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Dehydrogenative Coupling of Benzylic and Aldehydic C-H Bonds

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ABSTRACT: A photoinduced dehydrogenative coupling reaction between benzylic and aldehydic C–H bonds is reported. When a solution of an alkylbenzene and an aldehyde in ethyl acetate is irradiated with visible light in the presence of iridium and nickel catalysts, a coupled α -aryl ketone is formed with evolution of dihydrogen. An analogous C–C bond forming reaction occurs between a C–H bond next to the nitrogen of an *N*-methylamide and an aldehydic C–H bond to produce an α -amino ketone. These reactions provide a straightforward pathway from readily available materials leading to valued structural motifs of pharmacological relevance.

I twould offer a straightforward method to construct organic skeletons if two different C–H bonds are site-selectively cleaved and dihydrogen is removed to form a new C–C bond. Such a process of σ -bond metathesis is kinetically difficult to execute due to the inertness of C-H bonds. Furthermore, it is often unfavorable in terms of thermodynamic balances based on bond dissociation energies; generalized bond energies of C-H, C-C, and H-H bonds are ca. 98^2 , 81^2 , and 104 kcal/ mol,³ respectively. It is also formidable to facilitate crosscoupling in preference to homocoupling. The examples of such dehydrogenative C-H/C-H cross-coupling reported to date are limited to (1) those using phenols and tetrahydroisoquinolines, which possess low oxidation potentials,⁴ and (2) reactions using benzene derivatives substituted by heteroatom functional groups that direct metals to approach a specific aromatic C-H bond.⁵ Herein reported is a dehydrogenative C-H/C-H cross-coupling reaction of alkylbenzenes with aldehydes to form α -aryl ketones, which is promoted by collaboration of light, iridium, and nickel. An analogous C-H/ C-H cross-coupling reaction of N-methylamides with aldehydes furnishes α -amino ketones. The present study offers a direct access from readily available substances to α substituted ketones, which are valued structural motifs found in a number of biologically active molecules and their synthetic intermediates.

It has been reported that $C(sp^3)$ -H bonds undergo direct arylation,⁶ acylation,⁷ alkoxycarbonylation,⁸ alkenylation,⁹ alkylation,¹⁰ and carboxylation¹¹ reactions by cooperative actions of a nickel catalyst and a photocatalyst under photoirradiation. We tried to expand the scope of the reaction partner of $C(sp^3)$ -H bonds and examined the use of aldehydes. After a number of trials, we finally found conditions suitable for a dehydrogenative C-H/C-H coupling reaction between toluene derivatives and aldehydes, producing α -aryl ketones. A solution containing 4-methoxytoluene (1, 1.0 mmol, 5.0 equiv), octanal (2, 0.20 mmol, 1.0 equiv), Ir cat. (Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, 0.004 mmol, 2 mol %), and NiBr₂(dtbbpy) (0.01 mmol, 5 mol %) in ethyl acetate (4.9 mL) was irradiated with blue LEDs (40 W, $\lambda_{max} = 463$ nm) at ambient temperature for 20 h (Scheme 1). The ketone 3 was

Scheme 1. Dehydrogenative Coupling of 1 with 2



formed as the major product, and only a small amount of bibenzyl 4 (ca. 0.02 mmol) was detected. The excess amount of 1 remained unreacted. The formation of H_2 was confirmed by GC analysis of the gas phase in the headspace of the reaction vessel. Purification of the reaction mixture by silica gel chromatography afforded analytically pure ketone 3 in 73% yield based on 2.

A variety of substituted alkylarenes underwent the dehydrogenative coupling reaction with octanal (2) under analogous conditions to give the corresponding ketones 5-23 (Table 1). In the cases of methyl-substituted arenes (5-22), only small amounts (typically less than 0.02 mmol) of bibenzyl-type side products were observed. When 3,4-dimethylanisole was employed as the toluene derivative, the

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Table 1. Scope of Alkylbenzenes^a



^{*a*}Reaction conditions: alkylarenes (1.0 mmol, 5.0 equiv), octanal (2, 0.2 mmol, 1.0 equiv), NiBr₂(dtbbpy) (0.01 mmol, 5 mol %), Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (0.004 mmol, 2 mol %), AcOEt (4.9 mL), blue LEDs (40 W, $\lambda_{max} = 463$ nm), ambient temperature, 20 h. ^{*b*}Alkylarenes (1.4 mmol, 7.0 equiv). ^{*c*}Alkylarenes (1.6 mmol, 8.0 equiv). ^{*d*}Alkylarenes (0.40 mmol, 2.0 equiv). ^{*e*}Alkylarenes (10 mmol, 50 equiv). ^{*f*}72 h.

benzylic C-H bond para to the methoxy group preferentially participated in the acylation reaction to give 10 as the major product (para/meta = 89:11). Whereas electron-donating groups such as tert-butyl (11) and siloxy (12) groups were eligible substituents on the benzene ring, electron-withdrawing substituents such as alkoxycarbonyl, acyl, and cyano groups gave no cross-coupling products. This electronic contrast suggests that the benzylic hydrogen is abstracted in an electrophilic fashion. The reaction of *p*-cresol afforded benzyl ketone 13, i.e., C-acylated product in 32% yield along with the formation of the O-acylated product (27% yield). The toluene substrate having an ester moiety not on the benzene ring but on the alkoxy side chain afforded the product 14 in 58% yield. On the other hand, an analogous substrate having a nitrile in place of an ester gave 15 in 27% yield. The lower yield is probably because of the coordination of the nitrile moiety to

nickel. The reactions of halo-substituted toluenes were sluggish under the standard reaction conditions (5.0 equiv). When 50 equiv of toluene derivatives were used, however, the corresponding ketones 16-18 were obtained in yields ranging from 51% to 66%. Of note was that the chloro and even the bromo substituents remained intact in the products. In addition to toluene derivatives, 2-methylthiophene proved to be an eligible substrate, giving the product 20 in 62% yield. The reactions of 2,5-dimethylfuran and N-acetyl-2-methylindole also gave the corresponding cross-coupling products 21 and 22, respectively, albeit less efficiently. In the case of ethylbenzene, the secondary benzylic C-H bond was siteselectively abstracted to furnish the substituted ketone 23 in 46% yield together with a small amount of bibenzyl-type byproduct (2,3-diphenylbutane, 0.033 mmol as a diastereomer mixture). The lower yield of the cross-coupling product 23 can be ascribed to steric hindrance. Accordingly, sterically more congested isopropylbenzene failed to undergo the dehydrogenative cross-coupling reaction, and instead, the corresponding bibenzyl (2,3-dimethyl-2,3-diphenylbutane, 0.22 mmol, 44%) was formed as the major product.

Shown in Table 2 are the results using various aliphatic aldehydes, which successfully underwent the dehydrogenative cross-coupling reaction with 1 to give the corresponding ketones 24-34. Both linear (24-26) and α -branched (27-29) aldehydes could be employed. Acetal (32), hydroxy (33), and carbamate (34) functionalities remained intact under the present reaction conditions. The reaction of benzaldehyde was sluggish and the dibenzyl 4 was formed as the major product, suggesting the abstraction of aldehydic hydrogen is slow due to the electron-withdrawing nature of the phenyl group.

 α -Aryl ketones often serve as the key intermediates for the synthesis of various pharmaceuticals. For example, ketone 37 (Scheme 2) is the intermediate in the synthesis of Tofisopam,¹² which is an anxiolytic agent marketed in several countries. The present method offers a straightforward access to 37 starting from acetaldehyde (36) and methyl eugenol, an abundant naturally occurring compound. First, hydrogenation of methyl eugenol quantitatively gave 35. It successfully underwent the dehydrogenative C-H/C-H cross-coupling reaction with acetaldehyde (36) at the benzylic position to furnish 37 (0.22 mmol, 22%, 22 equiv to Ni).

Constructive mechanistic information was obtained by the following experiments. When Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ was treated with NiBr₂(dtbbpy) in CDCl₃, the hexafluorophosphate anion was replaced with a bromo ligand to form $Ir[dF(CF_3)ppy]_2(dtbbpy)Br$, which was supported by ¹H NMR spectroscopy.¹³ It has been reported that photoirradiation of Ir[dF(CF₃)ppy]₂(dtbbpy)Br induces singleelectron transfer from the bromide anion to iridium,¹⁴ and that the resulting bromine radical abstracts hydrogen from alkanes and aldehydes. No coupling product 3 was formed from toluene 1 and aldehyde 2 when $NiBr_2(dtbbpy)$ was replaced with a catalyst formed in situ from Ni(OAc)₂ and dtbbpy.¹⁵ The product formation resumed upon addition of $(n-Bu)_4$ NBr to the Ni(OAc)₂/dtbbpy catalyst. Replacement of NiBr₂(dtbbpy) with its chloride counterpart, NiCl₂(dtbbpy), decreased the yield of 3 to 9%, presumably because of the higher oxidation potential of a chloride anion than that of a bromide anion.¹⁶ All the experimental results mentioned above are consistent with the mechanism which involves an oxidation of a bromide anion to a bromine radical.

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Table 2. Scope of Aldehydes^a



"Reaction conditions: *p*-methoxytoluene (1, 1.0 mmol, 5.0 equiv), aldehydes (0.2 mmol, 1.0 equiv), NiBr₂(dtbbpy) (0.01 mmol, 5 mol %), Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (0.004 mmol, 2 mol %), AcOEt (4.9 mL), blue LEDs (40 W, λ_{max} = 463 nm), ambient temperature, 20 h.



We also performed the reaction of 1 with 2 in the presence of TEMPO under the conditions that were otherwise identical to those shown in Scheme 1 (Scheme 3). The TEMPO adducts 38 and 39 were produced, corroborating the intermediacy of both benzylic and acyl radical species.

Depicted in Scheme 4 is one of the possible mechanistic scenarios for the formation of the cross-coupling product. It consists of five steps (Steps 1–5). Step 1: Anion exchange between cationic iridium(III) hexafluorophosphate A and nickel(II) bromide B forms iridium(III) bromide complex C. Step 2: When C absorbs light to get excited, a single electron transfers from the bromide anion to iridium(III) to produce iridium(II) species E and a bromine radical.^{13,14} The

Scheme 3. Reaction in the Presence of TEMPO







iridium(II) E $(E_{1/2}[\text{Ir}(\text{III})/\text{Ir}(\text{II})] = -1.37 \text{ V vs SCE})^{17}$ donates a single electron to Ni(II) species B $(E_{1/2}[\text{Ni}(\text{II})/\text{Ni}(0)] = -1.2 \text{ V vs SCE})$,¹⁸ giving rise to Ni(I) species F and the iridium(III)bromide C. Step 3: The bromine radical generated in Step 2 abstracts hydrogen atoms from benzylic and aldehydic C-H bonds to furnish benzylic and acyl radical species^{13,19} along with HBr. Step 4: The acyl and benzylic radical species sequentially add to the nickel(I) species F to produce nickel(III) complex H. The following reductive elimination gives the ketone 3 and the nickel(I) species F.^{20,21} Step 5: The nickel(I) species F reacts with HBr to generate H₂²² and the Ni(II)Br₂ species B, which re-enters the catalytic cycle of Step 1.

Aromatic groups participate in the stabilization of benzylic radicals. Similarly, a nitrogen atom also stabilizes its bound carbon radical species. We briefly examined whether C-H bonds next to nitrogen atoms could take part in the dehydrogenative coupling with an aldehydic C-H bond, and suitable reaction conditions were found by modifying the conditions for alkylarenes (Scheme 5). When a solution

Scheme 5. Synthesis of α -Amino Ketones



containing a large excess of *N*,*N*-dimethylacetamide (40, 20 mmol, 100 equiv) was subjected to the reaction with octanal (2) under the conditions shown in Scheme 1, α -amino ketone 41 was produced in 70% yield based on 2. *N*,*N*-Dimethylformamide (42) also underwent the dehydrogenative coupling reaction with 2 under the same conditions.

In summary, we have developed the photoinduced dehydrogenative C–H/C–H cross-coupling reaction between alkylbenzenes and aldehydes. It offers a convenient and straightforward synthetic method of α -aryl ketones, which are a valued structural motif relevant to pharmaceuticals. α -Amino ketones are also synthesized from N-methylamides through an analogous C–C bond forming reaction with aldehydes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b13920.

Details of experimental procedures including spectroscopic data of products (PDF)

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Notes

The authors declare no competing financial interest.

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