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Communication

Photocatalytic Dehydroxymethylative Arylation by Synergistic Cerium and Nickel Catalysis

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ABSTRACT: Under mild reaction conditions with inexpensive cerium and nickel catalysts, easily accessible free alcohols can now be utilized as operationally simple and robust carbon pronucleophiles in selective C(sp^3)−C(sp^2) cross-couplings. Facilitated by automated high-throughput experimentation, sterically encumbered benzoate ligands have been identified for robust cerium complexes, enabling the synergistic cooperation of cerium catalysis in the emerging metallaphotoredox catalysis. A broad range of free alcohols and aromatic halides can be facilely employed in this transformation, representing a new paradigm for the C(sp^3)−C(sp^2) bond construction between free alcohols and aryl halides with the extrusion of formaldehyde. Moreover, mechanistic investigations have been conducted, leading to the identification of a tribenzoate cerium(III) complex as a viable intermediate.

The development of efficient photocatalysts is central to the utilization of visible-light energy for sustainable synthesis, yet the exploitation of abundant and economical metals instead of Ru and Ir remains a prominent challenge.[1] In particular, earth-abundant cerium compounds have emerged as promising lanthanide photocatalysts, owing to their intriguing redox capacities to engage single-electron transfer (SET) activations upon metal-centered charge-transfer excitation or ligand-to-metal charge-transfer (LMCT) excitation.[2] The recent exploitation of cerium bis(guanidinate) complexes,[3] cerium chloride,[4] and the oxo-bridged cerium cluster[5] as practical photocatalysts has enabled diverse radical-mediated transformations with reactive radical acceptors, such as dehalogenative arylation and borylation, decarboxylative amination and oxidation, C−C bond cleavage of alkanols, and C−H functionalization of alkane feedstocks. Nevertheless, ligand design and modification, one main strategy to tune photoexcitation and redox properties, has remained relatively underexploited for cerium,[6] in which significant challenges have been imposed by ligand redistribution, unpredictable coordination geometry, and variable coordination numbers.[7] Herein we describe the synergistic combination of cerium−LMCT catalysis and nickel catalysis for an unprecedented dehydroxymethylative cross-coupling, enabled by robust and sterically demanding benzoate ligands (Figure 1).

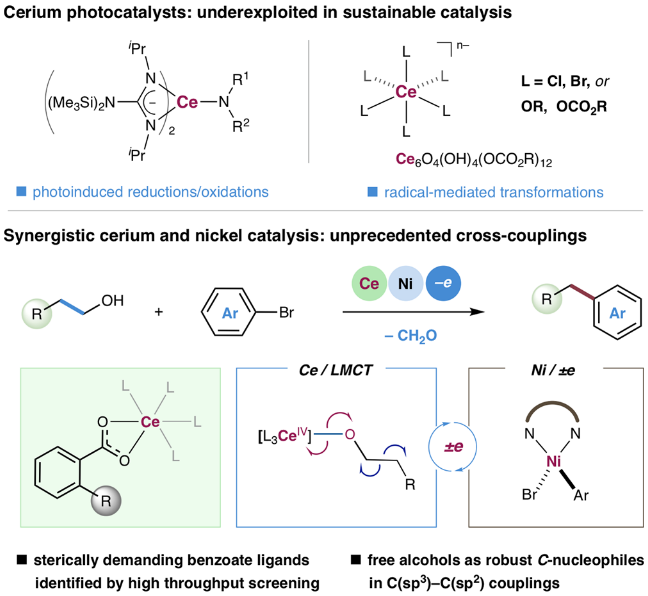

Figure 1. Synergistic cerium and nickel catalysis for the dehydroxymethylative arylation of free alcohols.

C−C bond cleavage has been demonstrated as a versatile but fickle platform to develop innovative transformations of feedstock chemicals to streamline the synthesis of complex molecules.[8] Direct dehydroxymethylation of alcohols, in which the α-C(sp^3)−C(sp^3) bond is selectively cleaved, remains a challenging task due to the lack of thermodynamic driving forces; nevertheless, this reaction provides intriguing opportunities to harness abundant and readily accessible alcohol feedstocks for rapid molecular complexity constructions.[9] The implementation of this reactivity mode for transition-metal-catalyzed cross-coupling, avoiding the discrete prefunctionalization of premetalation steps, however, currently remains elusive.[10] Encouraged by the generality and selectivity demonstrated in our recent study of cerium-catalyzed C−C bond cleavage and alkylations of alkanols,[4g] we posited that a practical dehydroxymethylative arylation could be achieved through the synergistic implementation of metallaphotoredox

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catalysis.[11] In our design, cerium−LMCT followed by β-scission processes would convert alcohols into nucleophilic alkyl radicals, which could be readily intercepted by a nickel cross-coupling cycle, establishing a new paradigm for the $C(sp^3)-C(sp^2)$ bond construction between free alcohols and aryl halides with the extrusion of formaldehyde.

We initiated the investigation of the proposed synergistic catalytic system using *N*-Boc-prolinol and 4-bromobiphenyl as template substrates under the irradiation of LED light (center wavelength, 400 nm; light intensity, 0.30 W/cm^2) (Figure 2).

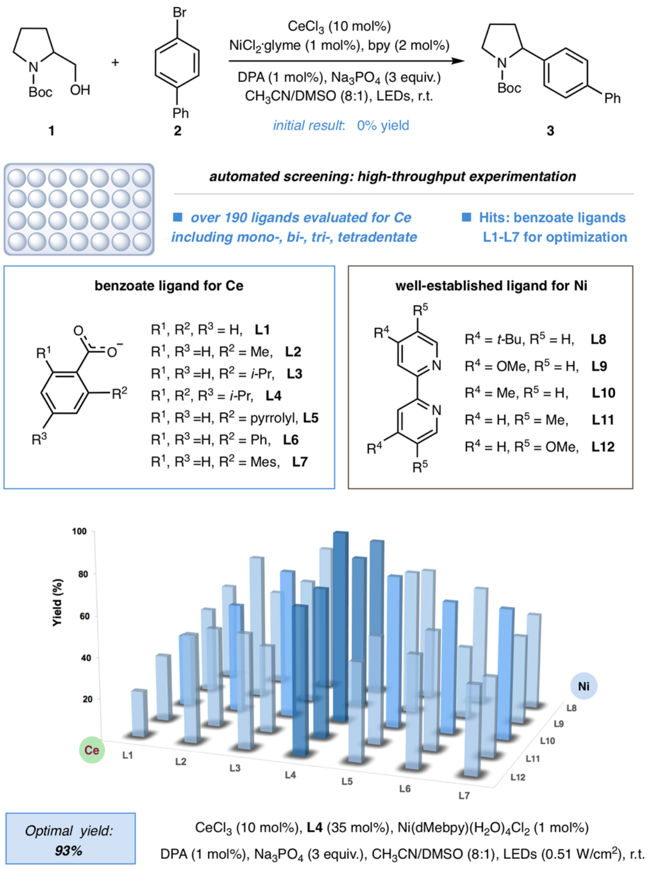

Figure 2. Reaction development. Automated high-throughput experimentation and subsequent cross-examination were carried out to identify the optimal catalyst combination. See the Supporting Information for details.

Our initial attempts failed to provide any dehydroxymethylative arylation product, even with 9,10-diphenylanthracene (DPA) added as an electron-shuttle; nevertheless, the detection of biphenyl and 4-chlorobiphenyl confirmed that the nickel cycle driven by the catalyst composition of $NiCl_2\cdot$glyme and 2,2′-bipyridine was functional under this condition. The indication of the cerium−LMCT pathway being inhibited, possibly by bipyridine, promoted us to search for suitable cerium photocatalysts to operate synergistically with nickel catalysis. Distinct from traditional approaches of photoredox catalysis where iridium/ruthenium photocatalysts need to be synthesized and purified before evaluation, the LMCT catalysis mode can harness the *in situ* formed cerium alkoxide complexes for direct photoactivation with additional ligands, providing an advantageous opportunity to conduct rapid evaluations of ligands for the optimal cerium photocatalyst. With the assistance of an automated high-throughput experimentation platform, we were able to evaluate a large collection of ligands for cerium trichloride, including various mono-, bi-, tri-, and tetradentate ligands. (Over 190 ligands were screened; see the Supporting Information for details.) The rapid, automated evaluation identified benzoate ligands as effective for enabling the desired dehydroxymethylative arylation, which were subsequently carried into a second round of optimization. Interestingly, several previously reported ligands for cerium catalysis, such as multidentate-amine-type ligands, were found to be inactive in this photocatalytic system. Under an operationally simple laboratory setup with enhanced light intensity of 0.51 W/cm^2, a cross-examination of the seven benzoate ligands for cerium with well-established bipyridine-type ligands for nickel then revealed the optimal catalyst combination, cerium trichloride and benzoate **L4**, with nickel chloride and **L10**. Notably, the ortho substitution of the benzoates could affect the efficiency dramatically, as electron-donating groups with some degree of steric hindrance exhibit a more positive effect, with isopropyl groups demonstrating the best efficiency. (See Table S1.) Further improvement of the catalytic efficiency was observed when the preformed nickel complex $Ni(dMebpy)(H_2O)_4Cl_2$ was used instead of the separate addition of the nickel salt and **L10**.[12] Under the optimal conditions, the desired arylation product **3** could be obtained in 93% yield, with no α-C−H arylation or C−O cross-coupling products observed, demonstrating high levels of chemoselectivity. Moreover, control experiments revealed that cerium catalyst, nickel catalyst, DPA, and light are all essential for the desired photoactivity. (See Table S2.)

With the optimal conditions in hand, we then examined the generality of this synergistic catalytic system. As demonstrated in Scheme 1, a broad range of primary alcohols could be utilized as operationally simple carbon pronucleophiles in the dehydroxymethylative cross-couplings with 4-bromobiphenyl under mild reaction conditions, demonstrating an unconventional strategy directly utilizing readily accessible free alcohols as robust coupling reagents in $C(sp^3)-C(sp^2)$ constructions. Importantly, the cleavage of the α-$C(sp^3)-C(sp^3)$ bond mediated by the β-scission of alkoxy radicals was universally achieved with a high level of selectivity, as activated $C(sp^3)-H$ bonds or alkenes were left unscathed, despite their tendencies to react with alkoxy radicals via hydrogen atom transfer or addition processes. Commonly occurring functional groups such as aromatic halides, heteroarenes, alkenes, alkyne, ethers, and amides can be well-tolerated. Primary alcohols with β-substitutions can be readily converted into stabilized benzylic-type radicals by a cerium catalyst to forge a new C−C bond, and the reaction efficiency was found in correlation with the electronic and steric properties of the resultant radicals. Alcohols equipped with electron-rich arenes that would render more nucleophilic carbon-centered radicals tend to provide enhanced efficiency (products **5**, **14**−**17**), whereas electron-withdrawing functionalities including nitrile (**6**), trifluoromethyl (**7**), and ester (**8**) groups lead to slightly declined yields. This cross-coupling arylation was sensitive to the steric hindrance of the alcohol, as the presence of ortho substitutions of the resultant benzylic radicals such as methyl and chloride groups has a detrimental effect on the catalytic efficiency and requires the use of a higher loading of nickel catalyst (products **11**−**13**). Importantly, a variety of homoallylic alcohols can be selectively activated and utilized as robust allylic nucleophiles in $C(sp^3)-C(sp^2)$ cross-couplings (products **18**−**20**). No

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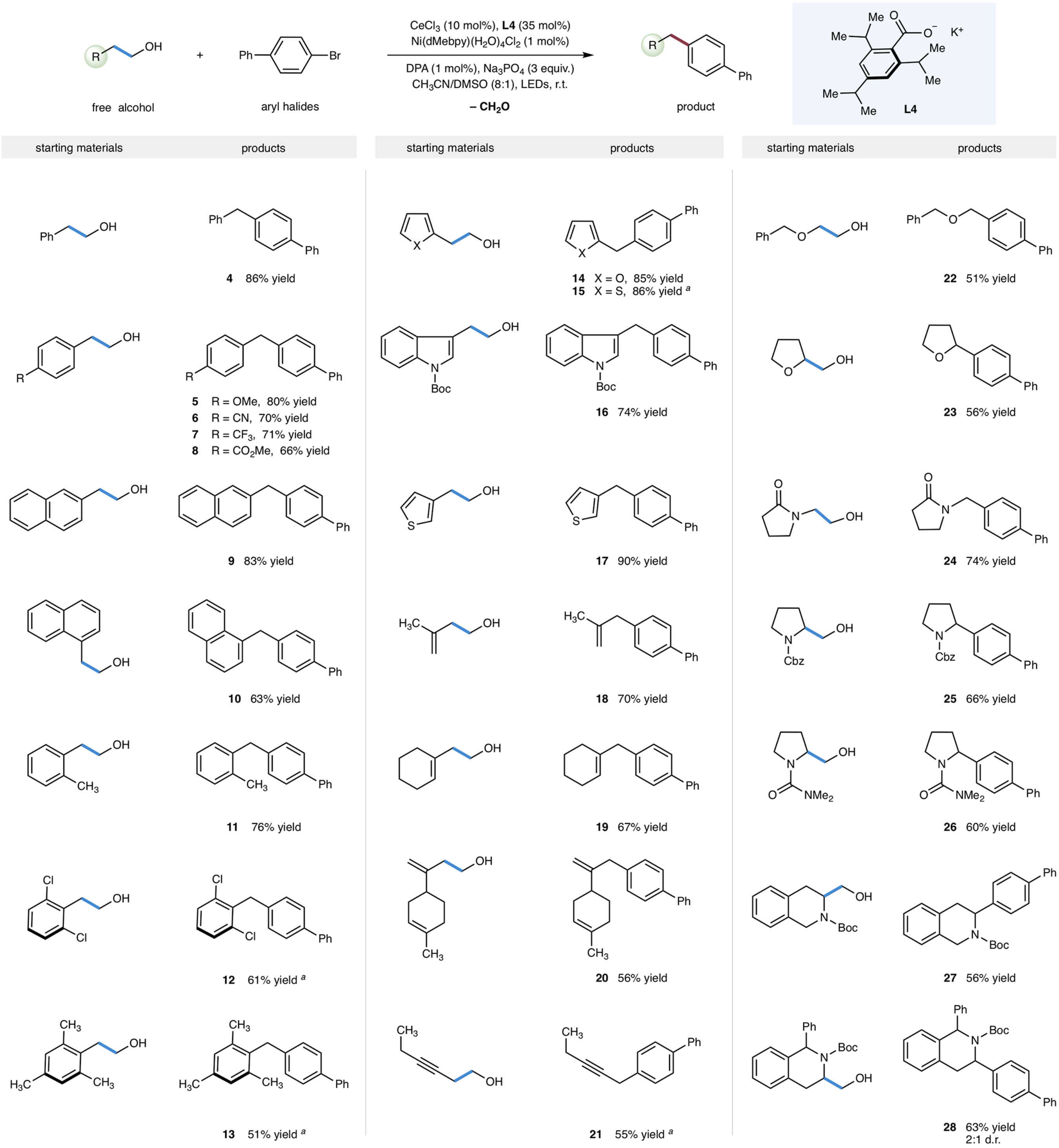
Scheme 1. Dehydroxymethylative Arylation Scope of Alcohols[a]

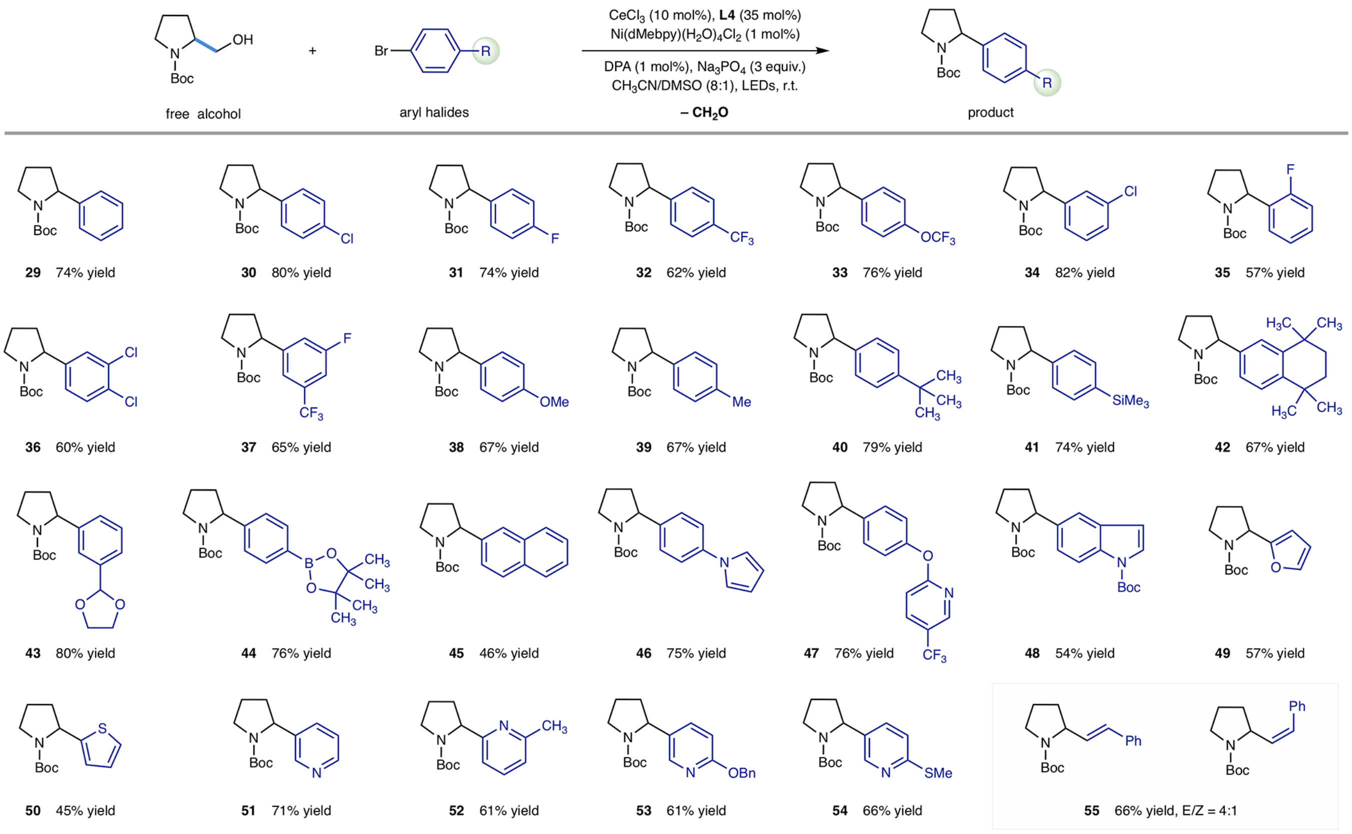


[a]General reaction conditions: alcohol substrate (0.4 mmol), 4-bromo-1,1′-biphenyl (0.2 mmol), Ni(dMebpy)$(H_2O)_4Cl_2$ (0.002 mmol), DPA (0.002 mmol,), **L4** (0.07 mmol), $CeCl_3$ (0.02 mmol), Na_3PO_4 (0.6 mmol), CH_3CN (2 mL) and DMSO (0.25 mL), blue LEDs. All yields are isolated yields. [b]Reaction performed with Ni(dMebpy)$(H_2O)_4Cl_2$ (0.01 mmol).

isomerization of the trisubstituted double bond in product **19** was observed. Moreover, homopropargylic alcohol can be employed in dehydroxymethylative arylation, albeit with moderate efficiency, even at an increased loading of nickel catalyst (**21**). A variety of primary alcohols with oxygen or nitrogen functionalities can be accommodated, delivering the corresponding arylation products (**22**–**26**). Primary hydroxyls appended to the tetrahydroisoquinoline moieties proved to be efficient functional handles, enabling the direct coupling of tetrahydroisoquinoline to the aryl bromide.

We were pleased to find that a variety of aromatic bromides can be accommodated in the dehydroxymethylative arylation. As shown in Scheme 2, both electron-withdrawing groups (**30**–**37**) and electron-donating groups (**38**–**43**) on the aryl

Scheme 2. Dehydroxymethylative Arylation Scope of Aryl Halides



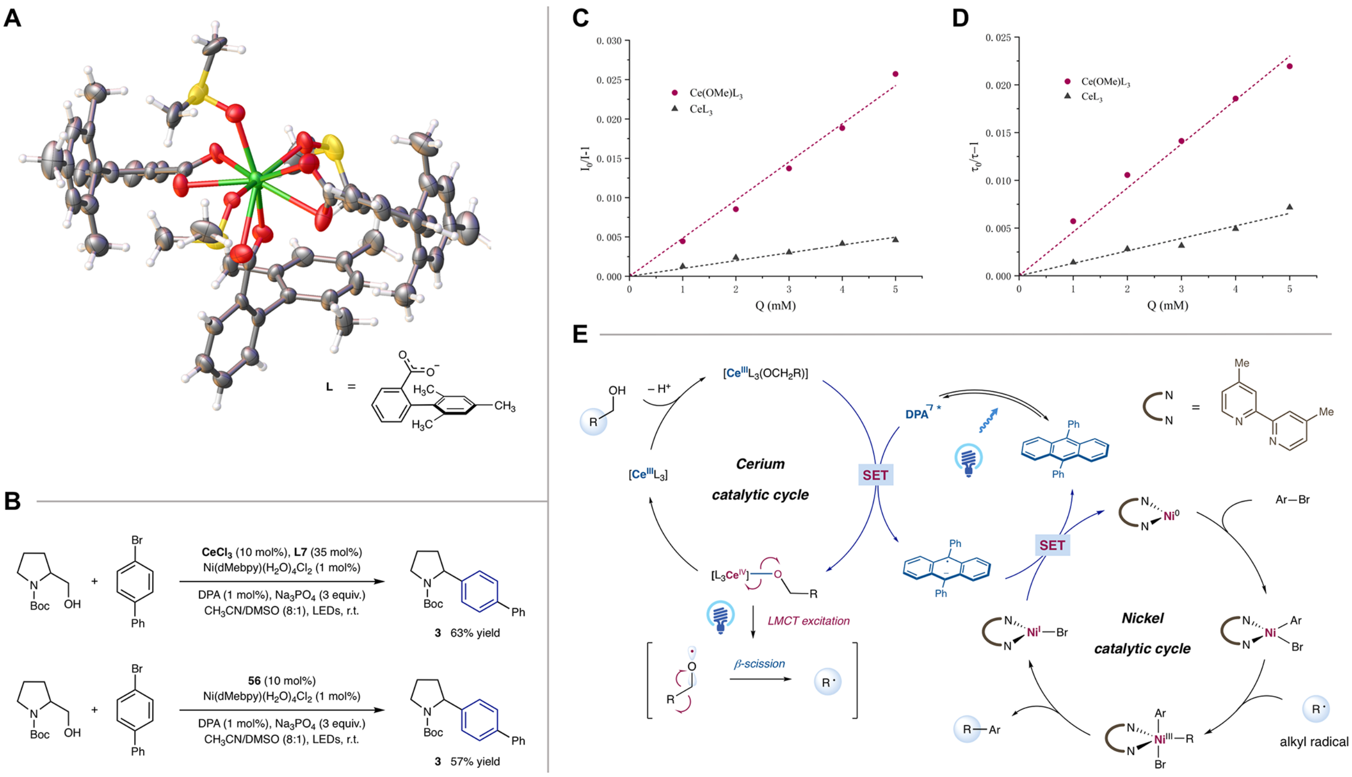


Figure 3. Mechanistic studies. (A) Molecular structure of **56** with 30% probability ellipsoids. (B) Evaluation of the catalytic efficiency of the cerium complex. (C) Stern−Volmer plot based on the steady-state emission experiment. (D) Stern−Volmer plot based on the time-resolved emission experiment. See the Supporting Information for a detailed description. (E) Proposed catalytic cycle.

ring could be incorporated, with trivial differences in catalytic efficiencies. Furthermore, aryl bromides installed on heterocycles such as indole (**48**), furan (**49**), thiophene (**50**), and pyridines (**51**−**54**) could also be employed as effective coupling partners. A broad range of functionalities could be well-tolerated, including halogen atoms (**30**, **31**, **34**−**37**) and silane (**41**), ether (**33**, **38**, **47**, **53**), and ketal groups (**43**). Interestingly, the boronic ester functional handle in **44** was kept intact during this synergistic cross-coupling. Moreover, β-bromostyrene could be employed for dehydroxymethylative vinylation under the same set of reaction conditions, although alkene isomerization was observed in the products.

Encouraged by the generality of this dehydroxymethylative cross-coupling, we next carried out mechanistic investigations to elucidate the enabling effect of the benzoates in promoting cerium/nickel synergistic catalysis. Control experiments have demonstrated the critical role of benzoate salts. During optimization, a 3.5:1 benzoate/cerium loading was found to be optimal, and increased loadings of benzoate would shut down the dehydroxymethylative arylation. Moreover, the ortho substitution effect revealed in the optimization study clearly precludes the benzoate being a mild or soluble base. We were intrigued by the fact that aromatic carboxylic acids were previously demonstrated to be viable LMCT substrates and converted into lactones in the oxidative decarboxylation developed by the Mashima group.[5] Although in their seminal report, cerium(IV) *tert*-butoxide was employed as a precatalyst and an oxo-cerium(IV) cluster was demonstrated as the active intermediate, this promoted us to investigate whether the benzoate was consumed in this dehydroxymethylation reaction. Even after 36 h of irradiation under our conditions, benzoic acid derived from **L4** could be almost completely recovered (93%) after acidification of the reaction mixture, and no corresponding lactone could be detected using gas chromatography−mass spectrometry (GC−MS). (See Figure S8.)

The crystallizations of cerium trichloride with benzoate ligand **L7** resulted in a crystallized compound **56** (Figure 3). X-ray analysis of **56** revealed that three benzoate ligands were ligated to the cerium center in the κ^2 chelating mode with the Ce−O bond length ranging from 2.501 to 2.613 Å. Three solvent molecules of DMSO were also found ligated to the cerium(III) center. The steric shielding around the cerium center caused by ortho-substitution groups of the benzoates probably helped to prevent the formation of dimeric or polymeric structures that typically prevail in lanthanide carboxylate complexes,[13] rendering multiple open coordination sites for the *in situ* ligation of alkoxide. In cyclic voltammogram measurements, complex **56** showed an irreversible redox wave in CH_3CN/DMSO solution ($E_{p/2}$ = 0.46 V vs SCE). Because of the difficulties in isolating Ce(IV) compounds,[7d] we were only able to conduct ^1H NMR spectroscopic analysis on the *in situ* formed Ce(IV) carboxylate complexes. (The ^1H NMR spectrum reveals an approximate carboxylate/Ce ratio of 3:1; see Figure S11.)

Under the standard reaction conditions, cerium complex **56** demonstrated identical catalytic efficiency compared to the addition of cerium trichloride with **L7**. This finding together with the optimal 3.5:1 ligand/cerium loading that we identified during the optimization lends support for the *in situ* formation of CeL_3 alkoxide complexes. The distinct coordination pattern we observed, in comparison with the oxo-cerium cluster discovered by the Mashima group, would have resulted in different patterns of photoactivity, further demonstrating the intriguing potential and underexploited properties of cerium catalysis. Importantly, both steady-state and time-resolved emission quenching experiments revealed the linear photoluminescence quenching of the cocatalyst DPA by cerium(III) complexes.[14] As shown in the Stern−Volmer plots, CeL_3 alkoxide complexes exhibit higher quenching efficiency compared with CeL_3 complexes at the same concentration, which indicates a favorable SET between photoexcited DPA (E^* = 1.19 V vs SCE in DMSO) and CeL_3 alkoxide for the *in situ* generation of $Ce(IV)L_3(OR)$ complexes.

In light of these experiments, a synergistic catalytic cycle was proposed. The coordination of free alcohol with a cerium benzoate complex followed by photoinduced electron transfer with DPA generates a photoactive Ce(IV) alkoxide species. Under LED irradiation, one electron of the higher lying alkoxide ligand orbital will be promoted to the empty 4f orbital of cerium, resulting in the homolysis of the Ce−O bond. The bond homolysis leads to the generation of Ce(III) benzoate and alkoxy radicals, which would undergo β-scission to form alkyl radicals. Meanwhile, in the nickel catalytic cycle, low-valent Ni complexes undergo oxidative addition to generate Ni(II) aryl complexes. The radical interception with the Ni(II) aryl complex forms a Ni(III) species that undergoes rapid reductive elimination to deliver the desired dehydroxymethylative arylation product. The SET events enabled and coordinated by the DPA cycle, including the reduction of Ni(I) by a radical anion of DPA and the oxidation of Ce(III) by excited DPA, have furnished cerium and nickel catalytic cycles and, more importantly, have established a synergy between radical generation and conversion.

In summary, the photocatalytic dehydroxymethylative arylation of free alcohols with aryl halides has been achieved under mild and practical conditions. Enabled by the synergistic utilization of cerium and nickel catalysts, the α-C(sp^3)−C(sp^3) bond of free alcohols can be selectively cleaved and harnessed as an unconventional synthon in cross-couplings. Sterically encumbered benzoate ligands have enabled the incorporation of cerium catalysts in metallaphotoredox catalysis, providing intriguing opportunities for the exploitation of abundant cerium catalysts in sustainable synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00618.

Experimental procedures and compound characterization data (PDF)

Accession Codes

CCDC 2056187 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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