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Skeletal Editing of Dibenzolactones to Fluorenes via Ni- or Pd-Catalyzed Decarboxylation

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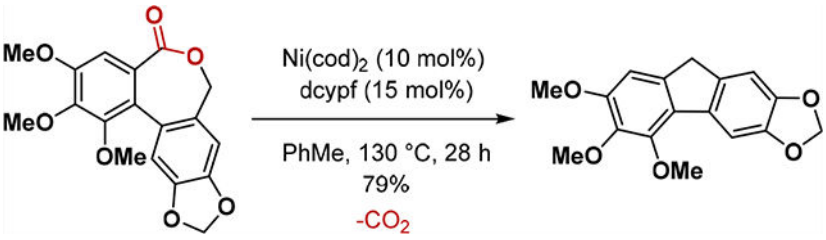
Abstract

The skeletal editing of dibenzolactones to fluorenes by Ni- or Pd-catalyzed decarboxylation is reported. In contrast to previously reported intramolecular decarboxylative couplings, inductively electron-withdrawing *ortho* substituents on the aryl carboxylate moiety and metal additives are not required. The decarboxylation reaction proceeds cleanly and can be applied to the skeletal editing of a natural product analogue. Mechanistic observations are consistent with stabilization of the carboxylate-ligated Ni complex over the Ni-carboxylate ion pair, which is the key factor in promoting the challenging decarboxylation step in the catalytic cycle.

Graphical Abstract



Skeletal rearrangements of a molecular framework generate new carbon skeletons with or without the introduction of new functionality, enabling expedited access to polycyclic natural product-like frameworks without the need for *de novo* synthesis.[1] Recent developments in *skeletal editing* aim to make precise changes to the molecular framework.[2] In this vein, our group recently reported an “atom-swapping” reaction sequence for the net substitution of a CH_2 group with an oxidized O within the molecular framework.[3] The key

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ASSOCIATED CONTENT

Supporting Information

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Experimental details, characterization data, and NMR spectra of new compounds and results of optimization reactions for the Pd-catalyzed decarboxylation reaction (PDF)

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.3c00700

step in this process utilizes a nickel-catalyzed decarbonylation that proceeds via oxidative addition to the C(acyl)–O bond (Scheme 1A). Guided by decarboxylative-intramolecular coupling reactions first described by Tsuji[4a] and Saegusa[4b] and their variants[5–7] (Scheme 1B), we reason that, for lactones such as dibenzo[*c,e*]oxepin-5(7*H*)-ones containing a benzyl ester, oxidative addition would instead occur at the benzylic Csp^3–O bond.[8] This would allow for decarboxylation followed by intramolecular cross-coupling to occur (Scheme 1C), thus enabling the skeletal editing of dibenzolactone motifs found in Graphislactone D and related natural products[9] into fluorenes, which are important substructures in pharmaceuticals,[10] natural products,[11] and fluorophores.[12]

A notable feature of the Pd-catalyzed decarboxylative intramolecular coupling of aryl carboxylic esters is that the aryl component typically contains inductively electron-withdrawing groups *ortho* to the carboxyl moiety to promote decarboxylation[6a,b] in the absence of silver additives (Scheme 1B).[6c] It is hypothesized that these substituents are needed to stabilize the incipient negative charge in the transition state for decarboxylation.[13]

Metal additives such as silver,[14] copper,[15] or zinc[16] salts have also been used to promote decarboxylative processes. In this Note, we report a nickel- and palladium-catalyzed decarboxylation reaction of dibenzo[*c,e*]oxepin-5(7*H*)-ones (Scheme 1C). *Ortho* electron-withdrawing groups and additives are not required for this reaction.

We began our investigations by identifying the optimal ligand. Using $Ni(cod)_2$ as the Ni source, dcypf afforded the highest product yield among the ligands tested (Table 1, entry 1, 91%). Changing the cyclohexyl groups in dcypf to phenyl in dppf lowered the yield by 30% (entry 2, 61%). Dcype, with a smaller bite angle, was ineffective (entry 3, <5%). PCy_3, known to achieve C(benzyl)–O oxidative addition in benzylic carbamates,[17] gave a moderate yield (entry 4, 59%). Using dcypf, the temperature can be lowered to 100 °C for full conversion of **1a** within 16 h (entry 5). The reaction also proceeded at 80 °C (entry 6) to give 52% yield after 24 h. In all cases, the reactions proceeded cleanly without formation of side products. The reaction did not proceed without the Ni catalyst at 130 °C (see the Supporting Information for full optimization studies).

With the optimal conditions in hand, we investigated the substrate scope (Scheme 2). The reaction works for both electron-withdrawing (**2b**, 81%; **2c**, 93%) and electron-donating groups (**2d**, 60%) *para* to the carboxyl moiety. Electronic effects were more pronounced for substrates with electron-withdrawing and electron-donating groups on each of the arenes under the standard reaction conditions (**2e**, 31%; **2f**, <5%). However, good yields were obtained for both substrates at a higher temperature of 130 °C for 24 h (**2e**, 73%; **2f**, 88%). Substrates with an electron-withdrawing group at the *para* position relative to the COO moiety and an electron-donating group *para* to the bridging methylene provided **2g** in 70% yield. Switching the electronics of the two aryl groups provided **2g** in 84% yield. Substituents *ortho* to either the COO motif or the bridging methylene were tolerated, generating **2h** in 96% yield when R^1 = *o*-OMe and R^2 = H and 95% yields when R^1 = H and R^2 = *o*-OMe. However, decarboxylation of the substrate with two *ortho*-methoxy substituents *ortho* to the COO motif and the bridging methylene led to no conversion (**2i**,

<5%). The reaction was not tolerant toward the MOM and Boc protecting groups (**2j**, 19%; **2k**, 26%). Thiophene-containing **2l** was obtained in 96% yield.

During the course of preparing the lactones for decarboxylation, we utilized a Suzuki–Miyaura cross-coupling reaction between an oxaborole and an aryl halide to give a biaryl product that undergoes *in situ* lactonization to generate the desired lactone. During the synthesis of **1ga** and **1gb**, we isolated fluorene product **2g** in both reactions, indicating that the Pd catalyst used for the cross-coupling reaction was also capable of promoting decarboxylation (Scheme 3A). We optimized the conditions for the decarboxylation of **1a** for palladium catalysis, which required 0.2 equiv of Cs_2CO_3 for good conversion. At 130 °C, the Pd/RuPhos catalyst gave yields similar to that of the $Ni(cod)_2$/dcypf catalyst for the decarboxylation of **1a** (Table 1, entry 1 vs Scheme 3B, top). However, only the Pd catalyst was able to promote the decarboxylation of **1m**, which has a substituent at the benzylic position (Scheme 3B, bottom). The decarboxylation product was formed in 23% yield, with no conversion observed with $Ni(cod)_2$/dcypf even at 130 °C.

To test if our decarboxylation protocol can be applied to the skeletal editing of natural product-like structures similar to those in Scheme 1C, we synthesized **1n**, which contains multiple alkoxy substituents typically found in natural products. Decarboxylation under 130 °C for 28 h on a 1.0 mmol scale gave a 79% yield of the desired fluorene product, and benzylic oxidation on a 0.1 mmol scale then gave **5** in 95% yield (Scheme 4). This decarboxylation–oxidation sequence represents a skeletal editing of a lactone to a fluorenone, which are substructures in >60 natural products.[18]

Finally, we made some mechanistic observations about the Ni-catalyzed decarboxylation reaction. The putative catalytic cycle is a sequence of oxidative addition, CO_2 deinsertion (decarboxylation), and reductive elimination (Figure 1A). When a 1:1 mixture of $Ni(cod)_2$, dcypf, and **1b** was heated in C_6D_6, intermediate species **dcypf-Ni-I** with a signal at −61.96 ppm in ^{19}F NMR and at 174.8 ppm in ^{13}C NMR was observed at 70 °C within 1 h (Figure 1B). At 90 °C, product formation was observed; at 100 °C, **dcypf-Ni-I** and **1b** were fully converted to the product **2b** within 1 h. We synthesized **dcypf-Ni-I** through an independent route. Based on assignment of the key NMR signals, we propose the structure of **dcypf-Ni-I** to be the product of oxidative addition at the C(benzyl)–O bond shown in Figure 1C, top.[19] **Dcypf-Ni-I** can be used as a precatalyst in the decarboxylation reaction (Figure 1C, bottom). The observation of **dcypf-Ni-I** and not **dcypf-Ni-II** is consistent with literature precedent, which suggests that decarboxylation is the challenging step.

Under our standard reaction conditions, 8-membered lactone **1o** does not react (Figure 1D). Acyclic substrate **1p** gave only benzoic acid 7 with no products derived from decarboxylation observable by GC and NMR of the crude reaction mixture under stoichiometric conditions at 100 or 130 °C, indicating that oxidative addition occurred but not decarboxylation. Based on our observations and previous DFT studies on the mechanism of decarboxylation, we reason that the decarboxylation of **1b** can occur because the chelating effect stabilizes the carboxylate-ligated Ni complex **dcypf-Ni-I**, which then establishes the *ipso*-interaction between the arene and the Ni center crucial for CO_2 deinsertion.[13b,20] The weakening or lack of this chelating effect in the more

conformationally flexible **1o** and **1p** leads to carboxylate dissociation[21] to form an ion pair. The free carboxylate can only undergo thermal decarboxylation under more forcing conditions.[22] The stabilization of the ion pair by a coordinating solvent may also contribute to the low yield (44%) of the decarboxylation of **1a** when MeCN is used as the solvent.

In conclusion, we have developed a methodology for converting dibenzolactones into the corresponding fluorenes via Ni- or Pd-decarboxylative-intramolecular coupling. The transformation proceeds cleanly without the assistance of metal additives, and inductively electron-withdrawing *ortho* substituents are not required on the substrates. This reaction was applied to the skeletal editing of a highly oxygenated natural product analogue to generate the corresponding fluorenone. The methodology developed in this work extends a class of reactions that previously had severe substrate restrictions into a practical reaction for accessing useful fluorene motifs.

EXPERIMENTAL SECTION

Representative procedure for the Ni-catalyzed decarboxylation of **1a** to **2a**: An oven-dried 2-dram vial was charged with a magnetic stir bar and dibenzolactone (0.1 mmol, 1 equiv). The vial was brought into a glovebox, and dcypf (8.7 mg, 0.015 mmol, 15 mol %), $Ni(cod)_2$ (2.8 mg, 0.010 mmol, 10 mol %), and toluene (1.0 mL) were added sequentially. The vial was capped and brought out of the glovebox and placed on an aluminum heating block preheated at 100 °C. After stirring for 16 h, the reaction was allowed to cool to rt. The solvent was then removed by using a rotary evaporator. The reaction mixture was then redissolved in CH_2Cl_2, loaded onto a 25 g sample load cartridge prepacked with silica gel, and purified by automated silica gel chromatography (12 g RediSep Gold column, 100% hexanes for 13 CV) to afford **2a** (14.3 mg, 0.0860 mmol, 86%). NMR data match previously reported values. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.4 Hz, 2H), 7.57 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 6.9 Hz, 2H), 7.32 (td, J = 7.4, 1.2 Hz, 2H), 3.92 (s, 2H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ: 143.3, 141.8, 126.9, 126.8, 125.2, 120.0, 37.1.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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Data Availability Statement

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

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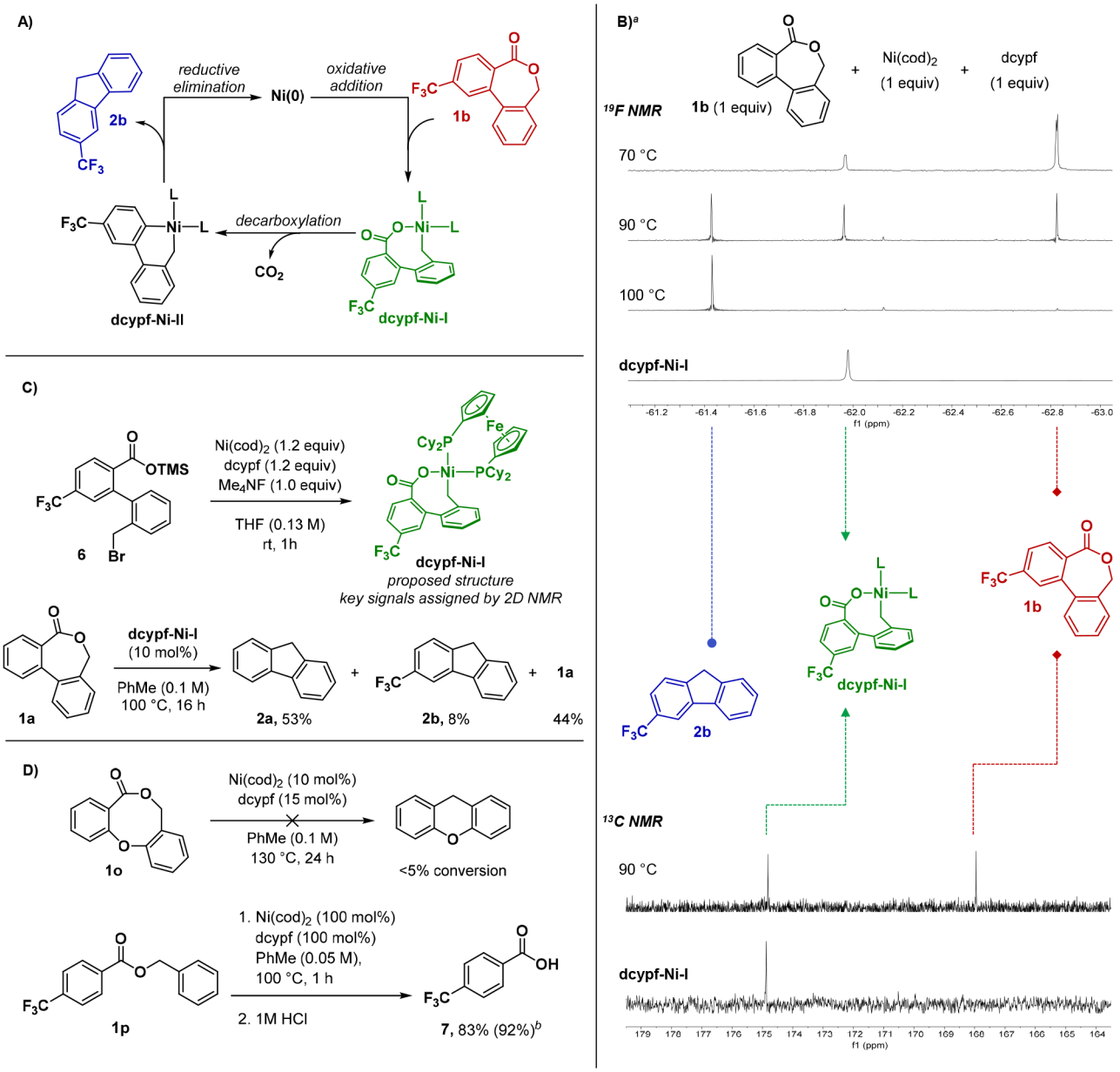
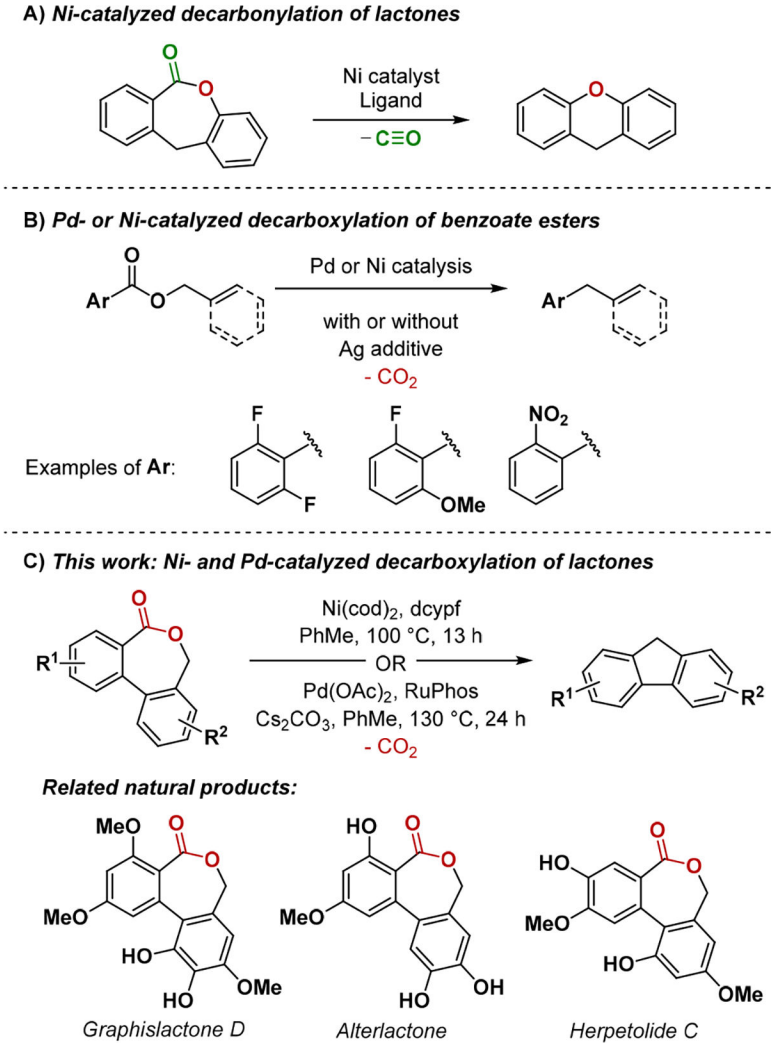


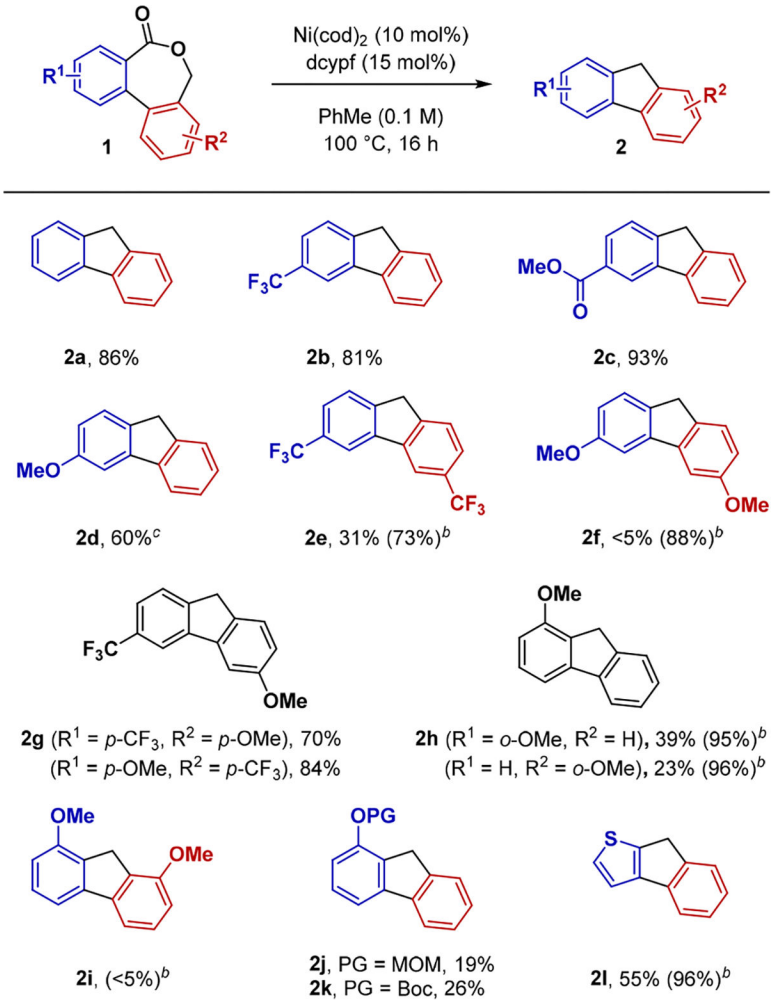
Figure 1.

Proposed mechanism of decarboxylation and experiments to probe the mechanism. [a]The reaction was run for 1 h at each temperature. [b]The reaction was run at 130 °C for 1 h. Yields shown are NMR yields.



Scheme 1.

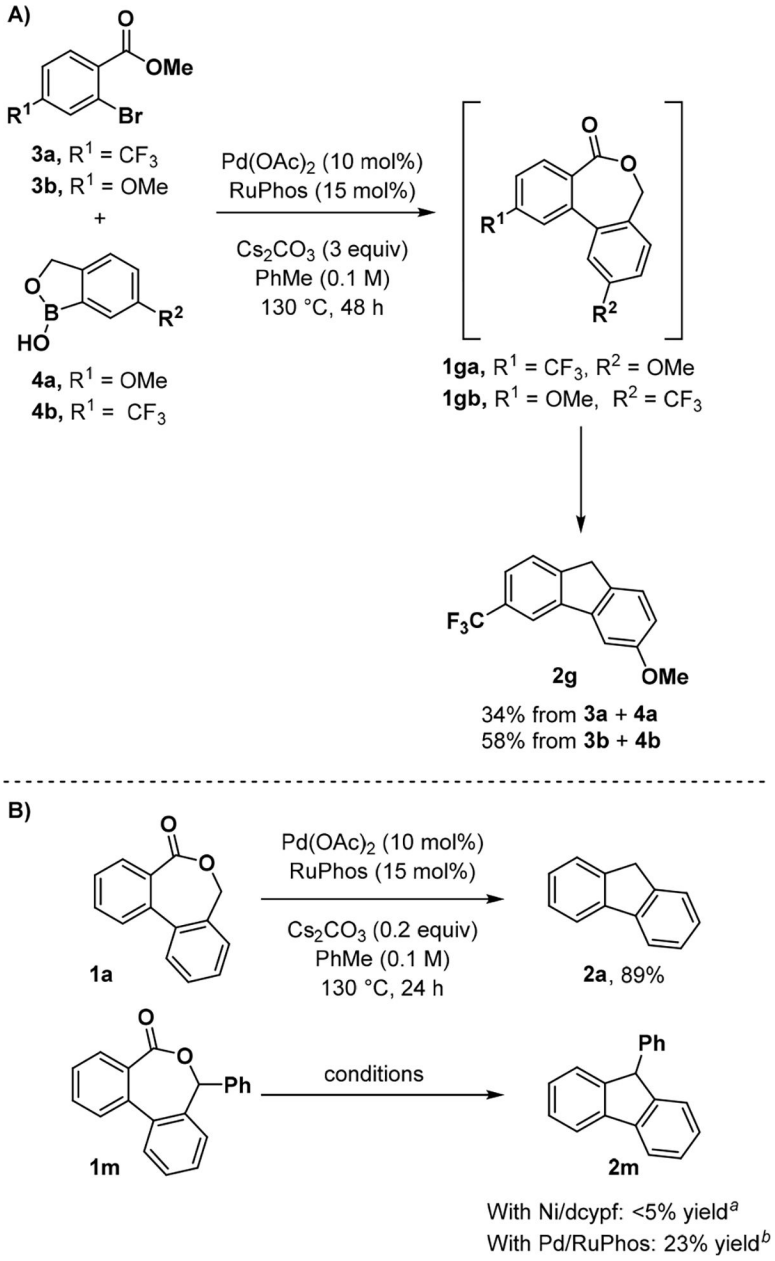
Molecular Editing of Esters by Decarbonylation and Decarboxylation (This Work)



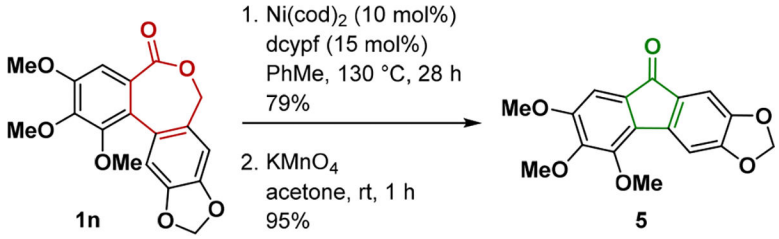
Scheme 2.

Substrate Scope of Lactones for Decarboxylation to Fluorenes[a]

[a]Reactions were run on a 0.10 mmol scale. Yields shown are isolated yields. [b]The reaction was run at 130 °C for 24 h. [c]Average yield of three reactions.



Scheme 3.

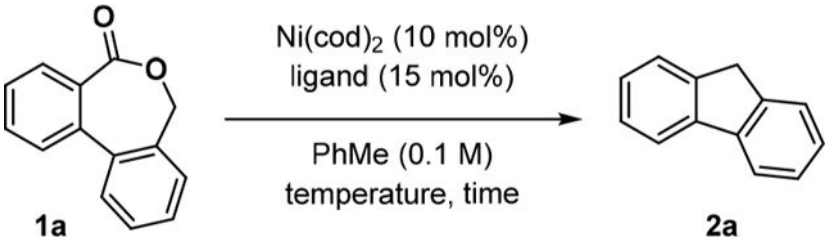


Scheme 4.

Skeletal Editing of Dibenzolactone 1n to Fluorenone 5

Table 1.

Optimization Table[a]



entry	ligand	temperature (°C)	time (h)	yield (%)
1	dcypf	130	24	91
2	dppf	130	24	61
3	dcype	130	24	<5
4	PCy_3[b]	130	24	50
5	dcypf	100	16	92
6	dcypf	80	24	52

[a]Reactions were run on a 0.050 mmol scale. Yields shown are NMR yields.

[b]25 mol % of ligand was used.