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Communication

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Practical Ni-Catalyzed Aryl–Alkyl Cross-Coupling of Secondary Redox-Active Esters

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Supporting Information

ABSTRACT: A new transformation is presented that enables chemists to couple simple alkyl carboxylic acids with aryl zinc reagents under Ni-catalysis. The success of this reaction hinges on the unique use of redox-active esters that allow one to employ such derivatives as alkyl halides surrogates. The chemistry exhibits broad substrate scope and features a high degree of practicality. The simple procedure and extremely inexpensive nature of both the substrates and pre-catalyst ($NiCl_2 \cdot 6H_2O$, ca. $9.5/mol) bode well for the immediate widespread adoption of this method.

Practical and simple methods to forge linkages between sp^2 and sp^3 hybridized carbons are of extreme importance in every branch of chemical science.[1] Thus far, the majority of contributions in this arena have focused on the use of alkyl halides or alkyl metal species for the sp^3 component.[2] Elegant demonstrations of the practicality and feasibility of such a disconnection using nickel catalysis (Figure 1A) can be found from the early examples of Kumada,[3] Corriu,[4] Kochi[5] or Negishi,[6] to the most recent studies from the Kambe,[7] Knochel,[8] Fu,[9] Biscoe,[10] and Hu[11] laboratories (just to name a few). A recurring theme in the mechanistic picture in these reactions involves a single-electron-transfer (SET)-based catalytic cycle.[12] Chatani[13] and Weix[14] have extended these radical-based processes to the realms of directed C–H functionalization and cross-electrophile coupling. Recently, the Molander,[15] MacMillan, and Doyle[16] groups reported the coupling of alkyl boron or ammonium alkylsilicates and α-heteroatom containing secondary carboxylic acids with aryl halides by combining photoinduced electron transfer (PET) with the Ni-SET cycle. Our studies in the synthesis of alkyl sulfinates from alkyl carboxylic acids led us to wonder if the classic Barton decarboxylation could be inserted into such a regime.[17] As illustrated in Figure 1B, this proved to be the case with an unexpected twist. When ester **1a** was irradiated with visible light in the presence of Ni-aryl complex **2**, a 51% yield of cross-coupled product **3** was observed in addition to the expected Barton byproduct **4**. Remarkably, when the same reaction was conducted in the absence of light at room temperature, it still afforded 54% yield of **3**. This fortuitous discovery led us to hypothesize that the nickel complex acts as a single electron reductant to the pyridothione group.

The resulting radical anion (**A**) presumably liberates acyloxy radical (**B**) along with the 2-thiopyridyl anion (**C**). Decarboxylation of the former followed by recombination with an aryl-Ni species ultimately leads to **3**.

In this Communication we report the initial ramifications of this finding with the invention of a simple, practical, general method for the cross-coupling of carboxylic acids (via their redox-active ester derivatives) with aryl zinc species. The simplicity of this method is evidenced by a monometallic catalytic cycle and operationally facile procedure.

Drawing from the inspiration of the initial discovery in Figure 1B, aryl zinc reagents were chosen for the aryl coupling partner due to their low basicity, functional group tolerance and documented ease of transmetalation.[18] After extensive optimization, ester **1g** (Figure 1C) could be coupled with PhZnCl·LiCl (3 equiv) in 92% isolated yield with 20 mol% of $NiCl_2$·glyme and 40 mol% of di-*t*Bubipy at room temperature. Two key challenges were overcome to arrive at these conditions: (1) the establishment of a catalytic cycle and (2) the identification of a simple and practical activated ester. A broad evaluation of solvents, ligands, and nickel sources was performed to address the first challenge (see Supporting Information (SI)). Here, we benefited from pioneering studies preceding ours.[7−16] The second challenge, however, was uncharted territory. In accord with our initial hypothesis, the choice of ester proved to be critical. For the purpose of this study, "redox-active" esters are defined as those which can accept an electron (to form a radical anion such as **A**) and gracefully depart as a stable and unreactive anion. Although the original Barton ester provided workable yields of the product (Figure 1C, entries 1, 2), such esters are not practical to employ on scale and readily form byproducts such as **4**. As a control, the acid chloride and methyl ester were screened (entries 3, 4) and no product was observed by GC/MS. Remarkably, when the classic HOAt and HOBt esters associated with peptide coupling were employed, good yields were observed of **3** (entries 5, 6). The underappreciated ability of such redox-active esters to readily accept an electron led us to evaluate other esters commonly employed in peptide-coupling. The pentafluorophenol ester (entry 7) failed perhaps due to the inability to productively fragment if a radical anion (such as **A**) is formed, and the NHS ester (entry 8) failed presumably due to its lower capacity of generating a radical

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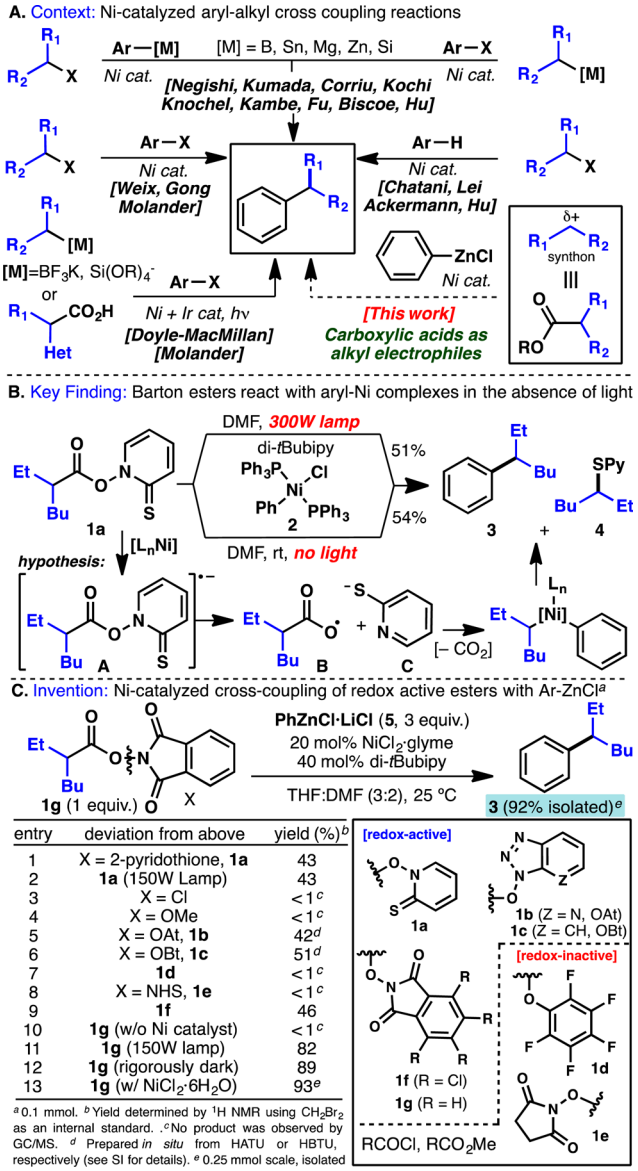


entry	deviation from above	yield (%)[b]
1	X = 2-pyridothione, **1a**	43
2	**1a** (150W Lamp)	43
3	X = Cl	<1[c]
4	X = OMe	<1[c]
5	X = OAt, **1b**	42[d]
6	X = OBt, **1c**	51[d]
7	**1d**	<1[c]
8	X = NHS, **1e**	<1[c]
9	**1f**	46
10	**1g** (w/o Ni catalyst)	<1[c]
11	**1g** (150W lamp)	82
12	**1g** (rigorously dark)	89
13	**1g** (w/ $NiCl_2·6H_2O$)	93[e]

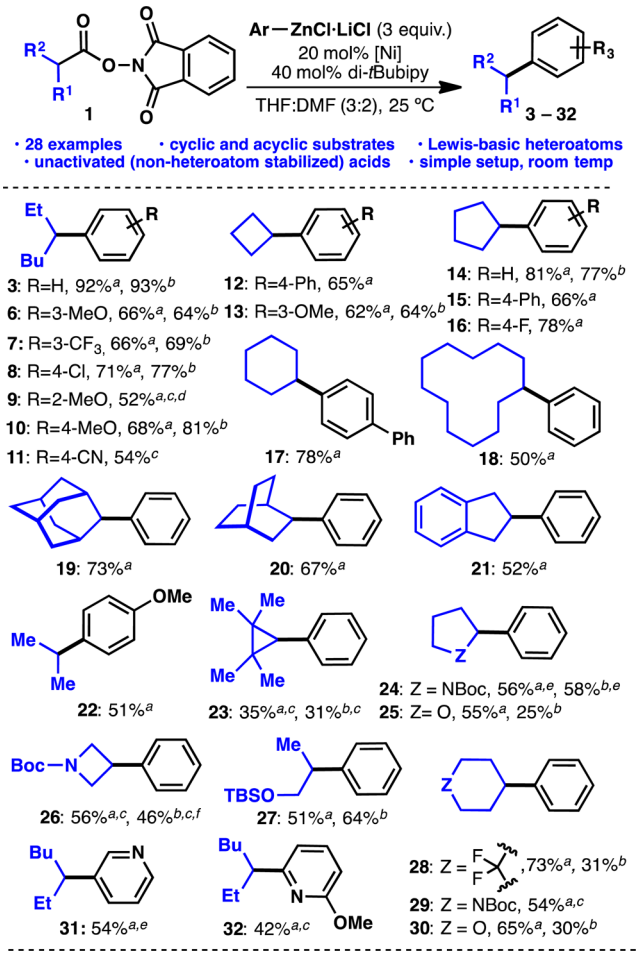
[a] 0.1 mmol. [b] Yield determined by ^1H NMR using CH_2Br_2 as an internal standard. [c] No product was observed by GC/MS. [d] Prepared *in situ* from HATU or HBTU, respectively (see SI for details). [e] 0.25 mmol scale, isolated

Figure 1. (A) A brief historical perspective of Ni-catalyzed alkyl-aryl cross-coupling. (B) An attempted intercepted Barton decarboxylation leads to a new hypothesis. (C) Invention of a new Ni-catalyzed decarboxylative cross-coupling.

anion. An ideal balance of reactivity, stability, and practicality was finally found in the *N*-hydroxyphthalimide (NHPI, ca. $19.5/mol) ester (**1g**, standard conditions). Replacing this ester with the more electron deficient tetrachloro derivative did not increase the yield (**1f**, entry 9). Control reactions demonstrated the necessity of the nickel catalyst (entry 10) and that the reaction is a purely thermal process (entries 11, 12). Gratifyingly, when the nickel source was replaced by the inexpensive $NiCl_2·6H_2O$ (entry 13), comparable yields were also obtained, thus showcasing the robustness of the method.

With an optimized set of conditions in hand, the scope of this reaction was evaluated as shown in Table 1. To our delight this reaction exhibits broad substrate scope. A range of carboxylic acids were converted to the corresponding NHPI-esters and coupled with a variety of aryl zinc reagents (prepared according to Knochel's procedure).[19] One of the striking features of this reaction is that acids lacking any radical stabilizing groups react smoothly. For example, the NHPI ester

Table 1. Initial Scope of the Nickel-Catalyzed Cross-Coupling of Redox-Active *N*-Hydroxyphthalimide Esters with Aryl Zinc Reagents



Reaction conditions: "redox-active" ester (1 equiv), [Ni] (20 mol%), di-*t*Bubipy (40 mol%), ArZnCl·LiCl (3 equiv) in DMF:THF (2:3) at 25 °C for 16 h. [a] $NiCl_2$·glyme. [b] $NiCl_2·6H_2O$. [c] Tetrachloro *N*-hydroxyphthalimide ester instead. [d] Reaction performed at 60 °C. [e] HOAt ester preformed *in situ* with 1 equiv of HATU and 1 equiv of Et_3N. [f] 2,2′-Bipyridine used as ligand.

of 2-ethylhexanoic acid was coupled with seven different aryl zinc reagents in 51–93% yield using either $NiCl_2$·glyme complex or simply $NiCl_2·6H_2O$ (**3**, **6**–**11**). In contrast, attempted decarboxylative PET arylation[16] on this system failed to deliver any arylated product **8** in our hands (see SI for details).

Simple feedstock carboxylic acids such as cyclobutane- (ca. $30/mol), cyclopentane- (ca. $82/mol), and cyclohexanecarboxylic acids (ca. $9/mol) also coupled smoothly after activation (**12**–**17**). It is worth pointing out that these acids are among the most inexpensive and stable sources of cyclobutyl, cyclopentyl, and cyclohexyl groups. Larger ring sized acids such as cyclododecanecarboxylic acid (**18**) or polycyclic acids such as 2-adamantane, [2.2.2]bicyclooctane, or 2-indane acids afforded the corresponding arylated compounds in excellent yields (**19**–**21**). Additionally, the smallest aliphatic secondary carboxylic acid smoothly reacted (**22**), and even an exotic and sterically encumbered tetramethylated cyclopropane could be prepared, albeit in diminished yield (**23**). Heteroatom containing carboxylic acids could also be employed such as the

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N-Boc proline, *N*-Boc azetidine, and tetrahydrofuroic acids (**24**–**26**). In addition, silyl-protected hydroxy acid and pyran bioisosteric difluorocyclohexanecarboxylic acid could also be smoothly coupled (**27** and **28**). The ever-present piperidine and pyran motifs, found in thousands of medicinally important structures, could also be used in this reaction (**29** and **30**). Industrially relevant preparations of such compounds usually start from piperidone and employ a three-step protocol consisting of either triflation/cross-coupling/hydrogenation or Grignard/dehydration/hydrogenation. Finally, simple pyridine zinc reagents could be satisfactorily coupled albeit in lower yields as exemplified by **31** and **32**. As anticipated, in cases where hydrolysis of the parent ester might represent a challenge, $NiCl_2$·glyme proved to be a superior pre-catalyst. The feasibility of employing carboxylic acids directly with *in situ* activation was demonstrated with substrates **24** and **31**. Finally, two different NHPI ester precursors were evaluated by DSC and found to be stable well within the reaction operating ranges (see SI for details).

To showcase the scalability of this process, a gram-scale reaction was performed with activated ester **1g**. Gratifyingly, a satisfactory 79% isolated yield of cross-coupled product **3** could be obtained without modification of the optimized conditions (Figure 2).

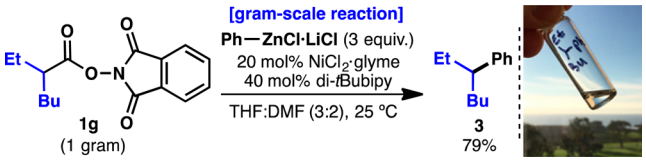

Figure 2. Nickel-catalyzed decarboxylative cross-coupling performed on gram scale.

A mechanism for this transformation is depicted in Figure 3A. By analogy to prior mechanistic investigations of Ni-catalyzed cross-coupling reactions with alkyl halides,[12] a related pathway is postulated for the coupling of redox-active esters. Thus, it is reasonable to propose that aryl–Ni(I) complex **I** transmetalates with an aryl zinc reagent to produce aryl–Ni(I) complex **II**. Next, this complex would then act as a reducing agent and deliver an electron into redox-active ester **1g**,[20] thus generating the radical anion of the activated ester **III** with concomitant formation of Ni complex **IV**. Fragmentation of the former followed by extrusion of CO_2 would generate the phthalimide anion and the desired secondary alkyl radical species. At this point, recombination of the radical species and the phthalimide anion with complex **IV** would render the Ni(III) intermediate **V**, which upon reductive elimination would afford the desired cross-coupling product and close the catalytic cycle.[21] In support of intermediate **V**, varying amounts of aryl-phthalimide adducts were observed, presumably as a consequence of an undesired C–N bond forming reductive elimination pathway.

Mechanistic evidence for the generation of an alkyl radical is provided in Figure 3B,C. Stoichiometric reaction of the HOAt ester of enantiopure (*S*)-tetrahydrofuroic acid with **2** in the presence of di-*t*Bubipy smoothly afforded **25** as a racemic mixture. Additionally, when the cyclopropane-containing keto acid **34** was subjected to the reaction conditions, 74% of ring-opened product **35** was obtained (Figure 3C). The observation of racemic product **25**, complete product suppression in the

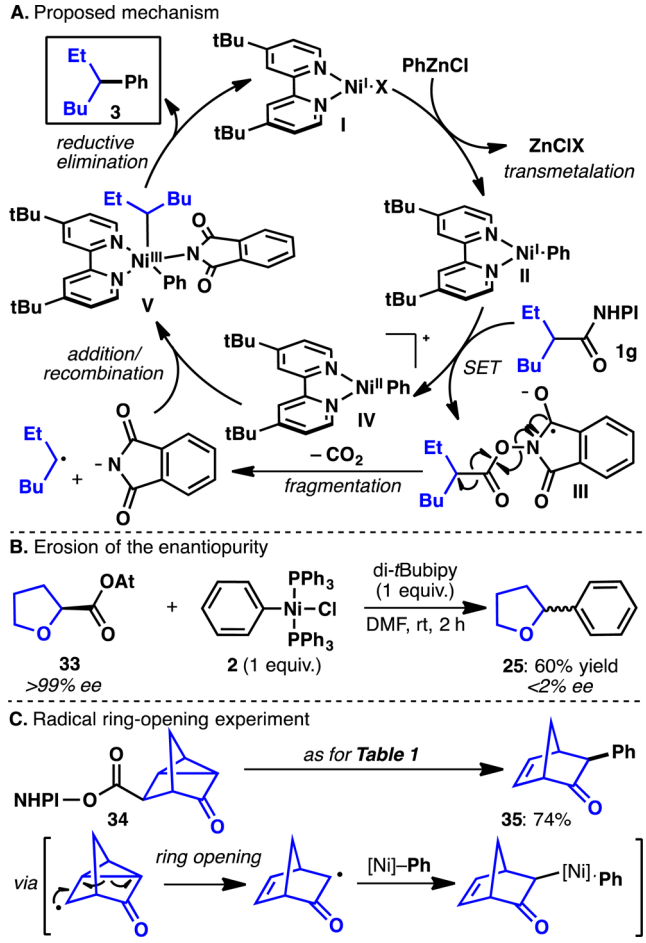

Figure 3. (A) Working hypothesis for the "redox-active" ester cross-coupling with aryl zinc reagents. (B) A stoichiometric experiment in support of a radical intermediate. (C) Ring opening of a carboxylic acid bearing a cyclopropane moiety.

presence of TEMPO and the opening of the cyclopropane in **34** supports the hypothesis of a radical intermediate.

This work has established a framework from which to employ simple alkyl carboxylic acids in cross-coupling chemistry as proxies for alkyl halides. It thus serves as a new and complementary bond disconnection strategy that is likely to find broad application since carboxylic acids are among the most widespread, stable, and inexpensive carbon-based building blocks. The use of a redox-active ester simplifies and enables the process allowing for a thermal, monometallic system with an abundant nickel source. A myriad of exciting extensions of this chemistry can be envisaged such as the formation of quaternary centers, sp^3–sp^3 couplings, alternative transition metal catalysts, and asymmetric variants; all of these and more are the subject of current investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00250.

Experimental procedures and analytical data (^{1}H and ^{13}C NMR, MS) for all new compounds (PDF)

X-ray crystallographic data for **1f** (CIF)

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Notes

The authors declare no competing financial interest.

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