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Cu(II)-catalyzed 'in-water' *N*-arylation of electron-deficient NH-heterocycles†

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Cu(II)-catalyzed *N*-arylation of electron-deficient NH-heterocycles 'in-water' at room temperature is described. A wide substrate scope with respect to structural and electronic variation of NH-heterocycles plus arylboronic acids allows product diversity. The functional group tolerance, 'gram-scale' synthesis, synthetic elaboration of *N*-arylated products and late-stage arylation are the distinct advantages.

Introduction

N-containing heterocycles are omnipresent as subunits in many natural products, are present as backbones of several bio-active molecules and exhibit diversified biological activities.¹ Several prescribed approved drugs and marketed pharmaceutical agents are enriched with N-heterocycles as essential structural cores.² Typically, the substitution of a CH-group by an N-atom in (hetero)arene systems may induce vital features in terms of physicochemical properties and molecular interactions of a new therapeutic lead, which can be translated into enhancing pharmacological profiles during the identification of safe and efficacious drug candidates as well as exploring the space of high-quality drugs.³ Thus, synthesis and/or chemical modifications of small molecule N-based heterocycles have received significant attention in drug design, discovery medicinal chemistry and drug development efforts.⁴

Moreover, the *N*-arylated analogues of NH-heterocycles are prevalent components in numerous medicinal compounds and key building blocks of biologically active natural products and have found numerous applications in medicinal chemistry, pharmaceutical research, and drug discovery.⁵ Due to a

broad range of biological activities and extensive applications in medicinal and pharmaceutical sciences, the *N*-arylated heterocycles have attracted considerable interest from synthetic organic/medicinal chemists, and the C–N bond constructions have been under continuous investigation in the synthetic chemistry community.⁶

The copper-mediated oxidative cross-coupling reaction of NH-(hetero)arenes with arylboronic acids, popularly known as Chan–Lam coupling,⁷ offers a straightforward synthetic method for (hetero)arene *N*-arylation.⁸ Recently, copper-catalyzed Chan–Lam coupling has also been explored as a prominent and broadly applicable powerful tool for coupling of N-nucleophiles to access N–C(aryl) bonds.⁹ The copper-catalyzed Chan–Lam coupling has been extensively studied with electron-rich heteroarenes (*e.g.*, imidazole, benzimidazole, pyrazole, indazole, 1,2,3-benzotriazole),^{5b,6d,8c,9a,10} primarily because of their high nucleophilicity, which facilitates coordination of N-atom to copper centre. In contrast, the participation of moderate/strong electron-deficient NH-heterocycles in copper-catalyzed Chan–Lam coupling remains elusive^{10e,11} and only one or two examples have been included for each structural class of NH-heterocycles, such as cyclic amide, imide, cyclic urea, cyclic sulfonamide, cyclic carbamate, and 2,4-thiazolidinedione, under copper-promoted conditions using undesirable hazardous halogenated CH₂Cl₂ solvent.^{7a,c,8a,c} Perhaps poor nucleophilicity of electron-deficient NH-heteroarenes inhibits easy coordination of N-atom to copper centre and prevents easy reductive elimination of the copper centre at the elementary steps during catalytic turnover. The slow reaction rate of electron-deficient NH-heterocycles eventually necessitates a long duration of reaction (12 h–72 h) under both Cu-catalyzed and Cu-mediated conditions^{7c,8a,11} and the participation of electron-rich arylboronic acids as coupling partners.^{8a,11} Furthermore, non-reactivity or poor conversion,^{7a,c} or inadequate examples of moderate or strong electron-deficient arylboronic acids,^{7a,c,11a} lead to a lack of generality in substrate scope, and use of undesirable high-boiling (DMSO)^{11a} or hazardous halogenated solvents (CH₂Cl₂)^{7a,c,8a,c,11b} further highlight the notable

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limitations of electron-deficient NH-heterocyclic scaffolds for Chan–Lam coupling. Therefore, the Chan–Lam coupling of electron-deficient NH-heterocycles typically represents a formidable challenge. Thus, there is a need to develop a mild, robust, efficient, and more generalized strategy for Chan–Lam coupling of electron-deficient NH-heterocycles.

The ever-growing demand for the application of green chemistry tools in medicinal chemistry research and chemistry-based organizations urges the use of green reaction media.¹² The improvement of reaction methodologies, which is associated with deficiencies in atom economy, cost-effectiveness, safety, poor reactivity, and scalability, drives the working philosophy of medicinal chemistry research to find a better synthetic approach to enrich the medicinal chemist's toolbox.¹³ In an endeavour toward sustainable practices as part of our synthetic medicinal chemistry program to identify new therapeutic leads *via* the functionalization of heterocyclic scaffolds, recently, we became interested in exploring the Chan–Lam coupling of electron-deficient bio-relevant NH-heterocycles in a water medium. Growing interest in using water as a preferred non-conventional reaction medium^{12a,14} in designing green chemical syntheses¹⁵ is mirrored by significant efforts in the execution of a variety of organic reactions in an aqueous medium.¹⁶ The use of water as a reaction medium replacing common volatile organic solvents (VOSs) can circumvent the environmental non-benignity of VOSs, as these are major contributors to environmental pollution because of their frequent, abundant use (on average contributing 85–90% of the overall mass of a chemical process) as well as incomplete recovery efficacy.¹⁷ However, most organic compounds are poorly soluble in water, which may restrict the application of water-mediated organic reactions.¹⁸ The solubility issue has been cleverly addressed using surfactants in water-mediated organic reactions, wherein the surfactants generate micellar nanoreactors by self-aggregation in an aqueous medium to entrap organic reactants to promote or accelerate organic transformations.¹⁹ The catalytic applications of different transition metals in aqueous media benefitting various organic transformations have been well established,^{19a,c,20} which prompted us to devise an efficient, mild, and robust strategy for the Chan–Lam coupling of electron-deficient NH-heterocycles. Herein, we describe Cu(II)-catalyzed water-mediated Chan–Lam coupling of electron-deficient bio-relevant NH-heterocycles, such as isatin, 4(3*H*)-quinazolinone, and 2-oxazolidinone, in line with the 'triple bottom line' philosophy²¹ of green chemistry practice.

The isatin, 4(3*H*)-quinazolinone, and 2-oxazolidinone scaffolds have proved to be privileged structural units present in several naturally occurring compounds having divergent biological and pharmacological properties. For example, the isatin core and many of its derivatives display inhibitory activities, such as those against CNS-MAO B (monoamine oxidase B) and SARS protease, act as GAL₃ receptor antagonists, and are present in clinically approved drugs (*e.g.*, sunitinib, semaxanib, *etc.*) (Fig. 1A).²² The 4(3*H*)-quinazolinone core is widely distributed as a building block in several synthetic and natural

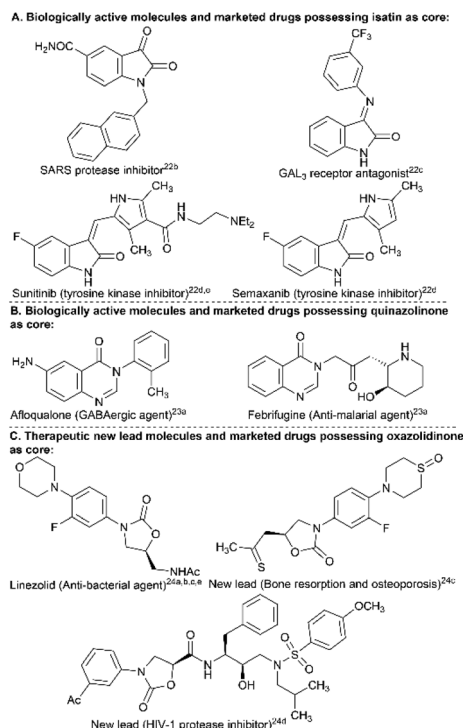
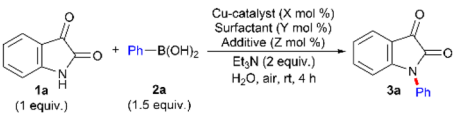


Fig. 1 A few selected examples of biologically active molecules, new therapeutic leads and marketed drugs that contain isatin, 4(3*H*)-quinazolinone, and 2-oxazolidinone as the structural core.

product-based drugs to treat various disease conditions and exhibits a broad spectrum of biological functions, including anti-malarial, anti-cancer, anti-convulsant, anti-inflammatory, anti-diabetic, anti-fungal, kinase inhibitory and many more activities.²³ The 2-oxazolidinone nucleus is present as the backbone in medicinally significant molecules expressing a broad range of pharmacological activities, such as HIV-1 protease inhibition, anti-bacterial, MAO inhibition, effective agents in the treatment of bone resorption and osteoporosis, *etc.*²⁴ The functionalization (*e.g.*, *N*-arylation) of these bio-relevant NH-heterocycles has, therefore, been desired to broaden the chemical and molecular space²⁵ to identify new therapeutic lead molecules for drug discovery efforts in a medicinal chemistry program.

Results and discussion

The popularity of Cu(II)-catalyzed Chan–Lam coupling^{9–11} prompted us to initiate the investigation by assessing *N*-arylation in a model study of isatin (**1a**) (1 equiv.) with phenylboronic acid (**2a**) (1.5 equiv.) using various Cu-based catalysts applying different conditions in a water medium (Table 1). We started optimization of the reaction conditions by using 1 equiv. of Cu(OAc)₂ in the presence of catalytic surfactant sodium dioctylsulfosuccinate (SDOSS) (20 mol%) and Et₃N (2 equiv.) as a base in H₂O at rt under air, which afforded the desired *N*-phenylisatin (**3a**) in 24% isolated yield (entry 1).

Table 1 Representative data of optimization of the reaction conditions for *N*-arylation of **1a** with **2a** to form **3a**^a


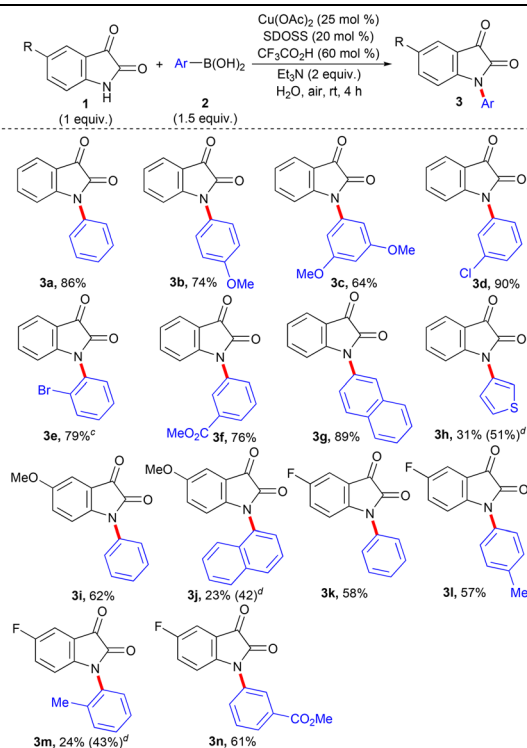
Entry	Catalyst (X)	Surfactant ^b (Y)	Additive ^b (Z)	Yield ^c (%)
1	Cu(OAc) ₂ (100)	SDOSS (20)	None	24
2	Cu(OAc) ₂ (50)	SDOSS (20)	None	15
3	Cu(OAc) ₂ (25)	SDOSS (20)	None	0 ^d
4	Cu(OAc) ₂ (25)	SDOSS (20)	en (30)	0 ^d
5	Cu(OAc) ₂ (25)	SDOSS (20)	<i>N,N</i> -DMEDA (30)	0 ^d
6	Cu(OAc) ₂ (25)	SDOSS (20)	AcOH (20)	38
7	Cu(OAc) ₂ (25)	SDOSS (20)	AcOH (40)	47
8	Cu(OAc) ₂ (25)	SDOSS (20)	AcOH (60)	58
9	Cu(OAc) ₂ (25)	SDOSS (20)	CF ₃ CO ₂ H (60)	86
10	Cu(OAc) ₂ (25)	SDOSS (10)	CF ₃ CO ₂ H (60)	29
11	Cu(OAc) ₂ (25)	None	CF ₃ CO ₂ H (60)	19
12	Cu(OAc) ₂ (10)	SDOSS (20)	CF ₃ CO ₂ H (60)	0 ^d
13	None	SDOSS (20)	CF ₃ CO ₂ H (60)	0 ^d
14	CuI (25)	SDOSS (20)	CF ₃ CO ₂ H (60)	10
15	Cu(acac) ₂ (25)	SDOSS (20)	CF ₃ CO ₂ H (60)	0
16	Cu(BF ₄) ₂ ·xH ₂ O (25)	SDOSS (20)	CF ₃ CO ₂ H (60)	0
17	CuSO ₄ (25)	SDOSS (20)	CF ₃ CO ₂ H (60)	0
18	CuBr ₂ (25)	SDOSS (20)	CF ₃ CO ₂ H (60)	0
19	Cu(OAc) ₂ (25)	SDOSS (20)	CF ₃ CO ₂ H (60)	0 ^{d,e}
20	Cu(OAc) ₂ (25)	SDS (20)	CF ₃ CO ₂ H (60)	63
21	Cu(OAc) ₂ (25)	SDOSS (20)	NH ₄ OH + NH ₄ Cl (100)	12 ^f
22	Cu(OAc) ₂ (25)	SDOSS (20)	NH ₄ OH + NH ₄ Cl (260)	16 ^f

^a **1a** (1 mmol) was treated with **2a** (1.5 mmol, 1.5 equiv.) under various conditions in the presence of Et₃N (2 equiv.) in H₂O (2 mL) at rt for 4 h. ^b The amount used is with respect to **1a**. ^c Isolated yield of **3a**. ^d Both **1a** and **2a** were recovered. ^e In the absence of Et₃N. ^f In the absence of CF₃CO₂H and Et₃N. en = ethylenediamine; *N,N*-DMEDA = *N,N*-dimethyl ethylenediamine.

Reducing the amount of Cu(OAc)₂ to a catalytic quantity of 50 and 25 mol% either gave poor yield (15%) of **3a** (entry 2) or did not work (entry 3). The N-donor chelating ligands, separately or in combination, are capable of facilitating/accelerating coinage metal-catalyzed *N*-arylation of NH-heterocycles.^{9f,26} So, we tested N-chelating ligands, such as ethylenediamine (en) and *N,N*-dimethyl ethylenediamine (*N,N*-DMEDA). However, neither en and *N,N*-DMEDA separately nor a combination of en plus *N,N*-DMEDA was successful (entries 4 and 5 and ESI†). At this point, we hypothesized enhancing the electrophilicity of the Cu(II) centre, which could have a few advantages. An acidic reaction environment is known to enhance the electrophilic character of a metal centre transiently²⁷ and the application of a strong acid during C–H activation/functionalization to increase the electrophilicity of a metal centre by forming a cationic metal species²⁸ via the release of the coordinating acetate ion²⁹ is well documented. Moreover, it was reasoned that tuning the cationicity^{27–29} of the catalytic Cu(II) centre may endow better reactivity due to the following aspects: (i) the vacant active coordination site around the Cu(II) centre, generated after the dissociation of the coordinating acetate ion, would allow an easy N-atom coordination of poorly

nucleophilic **1a** circumventing its low reactivity; (ii) the high extent of electronic attraction between the Cu(II) centre and **1a**; (iii) accelerated transmetalation with **2a** driven by better electronic interaction; (iv) facile reductive elimination at the cationic copper centre for C–N bond formation;³⁰ and (v) potential application of overall mild reaction conditions.²⁹ Attracted by the observations and understanding mentioned above, we added catalytic (20 mol%) CH₃CO₂H (glacial) to the reaction system, which gave an improved yield (38%) of **3a** (entry 6). Increasing the amount of CH₃CO₂H (40 mol%) was not very effective, and the yield of **3a** was 47% (entry 7). However, 60 mol% CH₃CO₂H further improved the yield of **3a** to a decent level (58%) (entry 8). Gratifyingly, replacing CH₃CO₂H with a stronger acid, CF₃CO₂H (60 mol%), significantly enhanced the yield of **3a** to 86% (entry 9). Poor results were obtained on lowering the quantity of SDOSS and in the absence of it (entries 10 and 11), which suggests a distinct role for SDOSS in the transformation. The reaction failed when the Cu(OAc)₂ quantity was decreased to 10 mol% and without it (entries 12 and 13). The catalytic Cu(I) salt (e.g., CuI) and other Cu(II)-based catalysts, such as Cu(acac)₂, Cu(BF₄)₂·xH₂O, CuSO₄, and CuBr₂ either gave poor results (entry 14) or were not effective (entries 15–18). The base Et₃N was essential, as otherwise **3a** did not form (entry 19). The use of different surfactant, sodium dodecylsulfate (SDS), provided a poor result compared to that with SDOSS (entry 20). Replacing CF₃CO₂H and Et₃N with a weak basic buffer solution NH₄OH + NH₄Cl (1 equiv. and 2.6 equiv.) proved to be inferior (entries 21 and 22). After careful screening of several reaction parameters, the best reaction conditions was identified as those stated in entry 9, Table 1. The solvent plays a crucial role, and water was the most effective solvent to effectuate the transformation. Other solvents, such as *N,N*-dimethyl formamide (DMF), *N,N*-diethyl formamide (DEF), *N,N*-dimethyl acetamide (DMA), MeOH, ⁿBuOH, and THF were either ineffective or provided inferior results (please see Tables A, B, C, D, E, F, and G in the ESI† for a detailed description of reaction condition optimization).

With the optimized reaction conditions in hand, we attempted to generalize the transformation with respect to structural and electronic variations of **1** and **2** (Table 2). Subsequently, the influence of electronic and steric factors of substituents on the aryl ring of both **1** and **2** was assessed. The reaction proceeded smoothly with moderate/strong electron-donating groups (4-Me, 4-OMe, and 3,5-di-OMe), a strong electron-withdrawing group (3-CO₂Me), and halogen functionalities (3-Cl, 2-Br) on the aryl unit of **2** affording the corresponding *N*-arylated products (**3b–f**, and **3l**) in moderate to excellent yields. The survival of sensitive Cl and Br groups on the aryl ring of **2** establishes excellent chemoselectivity of the reaction conditions and provides scope for further synthetic elaboration. Unlike the transition metal-catalyzed amidation of the ester functionality,³¹ the present catalytic conditions were compatible with the ester group on the aryl ring of **2**. The result further highlights the mild, robust, and highly chemoselective nature of the developed catalytic system. Moreover, no ester hydrolysis was observed. The OMe and F groups at the

Table 2 Substrate scope study of *N*-arylation of isatin scaffold (**1**) with arylboronic acid (**2**) to form **3**^{a,b}

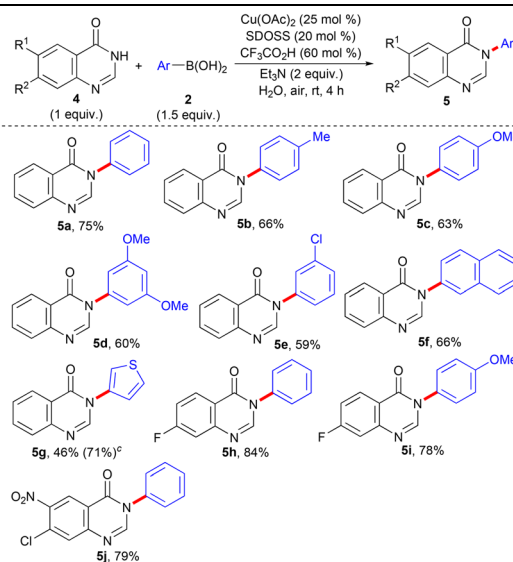
^a Reaction condition: **1** (1 mmol), **2** (1.5 mmol, 1.5 equiv.), Cu(OAc)₂ (25 mol%), SDOSS (20 mol%), CF₃CO₂H (60 mol%), Et₃N (2 equiv.) in H₂O (2 mL) at rt, 4 h. ^b Isolated yield of **3**. ^c No proto-debromination was observed. ^d The figure in parentheses is the total yield based on recovery and reuse of both the unreacted starting materials after the first attempt and further calculated with respect to **1**.

C5-position of **1** also worked well and furnished the *N*-arylated products (**3i**, **3k**, **3l**, and **3n**) in synthetically useful yields. Fused π -systems, such as a 2-naphthyl unit on **2**, afforded the *N*-arylated derivative (**3g**) in an excellent yield. Sterically congested aryl rings of **2**, such as 1-naphthyl and *ortho*-tolyl, participated in the transformation, albeit the product yields being low (**3j** and **3m**). However, the sterically demanding *ortho*-Br aryl unit of **2** delivered **3e** in good yield. Interestingly, the heteroarene, such as the 3-thienyl unit from **2**, could also be accommodated as a coupling partner. However, the conversion of the product was less (**3h**).

Next, we turned our attention to performing *N*-arylation of the electron-deficient NH-heterocyclic scaffold quinazolinone (**4**) with the same optimized reaction condition as stated in entry 9 of Table 1. The Chan–Lam coupling of **4** has been demonstrated under both Cu(II)-promoted³² and Cu(I)-catalyzed³³ conditions. The Cu(I)-catalyzed *N*-arylation of **4** has been performed in high boiling point environmentally non-preferred solvent DMSO,^{12a,14b,15b} requires a long reaction period (16 h–18 h),³³ and reveals insufficient substrate scope with limited derivatization.³³ The *N*-phenylation of 4(3*H*)-quinazolinone (**4a**) with C-based electrophile iodobenzene has also been reported earlier under Cu(I) catalysis,³⁴ which pri-

marily requires a long period of reaction (24 h) in the presence of environmentally non-benign high boiling point solvent DMF^{12a,b,14b,15b} at 100 °C and demonstrates only one single example of *N*-arylation of **4a** without an attempt to expand the substrate scope study with further derivatization. A wide range of **4** and **2**, having variations in their structural and electronic properties, were subjected to *N*-arylation (Table 3). The reaction conditions worked nicely, irrespective of any prominent electronic bias from the substituents on the aryl ring of both **4** and **2**. The corresponding *N*-arylation products (**5a–f**, and **5h–j**) were obtained in decent yields. Gratifyingly, a heteroarene moiety 3-thienyl ring from **2** also afforded the desired product (**5g**), although the conversion was less.

Furthermore, we planned to extend the scope of NH-heterocycles, such as the 2-oxazolidinone moiety for *N*-arylation with **2** under the optimized condition of entry 9, Table 1. An early report describes Cu(I)/1,2-diaminocyclohexane-catalyzed *N*-arylation of the 2-oxazolidinone scaffold with bromoarenes in refluxing 1,4-dioxane overnight, which exemplifies inadequate substrate scope.^{5e} The Cu(I)-catalyzed *N*-arylation of structurally related heterocycle 2-pyrrolidinone with iodo-/bromoarenes has also been reported, wherein typically, the 2-oxazolidinone moiety plays a crucial role in the ligand to effectuate the transformation.³⁵ Treating 2-oxazolidinone (**6a**) with **2a** under the established condition of entry 9, Table 1 failed to deliver the desired *N*-arylation product and both the starting materials **6a** and **2a** were recovered. Pleasingly, the inclusion of an additional cationic surfactant tetrabutylammonium bromide (TBAB) (20 mol%) with the optimized

Table 3 Substrate scope study of *N*-arylation of quinazolinone scaffold (**4**) with arylboronic acid (**2**) to form **5**^{a,b}

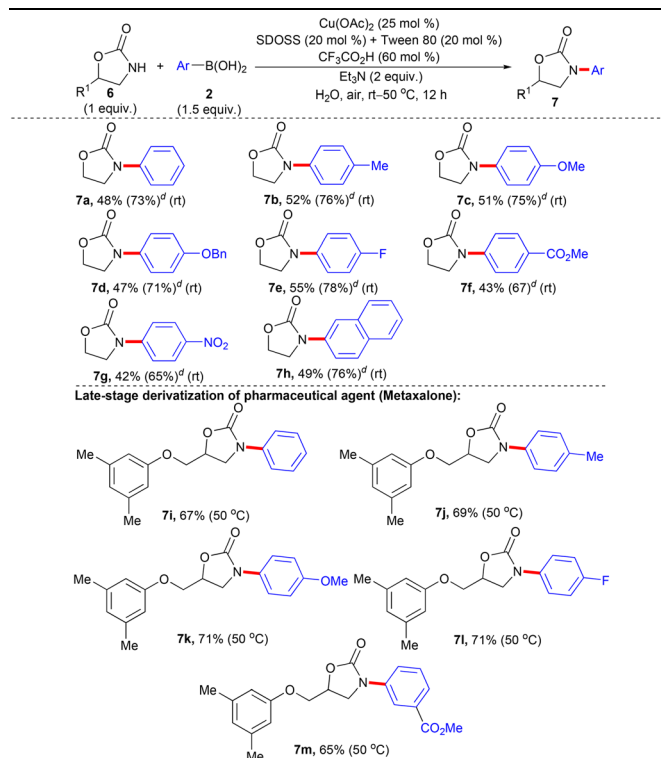
^a Reaction condition: **4** (1 mmol), **2** (1.5 mmol, 1.5 equiv.), Cu(OAc)₂ (25 mol%), SDOSS (20 mol%), CF₃CO₂H (60 mol%), Et₃N (2 equiv.) in H₂O (2 mL) at rt, 4 h. ^b Isolated yield of **5**. ^c The figure in parentheses is the total yield based on recovery and reuse of both the unreacted starting materials after the first attempt and further calculated with respect to **4**.

condition of entry 9, Table 1 provided the expected *N*-arylation product **7a** after 12 h, although the yield was poor (17%). Encouraged by this result we screened different cationic and non-ionic surfactants with varied alkyl chain lengths in combination with equimolar SDOSS to assess their efficiency. After careful screening, we have identified the best optimized condition for *N*-phenylation of **6a** with **2a** as Cu(OAc)₂ (25 mol%), SDOSS (20 mol%), Tween 80 (20 mol%), CF₃CO₂H (60 mol%), and Et₃N (2 equiv.) in water at room temperature, which afforded **7a** in 48% isolated yield after 12 h (please see Table H in the ESI† for the detailed optimization study). Better efficiency of the combination of SDOSS and Tween 80 (20 mol% each) to effectuate the transformation could be attributed to synergistic interactions of anionic and non-ionic binary surfactants driven by the increase in hydrophobicity induced by large alkyl chains (tails), which in turn may enhance the solubility of organic reactants through tuning the property of generated mixed micelles.³⁶ The optimized reaction conditions are viable for the electronically distinct **2** possessing various functionalities for the *N*-arylation with **6a** and afforded the desired products (**7a–h**) in synthetically acceptable yields (Table 4). The sensitive –OBn group on the aryl unit of **2** survived the reaction conditions. Interestingly, strong electron-deficient aryl rings of **2** having an ester and nitro group participated in the transformation. No hydrolysis was observed for the ester functionality. The results mirror the mild, robust, and dynamic characteristics of the present protocol. Although the reactivity of **6** appears less than 1/4, no homo-coupling of **2** was observed.

Transition metal-catalyzed late-stage functionalization (LSF) of pharmaceutical agents, lead molecules, and bio-active natural products provide an opportunity to rapidly optimize and elaborate their pharmacokinetic and pharmacodynamic properties by synthesizing new analogues and has gained momentum as an increasingly powerful tool for the structural diversification of value-added molecular entities during the drug development program.^{37,38} Metaxalone, housing 2-oxazolidinone as the core nucleus, has long been identified as a muscle relaxant.³⁹ Gratifyingly, the developed protocol allowed smooth *N*-arylation of metaxalone with electronically divergent **2** and the corresponding products (**7i–m**) were delivered in decent yields at 50 °C. The reaction condition were compatible with the ether linkage of metaxalone and the ester group present in the aryl ring of **2**. The results reflect the promising scope to streamline late-stage modification of pharmaceuticals, nutraceuticals, and agrochemicals by generating novel valuable derivatives.

The green chemistry metrics, such as atom economy (AE) and environmental factor (*E*-factor) values of all the synthesized *N*-arylation derivatives presented in Tables 2–4 have been assessed to evaluate the green credentials (please see Table I, J, and K in the ESI† for detailed descriptions). The AE values were in the range of 78.1–88.6% and the *E*-factor scores appeared in the range of 2.33–6.03. The calculated high AE value and *E*-factor count, albeit relatively poor, indicate the present methods as being green and sustainable.⁴⁰ We

Table 4 Substrate scope study of *N*-arylation of oxazolidinone scaffold (**6**) with arylboronic acid (**2**) to form **7**^{a,b,c}



^a Reaction condition: **6** (1 mmol), **2** (1.5 mmol, 1.5 equiv.), Cu(OAc)₂ (25 mol%), SDOSS (20 mol%), Tween 80 (20 mol%), CF₃CO₂H (60 mol%), Et₃N (2 equiv.) in H₂O (2 mL) at rt–50 °C, 12 h. ^b Isolated yield of **7**. ^c No homo-coupling of **2** was observed. ^d The figure in parentheses is the total yield based on recovery and reuse of both the unreacted starting materials after the first attempt and further calculated with respect to **6**.

observed that the electronic and steric properties of **1**, **2**, **4**, and **6** have been the primary factors controlling their individual reactivity for *N*-arylation, which along with the homogeneous nature of the catalytic system,^{40e} in turn, governs the AE and *E*-factor. The relatively poor *E*-factor score could be mitigated by further customization of the reaction parameters to enhance the reactivity profiles of **1**, **2**, **4**, and **6** in overcoming their kinetic barrier of reactivity.

We have compared the AE value and *E*-factor score as well as reaction conditions of our method with prior literature reports (please see Tables L–P in the ESI†). Comparable AE values have been obtained in all cases. In most of the cases, our method provided a better *E*-factor score compared to prior literature reports (Tables L–N, and Table P†), except in one case, in which the *E*-factor count of our method was inferior (Table O†). However, the prior reports (Tables L–P†) are associated with the requirement of stoichiometric Cu(OAc)₂ (1 equiv.), undesirable hazardous halogenated solvent (CH₂Cl₂), hazardous high-boiling point solvent (DMSO), and a long period of reaction (18 h–72 h). Thus, an overall consideration of all the aspects endorses our method as a more ‘green technology’.⁴¹

The catalytic conditions could be readily applied to a 'gram-scale' reaction of **1a** (1.47 g) with **2a** to prepare **3a** in 84% isolated yield (Scheme 1A). The result proves the scalability, reproducibility, and potential practical utility of the developed protocol of *N*-arylation. Furthermore, compound **3e** was synthetically modified by introducing a phenyl unit at the *ortho* C–Br bond following the Suzuki cross-coupling reaction with **2a**, which furnished *ortho*-heterocycle-tethered biphenyl system **8a** in 40% isolated yield (Scheme 1B). Moreover, **3a** was further derivatized at the C3-position through the nucleophilic addition of the –CH₂CN moiety, generated *via* the sp³C–H activation of acetonitrile **9**, under Pd(OAc)₂-catalyzed condition⁴² and the corresponding product **10a** was obtained in good yield (69%) (Scheme 1C). These outcomes reflect the possible usefulness of the developed *N*-arylation method, allowing further synthetic elaboration.

Control experiments were conducted to probe the effect of various oxidants on the reaction outcome because the Chan–Lam coupling between two nucleophiles, N-based and C-based, under the catalytic influence of Cu(II) salts typically relies on an oxidative environment (air or O₂).^{8c,9c,f,10g,11b,43} SDOSS in catalytic quantities is well known to activate aerial oxygen through the oxygen reuptake mechanism facilitating the oxidation process in water-mediated organic transformation⁴⁴ to promote green aerobic oxidation practice. Therefore, we first investigated the effect of aerial oxidation, O₂ balloon and N₂ atmospheres during the reaction of **1a** with **2a** (entries 1–3, Table 5). While aerial oxidation and the use of an O₂ balloon gave comparable results having higher conversions of **3a**, the use of an N₂ balloon provided poor results and established the indispensable role of the oxidative environment (aerial oxidation) for the transformation. We tested several other metal-based and non-metal-based oxidants (entries 4–7, Table 5 and Table G in the ESI†). Water-soluble oxidant, oxone, completely converted **2a** to phenol⁴⁵ (isolated in 96% yield) and thereby, did not allow **2a** to further participate in the catalytic cycle (entry 4). H₂O₂ and ^tBuOOH gave inferior results as an oxidant (entries 5 and 6). Other toxic and corros-

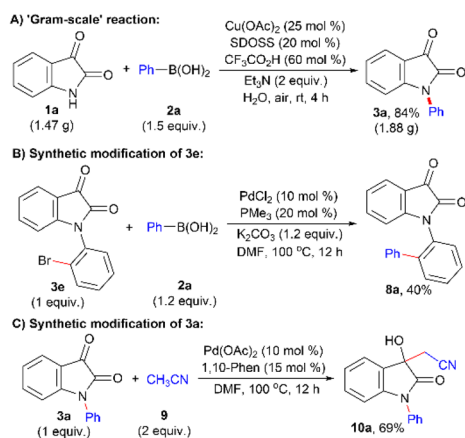
Table 5 Representative study of the effect of various oxidants on the *N*-arylation of **1a** with **2a** to form **3a**^a

Entry	Oxidant ^b	Yield ^c (%)
1	Aerial oxidation	86
2	O ₂ balloon	88
3	N ₂ balloon	10
4	Oxone	0 ^{d,e}
5	H ₂ O ₂	24 ^d
6	^t BuOOH	21 ^d
7	Ag ₂ O	0 ^d

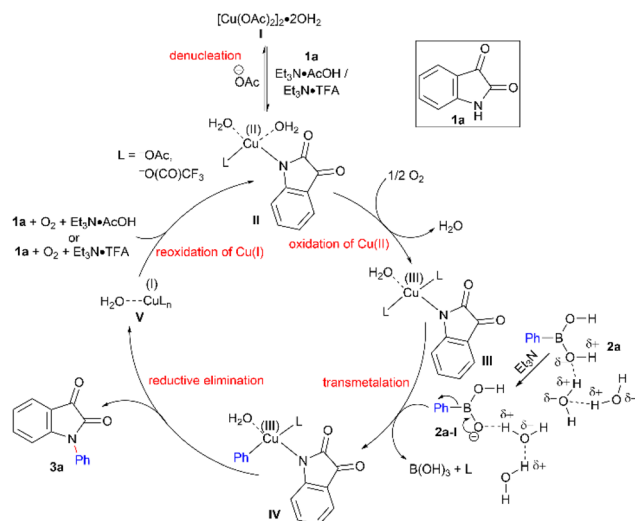
^a **1a** (1 mmol) was treated with **2a** (1.5 mmol, 1.5 equiv.) in the presence of Cu(OAc)₂ (25 mol%), SDOSS (20 mol%), CF₃CO₂H (60 mol%), Et₃N (2 equiv.) under different oxidative environments in H₂O (2 mL) at rt for 4 h. ^b The amount used is with respect to **1a**. ^c Isolated yield of **3a**. ^d Performed in a closed vessel. ^e Phenol was isolated in 96% yield.

ive stoichiometric non-metallic oxidants or costly metallic oxidants either failed or provided inferior results compared to aerial oxidation. Thus, use of catalytic SDOSS to dissolve aerial O₂ in water, effectuating the transformation, displays superior performance and is seemingly competent.

Based on the control experiments and prior literature report,⁴⁶ we have presented a plausible mechanism of coupling **1a** with **2a** to afford **3a** (Scheme 2). Cu(OAc)₂ may exist in equilibrium with the dimeric state **I**, which in turn may equilibrate with multinuclear forms as a resting state/reservoir.⁴⁶ At first, Et₃N abstracts the N–H proton from poorly nucleophilic **1a**, converting it to the anionic form, which is a better nucleophile and further denucleates **I** to monomeric Cu(II) complex **II** *via* N-coordination to the Cu(II) centre.⁴⁶ **II** then undergoes an easy oxidation to putative Cu(III) species **III** under aerial oxidation,⁴⁷ facilitated by a decrease in the reduction potential of



Scheme 1 (A) 'Gram-scale' production of **3a**; (B) derivatization of **3e** with **2a** to afford **8a**; and (C) derivatization of **3a** with **9** to afford **10a**.



Scheme 2 Proposed catalytic cycle of coupling of **1a** and **2a** providing **3a**.

the Cu(III)/Cu(II) couple⁴⁸ following N-coordination from **1a**. Transmetalation of the phenyl moiety from the *ate* species⁴⁹ **2a-I**, generated from **2a** aided by Et₃N,⁴⁶ to species **III** provides another Cu(III) species **IV**. A facile (Ph)C–N bond-forming reductive elimination from the high-valent Cu(III) centre⁵⁰ of **IV** delivers the *N*-arylation product **3a** along with Cu(I) species **V**. Finally, reoxidation of the Cu(I) centre of species **V**, assisted by Et₃N under aerobic condition and promoted by **1a**, regenerates the Cu(II) complex⁴⁶ **II**, thereby, the catalytic cycle closes and complex **II** is available for the next run.

Moreover, the formed B(OH)₃ in the elementary step (transmetalation) may further speed up the reoxidation of Cu(I) to Cu(II) in the presence of Et₃N and AcOH.⁴⁶ Perhaps, during the oxidation of Cu(II) to Cu(III), hydrogen peroxide could also be generated in the catalytic step, which may decompose **2a** *via* oxidation,⁵¹ and accounts for the requirement of 1.5 equivalents of **2** for a better conversion of the desired product. The better reactivity of the Chan–Lam coupling in the presence of Et₃N is well known.^{7a,c,47} The profound effect of Et₃N in the proposed catalytic cycle (Scheme 2) indicates that Et₃N eventually could play several fundamental roles: (i) abstracts the N–H proton from **1a**, rendering it more nucleophilic and favouring the denucleation of dimeric **I** by N-coordination to the Cu(II) centre; (ii) abstracts the O–H proton from **2a** forming an *ate* species **2a-I** and assisting in the effective transmetalation of the aryl unit; (iii) sequesters AcOH preventing reformation of dimeric **I** and other multinuclear catalytically inactive species; (iv) the resulting salt (Et₃N·AcOH) offers H⁺ and OAc[−] boosting the reoxidation of the Cu(I) centre to Cu(II).⁴⁶ Similarly, the amine substrate **1a** helps in (i) the denucleation of dimeric **I** to initiate the catalytic turnover and (ii) promotes reoxidation of the Cu(I) centre.⁴⁶ However, AcOH may play dual roles: (i) a detrimental effect by forming dimeric **I** and related catalytically incompetent species; and (ii) beneficial effects on the reoxidation of Cu(I) to Cu(II); and furthermore (iii) stabilizing the high-valent Cu(III) species⁵² **III** in the form of an ancillary ligand.⁵³ Possibly, catalytic CF₃CO₂H (i) promotes denucleation of **I** *via* the dissociation of the coordinating acetate ion²⁹ and enhances the cationicity^{27,28} of the Cu(II) centre, enabling the facile coordination of the NH-heterocycle, and (ii) may further stabilize the Cu(III) centre in **III**.

Water plays an indispensable role in performing this oxidative coupling reaction, otherwise the transformation either fails or gives inferior results in different organic solvents. While the role of water in promoting organic reactions is yet to be fully understood, various factors, such as the high cohesive energy density of water, enforced hydrophobic interactions, and hydrogen bonding (H-bonding) effect, could be envisaged as the unique features of water to accelerate the rate of an organic reaction.⁵⁴ The H-bonding effect has popularly been referred to as one of the factors for the rate enhancement of organic reactions in water originating from interfacial interactions of organic molecules with free hydroxyl groups of water molecules.⁵⁵ Thus, the benefit of the water medium could be anticipated to form an H-bond with the –OH group of **2a**, rendering the O–H proton more acidic, enabling its facile

abstraction by Et₃N, and subsequent stabilization of the resulting *ate* species **2a-I**, *via* an H-bonding interaction with O[−] atom, which in turn enhances the rate of phenyl unit transfer in the transmetalation step. Overall, the H-bond-promoted supramolecular assembly involving the reactant and water molecule(s) could be inferred as a favourable factor.^{20b,56}

Apart from the solubilizing aid of organic molecules within a micellar environment accounting for ‘in-water’ catalysis,^{19a-c,54a} the specific role of Tween 80 could be correlated with its H-bond donor (through terminal free –OH groups) and H-bond acceptor (through polyoxyethylene ethereal O-atoms and carbonyl O-atom) abilities. Moreover, it could be expected that the Tween 80 molecule may experience H-bonding interactions with the dangling –OH groups^{55b} of the interfacial water molecule(s) and further encapsulate and activate **2/6** through H-bonding interactions, resulting in better reactivity.

The hydrotropic effect of monoalkylglycerol ether molecules, controlled by the non-polar alkyl chain length, governs the hydrophobic interaction between a hydrotrope and solute and is the driving force of strong agglomeration of the hydrotrope around a solute in the water medium.⁵⁷ The hydrotropic effect of catalytic Tween 80 in solubilizing **2** and **6** in the water medium cannot be excluded.

Conclusions

In summary, this work describes Cu(II)-catalyzed simple, mild, powerful, and efficient *N*-arylation of poorly nucleophilic electron-deficient NH-heterocycles with arylboronic acids ‘in-water’ at room temperature. The catalytic effects of CF₃CO₂H and SDOSS/Tween 80, stoichiometric Et₃N, along with water molecule(s) have been found crucial for the coupling, and each component plays an indispensable role *via* synchronous interplay for an effective, sustainable transformation. The versatility and robustness of the protocol are established by accommodating different variations of (i) electron-deficient NH-heterocycles, (ii) arylboronic acids of moderate/strong electron-rich plus moderate/strong electron-deficient characteristics, (iii) execution of the reaction in an environmentally benign water medium, (iv) compatibility of sensitive functional groups, which illustrates notable advantages in diversity generation, (v) excellent chemoselectivity, (vi) high reaction rate, and (vii) operational simplicity mostly at room temperature. The promising practical applicability has been demonstrated through a ‘gram-scale’ synthesis, further synthetic manipulations of the resulting *N*-arylated scaffolds, and facile late-stage arylation of a pharmaceutical agent. Therefore, this strategy is expected to broaden the chemical, molecular and high-quality drug space by synthesizing small molecule-focused libraries⁵⁸ following sustainable medicinal chemistry practice.⁵⁹

Conflicts of interest

There are no conflicts to declare.

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References

- Selected representative examples: (a) A. N. Kim, A. Ngamnithiporn, E. Du and B. M. Stoltz, *Chem. Rev.*, 2023, **123**, 9447; (b) S. Chahal, P. Rani, Kiran, J. Sindhu, G. Joshi, A. Ganesan, S. Kalyaanamoorthy, Mayank, P. Kumar, R. Singh and A. Negi, *ACS Omega*, 2023, **8**, 17446; (c) K. R. Holman, A. M. Stanko and S. E. Reisman, *Chem. Soc. Rev.*, 2021, **50**, 7891; (d) M. A. Hardy, B. A. Wright, J. L. Bachman, T. B. Boit, H. M. S. Haley, R. R. Knapp, R. F. Lusi, T. Okada, V. Tona, N. K. Garg and R. Sarpong, *ACS Cent. Sci.*, 2020, **6**, 1017; (e) K. Seth, S. K. Garg, R. Kumar, P. Purohit, V. S. Meena, R. Goyal, U. C. Banerjee and A. K. Chakraborti, *ACS Med. Chem. Lett.*, 2014, **5**, 512; (f) A. Fürstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582; (g) K. C. Nicolaou, D. Vourloumis, N. Winssinger and P. S. Baran, *Angew. Chem., Int. Ed.*, 2000, **39**, 44.
- Selected representative examples: (a) J. Shearer, J. L. Castro, A. D. G. Lawson, M. MacCoss and R. D. Taylor, *J. Med. Chem.*, 2022, **65**, 8699; (b) M. M. Heravi and V. Zadsirjan, *RSC Adv.*, 2020, **10**, 44247; (c) R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845; (d) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257; (e) M. Baumann and I. R. Baxendale, *Beilstein J. Org. Chem.*, 2013, **9**, 2265; (f) M. Baumann, I. R. Baxendale, S. V. Ley and N. Nikbin, *Beilstein J. Org. Chem.*, 2011, **7**, 442.
- (a) H. Valluri, A. Bhanot, S. Shah, N. Bhandaru and S. Sundriyal, *J. Med. Chem.*, 2023, **66**, 8382; (b) L. D. Pennington and D. T. Moustakas, *J. Med. Chem.*, 2017, **60**, 3552.
- (a) K. R. Campos, P. J. Coleman, J. C. Alvarez, S. D. Dreher, R. M. Garbaccio, N. K. Terrett, R. D. Tillyer, M. D. Truppo and E. R. Parmee, *Science*, 2019, **363**, eaat0805; (b) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson and A. Wood, *Nat. Chem.*, 2018, **10**, 383.
- Selected representative examples: (a) A. Kumar, A. K. Singh, H. Singh, V. Vijayan, D. Kumar, J. Naik, S. Thareja, J. P. Yadav, P. Pathak, M. Grishina, A. Verma, H. Khalilullah, M. Jaremko, A.-H. Emwas and P. Kumar, *Pharmaceuticals*, 2023, **16**, 299; (b) S. Raju, P. E. Sheridan, A. K. Hauer, A. E. Garrett, D. E. McConnell, J. A. Thornton, S. L. Stokes and J. P. Emerson, *Chem. Biodivers.*, 2022, **19**, e202200327; (c) E. Kabir and M. Uzzaman, *Results Chem.*, 2022, **4**, 100606; (d) N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Molecules*, 2020, **25**, 1909; (e) A. Ghosh, J. E. Sieser, S. Caron, M. Couturier, K. Dupont-Gaudet and M. Girardin, *J. Org. Chem.*, 2006, **71**, 1258.
- (a) P. Oeser, J. Koudelka, A. Petrenko and T. Tobrman, *Molecules*, 2021, **26**, 5079; (b) J. Liu, J. Jiang, L. Zheng and Z.-Q. Liu, *Adv. Synth. Catal.*, 2020, **362**, 4876; (c) P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**, 12564; (d) C. Fischer and B. Koenig, *Beilstein J. Org. Chem.*, 2011, **7**, 59.
- (a) D. J. Cundy and S. A. Forsyth, *Tetrahedron Lett.*, 1998, **39**, 7979; (b) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan and A. Combs, *Tetrahedron Lett.*, 1998, **39**, 2941; (c) D. M. T. Chan, K. L. Monaco, R.-P. Wang and M. P. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933.
- (a) D. N. Shinde, R. Trivedi, J. V. S. Krishna, L. Giribabu, B. Sridhar, P. S. Khursade and R. S. Prakasham, *New J. Chem.*, 2018, **42**, 12587; (b) D. Rambabu, S. K. Kumar, B. Y. Sreenivas, S. Sandra, A. Kandale, P. Misra, M. V. B. Rao and M. Pal, *Tetrahedron Lett.*, 2013, **54**, 495; (c) K. S. Rao and T.-S. Wu, *Tetrahedron*, 2012, **68**, 7735; (d) K. S. Kumar, R. Adepur, S. Sandra, D. Rambabu, G. R. Krishna, C. M. Reddy, P. Misra and M. Pal, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 1146; (e) J. X. Qiao and P. Y. S. Lam, *Synthesis*, 2011, 829; (f) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, K. M. Averill, D. M. T. Chan and A. Combs, *Synlett*, 2000, 674.
- (a) J.-Q. Chen, J.-H. Li and Z.-B. Dong, *Adv. Synth. Catal.*, 2020, **362**, 3311; (b) V. H. Duparc, G. L. Bano and F. Schaper, *ACS Catal.*, 2018, **8**, 7308; (c) T. Garnier, R. Sakly, M. Danel, S. Chassaing and P. Pale, *Synthesis*, 2017, **49**, 1223; (d) S. Roy, M. J. Sarma, B. Kashyap and P. Phukan, *Chem. Commun.*, 2016, **52**, 1170; (e) D. N. Rao, S. Rasheed, S. Aravinda, R. A. Vishwakarma and P. Das, *RSC Adv.*, 2013, **3**, 11472; (f) J. P. Collman, M. Zhong, C. Zhang and S. Costanzo, *J. Org. Chem.*, 2001, **66**, 7892.
- Selected representative examples: (a) B. Adhikari, M. Teimouri, J. W. Akin, S. Raju, S. L. Stokes and J. P. Emerson, *Eur. J. Org. Chem.*, 2023, e202300620; (b) A. Mahanta, A. J. Thakur and U. Bora, *Curr. Res. Green Sustainable Chem.*, 2021, **4**, 100093; (c) X. Jia and P. Peng, *Org. Biomol. Chem.*, 2018, **16**, 8984; (d) V. H. Duparc and F. Schaper, *Dalton Trans.*, 2017, **46**, 12766; (e) N. Devarajan and P. Suresh, *ChemCatChem*, 2016, **8**, 2953; (f) A. Gogoi, G. Sarmah, A. Dewan and U. Bora, *Tetrahedron Lett.*, 2014, **55**, 31; (g) J. P. Collman and M. Zhong, *Org. Lett.*, 2000, **2**, 1233.
- (a) W. Gao, F. Gao, H. Yang, Z. Wang and Y. Huang, *Catalysts*, 2023, **13**, 1060; (b) T. Onaka, H. Umemoto, Y. Miki, A. Nakamura and T. Maegawa, *J. Org. Chem.*, 2014, **79**, 6703.
- (a) K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31; (b) C. Capello, U. Fischer and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927.
- (a) J. Boström, D. G. Brown, R. J. Young and G. M. Keserü, *Nat. Rev. Drug Discovery*, 2018, **17**, 709; (b) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451.

- 14 (a) M. Cortes-Clerget, J. Yu, J. R. A. Kincaid, P. Walde, F. Gallou and B. H. Lipshutz, *Chem. Sci.*, 2021, **12**, 4237; (b) D. Prat, J. Hayler and A. Wells, *Green Chem.*, 2014, **16**, 4546; (c) H. C. Hailes, *Org. Process Res. Dev.*, 2007, **11**, 114.
- 15 (a) F. Zhou, Z. Hearne and C.-J. Li, *Curr. Opin. Green Sustainable Chem.*, 2019, **18**, 118; (b) C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, *Green Chem.*, 2015, **17**, 3111; (c) M.-O. Simon and C.-J. Li, *Chem. Soc. Rev.*, 2012, **41**, 1415; (d) J. L. Tucker, *Org. Process Res. Dev.*, 2006, **10**, 315.
- 16 Selected representative examples: (a) M.-Z. Lu and T.-P. Loh, *Acc. Chem. Res.*, 2024, **57**, 70; (b) F. Scalambra, P. Lorenzo-Luis, I. de los Rios and A. Romerosa, *Coord. Chem. Rev.*, 2021, **443**, 213997; (c) M. B. Gawande, V. D. B. Bonifácio, R. Luque, P. S. Branco and R. S. Varma, *Chem. Soc. Rev.*, 2013, **42**, 5522; (d) R. N. Butler and A. G. Coyne, *Chem. Rev.*, 2010, **110**, 6302; (e) A. Chanda and V. V. Fokin, *Chem. Rev.*, 2009, **109**, 725; (f) S. Minakata and M. Komatsu, *Chem. Rev.*, 2009, **109**, 711; (g) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095.
- 17 D. J. C. Constable, C. Jimenez-Gonzalez and R. K. Henderson, *Org. Process Res. Dev.*, 2007, **11**, 133.
- 18 L. Chen, S. Zhang, X. Liu and X. Ge, *Curr. Opin. Colloid Interface Sci.*, 2023, **65**, 101691.
- 19 (a) B. H. Lipshutz, S. Ghorai and M. Cortes-Clerget, *Chem. – Eur. J.*, 2018, **24**, 6672; (b) D. Kumar, K. Seth, D. N. Kommi, S. Bhagat and A. K. Chakraborti, *RSC Adv.*, 2013, **3**, 15157; (c) B. H. Lipshutz and S. Ghorai, *Aldrichimica Acta*, 2012, **45**, 3.
- 20 Selected representative examples: (a) D. P. Satpute, G. N. Vaidya, S. K. Lokhande, S. D. Shinde, S. M. Bhujbal, D. R. Chatterjee, P. Rana, A. Venkatesh, M. Nagpure and D. Kumar, *Green Chem.*, 2021, **23**, 6273; (b) K. Seth, S. Raha Roy, B. V. Pipaliya and A. K. Chakraborti, *Chem. Commun.*, 2013, **49**, 5886; (c) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (d) C. Fischmeister and H. Doucet, *Green Chem.*, 2011, **13**, 741; (e) M. Lamblin, L. Nassar-Hardy, J.-C. Hierso, E. Fouquet and F.-X. Felpin, *Adv. Synth. Catal.*, 2010, **352**, 33.
- 21 P. Tundo, P. Anastas, D. S. Black, J. Breen, T. Collins, S. Memoli, J. Miyamoto, M. Polyakoff and W. Tumas, *Pure Appl. Chem.*, 2000, **72**, 1207.
- 22 CNS-MAO B: (a) S. N. Pandeya, S. Smtha, M. Jyoti and S. K. Sridhar, *Acta Pharm.*, 2005, **55**, 27; SARS protease: (b) L. Zhou, Y. Liu, W. Zhang, P. Wei, C. Huang, J. Pei, Y. Yuan and L. Lai, *J. Med. Chem.*, 2006, **49**, 3440; GAL₃ receptor antagonist: (c) M. J. Konkel, B. Lagu, L. W. Boteju, H. Jimenez, S. Noble, M. W. Walker, G. Chandrasena, T. P. Blackburn, S. S. Nikam, J. L. Wright, B. E. Kornberg, T. Gregory, T. A. Pugsley, H. Akunne, K. Zoski and L. D. Wise, *J. Med. Chem.*, 2006, **49**, 3757; Sunitinib and semaxanib: (d) R. Nath, S. Pathania, G. Grover and M. J. Akhtar, *J. Mol. Struct.*, 2020, **1222**, 128900; (e) Varun, Sonam and R. Kakkar, *Med. Chem. Commun.*, 2019, **10**, 351.
- 23 (a) P. S. Auti, G. George and A. T. Paul, *RSC Adv.*, 2020, **10**, 41353; (b) D. He, M. Wang, S. Zhao, Y. Shu, H. Zeng, C. Xiao, C. Lu and Y. Liu, *Fitoterapia*, 2017, **119**, 136; (c) I. Khan, S. Zaib, S. Batool, N. Abbas, Z. Ashraf, J. Iqbal and A. Saeed, *Bioorg. Med. Chem.*, 2016, **24**, 2361.
- 24 (a) C. Foti, A. Piperno, A. Scala and O. Giuffrè, *Molecules*, 2021, **26**, 4280; (b) M. F. Gordeev and Z. Y. Yuan, *J. Med. Chem.*, 2014, **57**, 4487; (c) G. Zappia, P. Menendez, G. D. Monache, D. Misiti, L. Nevola and B. Botta, *Mini-Rev. Med. Chem.*, 2007, **7**, 389; (d) A. Ali, G. S. K. K. Reddy, H. Cao, S. G. Anjum, M. N. L. Nalam, C. A. Schiffer and T. M. Rana, *J. Med. Chem.*, 2006, **49**, 7342; (e) G. G. Zhanel, C. Schroeder, L. Vercaigne, A. S. Gin, J. Embil and D. J. Hoban, *Can. J. Infect. Dis. Med. Microbiol.*, 2001, **12**, 379.
- 25 (a) T. Hoffmann and M. Gastreich, *Drug Discovery Today*, 2019, **24**, 1148; (b) J.-L. Reymond and M. Awale, *ACS Chem. Neurosci.*, 2012, **3**, 649; (c) J.-L. Reymond, R. van Deursen, L. C. Blum and L. Ruddigkeit, *MedChemComm*, 2010, **1**, 30.
- 26 (a) K. K. Gurjar and R. K. Sharma, *Heliyon*, 2020, **6**, e03233; (b) R. Das, M. Mandal and D. Chakraborty, *Asian J. Org. Chem.*, 2013, **2**, 579; (c) S. S. van Berkel, A. van den Hoogenband, J. W. Terpstra, M. Tromp, P. W. N. M. van Leeuwen and G. P. F. van Strijdonck, *Tetrahedron Lett.*, 2004, **45**, 7659.
- 27 (a) M. Maingle, S. Sunny, L. Sheeba, F. R. Pathan and K. Seth, *Synthesis*, 2024, **56**, 312; (b) U. Belluco, M. Giustiniani and M. Graziani, *J. Am. Chem. Soc.*, 1967, **89**, 6494.
- 28 C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones and K. I. Booker-Milburn, *Angew. Chem., Int. Ed.*, 2009, **48**, 1830.
- 29 T. Nishikata, A. R. Abela, S. Huang and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2010, **132**, 4978.
- 30 Redox ligand assisted reductive elimination: J. Jacquet, P. Chaumont, G. Gontard, M. Orio, H. Vezin, S. Blanchard, M. D.-E. Murr and L. Fensterbank, *Angew. Chem., Int. Ed.*, 2016, **55**, 10712.
- 31 (a) J. Buchspies, M. M. Rahman and M. Szostak, *Molecules*, 2021, **26**, 188; (b) R. Takise, K. Muto and J. Yamaguchi, *Chem. Soc. Rev.*, 2017, **46**, 5864; (c) L. Hie, N. F. F. Nathel, X. Hong, Y.-F. Yang, K. N. Houk and N. K. Garg, *Angew. Chem., Int. Ed.*, 2016, **55**, 2810.
- 32 K. Sreeramamurthy, E. Ashok, V. Mahendar, G. Santoshkumar and P. Das, *Synlett*, 2010, 721.
- 33 K. A. Kumar, P. Kannaboina, C. K. Jaladanki, P. V. Bharatam and P. Das, *ChemistrySelect*, 2016, **3**, 601.
- 34 G. N. Vaidya, A. Khan, H. Verma, S. Kumar and D. Kumar, *J. Org. Chem.*, 2019, **84**, 3004.
- 35 H. C. Ma and X. Z. Jiang, *Synlett*, 2008, 1335.
- 36 (a) X. Cui, Y. Jiang, C. Yang, X. Lu, H. Chen, S. Mao, M. Liu, H. Yuan, P. Luo and Y. Du, *J. Phys. Chem. B*, 2010, **114**, 7808; (b) M. S. Bakshi and G. Kaur, *J. Colloid Interface Sci.*, 2005, **289**, 551; (c) M. Ishikawa, K. Matsumura, K. Esumi and K. Meguro, *J. Colloid Interface Sci.*, 1991, **141**,

- 10; (d) A. Graciaa, M. B. Ghoulam, G. Marion and J. Lachaise, *J. Phys. Chem.*, 1989, **93**, 4167.
- 37 LSF *via* cross-coupling: (a) T. Zhou, P.-P. Xie, C.-L. Ji, X. Hong and M. Szostak, *Org. Lett.*, 2020, **22**, 6434; (b) P. S. Engl, A. P. Häring, F. Berger, G. Berger, A. Pérez-Bitrián and T. Ritter, *J. Am. Chem. Soc.*, 2019, **141**, 13346; (c) P. Tang, T. Furuya and T. Ritter, *J. Am. Chem. Soc.*, 2010, **132**, 12150.
- 38 Selected representative examples of LSF *via* C–H functionalization: (a) J. H. Docherty, T. M. Lister, G. McArthur, M. T. Findlay, P. Domingo-Legarda, J. Kenyon, S. Choudhary and I. Larrosa, *Chem. Rev.*, 2023, **123**, 7692; (b) C. M. Josephitis, H. M. H. Nguyen and A. McNally, *Chem. Rev.*, 2023, **123**, 7655; (c) S. D. Friis, M. J. Johansson and L. Ackermann, *Nat. Chem.*, 2020, **12**, 511; (d) H. Schönherr and T. Cernak, *Angew. Chem., Int. Ed.*, 2013, **52**, 12256.
- 39 J. F. Kurtzke and J. Gylfe, *Neurology*, 1962, **12**, 343.
- 40 (a) N. Fantozzi, J.-N. Volle, A. Porcheddu, D. Virieux, F. García and E. Colacino, *Chem. Soc. Rev.*, 2023, **52**, 6680; (b) S. G. Akakios, M. L. Bode and R. A. Sheldon, *Green Chem.*, 2021, **23**, 3334; (c) K. A. Waibel, R. Nickisch, N. Möhl, R. Seim and M. A. R. Meier, *Green Chem.*, 2020, **22**, 933; (d) M. M. Khan, Saigal, S. Khan, S. Shareef and S. C. Sahoo, *RSC Adv.*, 2018, **8**, 41892; (e) M. J. Climent, A. Corma, S. Iborra, M. Mifsud and A. Velty, *Green Chem.*, 2010, **12**, 99.
- 41 P. Jessop, *Green Chem.*, 2020, **22**, 13.
- 42 (a) J. R. Hummel, J. A. Boerth and J. A. Ellman, *Chem. Rev.*, 2017, **117**, 9163; (b) G.-W. Wang, A.-X. Zhou, J.-J. Wang, R.-B. Hu and S.-D. Yang, *Org. Lett.*, 2013, **15**, 5270.
- 43 (a) M. T. Wentzel, J. B. Hewgley, R. M. Kamble, P. D. Wall and M. C. Kozlowski, *Adv. Synth. Catal.*, 2009, **351**, 931; (b) J.-B. Lan, L. Chen, X.-Q. You and R.-G. Xie, *Chem. Commun.*, 2004, 188.
- 44 N. Parikh, D. Kumar, S. Raha Roy and A. K. Chakraborti, *Chem. Commun.*, 2011, **47**, 1797.
- 45 K. S. Webb and D. Levy, *Tetrahedron Lett.*, 1995, **36**, 5117.
- 46 J. C. Vantourout, H. N. Miras, A. Isidro-Llobet, S. Sproules and A. J. B. Watson, *J. Am. Chem. Soc.*, 2017, **139**, 4769.
- 47 D. A. Evans, J. L. Katz and T. R. West, *Tetrahedron Lett.*, 1998, **39**, 2937.
- 48 S. G. Bratsch, *J. Phys. Chem. Ref. Data*, 1989, **18**, 1.
- 49 Pd-catalysis: (a) K. Seth, P. Purohit and A. K. Chakraborti, *Org. Lett.*, 2014, **16**, 2334; (b) R. Narayanan and M. A. El-Sayed, *J. Phys. Chem. B*, 2005, **109**, 4357.
- 50 (a) K. L. Vikse and P. Chen, *Organometallics*, 2015, **34**, 1294; (b) L. M. Huffman and S. S. Stahl, *Dalton Trans.*, 2011, **40**, 8959; (c) A. Casitas, A. E. King, T. Parella, M. Costas, S. S. Stahl and X. Ribas, *Chem. Sci.*, 2010, **1**, 326; (d) L. M. Huffman and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 9196.
- 51 M. F. Lappert, *Chem. Rev.*, 1956, **56**, 959.
- 52 A. J. Hickman and M. S. Sanford, *Nature*, 2012, **484**, 177.
- 53 B. S. Billow, T. J. McDaniel and A. L. Odom, *Nat. Chem.*, 2017, **9**, 837.
- 54 (a) V. M. Kolb, *Green organic chemistry and its interdisciplinary applications*, CRC Press, Boca Raton, Taylor and Francis, 2016; (b) S. Mellouli, L. Bousekkine, A. B. Theberge and W. T. S. Huck, *Angew. Chem., Int. Ed.*, 2012, **51**, 7981.
- 55 (a) Y. Zheng and J. Zhang, *ChemPhysChem*, 2010, **11**, 65; (b) Y. Jung and R. A. Marcus, *J. Am. Chem. Soc.*, 2007, **129**, 5492.
- 56 Selected representative examples: (a) D. N. Kommi, D. Kumar, K. Seth and A. K. Chakraborti, *Org. Lett.*, 2013, **15**, 1158; (b) D. N. Kommi, P. S. Jadhavar, D. Kumar and A. K. Chakraborti, *Green Chem.*, 2013, **15**, 798; (c) I. Viotijevic and T. F. Jamison, *Science*, 2007, **317**, 1189; (d) E. Vöhringer-Martinez, B. Hansmann, H. Hernandez, J. S. Francisco, J. Troe and B. Abel, *Science*, 2007, **315**, 497.
- 57 (a) D. O. Abranches, J. Benfica, B. P. Soares, A. Leal-Duaso, T. E. Sintra, E. Pires, S. P. Pinho, S. Shimizu and J. A. P. Coutinho, *Chem. Commun.*, 2020, **56**, 7143; (b) G. Graziano, *Nat. Rev. Chem.*, 2020, **4**, 332.
- 58 T. W. J. Cooper, I. B. Campbell and S. J. F. Macdonald, *Angew. Chem., Int. Ed.*, 2010, **49**, 8082.
- 59 (a) C. T. A. Moermond, N. Puhlmann, A. R. Brown, S. F. Owen, J. Ryan, J. Snape, B. J. Venhuis and K. Kümmerer, *Environ. Sci. Technol. Lett.*, 2022, **9**, 699; (b) M. C. Bryan, B. Dillon, L. G. Hamann, G. J. Hughes, M. E. Kopach, E. A. Peterson, M. Pourashraf, I. Raheem, P. Richardson, D. Richter and H. F. Sneddon, *J. Med. Chem.*, 2013, **56**, 6007.