Benzylic C—H acylation by cooperative NHC and photoredox catalysis

Qing-Yuan Meng¹, Lena Lezius¹ & Armido Studer ⚫¹

Methods that enable site selective acylation of sp³ C-H bonds in complex organic molecules are not well explored, particularly if compared with analogous transformations of aromatic and vinylic sp² C-H bonds. We report herein a direct acylation of benzylic C-H bonds by merging N-heterocyclic carbene (NHC) and photoredox catalysis. The method allows the preparation of a diverse range of benzylic ketones with good functional group tolerance under mild conditions. The reaction can be used to install acyl groups on highly functionalized natural product derived compounds and the C-H functionalization works with excellent site selectivity. The combination of NHC and photoredox catalysis offers options in preparing benzyl aryl ketones.

¹ Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Münster, Germany. ⚫Email: studer@uni-muenster.de
The Friedel-Crafts acylation (FCA) is a very powerful and established method for the introduction of an acyl group to an electron-rich arene via electrophilic aromatic substitution. It is apparent that the rapid development of transition metal catalyzed arene C–H functionalization has offered strategies to conduct formal Friedel-Crafts acylations. In these modern variants, a stoichiometric amount of a corrosive Lewis acid, generally required in the classical FCA, is not necessary. Moreover, electron-neutral and even electron-poor arenes have become eligible substrates. Although significant progress has been achieved for the acylation of sp² C–H bonds, the analogous transformation on sp³ C–H bonds still remains a challenge.

Benzylic C–H bonds occur in many bioactive compounds and ~25% of the top-selling 200 pharmaceuticals contain this structural motif. Great efforts have been devoted to functionalize such C–H bonds and benzylic C–C bonds and C–N bonds, C–O bonds, C–F bonds, and C–F bonds formation among others have been realized. However, direct benzylic C–H bond acylation is not well explored. A problem is that the targeted aryl ketones can further react in a ketone-directed sp² C–H functionalization. Moreover, site-selective acylation is challenging in cases where various benzylic C–H bonds are present. Li and co-workers reported rhodium-catalyzed acylation of 8-methylquinolines with ketenes and cyclopropanones to deliver the corresponding benzylic acyl products.

Coordinating directing groups were required for the acylation of 8-methylquinolines with ketenes. Alkyl acyl NiIII species were proposed as the key intermediates in the C–H activation. However, excellent regio- and diastereoselectivity is still highly desirable. As is evident from these results, aryl halides, most of which would be incompatible with Ni catalysis, engage in this cascade, albeit a moderate yield was obtained for the iodo-congener (3f, 48%). α-Naphthoyl and β-Naphthoyl fluoride were successfully used in the direct arylation of 2a (3n, 47%; 3o, 76%). The latter was more reactive due to lower steric hindrance during formation of the β-naphthoyl azolium intermediate. Furthermore, heteroaryl fluorides containing the furan and thiophene moieties were also amenable to the coupling with 2a to afford 3p and 3q in 47% and 82% yields, respectively.

The scope of the reaction with respect to the benzylic component was explored next using benzylofluoride 1a as the acyl donor (Fig. 3b). A variety of functional groups are tolerated, giving rise to products bearing ester (3r, 82%; 3s, 60%), amide (3t, 84%), azide (3u, 47%), ketone (3v, 66%), and ether (3w, 31%) functionalities. It is important to note that the 1,2-dihydrobenzofuran and chroman substructures can be found in pharmaceutical drugs such as Darifenacin and Nabilol. With this in mind, we tested them as radical coupling partners and both systems worked well to afford the ketones 3x and 3y in 82% and 87% yields, respectively. Benzoylation in α-position to the O-atom was not observed, clearly showing that C-radical formation occurs with complete regioselectivity at the benzylic position. Compared with 4-ethyl anisole, 1-ethyl-4-phenoxycarbonyl showed a lower efficiency (3z, 47%). Primary benzylic C–H bonds could also be acylated to give the desired products (3aa, 48%).

Substrate scope. With the optimized conditions established, we examined the reaction scope with respect to the acyl fluoride first (Fig. 3a). A wide range of benzylofluorides bearing electron-donating or electron-withdrawing substituents could be used for the C–H arylation of 4-ethyl anisole, affording the desired products in moderate to excellent yields (3b–3m, 48–95%). As is evident from these results, aryl halides, most of which would be incompatible with Ni catalysis, engage in this cascade, albeit a moderate yield was obtained for the iodo-congener (3f, 48%). α-Naphthoyl and β-Naphthoyl fluoride were successfully used in the direct arylation of 2a (3n, 47%; 3o, 76%). The latter was more reactive due to lower steric hindrance during formation of the β-naphthoyl azolium intermediate. Furthermore, heteroaryl fluorides containing the furan and thiophene moieties were also amenable to the coupling with 2a to afford 3p and 3q in 47% and 82% yields, respectively.

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Results and discussion

Reaction conditions development. To test our hypothesis, we initiated the study by examining the cross-coupling between benzoyl fluoride 1a and 4-ethyl anisole 2a with the triazolium salt A as the catalyst, which has been shown to be efficient in multi component couplings. The protic Brønsted acid (IrCl(II)/IrCl(III)) in the presence of a base promotes the acylation reaction. However, when a stoichiometric amount of a corrosive Lewis acid, generally required in the classical FCA, is not necessary. Moreover, electron-neutral and even electron-poor arenes have become eligible substrates. Although significant progress has been achieved for the acylation of sp² C–H bonds, the analogous transformation on sp³ C–H bonds still remains a challenge.

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Coordinating directing groups were required to control the regioselectivity, thus limiting the applicability of this method. The merger of photocatalysis with other catalytic modes has opened avenues for acylation of sp³ C–H bonds. The merger of photocatalysis with other catalytic modes has opened avenues for acylation of sp³ C–H bonds. The merger of photocatalysis with other catalytic modes has opened avenues for acylation of sp³ C–H bonds.
reaction was sluggish and 48% of starting material was recovered. Owing to the steric hindrance of tertiary C–H bonds, lower yields were obtained for 3ab (28%). Importantly, an activating O-substituent decreasing the arene oxidation potential is not required and (4-bromobutyl)benzene could be benzoylated with 1a, albeit with moderate yield (3ac, 41%).

We next turned our attention to examine the site selectivity of the direct C-H benzylation. Even in the presence of weaker benzylic C–H bonds, exclusive functionalization of the ethyl moiety in para-position to the alkoxy group was noted (3ad, 65% yield). Along these lines, methoxy-substituted dihydroindene and tetrahydronaphthalenes reacted with excellent site selectivity at the benzylic position that is located ortho or para to the activating methoxy group (3ae, 44%; 3af, 74%; 3ag, 70%). Likely, intermolecular C–H abstraction with an electrophilic radical would be not regioselective in these cases, showing that the

**Fig. 1 Direct acylation of sp3 C–H bonds.**

- **a** RhI-catalyzed benzylic C–H acylation of 8-methylquinoline.
- **b** Cooperative photoredox/NHC catalysis for acylation of N-aryl tetrahydroisoquinolines.
- **c** Cooperative photoredox/Ni catalysis for acylation of C–H bonds.
- **d** Cooperative photoredox/NHC catalysis for site-selective acylation of benzylic C–H bonds via radicals cross-coupling (this work).
deprotonation of an arene radical cation under our conditions is a highly regioselective process. It is noteworthy that monobenzoylation of 5,6-dimethoxy-2,3-dihydro-1H-indene was achieved (3ah, 62% yield). 1,2-Dihydrobenzofuran and chroman bearing a methyl substituent adjacent to the reactive benzylic site delivered the targeted ketones with high diastereoselectivities in good yields (3ai, 69%, trans/cis = 98:2; 3aj, 57%, trans/cis = 91:9). Finally, to further demonstrate the potential of our method, we applied the

| Entry | Solvent | NHC precatalyst | 2a, (M) | Conversion (%)b | Yield (%)c |
|-------|---------|-----------------|--------|----------------|------------|
| 1     | CH₂Cl₂  | A               | 0.05   | 17             | 15         |
| 2     | CHCl₃   | A               | 0.05   | 24             | 22         |
| 3     | DMSO    | A               | 0.05   | 20             | 20         |
| 4     | DMF     | A               | 0.05   | 43             | 42         |
| 5     | 1,4-Dioxane | A | 0.05 | 5             | 5         |
| 6     | Toluene | A               | 0.05   | 5              | 4          |
| 7     | CH₃CN   | A               | 0.05   | 59             | 59         |
| 8     | Ethyl acetate | A | 0.05 | 4              | 4         |
| 9     | CH₃CN   | B               | 0.05   | 43             | 42         |
| 10    | CH₃CN   | C               | 0.05   | 3              | 3          |
| 11    | CH₃CN   | D               | 0.05   | 7              | 6          |
| 12    | CH₃CN   | E               | 0.05   | 0              | 0          |
| 13    | CH₃CN   | F               | 0.05   | 3              | 3          |
| 14    | CH₃CN   | G               | 0.05   | 0              | 0          |
| 15    | CH₃CN   | H               | 0.05   | 0              | 0          |
| 16    | CH₃CN   | A               | 0.07   | 77             | 77         |
| 17    | CH₃CN   | A               | 0.10   | 86             | 85         |
| 18    | CH₃CN   | A               | 0.17   | 92             | 88 (83)    |
| 19d   | CH₂CN   | A               | 0.17   | -              | 83         |
| 20e   | CH₂CN   | A               | 0.17   | 0              | 0          |
| 21f   | CH₂CN   | A               | 0.17   | 0              | 0          |
| 22g   | CH₂CN   | A               | 0.17   | 0              | 0          |

*Reaction conditions: unless otherwise noted, all the reactions were carried out with benzoyl fluoride (0.4 mmol), 4-ethyl anisole (0.1 mmol), NHC catalyst (0.02 mmol), Cs₂CO₃ (0.2 mmol), and [Ir(df(CF₃)ppy)₂(dtbbpy)]PF₆ (0.002 mmol) in anhydrous CH₃CN (2 mL), irradiation with blue LEDs at room temperature for 24 h.

bGC-FID conversion using 1,3,5-trimethoxybenzene as an internal standard.

c¹H NMR yield using 1,3,5-trimethoxybenzene as an internal standard and yield of isolated product is given in parentheses.

d4CzIPN (0.002 mmol) was used instead of [Ir(df(CF₃)ppy)₂(dtbbpy)]PF₆ as the photocatalyst.

eThe reaction was carried out in the dark.

fNo photocatalyst was added.

gNo NHC catalyst was added. 4CzIPN, 2,4,5,6-tetra(carbazol-9-yl)isophthalonitrile. rt, room temperature. NHC, N-heterocyclic carbene. LEDs, light-emitting diodes.

Fig. 2 Different NHC catalysts tested. A–D are precursors leading to triazol-5-ylidene-type carbenes, E and F provide imidazole-2-ylidines, and G and H deliver thiazol-2-ylidenes. NHC N-heterocyclic carbene.
radical/radical cross-coupling reaction to the late-stage benzylic benzoylation of biologically interesting compounds (Fig. 3c).

Highly regioselective benzoylation of the methylene moiety of a \( \delta \)-tocopherol analog was achieved and benzoylation of the methyl group did not occur (3ak, 34%, \( \text{dr} = 1:1 \)). Additionally, both epiandrosterone and dopamine analogs could be regioselectively functionalized at the benzylic positions, with no byproduct observed derived from reactions adjacent to the ketone or amide moieties (3al, 73%; 3am, 52%).

Control experiments. To gain insights into the reaction mechanism, control experiments were performed. C-H-benzoylation of chroman with 1a was fully suppressed in the presence of 2,2,6,6-tetramethyl-piperidin-1-oxyl (TEMPO) (Fig. 4a). When CD\(_3\)CN was used in place of CH\(_3\)CN, there was no deuterium incorporation into the product, as well as in the recycled starting chroman, which indicates that H-atoms or protons of the solvent do not participate in the cascade (Fig. 4b). Moreover, a kinetic isotope effect (KIE) was observed in the
intermolecular competition experiment, demonstrating that the deprotonation might be involved in the rate-determining step (Fig. 4c) 52.

**Reaction mechanism.** According to the above results and previous reports, a possible mechanism is suggested in Fig. 5. Under blue LEDs irradiation, [Ir(dF(CF3)ppy)2(dtbbpy)]PF6 will be excited and the excited state will be reductively quenched by the electron-rich arene 2, leading to an arene radical cation III with concomitant formation of a radical anion of [Ir(dF(CF3)ppy)2(dtbbpy)]PF6 (E1/2(P/P−) = −1.37 V vs SCE) or 4CzIPN (E1/2(P/P+) = −1.21 V vs SCE)47,49. The radical cation III will be deprotonated (Cs2CO3) at the benzylic position to generate a transient benzylic radical IV. Based on the KIE studies, the initial electron transfer from II to PC* is reversible. The reduced photocatalyst will then transfer an electron to the acyl azolium salt I (E1/2 = −1.29 V vs SCE)40 itself formed in situ from the acyl fluoride I and the NHC catalyst to generate a persistent ketyl type radical II, closing the photoredox catalysis cycle. Radical-radical cross coupling of the transient radical IV with the persistent ketyl radical II steered by the persistent radical effect53 will lead to

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**Fig. 4 Control experiments.** a Radical inhibition experiment. b Deuterium incorporation experiment. c KIE experiment. TEMPO 2,2,6,6-tetramethyl-piperidin-1-oxyl, KIE kinetic isotope effect.

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**Fig. 5 Plausible reaction mechanism.** Cooperative NHC/photoredox catalysis where the acylazolium ion I is involved in both catalytic cycles. PC photocatalyst, NHC N-heterocyclic carbene, SET single-electron-transfer.
intermediate V. Fragmentation of the NHC will eventually provide the product ketone 3 thereby liberating the NHC catalyst.

In this work, we have developed a strategy to accomplish acylation of benzylic C–H bonds via cooperative NHC and photocatalysis. The key step of the cascade is a radical/radical cross-coupling. The acylation occurs with excellent site selectivity and broad functional group compatibility. The protocol is amenable to functionalize important structural motifs with good to excellent diastereoselectivities, as well as to the late-stage benzylation of more complex natural product derived compounds. The method will open avenues in the area of direct C–benzoylation of more complex natural product derived compounds.

Methods

General procedure for the cross-coupling between an acyl fluoride and a benzylcarbamate pre-catalyst A (6.3 mg, 0.02 mmol), 4CzIPN (1.6 mg, 0.002 mmol) or [Ir(df(CF3ppy)ppy)(dbbbpy)]PF6 (2.2 mg, 0.002), and Cs2CO3 (65.2 mg, 0.2 mmol) were added. Then the reaction tube was evacuated and backfilled with argon two times. Subsequently, a benzyl component (0.10 mmol) and an acyl fluoride (0.40 mmol) (if solid, they should be added at the beginning) and CH3CN (0.6 mL) were added. The resulting mixture was degassed under vacuum two times and then the mixture was irradiated with blue LEDs at room temperature for 24 h. After that, the residue was purified by silica gel chromatography using a mixture of n-pentane and ethyl acetate or pentane and diethyl ether as an eluent to get the desired product. Each reaction was carried out twice and the average value was used as the final yield.

Data availability

Supplementary information is available in the online version of the paper. Data supporting the findings of this work are available within this paper or its Supplementary Information and also from the corresponding author upon reasonable request.

Received: 14 December 2020; Accepted: 25 February 2021;
Published online: 06 April 2021

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Acknowledgements
We thank the European Research Council ERC (advanced grant agreement No. 692640) and the Deutsche Forschungsgemeinschaft (DFG) for supporting this work.

Author contributions
Q.Y.M. and A.S. conceived and designed the experiments. Q.Y.M. and L.L. performed the experiments and analyzed the data. Q.Y.M. and A.S. wrote the manuscript.

Funding
Open Access funding enabled and organized by Projekt DEAL.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-021-22292-z.

Correspondence
and requests for materials should be addressed to A.S.

Peer review information
Nature Communications thanks the anonymous reviewer(s) for their contribution to the peer review of this work.

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