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Facile Preparation of Spirolactones by an Alkoxycarbonyl Radical Cyclization Cross-Coupling Cascade

Nicholas A. Weires, Yuriy Slutskyy,[a] and Larry E. Overman*

Abstract: An alkoxycarbonyl radical cyclization cross-coupling cascade has been developed that allows functionalized γ-butyrolactones to be prepared in one step from simple tertiary alcohol-derived homoallylic oxalate precursors. The reaction succeeds with aryl and vinyl electrophiles and is compatible with heterocyclic fragments in both coupling partners. This chemistry allows for the rapid construction of spirolactones, which are of interest in drug discovery endeavors.

The γ-butyrolactone fragment is a common structural motif found in myriad drugs and biologically active natural products.[1] As such, numerous synthetic strategies have been developed for the preparation of γ-butyrolactones, including lactonization of hydroxyacids, displacement of leaving groups with pendent carboxylic acid nucleophiles, and redox manipulations of furans and other oxygen heterocycles.[1] Among the most common strategies are cyclizations of carboxylic acids onto pendent C–C double bonds. Indeed, such cyclizations have been relied upon for decades, with classic examples such as Corey's iodolactonization approach to prostaglandin analogs[2] being mirrored by more modern methods, including photoredox- and transition metal-catalyzed processes.[3]

A strategically distinct approach to the formation of γ-butyrolactones involves cyclization of 2-oxygenated radicals onto pendent alkenes, allowing for the formation of a new C–C bond and a new carbon-centered radical that can be further functionalized. Such a radical cyclization strategy was leveraged by Sherburn and coworkers in their total synthesis of podophyllotoxin,[4] and later in their syntheses of other lignan natural products.[5] Utilizing a thionocarbonate radical precursor, these authors were able to realize a 5-exo radical cyclization/intramolecular arylation of a pendent alkene to give the functionalized γ-butyrolactone found in the core of the lignan natural products. Drawing inspiration from approaches such as Sherburn's, we sought to develop an alkoxycarbonyl radical 5-exo cyclization/bimolecular cross-coupling cascade that would accomplish an analogously rapid increase in molecular complexity, but under the mild conditions offered by photoredox catalysis.[6]

Given our group's interest in alcohol-derived oxalates as readily accessible precursors to carbon-centered radicals,[7] we reasoned that oxalates derived from homoallylic alcohols could serve as suitable substrates for photoredox-mediated alkoxycarbonyl radical 5-exo cyclization triggered by loss of a single equivalent of CO_2. Indeed, cyclizations of alkoxycarbonyl radicals have been utilized by the groups of Bachi,[8] Yokoyama,[9] and others to construct γ-butyrolactones from precursors such as homoallylic selenocarbonates and N-alkoxyoxalyl-2-thiopyridones. These earlier studies showed that 5-exo cyclizations of alkoxycarbonyl radicals are faster than decarboxylation even when a tertiary radical would be produced in the latter process.[10,11] Moreover, given the recent developments in the field of nickel-photoredox dual catalysis,[12,13,14,15] we expected that the carbon-centered radical generated upon cyclization could be intercepted by nickel, allowing for a further cross-coupling functionalization event to occur. Such a transformation would not only contribute to the burgeoning field of alkene difunctionalization,[16,17,18,19,20] forging two new C–C bonds in a single transformation, but would also allow for rapid and efficient access to functionalized γ-butyrolactones.
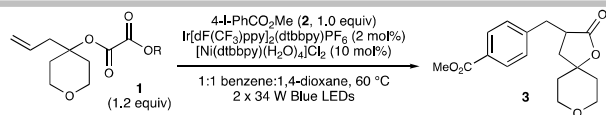
To initiate our study, we opted to employ homoallylic oxalate salts **1** derived from tetrahydropyran-4-one, as the product after cyclization and cross-coupling with aryl iodide **2** would be spiro-heterocyclic lactone **3** (Table 1). Notably, such spiro heterocycles are of interest in drug discovery as a result of their inherent three-dimensionality and uniquely rigid structures.[21,22] Under optimal conditions,[23] it was found that spirocycle **3** was formed in 87% yield when oxalate **1** was used in slight excess (1.2 equiv) to aryl iodide electrophile **2** in the presence of 2 mol% of the heteroleptic photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and 10 mol% of the nickel complex $[Ni(dtbbpy)(H_2O)_4]Cl_2$[24] (entry 1). The yield of **3** was significantly lower using the corresponding aryl bromide (entry 2). Using benzene as a cosolvent was found to be critical in order to minimize competitive C–H arylation of 1,4-dioxane.[25,26] Importantly, the reaction did not proceed in the absence of nickel, the iridium photocatalyst, or visible light (entries 3–5). To our surprise, the choice of cesium as the counterion of oxalate substrate **1** was found to be crucial for productive reactivity, as the corresponding lithium salt yielded none of the desired product (entry 6).[27]

Table 1. Optimized coupling conditions and control reactions.[a]

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[a] Reaction conditions: 0.10 mmol 4-I-PhCO$_2$Me (**2**), 1.2 equiv oxalate **1**, 2 mol% Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$, 10 mol% [Ni(dtbbpy)(H$_2$O)$_4$]Cl$_2$, 1:1 benzene:1,4-dioxane (0.033 M), 2 x 34W Blue LEDs, 60 °C, 2 h. [b] Yield determined by ^{1}H NMR spectroscopic analysis using 1,2-dibromo-4,5-methylenedioxybenzene as an external standard. dF(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine; dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl.

Having identified suitable reaction conditions, we sought to explore the generality of the coupling with iodide **2** with regard to the oxalate substrate (Scheme 1). The simplest possible homoallylic oxalate, derived from 3-buten-1-ol, coupled without event, producing lactone **4** in 73% yield. There did not appear to be a significant Thorpe–Ingold effect in the cyclization,[28] as the analogous oxalate possessing geminal dimethyl substitution furnished lactone **5** in 73% yield as well. Because of the aforementioned importance of spirocyclic scaffolds in drug development, elaboration of oxalate derivatives of cyclic tertiary alcohols was our major focus. A wide variety of spirocyclic lactone products could be fashioned in good yields, including those possessing 4, 5, and 6 membered rings (**6**–**8**, respectively). Oxygen heterocycles were readily incorporated in the coupling, as illustrated by the formation of dioxospirocyclic products **3** and **9**. Notably, formation of lactone **9** demonstrates that quaternary centers can be fashioned in the *5-exo* radical cyclization. Nitrogen-containing spirocyclic lactones harboring piperidine[29] and tropane functionalities, **10** and **11**, were formed in moderate to high yield. More complex carbocycles such as adamantane could also be employed, allowing for the formation of lactone **12** in 84% yield. Finally, an oxalate derived from estrone was utilized to prepare spirocycle **13** in 80% yield and 4:1 diastereoselectivity at the newly formed stereocenter.

**Scheme 1.** Scope of the oxalate in the coupling.[a]
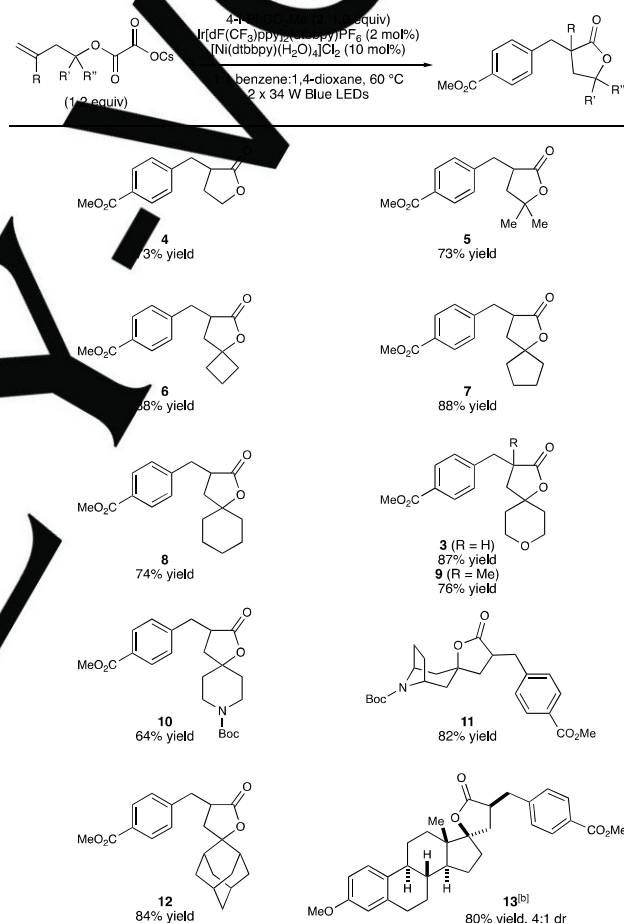
[a] Reaction conditions: 0.10 mmol 4-I-PhCO$_2$Me (**2**), 1.2 equiv oxalate, 2 mol% Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$, 10 mol% [Ni(dtbbpy)(H$_2$O)$_4$]Cl$_2$, 1:1 benzene:1,4-dioxane (0.033 M), 2 x 34W Blue LEDs, 60 °C, 2 h. Isolated yields of purified products shown. [b] 18 h. dF(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine; dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl.

In contrast to the efficiency of the coupling reaction for the formation of γ-butyrolactone products, the analogous *6-exo* cyclization cross-coupling cascade (e.g., **14** → **15**, Eq. 1) was much less efficient, yielding only 24% of δ-valerolactone **15**.

(Eq 1)
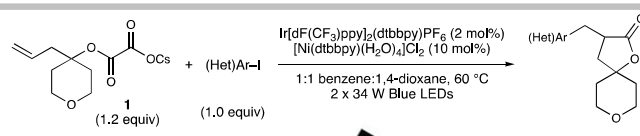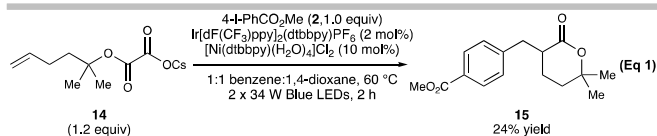
The scope of the cyclization/cross coupling reaction with respect to the iodide electrophile is summarized in Scheme 2.[21] Simple aryl iodides could be employed, including iodobenzene and 4-iodotoluene, delivering products **16** and **17**, respectively. Moreover, steric effects were not deleterious in the coupling, as illustrated by formation of lactone **18** in 75% yield. Electron-rich aryl iodides were well tolerated, as demonstrated by the production of lactones **19**–**21**. The formation of compound **21** illustrates the potential of using this transformation to diversify the structure of synthetic peptides. In addition, a biaryl iodide could be employed, furnishing coupled product **22**. The coupling was also tolerant of sensitive functionalities, including unprotected benzylic alcohols, free aldehydes, and enolizable ketones giving products **23**–**25**, whose syntheses by benzylation of the corresponding unsubstituted lactone enolates would be problematic. Heteroaryl iodides could also be utilized, furnishing pyridine **26** and indole **27** in 67% and 74% yields, respectively.

Scheme 2. Scope of the (hetero)aryl iodide in the coupling.[a]
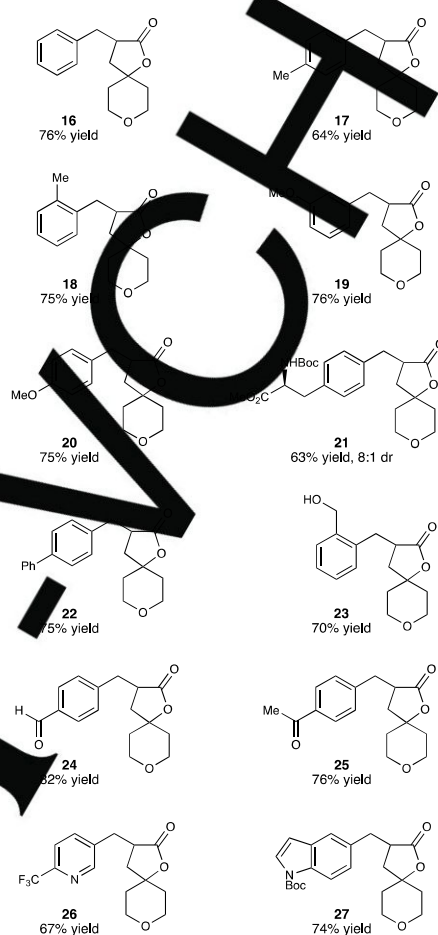
[a] Reaction conditions: 0.10 mmol (hetero)aryl iodide, 1.2 equiv oxalate **1**, 2 mol% Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, 10 mol% [Ni(dtbbpy) (H₂O)₄]Cl₂, 1:1 benzene:1,4-dioxane (0.033 M), 2 x 34W Blue LEDs, 60 °C, 2 h. Isolated yields of purified products shown. dF(CF₃)ppy = 2-(2,4- difluorophenyl)-5-trifluoromethylpyridine; dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl.

We also examined the utilization of vinyl iodides in the cross-coupling sequence (Scheme 3).[30] Both *E* and *Z* vinyl iodides derived from ethyl acrylate coupled with tropanone-derived oxalate **28** with complete stereoretention, delivering spirolactones **29** and **30** in good yields. In addition, more highly substituted electron-deficient vinyl iodides were also tolerated, as demonstrated by the formation of products **31** and **32**. Notably, unactivated vinyl iodides could also be employed in the coupling, delivering spiro tricyclic lactones **33** and **34**.
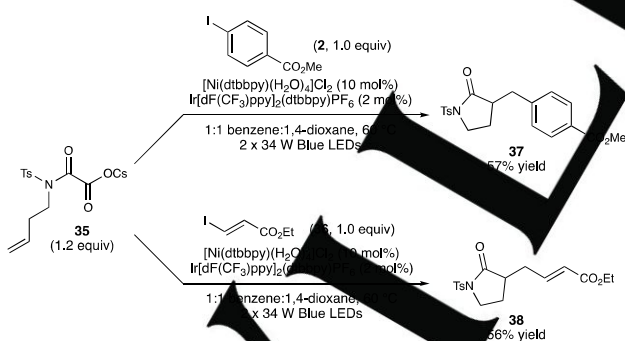
Scheme 3. Scope of the vinyl iodide in the coupling.[a]
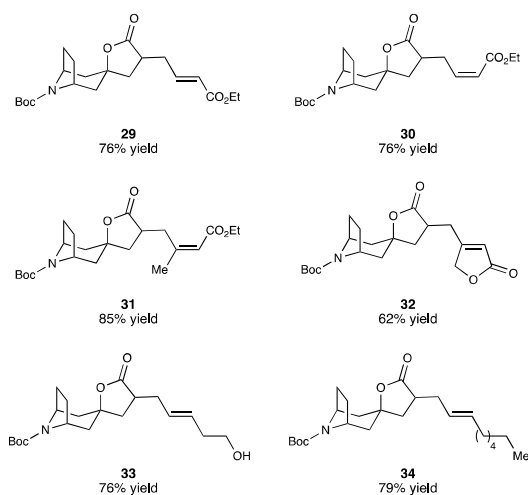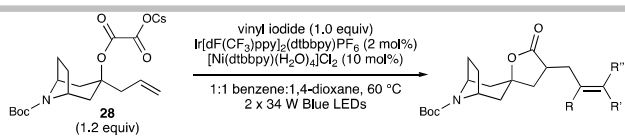
[a] Reaction conditions: 0.10 mmol vinyl iodide, 1.2 equiv oxalate **28**, 2 mol% Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, 10 mol% [Ni(dtbbpy)(H₂O)₄]Cl₂, 1:1 benzene:1,4-dioxane (0.033 M), 2 x 34W Blue LEDs, 60 °C, 2 h. Isolated yields of purified products shown. dF(CF₃)ppy = 2-(2,4- difluorophenyl)-5-trifluoromethylpyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl.

Although not a major focus of our study, we briefly examined couplings of an oxamate substrate in order to construct functionalized γ-butyrolactam products (Scheme 4). To our delight, oxamate **35**, derived from 3-buten-1-amine, could be coupled with both aryl iodide **2** and vinyl iodide **36**, furnishing functionalized lactam products **37** and **38** in 57% and 56% yields respectively.

**Scheme 4.** Couplings utilizing an oxamate substrate.[a]

[a] Reaction conditions: 0.10 mmol aryl or vinyl iodide, 1.2 equiv oxamate **35**, 2 mol% Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, 10 mol% [Ni(dtbbpy)(H₂O)₄]Cl₂, 1:1 benzene:1,4-dioxane (0.033 M), 2 x 34W Blue LEDs, 60 °C, 2 h. Isolated yields of purified products shown. Ts = tosyl; dF(CF₃)ppy = 2-(2,4- difluorophenyl)-5-trifluoromethylpyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl.

A plausible dual-catalytic mechanism for the *5-exo* radical cyclization cross-coupling cascade is outlined in Scheme 5. Irradiation of the heteroleptic iridium photocatalyst Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ with visible light generates the long-lived (τ = 2.3 μs) excited state *Ir^{III}, which is a strong oxidant ($E_{1/2}^{red}$ [*Ir^{III}/Ir^{II}] = +1.21 V vs saturated calomel electrode (SCE) in MeCN)[31]

capable of oxidizing the cesium oxalate ($E_{1/2}^{red}$ = +1.28 V vs SCE in MeCN for *t*-BuOCOCO₂Cs)[7] via single-electron transfer (SET). The oxidized substrate then undergoes decarboxylation, losing a single equivalent of CO₂ and yielding an intermediate alkoxycarbonyl radical that rapidly engages the pendent olefin in a *5-exo* cyclization, generating a new primary carbon-centered radical[32] and the reduced state of the photocatalyst, Ir^{II}. Concurrently, the Ni⁰ catalyst, likely generated by *in situ* reduction of the Ni^{II} precatalyst by the photocatalyst,[12b,13] undergoes oxidative addition into the aryl halide, furnishing an Ar–Ni^{II} species that is rapidly intercepted by the primary carbon-centered radical, producing a high-valent Ni^{III} intermediate.[13,34] This species is then poised to undergo reductive elimination, generating the functionalized γ-butyrolactone product and a Ni^{I} complex. Finally, SET from the reduced state of the photocatalyst [Ir^{II}, $E_{1/2}$ [Ir^{III}/Ir^{II}] = –1.37 V vs SCE in MeCN][31] to Ni^{I} ($E_{1/2}^{red}$ [Ni^{II}/Ni⁰] = –1.2 V vs SCE in DMF)[33] regenerates Ir^{III} and Ni⁰, simultaneously completing both catalytic cycles. Alternatively, a catalytic pathway involving trapping of the primary carbon-centered radical by Ni⁰ and oxidative addition of the resulting Ni^{I} species into the aryl halide to produce the key Ni^{III} intermediate is also plausible.[34] The quantum yield (Φ) for the lactonization cross-coupling cascade was determined to be 0.26 by the method of Scaiano and coworkers,[35,36] indicating that chain propagation likely does not occur under our reaction conditions.

Scheme 5. Plausible dual-catalytic mechanism of the coupling.
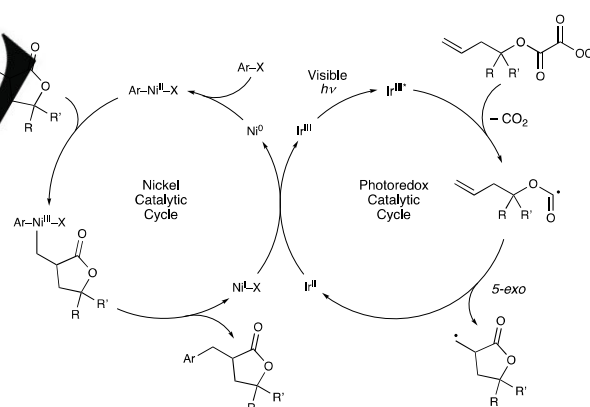
In summary, an alkoxycarbonyl radical *5-exo* cyclization cross-coupling cascade has been developed that allows for rapid access to functionalized γ-butyrolactones, notably ones having rigid spirocyclic structures. The coupling proceeds under mild conditions (i.e. visible light, nearly equimolar quantities of coupling partners, low reaction temperatures, etc.) and is tolerant of heterocyclic fragments on both the oxalate substrate and aryl iodide or vinyl iodide coupling partner. The homoallylic cesium oxalates used in this study were rapidly accessed in high yield in 2–3 steps from simple ketones,[36] allowing for facile access to a diverse array of functionalized lactone products in one additional step. These studies demonstrate that alkyl oxalate cesium salts serve as exemplary precursors to alkoxycarbonyl

radicals, with benefits including straightforward activation via visible-light photoredox catalysis and generation of CO_2 as the sole byproduct.

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23 examples
63–88% yield

6 examples
62–85% yield
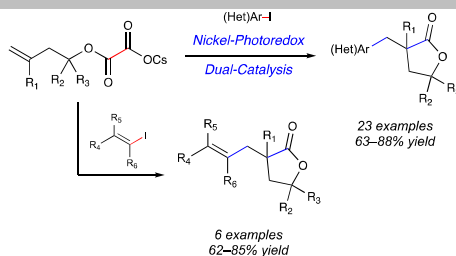
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