Stoichiometric Reactions of Acylnickel(II) Complexes with Electrophiles and the Catalytic Synthesis of Ketones

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ABSTRACT: Acylnickel(II) complexes feature prominently in cross-electrophile coupling (XEC) reactions that form ketones, yet their reactivity has not been systematically investigated. We present here our studies on the reactivity of acylnickel(II) complexes with a series of carbon electrophiles. Bromobenzene, α-chloroethylbenzene, bromooctane, and iodoctane were reacted with (dtbbpy) Ni(C(O)C5H11)(Br) (1b) and (dtbbpy)Ni(C(O)tolyl)(Br) (1c) to form a variety of organic products. While reactions with bromobenzene formed complex mixtures of ketones, reactions with α-chloroethylbenzene were highly selective for the cross-ketone product. Reactions with iodoctane and bromooctane also produced the cross-ketone product, but in intermediate yield and selectivity. In most cases the presence or absence of a chemical reductant (zinc) had only a small effect on the selectivity of the reaction. The coupling of 1c with iodoctane (60% yield) was translated into a catalytic reaction, the carbonylative coupling of bromoarenes with primary bromoalkanes (six examples, 60% average yield).

INTRODUCTION

The ketone is ubiquitous in organic synthesis because it is a synthetically useful functional group and a common motif in biologically active molecules. Among the many synthetic methods known, carbonylative cross-coupling of a carbon nucleophile with a carbon electrophile is attractive because it is convergent (eq 1).1 A common challenge for all of these carbonylative cross-coupling reactions is the availability and stability of the carbon nucleophile component, which has led to the development of alternative methods, such as C—H activation,10 and milder organometallic reagents.5

An alternative strategy to avoid the challenges of nucleophilic carbon reagents is the coupling of two different carbon electrophiles (Figure 1). Cross-electrophile coupling (XEC) has been much less studied than the cross-coupling of electrophiles with nucleophiles, but recent reports have demonstrated the generality of this approach3−6 and have shed light on the origins of selectivity.7 Two different nickel-catalyzed XEC approaches to ketones have been developed: the coupling of acid chlorides with alkyl and benzyl halides8 and the carbonylative coupling of aryl halides with alkyl halides.9 The carbonylative coupling approach has only been demonstrated with electrochemical reduction (Ni/Fe sacrificial anode), and high yields were only obtained with aryl iodides and benzyl bromides.9f

A common feature of many4−6,8 of these approaches (A and B, Figure 1) is the intermediacy of an acylnickel(II) intermediate (1) that is proposed to react with a carbon electrophile (R2X) to form the ketone product (R1C(O)R2). Studies of the generation of acylnickel(II) intermediates from nickel(0) have clearly delineated its formation, but no such systematic studies on the reactivity of 1 with carbon electrophiles have been reported.

Despite our recent success in developing and understanding the mechanism of nickel-catalyzed cross-electrophile coupling of aryl halides with alkyl halides, we foresaw several challenges for the carbonylative reaction. First, the coupling of two electrophiles with a third component (CO) results in a large number of potential products in comparison to two-component couplings.3,8 Second, the reactivity of the proposed acylnickel intermediates is relatively unknown, limiting our ability to troubleshoot reactions.

We report here our progress toward understanding the reactivity of acylnickel(II) complexes toward aryl, alkyl, and benzyl electrophiles and a cross-selective carbonylative coupling of unactivated primary alkyl bromides with aryl halides to form aryl alkyl ketones.

BACKGROUND

Stoichiometric reactions with Ni(CO)4 with electrophiles to form ketones are well-known to proceed via intermediate acylnickel(II) complexes (eq 2),9 but these reactions are not often used today due to toxicity concerns10 and limited availability.11,12 Catalytic versions of these stoichiometric reactions have proven to be difficult to develop.
The catalytic, carbonylative coupling of two organic halides has primarily been developed by the group of Troupel. Early work revealed that Fe(CO)$_5$ was a more convenient and reliable CO source for these reactions than CO gas, because the reaction was strongly inhibited by the formation of unreactive (L)Ni$_0$(CO)$_2$ at higher CO concentrations.

To date, the electrolysis conditions of Troupel are the best conditions for carbonylative XEC (Scheme 1). With 30 mol % of (bpy)NiBr$_2$, benzyl chlorides could be coupled with aryl iodides (2 equiv) to form aryl benzyl ketones in 43−88% yield, but yields were lower with aryl bromides (32−60%) and an unactivated alkyl iodide, iodooctane (35−42%). Functional group compatibility was promising, with free phenol and aniline groups coupling in good yield.

Troupel’s electrochemical mechanistic studies on this process implicated an acylnickel(II) intermediate, (bpy)Ni(COR)$_1$X (1), and examined the rate and mechanism of its formation under catalytically relevant conditions. Further reaction of 1 with another organic halide (R’SX) to form ketone (R’COR) was not studied, but it was proposed that it could occur through a number of pathways, including intermediate reduction of 1 from nickel(II) to nickel(I).

Acylnickel complexes may be generated by addition of CO to the corresponding organonickel(II) complex or by the reaction of nickel(0) with an activated ester. Phosphine-ligated acylnickel(II) halide complexes are reported to lose carbon monoxide over time or to reversibly eliminate CO and exchange it with other nickel complexes. Only one study has reported on the reactivity of an acylnickel(II) species with a bidentate N−N ligand (bpy). All of the reported ketone-forming XEC reactions call for N−N ligands of this type.

Yamamoto and co-workers explored the reactivity of 1 under thermolysis and with dioxygen, but the stoichiometric reactivity of 1 with organic electrophiles has never been systematically examined. Amatore and Jutand generated 1 under electrochemical conditions in their study on the acylation of benzyl bromides and showed it can easily be reduced to an acylnickel(I) species but did not study the reactivity of either species with organic electrophiles.

In studies related to the acylation of alkyl halides, Gong reacted (dmbpy)NiI$_3$ (dmbpy = 4,4′-dimethyl-2,2′-bipyridine) with a mixture of benzoic anhydride and a secondary alkyl bromide and reported that only the anhydride was consumed (Scheme 2). No ketone formation was observed from the resulting uncharacterized mixture unless a reductant (Zn$_0$) was added. A similar reaction with a mixture of anhydride and iodoalkane resulted in partial consumption of both electrophiles and no ketone formation. From these studies it appeared that the initial acylnickel(II) (1) had to be reduced to an acylnickel(I) before it could form ketone products from the reaction with secondary bromoalkanes.

An improved fundamental understanding of how (L)NiII(C−(O)R)X (1) reacts with electrophiles would be generally helpful to developing XEC reactions for ketone synthesis, especially for an improved method for the carbonylative XEC of aryl halides with alkyl halides to form aryl alkyl ketones. We also sought to improve upon the results of Troupel in the carbonylative coupling of aryl halides with unactivated alkyl halides (Scheme 1).
RESULTS AND DISCUSSION

Stoichiometric Studies. In order to study the key proposed bond-forming step, we synthesized the dark red (dtbbpy)NiII(C(O)C₅H₁₁)Br (1b) from the reaction of deep purple (dtbbpy)NiII(cod)Br (3) with hexanoyl bromide in THF, in analogy to several literature reports (Table 1).¹⁶ The reaction of 1b with α-bromoethylbenzene again produced a mixture of cross-aryl ketone products (Table 2, entries 3) in a yield that was comparable to those reported by Yamamoto's group for the reaction of α-bromoethylbenzene with acylnickel complexes.⁴c,d,e

Table 1. Synthesis of (dtbbpy)NiII(COR)Br and Selected Characterization Data

| Entry | [Ni] | Yield (%) | IR (cm⁻¹) | NMR (ppm) | UV-Vis (cm⁻¹) |
|-------|------|-----------|-----------|-----------|---------------|
| 1     | 1b   | 74        | 1612      | 3.12      | 20325         |
| 2     | 1c   | 89        | 1617      | 5         | 20576         |

"dtbppy = 4,4'-di-tert-butyl-2,2'-bipyridine. See the Supporting Information for full characterization data and procedures. "¹¹H NMR yield vs liberated cyclooctadiene; average of two runs. "C=O stretches reported that are characteristic of M=C(O)R complexes.¹⁵e "¹¹H NMR chemical shift and multiplicity for α-proton reported of M=C(O)CH₃.¹⁵c N/A = not applicable. "UV-Vis absorbances reported as wavenumbers (ε values are given in parentheses)."

Table 2. Reaction of (dtbbpy)NiII(COC₅H₁₁)Br with RX

| Entry | R⁻X | T (°C), t | Products (% yield) |
|-------|-----|----------|--------------------|
| 1     | PhBr | 60 °C, 14 h | 4 (12), 8 (11), 9 (11), 5 (8) |
| 2     | w/Zn | 60 °C, 14 h | 4 (22), 5 (13) |
| 3     | PhCl | 21 °C, 5 min | 4 (54) |
| 4     | w/Zn | 21 °C, 5 min | 4 (44) |
| 5     | H₂-CBr | 60 °C, 14 h | 4 (17), 5 (12) |
| 6     | w/Zn | 60 °C, 14 h | 4 (31), 5 (20) |
| 7     | H₂-Cd | 60 °C, 12 h | 4 (33), 5 (18) |

"Reactions run in a 1/1 THF-d₅/DMA mixture using freshly prepared 1b. See the Supporting Information for full experimental details and tables with all products formed. Yields are uncorrected GC yields of products formed in >7% yield.

is needed before it can react with organic halides, we also ran reactions with an added reductant, zinc flake. The reaction of 1b with bromobenzene produced similar amounts of cross-ketone (4) and symmetric ketone or diketone products (8 and 9; Table 2, entry 1). The addition of zinc flake eliminated the symmetric diketone products (8 and 9), but the reaction remains only marginally selective (entry 2).

Hexanoyl complex 1b reacts with α-chloroethylbenzene rapidly (under 5 min at room temperature) to exclusively form cross-ketone product 4 (Table 2, entry 3) in a yield that compares well with those reported for the XEC of acid chlorides with α-chloroethylbenzene (49–52% for similar conditions).⁴c,f The addition of zinc flake did not improve the reaction yield or selectivity (entry 4), suggesting that reduction of 1b is not required.

Finally, the reaction of 1b with bromoacetone or idooctane produced nearly equal amounts of cross-ketone product 4 and dioctyl ketone 5 (Table 2, entries 5–7). The addition of zinc flake improved the yield of ketone products (entry 6) but did not improve the selectivity for cross-ketone over symmetric ketone significantly (1.4/1 to 1.6/1). XEC of acid chlorides with alkyl halides is reported to be sensitive to the reductant and solvent, perhaps explaining the difference between these modest yields and those reported by Gong and ourselves.⁴d,e,f

The reactivity of aroylnickel 1c was examined in the same manner as 1b, and the results are shown in Table 3. Complex 1c was more stable than 1b, but we again prepared it fresh for each experiment.

Reaction of 1c with bromobenzene again produced a mixture of ketone products (Table 3, entry 1). The addition of zinc as a reductant improved the total yield of all coupled products from 1c (nearly quantitative from 70%) but also resulted in the formation of significant amounts of noncarbonylated cross-aryl product 7 (entry 2).
The reaction of aryl nickel(0) complexes with alkyl halides demonstrated that aryl halides do react more with the nickel catalyst. Our recent work on the reactivity of alkyl halides will work best if the aryl halide reacts, as shown in Scheme 3. Aroylnickel(II) complexes are well-known to decompose into diaryl ketones by disproportionation upon heating. The noncarbonylated product presumably arose when not enough CO was available in solution, allowing for the formation of 18. Consistent with these hypotheses, the addition of more alkyl bromide (2.25 equiv from 1 equiv) resulted in less diaryl ketone, although little effect was observed above 2.25 equiv (Table 4, entries 1–4). Increasing the amount of iron carbonyl eliminated noncarbonylated products, but too much iron carbonyl diminished yields (Table 4, entry 3 vs entries 5–7). The addition of iodide was essential for reactivity. A reaction with no NaI gave no ketone product (Table 4, entry 8), but substitution of NaI with LiI and KI provided results similar to those for NaI (Table 4, entry 3 vs entries 9 and 10). Lowering the catalyst loading from 7 to 5 mol % resulted in a 14% lower yield (entry 11). A reaction run without added reductant produced a small amount of 22. In this case, the Fe(CO)5 likely arose when not enough CO was available in solution, allowing for the formation of 18.

Examination of several metal carbonyls (Mn2CO10, W(CO)6, Mo(CO)6, Cr(CO)6) showed that iron carbonyl was best and that the reaction could be run in DMA instead of DMPU, but no significant improvements in yield were forthcoming.

The major reaction products were our desired aryl alkyl ketone, hydride, and diaryl bromide. We envisioned that both the diaryl ketone and the aryl alkyl ketone product could arise from the aryl nickel (1) formed by CO insertion into the aryl–nickel bond of 17 (Scheme 3). Aroylnickel(II) complexes are well-known to decompose into diaryl ketones by disproportionation upon heating. The noncarbonylated product presumably arose when not enough CO was available in solution, allowing for the formation of 18. Consistent with these hypotheses, the addition of more alkyl bromide (2.25 equiv from 1 equiv) resulted in less diaryl ketone, although little effect was observed above 2.25 equiv (Table 4, entries 1–4). Increasing the amount of iron carbonyl eliminated noncarbonylated products, but too much iron carbonyl diminished yields (Table 4, entry 3 vs entries 5–7). The addition of iodide was essential for reactivity. A reaction with no NaI gave no ketone product (Table 4, entry 8), but substitution of NaI with LiI and KI provided results similar to those for NaI (Table 4, entry 3 vs entries 9 and 10). Lowering the catalyst loading from 7 to 5 mol % resulted in a 14% lower yield (entry 11). A reaction run without added reductant produced a small amount of 22. In this case, the Fe(CO)5 likely arose when not enough CO was available in solution, allowing for the formation of 18.
acynickel complexes (Tables 2 and 3), the catalytic reactions were plagued by rapid dimerization of this reactive substrate.

**CONCLUSIONS**

In conclusion, our studies on acynickel complexes have revealed differential reactivity with respect to electrophiles. Both aryl- and alkanoynickel complexes react with secondary benzylic chlorides to form product without added reductant, but the arynickel complex reacts with alkyl iodides to produce more cross-ketone than the alkanoylnickel complex. Neither aryl- nor alkanoylnickel complexes react with secondary alkyl or benzyl halides but did improve the rate in one case, suggesting that reduction of acynickel(II) to acynickel(I) is not a necessary step in XEC ketone synthesis reactions and acetate more dramatic than the electron withdrawing effect we observed. However significantly different conditions. Finally, the observed reactivity of 1c with alkyl halides can be translated into the first carbonylative cross-coupling of bromoarenes with bromoalkanes. Further studies on the reactivity of acynickel complexes and translation to new reactions is ongoing.

**EXPERIMENTAL SECTION**

**Materials and Methods.** NiCl₂(1,2-dimethoxyethane) (NiCl₂(dme)) was purchased from Strem or synthesized according to the literature procedure.²⁰ Ni(cod)₂ was purchased from Strem. 4,4′-Di-tert-butyl-2,2′-bipyridine (dtbbpy) was purchased from Aldrich.

**EXPERIMENTAL SECTION**

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"Reactions were performed on a 0.75 mmol scale on the benchtop in 3 mL of DMA. Yields are uncorrected GC yields vs dodecane. The yield in parentheses is an additional 3% of benzophenone.

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5878
General Procedure for Aryl Bromides. A flame-dried 10 mL round-bottom flask (14/20 joint) containing a Teflon-coated magnetic stir bar was charged with NiCl₂(dme) (11.5 mg, 0.053 mmol), 4,4′-di tert-butyl-2,2′-bipyridine (14.5 mg, 0.054 mmol), anhydrous NaCl (28.1 mg, 0.1875 mmol), and zinc flake (98.0 mg, 2 equiv). The round-bottom flask was then fitted with a septum (14/20) and sealed tightly with a double strand of 20 gauge copper wire. The round-bottom flask was purged with nitrogen (1 min), and 2 mL of anhydrous DMA (<70 ppm of H₂O by KF titration) was added by syringe. The resulting mixture was stirred for 1 h at room temperature (∼21 °C) until the supernatant had turned dark gray. Alkyl bromide (1.69 mmol, 2.25 equiv), a solution of aryl halide (0.75 mmol in 1 mL of anhydrous DMA), and Fe(CO)₅ (35 μL, 0.27 mmol) were sequentially added by syringe. The reaction mixture was stirred (1000 rpm) at 60 °C (oil bath) until judged complete by GC analysis (less than 1% aryl bromide remaining, 17–36 h). The resulting mixture was filtered through a short silica gel pad (2 cm) in a pipet packed with glass wool. The filtrate was analyzed by GC.

Organometallics

Article

5879
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Ethyl 5-[(2-Methoxy-5-fluorophenyl)-5-oxopentanoate (25) [518789-85-3]. The general procedure was followed using 2-bromo-5-fluorooisole (97 µL, 0.75 mmol) and ethyl 4-bromobutate (240 µL, 1.68 mmol). The reaction was judged complete after 22 h. Following chromatography (8/1 hexanes/ethyl acetate, RF = 0.20, staining purple with p-anisaldehyde stain), the product was isolated as a white amorphous solid (132.1 mg, 62%). Mp: 30–33 °C. 1H NMR (400 MHz; CDCl3): δ 7.40 (dd, J = 7.1, 2.6 Hz, 1H), 7.14 (dd, J = 7.2, 5.9, 2.6 Hz, 1H), 6.90 (dd, J = 7.3, 3.2 Hz, 1H), 4.12 (q, J = 5.7 Hz, 2H), 3.87 (s, 3H), 3.02 (t, J = 5.7 Hz, 2H), 2.37 (t, J = 5.7 Hz, 2H), 2.00 (quintet, J = 5.8 Hz, 2H), 1.23 (t, J = 5.7 Hz, 3H). 13C NMR (126 MHz; CDCl3): δ 200.3, 172.8 (s, C=O, ester), 167.4 (s, C=O, ary ketone), EIMS (70 eV); m/z 268 (M+ 1). Ethyl 5-[(4-Trifluoromethylphenyl)-5-oxopentanoate (26) [59877-71-6]. The general procedure was followed using 4-bromobenzotrifluoride (105 µL, 0.75 mmol) and ethyl 4-bromobutyrate (240 µL, 1.68 mmol). The reaction was judged complete after 24 h. Following chromatography (15% ethyl acetate in hexanes, RF = 0.40, staining purple with p-anisaldehyde stain), the product was isolated as a white amorphous solid (102.9 mg, 48%). Mp: 29–32.5 °C. 1H NMR (500 MHz; CDCl3): δ 8.07 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.08 (t, J = 7.1 Hz, 2H), 2.44 (t, J = 7.1 Hz, 2H), 2.08 (quintet, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 4H). 13C NMR (126 MHz; CDCl3): δ 198.5, 173.3, 139.5, 134.5 (q, J = 32.7 Hz), 128.5, 125.8 (q, J = 3.7 Hz), 123.7 (q, J = 273 Hz), 60.6, 37.9, 33.3, 19.3, 14.3. 19F NMR (376 MHz; CDCl3): δ −60.66. IR (cm⁻¹): 1728 (s, C=O, ester), 1674 (s, C=O, ary ketone). EIMS (70 eV): m/z 288 (M+). 1-Phenyl-4-(2-butyl/dimethylsiloxy) 1-butanone (27) [14387847-47-1]. The general procedure was followed using bromobenzene (80 µL, 0.75 mmol) and 3-(2-tert-butyl(dimethylsiloxy)-1-bromopropane (427 mg, 1.68 mmol). The reaction was judged complete after 18 h. Following chromatography (4% diethyl ether in pentane, RF = 0.22, staining yellow with p-anisaldehyde stain), the product was isolated with 3% benzophenone impurity as a clear, colorless oil (135.7 mg, 65%). 1H NMR (500 MHz; CDCl3): δ 7.96 (d, J = 7.7 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 3.70 (t, J = 6.0 Hz, 2H), 3.05 (t, J = 7.2 Hz, 2H), 1.95 (quintet, J = 6.7 Hz, 2H), 0.88 (s, 9H), 0.03 (s, 6H). 13C NMR (126 MHz; CDCl3): δ 200.4, 137.3, 133.0, 128.7, 128.2, 62.4, 35.0, 27.6, 26.1, 18.5, −5.2. IR (cm⁻¹): 1686 (C=O ary ketone). EIMS (70 eV): m/z 221 (M+ − t-Bu).

ASSOCIATED CONTENT

1 Supporting Information
Tables S1 and S2, giving the full product distribution for Tables 2 and 3, respectively, pictures of the the reaction of 1c with electrophiles, and figures giving NMR spectra for 1b, c, 3, and 22–27. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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