A General Redox-Neutral Platform for Radical Cross-Coupling

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Abstract:

Sulfonyl hydrazides are disclosed as versatile radical precursors as exemplified with seven new C–C bond forming, redox-neutral cross-couplings with: (1) activated olefins, (2) alkyl halides, (3) redox active esters, (4) aryl halides, (5) alkenyl halides, (6) alkynyl halides, and (7) a trifluoromethylating reagent to forge $C(sp^3)$-$C(sp^3)$, $C(sp^3)$-$C(sp^2)$, and $C(sp^3)$-C(sp) bonds. Sulfonyl hydrazides are stable and usually crystalline substances that can be accessed in a variety of ways including transiently from hydrazones to achieve a net reductive arylation of carbonyl compounds. Exogenous redox (chemical, photo/electrochemical) additives are not necessary as these functional groups serve the dual role of radical precursor and electron donor. The operational simplicity (homogeneous, water tolerant, dump-and-stir) and practicality of the method are demonstrated as well as applications to streamlining synthesis and mild late-stage functionalization.

Introduction:

The use of radical cross-coupling in retrosynthetic analysis has experienced a renaissance over the past decade (*1-4*). This is due to the simple, convergent disconnections of challenging C–C bonds leading back to ever-present functional groups such as halides, acids, amines, alcohols, and olefins (Figure 1A) (*4-12*). In practice, all of these widely employed radical precursors require some sort of exogenous redox activation mode. Regardless of the choice of oxidative or reductive activation, this generally requires stoichiometric chemical additives, catalysts to facilitate photo-induced electron transfer, or electrochemistry (*5, 8, 13*). A simpler means to achieve radical cross-coupling without the use of exogenous redox methods would be highly attractive based on first principles reasoning as it would reduce cost and the complexity of reaction setup. Alkyl diazenes are a prime candidate for radical precursors that could achieve such an objective (*14, 15*). These species have been invoked since the late 1930's (*16, 17*) yet their use in organic synthesis has been sporadic and mainly relegated to $2e^-$-defunctionalization methods such as the classic Wolff–Kishner reduction and related reactions (*17-21*) (Figure 1B, left). A provocative report on the use of *in situ* derived diazenes from sulfonyl hydrazides was reported by Taber in 1993 wherein the radical cyclization of ketone **1** to octahydroindane **2** was achieved (Figure 1B, right) (*22*). Building on this precedent, we wondered if free radicals derived without redox-initiation from these intermediates could be enlisted in metal catalyzed cross-coupling events. Herein we disclose a remarkably general platform for redox-neutral radical cross-couplings driven by *in situ* derived alkyl diazenes to forge a variety of C–C bonds. Alkyl sulfonyl hydrazides are easily derived from carbonyl compounds and alcohols (N-sulfonyl regioisomers can be used interchangeably); these stable, crystalline substances can now be employed to generate a variety of useful sp^3-sp^3, sp^3-sp^2, and sp^3-sp linkages in a practical, "dump and stir" fashion, obviating the need for any external redox-activation.

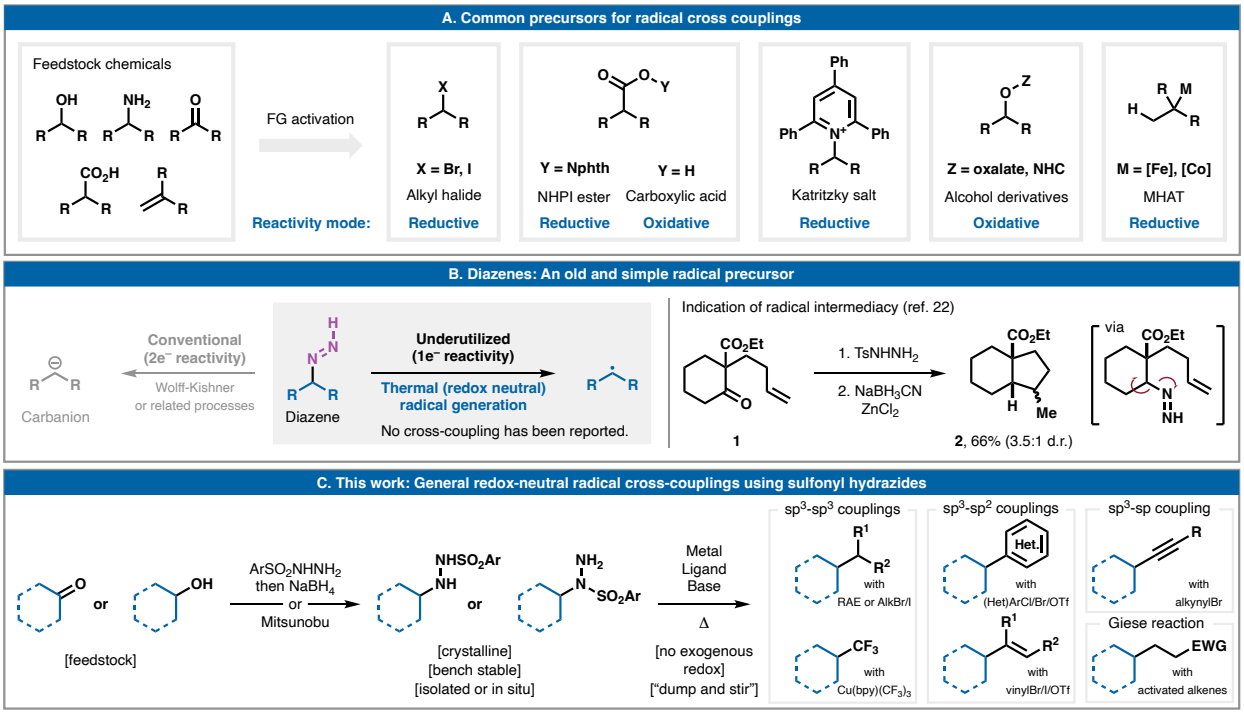

Figure 1. (A) Common radical cross coupling precursors; (B) alkyl diazenes as potential leads for redox-neutral cross-coupling; (C) realization of broadly general redox-neutral cross coupling using sulfonyl hydrazide precursors.

Table 1 vividly illustrates the versatility of sulfonyl hydrazides as redox-neutral coupling partners in six valuable C–C bond forming events. Each of these methods could warrant their own separate disclosure to describe their optimization and development. For the sake of brevity, this initial report describes an inaugural scope for each new reaction. A discussion of their optimization can be found in the Supplementary Materials and a detailed mechanistic study for each will be forthcoming. The simplest of radical couplings, namely Giese-type additions to unsaturated species was demonstrated first (Table 1A, top). For this reaction, dtbbpy was employed in concert with Ni(dme)Cl_2 along with Et_3N (3.0 equiv.) to furnish five representative adducts in 35-65% yield (**3–7**). Interestingly, the yield of this reaction was significantly reduced in the absence of a Ni/L system. Next, the direct formation of C(sp^3)-C(sp^3) linkages was explored using both alkyl halides and alkyl redox-active esters (RAEs) as coupling partners (Table 1A, bottom) (*23-25*). Using a near stoichiometric ratio of coupling partners (1.5 equiv. of sulfonyl hydrazide and 1.0 equiv. of alkyl halide or RAE) in the presence of Ni(dme)Cl_2, 2,6-bis(pyrazol-1-yl)pyridine (bpp), and Et_3N (3.0 equiv.) at 60 °C in DMF provided a range of secondary-secondary (**10–12**, **15**, and **16**) and secondary-primary adducts (**9**, **13**, and **14**) in good yield. From an operational standpoint

this reaction represents perhaps the most simple and inexpensive means of forming saturated C–C bonds (especially challenging 2°-2° linkages) (*3, 26*). A notable aspect of this coupling approach is that no exogenous redox chemistry is necessary even though RAEs and alkyl halides have historically required reductive radical generation (*27, 28*).

Turning to $C(sp^3)$-$C(sp^2)$ and $C(sp^3)$-C(sp) linkages, an array of viable coupling partners was identified to access broad regions of chemical space (Table 1B) (*29-34*). Alkenyl donors (bromides, iodides, and triflates), aryl halides (chlorides and bromides), and alkynyl bromides were all easily coupled with sulfonyl hydrazides (**23–29**, and **34**; **17–22**, and **33**; **30–32** and **35**, respectively) using similar conditions to that described above with the notable exception that the unique, but commercial, dNH_2-bpy ligand often led to higher yields. Notably, unlike the majority of reductive modes of accomplishing such transformations, protodehalogenation and/or homodimerization of the sp^2-halide substrate is greatly suppressed, thereby simplifying product isolation. The ability to utilize $C(sp^2)$-chlorides and triflates is of great utility and the deletion of pyrophoric reagents (Negishi and Kumada type) (*35-37*), palladium, or redox-focused reaction setups (photo/electrochemistry) (*3*) will reduce the barrier to employing radical cross-couplings.

The aforementioned reactions all rely on Ni-catalysis to facilitate productive C–C bond formation. However, the use of sulfonyl hydrazides is not limited to Ni as exemplified in Table 1C with the direct trifluoromethylation of these species (**36–42**) using Grushin's commercial Cu-based reagent (*38*), $Cu(bpy)(CF_3)_3$ (easily prepared on gram scale from $TMSCF_3$ and CuI). Unlike the related trifluoromethylation of alkyl halides or alcohols with the same reagent (*39, 40*), no exogenous redox activation is required. To the best of our knowledge, this method for alkyl-CF_3 bond formation is perhaps the most operationally simple option currently available.

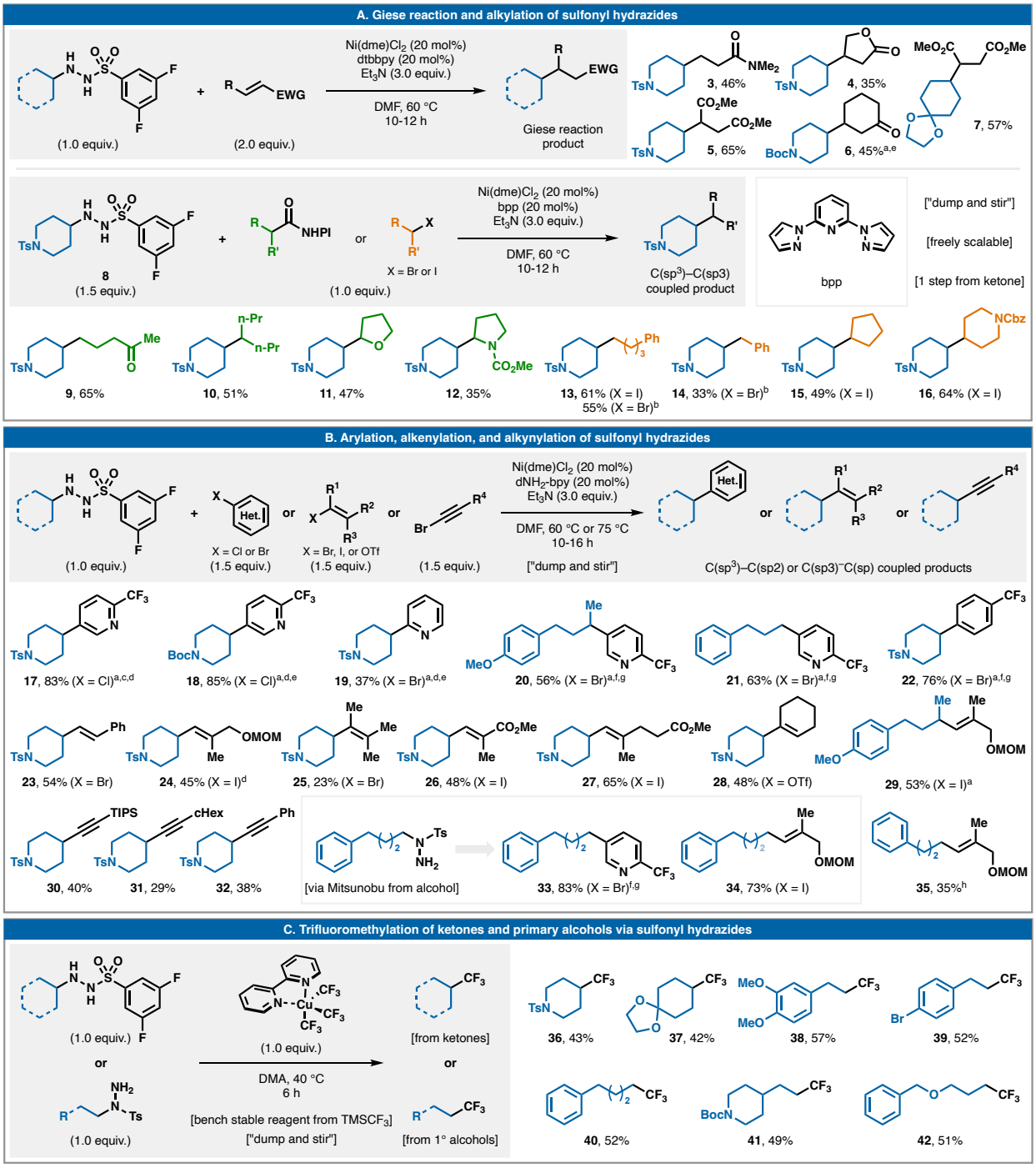

Table 1. Seven new classes of redox-neutral reactions with sulfonyl hydrazides: (A) Giese addition and cross coupling with alkyl halides and RAEs; (B) cross-coupling with C(sp^2) and C(sp) halides to create aryl-, alkenyl-, and alkynyl-alkyl linkages; and (C) Trifluoromethylation with Grushin's reagent. [a]The corresponding Ts hydrazide was used instead of the depicted difluorinated. [b]NaI (2.0 equiv.) was added. [c]Calibrated UPLC yield against PhNHAc as internal standard, ran as duplicate, average shown (84%, and 82% yield). [d]Pempidine was used as the base instead of Et_3N.

[e]Crude NMR yield against mesitylene or dibromomethane as internal standard. [f]dtbbpy was used as ligand instead of dNH_2-bpy. [g]1.0 equiv. of ArBr was used instead of 1.5 equiv.

In general, it was found that the 3,5-difluorophenylsulfonyl hydrazides exhibited the optimum reactivity for secondary cyclic radicals, but in many cases, such as primary derived radicals, the simple tosyl-substituted hydrazide can be employed (**33–35**, and **38–42**). However, in the case of arylation, simple tosyl hydrazides performed well (**17–22**). As a general matter, the byproducts resulting from hydrazide immolation are easily removed (N_2 gas and a sulfinate salt) upon aqueous workup. These reactions are ideal for parallel screening workflows as they can be conducted on very small scale. As discussed below they can also be scaled up with ease due to their homogeneity. Explorations thus far have revealed the majority of 2°-cyclic sulfonyl hydrazides to be bench stable substances, particularly in the case of tosyl hydrazides. 2°-acyclic and 1°-tosyl hydrazides obtained after hydrazone reduction should be used shortly after preparation whereas 1° hydrazides prepared through Mitsunobu (different NSO_2Ar regioisomer, Table 2B, box) are more stable (several days on a benchtop). A user guide based on current data is provided in the Supplementary Materials.

From an operational perspective it may be desirable to proceed directly from a hydrazone to obtain a coupled product without isolation of the corresponding sulfonyl hydrazide, analogous to the widely employed Barluenga coupling (*41-43*). In that reaction, a sulfonyl hydrazone is simply combined with a sp^2-boronic acid to deliver useful sp^2-sp^3 linkages by way of a diazo-intermediate. After extensive exploration, a simple silane ($PhSiMe_2H$, ca. $2/gram) could be added *in situ* to the standard reaction conditions thereby enabling the equivalent of a reductive Barluenga coupling using more convenient (hetero)aryl halides as illustrated in Table 2. Dozens of substrates were evaluated across a range of different hydrazones and aryl halides revealing the remarkable versatility of this method. In terms of the experimental protocol, it is operationally trivial to conduct as sulfonyl hydrazone formation is quantitative and isolation is optional. In cases where a hydrazone is used without purification, residual quantities of MeOH present after evaporation does not significantly impact the ensuing coupling. With the hydrazone in hand (isolated or used after evaporation of MeOH), the remaining materials are added (ArX, $Ni(dme)Cl_2$, dNH_2-bpy), followed by DMF under N_2 or Ar (pre-stirring until homogenous), followed by base and silane. The reaction is heated to 75 °C overnight (16-18 h) followed by standard aqueous workup. In terms

of the aryl electrophile scope, the trend is what one would expect based on known rates of Ni-oxidative addition into such systems. Using a highly electron rich ligand (dNH_2-bpy) and elevated temperature helps to extend this scope even further. Thus, electron-rich aryl bromides are competent (**43** and **44**), but electron-poor aryl bromides work better (**45** and **47**). Electron deficient aryl chlorides are suitable coupling partners (**17**, **18**, **54**, **58**, **60**, and **63–67**) as are aryl triflates (**18**). A wide variety of functional groups are tolerated including valuable handles for further functionalization: Bpin (**46**), polyhalogenated arenes (**50**), free glutarimide NH (**76**), free amino pyridine (**55**), aryl fluorides (**54**), SMe (**59**), tetrazole (**48**), benzylic CHF_2 groups (**68–72**, **74**, and **79**), nitriles (**45**, **52**, and **57**), esters (**65–71**, **73**, **74**, and **77–79**), amides (**51**), ortho substituents (**52**), and challenging heterocycles such as pyrimidines (**58–60**), pyrazines (**65–67**), indazoles (**61**), and azaindole (**62**).

The array of suitable carbonyl coupling partners appears to be vast. Cyclic ketones with ring sizes ranging from 4 to 6 are easily employed and it is anticipated that any ring size would be potentially suitable. Adjacent heteroatoms are tolerated (**63**, **71**, **72**, **78**, and **79**) and good to high d.r. is observed with ketones bearing pre-existing stereocenters (**68** and **69**). Complex bridged ketones also provide useful quantities of product in high diastereoselectivity (**67**, **70**, **71**, **73**, and **74**). Finally, aldehydes can be enlisted (**77–79**).

The ability to employ simple carbonyl groups in complex cross-couplings as outlined above opens a new opportunity for retrosynthetic planning as carbonyl groups are often used to generate carbon skeletons. Traditionally, the go-to strategy for such systems involves a sequence of vinyl-triflate or vinyl-boronic acid synthesis, Suzuki coupling, and hydrogenation which aside from being laborious (for example furan **72**) and non-chemoselective, is impossible to employ on non-enolizable systems such as **70**. Another popular approach is to convert a carbonyl group into a halide and employ it in conventional or reductive cross-coupling approaches; however, this multistep process suffers from limitations in the halogenation of certain alcohols. In some cases, it is desirable to employ a sulfonyl hydrazide directly rather than coupling a hydrazone directly (see Supplementary Materials for more details). Unlike the direct arylation of sulfonyl hydrazides presented in Table 1B, there are more byproducts observed using hydrazones with *in situ* reduction stemming from protodehalogenation and products resulting from reaction with reduced sulfinate (see Supplementary Materials for more details). The arylation method of Table 2 is thus better for rapid screening campaigns in medicinal chemistry where isolated yields are less important.

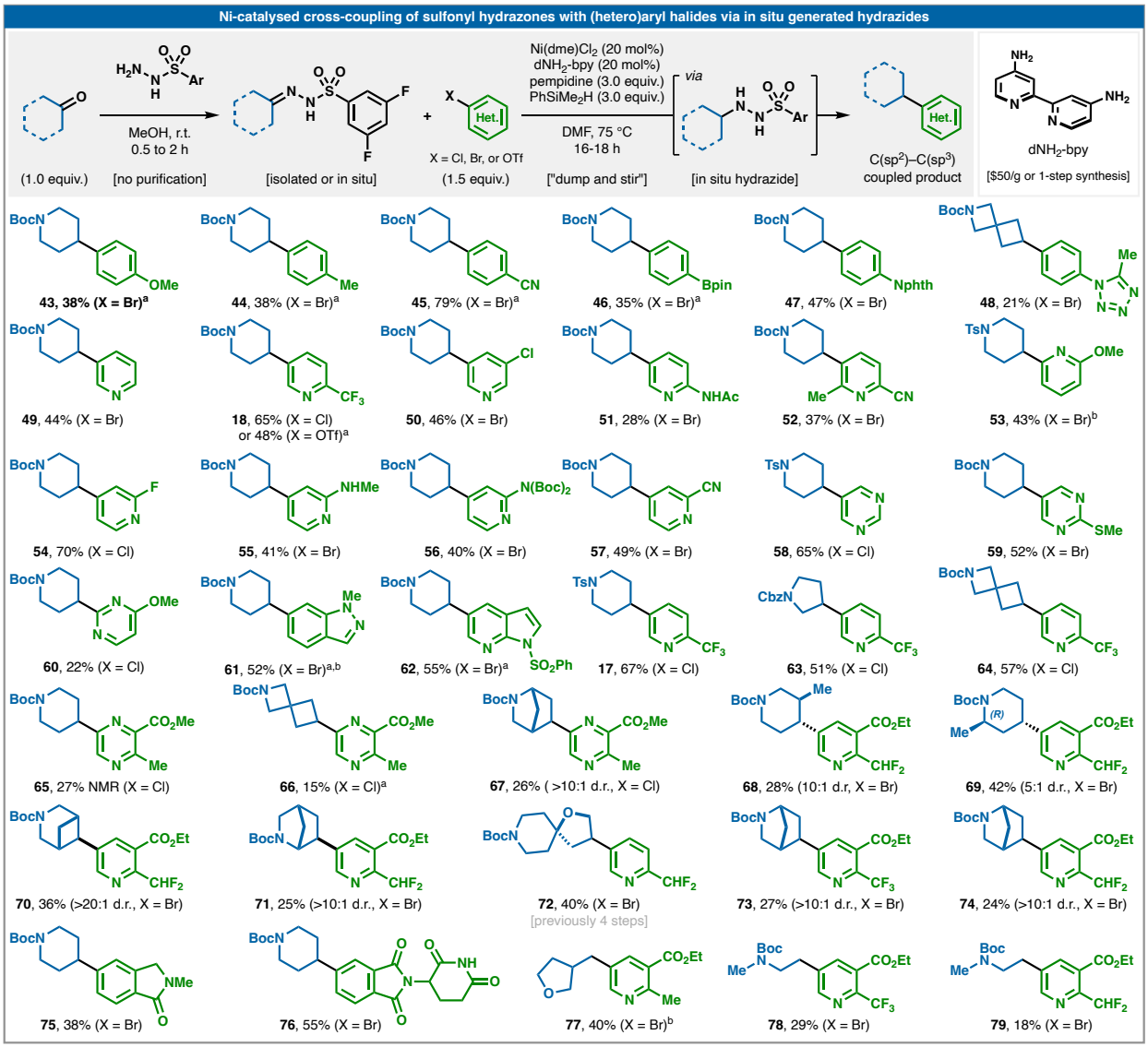

Table 2. A one-pot protocol for sulfonyl hydrazide couplings with aryl halides via hydrazones through *in situ* reduction with an inexpensive silane. [a]NMR yield against 1,3,5-trimethoxybenzene or mesitylene as internal standard. [b]NaCl (1.0 equiv.) was added.

Redox-neutral radical cross-couplings of alkyl sulfonyl hydrazides can dramatically simplify access to all sorts of useful building blocks. For instance, hydroxyethylated pyridine **80** (Figure 2A) is commercially available yet prohibitively expensive (ca. $500-1000/g). Retrosynthetically, numerous options can be envisaged using a variety of hydroxyethyl surrogates such as ethylene oxide (**82**), β-hydroxy acid/RAE (**83**), Katritzky salt **84**, boronic acid donor **85**, stannane **86**, and chloroethanol **87** (*44, 45*). Most of these building blocks are either unsuitable,

unstable (**83**), inaccessible (**85** and **86**), or inconvenient to employ (**82**). In stark contrast, commercial hydrazine **88** ($0.2/g) and chloropyridine **81** ($4-5/g) can be combined in a single-step process (chloropyridine **81**, TsCl, Ni(dme)Cl_2, and dNH_2-bpy are dissolved in DMF under Ar, then hydrazine **88** and Et_3N are added, stirred at r.t. for 30 min followed by heating to 75 °C for 6 hours) in 68% yield. The generally high chemoselectivity encountered in radical cross-couplings can be further leveraged for mild late-stage modifications such as in the case of the direct functionalization of Ticagrelor (Figure 2B). Without any protecting group chemistry, **89** can be subjected to Mitsunobu with $TsNHNH_2$ to install the sulfonyl hydrazide followed immediately (after aqueous workup) by radical cross-coupling to deliver arylated adduct **90** in 33% yield over 2 steps (along with *ca.* 20% recovered tosyl hydrazide). It is difficult to conceive of a more direct and simple way to achieve such a transformation.

The utility of these reactions will likely extend beyond a medicinal chemistry setting as its simple and homogenous nature bodes well for large scale applications. To exemplify this, gram-scale preparation of substrates **17** and **92** were performed by reacting sulfonyl hydrazide **8** with aryl bromide **93** and RAE **91**, respectively, in good yields. The clear advantage of eliminating exogenous redox in radical cross-coupling reach beyond reaction simplicity (no need for e-chem or photochem setups or expensive sensitizers), it can also facilitate transformations that are difficult to scale up or unworkable. For instance, as illustrated in Figure 2C, 1,4-trans substituted cyclohexanes **96** and **100** can be easily accessed in "dump-and-stir" homogenous reactions using sulfonyl hydrazide donor **94a** with arenes **95** and **99**, respectively (reactions run one time with no optimization). In the former case, an inconvenient flow photochemical scale-up is required for decarboxylative coupling and in the latter case the reaction did not proceed, necessitating a laborious workaround (*46*).

Although the Ni-catalyst loading reported in this disclosure is usually 20 mol%, no deliberate effort was made to reduce the loading. In the case of gram scale coupling of **8** and **93**, a 10 mol% loading was employed (delivering **17** in 80% yield), suggesting that much lower loadings of Ni are possible.

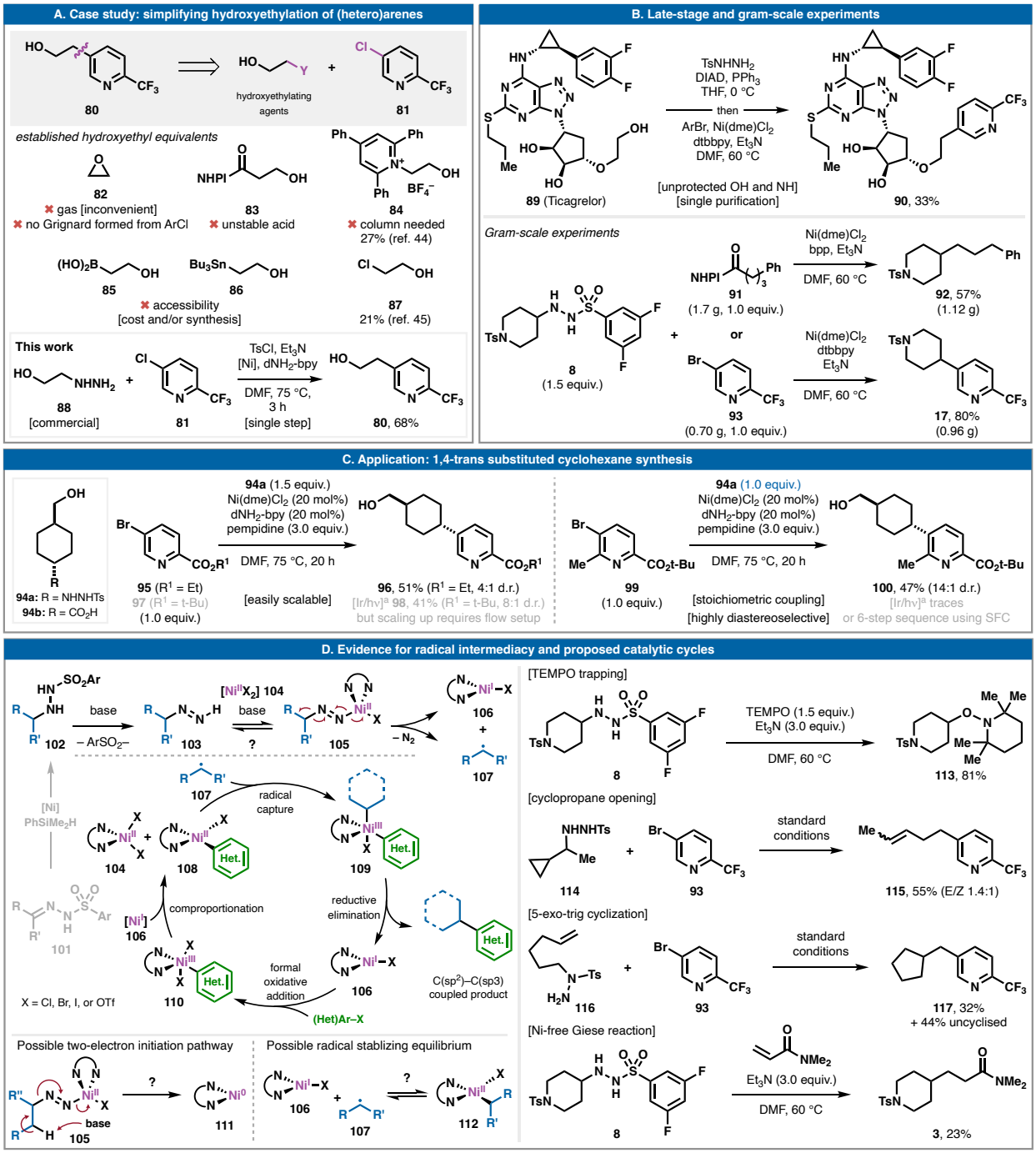

Figure 2. (A) Seemingly trivial hydroxyethylation of an aryl chloride can now be accomplished with ease; (B) application to late-stage functionalization and gram-scale examples; (C) A case study to compare simplified redox-neutral cross-coupling with conventional photo-induced electron transfer based decarboxylative coupling; and (D) current mechanistic working hypothesis and supporting studies. [a]**94b** was used instead of **94a** in the photochemical conditions.

The seven reaction classes disclosed in this report can each be individually studied to unearth their guiding mechanistic principles. As such, a definitive mechanism for redox-neutral radical cross-coupling using sulfonyl hydrazides is beyond the scope of this work. Nevertheless, we provide a general mechanistic picture focusing on $C(sp^2)$-$C(sp^3)$ bond formation that is consistent with findings made thus far, and literature precedent, as outlined in Figure 2D (left). As is well precedented in the literature (*47-49*), mild base undoubtedly liberates a diazine species **103** from the starting hydrazide **102** (generated in situ from hydrazone **101** by $PhSiMe_2H$ reduction which is perhaps mediated by a Ni-H species). The exact order of events following diazine liberation is currently unclear. For instance, it is conceivable that the diazene decomposes via homolysis-driven N_2 extrusion to an alkyl radical **107** (either thermally or mediated by Ni(II) species **104** via a discreet intermediate such as **105**) that is captured by a Ni-oxidative addition complex **108** giving high-valent Ni species **109**. Since Ni(II) is used and no exogenous reducing agent is present, it is possible that the hydrazide itself aids in the reduction of Ni(II) **104** to a catalytically competent low-valent species **106** that perpetuates the cycle (Figure 2D, top). Formal oxidative addition of low-valent Ni(I) into (Het)Ar-X bonds is well established in literature (from **106** to **110**), as is the comproportionation with **106** into **104** and **108** (*25, 50*). Radical capture of **107** has been shown to lead to high-valent Ni complexes such as **109** (*51*). Reductive elimination from **109** delivers the product and returns low-valent species **106** which, in turn, restarts the cycle. An alternative two-electron pathway to initiate the cycle can be imagined from **105** to Ni(0) species **111** via deprotonation and loss of N_2 gas (Figure 2D, bottom; details are currently unclear). This species can then engage in oxidative addition to give **108** directly thereby entering the catalytic cycle. As proposed, the alkyl radical **107** is generated in close proximity to Ni, therefore one could speculate a stabilizing associative equilibrium between Ni(I) **106** and the alkyl radical **107** to generate **112**. Various experiments in support of radical intermediacy are presented (Figure 2D, right). In accordance with findings in the literature, TEMPO trapped the radical generated from a hydrazide even in the absence of a Ni-catalyst (**8** to **113**). Further support of this hypothesis can be seen with cyclopropane opening/coupling of **114** with **93** to deliver linear adduct **115** and 5-exo-trig cyclization/coupling of **116** with **93** to afford cyclopentyl substrate **117** (*52*). In the latter case, the 5-exo-trig cyclisation was only partially complete before coupling resulting in a mixture of cyclized product **117** and its linear counterpart (not shown) in a 1:1.4 ratio, respectively. The

Giese reaction depicted in Table 1A to access **3** from **8** was facilitated with added Ni but in the absence of catalyst it was also observed in lower yield (46% vs. 23%, respectively).

CONCLUSION

Radical cross-coupling chemistry has had a profound impact on the practice of organic synthesis and has enabled simplifying radical retrosynthetic disconnections that did not exist a decade ago. Despite great strides in this field, the use of exogenous catalysts, stoichiometric reductants/oxidants, and photo/electrochemical setups diminishes its practical utility compared to conventional, redox-neutral C–C bond forming cross-couplings such as the venerable Suzuki reaction. The fundamental advance of this disclosure is the discovery that sulfonyl hydrazides can *serve not only as versatile radical progenitors but serve as their own electron donors*, driven by the loss of N_2, to facilitate a metal mediated catalytic cycle thereby obviating the need for external redox stimuli. From a practical perspective, sulfonyl hydrazides are generally stable, crystalline substances that do not need to be purified by chromatography and can often be used in crude form. Curiously, these groups are not very polar and are well-behaved on silica gel (nice round spots on TLC, see Supplementary Materials for pictures). Catalysis is demonstrated with Ni, but the same principle should be applicable to many other organometallic systems. In fact, preliminary experiments suggest that other metals such as Cu, Co, Pd, and Fe, can provide varying levels of product in $C(sp^3)$-$C(sp^2)$ coupling (see Supplementary Materials). This study outlines the invention of seven new transformations (Table 1), but a vast array of new reactions is now conceivable. Since easily prepared sulfonyl hydrazides divorce redox chemistry from radical cross-couplings, reaction setup is dramatically simplified (arguably as simple as a classic Suzuki coupling). Future studies will include applications to tertiary radical coupling, interfacing sulfonyl hydrazides with other organometallic reaction modes, further extending the scope to C–heteroatom bond cross coupling, and a deeper mechanistic inquiry. It is likely that these new C–C bond forming reactions will find application in nearly all branches of chemical synthesis when targeting novel materials, chemical biology probes, nucleic acids, peptides, sugars, natural products, agrochemicals, and medicines.

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Author contributions

Á.P. developed the in situ protocol described in Table 2 using hydrazones, project initiation, and underlying reactivity studies. **J.S.** developed coupling of sulfonyl hydrazides with aryl halides, redox active esters, alkyl halides, Giese addition, and related reactivity studies. **J.H.** developed the Cu-mediated trifluoromethylation of sulfonyl hydrazides. **J.T.** developed the coupling of sulfonyl hydrazides with alkenyl and alkynyl halides. **H.Z.** assisted with all aspects of the work. **B.P.V. D.S.P.**, **M.D.M.** and **M.D.P.** contributed to field testing reactions in a medicinal chemistry setting and adding numerous substrates to the scope. **Y.K.** assisted in experimental design. All authors contributed to writing the paper. **P.S.B.** helped to conceptualize the project, write the paper and secure funding.

Competing interest

The authors declare no competing financial interest.

Supporting Information

Experimental procedures including graphical guides; materials and methods; optimization studies; useful information including a user guide.