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A General Metallaphotoredox Platform for *N*-Alkylated Sulfoximines as Bioisosteric Building Blocks

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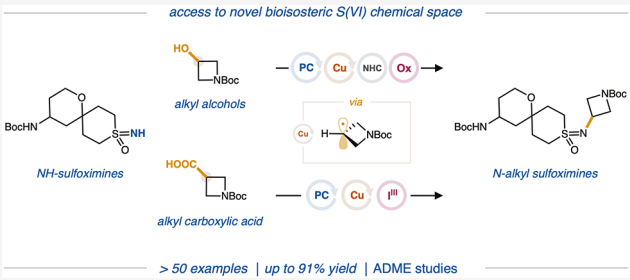
ABSTRACT: The precise modulation of physicochemical and ADME properties is critical in drug discovery. We report a unified, mild, and broadly applicable metallaphotoredox-enabled protocol for the *N*-alkylation of sulfoximines, a versatile S(VI) motif gaining prominence as a bioisostere. This method overcomes limitations of previous *N*-substitution approaches by accommodating diverse alkyl sources, including alcohols, alkyl bromides, and carboxylic acids, under visible-light irradiation. The strategy features high functional group tolerance and offers efficient access to both primary and secondary *N*-alkyl sulfoximines. Its utility is showcased through the late-stage functionalization of pharmacologically active compounds, natural product derivatives, and short peptides, enabling rapid access to novel analogues with enhanced structural diversity. Furthermore, we demonstrate the strategic coupling of bicyclo[1.1.1]pentyl moieties with sulfoximines to achieve a synergistic bioisosteric design. A preliminary drug optimization campaign, exemplified by an atuveciclib analogue, highlights the platform's potential for improving key ADME properties such as lipophilicity and cellular permeability, underscoring its value for lead diversification and refinement in medicinal chemistry.



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■ INTRODUCTION

In modern drug discovery, medicinal chemists routinely encounter major challenges in both hit identification and lead optimization. Key objectives include enhancing binding affinity and selectivity, mitigating toxicity, and improving physicochemical as well as ADME (absorption, distribution, metabolism, excretion) properties.[1,2] One powerful strategy to address these challenges is the use of bioisosteres, *i.e.* functional groups or frameworks that retain the biological activity of known motifs while offering improved therapeutic profiles.[3−5] This concept, known as bioisosteric replacement or scaffold hopping,[6−8] allows for the design of structurally distinct compounds through the strategic substitution of established motifs, often leading to enhanced potency, selectivity, and drug-like characteristics.

Sulfur(VI) functional groups, particularly sulfonyl and sulfonamide derivatives, are among the most common scaffolds used in modern drug design.[9−11] These motifs are present in over 150 FDA-approved drugs and are widely applied to treat a range of diseases due to their robust pharmacological properties and synthetic accessibility.[12] However, drawbacks such as limited lipophilicity, potential allergic reactions, risks of hepatotoxicity, and development of resistance motivate the search for alternative structures with improved profiles.[13−15]

Sulfoximines, the monoaza analogues of sulfones, have recently emerged as attractive alternatives in this context.[16−19] Their favorable features include adjustable polarity, unique hydrogen-bonding behavior, and the opportunity to introduce additional substituents at the nitrogen center.[20−22] These properties enable the fine-tuning of physicochemical characteristics and pharmacokinetics, including solubility, permeability, and protein binding. In the past decade, sulfoximines have seen increased adoption in medicinal chemistry, with several compounds advancing into clinical trials (Figure 1).[19,23,24] This trend has been supported by greater synthetic accessibility and a deeper understanding of their behavior in biological systems. Nevertheless, the vast majority of reported sulfoximine-containing structures remain unsubstituted at nitrogen, limiting their ability to serve as modular bioisosteres of sulfones or sulfonamides.

Substitution at the sulfoximine nitrogen has the potential to modulate pharmacological and metabolic profiles significantly, but practical methods to achieve such modifications remain scarce. Current methods for *N*-substitution—particularly alkylation—are often hindered by the poor nucleophilicity of the imine-like nitrogen, necessitating harsh reagents or conditions that restrict functional group compatibility.[25−28]

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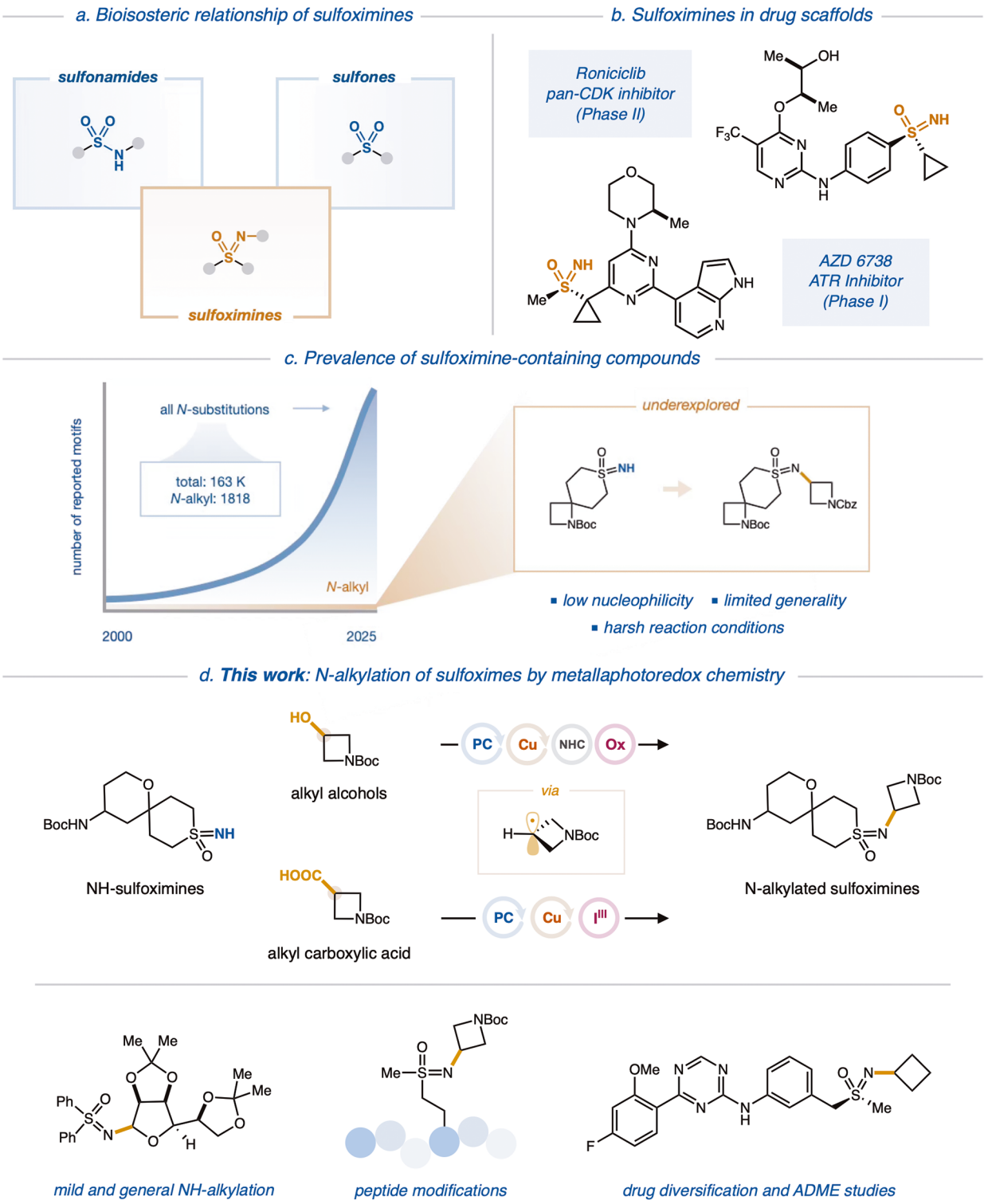

Figure 1. *N*-Alkylation of sulfoximines.

The development of mild and general strategies for *N*-alkyl sulfoximine synthesis remains a key challenge.

Previous studies have shown that both iron and copper catalysis can facilitate *N*-alkylation via radical intermediates thermally generated from peroxides;[29−32] however, these methods are hindered by safety concerns and substrate scope limitations. More recently, metallaphotoredox catalysis has emerged as a general approach for forming carbon−heteroatom bonds under mild conditions.[33] This technology relies on visible-light activation to generate reactive radical intermediates and has enabled a range of previously challenging transformations. Copper-based systems are particularly well suited for challenging coupling reactions, as they bypass oxidative addition and promote efficient reductive elimination.[34−37]

Building on our previous work using copper and photoredox catalysis to achieve alcohol-based alkylation of nitrogen heterocycles,[38] we sought to develop a unified strategy for

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the *N*-alkylation of sulfoximines. Our objective was to establish a modular protocol that could accommodate a wide array of radical precursors, including both alcohols and carboxylic acids, converging on a common bond-forming process that involves alkyl radical capture by an intermediate Cu(II) species. This approach would allow for orthogonal reactivity and broad late-stage functionalization potential.

Therefore, we have developed strategies to generate alkyl radical intermediates *in situ* from either alcohol or carboxylic acid precursors. Under this paradigm, alcohols are activated with benzoxazolium-based reagents under photoredox conditions to form alkyl radicals.[39] Carboxylic acids are converted to the corresponding radicals via decarboxylation using a hypervalent iodine reagent previously reported in our laboratory.[40] We demonstrate herein that this orthogonal reagent strategy enables the direct and selective *N*-alkylation of a wide range of sulfoximines, providing a general platform for the construction of valuable building blocks with potential applications in drug discovery and development.

Both activation pathways converge on a common mechanistic sequence for carbon−nitrogen bond formation. A proposed mechanism for the deoxygenative pathway is outlined in Figure 2. First, alcohol **1** reacts with the NHC

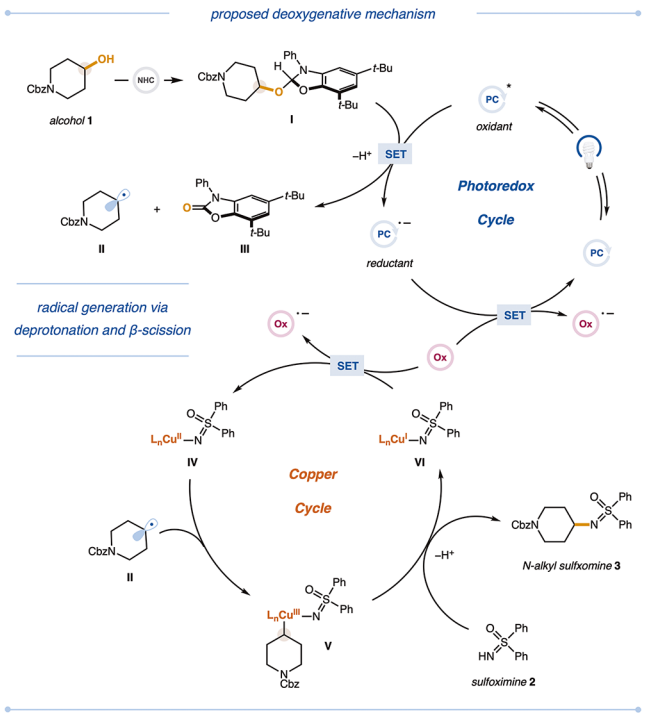


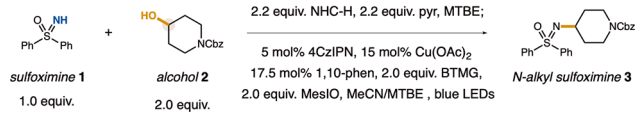
Figure 2. Plausible mechanism for the deoxygenative *N*-alkylation of sulfoximines; Cbz, benzyloxycarbonyl; PC, photocatalyst; Ox, oxidant.

salt under mildly basic conditions, forming NHC-alcohol adduct **I**. Subsequently, the employed photocatalyst (PC) is excited by visible, blue light yielding a sufficiently long-lived exited triplet state (PC*) to participate in bimolecular electron transfer. Using 4CzIPN as the photocatalyst ($E_{1/2}^{red}$ [PC*/PC$^{\bullet-}$] = +1.43 V vs. saturated calomel electrode (SCE) in MeCN),[41] the excited-state can be readily quenched by **I** ($E_{1/2}^{red}$ = 1.0 V vs. SCE in MeCN)[39] yielding the radical anion of the photocatalyst (PC$^{\bullet-}$) and a radical cation of **I**, which can undergo a deprotonation/β-scission sequence affording the desired alkyl radical **II** and inert carbamate byproduct **III**. The resulting radical **II** is intercepted by an *in situ* formed copper(II)−sulfoximine complex **IV** to form a putative copper(III) intermediate **V**. Facile reductive elimination from this species furnishes the cross-coupled product **3**, thereby opening a coordination site for another sulfoximine molecule (**2**). The resulting copper(I) complex **VI** is reoxidized to copper(II) by an external oxidant, which additionally allows for the turnover of the photocatalytic cycle regenerating 4CzIPN from the radical anion ($E_{1/2}^{red}$ [PC/PC$^{\bullet-}$] = − 1.24 V vs. SCE in MeCN).[41]

RESULTS AND DISCUSSION

We began our studies by optimizing the reaction conditions for the alcohol substrate class, using *S*,*S*-diphenyl sulfoximine (**1**) and Cbz-protected 4-hydroxypiperidine (**2**) as model substrates (Table 1). Under optimized conditions, **1** was

Table 1. Control Experiment for Deoxygenative *N*-Alkylation of Sulfoximines[a,b]



entry	deviation	yield[a]
1	none	79% (74%[b])
2	no light	<1%
3	no photocatalyst	<1%
4	no copper catalyst	<1%
5	no ligand	6%
6	no base	<1%
7	TMG as base (2.0 equiv.)	61%
8	no oxidant (N_2 atmosphere)	<1%
9	air as oxidant (18G needle)	8%

[a]Performed on a 0.05 mmol scale. The alcohol activation was stirred for 30 min at room temperature before being transferred to the reaction mixture, resulting in a 0.05 M reaction in 1:1 MeCN/MTBE. Irradiation for 8 h with 450 nm blue LEDs in the integrated photoreactor. Yields given as ^{1}H NMR assay yields against 1,3,5-trimethoxybenzene as internal standard. [b]Isolated yield on 0.5 mmol scale. Abbreviations: Ac, acetyl; BTMG, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine; Cbz, benzyloxycarbonyl; Mes, mesityl; MTBE: methyl *tert*-butyl ether; TMG, 1,1,3,3-tetramethylguanidine; Ph, phenyl; phen, phenanthroline pyr, pyridine. See the Supporting Information (SI) for further details.

combined with the NHC adduct of **2** in methyl *tert*-butyl ether (MTBE), with 4CzIPN as the photocatalyst, copper(II) acetate with 1,10-phenanthroline as the copper catalyst, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG) as base, and iodosomesitylene (MesIO) as oxidant in acetonitrile. Irradiation with blue light emitting diodes at 450 nm for 8 h afforded the desired carbon−nitrogen cross-coupled product **3** in 74% isolated yield on 0.5 mmol scale. Control experiments supported the proposed mechanism, as product formation beyond trace amounts was only observed when the photocatalyst, copper catalyst, base, and oxidant were all present under light irradiation. Omitting either the ligand or the external oxidant significantly reduced yields; similar reductions were observed when the reaction was conducted under air. Using 1,1,3,3-tetramethylguanidine (TMG) as a weaker base alternative to BTMG led to slightly diminished yields (see Supporting Information for optimization and control experiments).

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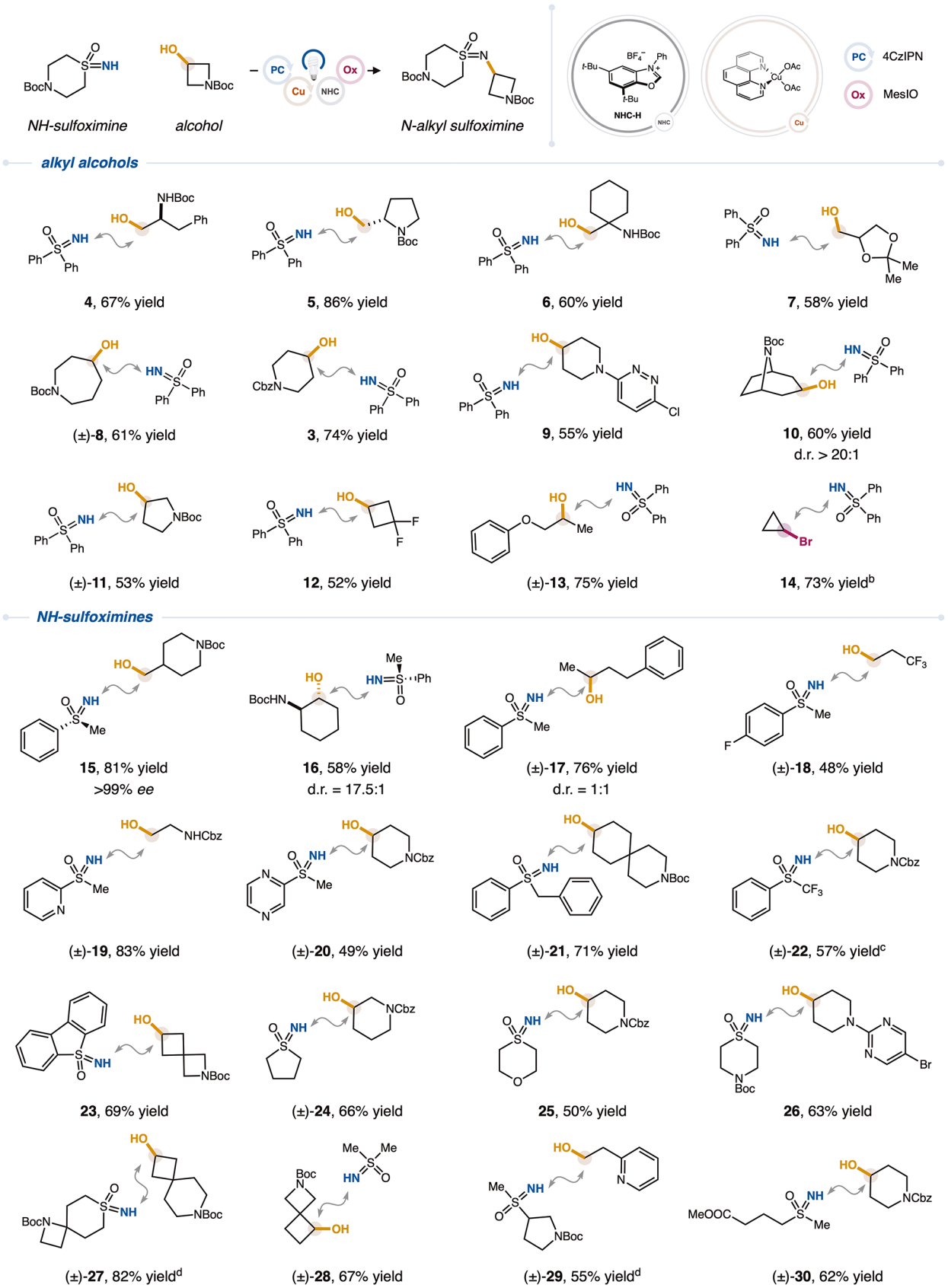
Table 2. Scope of Metallaphotoredox-Enabled Deoxygenative *N*-Alkylation of Sulfoximines[a,b,c,d]



[a]Performed on a 0.5 mmol scale with sulfoximine (1.0 equiv), alcohol (2.0 equiv),**NHC-H** (2.2 equiv), pyridine (2.2 equiv), 4CzIPN (5 mol %), $Cu(OAc)_2$ (15 mol %), 1,10-phenanthroline (17.5 mol %), BTMG (2 equiv), MesIO (2 equiv) in MeCN/MTBE (0.05 M) in the integrated photoreactor (450 nm, 75% light intensity for 8 h). [b]Performed on a 0.5 mmol scale with sulfoximine (1.0 equiv), bromide (2.0 equiv), $AdNHSi(TMS)_3$ (2.2 equiv) 4CzIPN (2 mol %), $Cu(OAc)_2$ (25 mol %), 1,10-phenanthroline (28 mol %), TMG (2 equiv) in MeCN (0.05 M)

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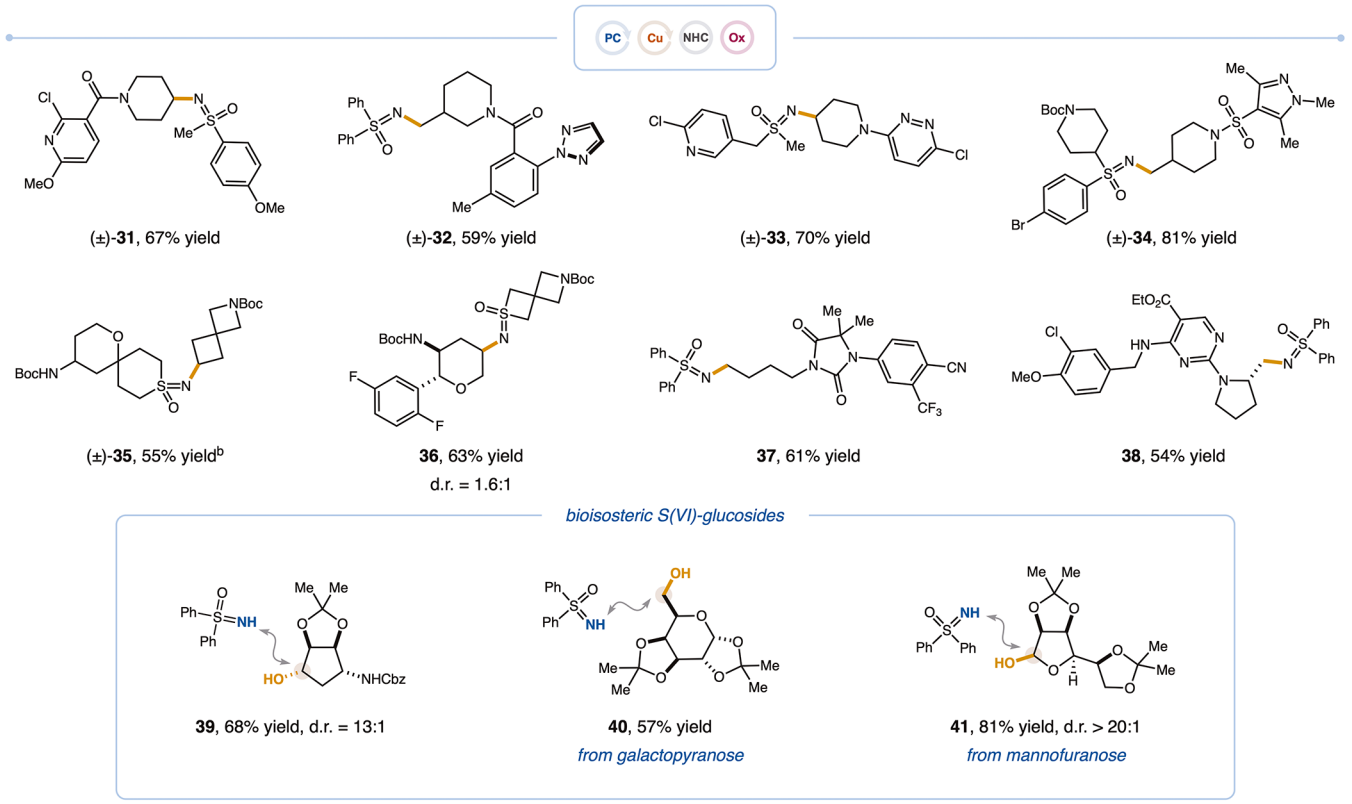
Table 2. continued

under air in the integrated photoreactor (450 nm, 10% light intensity for 12 h). [c]Use of TMG (2.0 equiv) instead of BTMG and neocuproine (17.5 mol %) instead of 1,10-phenanthroline. [d]Starting material was present as a diastereomeric mixture of 1:1. See the Supporting Information for experimental details.

Table 3. Scope of Complex Drug-like Substrates[a,b]



[a]Isolated yields are reported. See Supporting Information for experimental details. [b]Starting material was present as a mixture of diastereoisomers.

With these optimal conditions in hand, we set out to explore the applicability of this transformation to a variety of differently substituted alcohols and sulfoximines (Table 2). Owing to the versatility of the benzoxazolium reagent, a broad range of alcohols featuring diverse functional groups could be coupled to *S*,*S*-diphenylsulfoximine as the parent sulfoximine. Primary alcohols derived from chiral amino acids (**4** and **5**) provided the desired *N*-alkylated sulfoximines in high to excellent yields (67% and 86%). Moreover, sterically encumbered β-quaternary alcohols—challenging substrates in traditional cross-coupling reactions—proved competent coupling partners (**6**, 60%), as did alcohols containing acid-labile acetal protecting groups, such as solketal **7** (58%).

There are few reported methods for installing secondary alkyl residues at the sulfoximine nitrogen, and existing approaches often rely on specific alkyl scaffolds or harsh conditions, limiting their generality and efficiency.[31,42,43] We were therefore pleased to find that our system enables straightforward and efficient coupling of various secondary alkyl fragments with the parent sulfoximine. Seven- (**8**), six- (**3**, **9**, **10**), five- (**11**), and four-membered rings (**12**) were well tolerated, undergoing substitution at different ring positions in moderate to high yields (52−74%). Additionally, noncyclic secondary alcohols delivered the product in high yield (**13**, 75%).

The cyclopropyl moiety, due to the nature of its orbitals, is typically incompatible with S_N1 or S_N2 conditions, necessitating alternative activation strategies. Applying our methodology to cyclopropanol led to unsatisfactory conversion (<30%) presumably due to the low β-scission rate of the corresponding NHC-adduct upon single-electron oxidation and deprotonation ($<10^4$ $M^{-1}s^{-1}$). As a more practical entry point for this motif, we turned to bromocyclopropane. Building on prior work from our group employing adamantylaminosilane ($AdNHSi(TMS)_3$) as a potent halogen atom abstraction (XAT) reagent,[37,44] following oxidation and an aza-Brooks rearrangement, we reoptimized our protocol for alkyl halide substrates (see Supporting Information for proposed mechanism). This approach furnished *N*-cyclopropyl sulfoximine **14** in 73% yield, showcasing the complementary nature of our platform and its compatibility with diverse radical precursors and activation modes.

With a robust method for engaging a variety of alkyl fragments, we next explored the diversity of sulfoximine coupling partners as a means to further enhance molecular complexity. Our strategy allows coupling of enantiomerically pure sulfoximines with achiral alcohols with complete stereoretention, delivering product **15** in 81% yield and >99% *ee*. Furthermore, the introduction of a chiral alkyl fragment enabled construction of product **16** with three

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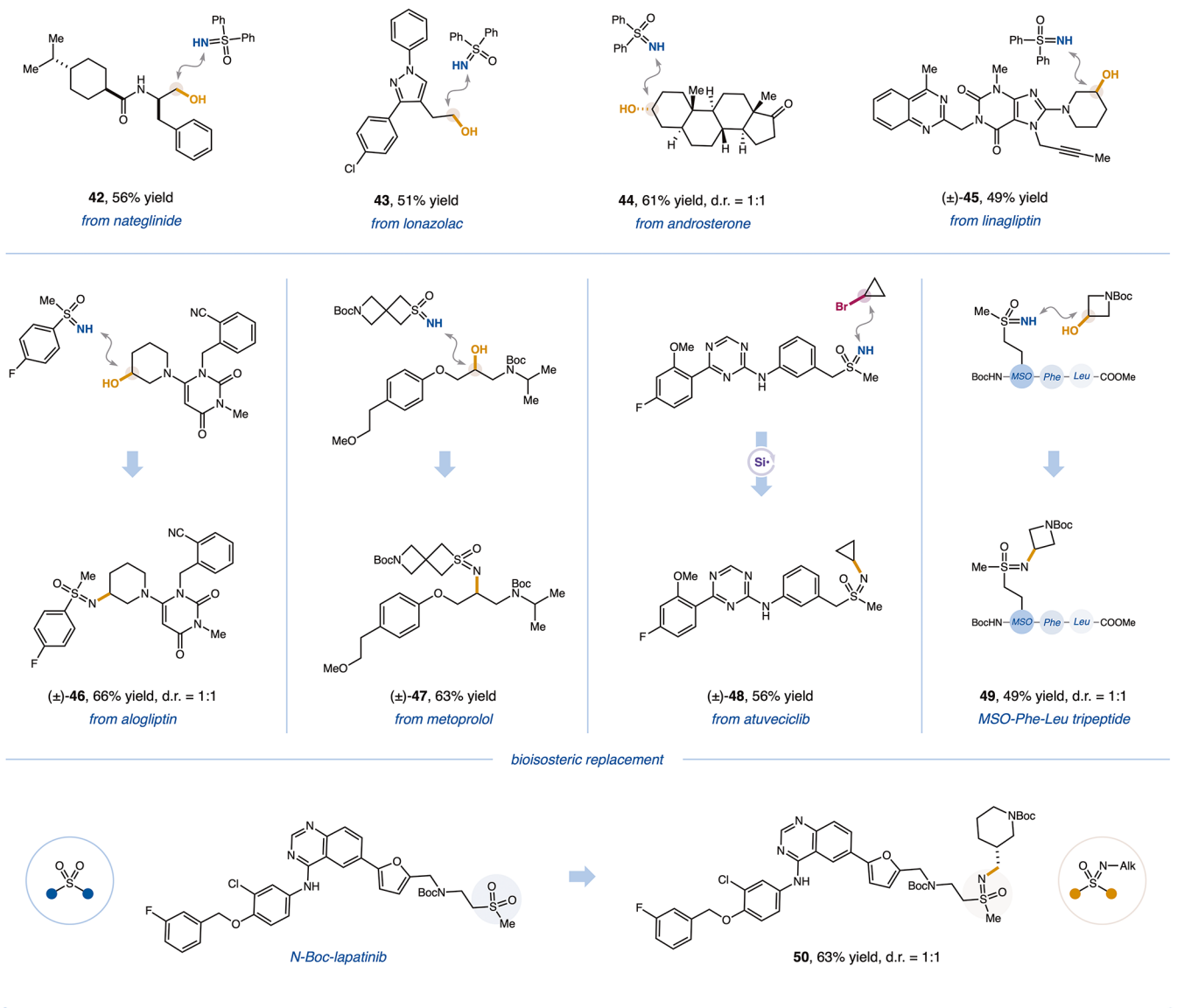
Table 4. Use of Drug Molecules and Bioactive Substrates[a]



[a]Isolated yields are reported. See Supporting Information for experimental details.

absolute stereogenic centers in a single step with high diastereoselectivity (58%, d.r. =17.5:1), exemplifying the power of this modular approach to generate stereochemical complexity.

We next evaluated arene−alkyl sulfoximines and found that a wide array of (hetero)aryl groups at the sulfoximine scaffold were tolerated, including phenyl (**17** and **18**), pyridyl (**19**), and pyrazinyl (**20**) substituents, all delivering products in moderate to high yields (48−83%). The methodology was also applicable to various alkyl sulfoximines, including benzylic variants (**21**, 71%). For an electron-deficient S(VI)−CF_3 derivative, changing the base to TMG and the ligand to neocuproine, afforded the desired product **22** in 57% yield. Cyclic sulfoximines also demonstrated high reactivity, including substrates derived from dibenzothiophene (**23**, 69%), tetrahydrothiophene (**24**, 66%), 1,4-oxathiane (**25**, 50%), thiomorpholine (**26**, 63%), and thiaazaspiro[3.5]nonane (**27**, 82%). Encouragingly, the successful coupling of fully *S*,*S*-alkyl-substituted sulfoximines was also extended to acyclic systems (**28**−**30**), with yields ranging from 55% to 67%.

A further advantage of this system is its tolerance to potentially reactive aryl halides (**9** and **26**), which remain intact under the reaction conditions due to the high kinetic barrier for oxidative addition to copper complexes. This feature enables the use of aryl halides as strategic handles for downstream diversification, greatly expanding the accessible chemical space.

We next aimed to apply our *N*-functionalization platform to more complex alcohols and sulfoximines, particularly those derived from naturally occurring biomolecules and scaffolds frequently found in pharmacologically active compounds (Table 3). The broad availability of alcohols, combined with the straightforward synthesis of sulfoximines via oxidation/nitrene transfer from thioethers,[45] enabled access to products from structurally diverse and complex starting materials. A range of differently substituted hydroxypiperidines, including

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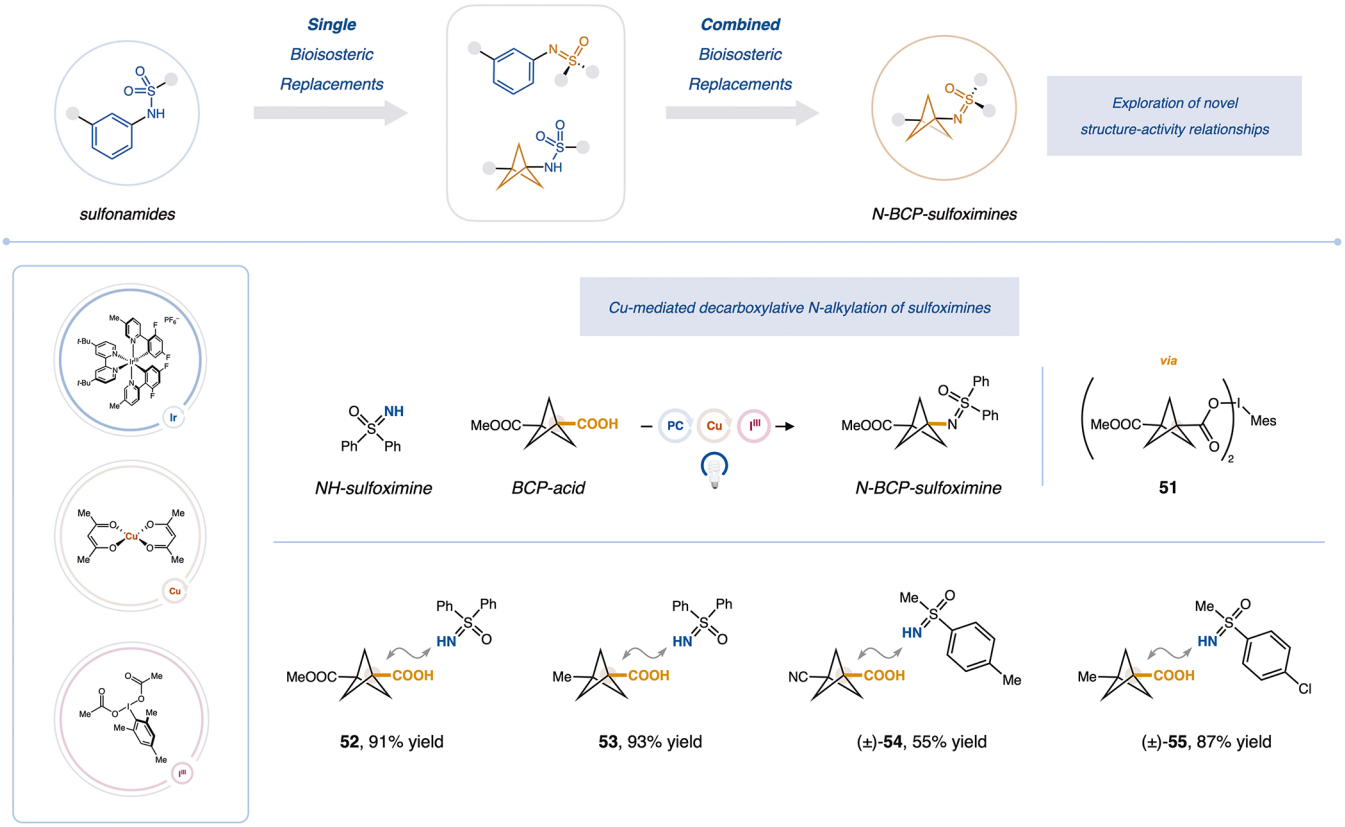
Table 5. Decarboxylative Amination of Bicyclo[1.1.1]Pentanes (BCPs)[a]



[a]Performed on a 0.4 mmol scale with corresponding iodonium carboxylate (1.0 equiv), sulfoximine (2.0 equiv), Ir[dF(Me)ppy]$_2$(4,4′-dtbbpy)PF$_6$ (2 mol %), Cu(acac)$_2$ (50 mol %), BTTP (1 equiv) in 1,4-dioxane (0.33 M) in the integrated photoreactor (450 nm, 25% light intensity for 1 h); BTTP: *tert*-butylimino-tri(pyrrolidino)phosphorane; I^{III}: iodomesitylene diacetate. See Supporting Information for experimental details.

N-heterobenzoylated (**31** and **32**), *N*-heteroarylated (**33**), and *N*-sulfonylated (**34**) alcohols were effectively employed as alkylating agents for sulfoximines bearing various substitution patterns, affording the desired products in high to very high yields (59−81%).

Given the growing emphasis on incorporating C(sp^3)-rich molecular frameworks into pharmaceutical candidates as a strategy correlated with clinical success,[46] we were especially pleased to obtain spirocyclic sulfoximines **35** and **36**, featuring an exceptionally high degree of C(sp^3) hybridization within their carbon skeleton in high yields (55% and 63%, respectively). Additionally, antiandrogen-derived **37** and an avanafil analog **38** were efficiently synthesized from the corresponding alcohols (61% and 54%, respectively).

The selective derivatization of glucosides, as well as the incorporation of bioisosteric elements into these structures, is of particular interest in drug discovery.[47] Functionalization of glucosides often proves challenging due to the difficulty of activating sugar-derived alcohols and the fragile nature of acetal protecting groups.[48] However, the mild activation and radical generation enabled by the NHC-based reagent allows for the direct conversion of native sugar alcohols into alkyl radicals suitable for coupling.

To demonstrate this utility, we applied the method to an unnatural nucleoside (**39**), galactopyranose (**40**), and mannofuranose (**41**). In each case, the corresponding alkylated sulfoximines were obtained in high to very high yields (57−81%) with excellent diastereoselectivity (d.r. = 13:1 for **39** and d.r. > 20:1 for **41**). Owing to the mild conditions of this protocol, this represents the first example of direct conversion of glucosides into their S(VI)-derivatives, offering valuable synthetic handles for future structure−activity relationship (SAR) studies.

Late-stage functionalization of complex molecules is a powerful strategy in drug discovery, enabling efficient structural diversification and optimization of physicochemical properties.[49,50] To highlight the utility of our method in this context, we applied it to the direct alkylation of drug-like and bioactive compounds. This approach provides a modular and broadly applicable route to libraries of alkylated sulfoximines, enabling late-stage installation of the sulfoximine moiety without the need for de novo synthesis.

We demonstrated our reaction platform on a selection of pharmacologically active compounds and their derivatives bearing alcohol groups, benchmarking its applicability for late-stage installation of sulfoximine bioisosteres (Table 4). To our delight, the sulfoximine group was readily incorporated into molecules derived from nateglinide (**42**), lonazolac (**43**), and linagliptin (**45**), affording the corresponding products in moderate to high yields (49−66%). Coupling with androsterone furnished sulfoximine **44** in 61% yield with a 1:1 diastereomeric ratio, providing access to both diastereomers for evaluation of potentially distinct biological activity or pharmacokinetic profiles. In addition, differently substituted complex sulfoximines were effective in the late-stage functionalization of alcohols derived from alogliptin (**46**) and metoprolol (**47**), delivering the desired products in high yields (66% and 63%, respectively), further underscoring the

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versatility of this methodology in connecting diverse and structurally complex building blocks.

This applicability was further demonstrated using racemic atuveciclib, a CDK inhibitor, as the sulfoximine coupling partner.[51] By employing our optimized conditions with bromocyclopropane and AdNHSi(TMS)$_3$, we obtained the corresponding *N*-cyclopropanated atuveciclib derivative **48** in 56% yield. This result highlights the practicality of the alkylation strategy, as the parent compound can be directly engaged in the transformation without the need for extensive prior modification.

Apart from small molecules, the late-stage modification of peptides represents a powerful strategy in medicinal chemistry, enabling the precise and efficient diversification of complex peptide scaffolds without the need for lengthy *de novo* synthesis.[52] By facilitating streamlined access to analogues, such methods significantly enhance the speed and precision of peptide-based drug development. To this end, we synthesized a tripeptide model substrate containing a Met−Phe−Leu sequence and subjected it to our established oxidation protocol for converting thioethers into sulfoximines. Exposure of the resulting NH-sulfoximine peptide (MSO−Phe−Leu) to our alkylation procedure enabled the installation of an azetidine moiety in synthetically useful yield (**49**, 49%, d.r. = 1:1). Notably, this transformation would not have been feasible using traditional substitution techniques or previously reported metal-catalyzed methods. We envision that this methodology could prove useful in peptide library synthesis by converting native methionine residues into unnatural amino acids in a straightforward and versatile manner.

We further applied our protocol to the synthesis of a lapatinib analogue (**50**), which was obtained in high yield (63%). In this case, compound **50** represents a direct bioisostere of the parent lapatinib, where the sulfone moiety, characterized by two hydrogen bond acceptors, was replaced by an alkylated sulfoximine that mimics these key acceptor features. Importantly, both bioisosteric compounds can be accessed from a common thioether precursor, thereby streamlining synthetic accessibility and enabling a late-stage divergence in the overall synthetic strategy.

Building on the successful use of alcohols and bromocyclopropane as alkylating agents for *N*-alkylation of sulfoximines, we sought to expand the molecular toolbox of viable starting materials. Carboxylic acids, among the most abundant and versatile functional groups in medicinal chemistry, serve as attractive functionalization handles due to their wide availability and commercial accessibility.[53] In parallel, bicyclo[1.1.1]pentanes (BCPs) have gained prominence as valuable bioisosteres for substituted phenyl rings and alkynes, offering superior physicochemical and pharmacokinetic properties.[54−56] Their rigid, saturated, and three-dimensional structure improves metabolic stability and lowers lipophilicity, while preserving essential spatial and electronic attributes of the original motifs.

In line with our group's long-standing interest in designing new methods to access C(sp^3)-rich bioisosteric chemical space,[57−59] we set out to incorporate BCP motifs into our reaction protocol. This approach would allow for the convergence of two bioisosteric elements in a single transformation, providing entry to synergistic bioisosteric chemical space that may serve as a replacement for aryl sulfones or sulfonamides (Table 5). By fine-tuning our reaction conditions and modifying the redox linchpins—including preactivating the carboxylic acids with iodomesitylene diacetate [MesI(OAc)$_2$] to generate diacetate **51** and using [Ir(dF(Me)ppy)$_2$(dtbbpy)]PF$_6$ as the photocatalyst and Cu(acac)$_2$ as the copper source—we successfully coupled a variety of differently substituted sulfoximines with BCP-carboxylic acids (**52**−**55**) in moderate to excellent yields (55−93%; see Supporting Information for details).

A mechanistic hypothesis for this transformation is presented in Figure 3. In contrast to the deoxygenative

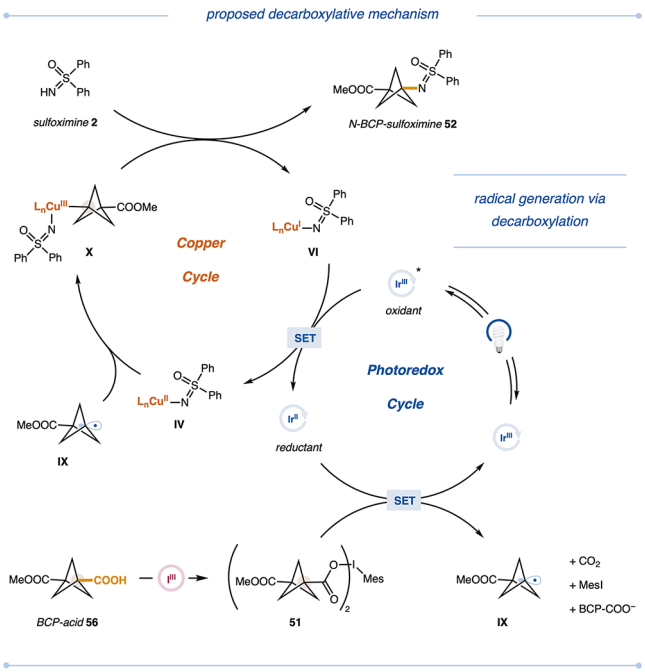

Figure 3. Plausible mechanism for the decarboxylative *N*-alkylation of sulfoximines; I^{III}: iodomesitylene diacetate.

approach, no external oxidant is required as the system is based on a redox-neutral catalytic cycle. *In situ* formed Cu(I) complex **VI** ($E_{1/2}^{red}$ [Cu^{II}(BPhen)$_2$/Cu^{I}(BPhen)$_2$] = +0.08 V vs. SCE in DMF, BPhen = 4,7-diphenyl-1,10-phenanthroline)[60] possesses the ability to reductively quench the exited state of the Ir-based photocatalyst ($E_{1/2}^{red}$ [*Ir^{III}/Ir^{II}] = +0.99 V vs. SCE in MeCN),[61] yielding the reduced Ir(II) photocatalyst as well as the required Cu(II)-sulfoximine complex **IV**. For the decarboxylative approach, we propose that iodomesitylene dicarboxylate **51**, generated from carboxylic acid **56** with iodomesitylene diacetate [MesI(OAc)$_2$], would undergo facile reduction by the Ir(II) species ($E_{1/2}^{red}$ [Ir^{III}/Ir^{II}] = − 1.41 V vs. SCE in MeCN);[61] E_p [**51**/**51**$^{\bullet-}$] = −1.14 V vs. SCE in MeCN),[40] leading to the formation of a carboxyl radical as well as the regeneration of the ground-state Ir(III) photocatalyst. Upon subsequent decarboxylation, the desired BCP-radical **IX** is obtained. In line with the mechanism for the deoxygenative approach, the putative Cu(III) intermediate **X** is formed upon coordination of radical **IX** to Cu(II) complex **IV**, which subsequently undergoes reductive elimination, furnishing the desired *N*-BCP sulfoximine **52**.

Finally, we evaluated the potential of our method in a small-scale drug optimization campaign as a blueprint for applications in drug discovery. Sulfoximines have gained prominence in medicinal chemistry due to their unique combination of physicochemical and pharmacokinetic advan-

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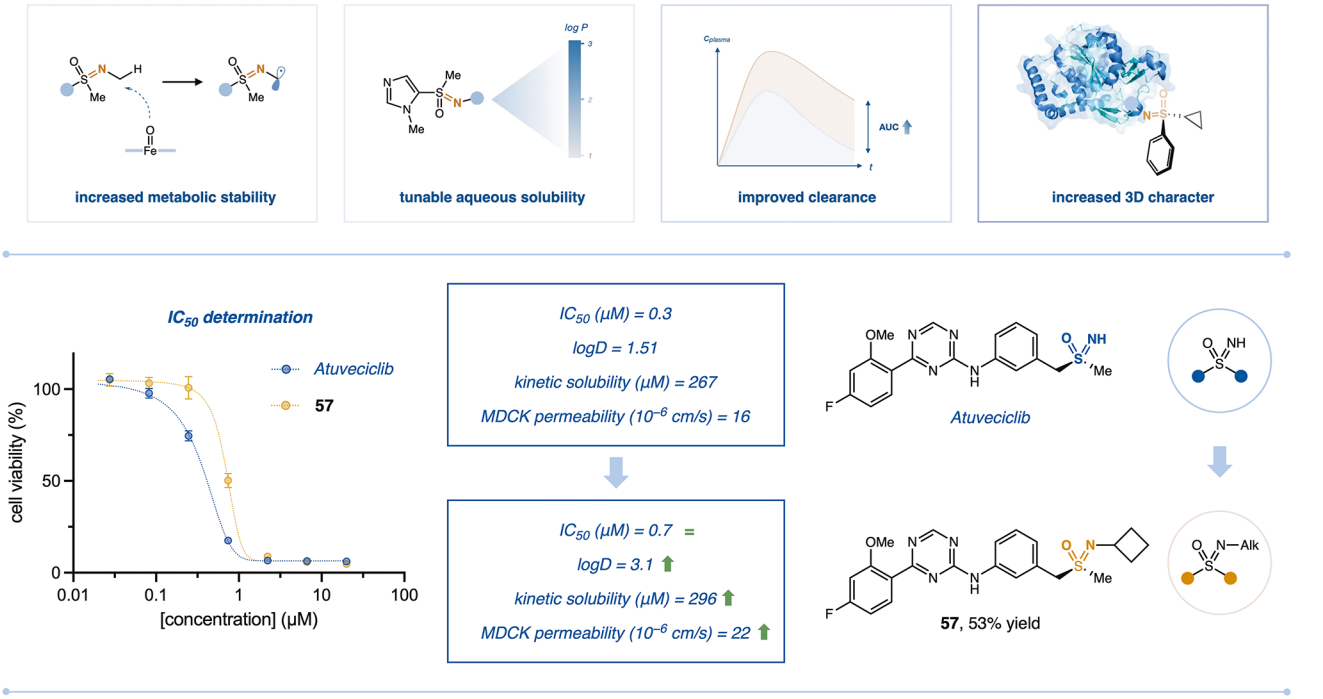

Figure 4. Tunability of pharmacological properties by bioisosteric replacement.

tages. Compared to traditional functional groups such as sulfones and sulfonamides, sulfoximines offer enhanced metabolic stability, reduced off-target effects, and lowered risk of undesired drug−drug interactions. Their tunable hydrogen bonding capacity often translates into improved aqueous solubility and oral bioavailability. The structural diversity of sulfoximines, supported by their three-dimensional, chiral architecture, enables precise tuning of molecular properties such as permeability and plasma protein binding, key determinants of *in vivo* clearance (Figure 2). As a result, sulfoximines are valuable functional groups for optimizing ADME profiles in drug development. To evaluate this potential, we selected atuveciclib, an established CDK inhibitor,[51] to assess whether the introduction of an alkyl group at the nitrogen atom of the sulfoximine would lead to improved pharmacological properties. Based on computational docking studies,[57] we selected the alkylated derivative **57** as a suitable candidate for our endeavor. Accordingly, we applied our NHC-based protocol using cyclobutanol as the alkylating reagent, affording **57** directly from atuveciclib in 53% yield with full retention of stereochemical configuration.

Compound **57** was subsequently evaluated in HeLa human cervical carcinoma cells (CCL-2) to assess its cellular potency relative to the parent compound (Figure 4). Gratifyingly, the IC_{50} value (0.7 μM) was comparable to atuveciclib (0.3 μM), indicating that *N*-alkylation does not compromise cellular activity. Encouraged by this result, we next examined whether *N*-alkylation improved the compound's physicochemical properties *in vivo*. An increase in logD was observed, suggesting enhanced lipophilicity, which may contribute to improved membrane permeability.[62] In parallel, kinetic solubility showed a notable improvement compared to atuveciclib (Figure 4). Together, these properties are expected to increase the fraction absorbed (Fa) in vivo, potentially resulting in higher oral bioavailability. To further assess its ADME profile, we measured the permeability of compound **57** in Madin-Darby canine kidney (MDCK) cells, a model for epithelial absorption. Compound **57** exhibited enhanced permeability compared to the parent compound, suggesting improved oral bioavailability or tissue distribution. Together, these results underscore the potential of *N*-alkylated sulfoximines as valuable motifs for modulating both physicochemical and pharmacokinetic properties in drug development.

■ CONCLUSIONS

In summary, we present an efficient and broadly applicable protocol for the *N*-alkylation of sulfoximines using aliphatic alcohols, alkyl bromides, and carboxylic acids as versatile alkyl sources. This unified strategy accommodates a diverse substrate scope, enabling the coupling of both primary and secondary alcohols—including complex, drug-like examples—with a wide range of structurally distinct sulfoximines. The method demonstrates exceptional functional group tolerance and broad applicability, offering direct access to *N*-alkyl sulfoximines from readily available starting materials.

The power of this approach in late-stage functionalization was exemplified by the successful modification of pharmacologically active molecules, natural product derivatives, and short peptides. These results highlight the potential for rapidly generating analogues with enhanced structural diversity and complexity. The platform was further expanded to include the modular synthesis of *N*-substituted sulfoximines bearing bicyclo[1.1.1]pentyl or cyclopropyl motifs, using carboxylic acids and bromocyclopropane as alkyl radical precursors, respectively.

We further applied this methodology in a preliminary drug optimization study, showcasing its value for structure−activity relationship exploration. A sulfoximine analogue of atuveciclib, synthesized in one step, demonstrated improved physicochemical and ADME properties, underlining the potential of this platform to streamline lead diversification and refinement. We

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anticipate that this reaction will be a valuable addition to the medicinal chemistry toolbox, facilitating the discovery of novel sulfoximine scaffolds and their strategic incorporation as bioisosteric replacements in drug development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c13726.

Detailed experimental procedures; optimization data; additional scope examples; characterization data of new compounds; biological studies; NMR spectra for new compounds (PDF)

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Notes

The authors declare the following competing financial interest(s): D.W.C.M. declares a competing financial interest with respect to the integrated photoreactor. A provisional U.S. patent has been filed by D.W.C.M. and J.J.G. based in part on this work, 63/736,215. The remaining authors declare no competing interests.

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■ ABBREVIATIONS

4CzIPN, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene; Ac, acetyl; ADME, absorption, distribution, metabolism, excretion; AdNHSi(TMS)$_3$, adamantylaminosilane; BCP, bicyclo[1.1.1]pentane; BTTP, *tert*-butylimino-tri(pyrrolidino)-phosphorane; BTMG, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine; Cbz, benzyloxycarbonyl; CDK, cyclin-dependent kinase; d.r., diastereomeric ratio; ee, enantiomeric excess; MDCK, Madin-Darby Canine Kidney (cells); Mes, mesityl; MesIO, iodosomesitylene; SAR, structure−activity relationship; TMG, 1,1,3,3-tetramethylguanidine; XAT, halogen atom abstraction

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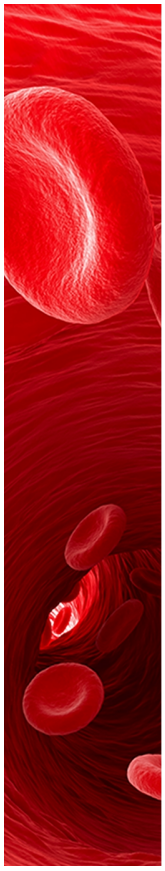
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