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Double Deoxygenative Coupling of Carboxylic Acids and Alcohols

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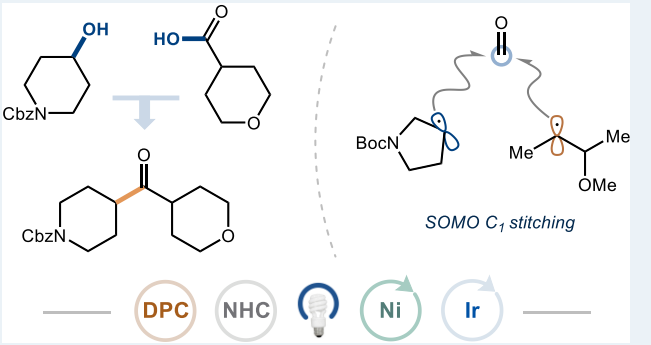
ABSTRACT: Ketones are highly valued for their versatility in functional group interconversions and prevalence in bioactive molecules. However, the synthesis of complex ketones often requires organometallic reagents or prefunctionalized substrates. Herein, we report a photoredox-catalyzed double deoxygenative fragment coupling between alcohols and carboxylic acids to access diverse, sp^3-rich ketone scaffolds. This transformation proceeds under mild conditions and leverages abundant starting materials. We further expand the logic of radical cross-coupling via a bis-radical SOMO stitching approach that unites two alcohol-derived fragments to forge C_1-connected ketone products.

KEYWORDS: *nickel catalysis, ketone, metallaphotoredox, photoredox, cross-coupling, C1 synthon*



Ketones are core functional groups in organic synthesis, valued for their versatility in a wide range of transformations such as condensations and reductive aminations − reactions central to both rapid small-scale screening and process-scale chemistry in pharmaceutical and agrochemical settings.[1−7] Their prevalence in bioactive compounds further underscores their synthetic value (Figure 1). Ketones are traditionally prepared via nucleophilic addition of organometallic reagents to Weinreb amides or aldehydes, the latter requiring additional functional group manipulations.[8−13] However, such strategies often suffer from the need to prepare and handle sensitive organometallic reagents and rely on multi-step protecting group sequences. As such, there remains a strong demand for methods that directly construct ketones from abundant, commercially available building blocks.

To this end, radical intermediates offer an attractive alternative to traditional organometallic reagents, enabling high-energy bond constructions without the need for preformed nucleophiles.[14] Significant advancements in cross-electrophile coupling have led to the development of tailored activated esters that undergo facile oxidative addition into nickel complexes.[15−24] These approaches, which offer improved stability and versatility, have become a mainstay in radical acylation; however, such methods remain limited by their reliance on presynthesized alkyl radical precursors and superstoichiometric reductants. Moreover, while acyl radicals have been harnessed for ketone construction,[25−30] existing protocols often suffer from limited substrate scope or require specific substrate design.[31] Photoredox catalysis has emerged as a powerful platform for radical generation, enabling challenging $C(sp^3)$−$C(sp^2)$ bond formations under mild, redox-neutral conditions.[32−34] Several groups have made developments towards this longstanding issue; however, few have offered a unified method with such diversity of feedstock pool.[35−39] This approach eliminates the need for superstoichiometric oxidants and reductants and is well suited to complex fragment coupling. Extending this paradigm, we recently introduced a benzoxazolium reagent (NHC) that directly activates alcohols for *in situ* photoredox-mediated deoxygenative radical generation without the need for workup or purification.[40] Alcohols, given their wide availability, offer an ideal source of $C(sp^3)$ fragments for building block synthesis and late-stage functionalization.

We envisioned a formal double deoxygenative fragment coupling (DDC) that merges the NHC−alcohol platform with an *in situ*-activated carboxylic acid to directly access a diverse array of ketones. This approach minimizes the need for prefunctionalization and leverages two abundant, orthogonal substrate classes: alcohols and carboxylic acids (Figure 1). The resulting structural diversity and modularity render this platform particularly well suited for small-molecule screening campaigns.

To introduce the carbonyl moiety, we envisioned using 2-pyridyl esters, well-established oxidative addition partners in nickel catalysis.[41−43] We hypothesized that these intermediates could be generated *in situ* from carboxylic acids, enabling the direct use of both alkyl and acyl fragments from abundant, commercially available sources.

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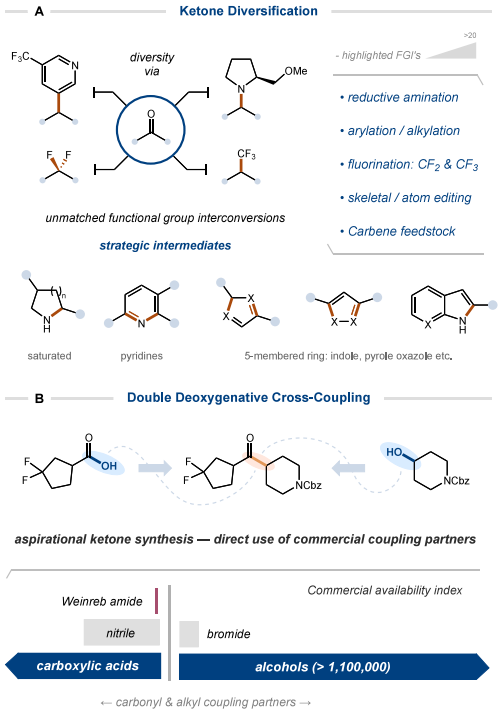
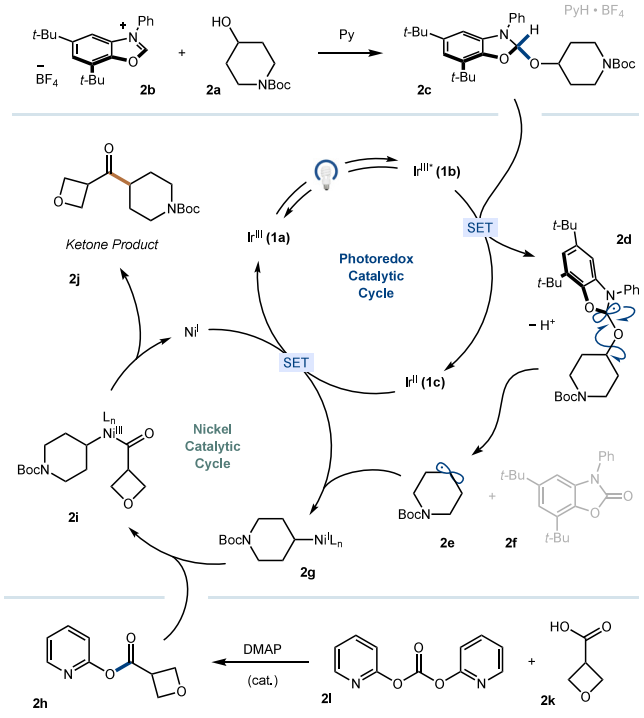


Figure 1. Expedited ketone access via double deoxygenative cross-coupling.

The proposed mechanistic design is outlined in Scheme 1. Alcohol **2a** condenses *in situ* with benzoxazolium salt **2b** to form the NHC−alcohol adduct **2c**. Upon irradiation with blue light (450 nm), photocatalyst **1a** is excited to its oxidizing state (**1b**), which is quenched via single-electron transfer (SET) from adduct **2c**, generating the reduced photocatalyst **1c**. Subsequent deprotonation yields α-hetero radical **2d**, which undergoes β-scission to cleave the C−O bond, releasing alkyl radical **2e** and inert byproduct **2f**.[9] The resulting radical engages a nickel(0) species to generate nickel(I)−alkyl intermediate **2 g**.[21] Oxidative addition into the *in situ*-formed pyridyl ester **2 h** furnishes a nickel(III) species, **2i**, which undergoes reductive elimination to afford the ketone product **2j** and regenerate nickel(I). Reduction of nickel(I) closes the catalytic cycle. It is envisaged that the use of 2-pyridyl esters should provide efficient oxidative addition to nickel(0/I) through pre-coordination via the pyridine nitrogen.[44] Further mechanistic details and photo-NMR studies are provided in the Supporting Information.

Scheme 1. Proposed Reaction Mechanism



2. RESULTS AND DISCUSSION

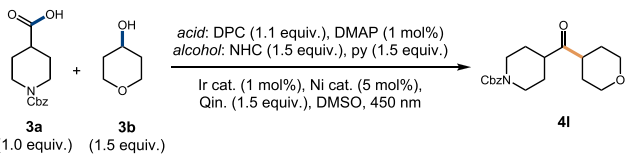
2.1. Optimization of Reaction Conditions

An optimization campaign identified conditions that effectively couple Cbz-protected piperidine-4-carboxylic acid (**3a**) and tetrahydro-4-pyranol (**3b**) to afford the corresponding ketone (**4 l**) in 85% yield (Table 1, entry 1). The reaction was relatively tolerant to variations in photocatalyst, base, and ligand (entries 1−4). However, DMSO proved critical to reaction efficiency, as alternative solvents such as DMA led to significantly diminished yields (entry 5). As expected, no product was formed in the absence of light (entry 6). Notably, use of isolated 2-pyridyl ester gave comparable results to in situ activation (entry 7), underscoring the efficiency of the in-situ activation strategy. Full optimization details are provided in the Supporting Information.

2.2. Reaction Scope

With optimized conditions in hand, we explored the scope of the deoxygenative coupling (Figure 2). The reaction proved

Table 1. Double Deoxygenative Coupling Optimization



entry[a]	deviation	yield[b]
1	none	85%
2	$NiBr_2$ • glyme and phenanthroline	78%
3	4-CzIPN	72%
4	BzOK	81%
5	DMA	16%[c]
6	no light	0%
7	isolated 2-pyridyl ester	85%

[a]Reactions performed on 0.05 mmol scale with acid (1.0 equiv), DPC (1.1 equiv), DMAP (1.0 mol %), DMSO (0.5 M); alcohol (1.25 equiv), NHC (1.5 equiv), pyridine (1.5 equiv), MTBE (0.10 M), 15 min; Quinuclidine (1.5 equiv), $NiBr_2$(dtbbpy) (5 mol %), [Ir[dF(CF_3)ppy]2(dtbpy)]PF_6 (1.0 mol %), DMSO/MTBE (1:1, 0.05 M), integrated photoreactor (450 nm, 100% light intensity), 15 h. [b]Yield determined by ultra-performance liquid chromatograph (UPLC). Di-2-pyridyl Carbonate (DPC), Quinuclidine (Quin.), NHC (**2b**), Integrated photoreactor (IPR). [c]The reaction with DMA provided lower yield in small scale due to formation of DMA-ketone side product; however, on 0.5 mmol scale reaction provided 62% yield.

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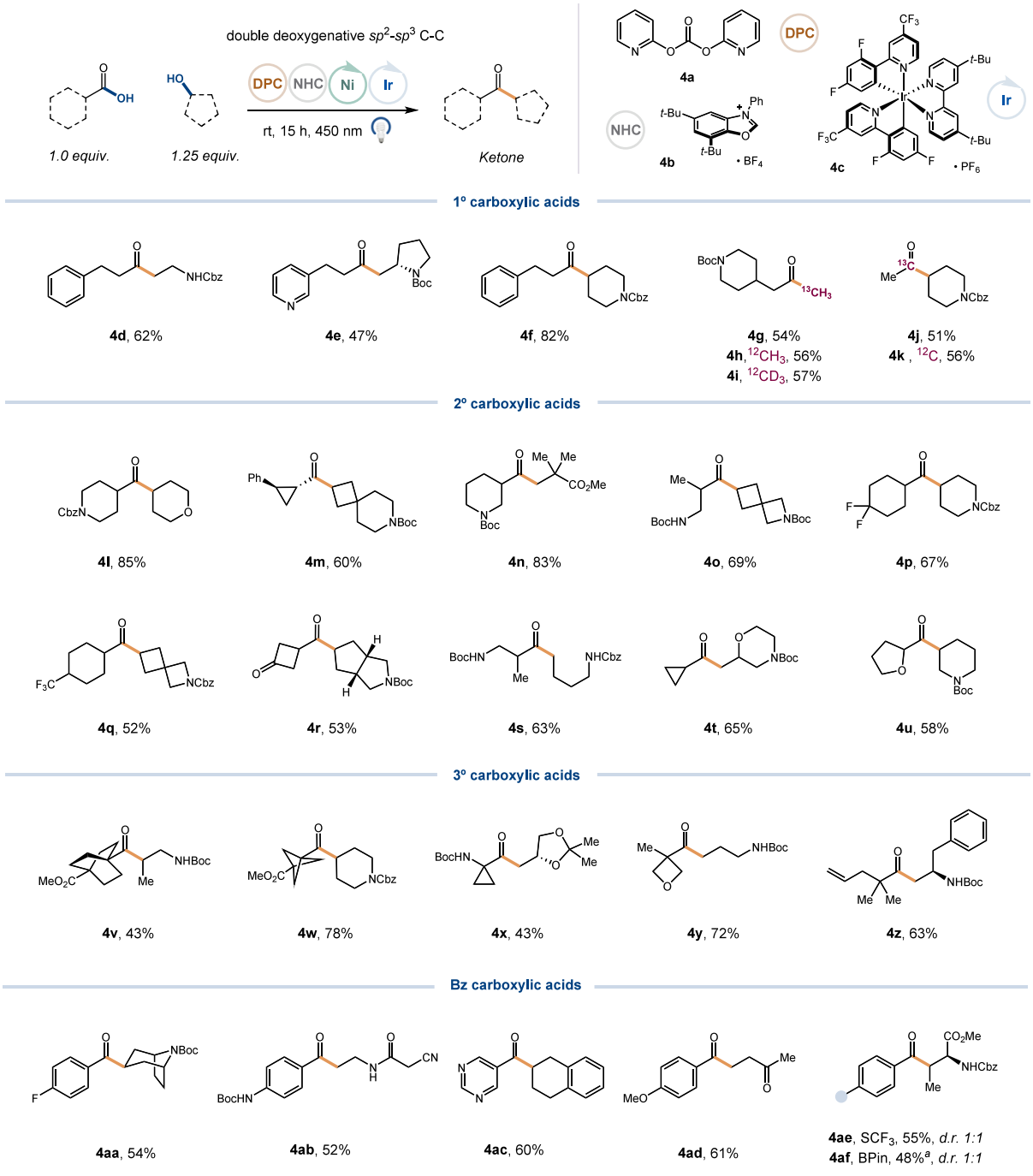

Figure 2. Carboxylic acid and alcohol scope. Reactions were performed on a 0.5 mmol scale with acid (1.0 equiv), DPC (1.1 equiv), DMAP (1 mol %), DMSO (0.5 M), 0.5–3 h; alcohol (1.5 equiv), NHC (4b, 1.5 equiv), pyridine (1.5 equiv), MTBE (0.1 M), 15 min; reaction: Ir (4c, 1 mol %), quinuclidine (1.5 equiv), $NiBr_2$(dtbbpy) (5.0 mol %)/BzOK (1.5 equiv), $NiBr_2$·glyme(phen) (5.0 mol %), DMSO/MTBE (1:1, 0.05 M), blue LEDs, 15 h. Isolated yields are reported. [a]UPLC assay yield. Deuterium retention determined by quantitative 1H NMR analysis.

general across a range of primary and secondary carboxylic acids and alcohols. Primary acids coupled with primary and secondary alcohols to afford ketones in good to excellent yields (47−82%, **4d**−**4k**). Notably, isotopically labeled units were readily introduced from inexpensive methanol and acetic acid. Secondary carboxylic acids also performed well, delivering ketones across a variety of alcohol coupling partners (52−85%, **4 l**−**4u**).

We then turned to more challenging substrates, including benzylic, benzoic, aryl, α-heteroatom, and tertiary acids. These substrates initially gave diminished yields due to significant formation of a bis-alcohol-derived ketone byproduct, consistent with high levels of decarbonylation.[45] We undertook a second optimization campaign and found that replacing dtbppy ligand with phenanthroline and quinuclidine base with potassium benzoate suppressed formation of the bis-alcohol byproduct and

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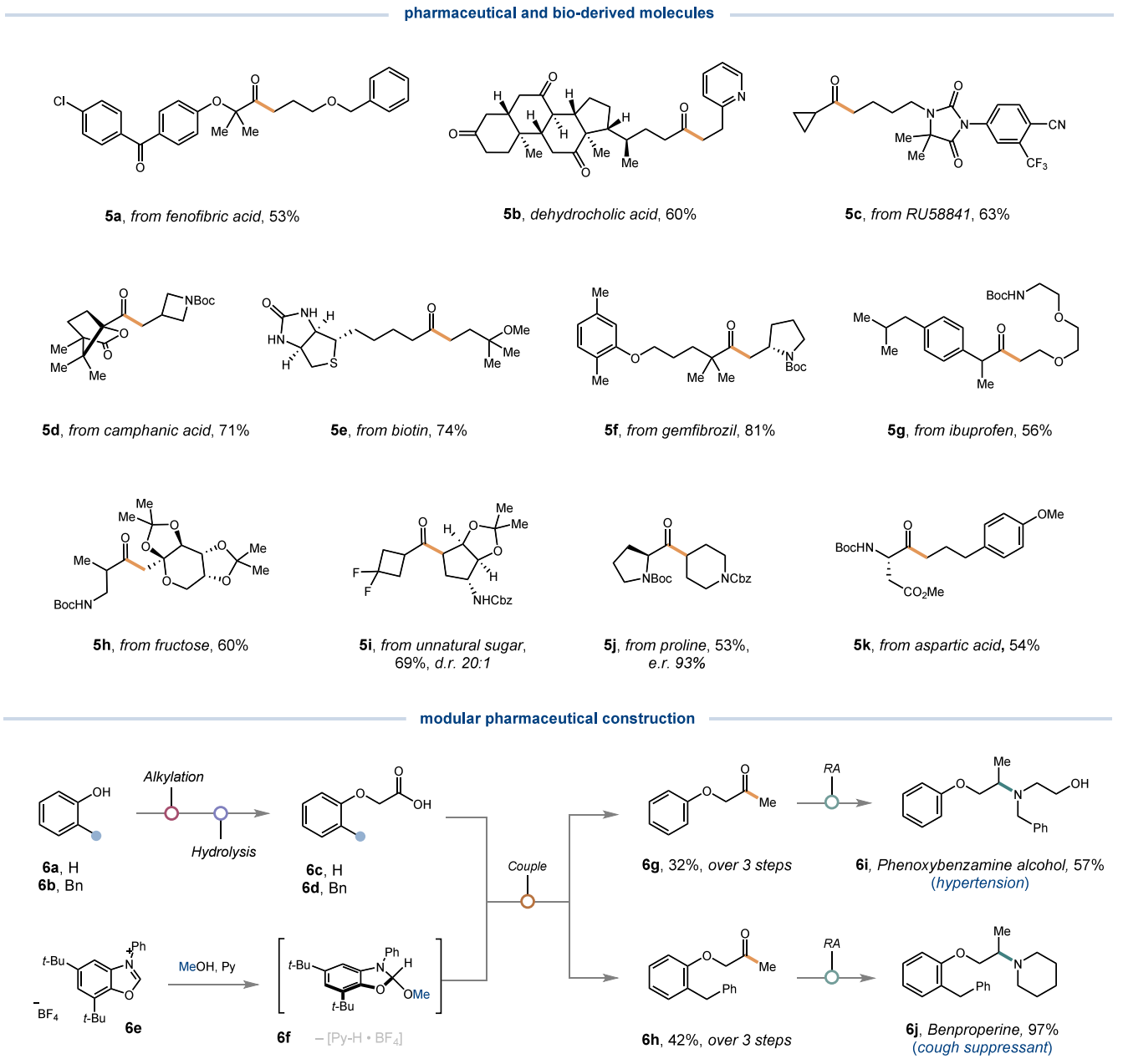

Figure 3. Complex molecule scope and pharmaceutical synthesis. See standard reaction details, Figure 2. RA: reductive amination.

afforded good to excellent yields with tertiary carboxylic acids. These modified conditions proved general across this set of challenging substrates.

Under these modified conditions, tertiary carboxylic acids underwent efficient coupling to afford ketones in good to excellent yield (**4v**–**4z**, 43–78%). We also gained access to bicyclo[1.1.1]pentane and bicyclo[2.2.2]octane scaffolds (**4w** and **4v**) – valuable bioisosteres of *para*-substituted phenyl rings.[46]

Importantly, this transformation was effective with both strained (**4w**, 78%; **4x**, 43%; and **4y**, 72%) and non-strained or caged, tertiary carboxylic acids (**4v**, 43% and **4z**, 63%). This finding is notable, as historically non-strained tertiary carboxylic acids have posed challenges in C–C coupling reactions; however, we were pleased to observe that these scaffolds are well tolerated under the present conditions. Aryl carboxylic acids proved effective, delivering products with varied electronic properties (**4aa**–**4af**, 48–61%). Moreover, 1,4-dicarbonyls (**4ad**) were effectively constructed using this approach, providing access to heterocyclic condensation pathways.

We next explored the applicability of the method to the functionalization of complex pharmaceutical and bio-relevant molecules (Figure 3). A range of pharmaceuticals was successfully coupled, including fenofibric acid (**5a**, 53%), dehydrocholic acid (**5b**, 60%), RU-58841 derivative (**5c**, 63%), gemfibrozil (**5f**, 81%), and ibuprofen (**5 g**, 56%). Bio-derived molecules, such as biotin (**5e**, 74%), camphanic acid (**5d**, 71%), and fructose (**5 h**, 60%), proved to be viable substrates, indicating the mild nature of these conditions. Unnatural sugars (**5i**, 69%) and simple amino acids, such as proline (**5j**, 53%) and aspartic acid (**5k**, 54%), were well tolerated. Moreover, coupling of enantiopure

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proline afforded enantioenriched ketone adduct **5j** in 93% e.r.- enantioenriched ketones are highly valued due to their importance in medicinal and synthetic chemistry.[47−49] Notably, the reaction conditions accommodate a range of sensitive functionalities. Specifically, ultra-performance liquid chromatography (UPLC) analysis confirmed retention of lactone (**5d**), preservation of ketal (**5h** and **5i**), and absence of E1cB byproducts (**5 h** and **5i**). Together, these examples highlight the potential of the method to facilitate the late-stage diversification of medicinally relevant compounds − offering a much-improved chemical space.[50]

While the current protocol requires pre-activation of both the alcohol and carboxylic acid coupling partners, the methodology enables the direct use of widely available native functional group precursors and provides reliable access to structurally complex, three-dimensional ketone architectures. At present, the reaction has been developed primarily for medicinal chemistry applications, where modularity, substrate availability, and rapid analogue synthesis are often prioritized over process-scale efficiency and atom economy. In this context, the platform has proven effective for the rapid construction of diverse compound libraries. Future efforts directed toward telescoped activation/coupling sequences, automated workflows, and more atom-economical variants may further improve the operational simplicity and scalability of the transformation.

To further demonstrate the synthetic utility of the method, we targeted the modular construction of pharmaceutical compounds from readily available starting materials. Specifically, we aimed to synthesize phenoxybenzamine alcohol (**6i**) and benproperine (**6j**) from simple starting materials: methanol and phenol (**6a**) or benzylphenol (**6b**). As shown in Figure 3, the sequence of ethyl bromoacetate alkylation, base hydrolysis, and methanol cross-coupling efficiently produced the precursors to phenoxybenzamine alcohol (**6 g**, 32% overall) and benproperine (**6 h**, 42% overall). These ketones underwent reductive amination to furnish the desired phenoxybenzamine alcohol (**6i**) and benproperine (**6j**) in 57% and 97% yield, respectively.

Given the natural variety and abundance of feedstock alcohols, we wondered whether it might be possible to construct ketones using only alcohol coupling partners. Recently, our group demonstrated that alcohols can undergo deoxygenative radical formation followed by trapping of *p*-toluenesulfonyl cyanide to afford the corresponding nitriles.[15] These nitriles serve as 'masked' carboxylic acids that can be revealed through acid or base hydrolysis. We envisioned a sequence wherein a nitrile species, generated from the alcohol coupling partner, would be converted to a carboxylic acid and, upon exposure to our reaction conditions, merge with a second alcohol to ultimately furnish a ketone product (Figure 4). This overall transformation exemplifies a formal double deoxygenative C1 coupling strategy we term 'SOMO stitching.'

In practice, we converted a range of alcohols (**7a**, **7d**, **7 g**, **7j**) into the corresponding nitriles (34−57%), which were hydrolyzed to the respective acids in excellent yields (81−98%). Acidic or basic conditions were interchangeable for all nitrile hydrolyses, making this an attractive strategy for substrates sensitive to either side of the pH scale; no column purification or recrystallization was required. These carboxylic acids were subsequently cross-coupled with alcohol partners (**7b**, **7e**, **7 h**, **7k**) to furnish complex ketone scaffolds in good yields (55−62%, **7c**, **7f**, **7i**, **7 l**). The SOMO-based C1 logic provides a strategic approach to target construction in cases where the corresponding carboxylic acid synthons are not readily accessible, despite the additional synthetic steps required. This SOMO C_1 stitching strategy complements and improves upon existing organometallic C_1 approaches in terms of chemoselectivity and late-stage capability.[15]

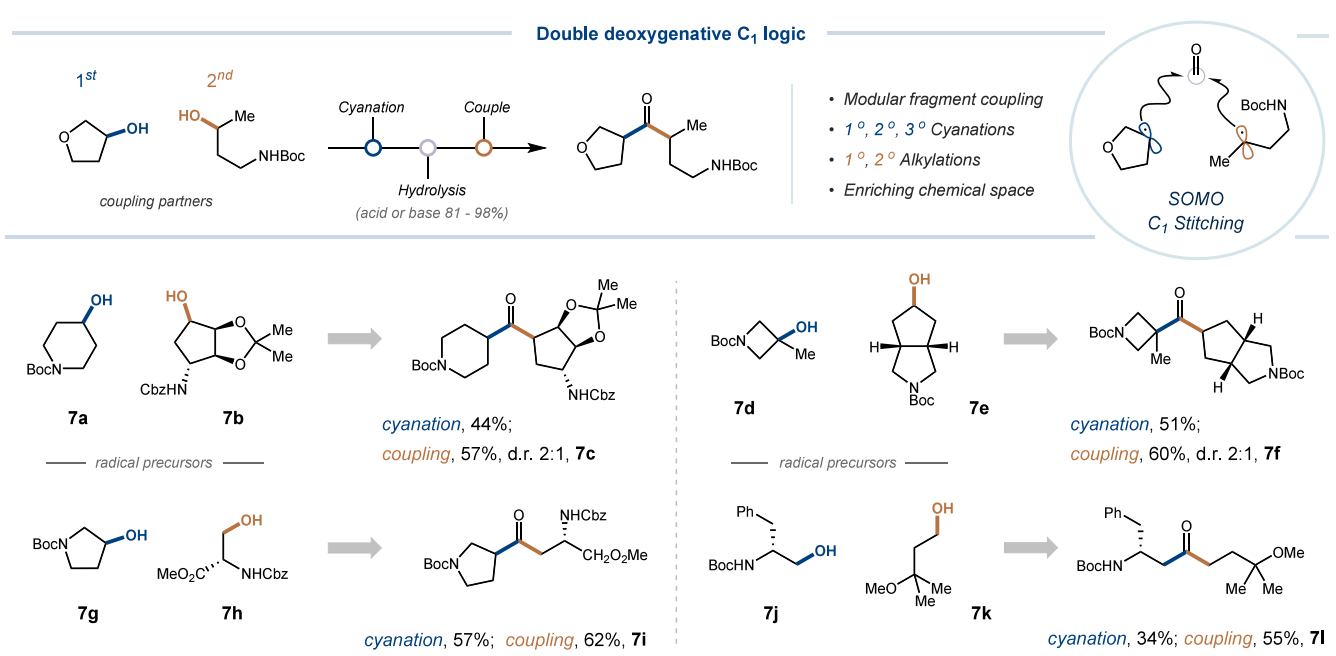

Figure 4. SOMO C1 stitching. Reactions were performed on a 0.5 mmol scale. Cyanations: alcohol (1.0 equiv), NHC (4b, 1.2 equiv), pyridine (1.5 equiv), MTBE (0.1 M), 30 min; 4-CzPN (5 mol %), TsCN (1.5 equiv), Bz_2O (1.0 equiv), 2,4,6-Trimethylpyridine (3.0 equiv), acetone:water (15:1, 0.03 M), blue LEDs, 8 h. Hydrolysis: nitrile (1.0 equiv), HCl (37%) 4 h, then Na_2CO_3 (3.0 equiv), Boc_2O (1.2 equiv), 16 h / NaOH (10.0 equiv), methanol: water (1:1, 0.25 M), 5 h. DDC: standard reaction details, Figure 2. Isolated yields are reported.

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3. CONCLUSIONS

In summary, we describe herein a double deoxygenative coupling of alcohols and carboxylic acids that enables the construction of diverse sp^3-rich ketone scaffolds from simple starting materials. The generality of this approach is reflected in its broad substrate scope (>80 unique coupling partners), encompassing multiple classes, including primary, secondary, tertiary, benzylic, benzoic, aryl, and α-heteroatom carboxylic acids, many of which are poorly tolerated under existing methods. The new platform is exceptionally mild, as evidenced by its ability to access enantioenriched α-amino ketones and achieve late-stage diversification of pharmaceuticals. Applications to downstream transformations are highlighted through the synthesis of relevant pharmaceuticals bearing hydrogen or carbon isotope enrichment. Finally, the method enables coupling of two alcohol partners via a SOMO C_1 stitching strategy. We anticipate that this method will find broad application in medicinal chemistry.

METHODS

General Procedure for Ketone Formation

Acid Activation. An 8 mL vial was charged with acid (0.5 mmol, 1.0 equiv), di-2-pyridyl carbonate (118 mg, 0.55 mmol, 1.1 equiv), DMAP (0.6 mg, 5.0 μmol, 1.0 mol %), followed by DMSO (1.0 mL, 0.5 M). The mixture was stirred for 0.5−4 h at rt before diluting with DMSO (5.0 mL).

Alcohol Activation. An oven dried 8 mL vial was charged with alcohol (0.625 mmol, 1.25 equiv, if liquid it was added after addition of MTBE) and NHC (297 mg, 0.75 mmol, 1.5 equiv). The vial was purged with nitrogen, followed by the addition of dry TBME (3.0 mL). The mixture was vigorously stirred for 5 min prior to the dropwise addition of pyridine (60 μL, 0.75 mmol, 1.5 equiv). The mixture was stirred at rt for 15 min. before syringe filtering and eluting with additional MTBE (3.0 mL).

Reaction. A 40 mL oven dried vial was charged with quinuclidine (84 mg, 0.75 mmol, 1.5 equiv), $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol %), $NiBr_2(dtppy)$ (12 mg, 25.0 μmol, 5.0 mol %) and solutions from acid and alcohol activation. The mixture was purged with nitrogen for 5.0 min.

The reaction mixture was diluted with EtOAc (100 mL), washed with water (2 × 100 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography using EtOAc/hexanes as eluent.

General Procedure for Nitrile Formation

1° and 2° Alcohols. To a vial containing alcohol (0.5 mmol, 1 equiv) and NHC (237 mg, 0.6 mmol, 1.2 equiv) was added MTBE (7.5 mL). The suspension was sonicated for 1 min. and stirred for 5 min before the slow dropwise addition of pyridine (1.5 equiv, 0.75 mmol, 60 μL). The mixture was stirred for 30 min. with occasional shaking. The mixture was diluted with MTBE (7.5 mL) and syringe filtered into a vial containing a solution of 4-CzIPN (8 mg, 5 mol %), TsCN (136 mg, 0.75 mmol, 1.5 equiv), Bz_2O (121 mg, 0.5 mmol, 1.0 equiv), 2,4,6-Trimethylpyridine (198 μL, 1.5 mmol, 3.0 equiv) and water (1 mL) in acetone (15 mL). The mixture was purged with nitrogen (5 min.) at 0 °C and put into PennPhD m1 integrated photoreactor (m2 450 nm LED plate, 100% intensity, 6800 rpm fans, 1000 rpm stirring) and irradiated for 8 h. The mixture was concentrated under nitrogen, redissolved in with EtOAc (50 mL) and washed with water (50 mL, spiked with brine). The aqueous was re-extracted with EtOAc (50 mL), organics combined, dried with Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by normal phase flash chromatography using EtOAc/hexanes as eluent.

3° Alcohols. To a vial containing alcohol (0.5 mmol, 1 equiv) and NHC-5 (278 mg, 0.6 mmol, 1.2 equiv) was added α, α, α-Trifluorotoluene (5 mL). The suspension was sonicated for 1 min. and stirred for 5 min before cooling to −20 °C and a slow dropwise addition of pyridine (1.5 equiv, 0.75 mmol, 60 μL). The mixture was stirred for 2 h, while allowing to warm in cooling bath. The mixture was diluted with α, α, α-Trifluorotoluene (10 mL) and syringe filtered into a vial as previously described. Sequence follows previous procedure.

General Procedure for Carboxylic Acid Formation

Acid. To a vial containing nitrile (1.0 equiv) was added HCl (37%, 0.25 M). The solution was stirred at 100 °C for 4 h. The solution was concentrated under nitrogen. To this vial was added Na_2CO_3 (3.0 equiv) followed by water and acetone (1:1, 0.25 M). The mixture was stirred for 10 min. before addition of $(Boc)_2O$ (1.2 equiv). The mixture was stirred overnight, diluted with EtOAc (50 mL) and washed with water (50 mL, spiked with 1 M HCl). The aqueous was re-extracted with EtOAc (50 mL), organics combined, dried with Na_2SO_4, filtered and evaporated *in vacuo*. Compounds needing purification are purified by preparative reverse phase HLPC (C18, 1% formic acid modifier); these compounds are noted as such.

Base. To a vial containing nitrile (1.0 equiv) was added NaOH (10.0 equiv) followed by water and MeOH (1:1, 0.25 M). The mixture was stirred for 5 h at 70 °C. The mixture was diluted with EtOAc (50 mL) and washed with water (50 mL, spiked with 1 M HCl). The aqueous was re-extracted with EtOAc (50 mL), organics combined, dried with Na_2SO_4, filtered and evaporated *in vacuo*. Compounds needing purification are purified by preparative reverse phase HLPC (C18, 1% formic acid modifier); these compounds are noted as such.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.6c02684.

Additional experimental details, mechanistic studies, optimization studies, compound characterization, and spectra (DOCX)

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Author Contributions

VC and REM designed and carried out the experimental work. EL, CNPK and DWCM aided in experimental design. VC and REM wrote the manuscript. All authors approved the manuscript.

Notes

The authors declare the following competing financial interest(s): D.W.C.M. declares a competing financial interest with respect to the integrated photoreactor.

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