Nickel-Mediated Photoreductive Cross Coupling of Carboxylic Acid Derivatives for Ketone Synthesis**

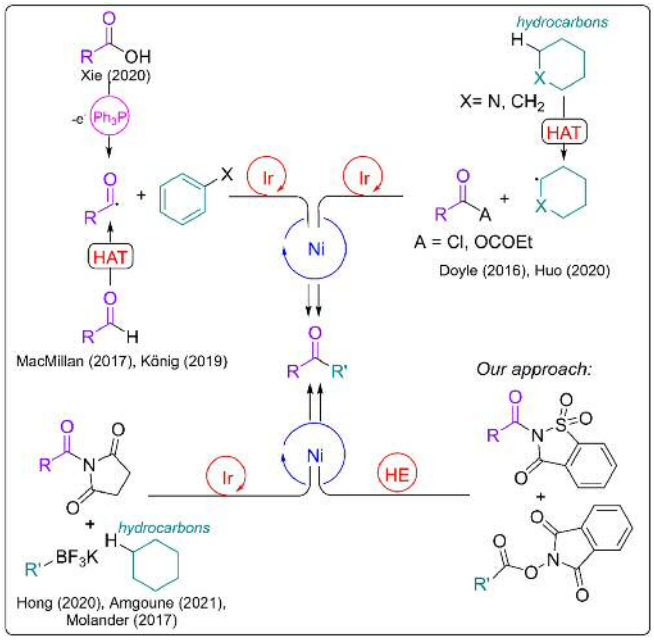
Jan Brauer,[a] Elisabeth Quraishi,[a] Lisa Marie Kammer,[a] and Till Opatz*[a]

Abstract: A simple visible light photochemical, nickel-catalyzed synthesis of ketones from carboxylic acid-derived precursors is presented. Hantzsch ester (HE) functions as a cheap, green and strong photoreductant to facilitate radical generation and also engages in the Ni-catalytic cycle to restore the reactive species. With this dual role, HE allows for the coupling of a large variety of radicals (1°,2°, benzylic, α-oxy & α-amino) with aroyl and alkanoyl moieties, a new feature in reactions of this type. With both precursors deriving from abundant carboxylic acids, this protocol is a welcome addition to the organic chemistry toolbox. The reaction proceeds under mild conditions without the need for toxic metal reagents or bases and shows a wide scope, including pharmaceuticals and complex molecular architectures.

Introduction

Ketones represent a widespread and important compound class in organic chemistry. Common methods for their synthesis include many textbook reactions such as the Weinreb ketone synthesis,[1] the Corey-Seebach Umpolung,[2] Negishi couplings[3] or the Suzuki-Miyaura reaction. Using amides as electrophilic acyl components in combination with transition metal catalysis permitted the transition from highly reactive organometallics to less reactive and more convenient nucleophilic coupling partners such as boronic acids.[4–7] However, those transformations rely on the use of expensive palladium catalysts, which is neither economically nor environmentally desirable. Even though palladium can often be replaced by nickel,[8] many transformations still require organometallic species[9] or additional metals as sacrificial reductants.[10] This comes at the cost of a larger environmental footprint[11] and limits functional group tolerance.

In the past few years, dual nickel-photoredox catalysis has been established as a greener alternative to palladium chemistry, permitting a plethora of transformations to form alkyl-aryl C–C bonds[12] or to produce ketones,[13] ethers[14] and other functionalities under mild reaction conditions.[15] For ketone synthesis, several options exist (see scheme 1): using α-ketoacids as radical precursors through oxidative decarboxylation[16] or aldehydes by utilizing hydrogen atom transfer (HAT)[17] in combination with aryl halides, the MacMillan group developed elegant synthetic strategies.



Scheme 1. Different methods for nickel-mediated photochemical ketone synthesis.

Related work by the König group showed that ketones can be synthesized from aldehydes and aryl bromides under visible light photoredox catalysis.[18] This elegant method, in which the product acts as the photocatalyst, is however limited to benzophenone derivatives. Xie et al. used dual nickel-photoredox catalysis in combination with stoichiometric amounts of triphenyl phosphine to access ketones directly from aromatic carboxylic acids and alkyl/aryl bromides.[19] However, only

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aromatic carboxylic acids could be used, excluding purely aliphatic ketones from the product scope.

The previously mentioned examples focus on the generation of acyl radicals and largely employ aromatic acyl moieties with their additional resonance stabilization, which limits the accessibility of aliphatic ketones.[20]

In 2017, the Molander group reported a method for the synthesis of aliphatic ketones using *N*-acylsuccinimides and potassium alkyltrifluoroborates.[21] Hong et al. recently published a method for C(sp^3)–H bond activation in hydrocarbons, which they also coupled with *N*-acylsuccinimides to afford ketones.[22] The hydrocarbons however need to be used in large excess to furnish the product in appreciable yield. Amgoune et al. developed similar procedure in which they additionally used LiCl, tripotassium phosphate and sodium tungestate to reduce the required excess of hydrocarbons to three equivalents.[23]

Doyle et al. showed that racemic α-amino ketones can be synthesized by C-acylation of C(sp^3)–H bonds in α-position to nitrogen with symmetric anhydrides or thioesters.[24] A similar strategy was utilized by Huo et al. for asymmetric acylations by using in situ activation of carboxylic acids with dimethyldicarbonate (DMDC) in combination with a chiral ligand.[25] The Fensterbank group employed alkyl bis(catecholato)silicates as suitable alkyl precursors in combination with acyl chlorides using dual catalysis, although primary aliphatic silicates worked only poorly.[26]

A major drawback of these methods is their reliance on rare and expensive iridium-based photocatalysts, making them less attractive for industrial applications and limiting their potential for the use in green synthesis protocols.

Two notable exceptions are the use of 4CzIPN as an organic photocatalyst instead of iridium by Fensterbank et al. in a net-oxidative Giese-type carbonylation with carbon monoxide[27] or of carbohydrate-based 1,4-dihydropyridines for the synthesis of *C*-acyl glucosides by in situ activation of carboxylic acids with DMDC by the Molander group.[28]

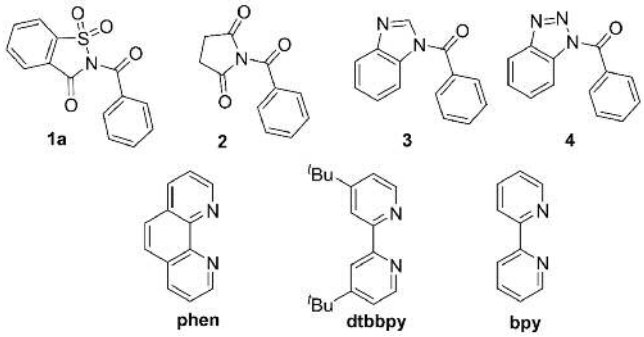
Recently, the latter group also presented a net-reductive nickel-catalyzed method for the formation of C(sp^3)–C(sp^2) bonds using a tandem-system consisting of Hantzsch ester (HE), Ni(II) and *N*-hydroxyphthalimide-esters (NHP-Esters) as redox active esters (RAE).[29] Due to HE's low excited-state-redox potential ($E_{1/2}^{red*} = -2.2$ V vs. SCE),[30] which enables the formation of Ni(0) and the ability to form electron donor acceptor complexes (EDA) with NHP-Esters, this system also proved highly efficient in our case.

Based on the same general strategy, we aimed to use active amide intermediates in a photochemical synthesis of ketones to capitalize on the structural diversity of carboxylic acids available from classical petrochemical processes as well as from renewable resources. A further advantage of exclusively using carboxylic acid substrates is the option to overcome limitations of the process by swapping the roles of acyl and alkyl precursor on the way to a given product.

Results and Discussion

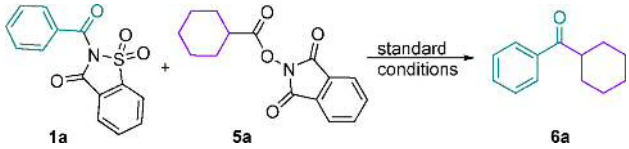
As a starting point for optimization of the reaction, the synthesis of benzoylcyclohexane (**6a**) and GC-MS/FID for efficient screening and yield determination were chosen. Four active amide-type acyl precursors (Scheme 2) were evaluated under different reaction conditions with *N*-(cyclohexanecarbonyloxy)-phthalimide (**5a**) as the corresponding coupling partner. *N*-benzoylsaccharins (**1a**) turned out to be most efficient while other amides such as Hong's *N*-benzoylsuccinimide (**2**) gave little or no product (Table 1, entries 2–4).

Different ligands for nickel were screened during optimization (Table 1, entries 10–11) and 1,10-phenanthroline turned out to be the ligand of choice with 88% isolated yield of **6a**. Interestingly, using an iridium-based photocatalyst proved detrimental (Table 1, entry 9). Changing the solvent from *N,N*-dimethylacetamide (DMAc) to other alternatives drastically decreased the yield of **6a** (Table 1, entries 7–8) and product



Scheme 2. Screened acyl precursors and ligands for the newly developed reaction.

Table 1. Variation of the optimized reaction conditions.



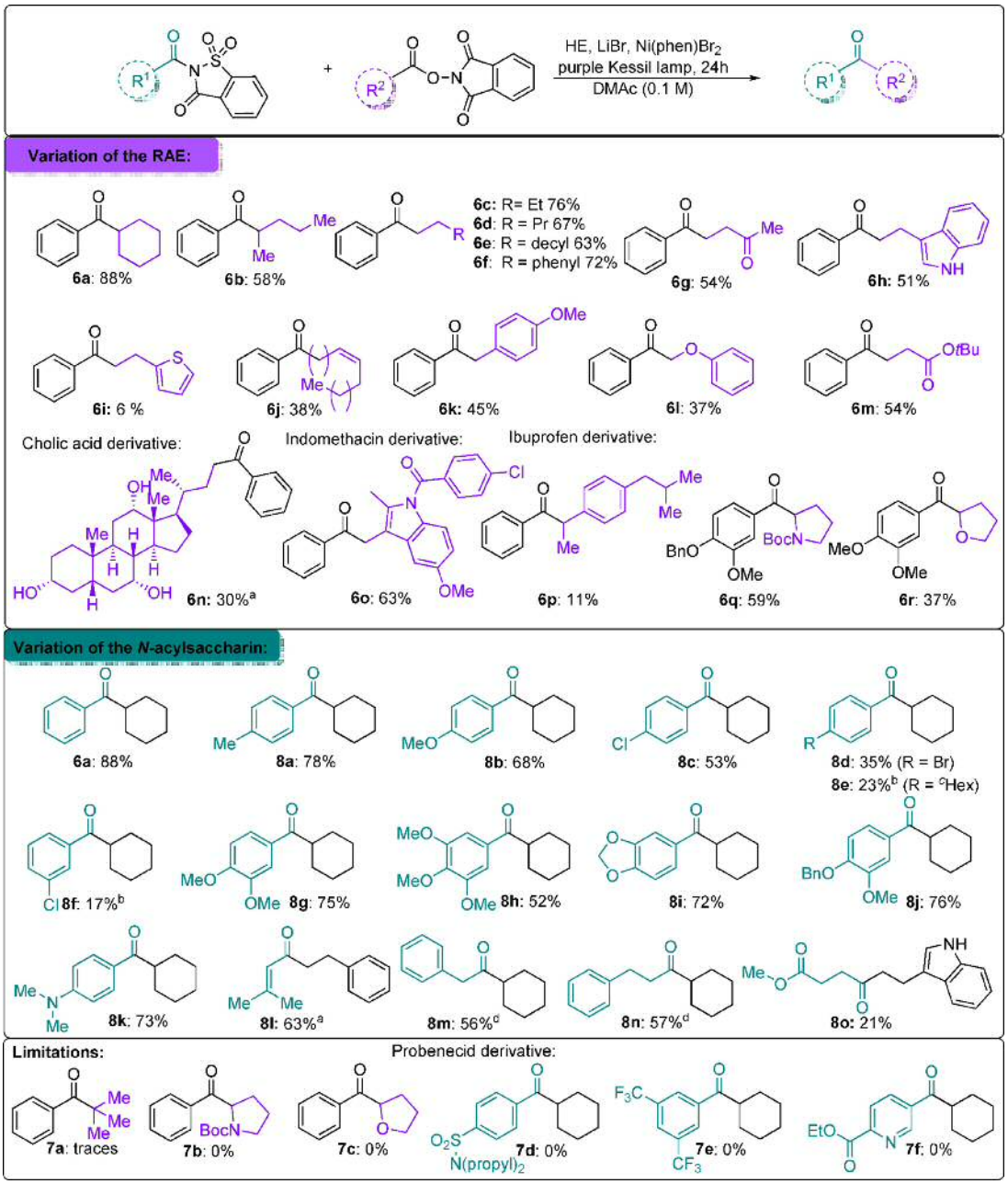
Entry	Conditions	Yield in %[a]
1	No deviation	89 (88)
2	**2** instead of **1a**	traces
3	**3** instead of **1a**	traces
4	**4** instead of **1a**	traces
5	no LiBr	73
6	1.5 equiv. of **5a**	70 (67)
7	solvent DMF	30
8	solvent MeCN	0
9	$Ir(ppy)_3$ (2 mol%) and NEt_3 (3 equiv.) instead of HE	0
10	$Ni(dtbbpy)Br_2$ instead of $Ni(phen)Br_2$	37
11	$Ni(bpy)Br_2$ instead of $Ni(phen)Br_2$	48
12	no $Ni(phen)Br_2$	0
13	no light, heating to 50 °C	traces
14	no HE	0

[a] Determined by GC-MS/FID, isolated yields in brackets; reaction conditions: *N*-benzoylsaccharin (0.1 mmol, 1 equiv.), RAE (0.2 mmol, 2 equiv.), Hantzsch ester (0.3 mmol, 3 equiv.), LiBr (0.2 mmol, 2 equiv.), $Ni(phen)Br_2$ (0.01 mmol, 10 mol%) and 1 mL DMAc (0.1 M).

formation could only be detected in solvents with Kamlett-Taft parameters similar to those of DMAc (Supporting Information, Table 1). The addition of anhydrous LiBr as well as a higher concentration of the RAE **5a** (entry 6) were found to improve the yield (compare Table 1, entries 5 and 6).

As shown in entries 12–14, control experiments were performed and each component proved indispensable. This is due to the insufficient redox potential of HE in its ground-state ($E_{1/2}^{red} = +1.0$ V vs. SCE),[31] which can neither generate radicals from NHP-esters ($E_{1/2} = -1.26$ V to -1.37 V vs. SCE)[32] in its ground state, nor regenerate the catalytically active Ni(0) species from Ni(I) ($E_P^{Ni(I)dtbpy} = -1.17$ V vs. SCE).[33]

Next, the scope of this method (Schemes 3) was investigated. Primary and secondary aliphatic radicals worked in good to excellent yields and also acids with long aliphatic chains (oleochemicals) worked very well. (**6a**–**6f**) Tertiary alkyl radicals (corresponding to **7a**) gave the corresponding products only in low yields, which is consistent with observations in related reactions.[22,34] As to be expected, ketone carbonyls are also tolerated, permitting access to 1,4-diketones (**6g**) which can be further utilized in the synthesis of five-membered

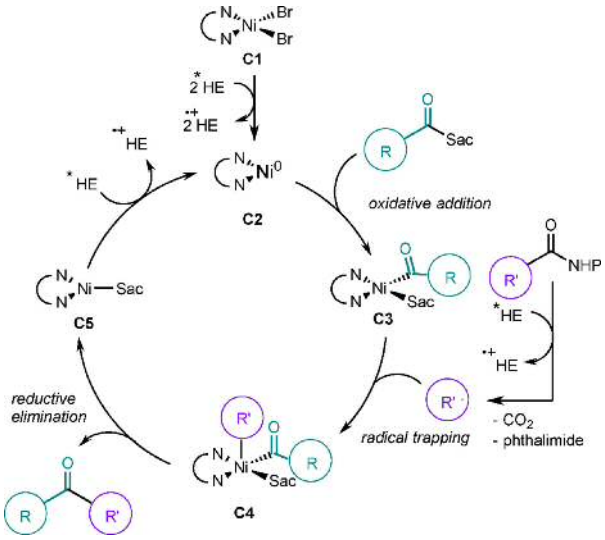


Scheme 3. Scope of the redox-active esters, Isolated yields unless stated otherwise. Reaction conditions: 0.4 mmol *N*-acylsaccharin, 0.4 mmol RAE, 0.6 mmol Hantzsch ester, LiBr 0.8 mmol, Ni(phen)Br_2 (0.04 mmol) and 4 mL DMAc (0.1 M). [a] Yield determined with internal standard (^{1}H NMR). [b] Side product **8e** was isolated, during the preparation of **8d**. [d] Yields estimated by ^{1}H NMR due to dicyclohexylketone remaining in the product after column chromatography.

heterocycles through Paal-Knorr synthesis. Aliphatic acids bearing heterocyclic systems like thiophene or indole moieties can also be used to deliver the corresponding ketones (**6i**, **6h**), with the free N–H group not affecting the reaction. Alkenes as in the derivative of erucic acid (**6j**) do not interfere with the orchestrated radical mechanism, highlighting the efficient reaction of the free radical with the nickel catalyst. For stabilized benzylic radicals (products **6k** and **6p**), dimers were observed as side products (see the Supporting Information), supporting the proposed free radical reaction mechanism (see Scheme 4).

α-Oxy- and α-amino acid derivatives (**6l**, **6q** and **6r**) could also be used as radical precursors, the latter giving access to α-amino ketones (e.g., **6q**) which are of synthetic and medicinally relevant structures.[35] These electron-rich radicals however reacted only with electron rich *N*-acylsaccharins but showed no reaction with **1a** (**7b**–**7c**). Finally, we were also able to generate ketones bearing a carboxy group (**6m**) using a ^{t}Bu-ester as a protecting group. The presented approach to ketone synthesis is also feasible for late-stage functionalization and more complex structures as shown with **6n** and **6o**, with even like indomethacin or cholic acid (**6n**) yielding the product in good yields.

Next, the scope of *N*-acylsaccharins was investigated. Aromatic derivatives gave moderate to good yields (17–88%, see Scheme 3). In contrast to aryl bromides which generally work better with decreasing electron density,[29] electron-deficient aromatic *N*-acylsaccharins seem to be less reactive than their electron-rich analogues (see **7d**–**7f**). Halogen substituents with their strong inductive effect diminish the electron density of the aromatic system and the carbonyl group, which leads to a decreased yield (**8c**–**8f**). For the *p*-bromo substituted phenyl ring (**8d**), the side product corresponding to the cross coupling of Br (**8e**) was also isolated in accordance with the literature.[29] Electron-rich *N*-acylsaccharins (**8g** to **8j**) performed very well, showing how an increase in electron density enhances their reactivity. According to this observation, aromatic carboxylic acids bearing a tertiary amine (**8k**) can also be used as acyl surrogates, where the purely reductive conditions of our method are superior to iridium-catalyzed reactions as for those conditions the oxidation of the amine is to be expected.[36] Gratifyingly, we found vinylogous acids (**8l**) to selectively generate the corresponding enone in good yield, again emphasizing the broad applicability of the method. No by-products of radical attack to the C=C double bond could be detected. Aliphatic *N*-acylsaccharins also performed well (**8m** to **8o**), allowing use of aliphatic carboxylic acid either as RAE or as acyl surrogates, granting our newly proposed method more synthetic flexibility. Methyl ester groups as shown in **8o** are stable during the reaction which makes aliphatic dicarboxylic acids also possible precursors for *N*-acylsaccharins.



Scheme 4. Proposed catalytic cycle of the developed nickel-catalyzed photochemical ketone synthesis.

Computational and spectroscopic studies

To gain a deeper understanding of the reactivity of *N*-acylsaccharins in this photochemical reaction, the stability of the amide bond was investigated via quantum chemistry. According to literature reports, the high reactivity of *N*-acylsaccharins in Pd-catalyzed cross-coupling reactions is due to the low resonance stabilization of the amide bond, originating from the high torsion angle.[7,37,38] A similar calculation was performed using the COSNAR-method[39,40] (carbonyl substitution nitrogen atom replacement). However, these calculations did not predict *N*-benzoylsaccharin to be the most reactive compound, as *N*-benzoylsuccinimide shows an even weaker amide resonance. E_{COSNAR} thus seems to be a poor predictor for the reactivity of the selected acyl precursors in this nickel-catalyzed reaction as it should correlate with the yield (compare Supporting Information, figure S8 and table S2, blue and red graph).

As would be expected, the bond dissociation energy E_D should govern the height of the activation barrier for the insertion of nickel into the amide bond. The quite low E_D of *N*-benzoylsaccharin arises as the π*-orbital of the exocyclic O–C–N bond is lowered in energy through overlap with the antibonding orbitals of the endocyclic N–S and N–C bonds, (see the Supporting Information). The bond dissociation energy appears to be a more reliable predictor for the reactivity of the different acyl precursors as it shows a better correlation to the detected yield of the compound in question (see the Supporting Information, S9 and table S3).

Additionally, cyclic voltammograms (CV) were recorded. *N*-benzoylsaccharin can be reduced irreversibly ($E_{p,1} = -0.95$ V vs. SCE and $E_{p,2} = -1.19$ V vs. SCE), at potentials which should also be reached by HE in its excited state ($E_{1/2}^{red*} = -2.2$ V vs. SCE).[30] To investigate whether this direct electron transfer also occurs during the reaction, possibly changing the reactivity of the acyl surrogate, a fluorescence quenching experiment was performed. In a Stern-Volmer plot, no quenching of the fluorescence of HE by *N*-benzoylsaccharin was evident (compare Supporting Information figure S3). This indicates that under the reaction conditions where the ratio of acyl precursor

to HE is much lower, no direct reduction of the saccharin derivative should occur. Ni(phen)Br_2 however quenched the fluorescence of HE as expected (compare Supporting Information figure S3), although, as indicated by the parabolic curve, the quenching is of both static and dynamic nature, suggesting an appreciable pre-association of HE and the nickel complex, possibly through π-π stacking with the phenanthroline ligand.

As reported by Molander et al., HE and the RAE form EDA complexes in their ground states showing characteristic absorption.[29] We could also observe the formation of those complexes by a bathochromic shift (see Supporting Information, figure S4). However, during the fluorescence quenching experiments, we could observe an increase of HE's fluorescence upon addition of RAE, which levels off at higher RAE concentrations (see Supporting Information, figure S5). As no changes in the absorption spectra at the concentrations used in the fluorescence experiments could be detected, the emitting species likely forms after excitation (see Supporting Information, figure S5). It is known that excimers form as a function of the concentration and show a characteristic fluorescence.[41] We therefore suggest that during the reaction, not only assembly in the ground state but also in the excited state plays a role in the generation of radicals. We were able to trap the intermediate alkyl radicals by the addition of styrene or TEMPO to the reaction mixture. However, smaller amounts of acyl radical adducts were also detected, which is in line with related reactions on amides.[22] Due to the small amounts relative to product and the adduct corresponding to the RAE radical, we suggest the generation of acyl radicals not to be a major pathway.

Based on these findings, the following reaction mechanism is proposed (Scheme 4): Ni(II) (**C1**) is first reduced by HE to generate the reactive Ni(0) species **C2**, which can undergo oxidative addition to the *N*-acylsaccharin, leading to intermediate **C3**. This species then traps the radical generated through EDA-complexation between HE and the RAE, producing the Ni(III) species **C4**. This highly reactive intermediate then undergoes reductive elimination, furnishing the ketone and forming the Ni(I) species **C5**, which is finally reduced by photoexcited HE to close the catalytic cycle.

We also acknowledge the possibility of the radical trapping to take place prior to the oxidative addition, which however contradicts the proposed mechanism of Hong et al.[22] and the low reactivity of the *N*-acylsuccinimide in our reaction.

Based on this mechanistic proposal, the hypothesis evolved that the Ni(II)-intermediate **C3** is much more electron deficient than the corresponding nickel(II)-intermediates derived from aryl bromides. This is probably due to the stronger σ-donor and weaker π-acceptor character of an aryl compared to the acyl group. The saccharinate anion (probably coordinated through the nitrogen atom[42]) is a weaker σ-donor and π-acceptor, not enhancing the electron density. Therefore, it was expected that electron donating substituents on the aromatic ring, for example, methoxy and benzyloxy groups in the acyl moiety, by weakening its π-acceptor character, would allow reactions with stabilized radicals. The latter are known to couple with aryl bromides in dual nickel photocatalysis.[29] Indeed, this could be observed for a secondary α-amino radical (**6q**) and a secondary α-oxy radical (**6r**), which instead showed no reaction with *N*-benzoylsaccharine.

To rule out that the high reactivity of the *N*-acylsaccharines is due to the release of free saccharine which may lead to the formation of a potentially reactive nickel saccharine complex[43] in solution, we performed the reaction using benzoyl chloride with and without addition of catalytic amounts of saccharine (10 mol%). As no significant change in the low but detectable yield could be observed, the role of the *N*-acylsaccharines appears to be only that of reactive acyl donors.

Conclusion

In summary, an eco-friendly protocol for the nickel-catalyzed synthesis of ketones from carboxylic acids using photoredox chemistry has been developed. The net process resembles the well-known pyrolytic decarboxylative coupling of calcium or thorium carboxylates[44] but operates under much milder conditions. To the best of our knowledge, this represents the first application of *N*-acylsaccharins in such a setting and it was possible to gain a deeper understanding of their high reactivity using computational chemistry combined with practical experiments. *N*-acylsaccharins and NHP-esters can both be prepared in a single step from the corresponding carboxylic acid and are both bench-stable. Phthalimide can be easily isolated and could be recycled to *N*-hydroxyphthalimide upon reaction with hydroxylamine,[45] while saccharin can be reextracted from the aqueous phase.

The developed methodology provides access to a variety of ketones in moderate to good yields and does not rely on the use of expensive iridium photocatalysts but employs Hantzsch ester as a cheap and eco-friendly photoreductant and photocatalyst instead.

Experimental Section

General procedure (1) for the synthesis of *N*-acylsaccharins

Starting from carboxylic acid chlorides (procedure 1a):[7] To a stirred solution of saccharin (549 mg, 3.0 mmol, 1.0 equiv.) and triethylamine (0.35 mL, 3.0 mmol, 1.0 equiv.) in DMAc (3 mL) at 0 °C the corresponding acid chloride (3.0 mmol, 1.0 equiv.) was added dropwise over the course of 10 minutes. The reaction mixture was stirred at 0 °C for 10 minutes and afterwards at room temperature for 1 h. The product was precipitated by addition of water (20 mL), filtered off, washed with water, saturated Na_2CO_3 solution and ice-cold methanol. The crude product was recrystallized from toluene to yield the product in sufficient purity.

Starting from carboxylic acids (procedure 1b): To a stirred suspension of the carboxylic acid (3.0 mmol, 1.0 equiv.) in EtOAc (10 mL) under N_2-atmosphere, thionyl chloride (0.25 mL, 3.3 mmol, 1.1 equiv.) was added. After stirring for one minute, one drop of dry DMF was added and the solution was refluxed until all starting material was consumed (ca. 3 h). The solvent was removed under reduced pressure. The crude product was immediately added dropwise (or portion-wise for solids) to a solution of saccharin

(549 mg, 3.0 mmol, 1.0 equiv.) and triethylamine (0.35 mL, 3.0 mmol, 1.0 equiv.) in DMAc (3 mL). The reaction mixture was stirred at 0 °C for 10 min and afterwards at room temperature for 1 h. The product was precipitated through the addition of water (20 mL), filtered off, washed with water, saturated Na_2CO_3 solution and ice-cold methanol. The crude product was recrystallized from toluene to yield the product in sufficient purity.

General procedure (2) for the synthesis of NHP-esters

Using DCC as coupling reagent (procedure 2a):[32] To a 25 mL flask, *N,N'*-dicyclohexylcarbodiimide (1.40 g, 6.7 mmol, 1.2 equiv.), 4-(dimethylamino)pyridine (DMAP) (60 mg, 0.56 mmol, 0.1 equiv.) and the corresponding acid (5.6 mmol, 1.0 equiv.) were added. THF (15 mL) was added, the solution stirred for 2 min. Then, *N*-hydroxyphthalimide (1.00 g, 6.1 mmol, 1.1 equiv.) was added and the resulting solution was stirred for 24 h at room temperature. The precipitate was filtered over silica and the resulting solution was evaporated under reduced pressure. The crude product was purified by recrystallization from ethanol.

Using EDC as coupling reagent (2b): To a 25 mL flask, EDC·HCl (460 mg, 2.2 mmol, 1.1 equiv.), DMAP (24 mg, 240.2 mmol, 0.1 equiv.), *N*-hydroxyphthalimide (391 mg, 2.4 mmol, 1.2 equiv.) and the corresponding acid (2.0 mmol, 1.0 equiv.) were added, followed by DCM (15 mL). The resulting solution was stirred at room temperature until no starting material could be detected by TLC (around 2 h). The organic phase was washed twice with 1 N HCl (10 mL), twice with saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure. Recrystallization from ethanol furnished the pure product.

General procedure (3) for the synthesis of ketones

To an 8 mL vial equipped with a magnetic stir bar and a rubber septum was added $NiBr_2$(phen) (10 mol%, 20 mg), Hantzsch ester (3.0 equiv, 1.2 mmol, 302 mg), redox-active ester (2.0 equiv, 0.8 mmol), LiBr (2.0 equiv, 0.8 mmol, 86 mg), and *N*-acylsaccharin (1.0 equiv, 0.40 mmol). The vial was evacuated three times and filled with argon. Dry, degassed DMAc (4 mL) was subsequently added. The vial was placed in front of two Kessil PR160 L-purple LED lamps (52 W, $\lambda_{max} = 390$ nm) and irradiated for 24 h. The reaction mixture was diluted with 20 mL water and extracted with three times with Et_2O (10 mL). The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using automatic flash column chromatography.

All characterization data can be found in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: carboxylic acids · ketones · nickel · photocatalysis · radicals

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