Redox Inversion: A Radical Analog of Umpolung Reactivity for Base and Metal-Free Catalytic C(sp^3)–C(sp^3) Coupling

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Cross-coupling, radical chemistry, photoredox catalysis

ABSTRACT: The construction of alkyl–alkyl bonds is a powerful tool in organic synthesis. Redox inversion–defined as the radical analog of polarity inversion–is used as a strategy for C(sp^3)–C(sp^3) coupling. Herein is reported a base and metal-free photocatalytic coupling of carboxylic acids to form biologically relevant bibenzyls through a radical-radical coupling. Mechanistic insight is gained through control reactions that implicate this new redox inversion strategy. In this work, the previously unexplored redox-opposite relationship between a carboxylic acid and its *in situ* activated redox active ester is implemented in catalysis.

The construction of C(sp^3)–C(sp^3) bonds is a critical challenge in organic synthesis.[1–3] Beyond the retrosynthetic disconnections enabled by this transformation, its value lies in the profound impact on a molecule's biological activity.[4,5] Although metal-catalyzed alkyl–alkyl cross-coupling has dominated this field, challenges still remain in the use of bench stable coupling partners that do not generate stoichiometric metal (Sn, Mg, Zn, B, etc.) and halide waste. [1–3] Baran, MacMillan, and others have popularized transition-metal catalyzed C(sp^3)–C(sp^3) coupling reactions using carboxylic acid derivatives paired with a traditional coupling partner such as alkyl Zn reagents and alkyl halides **(Figure 1a)**.[6–19] In their work, carboxylic acids are commonly used as alkyl radical precursors via oxidative decarboxylation (acting as a single electron donor), and redox active N-hydroxyphthalimide (NHPI) esters typically utilized as alkyl precursors via reductive decarboxylation (acting as a single electron acceptor).[6,20–24] However, to the best of our knowledge, the contrasting redox characteristics of these carboxylic acid-derived substrates have not been exploited in conjunction for radical-radical coupling to form C(sp^3)–C(sp^3) bonds.

To explore this redox-opposite relationship between the two carboxylic acid-derivatives for radical-radical coupling, we were inspired by the use of polarity inversion (also known as umpolung) in benzoin condensation, one of the oldest known C–C bond forming reactions in organic chemistry (**Figure 1b**).[25–28] In this transformation, one equivalent of benzaldehyde, an electrophile, is converted to a nucleophile via an *in situ* functionalization, inverting its polarity. Subsequently, another equivalent of the electrophilic aldehyde reacts with the newly formed nucleophile to form benzoin.

Herein we report redox inversion–defined as switching the redox profile of a functional group–as the radical analog of polarity inversion to form C(sp^3)–C(sp^3) bonds (**Figure 1c**). We hypothesized that through *in situ* activation, we could obtain a mixture of carboxylic acids and their redox-active ester derivatives in one-pot, which could allow for alkyl–alkyl coupling via a net redox-neutral single electron transfer. In this reaction design, the starting material acts as both the oxidant and the reductant, analogous to the role of benzaldehyde as both the nucleophile and the electrophile in benzoin condensation.

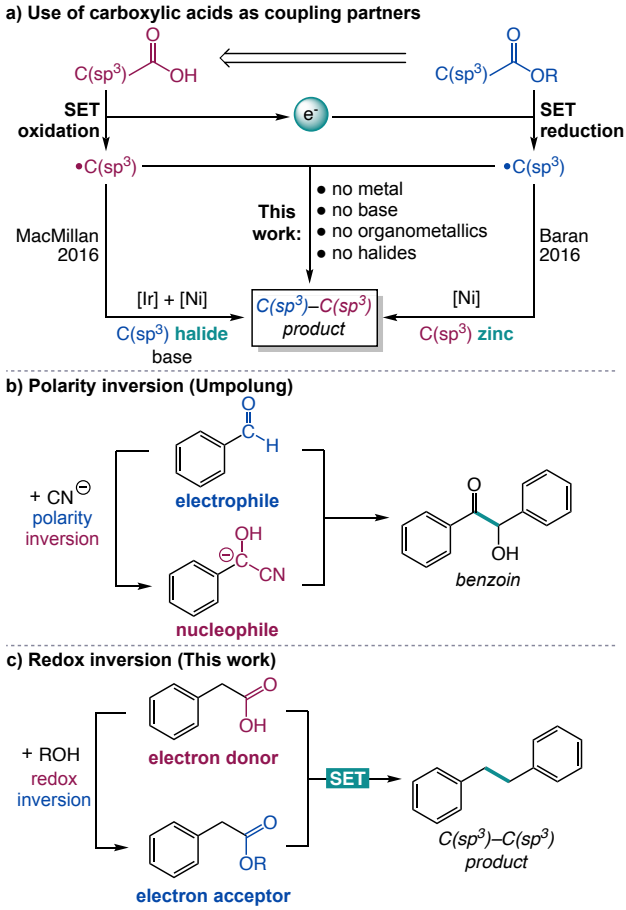


Figure 1. a) Previous examples of radical generation for C(sp^3)–C(sp^3) coupling. b) Benzoin condensation as a representative polarity inversion reaction. c) C(sp^3)–C(sp^3) coupling as a representative redox-inversion reaction.

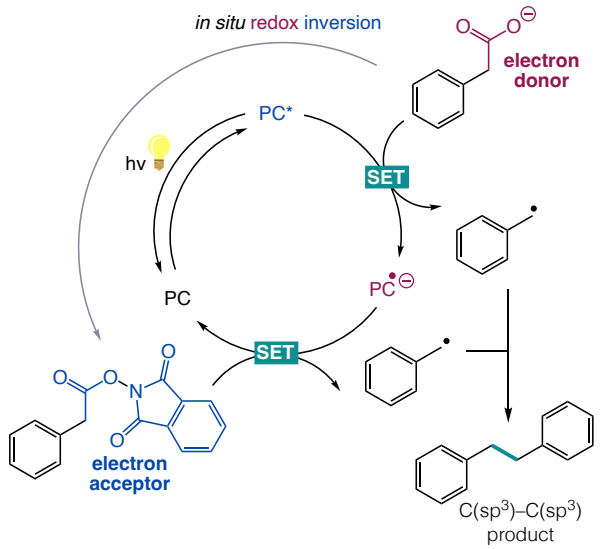
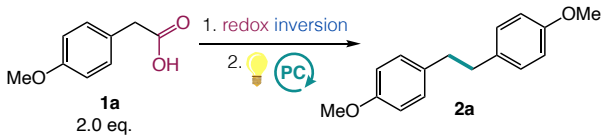


Figure 2. Proposed mechanism

To enable this strategy, we envisioned employing two equivalents of carboxylic acid and *in situ* functionalizing only one equivalent with N-hydroxyphthalimide to enable the generation of a single electron donor-acceptor pair (**Figure 2**). Single electron transfer would then be aided by an organic photocatalyst, followed by decarboxylative radical coupling to form C(sp^3)–C(sp^3) products in a metal-free process. To explore this concept,



Entry	PC	Solvent	Time (h)	Cs_2CO_3 (eq.)	Yield (%)[a]
1	**PC1**	MeCN	4	1.5	6
2	**PC2**	MeCN	4	1.5	66
3	**PC3**	MeCN	4	1.5	73
4	**PC3**	MeCN	4	1.0	63
5	**PC3**	MeCN	4	2.0	70
6	**PC3**	MeCN	4	-	51
7[b]	**PC3**	MeCN	4	-	12
8	**PC3**	DMSO	4	-	40
9	**PC3**	DMF	4	-	45
10	**PC3**	DCM	4	-	70
11[c]	**PC3**	DCM	16	-	**73**
12[d]	**PC3**	DCM	16	-	<2%
13	-	DCM	16	-	2%

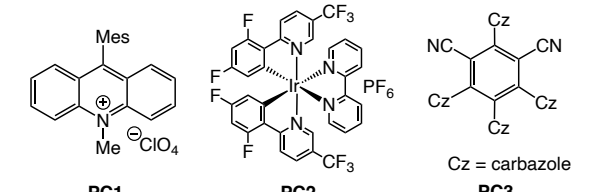


Figure 3. Optimization. Reaction was run in 0.1 mmol scale in 16.7 mM concentration. Reaction conditions: 1. DIC (1.0 eq.), NHPI (1.0 eq.), DMAP (0.1 eq.), DCM (0.5 mL), r.t., 1 h. 2. PC (2.5 mol%), Cs2CO3, Solvent (5.5 mL), 456 nm light. [a]Calculated via GC-FID calibration curve. [b]Functionalization reagents added with photocatalyst in 6 mL MeCN. [c]5.0 mol% PC instead of 2.5 mol%. [d]No light.

we focused on the use of C(sp^3)–C(sp^3) bond formation in the context of bibenzyl synthesis, which are prevalent across pharmaceuticals and natural products.[29–33] We hypothesized that the homocoupling of long-lived, stabilized benzylic radicals, would be an ideal proof-of-concept system for this new approach. To begin, acid **1a** was selected for optimization due to its precedent for undergoing light-induced one-electron decarboxylation (**Figure 3**).[6] Notably, the isolation of the pre-functionalized NHPI ester was not required. Instead, one equivalent of the NHPI ester is generated *in situ* by addition of DIC, N-hydroxyphthalimide, and catalytic DMAP without further workup. First, the identity of the photocatalyst (PC) was explored. Multiple well-established PCs were screened including acridinium salt **PC1** (Entry 1), iridium photocatalyst **PC2** (Entry 2), and cyanoarene 4-CzIPN **PC3** (Entry 3).[34–37] We were pleased to discover that the organic photocatalyst **PC3** provided the highest yield, thus precluding the need for less sustainable metal-based photocatalysts from our reaction conditions. Next, we investigated the amount of base necessary to deprotonate the carboxylic acid. Although 1.5 eq. of Cs_2CO_3 was preferred over 1.0 and 2.0 eq. (Entry 3-5) in standard acetonitrile conditions, excitingly, we discovered that external base could be omitted from the reaction, and still provide moderate yield (Entry 6). We hypothesized that the reaction could be run without external base, due to the basic phthalimide byproduct formed upon the reduction of the NHPI ester. To incorporate this additional layer of cooperativity between the acid and its NHPI ester, multiple solvents were screened in external base-free conditions (Entry 8-10), with DCM proving to be the best for this transformation (70%, Entry 10). Increasing the loading of PC from 2.5% to 5% and increasing the reaction time to 16 hours, gave the final optimized yield of 73%, with no metal catalyst or external base required (Entry 11). Finally, exclusion of the light or photocatalyst (Entries 12-13) from standard conditions formed trace to no yield of **2a**, demonstrating their crucial roles in the single electron transfer between the donor and the acceptor.

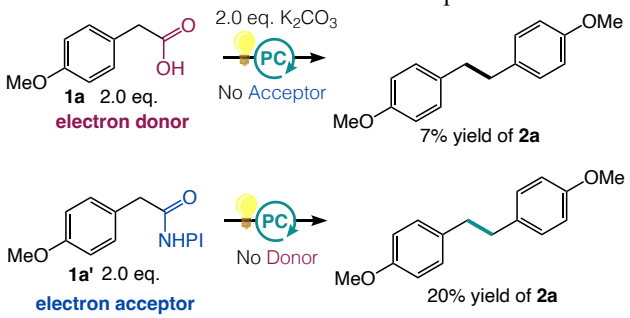


Figure 4. Mechanistic investigations to probe the necessity of both the electron donor and acceptor in the reaction

Next, the occurrence of redox inversion was probed. Control reactions demonstrated that both the electron donor and electron acceptor are necessary for the reaction to proceed (**Figure 4**). When 2.0 eq. of the acid **1a** was irradiated with photocatalyst without redox inversion, only 7% yield of **2a** was generated, likely due to a lack of electron acceptor (an NHPI ester) in the reaction (**Figure 4**). Likewise, when a pre-synthesized and isolated NHPI ester **1a'** was irradiated without an additional electron donor (a carboxylic acid), a diminished yield of 20% was obtained. This latter reaction (**Figure 4**) likely provided more product than the former, as side reactions of NHPI esters reported in the literature often involve hydrolysis of their acid counterparts.[38] This hydrolyzed phenylacetic acid could turn

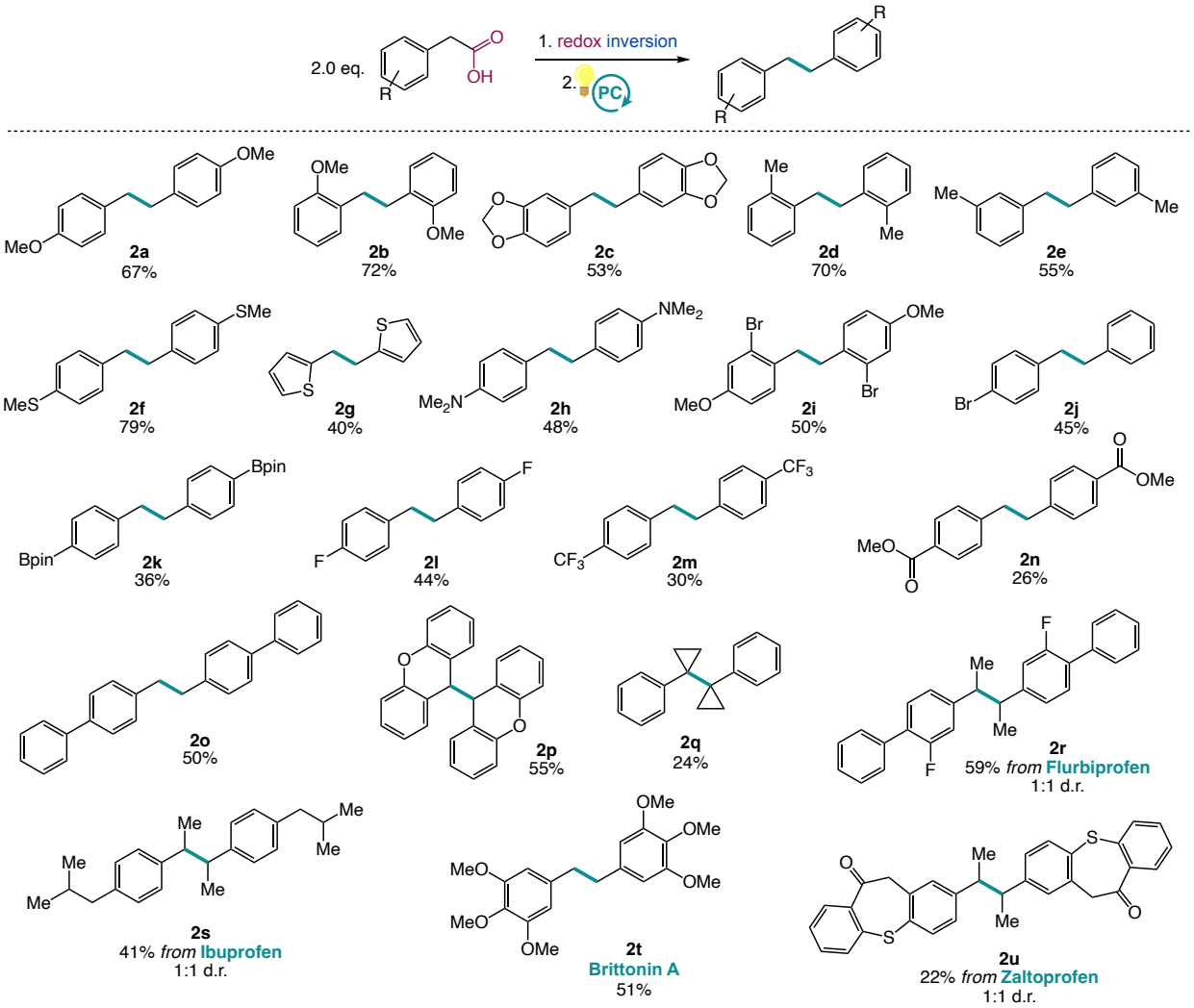


Figure 6. Substrate scope of bibenzyls

over the photocatalytic cycle, further alluding to the role of the acid as a single-electron donor. Regardless, the lower yields provided by the independent control reactions of **1a** and **1a'** emphasize the necessity of both the acid and the NHPI ester as donor-acceptor pairs in the reaction. With these results, as well as literature precedent, a proposed mechanism is depicted in **Figure 2**.[6]

To demonstrate the potential extension of this methodology beyond homocoupling, a reaction using two different carboxylic acids was carried out (**Figure 5**). The cross-coupled product of biphenylacetic acid and fluorophenylacetic acid (**2lo**) was produced in moderate isolated yield. This transformation highlights the potential of redox inversion to

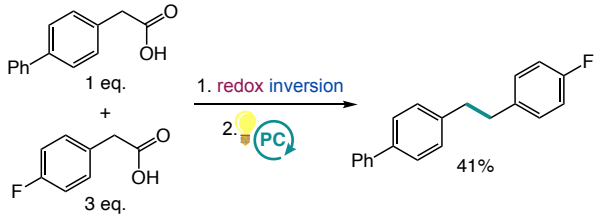


Figure 5. Cross-coupling mediated by redox inversion. See SI for experimental details.

access efficient radical cross-coupling of carboxylic acids. However, to understand the complementarity of functional group tolerance to metal-catalyzed processes, we turned back to homocoupling reactions which are higher yielding and do not require an excess of one carboxylic acid.

With optimized conditions, the scope of this transformation was found to be successful across a variety of carboxylic acids (**Figure 6**). Substrates with electron-rich substituents performed best (**2a-i**), likely due to the stabilizing effect of electron-donating groups on radical intermediates.[39] Additionally, *ortho*-substituted phenylacetic acid derivatives gave high yielding bibenzyl formation (**2b**, **d**) likely due to increased radical persistence in a more hindered environment.[40] A variety of heteroatoms (oxygen, sulfur, and nitrogen) provided good yields of the homocoupled products (**2a-c**, **f-i**), with the electron-donating *para*-thiophenol derivative giving the highest yield of 79% (**2f**). Unlike in traditional metal-mediated transformations, bromine substituents were well-tolerated across substitution patterns (**2i-j**). Similarly, boronic esters, typically non-innocent in coupling reactions, gave clean product formation in moderate yield, with no deprotected boronic acid detected (**2k**). This demonstrates, along with the bromine containing substrates, a versatile and flexible strategy to install sensitive functionality, and a simple approach for efficiently building molecular cores

with potential for further functionalization and diversification. Fluorine-containing substrates reacted smoothly, demonstrating facile access to valuable fluorine-containing motifs (**2l-m**). These results, along with the methyl-ester substituted bibenzyl, also demonstrate the ability to couple electron-deficient radical intermediates (**2n**). Finally, substrates typically challenging or unreactive in radical-radical transformations due to sterics can be employed as well.[13] Excitingly, secondary-secondary (**2p**) and tertiary-tertiary homocoupling (**2q**) can be achieved in moderate yields under these mild photocatalytic conditions (**Figure 6**).

After probing the scope of redox inversion, we wanted to apply the method to more complex, biologically relevant carboxylic acids. First, the secondary radical resulting from decarboxylation of flurbiprofen can be homocoupled in moderate yield (**2r, Figure 6**). Likewise, ibuprofen can undergo clean decarboxylation and radical combination (**2s**). The natural product Brittonin A can be accessed through this homocoupling in good yield as well (**2t**). Finally, Zaltoprofen, another medicinally relevant carboxylic acid, provides the desired product in moderate yield, demonstrating the ability to couple functionally dense carboxylic acids via redox inversion and metal-free photocatalysis (**2u**). Ultimately, the scope of this transformation highlights the versatility of the method, and its potential use as a strategy to rapidly build molecular complexity under mild conditions, using readily available carboxylic acids.

Finally, to further support that a radical-radical coupling was involved in the reaction, the enantiopure anti-inflammatory drug, *(S)*-Naproxen was subjected to the optimized conditions (**Figure 7**). The reaction resulted in racemization of the stereocenter, giving a 1.0 : 1.3 diastereomeric ratio of the homocoupled products.

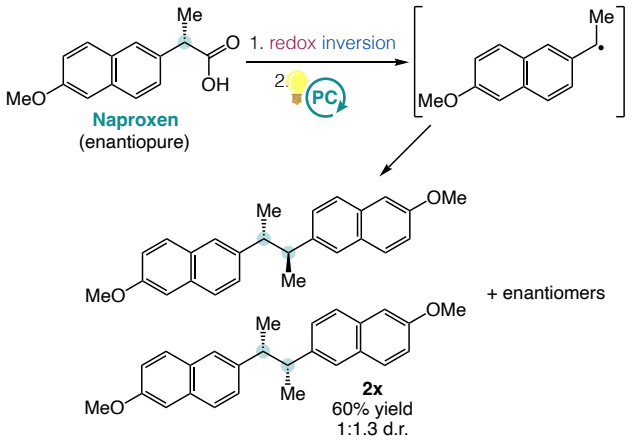


Figure 7. Racemization of stereocenter as a mechanistic investigation

In summary, we have developed redox inversion as a mechanistic strategy to access opposing redox characteristics from a single functional group. Specifically, this strategy was implemented to photocatalytically generate two radicals from readily available carboxylic acids in a redox-neutral process. These radicals can couple to produce biologically relevant bibenzyls at good to moderate yields, with no metal or external base. It was also demonstrated that by utilizing two different acids, unsymmetric bibenzyls can be formed, emphasizing potential for efficient $C(sp^3)$–$C(sp^3)$ cross-coupling. Ultimately, this work serves as an early utilization of the unexplored redox-opposite relationship of carboxylic acids and their redox-active esters for alkyl-alkyl bond formation. Ongoing work will investigate the cross-selectivity of this coupling process and an expansion of this radical-radical coupling to a wider range of substrates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. ‡These authors contributed equally.

Funding Sources

This work was supported in part by NSF Award CHE-1954751 and UMN startup funds.

ACKNOWLEDGMENT

This work was supported in part by NSF Award CHE-1954751 and UMN startup funds.

ABBREVIATIONS

DIC – N,N'-diisopropylcarbodiimide, DMAP – 4-dimethylaminopyridine, NHPI – N-hydroxyphthalimide, SET – single electron transfer, DCM – dichloromethane, DMSO – dimethylsulfoxide, DMF – N,N-dimethylformamide, TCNHPI – tetrachloro N-hydroxyphthalimide

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Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8

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