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A C-to-O atom-swapping reaction sequence enabled by Ni-catalyzed decarbonylation of lactones†

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Advances in site-selective functionalization reactions have enabled single atom changes on the periphery of a complex molecule, but reaction manifolds that enable such changes on the core framework of the molecule remain sparse. Here, we disclose a strategy for carbon-to-oxygen substitution in cyclic diarylmethanes and diarylketones to yield cyclic diarylethers. Oxygen atom insertion is accomplished by methylene and Baeyer–Villiger oxidations. To remove the carbon atom in this C-to-O "atom swap" process, we developed a nickel-catalyzed decarbonylation of lactones to yield the corresponding cyclic diaryl ethers. This reaction was enabled by mechanistic studies with stoichiometric nickel(II) complexes that led to the optimization of a ligand capable of promoting a challenging C(sp^2)–O(aryl) reductive elimination. The nickel-catalyzed decarbonylation was applied to 6–8 membered lactones (16 examples, 32–99%). Finally, a C-to-O atom-swapping reaction sequence was accomplished on a natural product and a pharmaceutical precursor.

Introduction

The impact of single atom changes in small molecules on the intermolecular interactions with their biological targets is well-documented.[1] With the development of site-selective functionalization reactions,[2] the isosteric replacement of an atom on the periphery of a complex molecule has become increasingly practical. In contrast, the analogous process for an atom embedded in the molecular skeleton remains challenging.[3] Although such an "atom swapping" process has been recognized as a highly desired transformation,[4] a strategy demonstrating its feasibility has yet to be reported (Fig. 1). Herein, we design a sequence of atom insertion and atom deletion events to realize a carbon-to-oxygen atom swap (Fig. 1). We reason that oxidation of a methylene group to a ketone will enable oxygen atom insertion by Baeyer–Villiger rearrangement, which generates a lactone. The lactone must then undergo a decarbonylative C–O bond-forming reaction to remove the carbon atom. However, despite the growing number of reports on intermolecular decarbonylative coupling reactions,[5] the proposed atom-swapping reaction sequence cannot be achieved due to the lack of a method for the decarbonylation of lactones.

In 2017, Yamaguchi and coworkers pioneered an intramolecular decarbonylative C–O coupling of esters, but non-heteroaryl substrates such as **1a** (Fig. 1) remain unviable to date.[6] In this work, we developed a catalytic system that overcomes this limitation. Lactone **1a** was chosen as the substrate for optimization as the dibenzolactone substructure can be derived from both diarylketone- and diarylmethane-containing natural products and pharmaceuticals. We first sought to understand the putative catalytic cycle for decarbonylation to identify the problematic step. The main steps involve oxidative

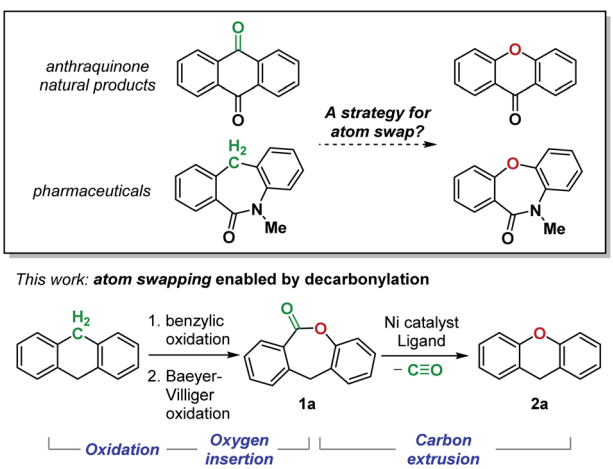

Fig. 1 A two-stage strategy for a carbon-to-oxygen atom swap comprising oxidation and carbon extrusion steps.

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† Electronic supplementary information (ESI) available: Full experimental details, characterization data, and NMR spectra of all new compounds. CCDC 2116181 and 2116182 contain the supplementary crystallographic data for **dcype-Ni-2a** and ***meso*-L2-Ni-2a**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc06968c

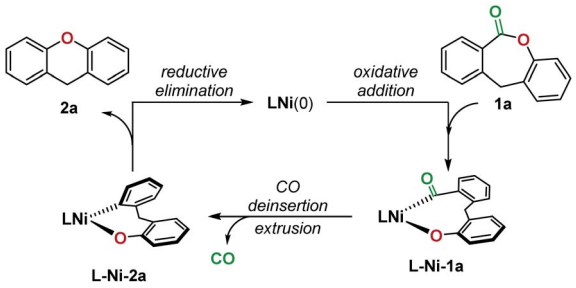

Fig. 2 A proposed catalytic cycle for the Ni-catalyzed decarbonylation of lactone **1a** to generate **2a**.

addition, migratory-deinsertion, and a Csp^2–O(aryl) reductive elimination (Fig. 2).

Results and discussion

The opposing ligand requirements[7] in the different steps of the putative catalytic cycle make this transformation challenging. Oxidative addition into the relatively inert C(acyl)–O bond of an ester[8,9] generally requires an electron-rich ligand on the metal complex.[10] The ligand also has to promote a challenging Csp^2–O reductive elimination from a Ni(II)(aryl)(aryloxo) complex,[11–14] which is faster from a more electron-deficient metal center bearing bulky ligands.[15] Dcype, a bisphosphine ligand used in Yamaguchi's decarbonylation reaction and a widely employed ligand for decarbonylative transformations,[9c,16] did not give any yield of **2a** from **1a**. We thus proceeded to examine the individual steps of the proposed catalytic cycle to determine the problematic step. In a stoichiometric experiment, heating a mixture of $Ni(cod)_2$, dcype, and lactone **1a** at 80 °C in C_6D_6 generated **dcype-Ni-2a** and $Ni(dcype)(CO)_2$, indicating that oxidative addition and decarbonylation occurred (Fig. 3A). The structure of **dcype-Ni-2a** was confirmed by independent synthesis, isolation, and characterization by X-ray crystallography (Fig. 3B). **dcype-Ni-2a** synthesized independently or formed *in situ* did not undergo reductive elimination to give **2a** at temperatures up to 150 °C and resulted only in decomposition.

To solve this reductive elimination problem, we synthesized and tested phosphine ligand classes that were successful for carbon–heteroatom bond formations under Ni(0)/Ni(II) catalysis[6,11a,b,17] (Fig. 4) and other ligands (see ESI for the full list, Section 3.1†). These ligands gave no or unsatisfactory yields of the desired product. However, bisphosphines bearing two bulky tetramethyltrioxaphosphaadamantyl moieties on an aryl backbone, first prepared by the Stradiotto group for C(aryl)–N cross couplings,[18,19] were effective, with ***meso*-L2** giving an 80% yield of the desired decarbonylation product (Fig. 4).

Stoichiometric experiments indicate that the successful formation of **2a** with the bulkier, less electron-rich ***meso*-L2** ligand compared to dcype can be attributed to its ability to promote reductive elimination from a Ni(II)(aryl)(aryloxo) complex. Heating a mixture of $Ni(cod)_2$, ***meso*-L2**, and **1a** at 110 °C in C_6D_6 resulted in no conversion, but increasing the

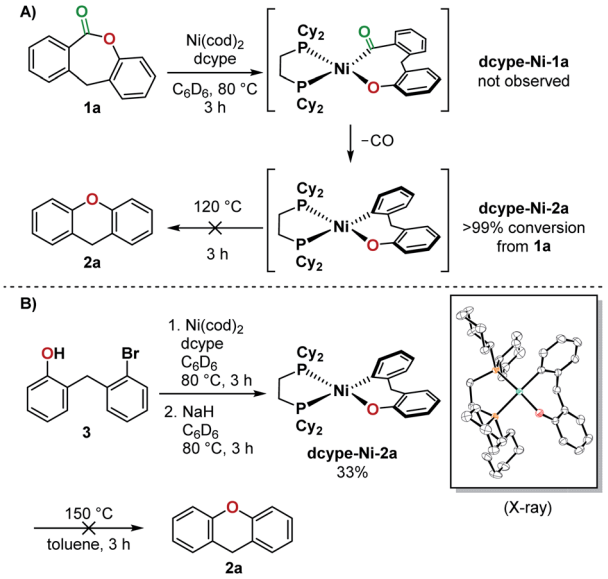

Fig. 3 (A) Stoichiometric experiment using dcype and **1a**, (B) independent synthesis of **dcype-Ni-2a** and a reductive elimination test.

reaction temperature to 120 °C then gave the product **2a** and ***meso*-L2-Ni(CO)$_2$** with no other Ni(II) intermediates detected by ^1H and ^{31}P NMR (Fig. 5A). This was further confirmed by independent synthesis and isolation of ***meso*-L2-Ni-2a** from **3**. At 110 °C, ***meso*-L2-Ni-2a** underwent reductive elimination cleanly to give **2a** in 99% yield (Fig. 5B).

Further experiments uncovered more differences between dcype- and ***meso*-L2**-ligated nickel(II) complexes in reductive elimination. Heating **dcype-Ni-2a** with $Cr(CO)_6$ at 80 °C resulted in the formation of lactone **1a** in 90% yield. In contrast, ***meso*-L2-Ni-2a** underwent reductive elimination under the same conditions to give **2a** in 98% yield (Fig. 6A). Since reductive elimination occurred at a lower temperature in the presence of CO than reductive elimination from ***meso*-L2-Ni-2a** in the absence of CO (Fig. 5B), a second catalytic cycle may be operating in the reaction employing $Ni(cod)_2$ and ***meso*-L2**. In

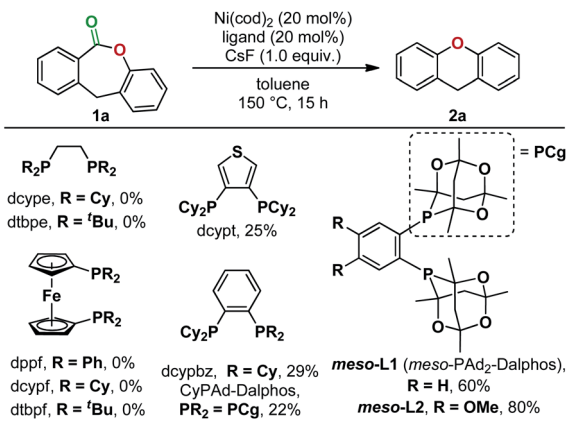

Fig. 4 Ligand optimization.

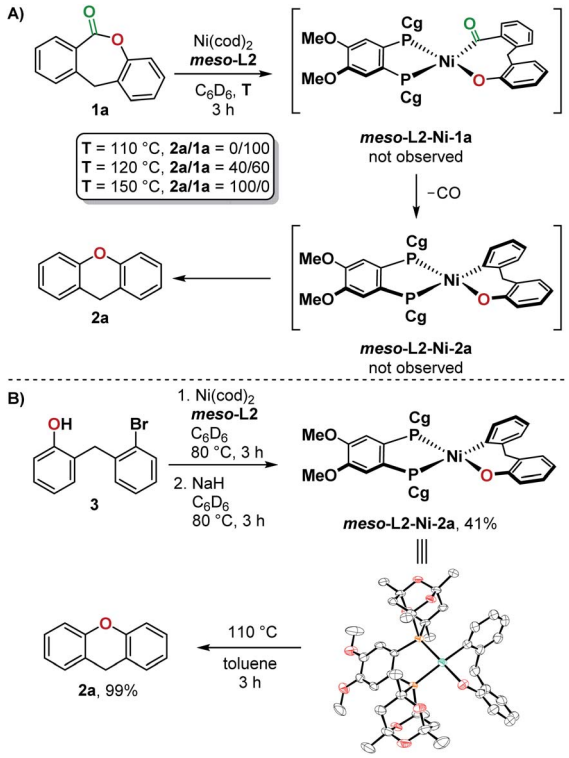

Fig. 5 (A) Stoichiometric experiment using ligand *meso*-L2 and 1a, (B) independent synthesis of *meso*-L2-Ni-2a and a reductive elimination test.

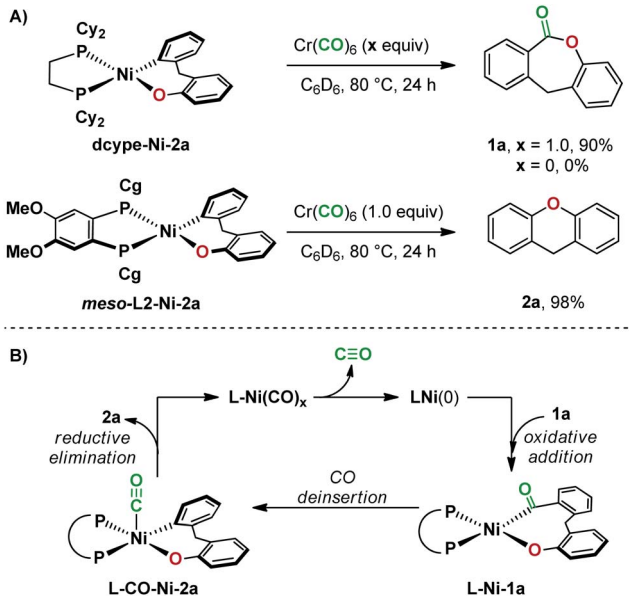

Fig. 6 (A) Carbonylation reactions with nickel complexes. (B) An alternative catalytic cycle with Ni/*meso*-L2.

this second pathway, CO deinsertion from **L-Ni-1a** generates a five-coordinate complex[20] **L-CO-Ni-2a**, which undergoes reductive elimination to give **2a** and complex **L-Ni(CO)$_x$**. The inactive complex **L-Ni(CO)$_x$** then re-enters the catalytic cycle after dissociation of carbon monoxide at high temperature (Fig. 6B).[20c,d] Reductive elimination from both a four-coordinate and five-coordinate dcype-ligated nickel complex are not feasible under the conditions examined.

Using Ni(cod)$_2$ and ***meso*-L2** as the catalyst, further optimization in solvent, temperature, concentration, and base led to 85% yield of **2a** (see ESI, Section 3†). The optimized conditions were then applied to different lactone substrates (Fig. 7). Electron-donating and electron-withdrawing substituents on either aryl rings of **1** significantly affected the reaction yields.[15] Two electron-withdrawing substituents at the *para* positions relative to the COO group gave a higher product yield than two electron-donating groups (**2b** *vs.* **2c**, 54% *vs.* 32%). Additionally, lactone **1d** with R^1 = CO$_2$Me and R^2 = OMe gave 67% yield of **2d**.

However, when the electronic character of the rings was reversed, the expected product **2e** was not detected. Overall, substrates with electron-donating groups *para* to the COO moiety gave noticeably lower yields (**2c**, **2e**, and **2n**). A range of R^3 substituents can be accommodated in the reaction, including both electron-donating and electron-withdrawing groups (**2f–2i**). Benzyl and MOM protecting groups are compatible (**2h** and **2i**), but not the Boc protecting group (**2j**). A benzyloxy and methoxy group as the R^4 substituent were tolerated with similar yields (45% and 48%, **2l** and **2m**). Dihydrodibenzooxepine **2o** can also be synthesized under the same conditions, albeit in decreased yield (42%). ***meso*-L2-Ni-2a** was also a competent pre-catalyst in place of Ni(cod)$_2$/***meso*-L2**, giving essentially the same yield of **2d** (see ESI, Section 5.7†) under otherwise identical conditions. Acyclic esters and alkyl lactones are currently outside the scope of this reaction (for details, see ESI Section 6.3†).

The successful development of the decarbonylation of lactones now opens the way for our proposed carbon-to-oxygen atom swap transformation. We first targeted the replacement of a ketone with an oxygen in an anthraquinone natural product

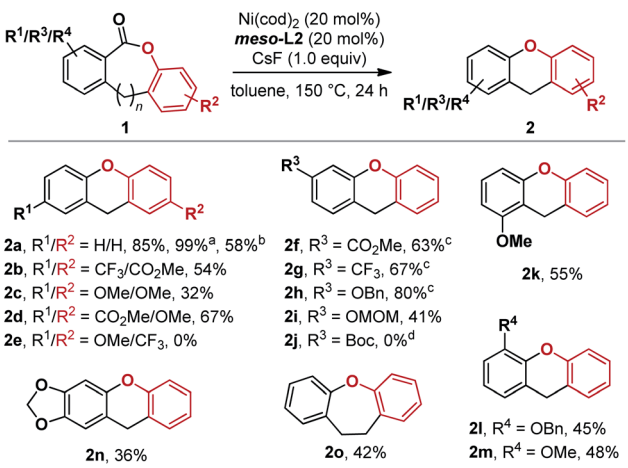

Fig. 7 Substrate scope. Reactions were run on a 0.20 mmol scale unless otherwise noted. Work-up and purification were carried out as described in the ESI.† [a] 0.050 mmol scale. [b] 1.00 mmol scale. [c] 0.10 mmol scale. [d] 29% yield of the deprotected lactone was obtained.

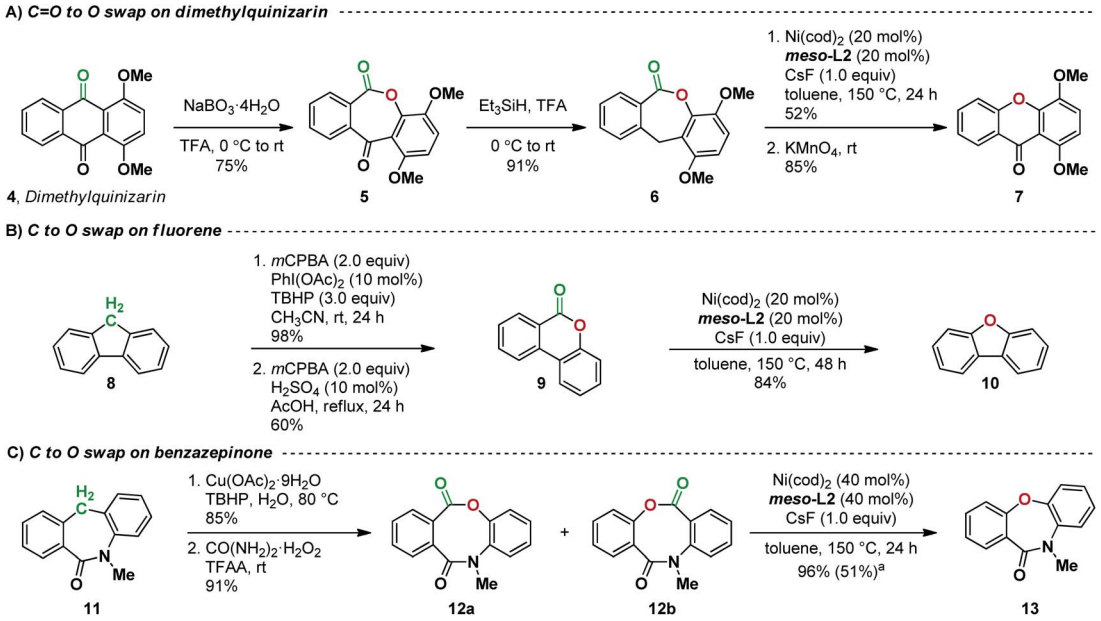

Fig. 8 Atom-swapping reaction sequences in (A) a natural product derivative; (B) fluorene; and (C) a pharmaceutical precursor. [a] Yield in parentheses is from a reaction using 20 mol% of $Ni(cod)_2$ and *meso*-L2.

derivative (Fig. 8A). A Baeyer–Villiger reaction[21] on dimethylquinizarin **4** followed by reduction with triethylsilane in trifluoroacetic acid gave lactone **6**. Subjecting **6** to the decarbonylation conditions we developed gave the desired diaryl ether in 52% yield. Oxidation with $KMnO_4$ then afforded the desired xanthone **7**. This sequence of reactions thus overall results in a C=O to O atom swap, transforming an anthraquinone to a xanthone. Our attempts to decarbonylate **5** without reduction to **6** led only to decomposition, suggesting that the decarbonylation is affected by the C–C–C bond angle at the carbon bridge in dibenzolactone **6**.

We next tested if CH_2-to-O atom swap can be realized (Fig. 8B). Indeed, a sequence of oxidation, Baeyer–Villiger reaction, and decarbonylation smoothly converts fluorene **8** to dibenzofuran **10** in an overall yield of 49%. This example also demonstrates that our decarbonylation reaction can be applied to the ring contraction of 6-membered dibenzolactones.

We then expanded our atom-swapping method to the conversion of a dibenzazepinone to a dibenzoxazepinone. Dibenzazepinones such as **11** (Fig. 8C) are versatile intermediates in the synthesis of a range of pharmaceuticals containing a dibenzoazepine motif, including mianserin, etazepine, epinastine, and perlapine.[22] Oxidation of dibenzazepinone **11** [22b] followed by Baeyer–Villiger rearrangement gave a mixture of regioisomeric lactones **12a** and **12b**. The regioselectivity of the Baeyer–Villiger oxidation was inconsequential since subsequent decarbonylation of the mixture gave the desired C-to-O atom-swapping product **13** in 96% yield. No other by-product was observed, indicating a complete selectivity for the C(acyl)–O bond activation over the C(acyl)–N bond[16j,23] during the decarbonylation step. In addition, the presence of two sp^2 atoms in the bridge is not detrimental to decarbonylation, presumably due to the greater flexibility in the larger ring.

Conclusion

In conclusion, we have achieved a carbon-to-oxygen atom swapping transformation comprising oxygen atom insertion and carbon atom deletion steps. To enable this overall process, we developed a Ni-catalyzed decarbonylation of lactones that overcomes the substrate limitations of previous ester decarbonylation reactions. The Ni/***meso*-L2** catalyst is capable of promoting a challenging Csp^2–O(aryl) reductive elimination from either a four- or five-coordinate Ni(II) complex. This report establishes the framework for creating new atom-swapping processes in complex molecules using transition metal-catalyzed decarbonylation reactions.

Data availability

Experimental data associated with this article are provided in the ESI.† Crystallographic data for ***meso*-L2-Ni-2a** and **dcype-Ni-2a** have been deposited at the CCDC under 2116181 and 2116182 and can be obtained from https://www.ccdc.cam.ac.uk/.

Author contributions

J. Li conceptualized the project. Q. H. Luu developed the methodology and performed most of the experiments. Both authors analyzed the data and wrote the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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