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Generalizing arene C−H alkylations by radical−radical cross-coupling

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The efficient and modular diversification of molecular scaffolds, particularly for the synthesis of diverse molecular libraries, remains a significant challenge in drug optimization campaigns.[1–3] The late-stage introduction of alkyl fragments is especially desirable due to the high sp^3-character and structural versatility of these motifs.[4] Given their prevalence in molecular frameworks, C(sp^2)−H bonds serve as attractive targets for diversification, though this process often requires difficult pre-functionalization or lengthy de novo syntheses. Traditionally, direct alkylations of arenes are achieved by employing Friedel–Crafts reaction conditions using strong Brønsted or Lewis acids.[5,6] However, these methods suffer from poor functional group tolerance and low selectivity, limiting their broad implementation in late-stage functionalization and drug optimization campaigns. Herein, we report the application of a novel strategy for the selective coupling of differently hybridized radical species, which we term *dynamic orbital selection*. This mechanistic paradigm overcomes common limitations of Friedel-Crafts alkylations via the in situ formation of two distinct radical species, which are subsequently differentiated by a copper-based catalyst based on their respective binding properties. As a result, we demonstrate herein a general and highly modular reaction for the direct alkylation of native arene C−H bonds using abundant and benign alcohols and carboxylic acids as the alkylating agents. Ultimately, this solution overcomes the synthetic challenges associated with the introduction of complex alkyl scaffolds into highly sophisticated drug scaffolds in a late-stage fashion, thereby granting access to vast new chemical space. Based on the generality of the underlying coupling mechanism, *dynamic orbital selection* is expected to be a broadly applicable coupling platform for further challenging transformations involving two distinct radical species.

In recent decades, the pace of drug discovery has become increasingly intertwined with advances in synthetic organic chemistry.[7,8] Notably, the need to rapidly diversify existing lead structures for structure-activity relationship (SAR) campaigns has underscored the importance of developing efficient, modular, and expedited synthetic protocols.[9] This synergy between drug discovery and chemical synthesis can significantly expedite the optimization of pharmacological properties in drug molecules.

In this context, the synthetic chemist aims to develop methods that harness abundant and structurally diverse functional groups as a means to maximize reaction applicability and generality.[10] Aromatic compounds, particularly those containing C(sp^2)−H bonds, are ubiquitous in drug molecules[11] and widely available from commercial sources. The ability to directly engage these native C(sp^2)−H bonds in functionalization reactions—without the need for prior installation of additional functional handles—would significantly streamline diversification efforts.[12] Recent years have seen growing interest in reactions that enable the direct functionalization of arenes, especially those that form C(sp^2)−C(sp^2) and C(sp^2)−heteroatom (C(sp^2)−Het) bonds.[13,14] Despite these efforts, few methods are capable of directly forging C(sp^2)−C(sp^3) bonds via C(sp^2)−H activation in the context of late-stage cross-couplings.[15–20] These methods often rely on alkyl halides, which are limited in both commercial availability and applicability, and generally offer attenuated scope. There is therefore great interest in developing a modular and general platform that achieves the selective alkylation of arene C−H bonds using abundant alkyl sources. To this end, alcohols are viewed as highly desirable synthetic building blocks due to their broad commercial availability, structural diversity, and benign nature (Fig. 1A).[10] Classical *Friedel-Crafts* alkylation strategies use alcohols, yet often require forcing reaction conditions that severely limit their applicability in diversely functionalized systems. Furthermore, these methods typically necessitate highly electron-rich aromatic compounds and are prone to overalkylation due to increased electron density in the aromatic system upon alkylation, further constraining their use in complex synthetic contexts.[5]

A robust, general catalytic platform that achieves the functionalization of a wide range of C(sp^2)−H bonds with alcohol alkylating agents would enable a vast expansion of accessible chemical space for alkyl–aryl substitution

patterns.[21] Moreover, a robust direct C(sp^2)−H alkylation protocol would facilitate retrosynthetic analysis of complex drug targets and, in the context of late-stage functionalization, would allow for the tailored one-step diversification of structurally sophisticated molecules, including natural products, biomolecules, and small-molecule therapeutics, circumventing the need for lengthy *de novo* syntheses (Fig. 1B).

Reaction Conceptualization

In recent years, the synergistic merger of transition metal catalysis and photoredox chemistry has led to the introduction of new cross-coupling methods that offer exceptional selectivity under mild reaction conditions.[22] Nickel-based metallaphotoredox catalysis strategies have been developed to forge C(sp^2)−C(sp^3) bonds; these mechanisms typically involve oxidative addition of a nickel complex into a C(sp^2)−halide bond.[23–25] However, in the context of complex drug scaffolds, introduction of the halide group requires alteration of the starting materials or direct installation under forcing conditions, which can be unfeasible or proceed with poor chemo- and regioselectivity.

To address this challenge, we envisioned a synthetic platform that eliminates the need for a pre-installed functional handle by bypassing the traditional oxidative addition step. Specifically, we sought to leverage previous studies on late-stage C(sp^2)−H activation that employ sulfoxides to generate open-shell aryl radicals from C(sp^2)−H bonds *via* light-induced electron transfer.[26–28] We anticipated that this aryl radical could be induced to selectively couple with a transient alkyl radical derived *in situ* from an alcohol precursor.

A long-standing paradigm in radical–radical cross-coupling asserts that to achieve satisfactory selectivity and prevent undesired side reactions, one of the coupling partners must be long-lived.[29] Recently, our group introduced the concept of *radical sorting* as a means to achieve cross-selectivity in radical–radical couplings. Under this strategy, two differentially substituted radicals are generated in solution, and selectivity is achieved through preferential capture of the less-substituted radical by the metal catalyst, followed by homolytic substitution with the more nucleophilic, higher substituted radical.[30–32]

While the logic of *radical sorting* relies on steric differences between coupling partners, one might also consider other properties that influence the strength of radical binding to a metal center. Inspired by seminal observations on the stabilization of distinct radical species by a metal center,[33] we sought to pursue *dynamic orbital selection* as a means to differentiate coupling partners by exploiting the different binding properties of radical orbitals to metals. Specifically, we envisioned simultaneously generating an alkyl p-radical and an aryl sp^2-radical in the presence of a Cu(I) catalyst (Fig. 1C). The dynamic equilibrium between the two free radicals and their respective metal-bound states is governed by differences in bond dissociation energies between the radical and the metal catalyst and can be used to enable cross selectivity in radical-radical couplings. We expected that the Cu(I) complex would preferentially bind to the sp^2-hybridized aryl radical over the alkyl p-radical, which would remain in equilibrium between the free and metal-bound states.[34] For the second radical capture, an additional selection event would occur based on the unfavorable coordination of an alkyl radical to an intermediate Cu(II)−alkyl species, as well as the inherently challenging reductive elimination leading to the alkyl homocoupled product. Instead, the reversibility of alkyl radical coordination, coupled with dynamic selection by the catalyst, would enable the system to selectively funnel to the desired high-valent aryl-alkyl Cu(III) species, poised to undergo facile reductive elimination.[35] Execution of this new *dynamic orbital selection* logic would allow the direct alkylation of C(sp^2)−H bonds using abundant feedstock precursors.

To maximize the scope and modularity of the reaction platform, we sought to employ both alcohols and carboxylic acids as alkylating agents. The use of these two distinct alkyl radical precursors would allow for orthogonal functionalizations of two different lynchpins. Previous work by our group has demonstrated the versatile use of benzoxazolium-based reagents, known as NHC reagents, for the activation of alcohols and the release of alkyl radicals by means of photoredox chemistry.[36] For alkyl-substituted carboxylic acids, we envisioned a copper-assisted direct oxidation followed by irreversible decarboxylation to generate the corresponding alkyl radical (Fig. 1D).[37]

Development of the cross-coupling platform

We first sought to optimize a general alkylation protocol using alcohols as the alkyl radical source. To benchmark our method against a traditional approach for direct alkylation of aromatic compounds—*Friedel-Crafts* alkylation—we selected fluorobenzene, an electron-poor arene, and Cbz-protected 4-hydroxypiperidine as the coupling partners.

The arene was activated with dibenzothiophene oxide (DBTO) and triflic anhydride to generate adduct **II** in a telescoped protocol without additional column purification. Under our optimized conditions, direct addition of

NHC-OMe-alcohol adduct **I**, Cu(I)Cl, Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6, cesium acetate (CsOAc), tetrabutylammonium chloride (TBACl), dimethyl sulfoxide (DMSO), and methyl *tert*-butyl ether (MTBE), followed by irradiation with blue light-emitting diodes (LEDs) for 2 hours, led to formation of the desired cross-coupled product in high yields. Interestingly, only copper-based catalysts, particularly Cu(I)Cl, were capable of acting as efficient *dynamic orbital selection* catalysts, delivering the cross-coupled product in satisfactory yields. In contrast, the nickel-based catalysts previously employed for radical sorting[31,32,38,39] produced only minor amounts of the desired product (see Supplementary Information for details).

The superior performance of the more electron-rich NHC-OMe, compared to its NHC-H analog, can be attributed to its lower reduction potential of $E_{1/2}$ (NHC-alcohol$^{+\bullet}$/NHC-alcohol) = +0.45 V (*vs.* SCE) (see Supplementary Information for cyclic voltammetry measurements), which allows it to outcompete competitive quenching of the excited state photocatalyst by Cu(I). Moreover, the addition of TBACl significantly enhanced the reaction yield and suppressed undesired olefin formation caused by overoxidation of the alkyl radical by *in situ*-formed Cu(II) species. We hypothesize that TBACl modulates the ligand environment of the copper catalyst, reducing its oxidative power in its Cu(II) state, analogous to other reported copper-based systems (see Supplementary Information for a detailed discussion).[40,41] Notably, other ligands commonly used in copper-mediated reactions did not improve the yield compared to TBACl. Both aryl and alkyl radical species were detected by radical trapping studies, including intramolecular cyclization experiments and TEMPO adduct formation. Control experiments further support the existence of a copper-mediated *dynamic orbital selection* pathway, as exclusion of metal catalyst led to a statistical amount of cross-coupled product and predominantly resulted in formation of the protodeoxygenated byproduct and reformation of the arene by hydrogen atom transfer (HAT).

Density functional theory (DFT) calculations support the existence of a reaction network initiated by selective radical capture by Cu(I), leading to the formation of Cu(II)−alkyl and Cu(II)−aryl species. Due to differences in bond dissociation energies, aryl radical coordination is an irreversible process, whereas alkyl radical coordination is reversible. This results in the immediate and irreversible capture of free aryl radicals by the Cu(I) catalyst, forming a Cu(II)−aryl species. This intermediate can subsequently capture either an aryl or an alkyl radical, leading to aryl homocoupling or the desired heterocoupled product, respectively, following reductive elimination from a high-valent Cu(III) species.[42] The high cross-coupling selectivity arises from the low temporal concentration of free aryl radicals in solution, a result of their barrierless and irreversible capture by Cu(I). This minimizes the statistical likelihood of aryl homocoupling. Furthermore, our calculations reveal a secondary selection process at the Cu(II) stage when an Cu(II)−alkyl species is formed. Reversible capture of a second alkyl radical by the Cu(II)−alkyl intermediate is thermodynamically less favored than irreversible aryl radical capture, therefore funneling the reaction toward the thermodynamically favored Cu(III) aryl-alkyl species, which rapidly undergoes reductive elimination to form the cross-coupled product.

The copper catalyst thus dynamically selects the appropriate radicals based on their binding properties, thereby governing cross-selectivity by guiding the reaction towards the desired high-valent Cu(III) aryl-alkyl species. Further mechanistic details are provided in the Supplementary Information.

Scope Evaluation

With optimized conditions in hand, we next set out to explore the scope of the aromatic alkylation strategy with respect to the alcohol coupling partner (Fig. 2). A range of primary alcohols with varying electronic and steric properties were productively engaged in radical–radical cross-coupling with (hetero)arene partners, generating the corresponding products in good to high yields (46–67% yield). Notably, the reaction tolerated a variety of different substitution patterns in the β-position, including secondary (**1**–**3**), tertiary (**4**), and even quaternary carbon centers bearing a neopentyl substitution pattern (**5**). The latter finding is particularly noteworthy, as highly β-substituted coupling partners often pose significant challenges in traditional radical cross-coupling reactions with aryl halides in the presence of sterically sensitive nickel complexes. In contrast, the copper complex employed herein is more sterically accessible as it does not require the addition of exogenous ligands.

A wide variety of complex secondary alcohols bearing seven- (**6**), six- (**7** and **8**), five- (**9** and **10**), and four-membered rings (**11** and **12**) were found to be suitable alkylating agents, delivering cross-coupled products in good to excellent yields (54–77% yield). Furthermore, spirocyclic alcohols (**13** and **14**) equipped with Boc-protected amines, which are notoriously difficult to engage in traditional *Friedel-Crafts* alkylation or acylation reactions, were coupled in 54% and 62% yield, respectively. Even sterically hindered 2-adamantanol was successfully coupled, affording the corresponding cross-coupled product **15** in 81% yield. A nucleoside analogue, **16**, containing a highly labile acetal protecting group, served as a competent coupling partner in our protocol (44% yield). Moreover, naturally occurring alcohols such as (–)-menthol (**17**) and derivatives of natural alcohols such as the

methylester of hydroxyproline (**18**) were viable coupling partners, delivering the desired products in high yields (74% and 54%, respectively). To our delight, more complexly substituted six-membered ring systems incorporating structural motifs prevalent in drug discovery, including pyridine **19** and triazolopiperazine **20**, could be converted to the respective products in synthetically useful yields (55% and 50%, respectively).

As outlined in Figure 2, we found a range of benzylic and allylic alcohols to be viable substrates in the cross-coupling reaction. Linear benzylic alcohols (**21**–**23**), allylic alcohols such as myrtenol (**24**), and cyclic benzylic alcohols (**25**) were efficiently coupled with phenyl-based arenes or sterically encumbered pyridine to deliver the desired products in high yields (60–67% yield, see Supplementary Information for extended scope).

To further extend the generality of the *dynamic orbital selection* system, we questioned whether tertiary radicals could be employed *en route* to desirable, yet challenging, all-carbon quaternary centers. Particularly in the context of copper-catalyzed radical cross-couplings, only quaternary centers possessing heteroatoms or two sp^2-carbon substitutions had previously been reported,[42,43] and radical coupling using all-carbon tertiary radicals remained elusive. Although tertiary alcohols in combination with strong *Brønsted*- and/or *Lewis*-acids have been shown to alkylate C(sp^2)−H bonds through *Friedel-Crafts* alkylation, these transformations lack selectivity as well as functional group tolerance in more complex settings.[44]

We were pleased to find that, by switching from CsOAc to tetrabutylammonium benzoate (TBAOBz) and using a variant of the NHC reagent (NHC-CF_3) specifically designed to activate tertiary alcohols, we obtained good to high yields of coupled products (44–68% yield) across a variety of tertiary alcohols, including cyclic (**26** and **27**), spirocyclic (**28** and **29**), and non-cyclic (**30**) substrates. To our delight, despite detectable overoxidation of the tertiary radical by Cu(II), the cross-coupled product was the main reaction outcome in all cases, showcasing the robustness of this *dynamic orbital selection* approach and the efficiency of alkyl radical capture paired with reductive elimination from the Cu(III) species.

In a combinatorial approach, we explored the scope of the arene coupling partner. Multiple commercially available or easily accessible arenes with various (heterocyclic) substitution patterns and electronic features were successfully coupled with differently substituted alcohols (see Supplementary Information for more examples). We were pleased to note that halide-containing arenes served as effective coupling partners (**5**, **10**, **19** and **23**); importantly, the reaction conditions preserved these valuable functional handles for use in further downstream manipulations. This result highlights the functional group tolerance of this reaction and its orthogonality to established radical cross-coupling reactions, which often suffer from deleterious dehalogenation.

At present, the limitations of the system include highly electron-poor (hetero)arenes that do not undergo activation by DBTO, as well as functional groups prone to deleterious side reactions under the activation conditions. Additionally, alcohols containing alkyl bromides or highly coordinating motifs, such as 1,3-diols, yield the desired products in low yields due to halogen atom transfer to the aryl radical and complexation with the copper catalyst, respectively. Additional substrate tables, along with an overview of functional group and structural motif limitations may be found in the Supplementary Information.

Radical-radical cross-coupling of complex scaffolds

We next aimed to apply our *dynamic orbital selection* platform to more complex alcohols, particularly those derived from naturally occurring biomolecules and scaffolds commonly found in pharmacologically active compounds (Fig. 3). We successfully intercepted various aryl radicals with a range of complex alkyl radicals, including triazine **31** (51% yield) and 1,2-diols, as exemplified by the synthesis of **32** (55% yield) from an efinaconazole-derived diol. In this example, due to the exceptional regioselectivity of the NHC reagent, only the secondary alcohol was activated, leaving the tertiary alcohol untouched and available for further functionalization.

Complex alcohols derived from amino acids also proved to be excellent coupling partners, as demonstrated by the hydroxyproline derivative **33** (54% yield), which offers the potential for further couplings at the Boc-protected nitrogen atoms, and oxazolidinone **34** (64% yield). Additionally, we productively harnessed biomolecules, including sugars and steroids, as alkyl radical sources, generating the galactopyranose derivative **35** (73% yield) and the androsterone derivative **36** (63% yield). Furthermore, both the antiandrogen derivative **37** and tetrahydropyran **38** were obtained in high to synthetically useful yields (48% and 63%, respectively).

A key advantage of this radical–radical cross-coupling approach is the use of native and ubiquitous C(sp^2)−H bonds without the need for substrate pre-functionalization. To highlight the utility of this direct C(sp^2)−H alkylation protocol, we subjected a variety of complex arenes to our optimized conditions. In general, the regioselectivity of DBTO activation is dictated by both steric factors and the electron density of the aromatic ring.[45] Particularly in (hetero)aromatic systems bearing electron-donating heteroatoms such as nitrogen or oxygen, excellent regioselectivity was observed, and the corresponding alkylated products were obtained in high yields (**39**, **41** and

42, 50–76% yield). In the context of neutral arenes, such as phenyls (**40**, 60% yield) or biaryls (**44**, 53% yield), both *ortho*- and *para*-products were observed, with a preference for the *para*-position. Importantly, despite variations in the electronic nature of the intermediate aryl radical, a wide range of substituted complex alkyl radicals could be coupled, including sugars, underscoring the modularity of this protocol. We also investigated the functionalization of complex scaffolds that do not permit the introduction of a halogen atom with established methods, as such structures would be incompatible with classical radical cross-coupling strategies. Pleasingly, both boscalid (**43**) and pyriproxyfen (**45**) were functionalized with excellent regioselectivity, affording the corresponding products in 45% and 50% yields, respectively.

Late-stage functionalization and expedited synthesis of biologically active compounds

In medicinal chemistry and drug development, methods to achieve the late-stage functionalization of biologically active molecules allow for straightforward diversification and open novel chemical space for SAR campaigns (*3*). In this context, we aimed to apply our method to the late-stage functionalization of drug molecules and other biologically active compounds, with the goal of offering a modular and general approach to accessing new alkylated chemical space without the need for lengthy, *de novo* syntheses (Fig. 4).

To our delight, multiple alcohol-containing drugs, including ticagrelor (**46**), losartan (**47**), and lonazolac (**48**), underwent radical–radical cross-coupling with fluorobenzene, yielding products in good to synthetically useful yields (41–67%). In the case of losartan (**47**), the scalability of the reaction was demonstrated by the successful generation of 1.24 g of the cross-coupled product in a single reaction setup. We sought to capitalize on the demonstrated functional group tolerance of this method to overcome longstanding challenges in arylating the 3'-position of a nucleoside, a modification that can alter the therapeutic properties of the nucleoside. To this end, application of our method to the functionalization of 5-methyl-2'-deoxycytidine provided the 3'-arylated product **49** in 38% yield with a diastereomeric ratio of 1.7:1.

Aromatic rings, among the most frequently represented structural motifs in drug compounds, are particularly attractive targets for late-stage functionalization. Selective and mild conditions are needed to preserve complex molecular structures. We benchmarked our system on a series of structurally differentiated arene-containing drug molecules, including nateglinide (**50**), gemfibrozil (**51**), nefiracetam (**52**), ibuprofen (**53**) and flurbiprofen (**54**). In all cases, cross-coupling with a variety of alcohol partners yielded the desired products in good to high yields (45–64%) without impeding the structural integrity of the drug molecules. Delightfully, the aryl radical generated from l-phenylalanine was readily cross-coupled to generate unnatural amino acid **55** (35% yield), opening the possibility of rapidly synthesizing phenylalanine-derived libraries of unnatural amino acids bearing different substitution moieties and patterns (*ortho vs. para*).

Recognizing the well-documented "magic methyl effect",[46] whereby significant enhancements in drug efficacy can be attained through the introduction of a methyl group, we aimed to address the persistent challenge of introducing a methyl group at a late stage in drug synthesis. Pleasingly, we installed a methyl group on the type 2 diabetes drug empagliflozin (**56**, 37% yield) with complete regioselectivity, using methanol as a safe and benign methyl radical source. Encouraged by these results, we turned our attention to another challenge in organic synthesis: the late-stage *tert*-butylation of complex molecules. Despite recent advances that use Minisci-type additions for *tert*-butylation of heterocyclic compounds,[47,48] the mild and selective introduction of a *tert*-butyl group to non-heterocyclic arenes remains underdeveloped.[49] Using our tertiary alcohol reaction protocol, we obtained *tert*-butylated boscalid **57** in synthetically useful 33% yield and with complete control of regioselectivity.

A priority of drug discovery is to access synthetic targets in a streamlined and efficient manner. However, traditional arene alkylation methods used in the synthesis of drug targets, such as the multiple sclerosis drug fingolimod, often require multiple steps, including *Friedel-Crafts* acylation followed by reduction, both of which involve forcing conditions and suffer selectivity issues. By contrast, our *dynamic orbital selection* strategy delivered fingolimod (**59**) from benzene through the *n*-octylbenzene (**58**) intermediate in a total of two steps with an average yield of 50% per step. This route notably shortens the synthetic sequence without requiring additional redox interconversions or the use of hazardous chemicals and pressurized reactors.[50]

To further benchmark the applicability of *dynamic orbital selection* in the context of drug synthesis, we set out to compare our system to an industrially applied *Friedel-Crafts* alkylation *en route* to tetralone **60**, the direct precursor of the antidepressant drug sertraline (**61**). Our protocol delivered **60** in 69% yield using commercially available starting materials, making it comparable to the industrially applied synthesis.[51] Subsequent reductive amination of the ketone delivered sertraline (**61**) in 88% yield.

Engaging carboxylic acids in radical-radical cross-coupling

Aside from alcohols, carboxylic acids are among the most widespread functional groups in medicinal chemistry and serve as attractive functionalization lynchpins due to their commercial availability. Moreover, carboxylic acids have proven to be excellent precursors to alkyl radicals in metallaphotoredox catalysis.[52] Therefore, we envisioned establishing carboxylic acids as coupling partners as a means to further extend the accessible chemical space of this transformation.

Our group previously demonstrated that carboxylic acids can be converted to alkyl radicals *via* a metallaphotoredox pathway involving capture of the alkyl radical by a copper(II) species.[37] To our delight, the use of CuCN with *p*-tolyl terpyridine ligand enabled successful radical–radical cross-coupling of various carboxylic acids with different arenes *via* the proposed intermediate **III** (Fig. 5). We engaged primary (**62** and **63**) as well as tertiary (**64**) carboxylic acids in *dynamic orbital selection* with high to excellent yields (52–83% yield). Moreover, a series of biologically active drug molecules were subjected to late-stage functionalization under these conditions, including naproxen (**65**, 70% yield), flurbiprofen (**66**, 69% yield), tolmetin (**67**, 48% yield), carprofen (**68**, 42% yield) and indometacin (**69**, 53% yield).

Finally, we sought to showcase the potential for late-stage orthogonal functionalization *via* sequential acid–aryl and alcohol–aryl radical-radical cross-couplings. Using ibuprofen (**70**) as the model compound, we first cross-coupled the corresponding alkyl radical with fluorobenzene to generate **71** in 56% yield. Subsequent treatment with DBTO and Tf_2O, followed by exposure to the alcohol *dynamic orbital selection* protocol, led exclusively to alkylation of the more electron-rich dialkylated arene (**72**, 53% yield) in preference to the fluorinated aryl ring. This outcome highlights the orthogonality of the functionalization strategy and demonstrates the potential to modularly manipulate existing drug scaffolds, thereby accessing novel chemical space and more complex structures.

Outlook

Medicinal chemists require robust methods for the late-stage derivatization of biologically active molecules in order to expedite SAR campaigns and accelerate the drug discovery process. Suitable methods should be versatile, mild, compatible with a wide range of functionalities, and employ abundant, bench-stable reagents. In this work, we introduce a new synthetic strategy to selectively alkylate the $C(sp^2)$–H bond through an orbital-sorting radical–radical cross-coupling mechanism. We have shown that this method is capable of efficiently functionalizing complex aryl rings with a diverse range of alkyl groups derived from ubiquitous alcohol and carboxylic acid coupling partners. We anticipate that the *dynamic orbital selection* approach described herein will find widespread adoption across the applied chemical sciences.

Supplementary information

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Data availability

All data supporting the findings of this study are available in the main text or in the Supplementary Information.

Competing interests: D. W. C. M. declares an ownership interest in the Penn PhD photoreactor, which is used to irradiate reactions in this work. The other authors declare no competing interests.

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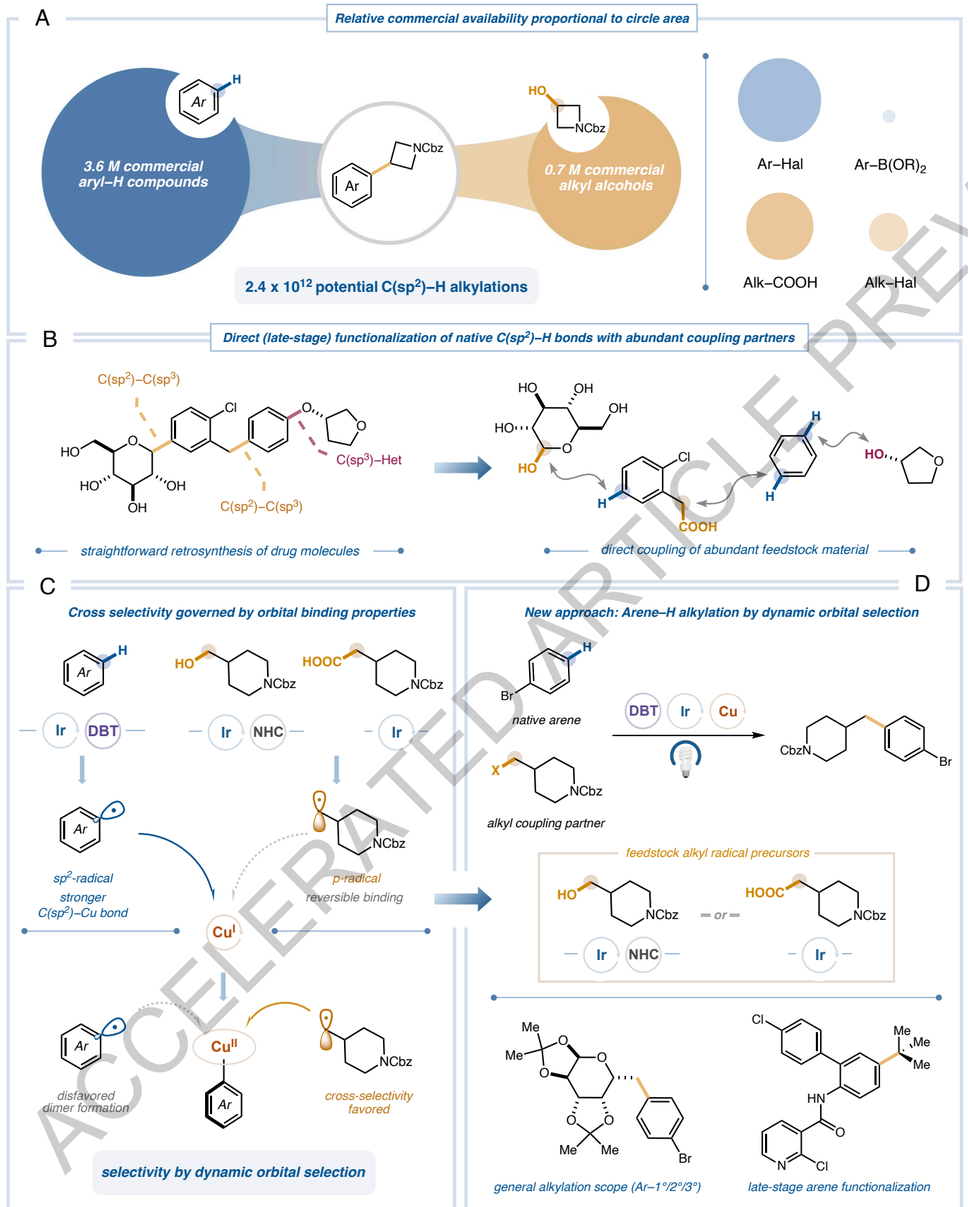
Fig 1 | Conceptualization of *dynamic orbital selection*. (A) Relative commercial abundance of common aryl and alkyl cross-coupling partners (heteroarenes not included; data retrieved from the Reaxys database as of November 2024). (B) Intuitive retrosynthetic disconnections enabling straight-forward syntheses of complex drug molecules. (C) Differences in binding properties of radical orbital enabling dynamic orbital selection. (D) General radical-radical cross-coupling of $C(sp^2)$−H bonds with abundant alkyl radical precursors (this work). Ar: aryl; Cbz, benzyl oxycarbonyl; DBT: dibenzothiophene 5-oxide; Me, methyl.

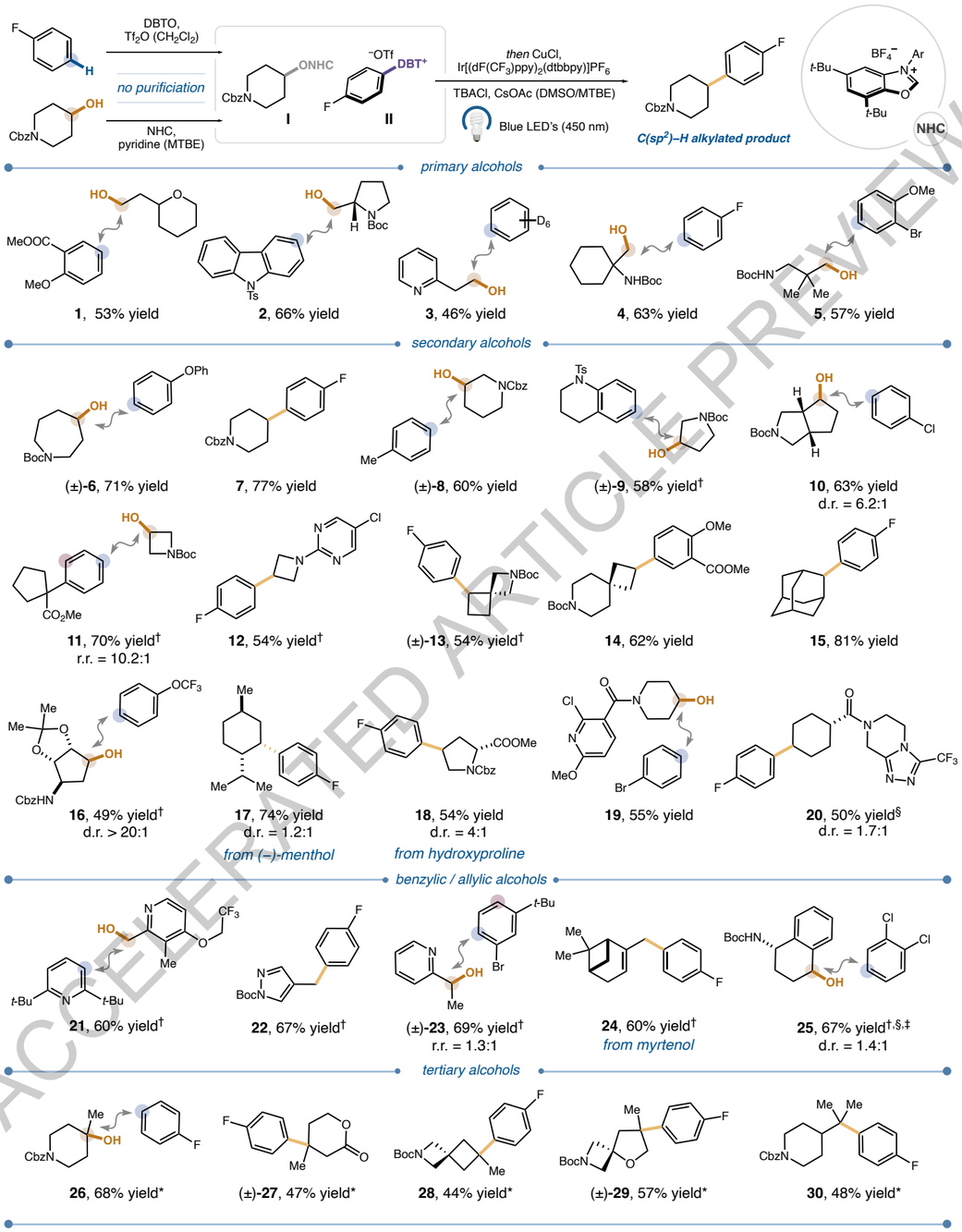
Fig 2 | Scope of the radical-radical cross coupling of arenes with alcohols. All yields are isolated and reactions were performed on a 0.5 mmol scale with alcohol (1.0 equiv.), NHC-OMe (Ar = *p*-OMe-Ph, 1.3 equiv.), pyridine (1.5 equiv.), *t*-BuOMe (0.1 M), arene (1.5 equiv.), DBTO (1.65 equiv.), Tf_2O (1.8 equiv.), CH_2Cl_2 (0.1 M), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.5 mol%), CuCl (30 mol%), CsOAc (3.0 equiv.), TBACl (3.5 equiv.), and DMSO [0.025 M (additional *t*-BuOMe) to 0.05 M] using an integrated photoreactor (450 nm, 50% light intensity) for 2 hours at room temperature. †With NHC-H (Ar = Ph, 1.2 to 1.3 equiv.), pyridine (1.2 to 1.5 equiv.), see Supplementary Information for full detailed experimental conditions. *With NHC-CF_3 (Ar = *p*-CF_3-Ph, 1.5 equiv.), pyridine (1.5 equiv.), TBAOBz (3.0 equiv.), CuCl (15 mol%), see Supplementary Information for detailed experimental conditions. ‡Preformed DBT-arene adduct and $Ir(ppy)_2(dtbbpy)PF_6$ (2.5 mol%) was used. §Alcohol starting material was a 1:1 mixture of diastereomers. Boc, *tert*-butyloxycarbonyl; Cbz, benzyl oxycarbonyl; d.r., diastereomeric ratio; Me, methyl; Ph, phenyl; Ts, 4-toluenesulfonyl; r.r., regioisomeric ratio; *t*-Bu, *tert*-butyl.

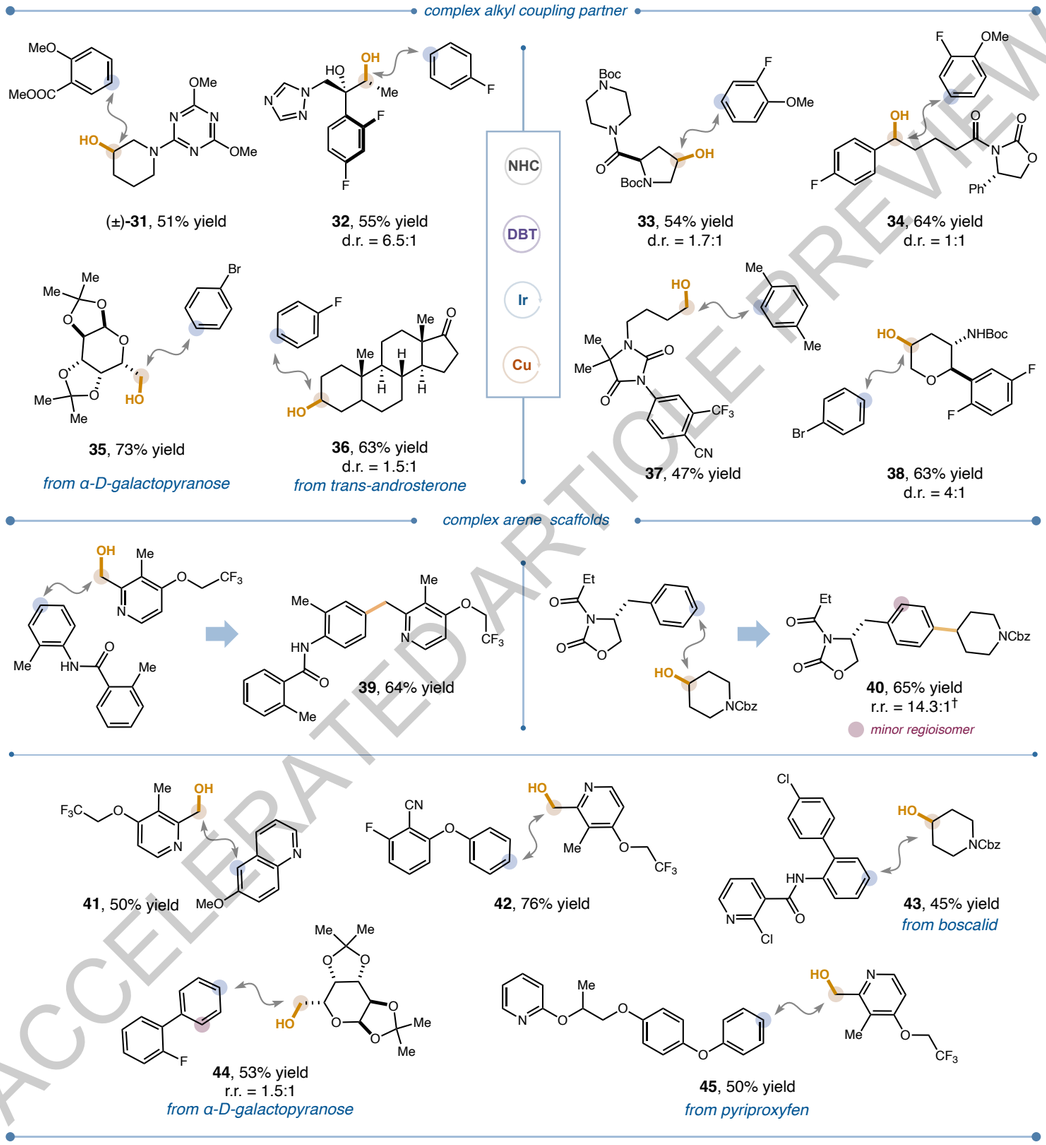
Fig 3 | Engagement of complex alcohols and (hetero)aromatic compounds in radical-radical cross coupling. All yields are isolated and reactions were performed on a 0.5 mmol scale, see supplementary materials for detailed experimental conditions. †TFA/TFAA in combination with DBTO was used for the arene activation. Boc, *tert*-butyloxycarbonyl; Cbz, benzyl oxycarbonyl; d.r., diastereomeric ratio; Et, ethyl; Me, methyl; Ph, phenyl; r.r., regioisomeric ratio.

Fig 4 | Late-stage functionalization and expedited synthesis of drug molecules. All yields are isolated, see supplementary materials for full detailed experimental conditions. *Performed on a 2.5 mmol scale. †Performed on a 1.5 mmol scale. ‡Use of preformed DBT-arene adduct. Ac: acetyl; Bz, benzoyl; Cbz, benzyl oxycarbonyl; DMT: dimethoytrityl; d.r., diastereomeric ratio; *i*-Pr, isopropyl; Me, methyl; *n*-Bu, normal butyl; *n*-Pr, normal propyl; Ph, phenyl; r.r., regioisomeric ratio; Trt: trityl.

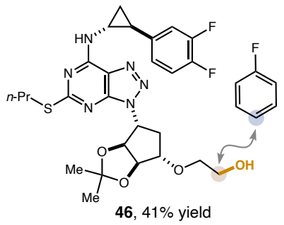
Fig 5 | Scope of the radical-radical cross coupling of arenes with carboxylic acid and orthogonal functionalization. All yields are isolated and reactions were performed on a 0.5 mmol scale with arene (1.0 equiv), DBTO (1.1 equiv.), Tf_2O (1.2 equiv.), CH_2Cl_2 (0.1 M), carboxylic acid (1.2 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.5 mol%), CuCN (20 mol%), *p*-TolTerpy (30 mol%), BTMG (3 equiv), and DMSO [0.065 M] using an integrated photoreactor (450 nm, 100% light intensity) for 12 hours at room temperature. ‡Performed on a 2 mmol scale. BTMG, 2-tert-butyl-1,1,3,3-tetramethyl-guanidine; Boc, *tert*-butyloxycarbonyl; Me, methyl; *p*-TolTerpy, 4-(*p*-tolyl)-2,6-bis(2-pyridyl)pyridine; r.r., regioisomeric ratio; Tol: *para*-tolyl.



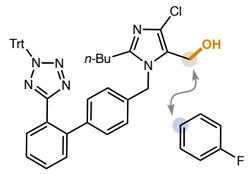




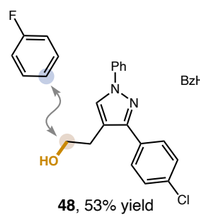
late-stage functionalization of biologically active compounds



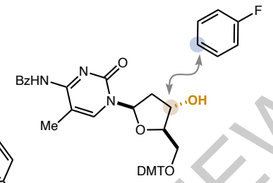
46, 41% yield
from ticagrelor



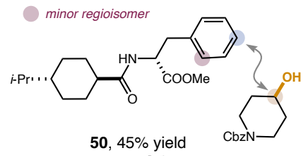
47, 67% yield*
from losartan



48, 53% yield
from lonazolac

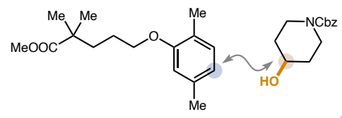


49, 38% yield
d.r. = 1.7:1
from methylcytidine

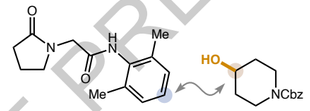


minor regioisomer

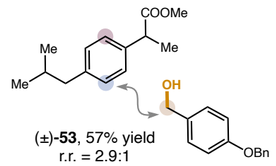
50, 45% yield
r.r. = 2:1
from nateglinide



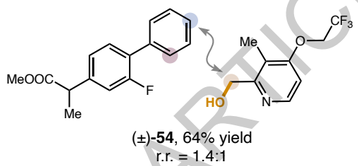
51, 54% yield
from gemfibrozil



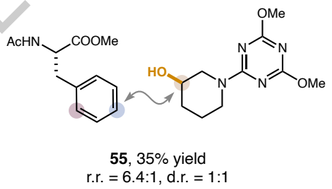
52, 43% yield
from nefiracetam



(±)-**53**, 57% yield
r.r. = 2.9:1
from ibuprofen

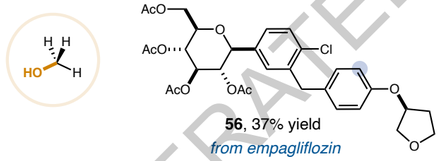


(±)-**54**, 64% yield
r.r. = 1.4:1
from flurbiprofen



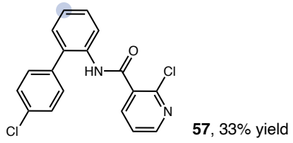
55, 35% yield
r.r. = 6.4:1, d.r. = 1:1
from L-phenylalanine

late-stage methylation



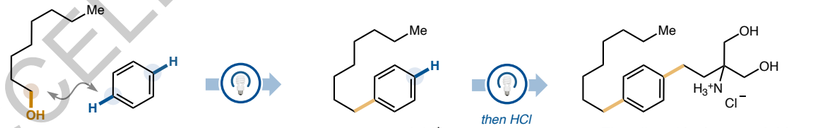
56, 37% yield
from empagliflozin

late-stage tert-butylation



57, 33% yield
from boscalid

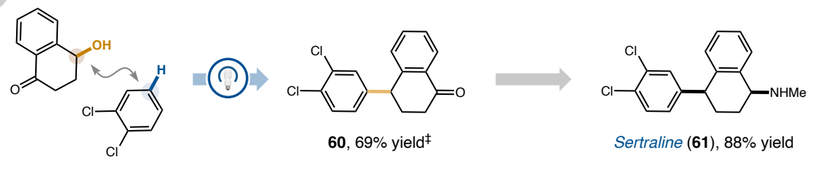
expedited synthesis of pharmacologically relevant molecules



58, 42% yield†

then HCl

Fingolimod (**59**), 57% yield



60, 69% yield‡

Sertraline (**61**), 88% yield

NHC
DBT
PC
Cu