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

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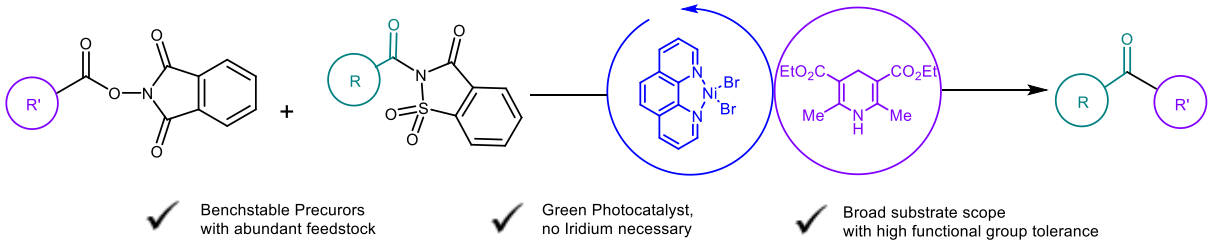


Abstract

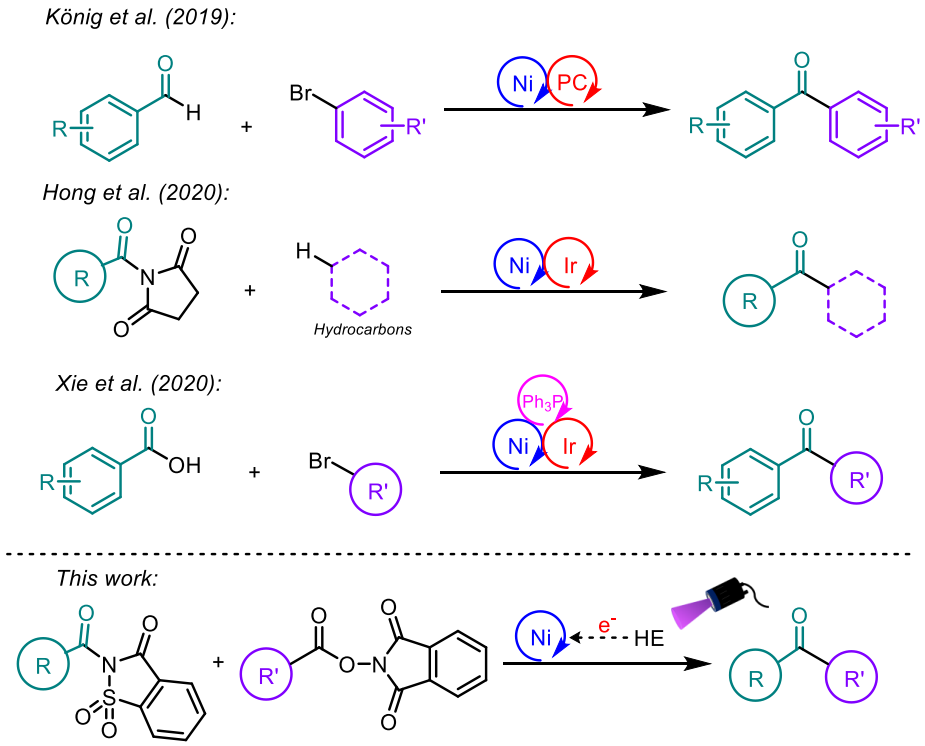
A simple photochemical, nickel-catalyzed synthesis of ketones starting from carboxylic acids is presented. Hantzsch-ester (HE) functions as a cheap, green and strong photoreductant upon visible-light excitation to facilitate radical generation and also engages in the Ni-catalytic cycle to restore the 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 the synthesis of ketones through dual nickel photoredox catalysis. 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 reactive organometallics to less reactive and more convenient nucleophilic coupling partners like boronic acids.[4–7] However, those transformations rely on the use of expensive palladium catalysts, which is neither economically nor environmentally favorable. Even though palladium can often be replaced by nickel[8], many transformations then again require organometallic species[9] or additional metals as sacrificial reductants.[10] This comes at the cost of a higher 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 bonds,[12] ketones,[13] ethers[14] and other structural moieties under mild reaction conditions.[15] For ketone synthesis, several options exist in this context, starting from various compounds such as α-ketoacids,[16] secondary aliphatic carboxylic acids,[17] amides,[18] and aldehydes,[19] amongst others.

The König group showed that ketones can be synthesized from aldehydes and aryl bromides under visible light photoredox catalysis.[19] 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.[17] However, only aromatic carboxylic acids could be used which excludes purely aliphatic ketones from the product scope.
The previously mentioned examples focus on the generation of acyl radicals and mostly employ aromatic acyl moieties with their additional resonance stabilization, which limits the accessibility of aliphatic ketones.[20] Hong et al. recently published a method for C(sp^3)–H bond activation in hydrocarbons which they coupled with *N*-acylsuccinimides to afford ketones.[18] These hydrocarbons however need to be used in large excess to furnish the product in appreciable yield.



Scheme 1: Different recent conditions for photochemical ketone synthesis and our newly developed method.

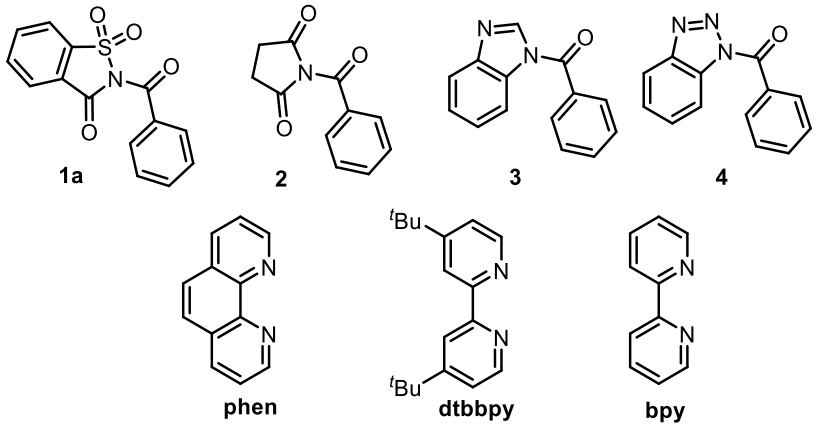
One major drawback of those photoredox methods is their reliance on very expensive iridium-based photocatalysts, which makes them less attractive for industrial applications and limits their potential for the use in green synthesis protocols. Recently, the Molander group presented a net-reductive nickel-catalyzed 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).[21] Due to HEs high excited-state-redox potential ($E_{1/2}^{red*}$ = –2.2 V vs. SCE)[22], which enables the formation of Ni(0) and the ability to form electron donor acceptor complexes (EDA) with NHP-Esters, this system proved to be highly efficient.

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.

Discussion

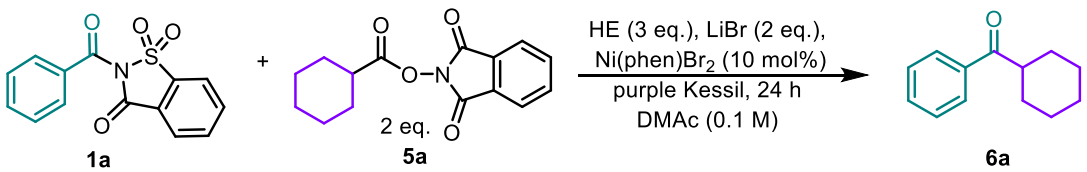
As a starting point for optimization of the reaction, the synthesis of benzoylcyclohexane (**6a**) and GC-MS/FID for efficient screening and yield determination were chosen. Four active amide-type acyl precursors (Scheme 2) were evaluated under different reaction conditions with *N*-(cyclohexanecarbonyloxy)phthalimide as the corresponding coupling partner. *N*-benzoylsaccharines (**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).



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

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 the desired product (**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 formation could only be detected in solvents with Kamlett-Taft parameters similar to those of DMAc (SI, Table X). We also found the addition of anhydrous lithium bromide as well as a higher concentration of the RAE **5a** (entry 6) to be beneficial for the product yield (compare Table 1, entries 5 and 6).

Table 1: Variation of the optimized reaction conditions.



#	conditions	yield in %
1	standard	89 (88)
2	**2** instead of **1a**	traces
3	**3** instead of **1a**	traces
4	**4** instead of **1a**	traces

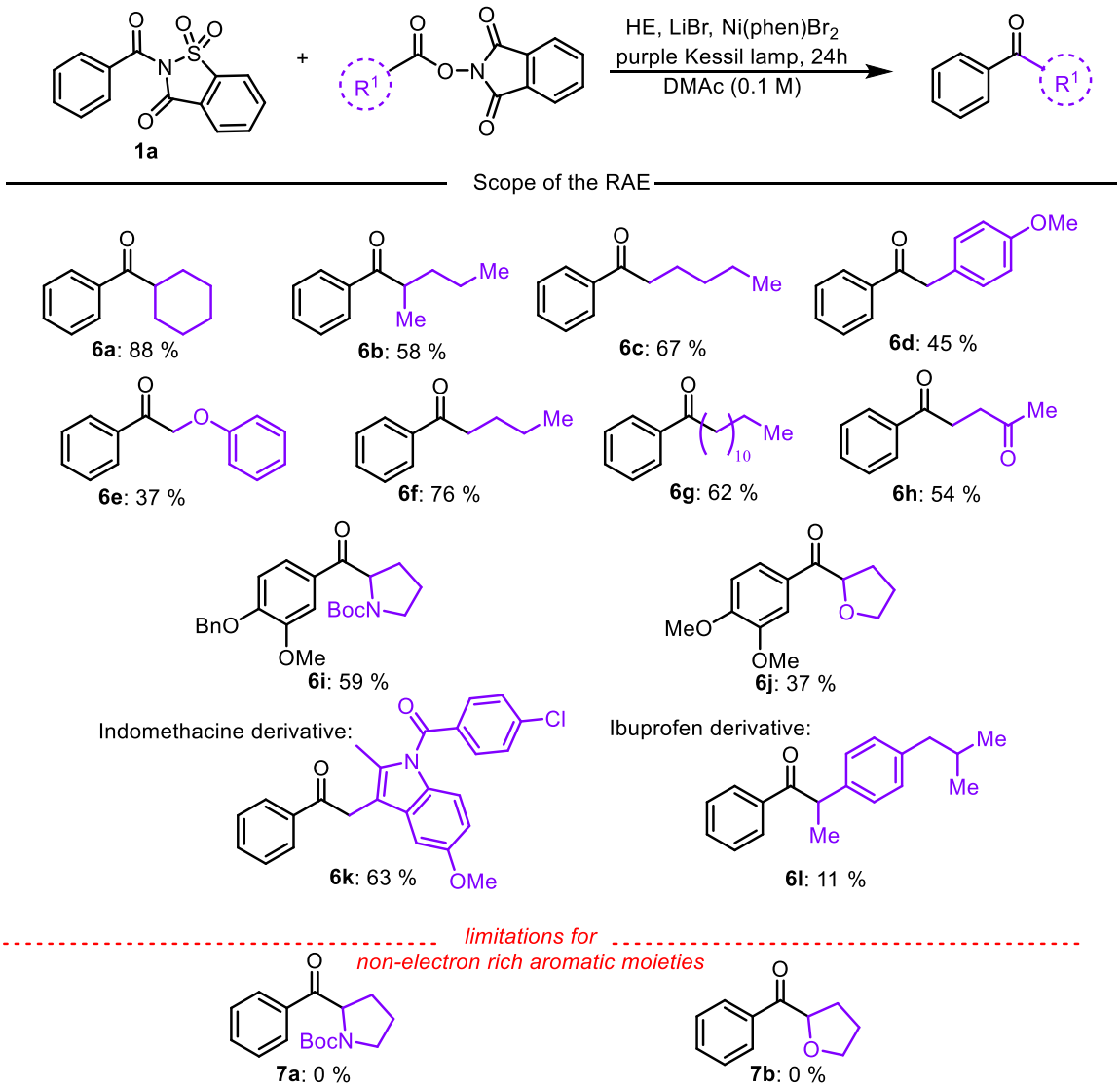
5	no LiBr	73
6	1.5 eq. of **5a**	70 (67)
7	solvent DMF	30
8	solvent MeCN	0
9	$Ir(ppy)_3$ (2 mol%) and NEt_3 (3 eq.) instead of HE	0
10	$Ni(dtbbpy)Br_2$ instead of $Ni(phen)Br_2$	37
11	$Ni(bpy)Br_2$ instead of $Ni(phen)Br_2$	48
12	no $Ni(phen)Br_2$	0
13	no light, heating to 50 °C	traces
14	no HE	0

Yields determined by GC-MS/FID by using calibration curve, isolated yields in brackets

reaction conditions: 0.1 mmol *N*-benzoylsaccharine, 0.2 mmol RAE, 0.3 mmol Hantzsch-ester, LiBr 0.2 mmol, $Ni(phen)Br_2$ (0.01 mmol) and 1 mL DMAc (0.1 M)

As shown in table 1, entries 12–14, control experiments were performed and every component proved to be indispensable for the reaction to proceed. This is due to the insufficient redox potential of HE in its ground-state ($E_{1/2}^{red}$ = +1.0 V vs. SCE)[23], which can neither generate radicals from NHP-esters ($E_{1/2}$ = –1.26 V bis –1.37 V vs. SCE)[24] 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).[25]

With these optimized reaction conditions, the scope of the developed ketone synthesis (compare Schemes 2 and 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 – 6c**, **6f - 6g**).
For the stabilized benzylic radicals (in accordance with products **6d** and **6l**), the dimerized products were observed as side products (see the supporting information), supporting the proposed free radical reaction mechanism (see Scheme 5).
With our method, it was also possible to generate 1,4-dieketones (**6h**), which can be further utilized in the synthesis of five-membered heterocycles like furans, pyrroles, or thiophenes utilizing the Paal-Knorr reaction.
α-Oxy carboxylic acids as well as amino acid derivatives (**6i** and **6j**) could also be used as radical precursors, the later giving access to α-amino ketones (e.g. **6i**) which are pharmaceutically important structures.[26] These stabilized and electron-rich radicals however reacted only with electron rich *N*-acylsaccharines, and showed no reaction with **1a** (**7a**-**7b**). The presented approach to ketone synthesis is also feasible for late-stage functionalization as shown with **6k** and **6l**, with even more complex structures like indomethacine can be functionalized in good yields.

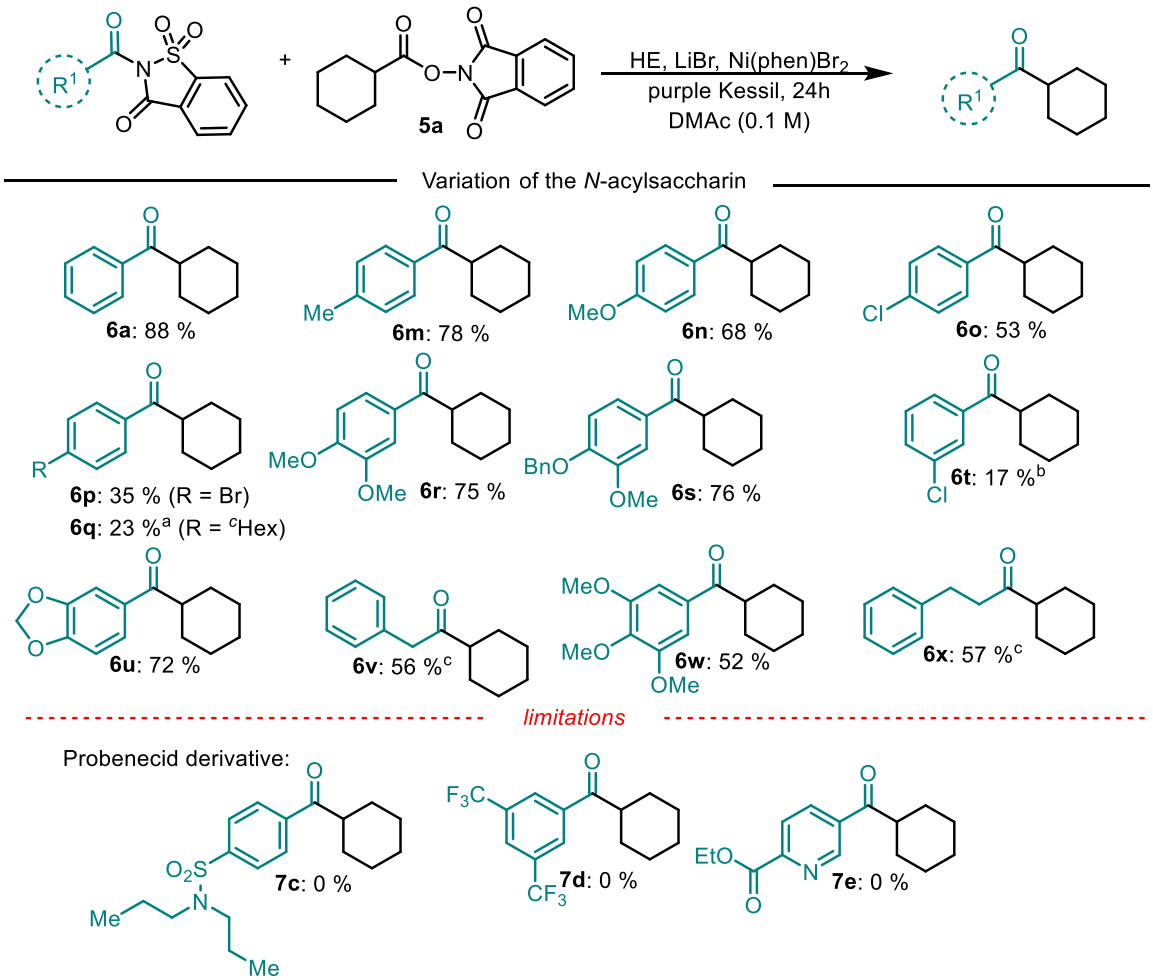


Scheme 3: Scope of the redox-active esters, Isolated yields unless stated otherwise. Reaction conditions: 0.4 mmol N-benzoylsaccharine **S1**, 0.4 mmol RAE, 0.6 mmol Hantzsch-ester, LiBr 0.8 mmol, $Ni(phen)Br_2$ (0.04 mmol) and 4 mL DMAc (0.1 M)

Next, the scope of *N*-acylsaccharines was investigated. Aromatic saccharine derivatives gave moderate to good yields (17-88 %, see Scheme 3). In contrast to aryl bromides which generally work better with decreasing electron density, electron-deficient aromatic *N*-acylsaccharines seem to react only poorly (see **7c**-**7e**).
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 (examples **6p**, **6o** and **6t**). For a chloro substituent, the meta position seems to be unfavorable (see **6o** vs. **6t**).

For the *p*-bromo substituted phenyl ring (**6p**), the side product corresponding to the cross coupling of Br (**6q**)was also isolated in accordance with the literature[21].
Surprisingly, we did not observe the insertion of nickel into the aryl bromide bond leading to the formation of 4-cyclohexylbenzoyl saccharine. Thus, the C(O)−N bond of this precursor is preferred for Ni-insertion over the C−Br bond.

Electron-rich *N*-acylsaccharines (**6r**, **6s** and **6u**) performed very well, as did aliphatic *N*-acylsaccharines (compare **6v** and **6x**).



Scheme 4: Scope of the *N*-acylsaccharine: Isolated yields unless stated otherwise, reactions were performed under standard conditions. [a]Side product **6q** was isolated, originating from the insertion of the Ni-catalyst into the Br–C(sp^2) bond. [b]Yield corrected with internal standard due to the presence of impurities. [c]Yields estimated by ^{1}H-NMR due to dicyclohexylketone remaining in the product after column chromatography.

Mechanistic and computational studies

To gain a deeper understanding of the special role of *N*-acylsaccharines in this photochemical reaction, the stability of the amide bond was investigated via quantum chemistry. According to literature reports, the high reactivity of *N*-acylsaccharines in Pd-catalyzed cross-coupling reactions is due to the low resonance stabilization of the amide bond, originating from the high torsion angle.[7,27,28]

A similar calculation was performed using the COSNAR-method[29,30] (carbonyl substitution nitrogen atom replacement). However, these calculations did not predict the *N*-benzoylsaccharine to be the most reactive compound, as the *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 SI, 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*-benzoylsaccharine arises because 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).

To gain a deeper understanding of the role of the *N*-acylsaccharines, cyclic voltammograms (CV) were recorded. *N*-Benzoylsaccharine can be reduced irreversibly ($E_{p,1}$ = –0.91 V vs Ag/AgCl and $E_{p,2}$ = –1.15 V vs Ag/AgCl), at potentials which should also be reached by HE in its excited state ($E_{1/2}^{red*}$ = –2.2 V vs. SCE)[22]. 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-benzoylsaccharine was visible. This indicates that under the reaction conditions (where the ratio of acyl precursor to HE is much lower), no direct reduction of the saccharine derivative should occur. Ni(phen)Br_2 however quenched the fluorescence of HE as expected (compare figure 2 right), although, as the parabolic curve indicates, the quenching is of both static and dynamic nature, suggesting an appreciable preassociation 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, which can then be excited by visible light.[21] We could also observe the formation of those complexes by a bathochromic shift (see SI, 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 concentration of the RAE (figure 1: left spectrum). As we could not detect any changes in the absorption spectra at the low concentrations used in the fluorescence experiments, the emitting species likely forms after excitation (see SI, figure S5). It is known that excimers form as a function of the concentration and show a characteristic fluorescence.[31] 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.

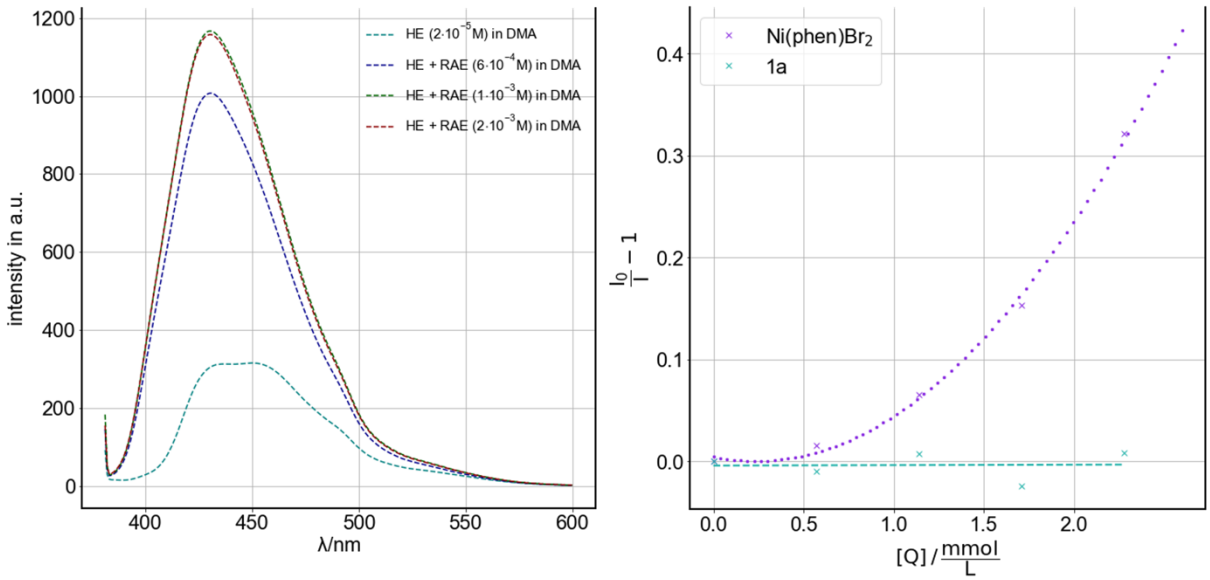
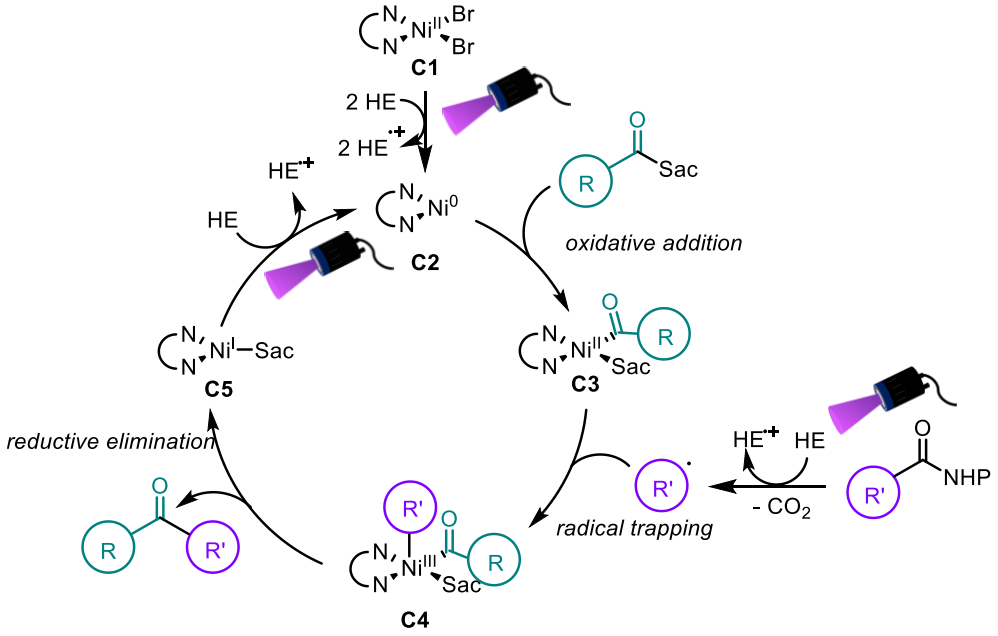


Figure 1: Left: Fluorescence spectra of Hantzsch-ester as a function of the concentration of the RAE. right: Stern-Volmer quenching of Hantzsch-ester with N-acylsaccharine (1a, blue line) and the nickel catalyst (violet line).

Based on these findings, the following reaction mechanism is proposed (Scheme 5): Ni(II) (**C1**) is first reduced by HE to generate the reactive Nickel(0) species **C2**, which can undergo oxidative addition to the *N*-acylsaccharine, 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 Nickel(I) species **C5**, which is finally reduced by photoexcited HE to close the catalytical cycle.



Scheme 5: Proposed catalytic cycle of the developed nickel-catalyzed photochemical ketone synthesis.

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 the end-on coordinated aryl carbanion compared to the acyl anion. The saccharinate anion (probably coordinated through the nitrogen atom[32]) 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, e.g., 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.[21] Indeed, this could be observed for a secondary α-amino radical (**6i**) and a secondary α-oxy radical (**6j**), 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[33] in solution, we performed the reaction using benzoyl chloride with and without addition of saccharine. 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. To the best of our knowledge, this represents the first application of *N*-acylsaccharines 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*-Acylsaccharines and NHP-esters can both be prepared in a single step from the corresponding carboxylic acid and are both bench-stable. The developed methodology provides access to a variety of ketones in moderate to good yields and does not rely on the use of very expensive iridium photocatalysts but employs Hantzsch-ester as a cheap and eco-friendly photoreductant and photocatalyst.

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