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Alcohols as Latent Coupling Fragments for Metallaphotoredox Catalysis: sp^3–sp^2 Cross-Coupling of Oxalates with Aryl Halides

Xiaheng Zhang and David W. C. MacMillan*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States

Supporting Information

ABSTRACT: Alkyl oxalates, prepared from their corresponding alcohols, are engaged for the first time as carbon radical fragments in metallaphotoredox catalysis. In this report, we demonstrate that alcohols, native organic functional groups, can be readily activated with simple oxalyl chloride to become radical precursors in a net redox-neutral C_{sp^3}–C_{sp^2} cross-coupling with a broad range of aryl halides. This alcohol-activation coupling is successfully applied to the functionalization of a naturally occurring steroid and the expedient synthesis of a medicinally relevant drug lead.

Over the last half-century, cross-coupling reactions, enabled mainly by Pd and Ni catalysts, have had a transformative impact on the synthetic chemistry community.[1] The capacity to generically couple nucleophilic fragments (i.e., boronic acids, organozincs, organostannanes, Grignard reagents, etc.) with electrophilic partners (typically aryl or alkyl halides), with high regiospecificity and functional group tolerance has driven the wide-scale adoption of these methods within both industry and academia. Not surprisingly, practicality and cost issues have spurred ongoing efforts to develop new cross-coupling technologies that rely on naturally occurring, or native, organic functional groups as nucleophile partners in lieu of pregenerated, organometallic-based substrates.

One of the strategies used for engaging fragments bearing native functional groups in cross-couplings is the merger of nickel and photoredox catalysis, a form of metallaphotoredox.[2] In this reactivity paradigm, the photoredox catalyst can generate a nucleophilic radical species from the native functional group (nucleophile partner) as well as modulate the oxidation state of the nickel catalyst, which subsequently serves as a platform for reductive elimination and fragment coupling. Since 2014, our group and others have demonstrated that alkyl radical fragments generated from ubiquitous yet traditionally inert functionality (e.g., carboxylic acids,[3] aliphatic C–H bonds[4]) can be successfully coupled with aryl or alkyl halides to create challenging and/or valuable C_{sp^3}–C_{sp^2} and C_{sp^3}–C_{sp^3} bonds.

Alcohols are among the most widely occurring, naturally abundant organic compounds known[5] and in many cases are considered feedstock chemicals. On this basis, we recently initiated a program to determine if C_{sp^3}–OH bonds could be activated to form nucleophilic partners for metallaphotoredox-based coupling technologies. The advantages of such a method are readily appreciated in that a range of alcohols, from simple to complex, are commercially available, whereas the corresponding boronic acids or esters are not yet broadly accessible or cost-effective. Recently, the Overman group, in collaboration with our lab, reported that relatively strong C–O bonds (~96 kcal/mol)[6] can be generically cleaved to access C_{sp^3} radical fragments from alkyl oxalates under photoredox conditions.[7,8] With this in mind, we questioned whether alkyl radicals generated in a similar manner could be merged with our metallaphotoredox platform as a means to expediently produce C–C bonds from C–O functionality. Moreover, we hoped to employ alcohols as the formal coupling partner via the rapid formation of alkyl oxalates (with inexpensive oxalyl chloride and without purification) prior to addition of the nickel catalyst or electrophile partner. Notably, activation of alcohols as C_{sp^3}-nucleophiles via oxalates would also mask the intrinsic reactivity of the alcohols toward C–O cross-coupling to form ethers.[9] Herein we report our efforts to develop

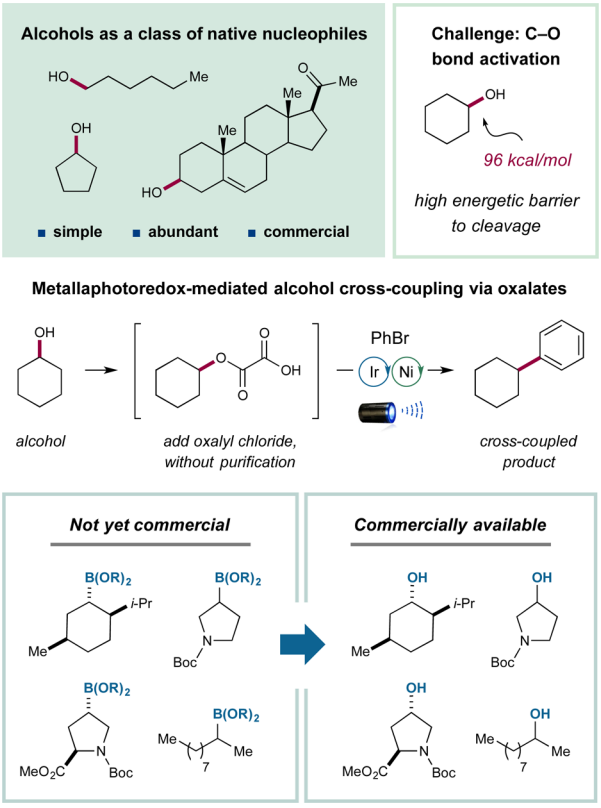

Figure 1. C–C Coupling of alcohols via oxalate activation.

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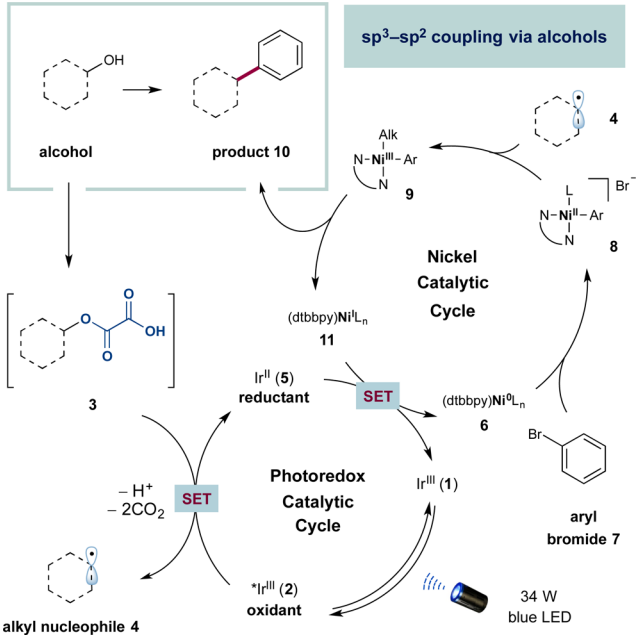
the first general route for efficiently converting a variety of alcohols via their corresponding oxalates into C_{sp^3}–C_{sp^2} coupled products with aryl halides by way of the synergistic action of nickel and photoredox catalysis (Figure 1).[10,11]

The mechanistic details of our proposed transformation are outlined in Scheme 1. Photoexcitation with visible light of the

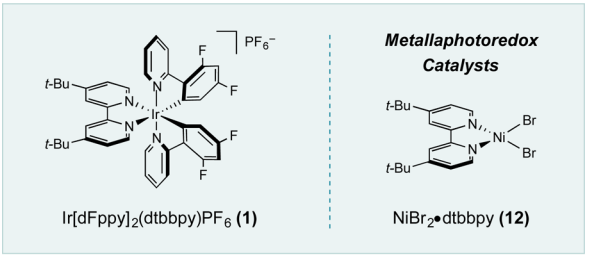
Scheme 1. Steps of Proposed Metallaphotoredox Reaction



iridium(III) photocatalyst, $Ir[dFppy]_2(dtbbpy)PF_6$ (**1**), is known to produce an excited state, $*Ir^{III}$ **2**, which is a strong oxidant ($E_{1/2}^{red}[*Ir^{III}/Ir^{II}]$ = +1.1 V vs saturated calomel electrode (SCE) in MeCN).[12] Based on the previous work by Overman and collaborators, the oxidation of the oxalate after deprotonation of **3** ($E_{p/2}$ = +1.26 V vs SCE in MeCN for the cesium oxalate derivative of *N*-Boc-4-hydroxypiperidine)[13] via single-electron transfer (SET) should be thermodynamically feasible, generating the reduced Ir^{II} species **5** and the alkyl radical **4**, via successive loss of two equivalents of CO_2. At the same time, oxidative addition of aryl bromide **7** to L_nNi^0 species **6** will form the aryl-Ni^{II} species **8**, which should be rapidly intercepted by radical **4** to form the resulting Ni^{III} complex **9**. At this stage, reductive elimination should then enable the desired C_{sp^3}–C_{sp^2} bond formation to deliver the coupled product **10** and Ni^I species **11**. Finally, the two catalytic cycles merge via electron transfer from the reduced Ir^{II} species **5** ($E_{1/2}^{red}[Ir^{III}/Ir^{II}]$ = −1.42 V vs saturated calomel electrode (SCE) in MeCN)[12] to the Ni^I complex **11** ($E_{1/2}^{red}[Ni^{II}/Ni^0]$ = −1.2 V vs SCE in DMF)[14] thereby regenerating both photocatalyst **1** and the Ni^0 catalyst **6**.

Our investigation into this new coupling reaction began with exposure of the oxalate of *N*-Boc-4-hydroxypiperidine (formed using oxalyl chloride, water, and without purification) to methyl 4-bromobenzoate, photocatalyst **1**, $NiBr_2$·dtbbpy (**12**), and a blue LED lamp in the presence of $CsHCO_3$ as base. Initial experiments revealed a significant solvent effect, as the desired coupling adduct was obtained only in tetrahydropyran (THP) (Table 1, entry 2, 8% yield), along with an ester side-product that arises from monodecarboxylation of the oxalate substrate.[15] Notably, an improvement in efficiency was obtained using DMSO as a cosolvent (entry 3, 39% yield). Next, we

Table 1. Optimization of the Oxalate Cross-Coupling[a]



entry	conditions	solvent	temp. (°C)	yield (%)[b]
1	as shown	DMSO	25	0
2	as shown	THP	25	8
3	as shown	THP/DMSO 5:1	25	39
4	as shown	THP/DMSO 5:1	50	52
5	as shown	THP/DMSO 5:1	70	65
6	as shown	dioxane/DMSO 5:1	70	62
7	no photocatalyst	THP/DMSO 5:1	70	0
8	no Ni catalyst	THP/DMSO 5:1	70	0
9	no base	THP/DMSO 5:1	70	0
10	no light	THP/DMSO 5:1	70	0

[a]Performed with photocatalyst **1** (1 mol %), $NiBr_2$·dtbbpy **12** (5 mol %), aryl halide (1.0 equiv), oxalate (1.3 equiv) and $CsHCO_3$ (1.5 equiv). [b]Yields were obtained by ^1H NMR analysis of the crude reaction mixtures using an internal standard.

hypothesized that increased temperature should improve the rate of the desired double decarboxylation step. Indeed, superior yields, along with minimal quantities of ester formation, were obtained when the transformation was performed at 70 °C (entry 5, 65% yield). It should be noted that comparable yields are also possible when 1,4-dioxane is employed as the reaction medium in lieu of THP. Control experiments conducted in the absence of photocatalyst, nickel catalyst, base, or light resulted in no product, emphasizing the crucial role of all these components in the dual catalytic cycle.

With these optimized conditions in hand, we next began an exploration of the scope of the aryl bromide component. As shown in Table 2, aryl rings that incorporate a large variety of functional groups are readily tolerated. In summary, electron-deficient aryl bromides bearing carbonyl, sulfonyl, trifluoromethyl, and nitrile moieties provide good yields (>55%, products **13**–**21**), whereas the coupling of electron-rich 4-bromotoluene was achieved with moderate efficiency (**22**, 42% yield). Given the importance of nitrogen-containing heterocycles in the production of bioactive molecules, we were delighted to find that a diverse array of substituted pyridyl bromides readily participate in this new coupling (products **23**–**28**). Chemoselective oxidative addition to the bromide substituent was observed when 2-chloro-4-bromopyridine was employed to generate **24** in 56% yield.

We next sought to explore the generality of this transformation with respect to the alcohol and the corresponding oxalate adduct. Further underscoring the practicality of this method, all oxalates were obtained by treatment of the alcohol with oxalyl chloride, which upon aqueous workup was employed directly (and

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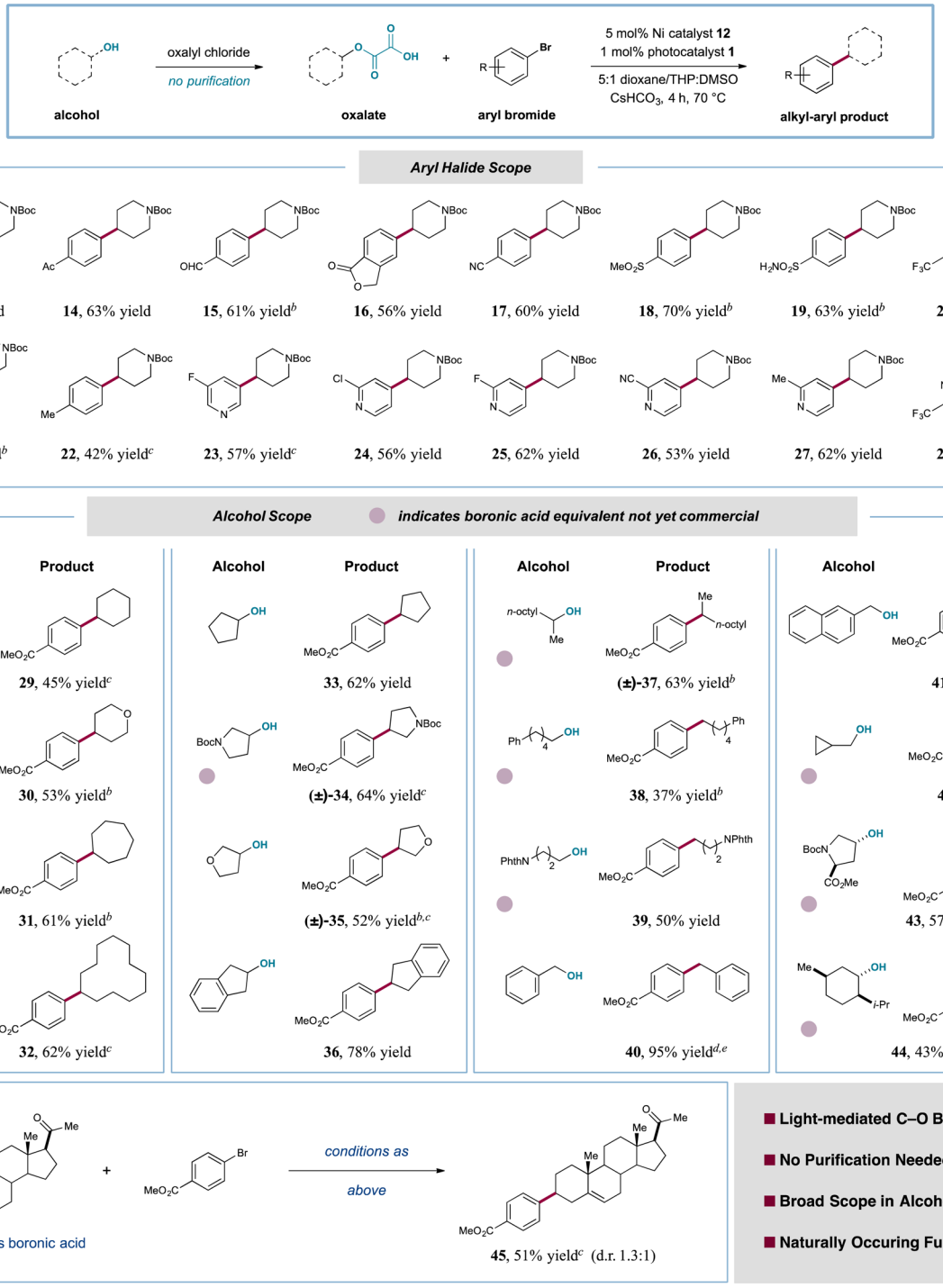
Table 2. From Alcohols to Alkyl-Aryl Products: Scope of Metallaphotoredox Reaction of Oxalates with Aryl Bromides[a]



[a]All yields are isolated. Performed with photocatalyst **1** (1 mol %), $NiBr_2$·dtbbpy **12** (5 mol %), aryl halide (1.0 equiv), oxalate (1.3 equiv) and $CsHCO_3$ (1.5 equiv). Ratios of diastereomers determined by ^1H NMR. For detailed experimental procedures, see the Supporting Information. [b]80 °C. [c]10 mol % **12**. [d]25 °C, 15 h. [e]Dioxane as solvent only. [f]50 °C, 15 h. [g]15 mol % **12**.

without purification) in the metallaphotoredox protocol. Oxalates derived from secondary alcohols were found to be generically successful in this transformation. For example, *N*-Boc-piperidinyl, cyclohexyl, and tetrahydropyranyl oxalates as well as larger ring oxalates were found to readily undergo fragment coupling (45−62% yield, products **29**−**32**). Moreover, 5-membered ring oxalates, including *N*-Boc-pyrrolidine and tetrahydrofuran derivatives, were also effective nucleophile partners (52−78% yield, products **33**−**36**). Notably, oxalates derived from acyclic secondary alcohols provide the desired adducts (e.g., **37**, 63% yield). The union of primary alcohol-derived oxalates with aryl rings can also be accomplished using this metallaphotoredox dual catalysis method (37−95% yield, products **38**−**42**). Despite moderate efficiency in some cases (with the exception of benzyl alcohols), we anticipate that these alcohol substrates will find broad utility throughout medicinal chemistry studies. As expected, when the oxalate of cyclopropanemethanol was employed, ring opening was observed,

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consistent with a radical intermediate,[16] to generate the homoallyl-bearing product **42**. Complex oxalates were also successfully employed, showcasing the wide utility of this transformation. For example, substituted *N*-Boc-proline methyl ester and highly substituted cyclohexyl fragments were coupled with methyl 4-bromobenzoate to provide adducts **43** and **44** in useful yields and in good d.r. (7:1 and >20:1, respectively). Additionally, adduct **45** was obtained from the oxalate of pregnenolone, a naturally occurring steroid, further emphasizing the potential of employing native functionality to access new structural analogues or to perform late stage functionalization.

Last, to emphasize the synthetic value of using alcohols as C_{sp^3}-nucleophiles, we applied this metallaphotoredox protocol to the synthesis of **46**, a valuable intermediate used in the production of Q203, a promising candidate for the treatment of tuberculosis.[17] As summarized in Figure 2, the 4-aryl-*N*-Boc-piperidine adduct

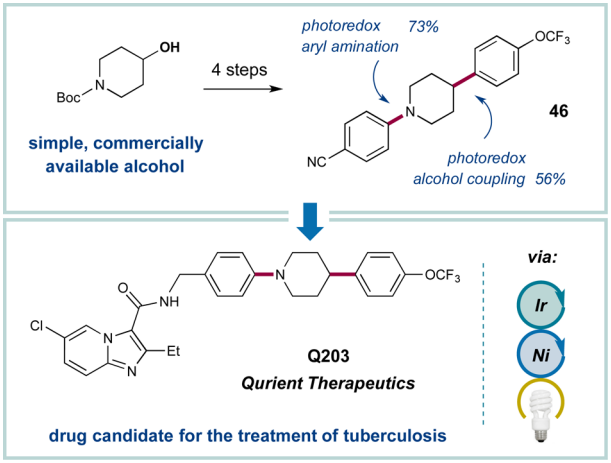

Figure 2. Synthesis of a precursor to Q203 via sequential visible light photoredox C−C and C−N coupling reactions.

was obtained in good yield using the optimized oxalate coupling conditions. After removal of the Boc group, the secondary amine was subsequently coupled with 4-cyanophenyl bromide using our previously published metallaphoto amination protocol[18] to deliver precursor **46** in excellent yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09533.

Experimental details (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*dmacmill@princeton.edu

Notes

The authors declare no competing financial interest.

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