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

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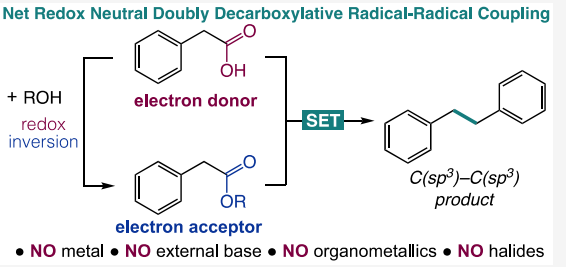
ABSTRACT: The construction of alkyl−alkyl bonds is a powerful tool in organic synthesis. Redox inversion, defined as switching the donor/acceptor profile of a functional group to its acceptor/donor profile, is used for C(sp^3)−C(sp^3) coupling. We report a photocatalytic coupling of carboxylic acids to form bibenzyls through a radical−radical coupling. Mechanistic insight is gained through control reactions. This unexplored redox-opposite relationship between a carboxylic acid and its 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 coupling has dominated this field, challenges remain in the use of bench-stable coupling partners that do not generate stoichiometric metal 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] During the preparation of this Note, more studies have paired carboxylic acids with nontraditional coupling partners.[25,26] However, to the best of our knowledge, the contrasting redox characteristics of these carboxylic acid-derived substrates have not been exploited in conjunction with radical−radical coupling to form C(sp^3)−C(sp^3) bonds.

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).[27−30] In this transformation, 1 equiv of benzaldehyde, an electrophile, is converted to a nucleophile via an *in situ* functionalization, inverting its polarity. Subsequently, another equiv of the electrophilic aldehyde reacts with the newly formed nucleophile to form benzoin. Herein, we report redox inversion, which we define as switching the donor/acceptor profile of a functional group to its acceptor/donor profile, as the radical analogue 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 (SET). 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. An initial version of this work was deposited in *chemRxiv* on August 22, 2022.[31]

To enable this strategy, we envisioned employing 2 equiv of carboxylic acid and *in situ* functionalizing only 1 equiv with NHPI to enable the generation of a single-electron donor−acceptor pair (Figure 2). SET would then be aided by a photocatalyst, followed by decarboxylation to generate alkyl radicals. Two of these radicals can couple to form C(sp^3)−C(sp^3) products in a metal-free process. To explore this concept, 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.[32−36] Other methods for generating bibenzyls through non-redox inversion methods are known.[37−41] We hypothesized that the homocoupling of long-lived, stabilized benzylic radicals would be an ideal proof-of-concept system. First, 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 prefunctionalized NHPI ester was not required. It could be generated *in situ* by addition of *N*,*N*′-

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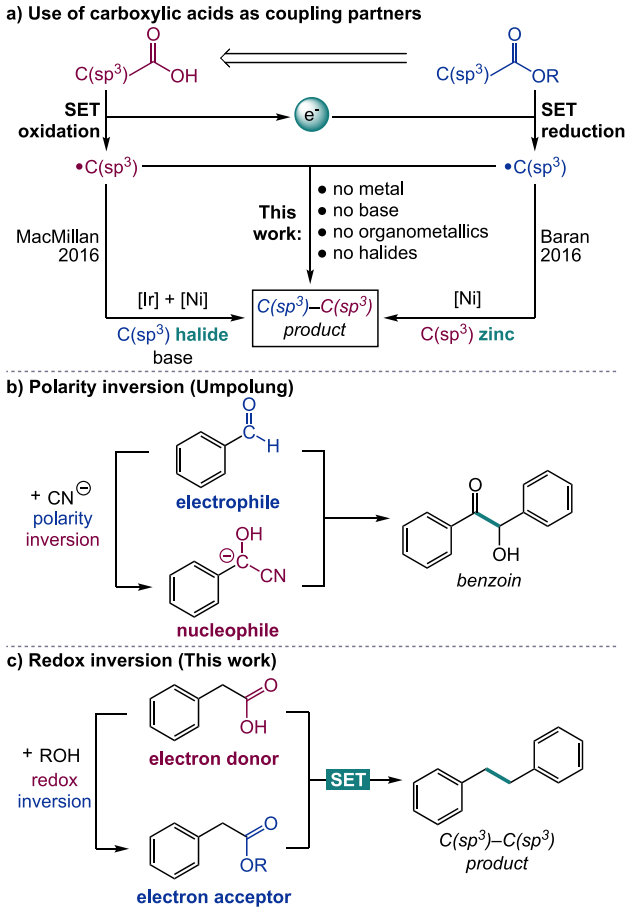


Figure 1. (a) Previous examples of radical generation for $C(sp^3)$–$C(sp^3)$ coupling. (b) Benzoin condensation as a representative polarity inversion reaction. (c) $C(sp^3)$–$C(sp^3)$ coupling as a representative redox inversion reaction.

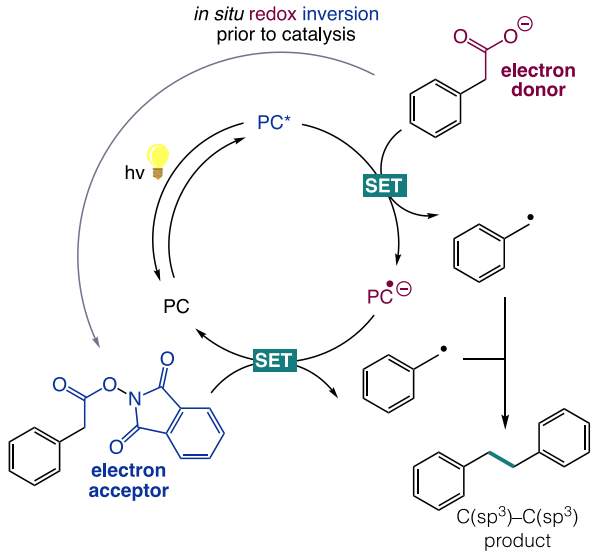
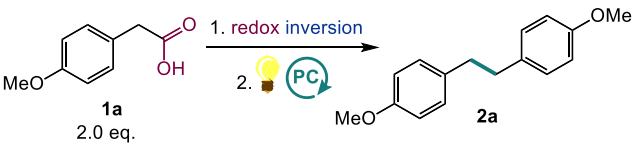


Figure 2. Proposed mechanism.

diisopropylcarbodiimide (DIC), NHPI, and catalytic 4-(dimethylamino)pyridine (DMAP) without further workup. First, the identity of the photocatalyst (PC) was explored. Multiple well-established PCs were screened (entries 1–3).[42−45] We were pleased to discover that the organic



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
14[e]	**PC3**	DCM	16	-	32

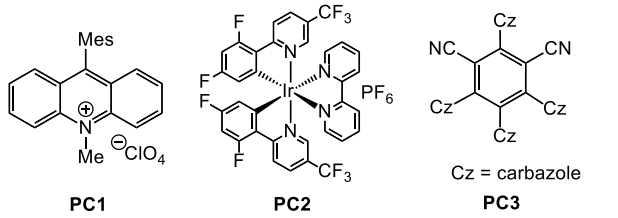


Figure 3. Optimization. The reaction was performed on a 0.1 mmol scale at a concentration of 16.7 mM. Reaction conditions: (1) DIC (1.0 equiv), NHPI (1.0 equiv), DMAP (0.1 equiv), DCM (0.5 mL), rt, 1 h; (2) PC (2.5 mol %), Cs_2CO_3, solvent (5.5 mL), 456 nm light. [a]Calculated via the GC-FID calibration curve. [b]Functionalization reagents added with a photocatalyst in 6 mL of MeCN. [c]With 5.0 mol % PC instead of 2.5 mol %. [d]No light. [e]With 0.25 equiv of $(PhO)_2P(O)OH$ added with a photocatalyst.

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 equiv of Cs_2CO_3 was optimal (entries 3–5) under standard acetonitrile conditions, excitingly, we discovered that an external base could be omitted from the reaction and it could still provide a moderate yield (entry 6). We hypothesized this was the case, due to the basic phthalimide byproduct formed upon the reduction of the NHPI ester. To improve this additional layer of cooperativity between the acid and its NHPI ester, multiple solvents were screened under external base-free conditions (entries 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 h gave the final optimized yield of 73%, with no metal catalyst or external base required (entry 11). Finally, the exclusion of light or a photocatalyst (entries 12 and 13) from standard conditions formed a trace to no yield of **2a**, demonstrating their crucial roles in the SET between the donor and the acceptor. It is also worth noting that the addition of diphenylphosphate did not increase the yield (entry 14), showing that the reaction does not benefit from a proton-coupled electron transfer.[46]

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Next, the occurrence of redox inversion was probed. Control reactions demonstrated that both the electron donor and the electron acceptor are necessary for the reaction to proceed to high conversion (Figure 4). When 2.0 equiv of acid **1a** was

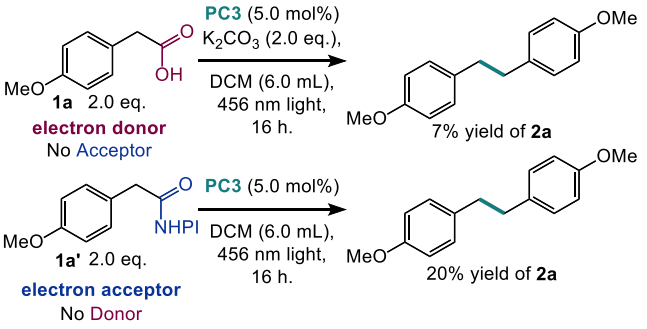

Figure 4. Mechanistic investigations for probing the necessity of both the electron donor and acceptor in the reaction.

irradiated with a photocatalyst without redox inversion, only 7% yield of **2a** was generated, likely due to the lack of an electron acceptor (NHPI ester). Likewise, when isolated NHPI ester **1a′** was irradiated without an additional electron donor (a carboxylic acid), a diminished yield of 20% was obtained. This latter reaction likely provided more product than the former, as side reactions of NHPI esters reported in the literature often involve hydrolysis of their acid counterparts.[47] This hydrolyzed phenylacetic acid could turn 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 the literature precedent, a proposed mechanism is depicted in Figure 2.[6]

With optimized conditions, the scope of this transformation was found to be successful across a variety of carboxylic acids (Figure 5). Substrates with electron-rich substituents performed best (**2a−i**), likely due to the stabilizing effect of electron-donating groups on radical intermediates.[48] Additionally, *ortho*-substituted phenylacetic acid derivatives gave moderately high-yield bibenzyl formation (**2b** and **2d**) likely due to increased radical persistence in a more hindered environment.[49] A variety of heteroatoms (oxygen, sulfur, and nitrogen) provided good yields of the homocoupled products (**2a−c** and **2f−i**), with the electron-donating *p*-thiophenol derivative giving the highest yield of 79% (**2f**). Unlike in traditional metal-mediated transformations, bromine substituents were well-tolerated across substitution patterns (**2i** and **2j**). 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 strategy for installing sensitive functionality, and a simple

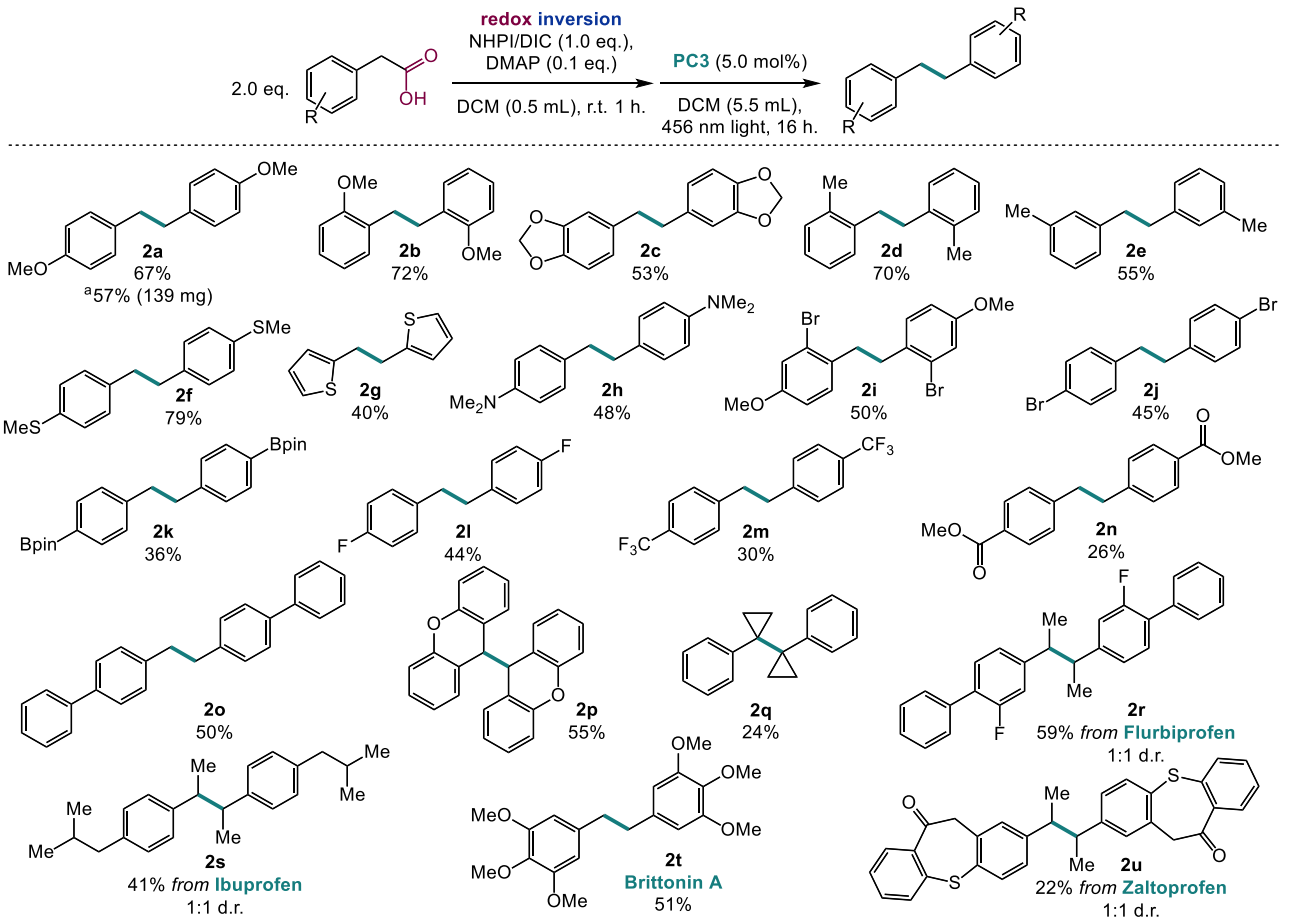

Figure 5. Substrate scope of bibenzyls with isolated yields. The reaction was performed on a 0.1 mmol scale at a concentration of 16.7 mM. [a]Reaction performed on a 1.0 mmol scale.

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approach for efficiently building molecular cores with potential for further functionalization and diversification. Fluorine-containing substrates were tolerated, demonstrating facile access to valuable fluorine-containing motifs (**2l** and **2m**). 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 (**2p** and **2q**).[13] For lower-yielding substrates, H atom abstraction and phthalimide-based by-products were the majority of the mass balance.

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**). 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, the decarboxylative coupling of Zaltoprofen provides the desired product in moderate yield, demonstrating the ability to couple functionally dense carboxylic acids via redox inversion and metal-free photocatalysis (**2u**).

To demonstrate the potential extension of this methodology beyond homocoupling, a reaction using two different carboxylic acids was carried out (Figure 6). The cross-coupled

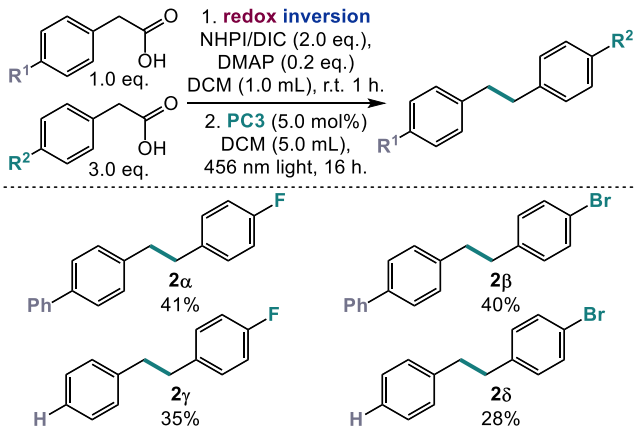

Figure 6. Cross-coupling mediated by redox inversion.

products (**2α**, **2β**, **2γ**, and **2δ**) were produced in moderate yield, with the remaining mass balance being homodimers of the starting materials. These transformations highlight the potential of redox inversion to access radical cross-coupling of carboxylic acids.

Finally, to further support the idea 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.

In summary, we have developed redox inversion as a mechanistic strategy for accessing 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

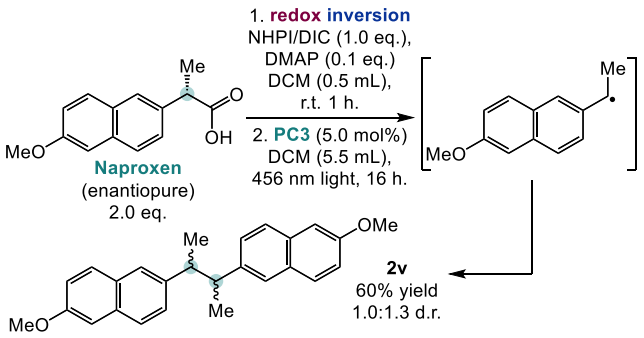

Figure 7. Racemization of the stereocenter.

different acids, unsymmetric bibenzyls can be formed, emphasizing the potential for 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

Data Availability Statement

The data underlying this study are available in the published article and Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c02877.

Experimental details, procedures, and ^{1}H and ^{13}C NMR spectra and characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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