Stereoretentive Radical Cross-Coupling

Authors: Jiawei Sun,[†1] Jiayan He,[†1] Luca Massaro,[†1] David A. Cagan,[1] Jet Tsien,[1] Yu Wang,[1] Flynn C. Attard,[1] Jillian E. Smith,[2] Jason S. Lee,[2] Yu Kawamata,[1] Phil S. Baran*[1]

Affiliations:

[1]Department of Chemistry, Scripps Research, 10550 North Torrey Pines Road, La Jolla, CA, 92037, United States.

[2]Automated Synthesis Facility, Scripps Research, 10550 North Torrey Pines Road, La Jolla, CA, 92037, United States.

[†]These authors contributed equally to this work.

[*]Correspondence to: pbaran@scripps.edu

Introduction:

Free radicals were first discovered over 120 years ago by Gomberg[1] and the first radical cross-couplings demonstrated by Kochi in the 1970's.[2] Fueled by the need for general methods to couple C(sp^3)-fragments, this area has seen an explosion of renewed interest. In contrast to widely employed polar cross-coupling chemistry to forge C(sp^2)–C(sp^2) bonds (Suzuki, Negishi, Kumada, etc.), radical cross-coupling is advantageous when applied to the coupling of saturated systems due to the mild conditions employed and enhanced chemoselectivity associated with single electron chemistry. Indeed, the ability to employ ubiquitous carbon-based fragments (carboxylic acids, alcohols, amines, olefins, etc.) in cross-coupling has dramatically simplified access to a variety of complex molecules.[3-9] Despite these advantages, enantiospecific coupling reactions involving free radicals are unknown and generally believed to be impossible due to their near-instantaneous racemization (picosecond timescale).[10] As a result, controlling the stereochemical outcome of radical cross-coupling can only be achieved on a case-by-case basis using bespoke chiral ligands[11] or in a diastereoselective fashion guided by nearby stereocenters.[12] Here we show how readily accessible enantioenriched sulfonylhydrazides and low loadings of an inexpensive achiral Ni-catalyst can be enlisted to solve this vexing challenge for the first time thereby enabling enantiospecific, stereoretentive radical cross-coupling between enantioenriched alkyl fragments and (hetero)aryl halides without exogenous redox chemistry or chiral ligands. Calculations support

the intermediacy of a unique Ni-bound diazene-containing transition state with C–C bond formation driven by loss of N_2.

Main text:

The physical organic chemistry of free radicals has been widely studied and it is well known that instantaneous racemization occurs upon generation from enantiopure precursors (Figure 1A).[13] The rate of this process has been measured to be in the picosecond range which is on the time scale of molecular rotations.[10, 14, 15] As such, retaining the chirality of radicals has only been observed in special settings.[16, 17] This basic property of alkyl radicals has rendered their stereoretentive capture with transition metals an elusive goal that is generally regarded as impossible. This has been experimentally verified in multiple contexts such as the reductive cross-coupling of enantiopure alkyl bromides such as **3**,[18] the decarboxylative Negishi coupling of **1**,[19] or the diastereocontrolled coupling of redox-active ester **6**.[20] As such, it is generally assumed that the only conceivable way to achieve enantiocontrolled radical cross-coupling is through radical capture onto a metal center adorned with chiral ligands.[11, 21] Enantioconvergent couplings of this type have been reported, requiring specially designed and optimized ligands for each individual reaction and substrate type.[21, 22] In addition, radical cross-couplings utilizing this strategy often requires stabilized radical donors (benzylic, adjacent to a heteroatom or electron-withdrawing group).[22, 23] This stands in stark contrast to widely employed asymmetric hydrogenation chemistry wherein a relatively small set of chiral ligands can be used to enantioselectively reduce almost every type of olefin.[24-28] Unlike olefins, which are inherently less structurally diverse, alkyl radical structures encompass much broader 3D chemical space, rendering the identification of general ligand classes that can reliably impart stereocontrol an intractable problem. Further complicating this puzzle from a practical standpoint is the ever-present need for redox chemistry to activate radical precursors.[29-31]

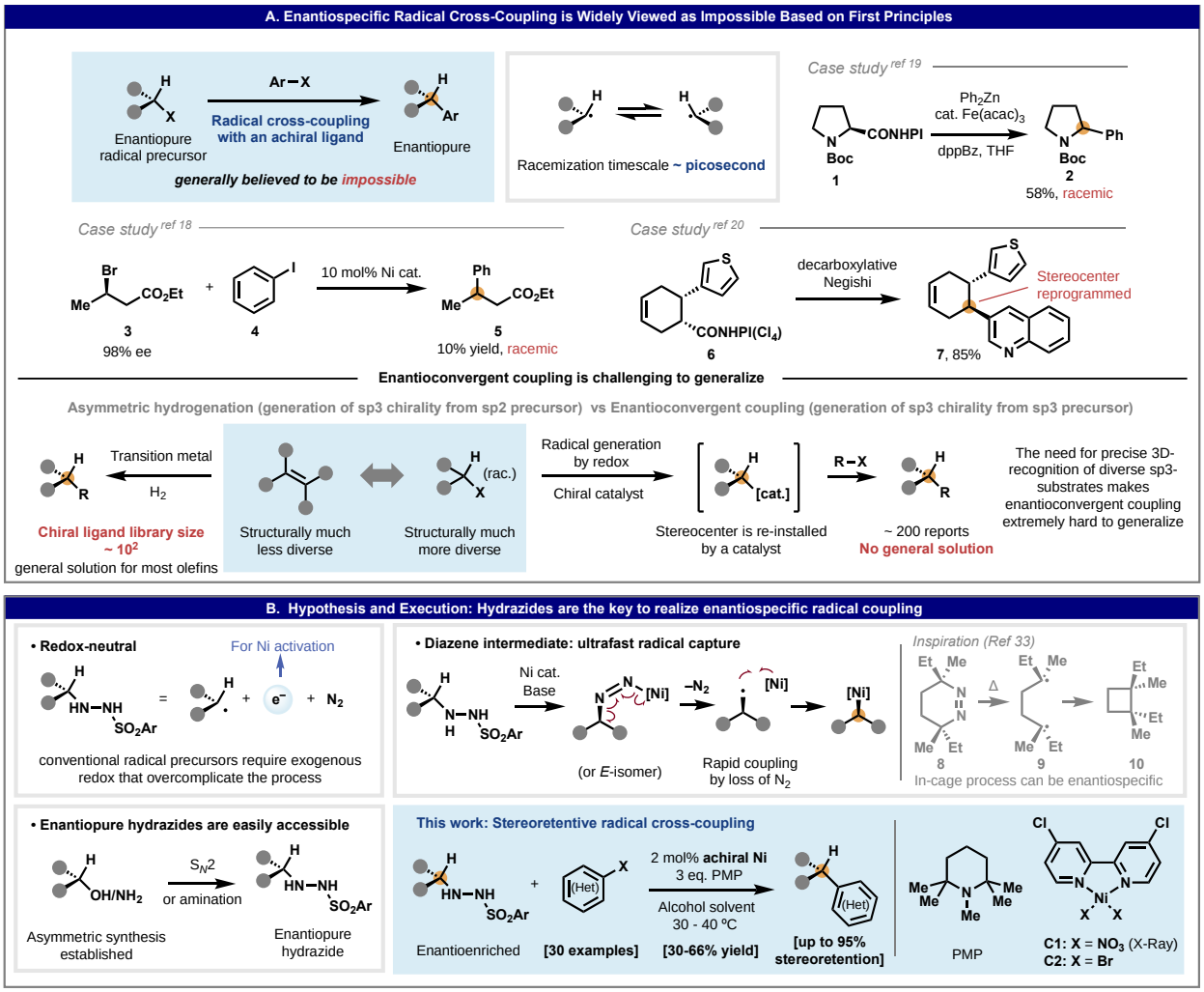

Figure 1. (A) Reported studies on radical cross-coupling of chiral substrates showed no retention of the stereocenter configuration. The design of chiral ligands for enantioconvergent radical cross-coupling is challenging and not as general as for the case of asymmetric hydrogenation. (B) Realization of stereoretentive radical cross-coupling using easily accessible enantiopure sulfonylhydrazides. The gray circles represent general substitution. The orange circles highlight the presence of the stereocenters involved in the transformations. X refers to redox active functionalities. Ar, (hetero)aromatic rings; dppBz, 1,2-Bis(diphenylphosphino)benzene; NHPI(Cl_4), tetrachloro-N-hydroxyphthalimide; PMP, 1,2,2,6,6-Pentamethylpiperidine.

Recently, we disclosed sulfonylhydrazides as redox-neutral radical precursors for cross-coupling that benefit from simple, "Suzuki-like" reaction conditions: an inexpensive Ni-catalyst, mild base, gentle heat, rapid setup, no pyrophoric reagents (alkyl zinc/magnesium), and no external redox additives/catalytic systems (Figure 1B).[32] Sulfonylhydrazides are uniquely useful radical precursors as they serve as electron donors to activate Ni, and are easily accessible from carbonyl

compounds, alcohols, amines, and hydrazines. It was hypothesized that if a tethered Ni-diazene species serves as intermediate in these reactions, it might be possible to capture the radical generated after loss of N_2 to retain the stereochemistry of an enantiopure sulfonylhydrazide by analogy to known in-cage enantiospecific decomposition of dialkyl diazenes.[33, 34]

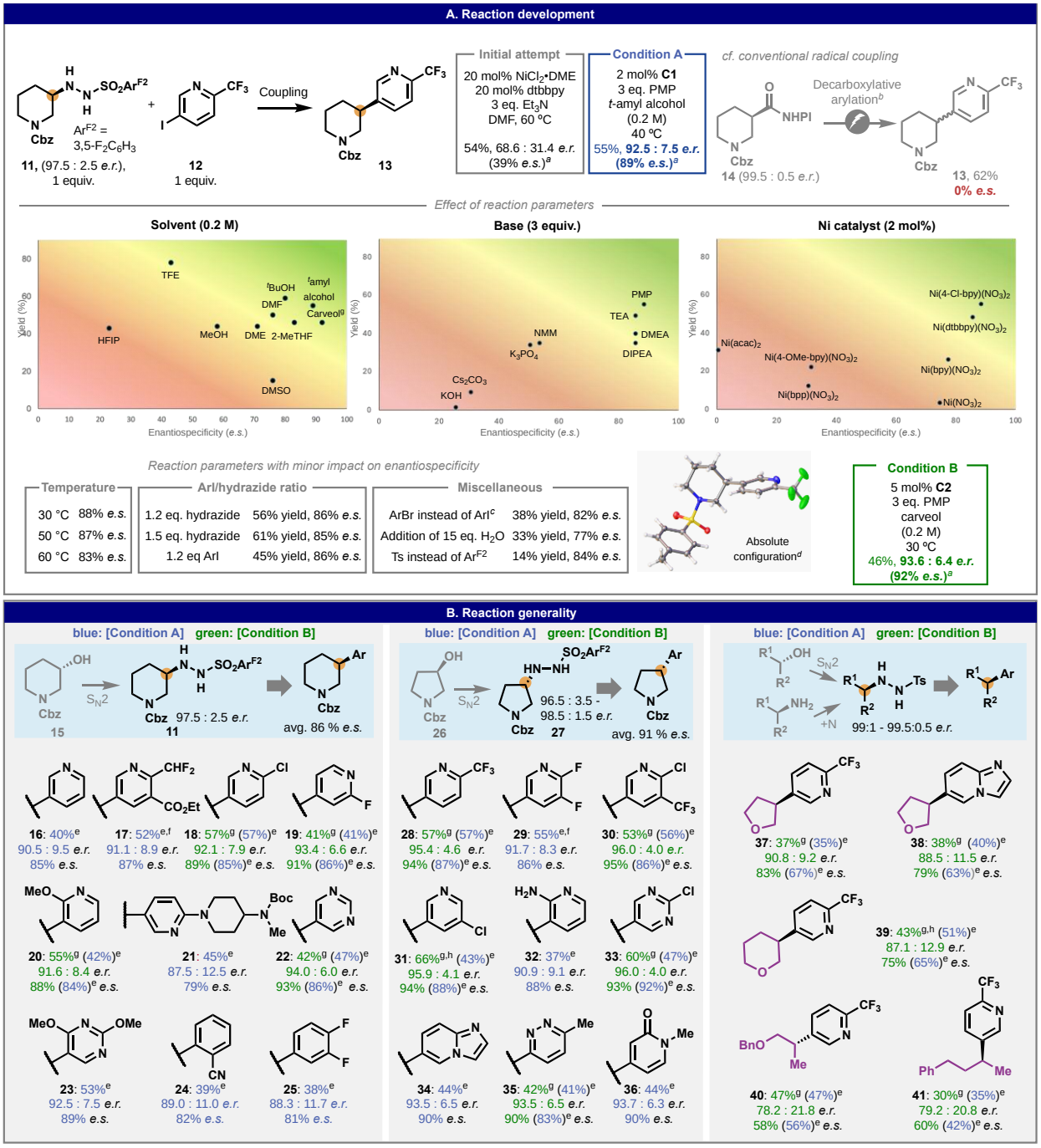

Table 1 (A) Selected examples of intensive reaction screening focused on improving stereoretention. [a] *e.s.* indicates enantiospecificity considering enantiopurity of the starting material **11**. [b] reaction conditions: 20

mol% $NiCl_2$•DME, 20 mol% bpy, 0.5 eq. $AgNO_3$, $TBABF_4$, DMA, (+)Mg/(–)RVC, 4 mA, 4 F/mol. [c] With 2 mol% Ni(dtbbpy)$(NO_3)_2$. [d] Absolute configuration was determined by X-Ray after protecting group swap of **11** from Cbz to Ts. (B) Scope and generality of stereoretentive cross-coupling featuring piperidines, pyrrolidines, furan and pyran coupled with diverse (hetero)aromatic halides. [e] Condition A. [f] 1 equivalent of aryl bromide was employed in place of aryl iodide. [g] Condition B. [h] 40 ºC

Abbreviations: DMA, Dimethylacetamide; DME, Dimethoxyethane; DMF, Dimethylformamide; DMSO, Dimethyl sulfoxide, HFIP, Hexafluoroisopropanol; TFE, Trifluoroethanol; THF, Tetrahydrofuran; PMP, 1,2,2,6,6-Pentamethylpiperidine; TEA: Triethylamine, DMEA: Dimethylethanolamine, DIPEA: Diisopropylethylamine, NMM: N-methylmorpholine; bpy, 2,2'-bipyridine; TBA, Tetrabutylammonium; Boc, tert-Butyloxycarbonyl; Cbz, Benzyl chloroformate; Ts, toluenesulfonyl. 4-Cl-bpy, 4,4'-dichloro-2,2'-bipyridine; 4-OMe-bpy, 4,4'-dimethoxy-2,2'-bipyridine; dtbbpy, 4,4'-di-*t*-butyl-2,2'-bipyridine; bpp, 2,6-bis(1-pyrazoyl)pyridine; acac, acetylacetonate.

If such a reaction could be realized, the enormous pool of commercial enantiopure alcohols and amines (and the wide array of methods to prepare them) which serve as precursors to sulfonylhydrazides could be leveraged. Disclosed herein is the realization of this design thereby enabling the first stereoretentive radical cross-couplings. The reaction is scalable, homogeneous, uses a process-friendly solvent system (*t*-amyl alcohol), and is hypothesized to proceed via an unprecedented diazine-linked Ni-catalytic cycle as supported by computation (*vide infra*). Studies commenced using the enantioenriched sulfonylhydrazide **11** (97.5 : 2.5 *e.r.*, Table 1A) due to the fact that 3-(hetero)arylpiperidines are embedded in over 35,000 known molecules. Such structures are usually prepared through a four-step sequence involving: (1) vinyl triflate formation from N-protected 3-ketopiperidine, (2) Suzuki coupling, (3) Pd-catalyzed hydrogenation, and (4) SFC to separate enantiomers. Not surprisingly, racemic piperidine **13** could be prepared using decarboxylative arylation of the commercially available enantiopure carboxylic acid **14**. Using the previously developed conditions,[32] sulfonylhydrazide coupling procedure between **11** (1.0 equiv) and iodopyridine **12** (1.0 equiv), the desired adduct **13** (previously prepared with *N*-Boc through the Suzuki/hydrogenation route) was obtained in 54% yield with modest enantiospecificity (39% *e.s.*, 68.6 : 31.4 *e.r.*). This initial result was extremely encouraging and motivated a deeper investigation. A series of >500 experiments were performed to improve *e.s.* by evaluating concentration, solvent, temperature, base, Ni catalyst, and ligand as graphically illustrated in Table 1A. An exhaustive listing of those results is provided in the Supplementary Materials but at a high

level, the three key factors influencing reaction outcome were solvent, base, and Ni-catalyst choice. Of the many solvents screened, alcohols such as *t*-amyl alcohol and *cis/trans*-(−)-carveol (*ca*. $0.9/mL) were optimal perhaps as a consequence of their low dielectric constant, high viscosity, and weakly-coordinating nature. Hindered tertiary amine bases performed well, with pempidine (pentamethylpiperidine) emerging as the best. With regards to Ni-catalyst, electron deficient bidentate bpy-type ligands were the top performers. For the purposes of reproducibility and robustness, bench stable precatalysts **C1** and **C2** (Figure 1B) were easily prepared by simply mixing 4-Cl-bpy and the NiX_2 precursor in THF at 60 °C followed by precipitation. In general the reaction could be conducted from 30-60 °C, with 30-40 °C giving slightly improved *e.s.*. A 1:1 ratio of starting materials was employed but slightly increased yields could be obtained by increasing the amount of sulfonylhydrazide donor. Using the corresponding aryl-bromide also worked with a slight decrease in *e.s.* and the presence of excess water was tolerated. Two sets of optimized conditions emerged from this study (conditions A and B), differing in the solvent (*t*-amyl alcohol or *cis/trans*-(−)-carveol), catalyst (**C1** or **C2**), and temperature (40 or 30 °C) employed. Enlisting conditions A or B provided to a 46-55% isolated yield of **13** in [92.5 : 7.5 or 93.6 : 6.4 *e.r.* from sulfonylhydrazide **11** (97.5 : 2.5 *e.r.*), corresponding to 89 or 92% *e.s.*, respectively] whose absolute configuration (stereoretention) was confirmed through X-ray crystallography after exchange of the Cbz for a Ts group. The two final set of optimized conditions are remarkably simple and similar, utilizing inexpensive alcohols as solvents (at 0.2 M), simple tertiary amine base, gentle heat, and 2-5 mol% loading of inexpensive Ni-catalysts.

With an optimized set of conditions established for substrate **11**, attention turned to evaluate the generality of enantiospecific sulfonylhydrazide coupling. A focus was placed on 3-arylpiperidine and pyrrolidines given their prevalence in medicinal chemistry (>78,000 known molecules contain these substructures). Pyridine, pyrimidines, pyridazines, pyridones and arenes were evaluated and found to be well-tolerated. Various substituents such as electron-withdrawing groups, electron-donating groups and halogens (chloro and fluoro) on the (hetero)arenes were explored as well. Notably, ortho-substituents (products **20**, **23**, **24**, **32**) and even a free aniline (**32**) could be enlisted without diminishing the *e.s.*. The haloselectivity of the coupling, enabling the selective cross-coupling in the presence of reactive 2-chloro groups (**18**, **30**, **33**) is also notable for potential downstream diversification. Although most of the products of Table 1 (16 out of 23) were never reported before, not even in racemic form, the majority are prophetically claimed within the

Markush structures of several patents.[35, 36] Seven compounds (**18**, **19**, **24**, **25**, **28**, **31** and **34**) were previously synthesized exclusively in racemic form using methods like Suzuki-hydrogenation, photochemical coupling, and reductive coupling from bromides. For example, the patented compound **18** was synthesized via Suzuki cross-coupling and hydrogenation using PtO_2 as catalyst, followed by chiral SFC separation.[37] Structure **34** was previously procured via reductive coupling from aryl and alkyl-bromides followed by chiral HPLC separation.[38] Products bearing tetrahydrofuran **37**, **38** and tetrahydropyran **39** were also synthesized, though with slightly lower *e.s.* than the corresponding azacycles. Linear alkyl substrates were also tested, resulting in a promising 77.2 : 22.8 *e.r.* and 70.7 : 29.3 *e.r.* for product **40** and **41** respectively. Despite these unoptimized outcomes with linear substrates, the observed partial retention of stereochemistry highlights the vast potential of enantiospecific radical-coupling. The starting sulfonylhydrazides **11** and **27** were prepared on a decagram scale from the corresponding commercial enantiopure alcohols and were found to be stable, crystalline solids. Tetrahydrofuran- and tetrahydropyran-derived sulfonylhydrazides could be prepared either via a Mitsunobu reaction of the corresponding alcohols or amination of the amines by using O-(*p*-nitrobenzoyl)hydroxylamine. In the latter case, amination was preferable due to the lower cost of the corresponding enantiopure amine. For the sulfonylhydrazides leading to acyclic substrates, a simple S_N2 reaction with hydrazine followed by tosylation was employed. In terms of limitations for the current conditions, the yields are generally moderate (*ca.* 50%), with the majority of the mass balance consisting of recovered aryl halide and alkane/alkene byproducts from decomposition of the sulfonylhydrazide. Currently, benzylic systems do not perform well (7% *e.s.*, compound **S34**) presumably due to the faster racemization of such systems. The unusual solvent (carveol) employed in Condition B can often be replaced by the achiral protic solvent, cyclohexanol, thereby implicating solvent viscosity rather than solvent chirality as being a key trait for optimized stereoretention (for instance substrate 37 performed similarly (89.0 : 11.0 *e.r.*, 80% *e.s.*), using cyclohexanol in place of carveol). In this initial report all optimization studies were focused on improving stereoretention and future studies will be focused on yield enhancement. It is worth mentioning that the current yields are similar to that observed in canonical, non stereoretentive radical cross coupling chemistry (*vide infra*).

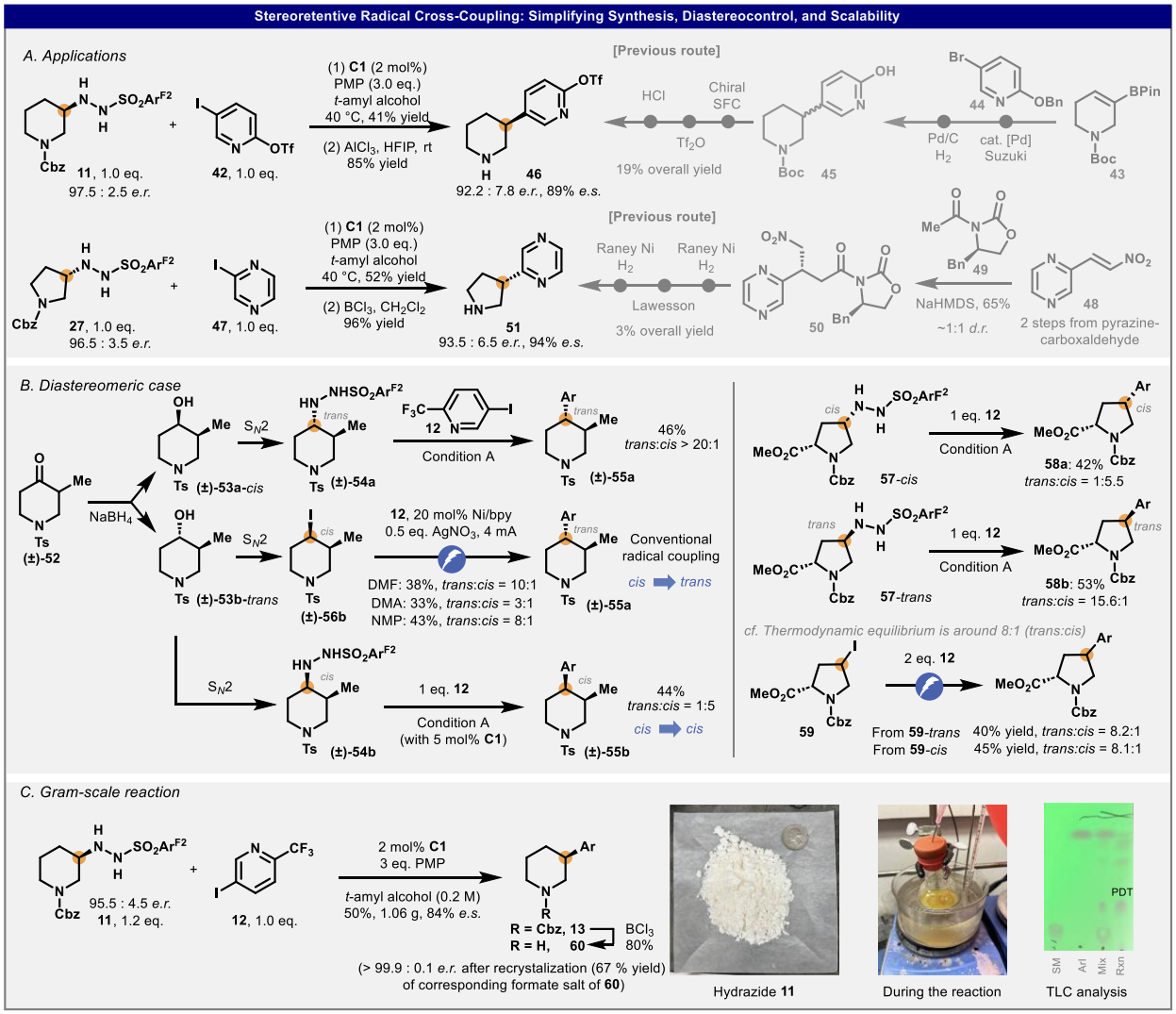

Figure 2. A. Applications of enantioretentive radical cross-coupling to patented drug intermediates. Two examples starting respectively from chiral piperidine and chiral pyrrolidine showcase the usefulness of the enantiospecific radical coupling, shortening each route of several steps. B. Diastereomeric studies demonstrates the different reaction outcomes between sulfonylhydrazides and canonical electrochemical coupling using iodide. C. Gram-scale reaction was performed to yield 1.06 g of product **13** which could be recrystallized up to 99.9 : 0.1 *e.r.* (recrystallization of the corresponding formate salt after Cbz-deprotection). Tf, trifluoromethanesulfonyl.

As an example of the unique retrosynthetic disconnections that enantiospecific Ni-catalyzed radical cross-coupling can enable (Figure 2), chiral piperidine **46** was targeted. This molecule was previously prepared using a standard strategy relying on polar-bond analysis, commencing from vinyl-BPin piperidine **43**, Suzuki coupling with 1.5 equiv. of Bn-protected pyridine **44**, Pd-catalyzed hydrogenation/deprotection, chiral SFC, triflation, and deprotection (19% overall

yield).[39] In stark contrast, iodopyridine **42** containing a sensitive triflate at C–2 could be directly coupled to sulfonylhydrazide **11** to deliver the same target after Cbz removal in 35% overall yield from **11** or 21% from the corresponding commercial alcohol and 92.2 : 7.8 *e.r.*. Another example that showcases the simplifying power of this transformation is the preparation of chiral pyrrolidine **51** ($1620/g in racemic form). The prior six-step route (3% overall yield) relies on a chiral auxiliary based conjugate addition onto vinyl-nitro containing pyrazine **48** which proceeds in 1:1 *d.r.* followed by separation of the diastereomers and multiple redox fluctuations to deliver enantiopure **51.**[40] In contrast, sulfonylhydrazide **27** can be directly coupled to iodopyrazine **47** in 52% isolated yield from **27** or 19% from the corresponding commercial alcohol, followed by Cbz deprotection to afford **51** with 93.5 : 6.5 *e.r.*.

The stereoretentive nature of this process was next explored in the context of achieving diastereocontrol. It is well precedented in the literature that radical cross-coupling resets the stereochemistry of the reaction center with the resulting stereochemical outcome being dictated by preexisting stereocenters. Towards this end, racemic piperidone **52** was reduced ($NaBH_4$) to afford alcohol **53** in a 3:1 *trans/cis*-mixture. The *cis*-isomer **53a** was converted to the corresponding *trans*-sulfonylhydrazide **54a** and after coupling with **12** afforded the *trans*-configured piperidine **55a** with 20:1 selectivity. Not surprisingly, the *cis*-configured iodide **56b**, prepared from *trans*-alcohol **53b**, delivered trans-**55a** as the major product under conventional electrocatalytic radical cross-coupling conditions in three different solvents.[41] In contrast, the *trans*-alcohol **53b** could be converted into *cis*-sulfonylhydrazide **54b** which retained the *cis*-configuration thereby affording *cis*-**55b** as the major product (5:1 *d.r.*, easily separated by silica gel chromatography). Similarly, 3-hydroxy proline-derived *cis*- and *trans*-sulfonylhydrazides **57**, respectively, could be coupled in a stereoretentive fashion with **12** to afford a high-degree of stereoretention in adducts **58-***cis* (1:5.5, *trans:cis*) and **58-** *trans* (15.6:1, *trans:cis*). Not surprisingly, "classic" electrocatalytic radical cross coupling conditions with **12** using either *cis* or *trans* iodide **59** furnished *trans* adduct **58** as the major product (8.1-8.2:1, *trans:cis*).

Finally, the robustness of the reaction was tested on a gram scale with the preparation of piperidine **13** from sulfonylhydrazide **11** and aryliodide **12**. Without any modification to the general protocol the reaction proceeded well to deliver adduct **13** in 50% isolated yield and 84% *e.s.*. Since it is well known in process chemistry that enantioenriched materials are easily upgraded via recrystallization, the Cbz group was removed and after a single round of recrystallization (using

the corresponding formate salt and a mixture of acetonitrile/ethyl acetate as solvent) delivered the corresponding deprotected piperidine in > 99.9 : 0.1 *e.r.*.

While a comprehensive mechanistic investigation will be the subject of future work, an initial mechanistic hypothesis for the sterorentive cross-coupling reaction was studied by dispersion corrected denisty functional theory (DFT) quantum chemical calculations performed in the ORCA 6 software package[42] (full details in the Supplemental Materials) using sulfonylhydrazide **11** as the model substrate (Figure 3). Building upon our previous disclosure,[32] catalysis is believed to be initated by the association of the precatalyst (**C1**) with diazene **61** (itself formed upon interaction of **11** with PMP base,[43] Figure 3A). Exergonic release of dinitrogen from **62** affords alkyl radical **63** and low-valent Ni(I)-complex **64** through a modest barrier. The latter undergoes oxidative addition with (hetero)aryl iodide **12** followed by comproportionation with **65** and a second equivalent of **64** to return **C1** and low-spin, square-planar Ni(II) complex **66**. Note that while the reaction commences with the nitrate-bound precatalyst, the iodo-bound complex necessarily accumulates with successive turnovers of **12**; computed free energies for both are shown in Figure 3A.

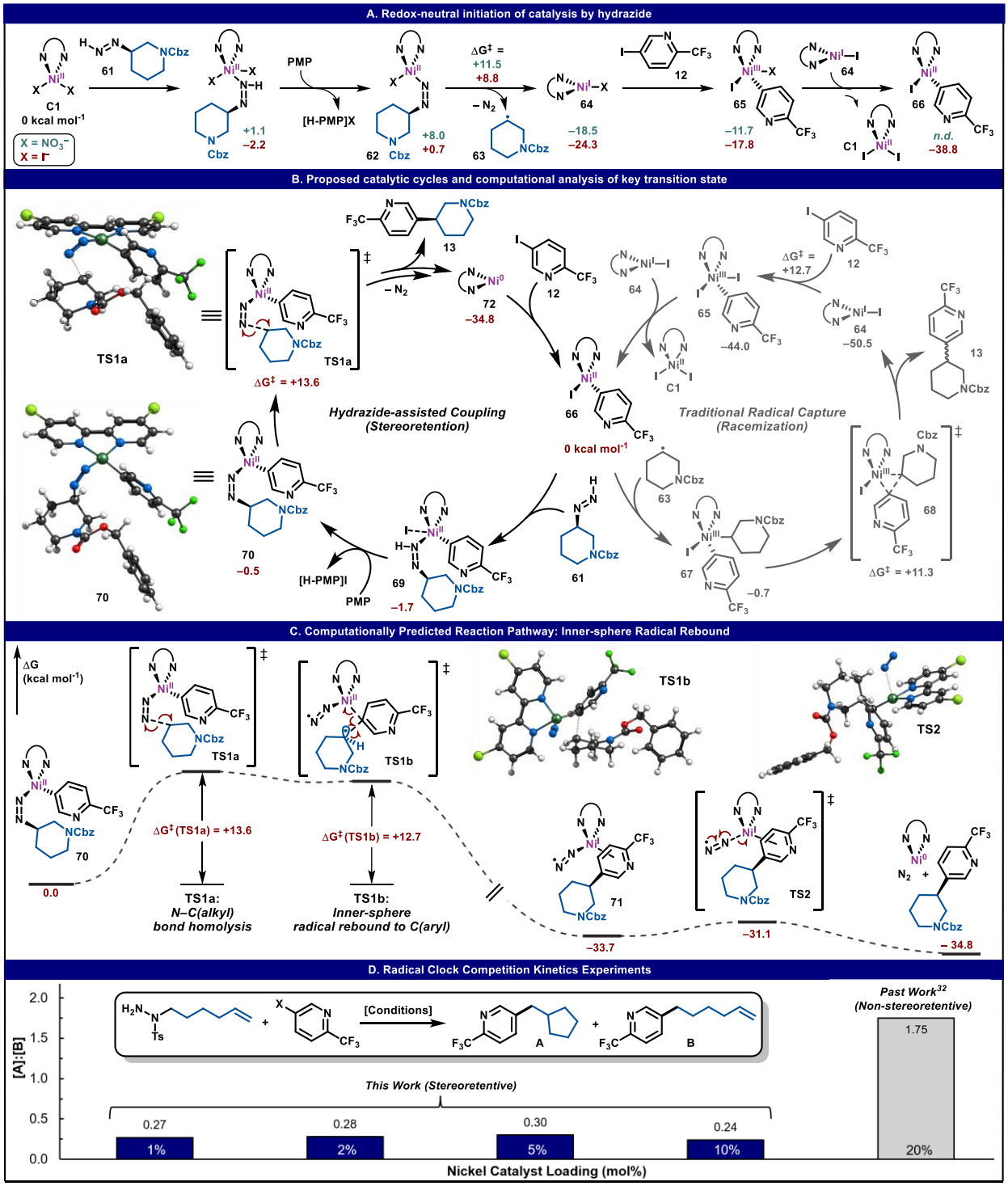

Figure 3. Proposed reaction pathways and associated mechanistic analysis. (A) Redox-neutral initiation proceeds with modest barrier and large driving force to give Ni(II) complex **66**. Free energies for the nitrate- and the iodo-bound complexes are shown in teal and maroon, respectively. (B) Proposed catalytic cycles, including sulfonylhydrazide-assisted stereoretentive pathway (left) and traditional free radical route (right) to give racemic product. Optimized structures of **70** and **TS1a** are shown. (C) Close examination of

https://doi.org/10.26434/chemrxiv-2025-h9snj **ORCID:** https://orcid.org/0000-0001-9193-9053

the inner-sphere radical rebound pathway to give enantiopure product. Optimized structures of **TS1b** and **TS2** are shown. Computations done at (U)TPSSh-D3(BJ) def2-TZVPP(Ni) def2-TZVP CPCM(2-methyl-2-propanol) // (U)B3LYP-D3(BJ) def2-TZVPP(Ni) def2-TZVP CPCM(2-methyl-2-propanol) level of theory. See Supplementary Information for more details. Computed free energies are given in kcal mol^{-1}; energies are for one turnover. (D) Results from competition kinetics radical clock experiments. Non-stereoretentive conditions:[32] 1.5 eq. sulfonylhydrazide, 1.0 eq. (hetero)aryl bromide, 3.0 eq. Et_3N, 20 mol% Ni(DME)Cl_2, 20 mol% dtbbpy, DMF (0.2 M), 70 °C. Stereoretentive conditions: 1.0 eq. sulfonylhydrazide, 1.0 eq. (hetero)aryl iodide, 3.0 eq. PMP base, 1–10 mol% **C1** precatalyst, *tert*-amyl alcohol (0.2 M), 40 °C.

Complex **66** is poised to enter either the traditional (leading to racemization) or sulfonylhydrazide-assisted, stereoretentive route for cross-coupling (Figure 3B). The former is well-known in the literature[44] and proceeds by capture of free radical **63** to give high-valent Ni(III) complex **67**. Free-radical capture by Ni(II)–bipyridine complexes has been experimentally determined to proceed with bimolecular rate constant of $k = 10^7$ M^{-1} s^{-1} ($\Delta G^{‡} \sim 8$ kcal mol^{-1}),[45] much slower than intramolecular free-radical racemization (ps timescale).[10] Thus, the subsequent reductive elimination gives exclusively the racemic product **13** via transition state **68** (calculated barrier height of $\Delta G^{‡} \sim 11.3$ kcal mol^{-1}, in good agreement with previously reported values).[46] The cycle is closed by oxidative addition of **12** to **64** followed by comproportionation, as above. On the other hand, entry into the stereoretentive cycle does not require free radical capture. Initial DFT calculations find that association of diazene **61** to form **69** is downhill ($\Delta G = –1.7$ kcal mol^{-1}). Introduction of PMP base gives Ni(II) intermediate **70** ($\Delta G = –0.5$ kcal mol^{-1}) with aryl and *Z*-coordinated diazene ligands. This step is likely driven by the precipitation of the [H-PMP]I salt (see Supplementary Information Section Gram-Scale synthesis). Homolytic cleavage of the nitrogen–carbon bond is possible through transition state **TS1a** ($\Delta G^{‡} = 13.6$ kcal mol^{-1}) from which several discrete pathways were found, including *i*) simple radical recombination to return **70**, *ii*) radical cage escape to form free radical **63**, and *iii*) radical rebound to the C(aryl) atom form **TS1b** ($\Delta G^{‡} = 13.6$ kcal mol^{-1}, Figure 3C). The latter of these is a *pseudo*-concerted, barrierless inner-sphere process; no stable minima between **TS1a** and **TS1b** could be found. Notably, the optimized geometry of **70** features the chiral C–H bond seated beneath the Ni atom (Ni–H distance ~ 2.47Å, Figure S7), possibly encouraging the alkyl fragment to remain in the inner-sphere via an agostic-type interaction.[47] Transition state **TS1b** is subsequently converted to formal Ni(I) complex **71** upon formation of the new $C(sp^2)$–$C(sp^3)$ bond, a strongly thermodynamically driving process ($\Delta G = –33.7$ kcal mol^{-1}). Dinitrogen release through **TS2** gives the enantiopure product **13** and Ni(0)

complex **72**, and the stereoretentive cycle is closed by oxidative addition of **12** to **72**, returning complex **66**. Because of the rapid nature of this radical rebound and the proximity of the active atoms, the stereochemistry is retained. As described in the Supplemental Materials, additional pathways were also considered but found to be unlikely (e.g., the possibility for a sulfonylhydrazide-assisted Ni(I)/Ni(III) cycle).

The identity of inner-sphere radical capture transition states **TS1a** and **TS1b** are supported by experimental observations. Yields and *e.r.* are increased when employing electron-withdrawing substituents on the heteroaryl coupling partner (Table S34). This observation can be rationalized by the substituents removing electron density from the critical Ni-bound carbon, thereby aiding the inner-sphere radical capture. Furthermore, radical clock competition kinetics experiments were performed using a 5-hexenyl sulfonylhydrazide (Figure 3D) as precursor to a 5-hexenyl primary radical. It was hypothesized that a free radical pathway (such as that proposed in our previous report for entry into a racemic Ni(I)/Ni(III) cycle)[32] would preferentially encounter the cyclized radical after irreversible 5-exo-trig ring closure when compared to the present reaction conditions; an inner-sphere radical rebound pathway that is fast enough for stereoretention will also kinetically out-compete 5-exo-trig cyclization.[48] From the product ratio it could be determined if there was a switch in mechanism between non-stereoretentive[32] and stereoretentive conditions (current study). Additionally, the ratio of cyclized product **A** to linear product **B** should demonstrate no dependence on Ni catalyst loading for an inner-sphere radical rebound mechanism,[49] whereas free radical capture processes are known to show a directly proportional relationship between **A**:**B** and catalyst loading.[45,18] From these experiments, a ratio of **A**:**B** = 1.75:1 under the non-stereoretentive conditions[32] was found, a result which strongly contrasted with the ratio of **A**:**B** = 0.28:1 under the stereoretentive conditions (Figure 3D). The clear switch to prefer the linear product under the present conditions supports a fast, unimolecular radical production and rebound mechanism. Furthermore, the competition kinetics experiments were repeated at varying Ni loadings. No dependence on the ratio of **A**:**B** and catalyst loading was found, again indicative of a caged, inner-sphere radical rebound mechanism (Figure 3D).[49] Altogether, these mechanistic analyses find that stereoretention is possible through an inner-sphere radical cross-coupling mechanism which circumvents the thermodynamic challenges typically assocated with $C(sp^2)$–$C(sp^3)$ bond formation from Ni(II).[50]

Conclusion:

Stereoretentive, transition metal-catalyzed radical cross-coupling has historically been regarded as a near-impossible transformation based on first principles. A simple solution is now disclosed using easily accessible enantioenriched sulfonylhydrazides as radical donors and an inexpensive, achiral Ni-catalyst. The realization of this longstanding challenge can be singularly attributed to the use of sulfonylhydrazide radical precursors for two reasons: (1) catalysis and reaction setup are simplified by removing exogenous redox-cycles and (2) a tethered diazene-Ni intermediate is presumably formed, as supported by calculations; loss of N_2 drives C–C bond formation. A myriad of future directions, avenues for additional improvement, and applications in organic synthesis based on these findings can be envisioned.

REFERENCES

1. Gomberg, M., An instance of trivalent carbon: Triphenylmethyl. *J. Am. Chem. Soc.* **1900**, *22*, 757-771.
2. Morrell, D. G.; Kochi, J. K., Mechanistic studies of nickel catalysis in the cross coupling of aryl halides with alkylmetals. Role of arylalkylnickel (II) species as intermediates. *J. Am. Chem. Soc.* **1975**, *97*, 7262-7270.
3. Smith, J. M.; Harwood, S. J.; Baran, P. S., Radical Retrosynthesis. *Acc. Chem. Res.* **2018**, *51*, 1807-1817.
4. Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S., Radicals: Reactive Intermediates with Translational Potential. *J. am. Chem. Soc.* **2016**, *138*, 12692-12714.
5. Palkowitz, M. D.; Emmanuel, M. A.; Oderinde, M. S., A Paradigm Shift in Catalysis: Electro- and Photomediated Nickel-Catalyzed Cross-Coupling Reactions. *Acc. Chem. Res.* **2023**, *56*, 2851-2865.
6. Laudadio, G.; Palkowitz, M. D.; El-Hayek Ewing, T.; Baran, P. S., Decarboxylative Cross-Coupling: A Radical Tool in Medicinal Chemistry. *ACS Med. Chem. Lett.* **2022**, *13*, 1413-1420.
7. Harwood, S. J.; Palkowitz, M. D.; Gannett, C. N.; Perez, P.; Yao, Z.; Sun, L.; Abruña, H. D.; Anderson, S. L.; Baran, P. S., Modular terpene synthesis enabled by mild electrochemical couplings. *Science* **2022**, *375*, 745-752.
8. Zhang, B.; He, J.; Gao, Y.; Levy, L.; Oderinde, M. S.; Palkowitz, M. D.; Dhar, T. G. M.; Mandler, M. D.; Collins, M. R.; Schmitt, D. C.; Bolduc, P. N.; Chen, T.; Clementson, S.; Petersen, N. N.; Laudadio, G.; Bi, C.; Kawamata, Y.; Baran, P. S., Complex molecule synthesis by electrocatalytic decarboxylative cross-coupling. *Nature* **2023**, *623*, 745-751.

9. Zhang, B.; Gao, Y.; Hioki, Y.; Oderinde, M. S.; Qiao, J. X.; Rodriguez, K. X.; Zhang, H.-J.; Kawamata, Y.; Baran, P. S., Ni-electrocatalytic Csp3–Csp3 doubly decarboxylative coupling. *Nature* **2022**, *606*, 313-318.
10. Johnston, L. J.; Ingold, K. U., Kinetics of cyclopropyl radical reactions. 2. Studies on the inversion of cyclopropyl and 1-methylcyclopropyl radicals and on the kinetics of some addition and abstraction reactions of 1-methylcyclopropyl and 1-methoxycyclopropyl radicals. *J. Am. Chem. Soc.* **1986**, *108*, 2343-2348.
11. Fu, G. C., Transition-Metal Catalysis of Nucleophilic Substitution Reactions: A Radical Alternative to SN1 and SN2 Processes. *ACS Cent. Sci.* **2017**, *3*, 692-700.
12. Yang, Y.-H.; Sibi, M. P., Stereoselective Radical Reactions. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*, 2012.
13. Bar, G.; Parsons, A. F., Stereoselective radical reactions. *Chem. Soc. Rev.* **2003**, *32*, 251-263.
14. Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D., Conformational Memory in Enantioselective Radical Reductions and a New Radical Clock Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 9386-9390.
15. Resendiz, M. J. E.; Family, F.; Fuller, K.; Campos, L. M.; Khan, S. I.; Lebedeva, N. V.; Forbes, M. D. E.; Garcia-Garibay, M. A., Radical Reactions with Double Memory of Chirality (2MOC) for the Enantiospecific Synthesis of Adjacent Stereogenic Quaternary Centers in Solution: Cleavage and Bonding Faster than Radical Rotation. *J. am. Chem. Soc.* **2009**, *131*, 8425-8433.
16. Gloor, C. S.; Dénès, F.; Renaud, P., Memory of chirality in reactions involving monoradicals. *Free Radical Research* **2016**, *50*, S102-S111.
17. Curran, D. P.; Porter, N. A.; Giese, B., *Stereochemistry of radical reactions: concepts, guidelines, and synthetic applications*. John Wiley & Sons: 2008.
18. Biswas, S.; Weix, D. J., Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 16192-16197.
19. Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S., Redox-Active Esters in Fe-Catalyzed C–C Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 11132-11135.
20. Chen, T. G.; Barton, L. M.; Lin, Y.; Tsien, J.; Kossler, D.; Bastida, I.; Asai, S.; Bi, C.; Chen, J. S.; Shan, M.; Fang, H.; Fang, F. G.; Choi, H.-w.; Hawkins, L.; Qin, T.; Baran, P. S., Building C(sp3)-rich complexity by combining cycloaddition and C–C cross-coupling reactions. *Nature* **2018**, *560*, 350-354.
21. Mondal, S.; Dumur, F.; Gigmes, D.; Sibi, M. P.; Bertrand, M. P.; Nechab, M., Enantioselective Radical Reactions Using Chiral Catalysts. *Chem. Rev.* **2022**, *122*, 5842-5976.
22. Yus, M.; Nájera, C.; Foubelo, F.; Sansano, J. M., Metal-Catalyzed Enantioconvergent Transformations. *Chem. Rev.* **2023**, *123*, 11817-11893.
23. Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D., Skeletal editing through direct nitrogen deletion of secondary amines. *Nature* **2021**, *593*, 223-227.
24. Chi, Y.; Tang, W.; Zhang, X., Rhodium-Catalyzed Asymmetric Hydrogenation. In *Modern Rhodium‐Catalyzed Organic Reactions*, 2005; 1-31.
25. Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G., Asymmetric Hydrogenation Using Monodentate Phosphoramidite Ligands. *Acc. Chem. Res.* **2007**, *40*, 1267-1277.
26. Roseblade, S. J.; Pfaltz, A., Iridium-Catalyzed Asymmetric Hydrogenation of Olefins. *Acc. Chem. Res.* **2007**, *40*, 1402-1411.

27. Noyori, R.; Kitamura, M.; Ohkuma, T., Toward efficient asymmetric hydrogenation: Architectural and functional engineering of chiral molecular catalysts. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5356-5362.
28. Knowles, W. S.; Noyori, R., Pioneering Perspectives on Asymmetric Hydrogenation. *Acc. Chem. Res.* **2007**, *40*, 1238-1239.
29. Gong, Y.; Hu, J.; Qiu, C.; Gong, H., Insights into Recent Nickel-Catalyzed Reductive and Redox C–C Coupling of Electrophiles, C(sp3)–H Bonds and Alkenes. *Acc. Chem. Res.* **2024**, *57*, 1149-1162.
30. Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C., Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis. *Chem. Rev.* **2022**, *122*, 1485-1542.
31. Payamifar, S.; Behrouzi, L.; Poursattar Marjani, A., The electrochemical coupling reactions of organic halides compound in a valuable and practical manner for CC and C–heteroatom formation: An overview. *Arab. J. Chem.* **2024**, *17*, 105822.
32. Sun, J.; Péter, Á.; He, J.; Tsien, J.; Zhang, H.; Cagan, D. A.; Vokits, B. P.; Peters, D. S.; Oderinde, M. S.; Mandler, M. D.; Richardson, P.; Chen, D.; Palkowitz, M. D.; Raheja, N.; Kawamata, Y.; Baran, P. S., Sulfonyl hydrazides as a general redox-neutral platform for radical cross-coupling. *Science*, **2025**, eadu6406.
33. Schultz, P. G.; Dervan, P. B., Photochemistry of 1,1-diazenes. Direct and sensitized photolyses of N-(2,2,5,5-tetramethylpyrrolidyl)nitrene, dl-N-(2,5-diethyl-2,5-dimethylpyrrolidyl)nitrene, and N-(2,2,6,6-tetramethylpiperidyl)nitrene. *J. Am. Chem. Soc.* **1982**, *104*, 6660-6668.
34. Movassaghi, M.; Ahmad, O. K.; Lathrop, S. P., Directed Heterodimerization: Stereocontrolled Assembly via Solvent-Caged Unsymmetrical Diazene Fragmentation. *J. Am. Chem. Soc.* **2011**, *133*, 13002-13005.
35. Horning, B.; Roy, N.; Patricelli, M.; Lam, B.; Kikuchi, S.; Cook Brian, N. Compounds Selective For JAK1 and Methods of Use. WO 2022/251280 A1, 2022.
36. Nagaraj Harish Kumar, M.; Bandodkar Balachandra, S.; Yellapu, S.; Sugandham Srinivas, R. A. O.; M, G.; Mukherjee, K.; Thimmappa Kiran, H.; Hanumesh Parimala, B. Piperidine Ureas as Cathepsin Cysteine Protease Inhibitors. WO 2016/027284 A3, 2016.
37. Buesking, A.; Combs, A.; Zhou, J.; Holmes, R.; Pawley, S.; Wu, X. CDK Inhibitors and Their Use as Pharmaceuticals. WO 2022/061273 A1, 2022.
38. Liu, P.; Miller Craig, A.; Yu, M.; Zhang, Z. Heteroaryl Carboxamide Compounds as Inhibitors of RIPK2. US 2018/0072717 A1, 2018.
39. Brooijmans, N.; Brubaker Jason, D.; Fleming Paul, E.; Hodous Brian, L.; Kim Joseph, L.; Waetzig, J.; Williams, B.; Wilson, D.; Wilson Kevin, J.; Cronin, M. Inhibitors of Activin Receptor-Like Kinase. WO 2017/181117 A1, 2017.
40. Whitten Jeffrey, P., Schwaebe, Michael, Regan, Collin Chiral pyrrolidine derivatives, and methods for preparing compounds thereof. US 2006/0025468 A1, 2006.
41. Palkowitz, M. D.; Laudadio, G.; Kolb, S.; Choi, J.; Oderinde, M. S.; Ewing, T. E.-H.; Bolduc, P. N.; Chen, T.; Zhang, H.; Cheng, P. T. W.; Zhang, B.; Mandler, M. D.; Blasczak, V. D.; Richter, J. M.; Collins, M. R.; Schioldager, R. L.; Bravo, M.; Dhar, T. G. M.; Vokits, B.; Zhu, Y.; Echeverria, P.-G.; Poss, M. A.; Shaw, S. A.; Clementson, S.; Petersen, N. N.; Mykhailiuk, P. K.; Baran, P. S., Overcoming Limitations in Decarboxylative Arylation via Ag–Ni Electrocatalysis. *J. Am. Chem. Soc* **2022**, *144*, 17709-17720.

42. Neese, F., Software update: The ORCA program system—Version 5.0. *WIREs Comput. Mol. Sci.* **2022**, *12*, e1606.
43. Myers, A. G.; Movassaghi, M.; Zheng, B., Mechanistic studies of the free-radical fragmentation of monoalkyl diazenes. *Tetrahedron Letters* **1997**, *38*, 6569-6572.
44. Cagan, D. A.; Bím, D.; Kazmierczak, N. P.; Hadt, R. G., Mechanisms of Photoredox Catalysis Featuring Nickel–Bipyridine Complexes. *ACS Catal.* **2024**, *14*, 9055-9076.
45. Lin, Q.; Spielvogel, E. H.; Diao, T., Carbon-centered radical capture at nickel(II) complexes: Spectroscopic evidence, rates, and selectivity. *Chem* **2023**, *9*, 1295-1308.
46. Yuan, M.; Song, Z.; Badir, S. O.; Molander, G. A.; Gutierrez, O., On the Nature of C(sp3)–C(sp2) Bond Formation in Nickel-Catalyzed Tertiary Radical Cross-Couplings: A Case Study of Ni/Photoredox Catalytic Cross-Coupling of Alkyl Radicals and Aryl Halides. *J. Am. Chem. Soc.* **2020**, *142*, 7225-7234.
47. Brookhart, M.; Green, M. L. H.; Parkin, G., Agostic interactions in transition metal compounds. *PNAS* **2007**, *104*, 6908-6914.
48. Newcomb, M., Radical Kinetics and Clocks. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*, John Wiley & Sons, Ltd, 2012.
49. Shevick, S. L.; Obradors, C.; Shenvi, R. A., Mechanistic Interrogation of Co/Ni-Dual Catalyzed Hydroarylation. *J. Am. Chem. Soc.* **2018**, *140*, 12056-12068.
50. Tasker, S. Z.; Standley, E. A.; Jamison, T. F., Recent advances in homogeneous nickel catalysis. *Nature* **2014**, *509*, 299-309.

Acknowledgements

This project is financially supported by NIH (GM-118176, P.S.B) and the Gates Foundation (INV-056603, P.S.B. and Y.K.), L. M. thanks the Swedish Research Council (Vetenskapsrådet, VR-2023-00499) for postdoctoral fellowship. F. C. A. acknowledges ARC Centre of Excellence for Innovation in Peptide and Protein Science for Capacity Building Grant CBG117. We also thank D.-H. Huang and L. Pasternack (Scripps Research) for NMR spectroscopic assistance; Gembicky, Milan (UCSD) for X-ray analysis; Brandon Orzolek, Brittany Sanchez, Quynh Nguyen Wong (Scripps Automated Synthesis Facility). We thank Dr. Baiyang Jiang, Dr. Matteo Costantini and Dr. Áron Péter for helpful discussions. The computations presented here were conducted in the Garibaldi High Performance Computing (HPC) cluster, a facility supported by Scripps Research, La Jolla.

Corresponding Author

*pbaran@scripps.edu

Author contributions

Conceptualization: JS, JH, LM, YK, PSB

Experimental investigation: JS, JH, LM, DAC, JT, YW, FCA, JES, JSL

Data analysis: JS, JH, LM, DAC, JT, YW, JES, JSL, YK, PSB

Manuscript writing: JS, JH, LM, DAC, JT, YK, PSB

Funding acquisition: YK, PSB

Project administration: PSB

Competing interest

The authors declare no competing financial interest.

Data Availability

All the data are available within the main text or Supplementary Information. Experimental and characterization data for all new compounds prepared during this study are provided in Supplementary Information. The X-ray crystallographic coordinate for Ni(4-Cl-bpy)$(NO_3)_2 \cdot 2H_2O$ and compound **13**-Ts has been deposited at the Cambridge Crystallographic Data Centre (CCDC)

with accession codes 2425076 and 2411035, respectively. Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.