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Mild ketone formation *via* Ni-catalyzed reductive coupling of unactivated alkyl halides with acid anhydrides[†]

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Ni-catalyzed ketone formation through mild reductive coupling of a diverse set of unactivated alkyl bromides and iodides with particularly aryl acid anhydrides was successfully developed using zinc as the terminal reductant. These conditions also allow direct coupling of alkyl iodides with aryl acids in the presence of Boc₂O and MgCl₂.

Transition-metal-catalyzed addition of alkyl metallic reagents to acid derivatives have attracted considerable attention for alkyl ketones.¹⁻⁶ Of special note is the development of the Ni-catalyzed addition of alkylzinc reagents to less reactive acid anhydrides by Rovis, which provides ketones in a highly stereoselective manner.⁶ Synthesis of ketones from chemically and electrochemically reductive coupling of readily accessible alkyl and acyl electrophiles has been reported^{7,8} but is generally limited to alkyl ketones from the coupling of alkyl iodides with alkyloyl chlorides, pyridylthiol and pyridyloxyl esters. To the best of our knowledge, no reports regarding unactivated alkyl bromides have been revealed. Meanwhile, the employment of anhydrides to the synthesis of ketones is still rare.^{8a,c} Only activated allylic and benzylic electrophiles under electrochemical conditions have been documented, which requires high loading of anhydrides but generally produce low yields of ketones.⁸

Recently, we and others have demonstrated efficient Ni-catalyzed reductive coupling methods for the coupling of alkyl halides with other electrophiles.^{9–11} This prompts us to study whether acid anhydrides are competent for reductive coupling with alkyl halides, particularly alkyl bromides.¹² In this paper, we report our studies of unactivated alkyl iodides and bromides with aryl acid anhydrides to ketones under a Ni-catalyzed reductive strategy. This work features the first reductive ketone formation employing unactivated alkyl bromides, and allows direct coupling of aryl acids and alkyl iodides through *in situ* generation of acid anhydrides. Preliminary mechanistic studies indicate that alkyl bromides may proceed *via* a Ni¹/Ni^{III} process that differs from the previously proposed acylation of Ni^{II} mechanism (Fig. 1).⁷

To begin with, we first investigated the reaction conditions for the coupling of 4-iodo-1-tosylpiperidine **1a** and benzoic anhydride.¹³



Fig. 1 Catalytic ketone formation employing unactivated alkyl halides and acid derivatives.

After tremendous efforts, we identified that a combination of Ni(COD)₂/**3a**/Zn in CH₃CN gave the desired ketone in a 38% yield (entry 1, Table 1).¹⁴ Interestingly, addition of 20% of MgCl₂ boosted the yields to 50% (entry 2). Use of 1.5 equiv. of MgCl₂ gave **2** in an 85% yield (entry 3). We speculate that roles of MgCl₂ are in part to activate anhydrides and Zn by coordination to the carbonyl oxygen and by removal of salts on Zn surface, respectively. Extensive screening of other ligands **3b-d**, **4-6** (Fig. 2) did not yield better results (entries 4–9), although ligand **5** is comparably effective.¹⁴ The reaction went to completion after 8 h (entry 10). The search for different Ni sources disclosed that the use of Ni(acac)₂ only slightly lowered the yield (entry 11).¹⁴ In general, the excess benzoic anhydride remained

 Table 1 Optimization of the reaction conditions^{a,b}

1a		O ^{Ph} Additive Zn (300 mol %) CH ₃ CN, 25 °C	2 Ph	
Entry	Ni/ligand	Additives (mol%)	Time/h	Yield (%)
1	Ni(COD) ₂ /3a	None	12	38
2	Ni(COD) ₂ /3a	MgCl ₂ (20)	12	50
3	Ni(COD) ₂ /3a	MgCl ₂ (150)	12	85
4	Ni(COD) ₂ /3b	$MgCl_{2}$ (150)	12	58
5	$Ni(COD)_2/3c$	$MgCl_{2}$ (150)	12	60
6	$Ni(COD)_2/3d$	$MgCl_{2}$ (150)	12	42
7	Ni(COD) ₂ /4a	$MgCl_{2}$ (150)	12	38
8	$Ni(COD)_2/5$	$MgCl_{2}$ (150)	12	80
9	$Ni(COD)_2/6$	$MgCl_{2}$ (150)	12	23
10	$Ni(COD)_2/3a$	$MgCl_{2}$ (150)	8	85
11	$Ni(acac)_2/3a$	$MgCl_2$ (150)	12	82

Ni source (10 mol %)

^{*a*} Reaction Conditions: **1a** (0.14 mmol, 100 mol%), benzoic anhydride (200 mol%), Ni source (10 mol%), ligand (15 mol%), Zn (300 mol%), CH₃CN (1 mL). ^{*b*} Isolated yields.

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Fig. 2 Structures of ligands.

Table 2 Substrate scope for R_{alkyl} -I^{*a,b*}



^{*a*} Reaction Conditions: alkyl iodide (0.14 mmol, 100 mol%), anhydride (200 mol%), Ni(COD)₂ (10 mol%), **3a** (15 mol%), Zn (300 mol%), MgCl₂ (150 mol%), CH₃CN (1 mL). ^{*b*} Isolated yields.

unreacted. Finally, use of 1.5 and 1 equiv. of benzoic anhydride reduced the yield to 70% and 65%, respectively.

Using the reaction conditions in entry 3, Table 1, a set of alkyl iodides were examined for the coupling with substituted benzoic anhydrides, delivering ketones 7–29 in moderate to excellent yields (Table 2). 4-*t*Bu-benzoic anhydride gave better result than methoxyl and methyl substituted ones as shown in 7–9. It should be noted that acetic acid anhydride also resulted in ketone 10 in 68%. Cyclic secondary alkyl iodides generally provided the desired ketones in good results (*e.g.* 11–18), which were more efficient than the open chain analogues (*e.g.* 19–26). The primary alkyl iodides also gave ketones 27–29 in good yields.

Next, we investigated ketone formation *via in situ* generation of anhydrides under the reductive conditions.¹⁵ By addition of Boc anhydride under the optimized reaction conditions, ketones **2**, **7–9**, **14–15**, **17–19**, **21**, **30–31**, and **33–34** were obtained successfully (Table 3), although 4 equiv. of acids appeared to be necessary. Raising the amount of Boc anhydride did not result in better yields. In general, moderate to excellent yields could be attained when secondary alkyl iodides were used. For primary alkyl iodides, low coupling yields were observed as evident in **28** and **34**. Notably, the use of electron-deficient aryl acid did not result in ketones, *e.g.* **32**. Although the coupling efficiency for this *in situ* anhydride method dropped as compared to those methods using purified anhydrides, to our knowledge, this work provides the first direct ketone formation from alkyl halides and acids.

Table 3 Coupling of alkyl iodides with aryl acids through *in situ* generation of anhydrides^{a,b}



^{*a*} Reaction Conditions: alkyl iodide (0.14 mmol, 100 mol%), acid (300 or 400 mol%), Ni(COD)₂ (10 mol%), **3a** (15 mol%), Zn (300 mol%), MgCl₂ (200 mol%), CH₃CN (1 mL). ^{*b*} Isolated yields. ^{*c*} 4 equiv of acid. ^{*d*} 3 equiv of acid. ^{*e*} Not detected.

Extension of the optimized reaction conditions for alkyl iodides to the coupling of 4-bromo-1-tosylpiperidine **1b** with benzoic anhydride only gave **2** in less than 40%. Extensive optimization gave the highest yield of 78% when using a combination of Ni(COD)₂/**4b**/Zn/MgCl₂ in a mixture of acetonitrile and DMF (*N*,*N*-dimethylforamide) (Table 4).¹⁴ Various unactivated 2° and 1° alkyl bromides were compatible, giving **2**, **7**, **12**, **18**, **23**, and **35–41** in moderate to excellent yields.

To understand whether a Negishi mechanism was involved, the coupling of cyclohexyl–ZnI with 2 equiv. of 4-*t*Bu-benzoic anhydride under the standard reaction conditions was conducted. Ketone **14** was obtained in a 78% yield, indicating an *in situ* Negishi mechanism is possible.⁶ However, Table 3 indicates the effectiveness of ketone formation in the presence of large excess aryl acids, which seemingly support that existence of

 Table 4
 Coupling of unactivated alkyl bromides with acid anhydrides^{a,b}



^{*a*} Reaction Conditions: alkyl bromide (0.14 mmol, 100 mol%), anhydride (200 mol%), Ni(COD)₂ (10 mol%), **4b** (15 mol%), Zn (300 mol%), MgCl₂ (150 mol%), CH₃CN–DMF 3:7 (v/v, 1 mL). ^{*b*} Isolated yields. ^{*c*} dr >20:1



Scheme 1 Coupling of 42 with benzoic anhydride.

organozinc is implausible.^{10*a*,16} Therefore for unactivated alkyl iodides, *in situ* Negishi mechanism cannot be unambiguously ruled out. For unactivated alkyl bromides, such a process is implausible since organozincs do not form under Ni-catalyzed reductive conditions at 25 $^{\circ}$ C.^{10*a*}

Next, an equimolar mixture of benzoic anhydride, $N(COD)_2/4b$ and **1b** revealed that benzoic anhydride consumed after 12 h, while **1b** remained unreacted. Addition of Zn and MgCl₂ to the resulting mixture gave **2** in 40% yield, suggesting a possible PhCO–Ni^{II} species as the initiation step of the catalytic process.^{6g,17} However, treatment of a 1 : 1 mixture of **1a** and benzoic anhydride with 1 equiv. of Ni(COD)₂ for 12 h, resulted in 55% recovered **1a**, and about 40% recovered anhydride, suggesting that alkyl iodides and aromatic anhydrides possess comparable oxidative addition rate to Ni⁰.

Although more studies are required, we propose at least for alkyl bromides, the reaction may proceed through one electron reduction of PhC(O)–Ni^{II}, leading to PhC(O)–Ni^{I.18} Subsequent oxidative addition of alkyl bromides generates R–Ni^{III}–C(O)Ph. Reductive elimination provides the ketone products and a Ni^I species, which could be reduced to Ni⁰ to allow the catalytic cycle to proceed.¹⁹ It should be noted that oxidative addition of alkyl halides to Ni^I generally involves radical intermediate. Coupling of **42** with benzoic anhydride gave a cyclization product **43**, conforming that this coupling event involves an alkyl radical (Scheme 1).²⁰

In summary, we have disclosed an efficient method for the coupling of unactivated alkyl iodides and bromides with anhydrides, providing ketones in good to excellent yields. This method allows direct use of carboxylic acids wherein *in situ* generation of anhydrides and formation of ketones can be achieved in one pot. Although the involvement of *in situ* organozincs is less likely, it cannot be unambiguously ruled out for alkyl iodides. Instead, the non-Negishi mechanisms that proceed through oxidative addition of anhydride to alkyl–Ni^{III}-C(O)Ph for alkyl halides may be operative, although previously proposed mechanism involving acylation of an alkyl–Ni^{III} intermediate is possible for alkyl iodides.⁷

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