excellent chemoselectivity of our reaction benefited from the intrinsic high preference of *S*-nucleophilicity of charge-free sulfinamides. The reaction was made possible by the strong driving force of strain-release of highly active arynes and cyclic alkynes.

In Figure 3, divergent synthetic applications of this method were demonstrated. The *S*-*tert*-butyl group of sulfoximines was removable in a stereospecific manner under mild conditions, affording an optically pure sulfinamide (**84**). Therefore, a formal S^{IV}-chirality transfer platform for the stereospecific synthesis of optically pure sulfinamides from the commercially available chiral *tert*-butylsulfinamides could be devised through sequential *S*-functionalization and debutylation. Chiral sulfinamides obtained thereof are valuable substrates in constructing new S^{VI} functional molecules through *S*-alkylation (**85**), *S*-arylation (**86**), and oxidative fluorination (**87**). Notably, the optically pure sulfonimidoyl fluorides were valuable warhead as covalent probes and key intermediate to sulfoximines, sulfonimidates, and sulfonimidamides.[18] Alternatively, free sulfoximines (=NH) was accessible under mild conditions (**88**), which allowed for further functionalization of the sulfonimidoyl nitrogen to deliver other functional derivatives of interest (**89**, **90**). Free sulfoximines also offered a complementary access to chiral sulfoxides by stereospecific removal of the imino group (**91**). As mentioned in the substrate scope section, our method tolerated a variety of functional groups that were valuable for late-stage diversifications. Here, we highlighted three of them as a proof-of-concept, including the cross-coupling of boronic ester (**92**), the nucleophilic substitution of alkyl bromide (**93**), and the click ligation of terminal alkynes (**94**). Finally, the use of our method toward a short synthesis of compound NSC 287474 was demonstrated (**95**-**98**). It was a potential reverse transcriptase inhibitor for the protection of lymphocytes against HIV.[30]

Conclusion

In summary, we have developed a new stereospecific and chemoselective *S*-arylation and *S*-alkenylation method for converting sulfinamides into sulfoximines. The use of strain-containing arynes and cyclic alkynes were essential to the success of this reaction. The origin of exclusive sulfur selectivity was supported by DFT calculations. The reaction proceeds via a stepwise or concerted five-membered ring transition state. One significant advantage of this method over previous reports was the excellent functional group tolerance, which enabled unprecedented chemical diversity attached to nitrogen (*N*-R). It was also valuable for functionalization of bioactive molecules at the very late stage.

Supporting information

All data are available in the main text or the supporting information. Additional data are available from the corresponding authors upon request. CCDC 2242867, 2218739, and 2218741 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac. uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

Acknowledgements

Financial support was provided by National Natural Science Foundation of China (22001065), the Science and Technology Foundation of Hunan Province (2021JJ30090), Guangdong Provincial Key Laboratory of Catalysis (2020B121201002), and Shenzhen Science and Technology Program (KQTD20210811090112004). Computational work was supported by Center for Computational Science and Engineering at SUSTech, and the CHEM high-performance supercomputer cluster (CHEM-HPC) located at the Department of Chemistry, SUSTech.

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