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Modular radical cross-coupling with sulfones enables access to sp^3-rich (fluoro)alkylated scaffolds

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Cross-coupling chemistry is widely applied to carbon-carbon bond formation in the synthesis of medicines, agrochemicals, and other functional materials. Recently single-electron-induced variants of this reaction class have proven particularly useful in the formation of C(sp^2)-C(sp^3) linkages, though certain compound classes have remained a challenge. Here we report the use of sulfones to activate the alkyl coupling partner in nickel-catalyzed radical cross-coupling with aryl zinc reagents. This method's tolerance of fluoroalkyl substituents proved particularly advantageous for the streamlined preparation of pharmaceutically-oriented fluorinated scaffolds that previously required multiple steps, toxic reagents, and non-modular retrosynthetic blueprints. Five specific sulfone reagents facilitate the rapid assembly of a vast set of compounds, many of which contain challenging fluorination patterns.

Cross-coupling proceeding through a single electron transfer pathway to forge new C–C bonds is complementary to the robust two-electron coupling paradigm of the venerable Heck, Suzuki, and Negishi reactions (*1*). In recent years metal-catalyzed radical cross-coupling (RCC) has proven effective for forging bonds to sp^3-hybridized secondary and tertiary carbon centers that remain challenging for the more widely applied two-electron Pd catalysis (*2*). To realize the full potential of RCC strategies, functional groups more versatile than alkyl halides (*3*–*8*) are needed to expand the range of compatible coupling partners (Fig. 1A). In this regard, alkyl carboxylic acids (*3*, *4*), alkylboron (*5*) and alkylsilicon (*6*) derivatives, olefins (*7*), alkyl pyridinium salts (derived from amines) (*8*) and alkyl dihydropyridines (*9*) have been identified as useful agents in RCC. Here we show that readily available sulfones (specifically bearing the 1-phenyl-1*H*-tetrazol-5-yl group) can be directly used as an orthogonal redox-active functional group for RCC-based synthesis. The sulfones present three specific advantages. First, they tolerate powerful anionic chemistry (α-alkylation, fluorination) for functional elaboration prior to the cross-coupling event (Fig. 1, A and B) (*10*, *11*); second, when attached to unsaturated systems they enable facile cycloadditions and Michael/Giese type additions (*12*); and lastly their stability and crystallinity allow for convenient manipulation.

The literature is replete with examples of sulfones serving a variety of different roles in synthesis from facilitating olefin formation and cycloadditions to their use in two-electron cross-couplings. In the latter regard, the independent work of the Crudden (*13*) and Li (*14*) research groups has stood out for their use of benzylic phenyl sulfones in a variety of Pd- and Ni-catalyzed desulfonylative cross-coupling methodologies. The first systematic study of the use of an unactivated alkyl sulfone for RCC emerged in 2013 from the Denmark lab's report of Fe-catalyzed Kumada cross-coupling to forge C(sp^2)–C(sp^3) bonds (*15*). These elegant studies pointed to the improvements needed for mainstream adoption of this chemistry. Indeed, an ongoing medicinal chemistry project at Pfizer could have used this reaction, but the limited scope prevented its wide adoption (beyond the use of PhMgBr). Thus, first forays into this area centered on identifying a suitably substituted sulfone that would be susceptible to reduction under mild (e.g., low-valent Ni) reaction conditions to generate an alkyl radical and unreactive sulfinate anion (*4*). A variety of sulfones differing in relative reduction potential, electronegativity, and size were evaluated under Ni-catalyzed Negishi-type conditions (Fig. 1C). In the case of aryl sulfone **3a**, used previously by Denmark, starting material was recovered with only traces of formation of the desired product **5a**; sulfones **3b**–**e** performed similarly. A primary breakthrough was the discovery that a redox-active phenyl-tetrazole (PT)

sulfone **3f** was uniquely capable of delivering the desired RCC product **5a** (71% isolated yield). As outlined in tables S1 to S8, a variety of conditions were surveyed, and Ni proved an effective catalyst whereas Fe did not; concurrent with our report, difluoromethyl 2-pyridyl sulfone was found to be a competent coupling partner under iron catalysis (*16*). The use of a bipyridine-type ligand was also imperative as performing the reaction in the absence of ligand resulted in exclusive formation of the biaryl byproduct**;** without the Ni precatalyst and bipyridine ligand, no reaction occurred.

From a pragmatic perspective, PT-sulfones can be easily derived from alcohols or alkyl halides using Mitsunobu conditions or S_N2 displacement with inexpensive and odor-free thiol **6** followed by straightforward oxidation to produce stable products that are often crystalline (*17*). As shown below, their ability to enable modular synthesis strategies inspired the development of five reagents (two of which are new chemical entities).

The robustness of the optimized reaction conditions for the desulfonylative RCC reaction is illustrated in the synthesis of over 60 products (Fig. 2, A to E). The scope of this methodology was initially evaluated with a variety of aryl zinc reagents (Fig. 2A). PT–sulfone **3f** reacted with thirteen different organozinc reagents to produce a series of arylated piperidine derivatives (**5a**, **12**–**23**). *Ortho*-substituted arylzinc reagents could be employed under the reaction conditions (**17** and **18**), and potential electrophilic coupling partners such as aryl chlorides were also tolerated on the arylzinc reagent (**21**). Both electron-rich and electron-deficient heterocyclic organozinc reagents proved competent coupling partners in this reaction manifold, as exemplified by indole **22** and pyridine **23**. To assess the disclosed method relative to the prior state of the art in the cross-coupling of unactivated alkyl sulfones, a direct comparison of substrates (**24**–**30**) previously evaluated under Fe catalysis was conducted. The conditions reported herein compared favorably in all cases to literature-reported yields and allowed access to compounds that were previously inaccessible via a desulfonylative cross-coupling route (*15*). Arylzinc reagents can also be accessed through lithium-halogen exchange/transmetallation or magnesium-halogen exchange/transmetallation and successfully employed under the reaction conditions in comparable yield to arylzinc reagents derived via Mg insertion (71% vs. 66% isolated yield for **5a**, for example).

Panel B demonstrates desulfonylative RCC as a means to synthesize a broad range of compounds from eighteen different readily-accessible sulfones. Primary (**31**–**35**, **47**, **50**), secondary (acylic and cyclic, **36**–**46**, **48, 49, 51, 52**), and benzylic (**47**) arylated products could be accessed from the corresponding sulfone. Alkyl chlorides (**35**) were tolerated under the reaction conditions despite their propensity to engage in single-electron chemistry under Ni catalysis, thereby establishing the orthogonality of these two alkyl electrophiles. Moreover, desulfonylative RCC provides a straightforward means to access A-ring modified steroids (**49** and **52**). As a testament to the mild reaction conditions, Roche ester derived **47** was successfully synthesized with no erosion of enantiomeric excess. Due to the well-studied reactivity of vinyl sulfones in cycloaddition chemistry, **7** was treated with cyclohexadiene in a Diels-Alder reaction and subsequently cross-coupled to afford [2.2.2]-bicycle **51**. Compound **7** is known to react with dienes under mild and more selective conditions than acrylates or the corresponding phenyl vinyl sulfone (*12*).

The primary advantage of this chemistry lies in its ability to simplify the retrosynthetic analysis of complex sp^3-rich organofluorine building blocks so that the C–C bond forming disconnection used is the same regardless of fluorine content. Whereas methods to install fluoroalkyl groups via cross-coupling chemistry exist, they are limited by the lack of facile access to the corresponding fluoroalkyl electrophiles (a full listing is provided in fig. S24) (*18*–*20*). In the case of simple monofluoromethyl or difluoromethyl groups, many reagents are difficult to handle (e.g., gaseous) or require additional steps to remove superfluous functionality (*21*). It is in this context that α-fluoroalkyl sulfones were evaluated; these are well regarded as stable reagents used in synthetic organic chemistry for a variety of applications (*22*) such as the installation of fluoroalkenes from carbonyl-containing compounds (*23*) as well as reacting as radical precursors under photoinduced electron transfer conditions (*24*). Redox-active α-fluoro-PT-sulfones were thus investigated to install fluorinated groups onto arenes by RCC (Fig. 2C). By employing bathophenanthroline as the ligand with a 1:2 ratio of Ni precatalyst to ligand, Negishi-type arylation of mono- and difluorinated sulfones could be achieved.

Fluoromethyl reagent **8** and difluoromethyl reagent **9** were prepared in a straightforward manner according to literature procedures from inexpensive CFH_2Cl and CF_2HCl, respectively (*25*). Difluoroethyl reagent **10** was accessed through anionic functionalization (deprotonation and quenching with *N*-fluorobenzenesulfonimide [NFSI]) of the parent ethyl PT-sulfone. Using the other corresponding alkyl radical precursors depicted in Fig. 1A, this anionic manipulation would not be possible; thus, redox-active PT-sulfones offer a distinct advantage to more traditional alkyl electrophiles in that they engender a modular solution for installation of monofluoro and difluoroalkyl groups onto an aryl group from a single sulfone starting material. These reagents were successfully employed to access mono- and difluoroalkyl arenes (**53**–**55**, **56**–**58**, **59, 60**) and could be used to shorten synthetic routes to compounds found in the literature (**55**, **58**) (*21*, *25*). Although CH_2F and CF_2H moieties

can be installed from the corresponding halides, such procedures are inconvenient because they often require an excess of gaseous reagents. The synthesis of additional tertiary fluorides (**62** and **63**) was similarly achieved, thereby presenting a useful alternative to traditional tertiary fluoride synthesis from the corresponding tertiary alcohol and treatment with diethylaminosulfur trifluoride (DAST, a highly toxic and dangerous reagent), a transformation that often proceeds in low yield (*26*). A current limitation is that the trifluoromethyl group cannot be readily installed using this method (**64**).

Reagents such as **7** and **11** open up unique possibilities for stepwise, successive RCC chemistry as the PT-sulfone is known to enhance the rate of Giese-type radical additions (*12*). Indeed a variety of olefin- and carboxylic acid-derived radicals could be smoothly intercepted with **7** or **11** followed by desulfonylative RCC to generate structures that in some cases would be challenging to otherwise procure (*27*, *28*). For example, **66** is prepared in the literature using an elegant deborylative cyclization (*29*); the current modular approach starts with commercial cyclohexenyl boronic ester followed by olefin RCC and then desulfonylative RCC. Similarly, quaternary-center bearing substrates **72**, **74**, **76**, and **78** are easily produced from either readily available acids or olefins by concurrent RCC chemistry thus obviating the need for either deoxyfluorination or vexing cross-coupling challenges. Finally, the success of this process points to the orthogonality of redox-active PT-sulfones both in the context of reductive chemistry (olefin HAT and acid Giese) and known radical precursors (boronic esters).

Mechanistically (fig. S9), alkyl radicals are posited intermediates under the reaction conditions, as evidenced by radical probe substrates **79** (cyclopropane ring-opening), **80** (*5-exo-trig* cyclization), and **81** (racemic product from a chiral sulfone) as shown in Panel E (*30*).

In collaboration with Asymchem, **7**, **8**, **9**, **10**, and **11** have been prepared on large scale (see SM for a graphical procedure).

As illustrated in Fig. 3, the strategic impact of this chemistry shines in the preparation of complex medicinally oriented building blocks containing varying levels of fluorination. Traditionally, retrosynthetic analysis of these targets has centered around the installation of the fluorine atom; carbonyl chemistry and deoxyfluorination are therefore of prime importance. Moreover, such routes typically rely on highly toxic and dangerous reagents (e.g., DAST). Panels A–D are examples from modern medicinal chemistry where this challenge is vividly displayed and contrasted with an RCC approach. In such contexts, fluorine atoms are often incorporated into scaffolds to alter solubility, efficacy, or metabolic properties. The often empirical nature of structure-activity relationships requires targeting of multiple fluorinated variants as bioisosteric replacements (*31*) and such case studies are widespread in the medicinal chemistry literature. For instance (Fig. 3A), Schering scientists targeted building blocks **83a**–**b** differing only in the substitution at a single carbon (containing one or two fluorine atoms) (*32*). To access these simple structures, an eight-step sequence was devised from phenol **84**; only two of these steps are strategic and produce C–C bonds. In striking contrast, acetal **82** could be directly coupled with reagent **8**, **9**, or **10** to deliver **83a**–**b** and a new analog **83c** after simple oxidation (the acetal is deprotected during the RCC workup with 1N HCl) thus avoiding tin-based reagents, ozonolysis, and deoxyfluorination steps.

A case-study from a recent Merck campaign demonstrates the power of a concurrent RCC strategy for modularly generating C(sp^3)-rich scaffolds (Fig. 3B) such as **87a**–**b** (*33*, *34*). In the original preparation, the absence or presence of fluorine atoms dictates the starting materials and methods employed. In the preparation of the unfluorinated compound (five steps), an aryl aldehyde is employed in concert with a Wittig reaction to forge the central C–C bond followed by hydrogenation to furnish **87a**. To access the latter, fluorine-substituted analog (**87b**, eight steps), a different route is required as the difluorinated carbon must be installed via deoxyfluorination of an aryl ketone thus requiring a different starting material, protecting group swaps due to harsh reagents (Boc → Cbz → Boc), thiols, and toxic HF. Using RCC-based logic, the same starting material can be used to make both **87a** and **87b** by employing acid **85** (n = 1) in two successive RCC steps, the first of which uses the redox-active NHPI ester derived from the acid in a Giese-type addition to PT-sulfone reagent **7** to yield **86**. In the case of **87a**, redox-active PT-sulfone **86** is directly subjected to RCC to furnish **87a** whereas for **87b**, anionic α-fluorination followed by RCC delivers **87b**. Both routes proceed in a fraction of the steps previously required and obviate the need for superfluous steps and/or toxic reagents.

A recent (2017) patent from the Shanghai Institute of Organic Chemistry (Fig. 3C) serves as a good example for the advantage of using the redox-active PT-sulfone over an alkyl halide for achieving the modular synthesis of a simple fluorinated scaffold (*35*). In the reported approach to **91** (six steps), an alkyl bromide is homologated with malonate and fluorinated with Selectfluor® to produce a diester, which in turn undergoes decarboxylation and Hunsdiecker iodination to furnish a geminal-dihalide suitable for Ni-catalyzed Suzuki coupling. Alternatively, hydrocinnamic acid **92** could be homologated via the corresponding redox-active ester using reagent **11** through Giese addition followed by RCC to deliver **91** in only two steps. In such a case, the fluorine atom in **91** was handled from a planning perspective as if it were any other substituent (methyl, aryl, hydrogen), circumventing the fluorine-specific logic normally required.

The fourth case study (Fig. 3D) drawn from the patent literature (Novartis), demonstrates the advantage of a modular approach that diverges from the same intermediate even when the overall step-count is similar (*11*). Targets **96a–c** differ only in the presence or absence of benzylic fluorine atoms (0, 1, or 2), yet their preparation is guided not by the carbon skeleton (which comprises >90% of the molecular weight of **96b–c**) but rather by fluorine atom incorporation. Whereas desfluoro analog **96a** is prepared from acid **97** via a Heck/hydrogenation sequence, mono- and difluoro analogs **96b–c** require a pyridine-based starting material (**98**) which must be saturated, converted to a Grignard reagent, and added into an aryl subunit to afford a carbonyl group that serves as a gateway to introduce fluorine through deoxyfluorination. A very different blueprint emerges when employing RCC. Thus, simple isonipecotic acid can be subjected to decarboxylative alkyl-alkyl RCC with an alkyl-chloride bearing zinc reagent followed by S_N2 displacement with **6** and oxidation to afford **95,** from which **96a–c** can all be accessed. Similarly, direct RCC, α-fluorination/RCC, or α-difluorination/RCC affords **96a**, **96b**, or **96c**, respectively. Thus, the aforementioned case studies (panels A–D) point to disconnection strategies that retain focus on the carbon skeleton during synthesis planning rather than allowing a single fluorine atom to completely alter the logic employed.

In a final demonstration of the unique potential of RCC in synthesis (Fig. 3E), lithocholic acid was converted to a compound containing both a redox-active ester and sulfone, and controlled sequential RCC was demonstrated. Decarboxylative cross-coupling (DCC) proceeded selectively to afford products of Suzuki arylation (**101**) (*36*), Negishi arylation (**103**) (*37*), alkylation (**105**) (*38*), alkenylation (**107**) (*39*), and alkynylation (**109** and **111**) (*40*). Subsequently, those products underwent clean SCC arylation delivering an array of useful diversity (**102**, **104**, **106**, **108** and **110**). In the case of alkyne **111**, a classic two-electron cross-coupling (Sonogashira) could be conducted in an orthogonal manner before the final SCC to deliver **112**. Clearly, the choreography of both one- and two-electron based cross-coupling protocols holds great potential not only for modular scaffold design but also for emerging programmed automated synthesis paradigms. Competition experiments suggest that the general order of reactivity in RCC chemistry correlates to the following qualitative trend: Cl/Br < SO_2PT < NHPI/TCNHPI [experiments run under SCC conditions with primary alkyl systems (fig. S1)].

It is worth reflecting on the complementarity of the sulfone and decarboxylative cross-coupling processes. The decarboxylative manifold has a distinct advantage in that the starting materials are ubiquitous whereas the sulfone system stands out on the basis of privileged reactivity preceding the cross-coupling event and circumvention of pre-functionalization steps (ester hydrolysis and/or activation). Reagents **7** and **11**, stable crystalline solids, are illustrative of the practical advantage of PT-sulfones over analogous carboxy congeners that are not only toxic but also highly volatile. For example, the carboxy analog of reagent **8** (monofluoroacetic acid) is toxic and the carboxy analog of reagent **9** does not currently participate in RCC. Anionic α-fluorination of esters is rare, and the common route to such α-substituted mono and difluorinated systems involves α-oxidation/deoxyfluorination. In addition, crystalline and easily handled redox-active PT-sulfones can be employed in concert with other single-electron and two-electron cross-coupling steps to enable another dimension of modular synthesis planning. Although there are some low-yielding substrates, most cross-couplings attempted reliably produced the desired cross-coupled product. The mass balance of reactions includes recovered starting material and biaryl products resulting from cleavage of bond b (Fig. 1C). The safety profiles (thermal onset, friction and shock sensitivity) of all reagents have been evaluated (table S20) and were found to be non-hazardous.

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SUPPLEMENTARY MATERIALS

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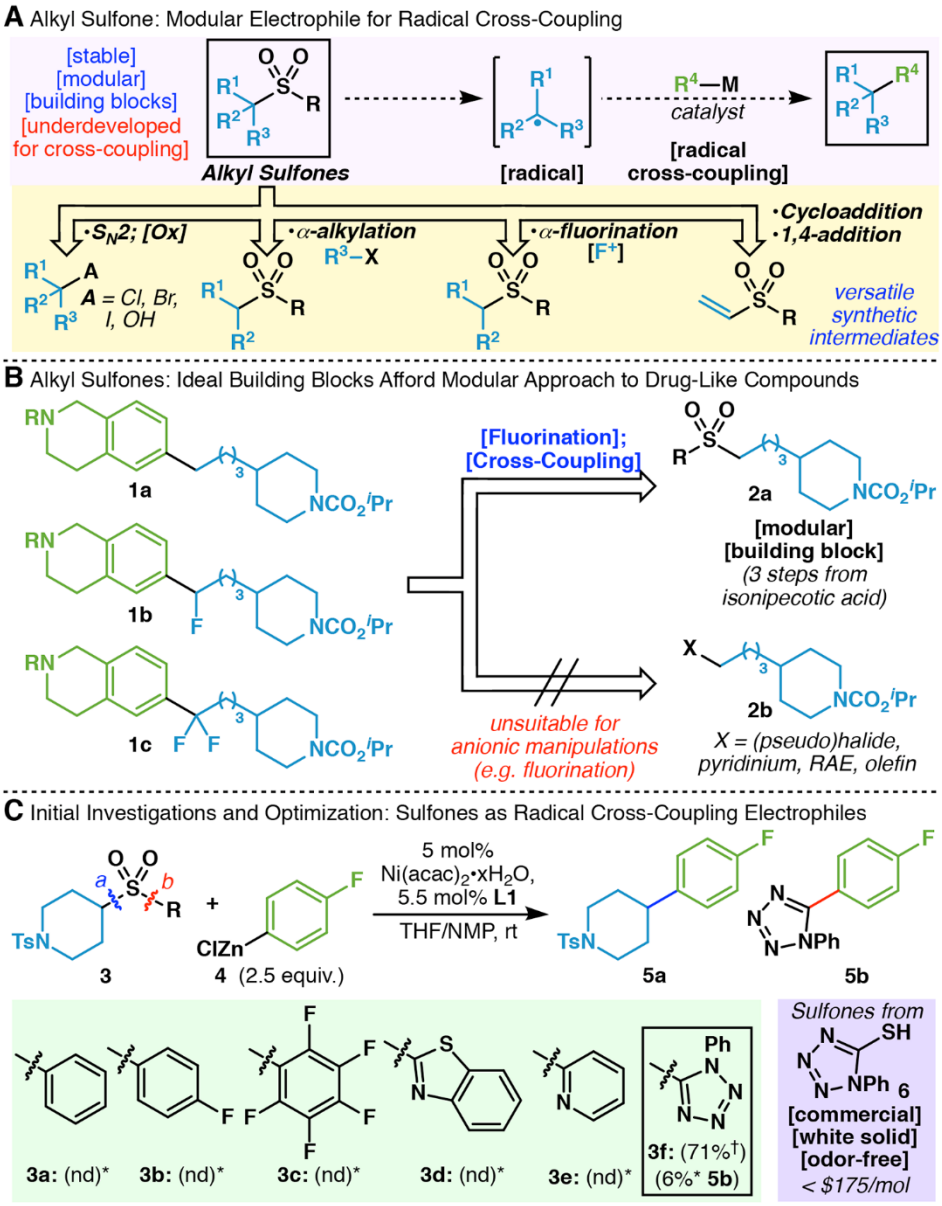

Fig. 1. Sulfone cross-coupling. (A) Alkyl sulfones represent a promising and underexplored functional group for one-electron cross-coupling processes due to their unique reactivity; (B) The potential to achieve modular synthesis of fluorine-containing C(sp^3)-rich architectures; (C) Identification of a redox-active sulfone and conditions to achieve selective cross-coupling under Ni-catalysis. *Yields determined by ^{19}F NMR with 1-fluoronapthalene as an internal standard. †Isolated yield. THF, tetrahydrofuran; NMP, 1-methylpyrrolidin-2-one; nd, not detected by ^{19}F NMR.

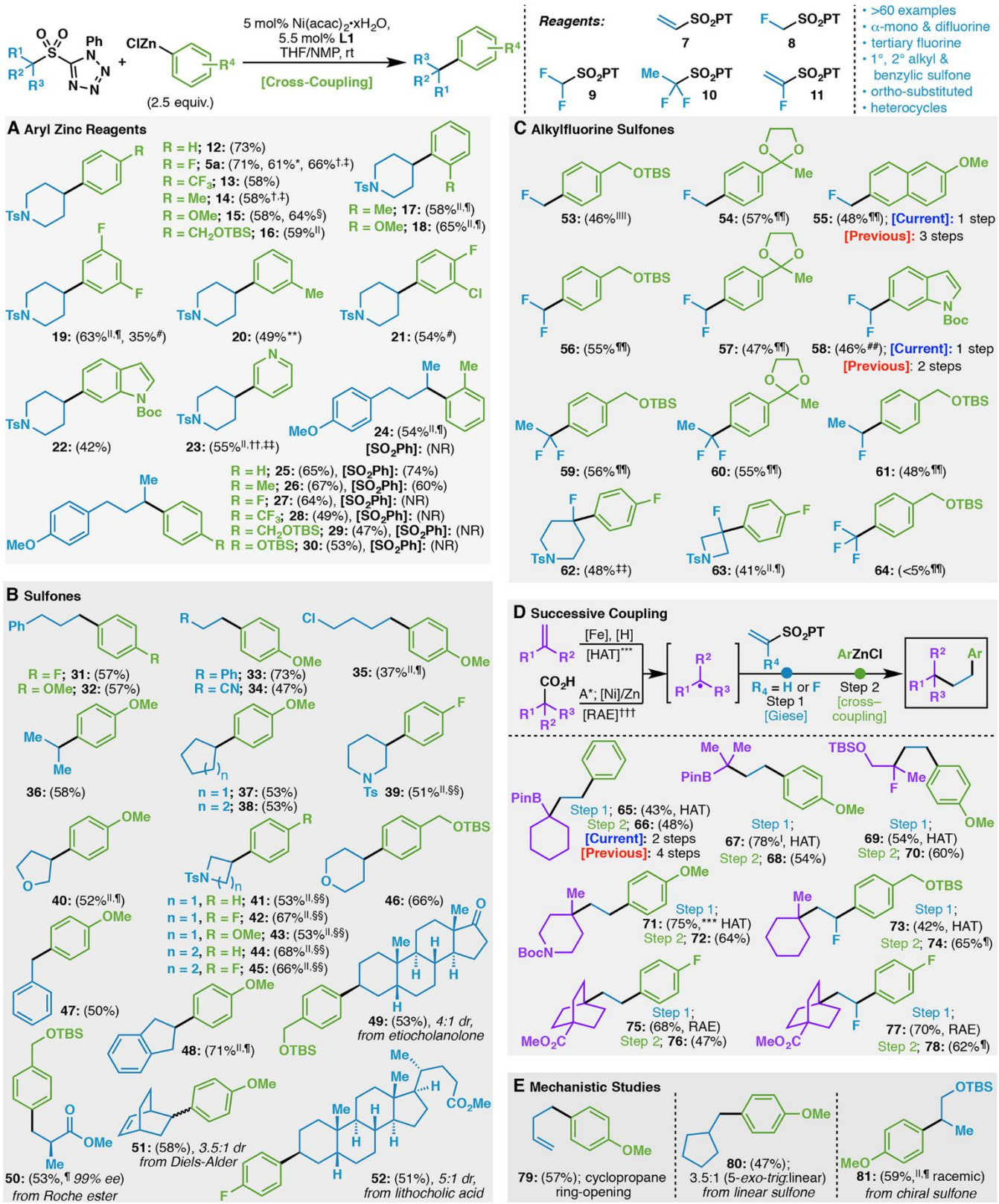

Fig. 2. Scope of the Ni-catalyzed cross-coupling of redox-active PT-sulfones. See the Supplementary Materials for experimental details. *2.5 mmol scale. †Arylzinc reagent prepared by lithium-halogen exchange with *n*-BuLi/transmetallation with $ZnCl_2$. ‡10 mol% $Ni(acac)_2 \cdot xH_2O$, 11% 2,2'-bipy. §0.5 mmol scale. ||60°C. ¶20 mol% $Ni(acac)_2 \cdot xH_2O$, 22 mol% 2,2'-bipy, 3.0 equiv. arylzinc reagent. #Arylzinc reagent prepared by magnesium-halogen exchange with *i*PrMgCl·LiCl/transmetallation with $ZnCl_2$. **Arylzinc reagent was prepared using commercial solution of $ZnCl_2$ in 2-MeTHF. ††DMF instead of NMP. ‡‡20 mol% $Ni(acac)_2 \cdot xH_2O$, 40 mol% 2,2'-bipy, 3.0 equiv. arylzinc reagent. §§30 mol% $Ni(acac)_2 \cdot xH_2O$, 33 mol% 2,2'-bipy, 4.0 equiv. arylzinc reagent. ||||30 mol% $Ni(acac)_2 \cdot xH_2O$, 60 mol% bathophenanthroline, 3.0 equiv. arylzinc reagent. ¶¶20 mol% $Ni(acac)_2 \cdot xH_2O$, 40 mol% bathophenanthroline, 3.0 equiv. arylzinc reagent. ##1.0 equiv. $Ni(acac)_2 \cdot xH_2O$, 1.1 equiv. bathophenanthroline, 6.0 equiv. arylzinc reagent. ***See (*27*) for experimental details and preparation. †††See (*28*) for experimental details. rt, room temperature; 2,2'-bipy, 2,2'-bipyridine; THF, tetrahydrofuran; NMP, 1-methylpyrrolidin-2-one; NR, no reaction; HAT, hydrogen atom transfer; A*, activation with N-hydroxyphthalimide (NHPI); RAE, redox-active ester; DMF, *N,N*-dimethylformamide.

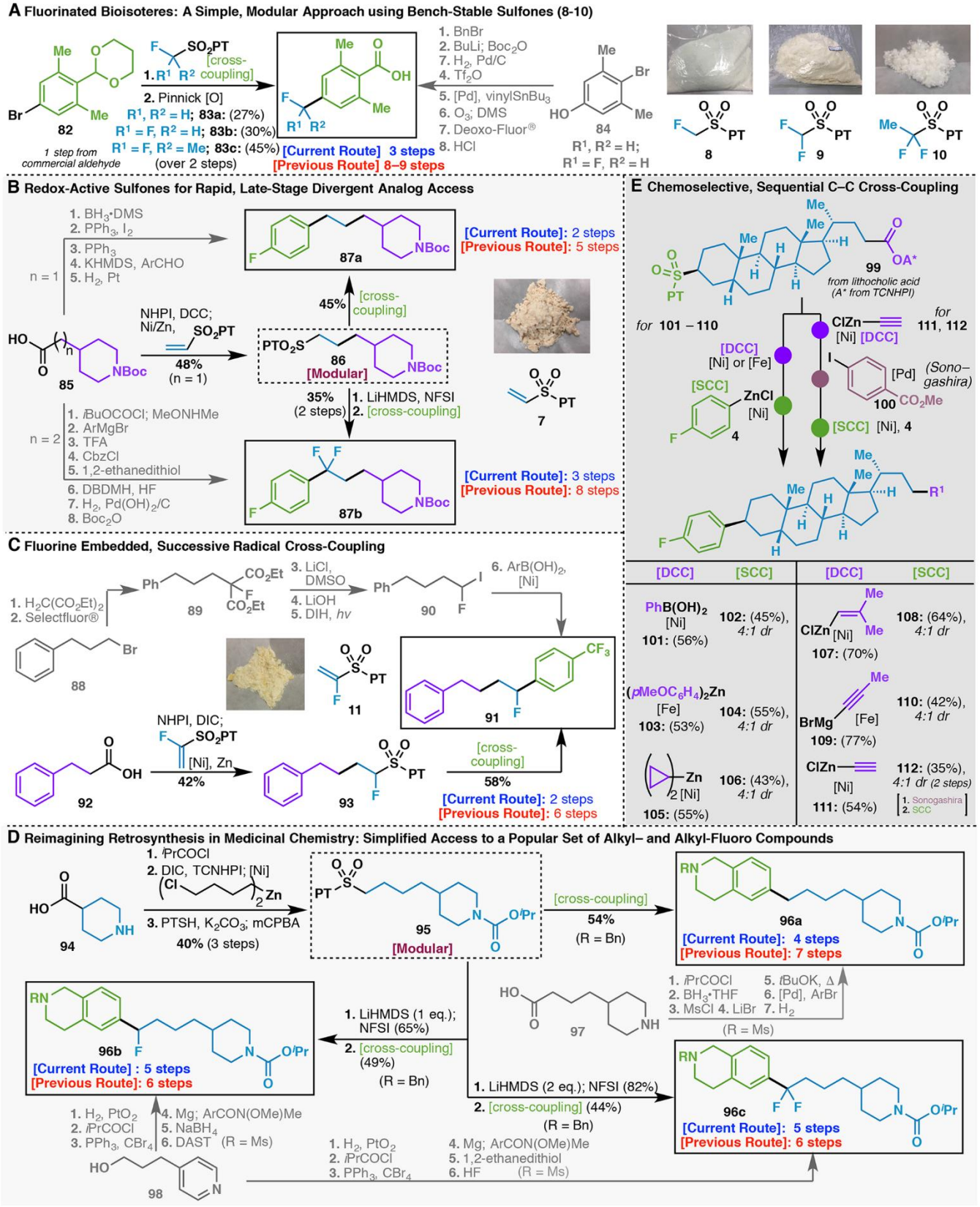

Fig. 3. Simplification of synthesis using sulfone-cross-coupling logic. See the Supplementary Materials for experimental details. DCC, decarboxylative cross-coupling; SCC, desulfonylative cross-coupling; DBDMH, 1,3-dibromo-5,5-dimethylhydantoin.

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Modular radical cross-coupling with sulfones enables access to sp^3-rich (fluoro)alkylated scaffolds

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