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Ni-Catalyzed Suzuki−Miyaura Cross-Coupling of Aliphatic Amides on the Benchtop

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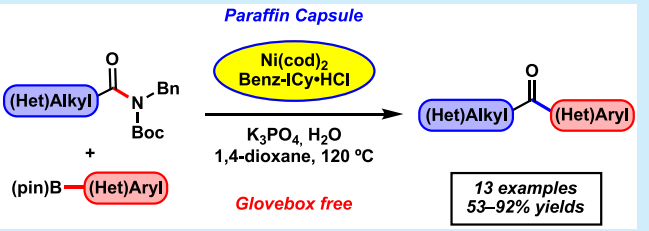
Supporting Information

ABSTRACT: Suzuki−Miyaura cross-couplings of amides offer an approach to the synthesis of ketones that avoids the use of basic or pyrophoric nucleophiles. However, these reactions require glovebox manipulations, thus limiting their practicality. We report a benchtop protocol for Suzuki−Miyaura cross-couplings of aliphatic amides that utilizes a paraffin capsule containing a Ni(0) precatalyst and NHC ligand. This methodology is broad in scope, is scalable, and provides a user-friendly approach to convert aliphatic amides to alkyl−aryl ketones.



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The conversion of carboxylic acid derivatives to ketones is a fundamental transformation in synthetic chemistry (Figure 1).[1] A common strategy to achieve this conversion is

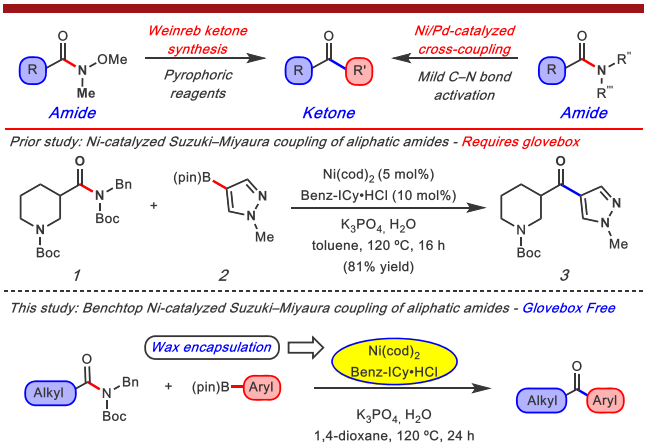

Figure 1. Methods for the conversion of amides to ketones, prior studies of Ni-catalyzed Suzuki−Miyaura couplings that utilize a glovebox, and paraffin encapsulation strategy for benchtop delivery (present study).

the Weinreb ketone synthesis, in which a *N*-methoxy-*N*-methyl amide undergoes net substitution with an organometallic nucleophile.[2] An alternative strategy lies in the development of transition-metal-catalyzed cross-couplings of acyl electrophiles,[1c,3] which avoid the use of strongly basic and pyrophoric organometallic reagents. Our laboratory and others have shown that amides, which are well suited for multistep synthesis due to their pronounced stability, are particularly useful in this context.[4] Specifically, Ni-[5,6] and Pd-catalysis[7] have enabled the mild activation of the amide C−N bond for cross-coupling with boronic acids and esters,[8] as well as organozinc reagents.[9]

We recently reported a Ni-catalyzed Suzuki−Miyaura coupling of aliphatic amides to generate alkyl−aryl ketones (Figure 1, e.g. **1** + **2** → **3**).[10,11] This methodology is broad in scope, but requires the use of a glovebox, thus limiting its practical utility.[12] We questioned if a paraffin-encapsulation strategy, analogous to that pioneered by Buchwald, could prove useful.[13] In this approach, air-sensitive reagents are stored in paraffin capsules, ultimately providing a user-friendly means to perform air-sensitive transition-metal-catalyzed reactions. Previously, we showed the promise of this strategy for the Suzuki−Miyaura cross-coupling of a single benzamide-derived substrate utilizing paraffin−Ni(cod)$_2$/SIPr capsules.[14] However, this precatalyst and ligand combination is ineffective in the coupling of amides derived from aliphatic carboxylic acids.[10] Moreover, only a single example of a glovebox free arylation of an aliphatic amide derivative has been reported, which uses a bench-stable Pd(II) precatalyst.[15] We report the realization of a paraffin encapsulation strategy to achieve the nickel-catalyzed Suzuki−Miyaura coupling of aliphatic amides on the benchtop.

Our studies were initiated by preparing the desired paraffin capsules, using a molding process analogous to one we had previously reported (Figure 2).[14] These capsules were charged with Ni(cod)$_2$ and Benz-ICy·HCl, as this precatalyst/ligand combination had proven effective in our original studies on the Suzuki−Miyaura coupling of aliphatic amides using a glovebox.[10] Next, we assessed the utility of these capsules in the benchtop Suzuki−Miyaura coupling of amide **4** with *N*-methylpyrrole-2-boronic acid pinacol ester (**5**), using 5 mol% Ni. Unfortunately, the use of our literature conditions resulted in a poor yield of ketone **6**.[16] Specifically, the coupling of **4** and **5** employing paraffin-encapsulated Ni(cod)$_2$/Benz-ICy·HCl,

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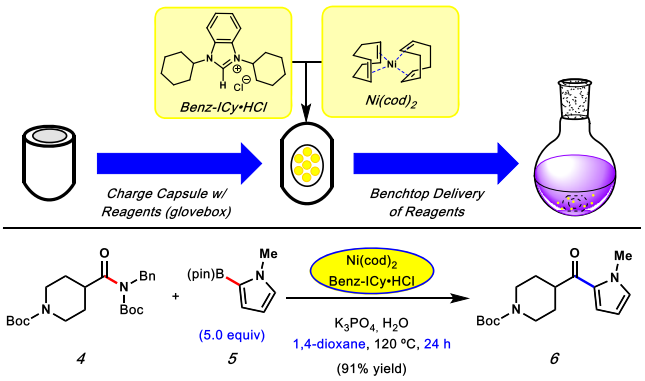

Figure 2. Preparation of $Ni(cod)_2$/Benz-ICy·HCl–paraffin capsules and their use in the benchtop Suzuki–Miyaura coupling of piperidinyl amide **4** and pyrrole boronic ester **5** under optimized conditions. Yield was determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

2.5 equiv of **5**, toluene as the reaction solvent, and a stir rate of 400 rpm for 16 h at 120 °C provided ketone **9** in 28% ^1H NMR yield.[17] After extensive experimentation, it was found that employing higher equivalents of **5** (2.5 to 5.0), utilizing 1,4-dioxane as the reaction solvent, and extending the reaction time to 24 h proved beneficial. This provided ketone **6** in 91% yield on the benchtop. Additionally, these capsules displayed long-term air and moisture stability when stored outside of a glovebox. After two months of storage, a benchtop coupling of **4** and **5** generated **6** in comparable yield.[16] These capsules are currently undergoing commercialization to enable their widespread use.[18]

Having validated our encapsulation approach and arrived at optimized reaction conditions, we evaluated the scope of this transformation with respect to the boronate ester coupling partner. A variety of aryl boronate esters were assessed in couplings with piperidinyl amide **4** (Figure 3). The methodology was found to be tolerant of medicinally privileged *N*-heterocyclic aryl boronates,[19] as evidenced by the formation of ketones **6**–**8**, in good to excellent yields. Additionally, electron-poor *p*-CF_3 and sterically encumbered *o*-CH_3 substituted phenyl boronate esters could be employed in the coupling, providing ketones **9** and **10** in 53% and 74% yields, respectively. Boronate esters featuring extended aromatic ring systems were also competent nucleophiles in the methodology, as demonstrated by the formation of naphthyl ketone **11** in 71% yield. Of note, in all cases, benchtop yields of the desired ketone products were comparable to those obtained when using literature conditions requiring a glovebox (yields using the glovebox protocol are shown in parentheses in Figures 3 and 4).[10]

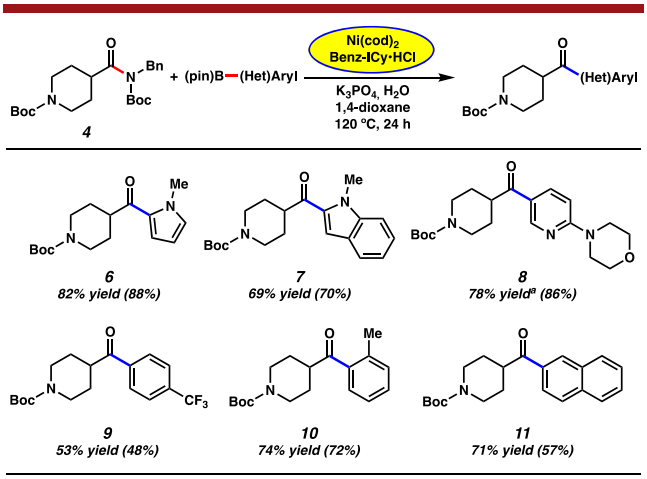

Figure 3. Scope of the boronic ester coupling partners. General conditions unless otherwise stated: substrate **4** (1.0 equiv, 0.4 mmol), K_3PO_4 (4.0 equiv), boronic ester (5.0 equiv), $Ni(cod)_2$ (5 mol%), Benz-ICy·HCl (10 mol%), and 1,4-dioxane (1.0 M) heated at 120 °C for 24 h in a sealed vial under an atmosphere of N_2. Unless otherwise noted, yields reflect the average of two isolation experiments. Yields in parentheses were obtained by carrying out the reaction in a glovebox utilizing literature conditions without encapsulating $Ni(cod)_2$ and Benz-ICy·HCl in paraffin. [a] Yield was determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

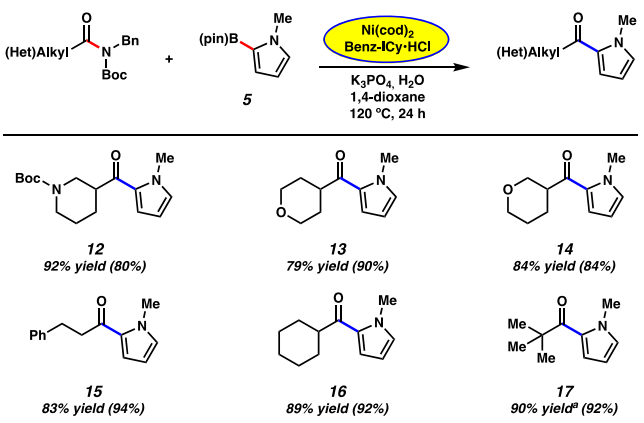

Figure 4. Scope of the amide substrate. General conditions unless otherwise stated: amide substrate (1.0 equiv, 0.4 mmol), K_3PO_4 (4.0 equiv), boronic ester **5** (5.0 equiv), $Ni(cod)_2$ (5 mol%), Benz-ICy·HCl (10 mol%), and 1,4-dioxane (1.0 M) heated at 120 °C for 24 h in a sealed vial under an atmosphere of N_2. Unless otherwise noted, yields reflect the average of two isolation experiments. Yields in parentheses were obtained by carrying out the reaction in a glovebox utilizing literature conditions without encapsulating $Ni(cod)_2$ and Benz-ICy·HCl in paraffin. [a] Yield was determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

We next surveyed a range of amide substrates in the Suzuki–Miyaura coupling with pyrroloboronate **5** (Figure 4).[20] An additional piperidine-derived amide substrate could be used in the coupling to furnish **12** in excellent yield. Furthermore, amides derived from isomeric 3- and 4-tetrahydropyran-carboxylic acids were competent substrates, giving rise to ketones **13** and **14** in 79% and 84% yields, respectively. We also evaluated the coupling of non-heterocyclic amides. Linear and carbocyclic amides underwent the reaction smoothly, as demonstrated by the formation of **15** and **16** in 83% and 89% yield, respectively. Notably, steric bulk adjacent to the amide carbonyl did not hinder the Suzuki–Miyaura coupling, as the use of a pivalamide substrate gave ketone **17** in 90% yield.

Finally, we assessed the Suzuki–Miyaura coupling of piperidine amide **1** with *N*-methylindole-2-boronic ester **18** on gram-scale as shown in Figure 5. Using 5 mol% Ni, the coupling proceeded smoothly to deliver ketone **19** in 73% yield. We view this result as promising in the context of the scalable construction of biologically relevant bis-heterocyclic ketones[19] where the enolizable alkyl–aryl ketone provides a valuable synthetic handle for further manipulation.

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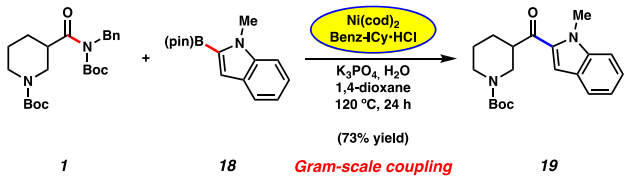

Figure 5. Gram-scale Suzuki–Miyaura coupling of amide **1** with boronate ester **18** to generate ketone **19**.

We have developed a benchtop protocol for the Suzuki–Miyaura cross-coupling of aliphatic amides to access alkyl–aryl ketones. Our strategy leverages mild Ni-catalyzed C–N bond activation to avoid the use of strongly basic and pyrophoric reagents typically employed in amide to ketone conversions. Additionally, the Ni(cod)$_2$/Benz-ICy·HCl–paraffin capsules, which are currently undergoing commercialization,[18] obviate the need to set up the reactions in a glovebox. Notably, this methodology enables the coupling of heterocyclic and aliphatic amides with a variety of aryl boronic esters for the formation of C–C bonds. Moreover, this transformation is scalable and, further, provides a valuable approach to the synthesis of alkyl–aryl ketones from amides, which benefits further from the use of base-metal catalysis and commercially available boronic ester nucleophiles. Thus, we hope these studies promote the use of Ni-mediated Suzuki–Miyaura couplings of aliphatic amides as a complement to traditional synthetic strategies.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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