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Silyl radical mediated cross-electrophile coupling of *N*-acyl-imides with alkyl bromides under photoredox/nickel dual catalysis

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ABSTRACT: *A photoredox Ni-catalyzed cross-coupling of N-acyl-imides with unactivated alkyl bromides has been developed that enables efficient access to a variety of functionalized alkyl ketones, including unsymmetrical dialkyl ketones, under very mild and operationally practical conditions. The reaction that operates without the need for any preformed carbon nucleophile proceeds via the combination of two different bond activation processes, i.e. Ni-catalyzed imide activation via C(acyl)-N bond cleavage, and (TMS)₃Si radical-mediated alkyl halide activation via halogen-atom abstraction.*

Transition metal-catalyzed acylation of organometallic compounds is a well-established key transformation in organic chemistry that is of high relevance to the synthesis of a plethora of carbonyl-containing compounds, including ketones.¹ Besides classical acyl-transfer reagents (*e.g.*, acyl chlorides, anhydrides, and thioesters) that are typically employed in these reactions, resonance destabilized amides have recently emerged as new potent electrophiles. These bench-stable acyl electrophiles are equally well accessible from abundant carboxylic acids, and have been shown to engage in cross-coupling reactions with organometallic nucleophiles.² Nickel catalysis has been particularly highlighted as a very powerful strategy to forge C(acyl)-C(sp²) bonds *via* C-N bond activation of amides, allowing the efficient preparation of valuable ketones.³ While the remarkable properties of nickel⁴ unlocked the development of challenging cross-coupling reactions with C(sp³)-hybridized substrates,^{4a} it is striking to note that the conversion of amides to alkyl ketones *via* C(acyl)-C(sp³) bond formation remains extremely rare. It is even more surprising that it could provide convenient synthetic methods to this versatile class of carbonyl compounds with notable applications spanning drug lead and natural product synthesis, as well as for their propensity to undergo functional group interconversion. The very few examples documented so far consist of nickel-catalyzed cross-couplings with organometallic reagents that are reminiscent of Negishi and Suzuki reactions. For instance, Garg and co-workers reported the acylation of alkylzinc reagents with *N*-tosyl and *N*-Boc amides.⁵ The group of Rueping investigated the cross-coupling of *N*-(Me)Ph amides with alkylboranes.⁶ In a different approach, Molander and co-workers developed the cross-coupling of *N*-acyl-succinimides with alkyltrifluoroborates *via* single-electron transmetalation with the aid of visible-light mediated photoredox catalysis (Scheme 1a).^{7,8}

Another highly valuable, yet unknown, strategy to convert amides into alkyl ketones would involve direct cross-electrophile coupling with abundant and bench stable alkyl halide electrophiles, avoiding the use of organometallic reagents.⁹ Cross-coupling reactions between two electrophiles have rapidly developed as a very appealing method to forge carbon-carbon bonds starting from alkyl halide reagents.¹⁰ For the preparation of ketones, reported methods rely on nickel catalyzed reductive acyl cross coupling between aroyl chlorides or anhydrides with alkyl halides, and require a stoichiometric amount of metal reductants.¹¹ In this work, we aimed to develop a direct cross-coupling of amides with alkyl bromides under mild conditions using cooperative nickel and photoredox catalysis (Scheme 1b). Since its introduction in 2014 by the

groups of McMillan, Doyle¹² and Molander,¹³ nickel/photoredox dual catalysis has burgeoned into one of the most appealing strategies for introducing C(sp³)-centers onto organic frameworks under very mild reaction conditions.¹⁴ This new methodology exploits the inherent ability of nickel complexes to undergo single electron transfer and accept alkyl radical species, issued here from a photoredox cycle. A tremendous progress has been made recently in this field by the group of MacMillan,¹⁵ with the sophisticated design of a nickel/photoredox cross-electrophile coupling of two organobromides. The key point of the mechanistic design relied on the documented ability of silyl radical intermediates, that are photocatalytically generated, to activate an alkyl bromide *via* halogen-atom abstraction.¹⁶ This procedure enables efficient C(sp²)-C(sp³) bond formation without the need for any preformed carbon nucleophiles.¹⁷ Inspired by this seminal breakthrough, we report herein the successful application of silyl radical-mediated activation of alkyl bromides to the development of a catalytic cross-electrophile coupling of amides with alkyl bromides. This method provides facile access to alkyl ketones, including primary and secondary alkyls, under very mild conditions.

Scheme 1. Ni-catalyzed C(acyl)-C(sp³) cross-coupling reactions of amide-derived electrophiles.

a) Cross-coupling with acyl imidate reagents

b) Cross-electrophile coupling with alkyl bromides [this work]

c) Reaction Design

The reaction design relies on the combination of two distinct modes of bond activation: (i) C(acyl)-N bond activation of the amide via oxidative addition to Ni(0) catalyst, and (ii) C(alkyl)-Br activation of the alkyl bromide via halogen-atom abstraction by a stabilized (TMS)₃Si radical, deriving from photocatalytic activation of tris(trimethylsilyl)silane [(TMS)₃SiH].¹⁶ These two activation processes would then merge through the capture of the alkyl radical by the acyl-Ni(II) complex (A), which would then be followed by C(alkyl)-C(acyl) reductive elimination from high-valent Ni(III)-amidate complex (B) (Scheme 1c). In this process, the photocatalyst would be required for the generation of the silyl radical species, and for reducing Ni(I) to Ni(0) so as to restart the nickel catalytic cycle.

We began our study with the reaction of *N*-benzoyl-succinimide¹⁸ **1aa** with 4-bromotetrahydropyran **2a** in the presence of stoichiometric amount of [(TMS)₃SiH] to assess the feasibility of the process. The selected dual catalytic system was composed of the bench-stable [Ni(dtbppy)(H₂O)₄]Cl₂ complex **I**, and Ir[dF(CF₃)ppy]₂(dtbbpy)]PF₆ complex **II** as the photocatalyst (Table 1).

Table 1. Selected preliminary optimization experiments^[a]

Entry	Deviation from optimal reaction conditions	Yield (%) ^[b]
1	none	74 (59)
2	48 h with one 30W blue LED lamp ^[c]	76
3	EtOAc as solvent	57 ^[d]
4	72 h with one 30W blue LED lamp in EtOAc ^[c]	74
5	no base	0
6	no photocatalyst	0
7	no light (dark)	0
8	no Ni catalyst	0
9	no silane	0
10	0.5 mol% of photocatalyst II	66
11	Ni(COD) ₂ /dtbbpy instead of I	63
12	0.5 mol% of Ni complex I , 24 h	61
13	Glutarimide derivative 1ab as substrate	68
14	NaBr instead of Na ₂ CO ₃	7
15	NaBr additive (1 equiv.)	69

^[a] Unless otherwise stated, reactions were performed using *N*-acyl-succinimide **1aa** on a 0.5 mmol scale under the irradiation of two 40W blue LED Kessil® lamps (455 nm). See the Supporting Information for details regarding lighting set-ups. Dtbppy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl; ppy = 2-phenylpyridine. ^[b] Yields were determined by ¹H NMR spectroscopy using dibromomethane as an internal standard. Yields in parentheses refer to isolated pure compound. ^[c] Reaction performed using EvoluChem™ PhotoRedOx Box device equipped with one 30W LED lamp (450 nm). ^[d] At this point (after 18 h) c.a. 20% of unreacted starting imide was still present in the reaction mixture.

A brief survey of several solvents (*e.g.*, DME, 1,4-dioxane, 2-MeTHF, MeCN, DMF, DCM, acetone, ethyl acetate) and bases (*e.g.*, alkali carbonates, K₃PO₄, CsF, AcONa, Et₃N, 2,6-lutidine), revealed that the desired alkyl ketone **3a** could be obtained in good yields with sodium carbonate as the base, and acetone or ethyl acetate as the solvent (Table 1, entries 3-4).¹⁹ Evaluation of the blue LED light irradiation setting indicated that the transformation proceeds equally well using direct irradiation with two 40W blue LED Kessil® lamps (455 nm) (74% yield, 18 h) or using the EvoluChem™ PhotoRedOx Box device equipped with one 450 nm 30W blue LED lamp (76% yield, albeit in 48 h). Control experiments revealed that the dual catalytic system, silane, base and light irradiation are essential for this transformation (Table 1, entries 5-9). From a practical point of view, it is interesting to note that the bench-stable Ni(II) complex **I** provides better results than the air-sensitive Ni(COD)₂/dtbbpy catalytic system (entry 11). Furthermore, the reaction proceeds well with very low nickel catalytic loading (down to 0.5 mol %, Table 1, entry 12). Finally, glutarimide derivative **1ab** also proved to be a reactive substrate, affording **3a** in 68 % yield (Table 1, entry 13).

Table 2. Scope of alkyl bromides and imides.^[a]

[a] Reactions performed on a 0.5 mmol scale. Conditions A: Acetone was used as solvent under the irradiation of two 40W blue LED Kessil® lamps (455 nm) for 18-24 h; Conditions B: Ethyl acetate was used as solvent under the irradiation of a 30W blue LED lamp (450 nm) for 24-72 h using the EvoluChem™ PhotoRedOx Box device. Isolated yields are given. [b] The reaction was run in acetone. [c] Obtained from the corresponding *N*-acylglutarimide.

With a set of suitable conditions in hand, we investigated the applicability of the methodology across a broad range of succinimide derivatives and commercially available alkyl halides (Table 2). The scope of alkyl bromides that underwent the transformation encompassed a range of primary and secondary non-activated derivatives, bearing a variety of functional groups such as ester, nitrile, amine, fluoroalkyl, ether as well as sensitive acetals (**3a-3j**). Notably, the protocol proved capable of delivering β -alkoxy-substituted ketones, including galactopyranose derivative (**3j**). On the other hand, alkylation using the activated α -methoxymethyl bromide (MOMBr) failed to provide the corresponding α -oxygenated ketone. Alkyl bromides bearing terminal alkene moieties were also suitable substrates. The cross-coupling reaction with 7-bromohept-1-ene afforded the expected coupling product in fair yield (**3k**) leaving the double bond untouched. In contrast, the 6-hexen-1-yl homolog, as a radical-clock substrate, partially underwent 5-*exo*-trig cyclization, thus leading to a mixture of cyclic and linear cross-coupled products **3l'** and **3l**, respectively, with a ratio of 3:2. This observation provides strong support for the formation of alkyl radicals as intermediate species in the coupling process. Overall, the scope of reactive alkyl bromides is complementary to that reported using alkyltrifluoroborates as radical precursors under a similar dual catalytic system.^{7,21} With respect to the scope of imide counterparts, the reaction protocol allowed the coupling of a variety of aromatic derivatives with various functional groups and substitution patterns (**3m-3t**), including boronic acid pinacol (BPin) ester (**3q**) that provides a chemical handle for further elaboration. Importantly, the scope was also expanded to imides having saturated backbones, thus providing access to unsymmetrical dialkyl ketones (**3u-3w**). Finally, access to α,α -difluoroketones was envisioned as a highly valuable addition to the scope of the reaction. Indeed, this would provide an attractive

strategy for the direct difluoroacetylation of aliphatic backbones. However, *N*-(α,α -difluoroacetyl)-imides are challenging substrates that are vulnerable to decomposition when exposed to inorganic bases.²² Nevertheless, a promising preliminary result was obtained with the synthesis of α,α -difluoroalkylketone **3x**. To further demonstrate the synthetic utility of the cross-coupling reaction, a synthesis of **3a** was performed on a 1.5 mmol scale, and the product was obtained in 49% isolated yield.

From a mechanistic point of view, in light of previous documented studies^{7,15,17} and our own observations, a sequence of events as depicted in Scheme 3 may be proposed as a possible reaction pathway. Nickel(0) complex would undergo oxidative addition of the amide electrophile via C-N bond cleavage. Meanwhile, the alkyl bromide would be activated by (TMS)₃Si radical through the generation of a nucleophilic alkyl radical with concomitant production of bromotris(trimethylsilyl)silane. Capture of the alkyl radical by the acyl-Ni(II) intermediate **A**, followed by reductive elimination of the desired ketone from high-valent Ni(III)-amidate complex **B** would afford Ni(I)-amidate **C**. Then, reduction of the Ni(I) species to Ni(0) by Ir(II) would restart the nickel and iridium catalytic cycles and liberate a succinimide ligand. Importantly, silylated succinimide **4** could be identified as a co-product of the reaction. This hitherto unknown compound was isolated and characterized. It is most likely that it derives from nucleophilic substitution of the silyl bromide by succinimide anion,²³ thus terminating the silicon pathway. Concerning the generation of the (TMS)₃Si radical intermediate, two possible pathways may be envisioned. A single electron oxidation of released Br⁻ anion by the photoexcited *Ir(III) catalyst would generate a bromine radical that can abstract hydrogen from (TMS)₃SiH (not shown).^{14a} However, it has to be noted that the addition of NaBr as a bromide source did not

improve the reaction yield. Furthermore, only traces of the product were observed when NaBr was used instead of the base (Table 1, entries 14 and 15). Alternatively, the $(\text{TMS})_3\text{Si}$ radical intermediate could be generated directly via oxidative scission of the $(\text{TMS})_3\text{Si-H}$ bond by the strongly oxidizing photoexcited $^*\text{Ir}(\text{III})$ catalyst in the presence of a base (scheme 3).^{17d,e}

Scheme 3. Tentative mechanism.

In summary, we have described a new cross-electrophile coupling reaction using *N*-(acyl)-imides and alkyl bromides as readily available, bench stable coupling partners. The reaction was conducted under very mild and operationally simple conditions without the need for any air-free techniques. A wide range of substrates, including primary and secondary alkyl bromides as well as alkyl amides are reactive, underscoring the great value of this reaction for the synthesis of a variety of functionalized alkyl ketones

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, compound characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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