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Nickel-Catalyzed Deaminative Acylation of Activated Aliphatic Amines with Aromatic Amides via C–N Bond Activation

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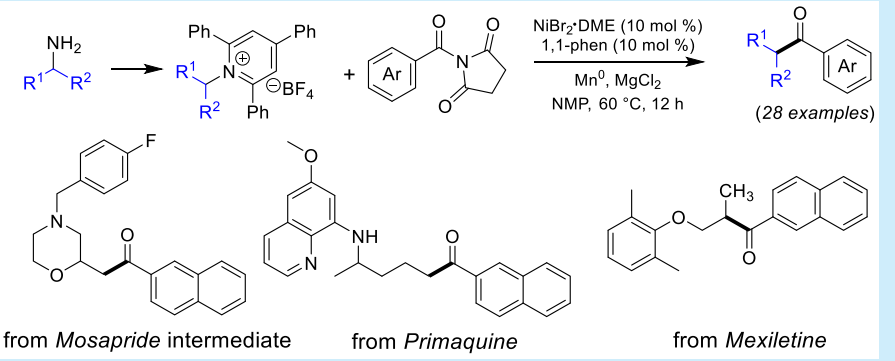

ABSTRACT: Deaminative functionalization of aliphatic primary amines has great synthetic utility. Herein, we describe a Ni-catalyzed reductive deaminative cross-electrophile coupling reaction between Katritzky salts and aromatic amides. This work provides examples of the synthesis of various ketones from alkylpyridinium salts, including both primary and secondary alkylamines. Given its mild reaction conditions and high functional group tolerance, this cross-coupling strategy is expected to be useful for late-stage functionalization of complex compounds.

Aliphatic primary amines are a feedstock with high natural abundance. They are also prevalent in many biologically active natural products, synthetic intermediates, and drug molecules.[1] The use of inexpensive, readily available, and abundant primary alkyl amines has the advantage of avoiding the use of halogenated hydrocarbons. Activation/functionalization of C–N bonds in amines has been used for C–C and C–X bond formation.[2] Notably, Watson and co-workers showed that Katritzky salts (2,4,6-triphenylpyridinium salts) can be used as alkyl radical precursors in Suzuki–Miyaura cross-coupling reactions (Scheme 1 A).[3] These redox-active species are prepared via a straightforward, chromatography-free process involving condensation of unactivated primary amines with a bench-stable, commercially available pyrylium salt.[4] In addition, Glorius et al. demonstrated that Katritzky salts can be used as alkyl halide surrogates to generate alkyl radicals in Minisci reactions under visible-light-induced photoredox conditions (Scheme 1A).[5] These exciting seminal reports have drawn much attention from organic chemists for the use of primary amines as radical precursors. Recent studies have demonstrated the great potential of Katritzky salts as radical precursors in deaminative functionalization, including borylation,[6] alkynylation/alkenylation,[7] arylation,[8] alkyl-Heck-type reactions,[9] allylation,[10] alkylation,[11] carbonylation,[9b,12] and C-heteroatom bond-forming reactions[13] (Scheme 1 A). In these examples, the Katritzky salts serve as electrophiles that react with nucleophilic reagents to realize deaminative functionalization. However, there have been few reports of cross-electrophile coupling transformations using amines as alkyl electrophile precursors. Very recently, one example of cross-electrophile coupling was achieved between Katritzky salts and halides (Scheme 1 B).[7b,c,14] However, the scope of these reactions remains limited and the pursuit of various electrophilic counterparts for use in reductive cross-electrophile coupling is necessary for deaminative functionalization of amines.

Amides play a key role in various areas of chemistry given their ubiquitous nature in proteins, polymers, and pharmaceuticals.[15] C–N bond cleavage remains a challenge in cross-coupling reactions due to the low reactivity of amides due to amidic resonance.[15a,16] In 2015, a mere handful of examples about activation of carbonyl C–N bonds were first reported.[17] Recently, transition-metal-catalyzed activation of carbonyl C–N bonds through a wide range of straightforward methods to generate acyl–metal intermediates through insertion of a metal into the amide bonds has become a thriving area in cross-

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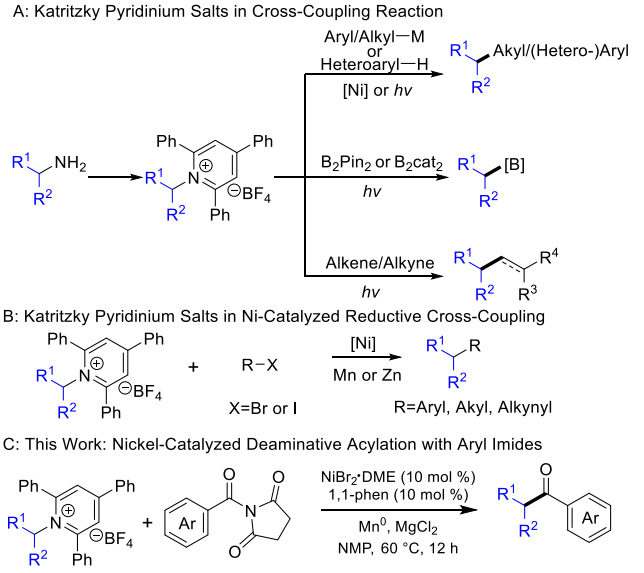
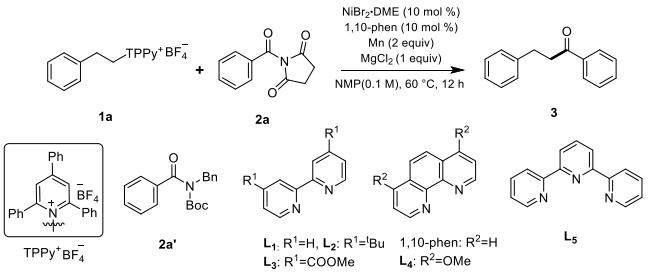
Scheme 1. Aliphatic Amines for Ketone Synthesis in Reductive Cross-Coupling



coupling reactions of amides.[18] Selective C−N bond cleavage has been developed into a powerful transformations for the synthesis of ketones and esters by Garg,[19] Zou,[20] Szostak,[21] Rueping,[22] and others.[23] However, the use of amides as electrophilic precursors remains limited,[24] especially in reductive cross-coupling reactions, which is one of the most active areas of research.[25] In this letter, we report the first nickel-catalyzed deaminative acylation of activated aliphatic amines with aromatic amides via acyl C−N bond activation by insertion of nickel into the bond (Scheme 1C).

We hypothesized that the acyl−nickel intermediates would be oxidized by alkyl radical generated from the pyridinium salt via single-electron transfer (SET),[14a−c] followed by generation of ketone as a reduction product. To investigate reductive cross-coupling reactions between aliphatic amines and aromatic amides, we began with Katritzky salt **1a** and activated amide **2a**. *N*-Acylsuccinimides **2a** with high reactivity results from the moderate twist and electronic activation of the amide bond (twist = approximately 70°, resonance energy = close to 0 kcal/mol) according to the literature.[16b] After evaluating various reaction parameters, we obtained the desired product in an acceptable yield with 10 mol % $NiBr_2$·DME as catalyst, 10 mol % 1,10-phenanthroline (1,10-phen) as a bidentate nitrogen ligand, and 2.0 equiv Mn^0 as a reducing agent at 60 °C under argon atmosphere (entry 1, in Table 1). In the process of optimizing the reaction conditions, we found that when $NiCl_2$·DME or $Ni(COD)_2$ was used as the catalyst, the yield decreased slightly (entries 2 and 3). Selecting amide **2a′** instead of **2a**, we observed no formation of the desired product, with recovery of starting material **2a′** (entry 4). The cleavage of C−N bond of amides is difficult due to amidic resonance,[16,17] so the recovery of starting material **2a′** under these standard conditions is acceptable. To examine the effects of different ligands, we used various nitrogen ligands instead of 1,10-phen (entries 5−9). The results show that suitable electron density on the ligand was crucial for the coupling reaction. When zinc was used as the reducing reagent, the yield decreased markedly to 45% (entry 10). This result well supports our presumption that a reductive metal species is important for this transformation. The choice of the solvent

Table 1. Optimization of the Reaction Conditions[a]



entry	modification from standard conditions	yield[b] (%)
1	none	78 (72)
2	$NiCl_2$·DME instead of $NiBr_2$·DME	67
3	$Ni(COD)_2$ instead of $NiBr_2$·DME	56
4	**2a′** instead of **2a**	0
5	L_1 instead of 1,10-phen	70
6	L_2 instead of 1,10-phen	43
7	L_3 instead of 1,10-phen	trace
8	L_4 instead of 1,10-phen	55
9	L_5 instead of 1,10-phen	16
10	Zn instead of Mn	45
11	DMA instead of NMP	66
12	DMF instead of NMP	40
13	THF instead of NMP	trace
14	dioxane instead of NMP	trace
15	no Mn or no Ni/1,10-phen	0
16	no $MgCl_2$	68

[a]Reaction conditions: Katritzky salts **1a** (1.2 equiv), **2a** (0.2 mmol), $NiBr_2$·DME (10 mol %), 1,10-phen (10 mol %), Mn^0 (2.0 equiv), $MgCl_2$ (1.0 equiv), in 2.0 mL of NMP at 60 °C for 12 h under Ar atmosphere. [b]Yield determined by GC using benzophenone as an internal standard. Isolated yield in parentheses. See the Supporting Information for details.

markedly influenced the reaction outcome (entries 11−14), which is very common in cross-coupling reactions. Control experiments indicated that $NiBr_2$·DME, ligand, and Mn^0 are essential (entry 15) and that $MgCl_2$ has a beneficial effect on the reaction (entry 16).

Under the optimized reaction conditions, we turned our attention to exploring the substrate scope of this reductive deaminative acylation with various activated aliphatic amines and aromatic amides (Scheme 2). Various substituted aromatic amides underwent coupling in fair to good yield (**3**−**10**). Electron-rich aromatic amides (**4**, **6**, and **7**) could be used as substrates, but the presence of a mildly electron-withdrawing substituent (**5**) resulted in decreased yield. Disappointingly, reactions with aromatic amides bearing strong electron-withdrawing groups (−COOMe, $-CF_3$) failed to give the desired ketone products. It is worth noting that a nitrogen-containing heteroaryl amide (**8**) reacted to give the ketone product in moderate yield. An acylamino substituent (**9**), a protic functional group, was also a compatible structural motif. The reductive cross-coupling with naphthamide (**10**) successful generated a product that was easily detectable under a UV lamp.

A variety of functional groups in the Katritzky salt were tolerated. Alkyl pyridinium salts bearing an additional handle for further modification via Suzuki coupling, such as an aryl chloride (**11**), reacted to give the desired product in good yield. The substrate prepared from the dopamine derivative 2-(benzo[d][1,3]dioxol-5-yl)ethan-1-amine (**12**) smoothly

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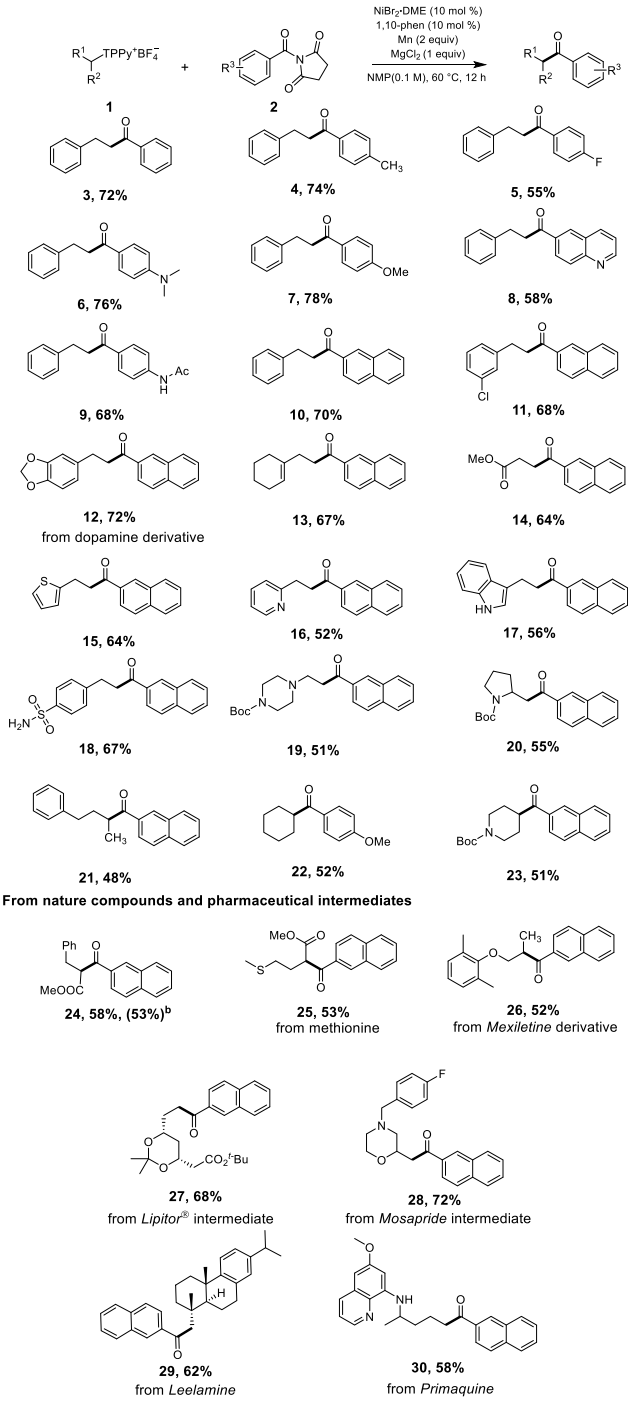
Scheme 2. Scope of Aryl/Heteroaryl Amides and Alkyl Pyridinium Salts[a]



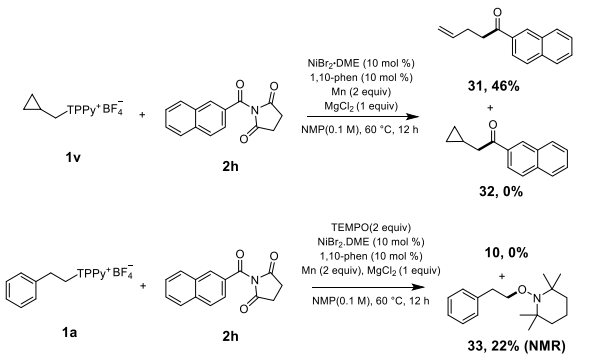
[a]As Table 1 (entry 1), 0.20 mmol scale, 60 °C, 12 h. Yields after purification. [b]Gram scale reaction (in 2 mmol), see the SI for details.

underwent the transformation. Importantly, this reaction process was shown to be suitable for obtaining products bearing various functional groups, such as alkenyl (**13**), electron-rich 2-thienyl (**15**), basic 2-pyridyl (**16**), and protic groups (indole **17**, unprotected sulfamine **18**). A Katritzky salt with a β-electron-withdrawing group was effective (**14**). Moreover, saturated heterocycles such as piperazine (**19**), pyrrolidine (**20**), piperidine (**23**), and ketal (**27**) were also tolerated. It is noteworthy that secondary alkyl-substituted pyridinium salts (**21**, **22**, and **23**) could be used in this protocol, though the yields were around 50%.

Furthermore, to examine the applicability of our developed protocol in late-stage functionalization, a series of Katritzky salts were synthesized from natural products and pharmaceutical intermediates. Gratifyingly, the acylation was successful with these druglike substrates (**24**−**30**). For example, Katritzky salts derived from amino acids (**24**, **25**) reacted smoothly. Also, acylation of the pyridinium salt of the antiarrhythmic drug mexiletine (**26**) was effective. Amine intermediates used for synthesizing the lipid-lowering drug atorvastatin (Lipitor, **27**) and the gastrokientic agent mosapride (**28**) also coupled well.[3,11c] Other biologically active derivatives from leelamine (**29**) and primaquine (**30**) could be transformed to the desired deaminative acylated products in fair yield.

To gain insight into the mechanism of this transformation, a series of mechanistic experiments were conducted (Scheme 3).

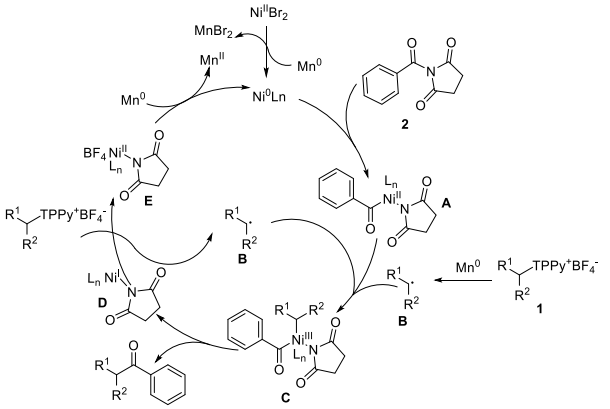
Scheme 3. Mechanistic Experiments



We observed ring-opened product **31** in 46% yield when cyclopropylmethylpyridinium **1v** was used. Also, when the radical scavenger TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] was added to the reaction system, the acylation was completely inhibited, with no product **3** being detected and the TEMPO-trapped adduct **33** being formed. These results suggest that this reaction likely proceeds via a radical mechanism.

Based on the literature on the nickel-catalyzed reductive cross-coupling of Katritzky salts and amides with aryl halides,[14,24] we propose a plausible mechanism (Scheme 4). Initially, the active Ni(0) catalyst, which is formed via reduction of Ni(II) salt by Mn^0, undergoes oxidative addition

Scheme 4. Proposed Mechanism



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into the C−N bond of amide **2** to give the intermediate Ni(II) complex **A**. Subsequently, reaction of Ni(II) complex **A** with alkyl radical **B** generated via reduction by Mn^0 or SET from $Ni(I)L_n$ of pyridinium salt **1** affords Ni(III) species **C**.[14a,c] Then, reductive elimination of Ni(III) species **C** releases the desired cross-coupling ketone product and generates a Ni(I) intermediate **D**, which can be subsequently oxidized to give the Ni(II) intermediate **E** by pyridinium salts via SET.[3] This Ni(II) intermediate **E** can be reduced by Mn^0 to regenerate the active Ni(0) catalyst used in the next catalytic cycle.

In summary, we developed a new Ni-catalyzed cross-electrophile coupling reaction between amides and alkyl amine−derived alkylpyridinium salts. Considering the availability and diversity of amides and alkyl amines and the ability to use primary and secondary alkylpyridinium salts, this method opens a new gateway to the synthesis of structurally diverse ketones. In addition, the reaction tolerated a broad substrate scope including compounds with protic functional groups and derivatives of bioactive molecules. Further studies using aliphatic amides are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04497.

Experimental procedures and ^1H and ^{13}C NMR spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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