C(sp³)–H Bond Acylation with N-Acyl Imides under Photoredox/Nickel Dual Catalysis

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Abstract A novel Ni/photoredox-catalyzed acylation of aliphatic substrates, including simple alkanes and dialkyl ethers, has been developed. The method combines C–N bond activation of amides with a radical relay mechanism involving hydrogen-atom transfer. The protocol is operationally simple, employs bench-stable N-acyl imides as acyl-transfer reagents, and permits facile access to alkyl ketones under very mild conditions.

Key words nickel catalysis, photocatalysis, acylation, radical relay, C–N bond activation, ketones

Ketones are ubiquitous chemical entities in everyday life. Found abundantly in nature, ketone groups are also present in numerous value-added pharmaceuticals and agrochemicals, as well as in fragrances, flavors, and fine chemicals. Alkyl ketones are extremely important scaffolds in multistep organic syntheses and offer multiple opportunities for late-stage derivatization of complex molecules.1

The invention of new methods and strategies for the introduction of acyl functionalities into aliphatic backbones is therefore an ever-present challenge that has significant potential in various fields of chemistry.

Over the last decade, dual visible-light photoredox and nickel catalysis has emerged as a powerful but operationally simple strategy for achieving, under very mild reaction conditions, challenging C(sp³)–C(sp³) bond disconnections that are beyond the reach of classical cross-coupling approaches.2,3 Hence, this method brings prospects for innovation in the area of catalytic acylation reactions of C(sp³)-hybridized substrates,4 and thereby offers a new paradigm for the synthesis of structurally diverse and highly functionalized alkyl ketones. Within this context, resonance-destabilized N-acyl imides stand amongst other carbonyl-type compounds as promising acyl electrophiles owing to their remarkable stability and the documented capability to engage in nickel-catalyzed cross-coupling reactions through C–N bond activation to forge C(acyl)–C(sp³) bonds.6 For instance, in 2017, Molander and co-workers7 reported the use of N-acylsuccinimides as suitable acyl-transfer reagents for photoredox nickel-catalyzed acylation of functionalized alkyl trifluoroborate nucleophiles.8 This provided a strong impetus to develop complementary methods that would exploit other readily available inexpensive aliphatic substrates.

Taking inspiration from recent progress in cross-electrophile coupling reactions, i.e. the direct catalytic joining of two different electrophiles that avoids the need for preformed carbon nucleophiles,9 we developed a novel dual-catalytic acylation process using nonactivated alkyl bromides as electrophilic partners for N-acylsuccinimides. The process was designed to follow a radical relay pathway where a silyl radical is generated photocatalytically and serves as an abstracting agent to activate the alkyl bromide through homolytic C–Br bond cleavage (Scheme 1A).10 Another exciting challenge that we subsequently considered was the design of an alternative strategy that would rely on the selective C(sp³)–H bond activation of simple alkanes through a radical hydrogen-atom transfer (HAT) process.11,12

The groups of Doyle and Molander independently demonstrated that organohalides could serve as both coupling partners and sources of halide radicals that act as potent H-abstraction agents in Ni/photoredox cross-coupling reactions with aliphatic substrates.13 Inspired by these sem-
In our initial exploratory studies, we used the coupling of N-benzoylsuccinimide (1a) with cyclohexane as a model system (Table 1). We found that the desired cross-coupling product 3a was formed in optimal yields by using [Ni(dtbbpy)(H2O)2]Cl2 (I; 4 mol%) (dtbbpy = 4,4’-di-tert-butyl-2,2’-bipyridine) and Ir[Ir(ppy)2(dtbbpy)]PF6 (II; 0.5 mol%) [df(CF3)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine] complexes as a dual-catalytic system under irradiation by a 40 W blue LED lamp. Remarkably, solvent evaluation indicated that only benzene was suitable for delivering the desired ketone. Another critical feature for the success of the coupling reaction was the need for an external source of halogen atoms. Lithium chloride was found to be the most effective source among the salts tested (LiCl, NaCl, KCl, TBAC, Et3N·BnCl, NH4Cl, and NaBr), and increasing the amount of this additive beyond one equivalent did not significantly increase the yield. Additionally, the reaction proceeded more efficiently by using a combination of tripotassium phosphate and sodium tungstate as a dual-base system (Table 1, entries 1–5). Control experiments revealed that the dual-catalytic system and light irradiation were essential for this transformation (entries 6–8). N-Benzoylglutarimide also proved to be a reactive substrate but gave 3a in a lower yield (entry 9). Notably, by employing up to five equivalents of cyclohexane, ketone 3a was isolated in a fair 53% yield after 24 hours of reaction. These conditions (entry 10) were therefore established as our standard conditions. Note that the use of cyclohexane as the solvent led essentially to no reaction, possibly due to the limited solubility of the catalyst and base in this reaction medium (entry 11).

Having a reliable acylation protocol in hand (Conditions A), we explored the reactivity of various acyl succinimides and potential HAT substrates (Scheme 2). Various electron-rich and electron-neutral aryl succinimides underwent coupling with cyclohexane in fair yields (3a–c), whereas electron-deficient derivatives were found to give significantly lower yields (3d and 3e). The scope was expanded to acyl succinimides bearing alkyl groups, as illustrated by 3f, thereby providing access to dialkyl ketones. Notably, other nonactivated cycloalkanes also participated in the coupling process (3g and 3h). We also attempted the acylation of alkyl ethers to access the corresponding α-functionalized ketones. For instance, we examined the use of dialkyl ethers as both alkylating reagents and solvents, as safer alternatives to benzene. In our initial experimental observations on the coupling of 1a with tetrahydrofuran, we found that...
the new procedure (conditions B) required higher catalyst loadings (10 mol% of catalyst I; 2 mol% of catalyst II), but proceeded efficiently without the need for sodium tungstate as an additive.18 This is illustrated by the synthesis of a series of 2-acetyl tetrahydrofurans 3i–l in moderate to good isolated yields. The same procedure successfully gave coupling products containing cyclic or linear aliphatic ethers such as 1,4-dioxane, diethyl ether, or 1,2-dimethoxyethane (3m–q). Notably, a separable 2.3:1 mixture of two regioisomeric products 3q and 3q′ was generated by the acylation of DME.

Interestingly, the byproducts regularly obtained from the reaction of N-acyl succinimides with alkanes were the symmetrical dialkyl ketones deriving from homocoupling of the alkane, together with the corresponding C(Ar)–C(sp²) bond-formation products. A series of experiments were carried out to gain information on the reaction pathway and the origin of these products (Scheme 3). As a prototypical example, the coupling of N-benzoylsuccinimide (1a) with cyclohexane afforded the desired cross-coupling product (3a), along with small amount of cyclohexylobenzene (4a; ≤10%) and dicyclohexylmethane (3f; ≤20%), suggesting the occurrence of a decarbonylative pathway.5b,6d Accordingly, an excess of 1a (10 equiv) was found to react spontaneously with (dtbbpy)Ni(COD) (1 equiv) to afford a mixture of complexes assigned to the corresponding Ni(II)-aryl complex III and the Ni(II)-acyl complex (IV) in a 3:2 ratio (1H NMR), together with the dicarbonyl complex (dtbbpy)Ni(CO)₂ (V) (Scheme 3A).16 By adjusting the stoichiometry of (dtbbpy)Ni(COD) (1.5 equiv) and 1a (1 equiv), the Ni(II)-aryl complex III could be obtained selectively and isolated for full characterization, including single-crystal X-ray diffraction analysis (Scheme 3A).19 The molecular structure of III displays a square-planar geometry of the nickel center, and represents a unique example of structural characterization of a Ni(II)–N succ complex formed by a C–N bond oxidative addition–decarbonylation sequence of amides with Ni(0).20 All attempts to generate the acyl complex IV selectively or to isolate it from the reaction mixture were unsuccessful. This result indicates that N-acyl succinimides undergo spontaneous oxidative addition to Ni(0) followed by facile decarbonylation, providing a plausible pathway to the symmetrical dialkyl ketones21 and the decarbonylative products.22 Comparatively, the reaction of benzoyl chloride with (dtbbpy)Ni(COD) led exclusively to the corresponding acyl-Ni(II) chloride complex VI.16,12b

We then compared the catalytic activity of complex I with that of other potent nickel catalytic intermediates (Scheme 3B). Surprisingly, the use of Ni(COD)₂ with dtbbpy as an exogenous ligand instead of complex I resulted in a very low 8% reaction yield. Furthermore, no reaction was observed with the Ni(II)-aryl intermediate III. On the other hand, the nickel(II)-acyl chloride complex VI was found to be catalytically competent, affording very similar results to those with complex I. Notably, only trace amounts of the desired product were observed in the absence of LiCl, confirming its key role in the reaction, probably through succinimide-to-chloride exchange at nickel. At this stage, the involvement in the catalytic cycle of active paramagnetic species generated in situ from nickel(II) complexes was envisioned. Indeed, as recently demonstrated by the group of Hazari,23 paramagnetic Ni(I) species with bipyridine ligands can participate as key intermediates in nickel-catalyzed C(sp³)–C(sp³) bond-forming reactions. We decided to examine this possibility, and we prepared the [(dtbbpy)Ni(Cl)]₂ dimer VII by the reported procedure.16 Remark-

![Scheme 2](image-url)
ably, the paramagnetic nickel species VII was found to be catalytically active and performed more efficiently than the nickel(II)-dichloro complex I.

These preliminary experiments suggest that the nickel-catalyzed acylation of C(sp³)-H bonds with N-acylsuccinimides does not follow the same pathway as that proposed

*Yields determined by GC-MS with benzophenone as an internal standard

**Scheme 3** (A) Reaction of 1a with (dtbbpy)Ni(COD) and (B) the catalytic behavior of several nickel species
for other acyl substrates. In related coupling processes involving chloroformates and acyl chlorides as substrates reported by the groups of Doyle\textsuperscript{10} and Shibasaki,\textsuperscript{12b} the oxidative addition of the acyl substrate proceeds at Ni(0) species. With N-acylsuccinimides, although oxidative addition of the C–N bond to Ni(0) readily occurs, our experiments suggest that the C–N bond-activation step proceeds at Ni(I) during the catalysis. Further mechanistic studies are clearly necessary to confirm the specific behavior of these acyl substrates, which might be exploited to design complementary mechanistic sequences.\textsuperscript{24}

In summary, we have described a new acylation reaction of C(sp\textsuperscript{3})–H bonds by using bench-stable N-acyl imide substrates. The dual-catalytic process combines nickel-catalyzed C–N bond activation with photocatalytic HAT, and provides operationally simple access to valuable alkyl ketones. Notably, N-acylsuccinimides were shown to undergo ready C–N bond oxidative addition to Ni(0), followed by decarboxylation, under mild conditions. Identification of by-products of the acylation reaction suggested that the development of decarboxylative cross-coupling pathways under mild conditions by using photoredox/Ni catalysis can be envisioned. Further investigations are underway to achieve a better understanding of the reaction mechanism.

**Funding Information**

Financial support from the Université de Lyon, IDEXLYON project (ANR-16_IDEX-0005) and the Agence Nationale de la Recherche (ANR-JCJC-2016-CHAUCACAO) is gratefully acknowledged. T.K. thanks the French Ministry of Higher Education and Research for a doctoral fellowship.

**Acknowledgment**

We thank Guillaume Pilet ([LMI], UMR 5615 CNRS-UCBL) for mass spectrometry analyses and C. Duchamp (Centre Commun de Spectrométrie de Masse, Université Lyon 1) for X-ray diffraction measurements, and C. Duchamp for X-ray diffraction measurements, and C. Duchamp (Centre Commun de Spectrométrie de Masse, Université Lyon 1) for X-ray diffraction analyses.

**Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707301.

**References and Notes**


(9) For a review of acylative cross-electrophile coupling reactions, see: Morigas, T.; Correa, A.; Martin, R. *Chem. Eur. J.* 2014, 20, 8242. For rare examples of cross-electrophile coupling reactions employing amides, see refs. 6c–e.


Cluster

Synlett 2020, 31, A–F

T. Kerackian et al.


(14) Doyle showed that external sources of chlorine atom such as TBACl can be used to cross-couple electrophiles that do not contain chloride (e.g., aryl triflates, bromides, or iodides); see refs. 13b and 13c.


(16) See the Supporting Information for more details.

(17) Cyclohexyl(phenyl)methanone (3a); Typical Procedure A

In an argon-filled glovebox, a 10 mL Schlenk tube equipped with a magnetic stirrer bar was charged with \( \text{Ir(}[\text{dF(CF}_3\text{)ppy}]_2(\text{dtbbpy})\text{PF}_6 \) (0.003 mmol, 3.2 mg), \([\text{Ni(dtbbpy)(H}_2\text{O})_4]\text{Cl}_2 \) (0.024 mmol, 11.2 mg), \( \text{K}_3\text{PO}_4 \) (1.2 mmol, 254 mg), \( \text{Na}_2\text{WO}_4·2\text{H}_2\text{O} \) (0.6 mmol, 200 mg), \( \text{LiCl} \) (0.6 mmol, 25 mg), \( \text{N}_\text{-benzoylsuccinimide} \) (0.6 mmol, 122 mg), cyclohexane (3.0 mmol, 325 mL), and anhyd benzene (6 mL). The sealed vessel was taken out of the glovebox, and the stirred mixture was irradiated by a 40 W blue LED Kessil lamp (455 nm) for 24 hours at RT. To remove solid residues, the mixture was filtered through a short pad of Celite with \( \text{CH}_2\text{Cl}_2 \) as eluent. The volatiles were removed under vacuum and the crude residue was purified by column chromatography [silica gel cyclohexane–EtOAc (10:1)] to give a colorless oil; yield: 60 mg (53%). The 1H NMR and 13C NMR spectra were consistent with values reported in the literature.8b

(18) Phenyl(tetrahydrofuran-2-yl)methanone (3i); Typical Procedure B

On the bench top, an 8 mL scintillation vial equipped with a magnetic stirrer bar was charged with \( \text{Ir(}[\text{dF(CF}_3\text{)ppy}]_2(\text{dtbbpy})\text{PF}_6 \) (0.008 mmol, 9 mg), \([\text{Ni(dtbbpy)(H}_2\text{O})_4]\text{Cl}_2 \) (0.04 mmol, 18.7 mg), \( \text{K}_3\text{PO}_4 \) (0.6 mmol, 127 mg), \( \text{LiCl} \) (0.4 mmol, 17 mg), \( \text{N}_\text{-benzoylsuccinimide} \) (0.4 mmol, 81.3 mg), and anhyd THF (3.2 mL, 0.125 M). The vial was sparged with argon then sealed, and the stirred mixture was irradiated by a 30 W blue LED lamp (450 nm; EvolutChem Photoredox Box device) for 24 h at RT. To remove solid residues, the mixture was filtered through a short pad of Celite with \( \text{CH}_2\text{Cl}_2 \) as eluent. The volatiles were removed under vacuum and the crude residue was purified by column chromatography [silica gel cyclohexane–EtOAc (10:1)] to give a colorless oil; yield: 37.5 mg (53%). The 1H NMR and 13C NMR spectra were consistent with the values reported in the literature.12b

(19) CCDC 2018793 contains the supplementary crystallographic data for complex III. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(20) A single precedent has been reported for the formation of an acyl nickel(II) complex by amide C–N bond activation in which, after a ligand exchange between the transient amidate complex and a chloride ion, a Ni(II) chloride complex was isolated and structurally characterized; see: Hu, J.; Zhao, Y.; Liu, J.; Zhang, Y.; Shi, Z. Angew. Chem. Int. Ed. 2016, 55, 8718.

(21) The formation of alkyl ketones deriving from a decarbonylative process with ethyl chloroformate has been recently reported; see: Shi, R.; Hu, X. Angew. Chem. Int. Ed. 2019, 58, 7454.

(22) For the coupling of \( \text{N}_\text{-benzoylsuccinimide} \) (1a) with cyclohexane, 4a could also be formed by direct attack of the cyclohexyl radical on benzene. See the Supporting Information for more details.


(24) During the final stage of the preparation of this manuscript, a similar protocol for the acylation of C(sp3)–H bonds with N-acylsuccinimides was published, see: Lee, G. S.; Won, J.; Choi, S.; Baik, M.-H.; Hong, S. H. Angew. Chem. Int. Ed. 2020, 59, 16933.