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Letter

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Nickel-Catalyzed Decarboxylative Alkylation of Aryl Iodides with Anhydrides

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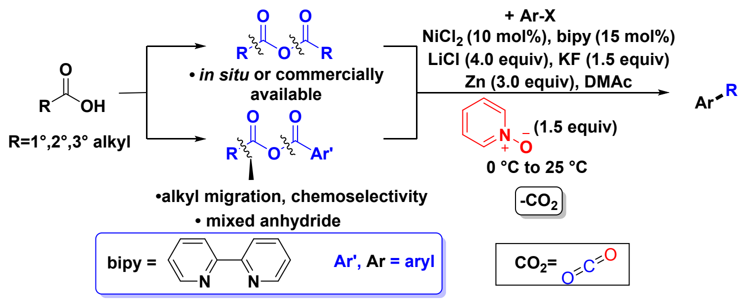
ABSTRACT: We present the anhydride-based decarboxylative alkylation of aryl iodides catalyzed by nickel. This method of decarboxylative coupling works with a broad scope of aliphatic carboxylic anhydrides and tolerates synthetically useful aromatic substituents. Assisted by a redox system of pyridine *N*-oxide and zinc additives, the current reaction occurs under mild conditions and without the assistance of photocatalyst. Notably, this method features high chemoselectivity towards alkyl migration with mixed aliphatic/aromatic anhydrides. Thus, it provides a powerful synthetic tool to modify high-valued aliphatic carboxylic acids by converting them into mixed anhydrides using readily available aryl carboxylic acids such as *p*-toluic acid. We propose a catalytic cycle that involves the key steps of free radical-based decarboxylation and subsequent alkyl transfer to nickel that precedes an oxidatively induced C-C reductive elimination from Ni(III).



KEYWORDS: decarboxylation, nickel catalysis, aliphatic acid anhydrides, cross-coupling, alkylation

In the past decades, the formation of C-C bonds catalyzed by transition metals has achieved great success in both academia and industry. [1] However, construction of the C(sp^2)-C(sp^3) bond remains underexplored. One of the main hurdles is that common alkyl coupling partners are less available compared to aryl coupling reagents. Alkyl halides as the major building blocks in this area were restricted due to their limited availability, toxicity and instability. Notably, aliphatic carboxylic acids are inexpensive, stable and non-toxic substances, and they are widely present in nature. This makes them appealingly as potential coupling partners for C(sp^2)-C(sp^3) bond formation. Herein, we aim to take another approach to decarboxylative C(sp^2)-C(sp^3) coupling by exploring aliphatic carboxylic anhydrides as the alkyl sources. In contrast to specialized esters as active substrates for decarboxylation (Scheme 1a), organic anhydrides are common building blocks that are either commercially available or readily prepared from the corresponding carboxylic acids. Catalytic application of carboxylic anhydrides in cross-coupling has been mainly focused on decarbonylative biaryl synthesis by Goossen[2-7] and other groups.[8-15] In 2003, Rovis and coworkers have reported an example of decarbonylative C(sp^2)-C(sp^3) bond formation [16] with cyclic anhydrides using a stoichiometric amount of nickel catalyst (Scheme 1b). We hypothesized that a corresponding catalytic decarboxylative coupling via free-radical processes could be promoted by using a suitable oxidizing reagent that both donates oxygen atoms and facilitate single-electron transfer (SET) redox chemistry (Scheme 1d).

More recently, decarboxylative cross-coupling has emerged as a powerful tool to form new C-C bonds. [17-45] MacMillan, Doyle, and other groups[17-19] (Scheme 1c) made major breakthroughs in this area and reported the couplings of aryl halides with secondary alkyl carboxylic acids by nickel catalysts with light assistance. Subsequently, asymmetric decarboxylative cross-coupling of α-amino acids was realized by Fu and MacMillan.[19] Pioneering work on decarboxylative coupling using the *N*-hydroxy-phthalimide esters (NHP esters) were reported by the Okada group and later by the Overman group (Scheme 1a). [20,21] In their studies, they used photocatalyst to convert the NHP esters into alkyl radicals that could be further used in numerous transformations. In 2016, the Baran and Weix groups (Scheme 1a) almost concurrently reported another elegant strategy on decarboxylative coupling, [24-29] which involved nickel-catalyzed C(sp^2)-C(sp^3) bond formation without assistance of light. In contrast to MacMillan's work, the aliphatic carboxylic acids in the Baran and Weix studies were required to be converted into the corresponding NHP [20,21] or other "redox-active" esters. [24-29]

Alternatively, we herein report a nickel-catalyzed decarboxylative coupling between aliphatic carboxylic anhydrides and aryl iodides using pyridine *N*-oxide as oxidant

(Scheme 1d). Furthermore, our approach requires no photocatalyst or preparation of NHP esters in advance. The catalytic method of C(sp^2)-C(sp^3) bond formation works well with a broad scope of symmetrical anhydrides derived from 1°, 2° and 3° alkyl carboxylic acids. Moreover, high chemoselectivity of alkyl- over aryl-migration was observed with unsymmetrical alkyl/aryl anhydrides. Thus, this method provides an attractive strategy to chemically modify high-valued aliphatic carboxylic acids by converting them into mixed anhydrides with low-priced benzenecarboxylic acids such as 4-toluic acid.

Scheme 1. Recent Development of Decarboxylative Couplings and Our Approach

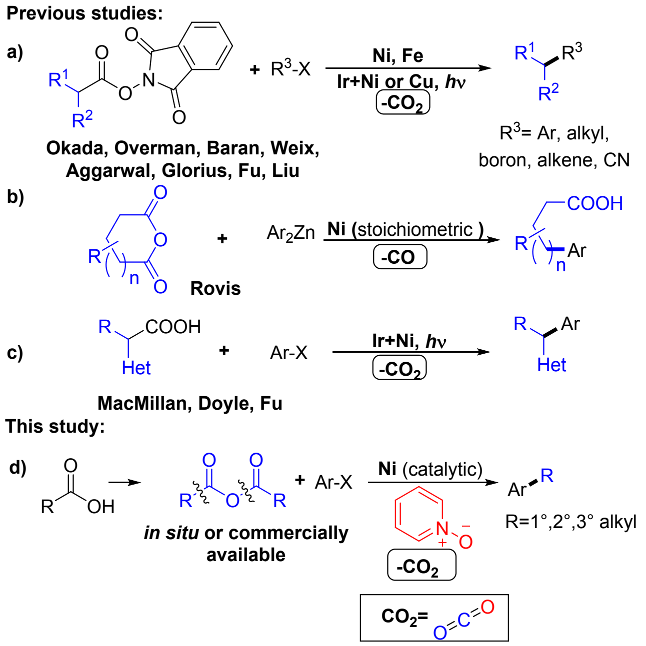
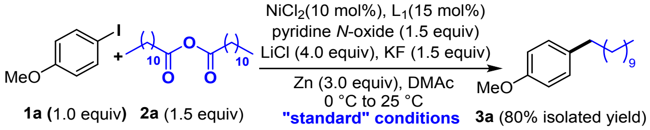
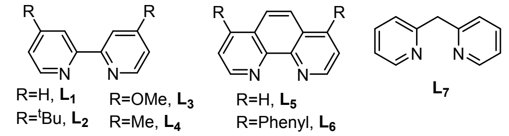


Figure 1. Ni-Catalyzed Cross-Coupling of Alkyl Acid Anhydrides with Aryl Iodides

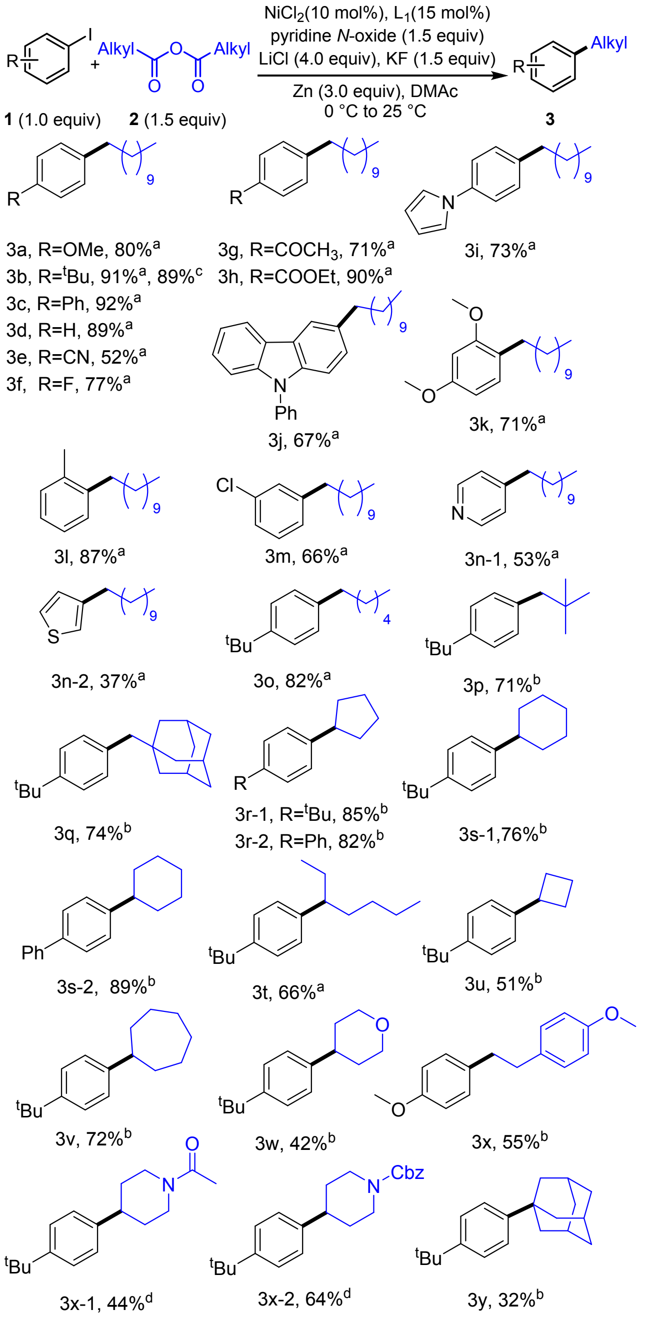


Entry	Deviation from above	Yield (%)	Entry	Deviation from above	Yield (%)
1	L_2	48	8	$Ni(PPh_3)_4$	72
2	L_3	55	9	$NiBr_2$	57
3	L_4	65	10	NiI_2	66
4	L_5	45	11	No nickel or ligand	0
5	L_6	47	12	No pyridine *N*-oxide	trace
6	L_7	33	13	1.2 equiv 2a	73
7	$Ni(COD)_2$	66	14	NMP instead of DMAc	61



Reactions were run on 0.2 mmol scale at 0 °C, 25 °C for 24h, respectively. Yields were determined by NMR using 1,3,5-trimethoxybenzene as the internal standard.

Table 1. Scope of Ni-Catalyzed Coupling of Aliphatic Acid Anhydrides with Aryl Iodides



3a, R=OMe, 80%[a]
3b, R=^{t}Bu, 91%[a], 89%[c]
3c, R=Ph, 92%[a]
3d, R=H, 89%[a]
3e, R=CN, 52%[a]
3f, R=F, 77%[a]
3g, R=COCH$_3$, 71%[a]
3h, R=COOEt, 90%[a]
3i, 73%[a]
3j, 67%[a]
3k, 71%[a]
3l, 87%[a]
3m, 66%[a]
3n-1, 53%[a]
3n-2, 37%[a]
3o, 82%[a]
3p, 71%[b]
3q, 74%[b]
3r-1, R=^{t}Bu, 85%[b]
3r-2, R=Ph, 82%[b]
3s-1,76%[b]
3s-2, 89%[b]
3t, 66%[a]
3u, 51%[b]
3v, 72%[b]
3w, 42%[b]
3x, 55%[b]
3x-1, 44%[d]
3x-2, 64%[d]
3y, 32%[b]

Reaction conditions: Reactions were run on 0.5 mmol scale with NiCl$_2$ as a catalyst in DMAc (5 mL) at 0 °C, 25 °C for 24h, respectively. Yields were isolated yields. (See Supporting Information (SI)). [a] Alkyl acid anhydrides were commercially available. [b] Alkyl acid anhydrides were prepared after simple filtration. [c] Reaction was run in the dark. [d] Using prepared mixed anhydrides of alkyl acids with *p*-toluic acids

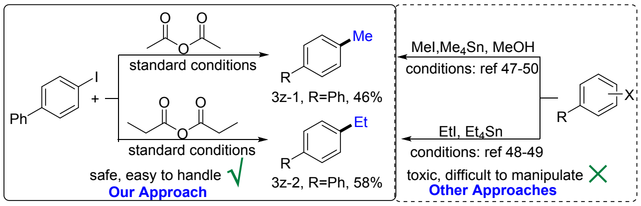
In our initial studies, the alkyl acid anhydrides were generated *in situ*, filtrated by sieves and directly used for the coupling reaction (Scheme 1d). [46] Different ligands, including bipyridines (Figure 1, entries 1-4), phenanthrolines (entries 5, 6), and phosphines (see Supporting Information (SI)) were first attempted. 2, 2'-bipyridine was the most efficient. Then, a variety of nickel catalysts were examined (entries 7-10) and NiCl$_2$ performed the best. Control reactions demonstrated that both nickel catalyst and ligand (entry 11) were essential for the reactions. Only a trace amount of desired product (entry 12) was detected without adding pyridine *N*-oxide. It is noteworthy that pyridine *N*-oxide was also nicely used as an additive for light assisted trifluoromethylation by Stephenson.[22,23] Reactions with an excess of anhydride (entry 13) resulted in a higher yield. A further optimization of the solvents (entry 14) revealed that DMAc (see Supporting Information (SI)) was optimal. In addition, zinc dusts and LiCl (see Supporting Information (SI)) were both indispensable in the catalytic reaction. Furthermore, addition of KF slightly increased the yield (see Supporting Information (SI)).

With the optimized conditions in hand, we first explored the scope of aryl iodides (Table 1, **3a-3n**). Electron-rich, -deficient and -neutral substituents were well tolerated (**3a-3m**). Different functional groups, including ester (**3h**), ketone (**3g**), cyano (**3e**), and protected nitrogen (**3i**, **3j**), were all compatible with the standard conditions. Substituents at the *ortho*- and *meta*-position did not have much impact on the yields (**3k-3m**). Remarkably, heterocyclic iodide (4-iodopyridine, **3n-1**) could be coupled, providing the corresponding product in a modest yield.

Next, a variety of carboxylic acid anhydrides, either commercially available or generated from the corresponding acids, were coupled with aryl iodides (Table 1, **3o-3z**). As anticipated, reaction using primary and secondary carboxylic acid anhydrides proceeded smoothly (**3o-3x**). Among them, cyclic alkyl acid anhydrides (**3r**, **3s**, **3u**) were coupled with iodoarenes resulting in good yields. Large ring sized acid anhydrides, such as cycloheptanecarboxylic anhydride (**3v**), also generated the corresponding arylated product in a good yield. Substrate (**3w-3x-2**) containing heteroatom also worked smoothly under the optimized conditions. In addition, reactions with the tertiary carboxylic acid anhydride (**3y**), considered as a challenging coupling partner, also gave the desired product, albeit in a lower yield.

Notably, methylation and ethylation (**3z-1**, **2**) of arenes (Figure 2),[47-50] which traditionally involved the use of difficult to manipulate organometallic reagents[47] or toxic methyl,[48,49] or ethyl iodides in medical chemistry,[49] were achieved in comparable yields using commercially available alkyl acid anhydrides.

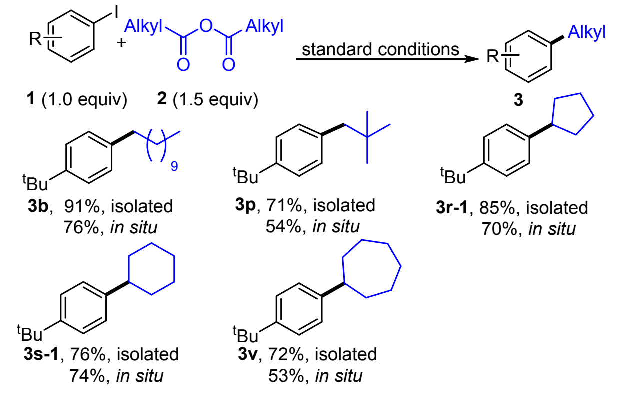
Figure 2. Methylation or Ethylation of Arenes



Reaction conditions: Reactions were run on 0.5 mmol scale with $NiCl_2$ as a catalyst in DMAc (5 mL) at 0 °C, 25 °C for 24h, respectively. Yields were isolated yields. (See Supporting Information (SI)).

Gratifyingly, this method proceeded smoothly when *in situ* generated anhydrides were directly used without filtration (Figure 3). The yields were only slightly lower than those with preformed alkyl acid anhydrides. For example, we got the decarboxylative coupling product (**3s-1**) in 76% yield when isolated alkyl acid anhydride was used. Only 2% decreased in the yield if we operated the reaction without any purification of anhydrides.

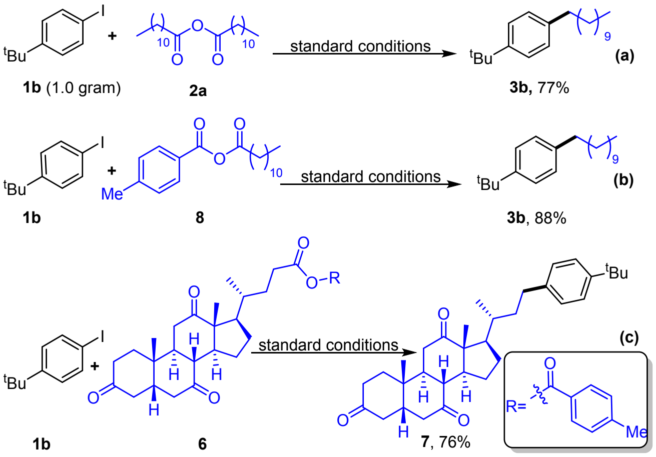
Figure 3. Ni-Catalyzed Coupling of Alkyl Acid Anhydrides (Generated *in situ*) with Aryl Iodides



Reaction conditions: Reactions were run on 0.5 mmol scale with $NiCl_2$ as a catalyst in DMAc at 0 °C, 25 °C for 24h, respectively. Yields were isolated yields. (See Supporting Information (SI)). [Isolated] = alkyl anhydrides were prepared after simple filtration of related impurities. [In situ] = alkyl anhydrides were prepared without any purification and reaction was taken in one flask. Preparation of symmetric anhydrides (See Supporting Information (SI)).

Furthermore, the reaction was performed at a large scale to showcase the utility of our protocol, and the decarboxylative product was obtained in satisfactory yield (Figure 4a). It was noteworthy that this method featured high chemoselectivity towards alkyl migration with mixed aliphatic/aromatic anhydrides (Figure 4b, c). Thus, it provided a powerful synthetic tool to modify high-valued aliphatic carboxylic acids by converting them into mixed anhydrides using readily available aryl carboxylic acids such as *p*-toluic acid (Figure 4c). More intriguingly, by testing electronically different benzoates as part of mixed anhydrides, it was reasonable to assume that the carboxylate anion may affect catalyst reactivity in some way (see Supporting Information (SI), part 6, S12). This implied that we could potentially tune the reactions by employing

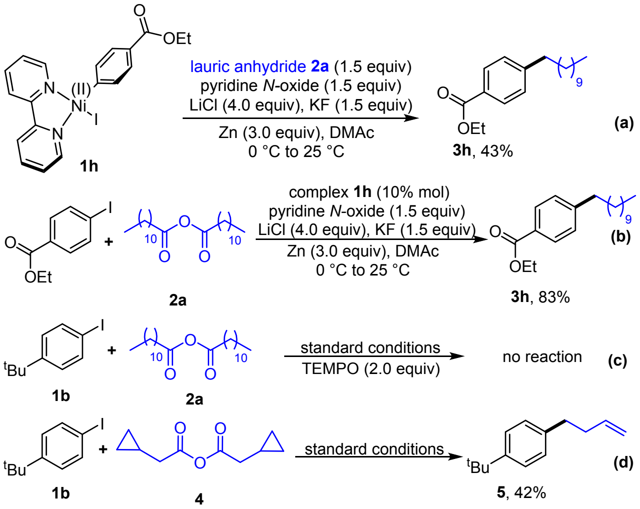
Figure 4. Gram Scale of Reaction and Chemical Selectivity of Reaction



Standard conditions: Reactions were run on 0.5 mmol with $NiCl_2$ as the catalyst in DMAc at 0 °C, 25 °C for 24h, respectively. Aryl iodide (1b) was 1 equiv, anhydrides 2a is 1.2 equiv, 6 and 8 was 1.5 equiv. Yields were recorded after isolation and purification. (See Supporting Information (SI)).

different aryl carboxylate anion as auxiliary ligands in the catalysis.

Figure 5. Mechanistic Studies

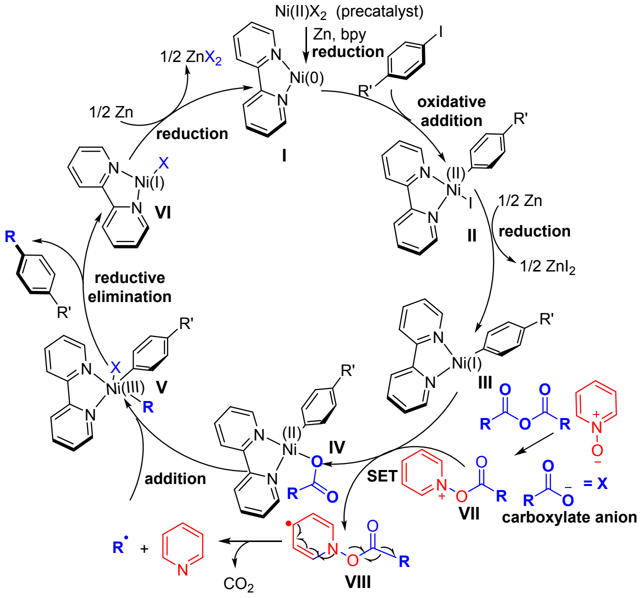


Standard conditions: Reactions were run on 0.5 mmol with $NiCl_2$ as the catalyst in DMAc at 0 °C, 25 °C for 24h, respectively. 1h and aryl iodide were 1 equiv, and the anhydrides were 1.5 equiv. Yields were recorded after isolation and purification. (See Supporting Information (SI)). Equation (a): If no pyridine *N*-oxides were added, no products were detected.

Finally, to elucidate the mechanism, we performed a stoichiometric reaction of an organonickel complex (**1h**) with acid anhydride (**2a**). The desired product (**3h**) was obtained in 43% yield (Figure 5a).[51-55]In addition, when **1h** was used as catalyst, the decarboxylative coupling product was obtained in 83% yield (Figure 5b). Both results suggested that **1h** was a key intermediate in the catalytic cycle. The other stoichiometric reaction indicated that pyridine *N*-oxide was essential in the catalytic process (Figure 5a).[56,57] Presumably, pyridine *N*-oxide was used as an additive for the formation of reducible anhydride adducts (Figure 6, **VII**). Although we could not isolate the combined intermediate, Stephenson [22,23] and others [56,57] have done a number of studies to confirm the existence of such types of reducible compounds. Thus, it was reasonable to propose that the anhydride adduct was reduced by Ni-complex to form alkyl radical, pyridine, and CO_2 (Figure 6). In line with this hypothesis, we also detected the formation of pyridine and gas in the reactions. Additionally, the coupling proceeded well in the dark (Table 1, **3b**[c]) and the effect of light was ruled out (Table 1, **3b**) and the formation of organozinc regent from aryl iodides were excluded (see Supporting Information (SI), part6, S13). Moreover, the reaction without addition of zinc powder or LiCl only provided a trace amount of the desired product (See Supporting Information (SI)), which indicated that two additives were necessary in the catalytic cycle. Finally, the reaction was completely suppressed in the presence of TEMPO (Figure 5c), and the ring-opening product (**5**) (Figure 5d) further strongly supported the hypothesis of SET process.

Based on these studies (Figure 5) and pioneering works by other groups, one possible catalytic cycle is proposed in Figure 6. Pre-catalyst $NiCl_2$ was reduced by zinc to generate bipyridine-ligated nickel (0) **I**. [51-53] Then, Ni (0) underwent oxidative addition with aryl iodide to form arylnickel (II) species **II**. This species was then reduced to arylnickel (I) complex **III**. [51-53] Next, complex **III** delivered an electron into aliphatic carboxylic anhydride adduct **VII**, thus producing the radical of adduct **VIII** with concomitant formation of Ni (II) complex **IV**. [24-29] The desired alkyl radical was produced with the fragmentation of **VIII** by release of CO_2 and generation of pyridine. Later, complex **IV** was combined with a alkyl radical to provide Ni (III) intermediate **V**, which then underwent reductive elimination to afford the desired product and Ni (I) species **VI**. At this point, complex **VI** (I) was reduced to regenerate Ni (0) complex **I** using zinc powder.

Figure 6. Proposed Mechanism



In conclusion, we develop the nickel-catalyzed decarboxylative alkylation of aryl iodides with alkyl acid anhydrides. This reaction exhibits broad substrate scopes, good functional group tolerance and chemical selectivity. In particular, this method provided a powerful tool to modify high-valued aliphatic carboxylic acids by simply converting them into mixed acid anhydrides with the cheap *p*-toluic acid. The decarboxylative cross-coupling of alkyl acid anhydride is believed to involve a SET process. Initial mechanistic studies on both the stoichiometric reactions and the catalytic reaction of the isolated (bpy)Ni(4-benzoate)I with alky acid anhydride support the arylnickel(II) complex as a key intermediate involved in the catalytic cycle. Additional mechanistic studies to further elucidate the detailed reaction mechanism are underway.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on ACS Publications website.
Detail experimental procedure and spectral data (^1H, ^{13}C, MS, HRMS) for compounds.

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Notes

The authors declare no competing financial interests.

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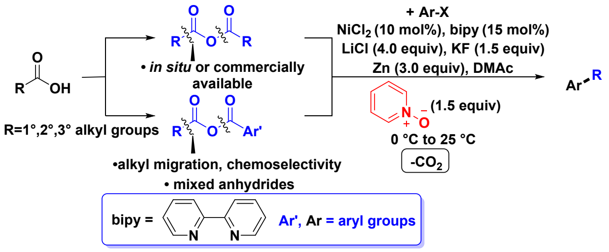
R=1°,2°,3° alkyl groups
• *in situ* or commercially available
•alkyl migration, chemoselectivity
• mixed anhydrides
+ Ar-X
NiCl$_2$ (10 mol%), bipy (15 mol%)
LiCl (4.0 equiv), KF (1.5 equiv)
Zn (3.0 equiv), DMAc
(1.5 equiv)
0 °C to 25 °C
-CO$_2$
bipy =
Ar', Ar = aryl groups