

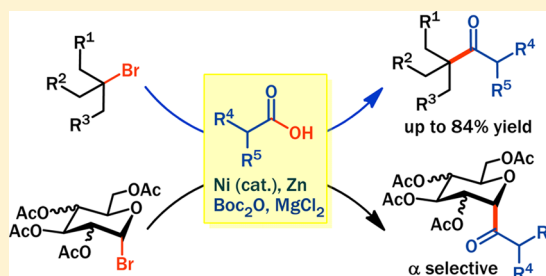
Ni-Catalyzed Reductive Coupling of Alkyl Acids with Unactivated Tertiary Alkyl and Glycosyl Halides

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Supporting Information

ABSTRACT: This work highlights Ni-catalyzed reductive coupling of alkyl acids with alkyl halides, particularly sterically hindered unactivated tertiary alkyl bromides for the production of all carbon quaternary ketones. The reductive strategy is applicable to α -selective synthesis of saturated, fully oxygenated C-acyl glycosides through easy manipulations of the readily available sugar bromides and alkyl acids, avoiding otherwise difficult multistep conversions. Initial mechanistic studies suggest that a radical chain mechanism (cycle B, Scheme 1) may be plausible, wherein MgCl_2 promotes the reduction of Ni^{II} complexes.



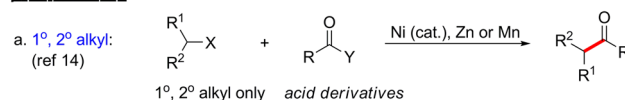
1. INTRODUCTION

In catalytic coupling reactions, tertiary alkyl–metallic reagents^{1,2} or tertiary alkyl electrophiles^{3,4} generally display pronounced difference and challenges as compared to their primary and secondary alkyl analogs, which require special and independent attentions. For instance, the recent development of catalytic coupling of unactivated secondary alkyl zinc reagents with aryl halides^{5,6} has only been extended to adamantylzinc reagents.⁷ Moreover, although catalytic formation of ketones involving alkyl nucleophiles has been widely explored,^{8–11} the employment of tertiary alkyl–metallic reagents is very rare.^{7,12} The challenge for the coupling of tertiary alkyl halides can be manifested in Oshima and Fu's recent construction of quaternary carbon centers through Kumada coupling of allyl-/benzyl-Mg and Suzuki coupling of aryl-9-BBN, respectively. While the former is limited to special organometallics, the latter is very sensitive to the electronic nature of aryl moieties.^{3,4}

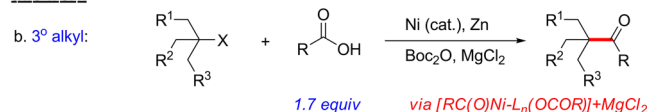
Therefore, it is not surprising to notice that although recent Ni-catalyzed reductive coupling of primary and secondary alkyl halides with other electrophiles including acid derivatives effectively generates $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ and $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ products (Figure 1),^{13–16} tertiary alkyl halides are not competent. Moreover, although we have extended the reductive protocol to ketone formation through the coupling of alkyl halides with in situ activated aryl acids, four equiv of aryl acids are necessary to ensure low to moderate coupling efficiency, and only alkyl iodides are compatible with limited aryl acids; alkyl acids prove to be ineffective.^{16a} Hence, development of reductive ketone synthesis that allows for tertiary alkyl halides and alkyl acids is important.

In addition, although C-glycosides including C-acyl glycosides are believed to be important bioactive candidates,^{17,18} their preparation has not been achieved by reductive coupling of two electrophiles. The conventional transition-metal-catalyzed coupling methods, though have succeeded in C-aryl

previous work



this work



c. acyl C-glycosides:

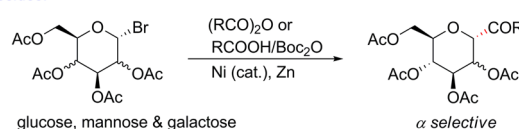


Figure 1. Ni-catalyzed ketone formation via alkyl halides.

and alkyl glycosides,^{19–21} are generally not applicable to C-acyl glycosides. The challenges are apparent; glycosyl C1 (sp^3) and acyl nucleophiles are notoriously difficult to prepare and participate in coupling reactions.^{22,23} Thus, far, benzoyl β -C-glucoside has been the sole example documented in a Pd-catalyzed acylation of 1-glycosyl-Sn method.²⁴ As a result, much less efficient multistep conversions from 1-glycosyl acids, cyanides, alkyne and allenes dominate the current synthesis of C-acyl glycosides.^{25,26} The development of a general and straightforward method to C-acyl glycosides particularly the α -anomers is therefore highly needed.

We herein report an efficient Ni-catalyzed alkyl–alkyl ketone formation method with emphasis on the coupling of tertiary alkyl and glycosyl halides with alkyl acids using Zn as the reductant (Figure 1). To the best of our knowledge, this work

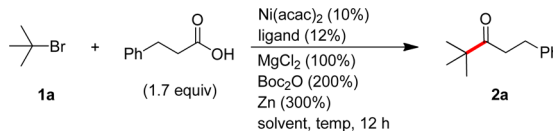
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demonstrates the first construction of all carbon quaternary centers via the reductive coupling of unactivated tertiary alkyl halides with a second electrophile other than Barbier-type radical addition to carbonyl or activated alkenes.^{27,28} It also represents the first reductive synthesis of C-glycosides via readily available electrophiles featuring α -selectivities. Finally, the initial mechanistic studies seem to support a radical chain mechanism, wherein MgCl_2 accelerates the reduction of the Ni^{II} complexes by Zn.

2. RESULTS AND DISCUSSIONS

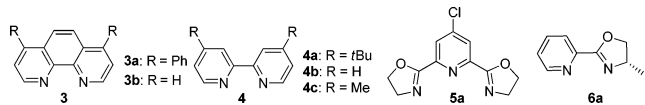
2.1. Coupling of Tertiary Alkyl Halides with Alkyl Acids. To identify whether alkyl acids and tertiary alkyl halides are competent, the coupling of *t*BuBr (**1a**) with 1.7 equiv of 3-phenylpropanoic acid was intensively surveyed in the presence of $\text{Boc}_2\text{O}/\text{Zn}$ and 1.5 equiv of MgCl_2 (Table 1).²⁹ With

Table 1. Optimization for the Reaction of *t*BuBr (1a**) with 3-Phenylpropanoic Acid^a**



entry	ligand	solvent	<i>i</i> Pr ₂ NEt (%)	MgCl_2 (%)	°C	yield (%) ^b
1	3a	THF	0	150	25	16
2	3b	THF	0	150	25	7
3	4a	THF	0	150	25	24
4	4a	DMSO	0	150	25	25
5	4a	DME	0	150	25	34
6	4a	DMSO/DME = 8:2	0	150	25	44
7	4a	DMSO/DME = 2:8	0	150	25	36
8	4a	DMSO/DME = 2:8	150	150	25	47
9	4b	DMSO/DME = 2:8	150	150	25	19
10	4c	DMSO/DME = 2:8	150	150	25	46
11	5a	DMSO/DME = 2:8	150	150	25	<10
12	6a	DMSO/DME = 2:8	150	150	25	<10
13	4a	DMSO/DME = 2:8	150	100	25	39
14	4b	DMSO/DME = 2:8	150	100	25	65
15	4b	DMSO/DME = 2:8	85	100	25	79
16	4b	DMSO/DME = 2:8	85	100	30	82
17	4a	DMSO/DME = 2:8	85	100	30	39

^aReaction Conditions: *t*BuBr (0.3 mmol, 100 mol %), acid (170 mol %), $\text{Ni}(\text{acac})_2$ (10 mol %), ligand (12 mol %), Boc_2O (200 mol %), Zn (300 mol %), MgCl_2 (100 mol %), solvent (1 mL). ^bGC yields using dodecane as the internal standard (calibrated).

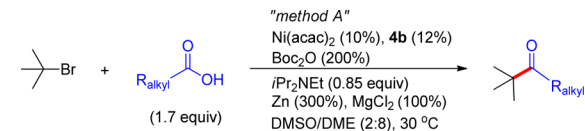


$\text{Ni}(\text{acac})_2$ being the precatalyst, ligand **4a** gave the ketone **2a** in 24% yield in THF, which is superior than **3a** and **3b** (Table 1, entries 1–3). The effects of solvents were next carefully examined. With **4a** as the ligand, DME was slightly better than DMSO (entries 4–5). While a mixture of DMSO/DME in a ratio of 8/2 (v/v) worked better than that of 2/8 (entries 6 and 7), addition of 1.5 equiv of *i*Pr₂NEt to the latter conditions increased the yield to 47% (entry 8). Other ligands, e.g., **4b–c**, **5a**, and **6a** did not yield better results (entries 9–12). Interestingly, whereas reduction of the amount of MgCl_2 from 1.5 to 1 equiv diminished the yield using ligand **4a**

(entries 8 vs 13), the yield was boosted to 65% from 19% when ligand **4b** was employed (entries 9 vs 14). Decrease of *i*Pr₂NEt from 1.5 to 0.85 equiv further enhanced the yield to 79% (entries 15). Raising the temperature from 25 to 30 °C resulted in a slight increase of the yield to 82% (entry 16). With these conditions (*method A*), ligand **4a** turned out to be much less efficient (entry 17).

With the optimized conditions (*method A*, Table 1, entry 16) in hand, a wide set of acids were able to generate good to excellent yields when coupling with *t*Bu-Br as evident in **2a–f**, except that a low yield was obtained for **2g** using a secondary acid. The excellent compatibility of sterically more hindered *tert*-alkyl bromides was illustrated in **7–15** (Table 2). Notably, compound **14** was obtained in high *trans*-diastereomeric selectivity (*trans*-4-acyl/phenyl) from its *cis*-bromo precursor (*cis*-4-bromo/phenyl).²⁹

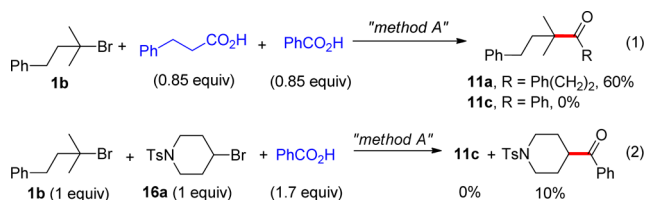
Table 2. Coupling of Unactivated *tert*-Alkyl Bromides with Acids^a



entry	alkyl bromide	alkyl acid	yield (%) ^b
2a	<i>t</i> Bu-Br	3-phenylpropanoic acid	83% ^b
2b	1-bromo-3-methylbutyl	3-phenylpropanoic acid	84% ^b
2c	1-bromo-3-methylbutyl	3-(4-methoxyphenyl)propanoic acid	74% ^b
2d	1-bromo-3-methylbutyl	3-phenylpropanoic acid	66% ^b
2e	1-bromo-3-methylbutyl	3-phenylpropanoic acid	50% ^b
2f	1-bromo-3-methylbutyl	3-phenylpropanoic acid	66% ^b
2g	1-bromo-3-methylbutyl	3-phenylpropanoic acid	40% ^c
7	1-bromo-3-methylbutyl	3-phenylpropanoic acid	60% ^b
8	1-bromo-3-methylbutyl	3-phenylpropanoic acid	45% ^b (52% ^{b,d})
9	1-bromo-3-methylbutyl	3-phenylpropanoic acid	50% ^{c,d}
10	1-bromo-3-methylbutyl	3-phenylpropanoic acid	50% ^c (60% ^{c,d})
11a	1-bromo-3-methylbutyl	3-phenylpropanoic acid	55% ^b
11b	1-bromo-3-methylbutyl	3-phenylpropanoic acid	53% ^c
12	1-bromo-3-methylbutyl	3-phenylpropanoic acid	50% ^b
13	1-bromo-3-methylbutyl	3-phenylpropanoic acid	50% ^c
14	1-bromo-3-methylbutyl	3-phenylpropanoic acid	70% (dr > 99:1) ^{c,e}
15	1-bromo-3-methylbutyl	3-phenylpropanoic acid	57% ^c

^aReaction Conditions (*method A*): *tert*-RBr (0.3 mmol, 100 mol %), acid (170 mol %), $\text{Ni}(\text{acac})_2$ (10 mol %), **4b** (12 mol %), MgCl_2 (100 mol %), *i*Pr₂NEt (85 mol %), Boc_2O (200 mol %), Zn (300 mol %), DMSO/DME (0.2:0.8, v/v, 1 mL). ^bIsolated yield after treatment of an inseparable mixture of product and *t*-butyl alkanoate (arising from Boc_2O) with TFA. ^cIsolated yield. ^d15 mol % of $\text{Ni}(\text{acac})_2$ and 15 mol % of **4b** were used. ^eThe dr for isolated **14** was determined by GC-MS analysis which is different from the crude reaction mixture (dr = 19:1); the relative stereochemistry of **14** was determined by single crystal X-ray diffraction analysis (see Supporting Information).

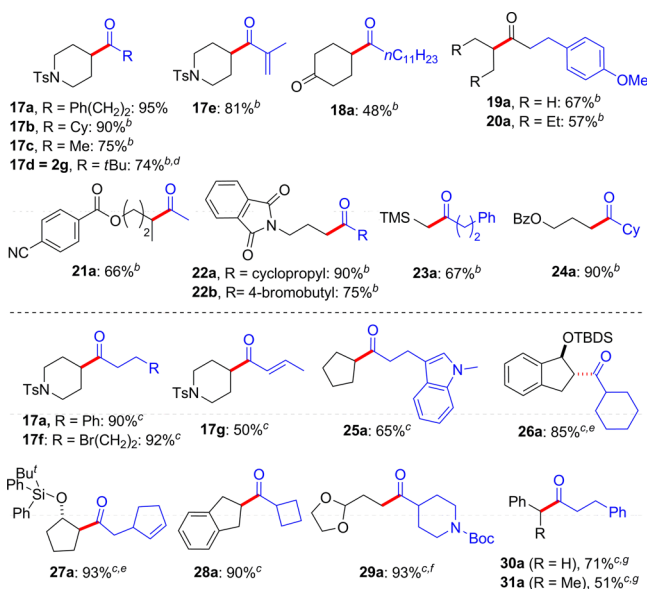
2.2. Coupling of Tertiary Alkyl Halides with Aryl Acids. With *method A* (Table 1, entry 16), coupling of benzoic acid (1.7 equiv) with (3-bromo-3-methylbutyl)benzene **1b** did not generate ketone **11c**, nor did benzoic acid anhydride; the majority of the tertiary halide remains unreacted, while benzoic acid and its anhydride were converted into *tert*-butyl benzoate or decomposed. A control experiment by exposure of equimolar mixture of 3-phenylpropanoic (0.85 equiv) and benzoic acids to **1b** gave ketones **11a** in 60% yield, while **11c** was not detected (eq 1). In addition, reaction of equimolar mixture of **1b** and 4-bromo-1-tosylpiperidine (**16a**) with



benzoic acid only generated 10% yield of the acylation product from the secondary halide, wherein most of **1b** was recovered and **16a** underwent hydrodehalogenation (eq 2). These results suggest that alkyl acids are more efficient than aryl acids for tertiary alkyl halides in the catalytic ketone formation, and secondary alkyl halides appear to be more reactive than the tertiary ones when reacting with benzoic acid.

2.3. Coupling of Primary and Secondary Alkyl Halides with Alkyl Acids. Extension of the conditions for tertiary alkyl bromides (*method A*) to secondary halides proved to be ineffective or not general.^{29,30} Optimization for the reaction of 4-iodo-1-tosylpiperidine (**16b**) with 1.5 equiv of 3-phenylpropanoic acid in the presence of Boc₂O/MgCl₂/Zn indicated that a combination of Ni(acac)₂/**3a** in CH₃CN/THF (v/v = 4:6) at 25 °C gave ketone **17a** in an optimal 95% yield (Table 3, *method B*). Likewise, the bromo-analogue **16a** gave **17a** in a

Table 3. Formation of Ketones from Alkyl Halides^{a,b,c}



^aIsolated yields. ^b*Method B*: Alkyl iodides (0.15 mmol, 100 mol %), acid (150%), Ni(acac)₂ (10 mol %), **3a** (12 mol %), Boc₂O (200 mol %), Zn (300 mol %), MgCl₂ (150 mol %), CH₃CN/THF (v/v = 4:6, 1 mL), 25 °C. ^c*Method C*: same as method B except alkyl bromides, **4a** and DMF/THF (v/v = 2:3, 0.5 mL) at 20 °C. ^d0.5 mL of solvents were used. ^edr > 20:1. ^fBu₄NI (50 mol %) was added, and the reaction was run at 30 °C. ^gBenzylic chlorides were used.

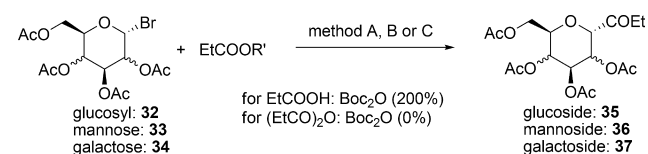
highest 90% yield using ligand **4a** in DMF/THF (v/v = 2:3) at 20 °C, with the initial concentration of **16a** being doubled (Table 3, *method C*).²⁹ The optimized conditions for **16b** was not applicable to **16a**, and vice versa (Supporting Information Table S3, entries 10 and 14).^{29,30}

With *methods B* and *C*, a variety of secondary and primary halides as well as benzylic chlorides were examined and proved to be competent, giving ketones **17b**–**31** in good to excellent yields (Table 3). The primary bromides were inert (e.g., **22b**

and **17f**) but can be activated by addition of Bu₄NI as evident in **29a**. Alkyl halides bearing neighboring groups that are more sterically demanding (e.g., **26a**–**27a**) or vulnerable to β-elimination as in **26a**–**28a**, and acids bearing Boc and conjugate double bond were compatible.

2.4. Application to the Synthesis of C-Glycosides. To showcase the applicability of this work, we extend the reaction conditions to the synthesis of C-acyl glycosides which are an important class of bioactive products or their intermediates.^{18,25,26} To our delight, the coupling of glucosyl bromides **32** with propionic acid and its anhydride (Table 4) using the

Table 4. Coupling of Glycosyl Bromides with Propionic Acid and Anhydride



entry	sugar	RCOOR'	method ^a	yield% ^b (α/β)
1	glucose	(EtCO) ₂ O (2 equiv)	A ^c	not detected
2	glucose	(EtCO) ₂ O (2 equiv)	B ^c	95 (2:1)
3	glucose	(EtCO) ₂ O (2 equiv)	C ^c	90 (3:1) ^d
4	glucose	EtCO ₂ H (1.5 equiv)	B	97 (2.2:1)
5	glucose	EtCO ₂ H (1.5 equiv)	C	82 (2.6:1)
6	glucose	EtCO ₂ H (1.5 equiv)	C1 ^e	99 (2.9:1)
7	glucose	EtCO ₂ H (1.5 equiv)	A	not detected
8	mannose	EtCO ₂ H (1.5 equiv)	B	87 (α)
9	galactose	EtCO ₂ H (1.5 equiv)	B	90 (7.5:1)
10	galactose	EtCO ₂ H (1.5 equiv)	C1 ^e	90 (8.7:1)

^aMethod A as in Table 2, Method B as in Table 3, Method C as in Table 3. ^bIsolated yields (α/β ratio was determined by ¹H NMR). ^cWith no Boc₂O. ^dThis result suffers from poor reproducibility. ^eSame as method C except DMF/CH₃CN = 1:4.

optimized *methods B, C* and *C1* (same as method C except DMF/CH₃CN = 1:4) produced the desired C-acyl glucoside **35** in up to 99% yield with moderate α selectivity (α:β ratio up to 3:1). Method A proved to be ineffective (entries 1–7). With method B and C1, high yields were obtained for mannosyl and galactosyl bromides **33** and **34**, giving **36** in pure α-form and **37** in high α selectivity (α:β = 8.7:1), respectively (entries 8–10).

The generality of the reductive method to C-acyl glycosides was exemplified in Table 5. A variety of alkyl acids were compatible when *method C1* (for glucosyl and galactosyl bromides) and *B* (for mannosyl bromide) were used, generating the corresponding ketones **38**–**46** in good to high yields, while retaining similar α/β ratios to those observed in Table 4.

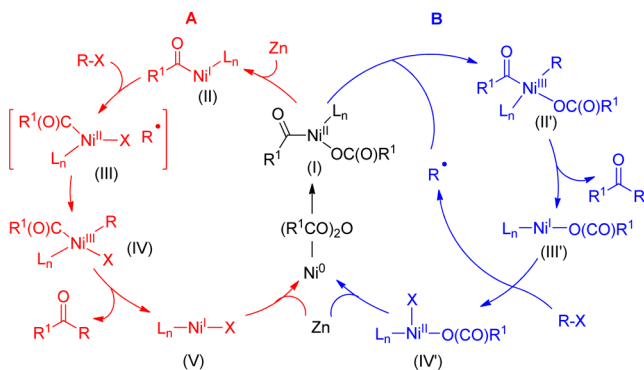
2.5. Radical Chain versus Double Oxidative Addition Mechanism. **2.5.1. Proposed Catalytic Cycles.** A control experiment indicated that 3-phenylpropanoic anhydride worked equally well as acid/Boc₂O when it couples with 2-bromo-2-methylbutane. We reasoned that in situ formation of acid anhydride³¹ followed by oxidative addition to Ni⁰ giving R¹C(O)–Ni^{II}–OC(O)R¹ (**I**) may constitute the first steps of the catalytic process.³² Intermediate **I** may be reduced to R¹C(O)–Ni^I (**II**) which undergoes oxidative addition of alkyl halide leading to a RC(O)Ni^{III}–R_{alkyl} (**IV**), possibly involving rapid combination of an alkyl radical and a Ni^{II} intermediate (**III**) that was generated by reduction of an alkyl halide with Ni^I (**II**) (Scheme 1, cycle A).^{33,34} An alternative radical chain

Table 5. Examples of C-Acyl Glycosides Using Methods B and C1^a

 38 (R = <i>i</i> Pr), 98% (α/β = 2.6:1) ^b	 39 , 99% (α/β = 2.7:1) ^b	 40 , 90% (α/β = 2.8:1) ^b
 41 , 76% (α only) ^c	 42 , 66%, (α only) ^c	 43 , (R' = cyclopropyl), 96% (α/β = 8.5:1) ^b
 44 , 94%, (α/β = 7.5:1) ^b	 45 , 92%, (α/β = 11:1) ^b	 46 , 99%, (α/β = 7.7:1) ^b

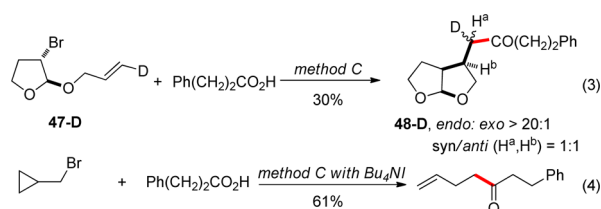
^aIsolated yields (α/β ratio was determined by ¹H NMR). ^bMethod C1: Same as method C except DMF/CH₃CN = 1:4. ^cMethod B.

Scheme 1. Double Oxidative Addition (Cycle A) And Radical Chain Mechanism (Cycle B)



process is possible via combination of an alkyl radical with intermediate **I**, similar to the recent Hu's Ni-catalyzed alkyl Kumada, Weix's reductive arylation and Fu's Negishi mechanisms (Scheme 1, cycle B).³⁵ The alkyl radical can be generated by reaction of alkyl halide with the Ni^I (**III'**) to give the Ni^{II} (**IV'**). Initial generation of intermediate **III'** may arise from halide abstraction of R-X with complex **I** to give R¹C(O)-Ni^{III}(OC(O)R)-X (**V'**), followed by reductive elimination of acyl-X.

2.5.2. Radical Process. The radical nature of the reaction was verified in the reductive cyclization/coupling of **47-D** with 3-phenylpropanoic acid giving *endo*-**48-D** with a 1:1 ratio of *syn/anti* for H^a/H^b (eq 3), as well as the ring opening/coupling of (bromomethyl)cyclopropane with 3-phenylpropanoic acid (eq 4).³⁶



2.5.3. Radical Chain versus Double Oxidative Addition Mechanism. Treatment of Ni(COD)₂ with **4a** and (*i*PrCO)₂O or (*n*PrCO)₂O in Et₂O gave isolatable **I-a** (Figure 2) and **I-b**

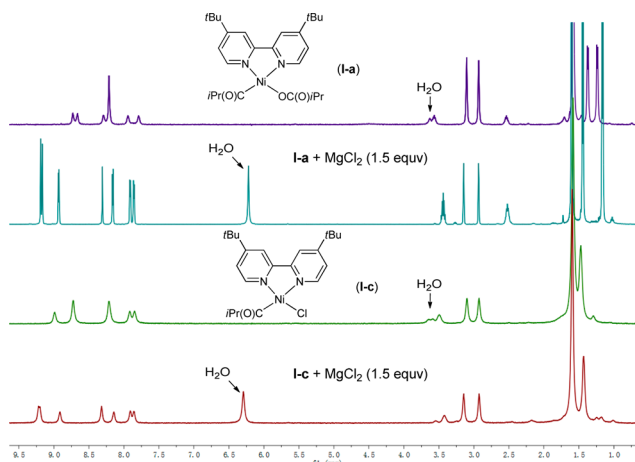
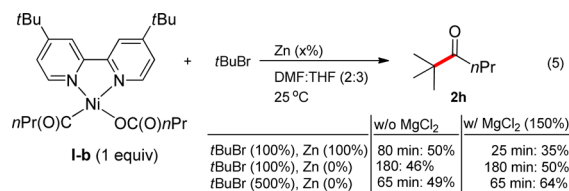


Figure 2. ¹H NMR spectra of **I-a** in DMF without (top) and with MgCl₂, and **I-c** without and with (bottom) MgCl₂.

(eq 5),^{32,37} which are stable in DMF and DMSO, respectively. Without Zn and MgCl₂, tracking the equimolar reaction of



*t*BuBr with **I-b** in DMSO/DME indicated that the reaction went to completion within 180 min, giving **2h** in 46% yield (Supporting Information Figure S7). With 5 equiv of *t*BuBr, the reaction completed much faster, delivering **2h** in 50% yield after 65 min.²⁹ Similar results were also detected for the reactions of **I-a** with **16a** (see Supporting Information Table S4), albeit much slower. The observations that Zn was not needed for the stoichiometric reactions of **I** with R_{alkyl}-X seem to be better explained by a radical chain mechanism (cycle B, Scheme 1), which involves addition of R_{alkyl} radical to **I**.^{35b} Cycle A is less likely as it would require reduction of **I** by Zn to be a key step. When Zn was introduced, the equimolar reactions of **I-b** with *t*BuBr went to completion faster than those without Zn (eq 5). If cycle B operates (Scheme 1), Zn would be unnecessary for the stoichiometric reaction of **I-b** with *t*BuBr except reduction of Ni^{II} complex (**IV'**) to Ni^I or Ni⁰. Generation of R_{alkyl} radicals by these low-valence Ni species is possible, which may in turn accelerate the reaction.^{36c}

Addition of MgCl₂ to the stoichiometric reactions of **I-b** with *t*BuBr without Zn did not seem to affect the yields and completion time as much as those with Zn (eq 5). In contrast, MgCl₂ appears to be indispensable for the catalytic conditions as evident in the coupling of (3-bromo-3-methylbutyl)benzene (**1b**) with Ph(CH₂)₂CO₂H, without which no **11a** formed. One of its key roles seems to be to significantly accelerate the reduction rate of the Ni(II) complexes. Without MgCl₂, most of **I-a** remained untouched after 3 h in the presence of excess Zn in DMF (Supporting Information Figure S2).²⁹ With it, ~80% and ~100% of **I-a** were consumed in DMF and DMF/THF (2:3, v/v) after 1 h, respectively (Supporting Information Figures S3 and S4).²⁹ ¹H NMR studies indicated that a different complex may form upon addition of MgCl₂ to **I-a** in DMF (Figure 2).^{29,38} This may involve Cl⁻/[*i*Pr C(O)O]⁻ anion metathesis and interaction of the resultant *i*PrC(O)-Ni(L_n)Cl

(I-c) intermediate^{29,39} with Mg^{2+} , since addition of MgCl_2 to I-c prepared from oxidative addition of $i\text{PrCOCl}$ to $\text{L}_n\text{-Ni}(0)$ resulted in identical ^1H NMR spectra as that of I-a/ MgCl_2 (Figure 2).^{37,40} It should be noted that reduction of I-c is much faster than I-a in the absence of MgCl_2 (Supporting Information Figure S5), indicating anion metathesis plays an important role in reduction of I-a/ MgCl_2 . However, the role of Mg^{2+} cannot be eliminated, as we also observed that MgCl_2 can markedly enhance the rate of reduction of $\text{L}_n\text{-NiBr}_2$ ($\text{L}_n = \mathbf{4a}$) by Zn. Without MgCl_2 , most of $\text{L}_n\text{-NiBr}_2$ remained intact after 3 h (Supporting Information Figure S6).^{29,40}

The effect of Zn^{2+} which is an in situ generated byproduct was also examined. By addition 1 equiv of ZnCl_2 to the catalytic reaction of $t\text{BuBr}$ with 3-phenylpropanoic acid, the yield of **2a** was comparable to the optimized one (Table 1). Equimolar mixture of ZnCl_2 with I-b in DMSO showed that I-b decomposed within 1 h; however, addition of 1.5 equiv of MgCl_2 significantly suppresses the decomposition,²⁹ suggesting that the effect of Zn^{2+} on the catalytic reactions is not important.

To further differentiate the proposed cycles A and B, a radical clock 6-iodohex-1-ene was examined for the coupling with 3-phenylpropanoic acid by varying the catalyst loading. According to Hu and Weix's studies on the Ni-catalyzed Kumada and reductive coupling processes,^{35a,b} a radical-cage-rebound process in cycle A (namely, rapid combination of alkyl radical with **III**) is accepted if the ratio of **49/50** remains constant, while a radical chain mechanism (namely, addition of alkyl radical to I) should give a linear dependence of the ratio of **49/50** on the catalyst loading. Figure 3 showed that by changing the loading of $\text{Ni}(\text{acac})_2$ from 2.5% to 15%, the ratio of **49/50** increased linearly, which supports the radical chain mechanism in cycle B.

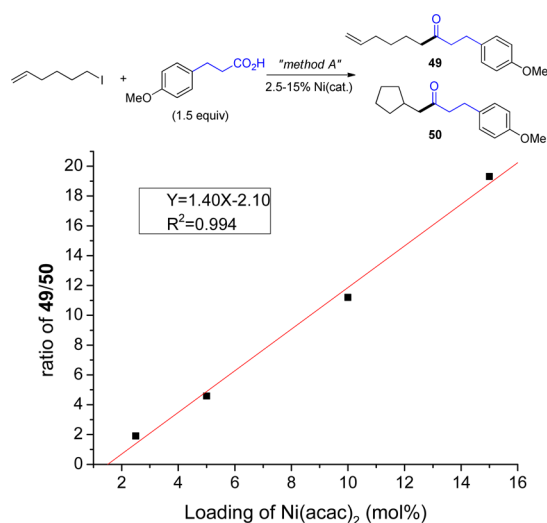


Figure 3. Dependence of the ratio of (**49/50**) on catalyst loading using a radical clock. Each ratio is averaged based on 4 independent runs.

The collective studies appear to favor the catalytic cycle B, although the details of the reaction mechanism require more evidence. For instance, the observation that Zn accelerates the stoichiometric reaction should not be simply attributed to reduction of complex **IV'** to Ni^0 which is significantly enhanced by MgCl_2 . Participation of Zn on promoting the formation of alkyl radicals cannot be excluded.³⁸

3. CONCLUSIONS

In summary, alkyl-alkyl ketones can be efficiently synthesized via Ni-catalyzed reductive coupling of alkyl halides with acids under mild conditions. The reactions accommodate various functional groups. A wide range of acids and alkyl halides are competent, particularly *tertiary* alkyl bromides. The easy-to-operate procedure avoids preparation of organometallic reagents and preactivation of acids, rendering it practical for ketone synthesis. The α -selective synthesis of potentially bioactive C-acyl glycosides is particularly intriguing, as it would otherwise be difficult to achieve using the conventional methods. The indispensable role of MgCl_2 in the catalytic process is evidenced by formation of a new complex with acyl- Ni^{II} (e.g., I-a), which appears to accelerate the reduction of Ni^{II} by Zn. The collective mechanistic studies seem to support a radical chain process proposed in cycle B, although more evidence are required for understanding the details.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization of new compounds. 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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■ REFERENCES

- (1) Coupling of *tertiary* R-MgX catalyzed by Cu: (a) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086. (b) Ren, P.; Stern, L. A.; Hu, X. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 9110. (c) Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, *134*, 11124. Co: (d) Iwasaki, T.; Takagawa, H.; Singh, S. P.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2013**, *135*, 9604.
- (2) Coupling of *tertiary* R-MgX catalyzed by Ni: (a) Lohre, C.; Dröge, T.; Wang, C.; Glorius, F. *Chem.-Eur. J.* **2011**, *17*, 6052. (b) Joshi-Pangu, A.; Wang, C.-Y.; Biscoe, M. R. *J. Am. Chem. Soc.* **2011**, *133*, 8478.
- (3) Coupling of *tertiary* alkyl halides with allylic and benzylic metalics: (a) Ghorai, S. K.; Jin, M.; Hatakeyama, T.; Nakamura, M. *Org. Lett.* **2012**, *14*, 1066. (b) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 969. (c) Mitamura, Y.; Asada, Y.; Murakami, K.; Someya, H.; Yorimitsu, H.; Oshima, K. *Chem.-Asian J.* **2010**, *5*, 1487. (d) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137.
- (4) Coupling of *tert*-alkyl halides with Ar-9BBN: Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624.

- (5) (a) Smith, S. C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 9334. (b) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532. (c) Thaler, T.; Haag, B.; Gavryushin, A.; Schober, K.; Hartmann, E.; Gschwind, R. M.; Zipse, H.; Mayer, P.; Knochel, P. *Nat. Chem.* **2010**, *2*, 125. (d) Joshi-Pangu, A.; Ganesh, M.; Biscoe, M. R. *Org. Lett.* **2011**, *13*, 1218. (e) Li, L.; Wang, C.-Y.; Huang, R.; Biscoe, M. R. *Nat. Chem.* **2013**, *5*, 607. (f) Liu, Z.; Dong, N.; Xu, M.; Sun, Z.; Tu, T. *J. Org. Chem.* **2013**, *78*, 7436.
- (6) For a review on alkyl-organometallics, see: Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.
- (7) Sämman, C.; Dhayalan, V.; Schreiner, P. R.; Knochel, P. *Org. Lett.* **2014**, *16*, 2418.
- (8) For leading reviews on catalytic ketone synthesis, see: (a) Johnson, J. B.; Rovis, T. *Acc. Chem. Res.* **2008**, *41*, 327. (b) Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177.
- (9) For selected examples with alkyl-Zn: (a) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1157. (b) Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1700. Alkyl-Sn: (c) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557. Alkyl-B: (d) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554. Alkyl-Mg: (e) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. Alkyl-Zr: (f) Coia, N.; Mokhtari, N.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2011**, *13*, 6292.
- (10) (a) Johnson, J. B.; Bercot, E. A.; Rowley, J. M.; Coates, G. W.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 2718. (b) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174. (c) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247. (d) Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 15964. (e) Johnson, J. B.; Yu, R. T.; Fink, P.; Bercot, E. A.; Rovis, T. *Org. Lett.* **2006**, *8*, 4307. (f) Kozuch, S.; Lee, S. E.; Shaik, S. *Organometallics* **2009**, *28*, 1303.
- (11) For selected examples of carbonylative coupling of alkyl-nucleophiles: (a) Ishiyama, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1999. (b) Lee, S. W.; Lee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, M.; Lee, P. H. *J. Org. Chem.* **2004**, *69*, 4852. (c) Gøgsig, T. M.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 798.
- (12) Rieke, R. D.; Hanson, M. V.; Brown, J. D. *J. Org. Chem.* **1996**, *61*, 2726.
- (13) For seminal examples and leading reviews on the Ni-catalyzed coupling of alkyl halides, see: (a) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (c) Hu, X. *Chem. Sci.* **2011**, *2*, 1867. (d) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726. (e) Devasagayaram, A.; Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2723. For Ni-catalyzed alkyl halides with CO₂: (f) Liu, Y.; Cornella, J.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 11212.
- (14) For recent reviews on reductive coupling of two electrophiles, see: (a) Knappe, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; von Wangelin, A. *J. Chem.—Eur. J.* **2014**, *20*, 6828. (b) Everson, D. A.; Weix, D. J. *J. Org. Chem.* **2014**, *79*, 4793. (c) Moragas, T.; Correa, A.; Martin, R. *Chem.—Eur. J.* **2014**, *20*, 8242.
- (15) (a) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442. (b) Wotal, A. C.; Weix, D. J. *Org. Lett.* **2012**, *14*, 1476. (c) Amatore, C.; Jutand, A.; Périchon, J.; Rollin, Y. *Monatsh. Chem.* **2000**, *131*, 1293. (d) d'Incan, E.; Sibille, S.; Périchon, J.; Moingeon, M.-O.; Chaussard, J. *Tetrahedron Lett.* **1986**, *27*, 4175. (e) Onaka, M.; Matsuoka, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, *10*, 531.
- (16) (a) Yin, H.; Zhao, C.; You, H.; Lin, Q.; Gong, H. *Chem. Commun.* **2012**, *48*, 7034. (b) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3044. (c) Lu, W.; Liang, Z.; Zhang, Y.; Wu, F.; Qian, Q.; Gong, H. *Synthesis* **2013**, *45*, 2234.
- (17) For recent reviews in C-glycoside biology and biosynthesis, see: (a) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742. (b) Hultin, P. G. *Curr. Top. Med. Chem.* **2005**, *5*, 1299. (c) Zou, W. *Curr. Top. Med. Chem.* **2005**, *5*, 1363. (d) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077. (e) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55.
- (18) Naturally occurring C-acyl-glycosides: (a) Wu, Q.; Cho, J.-G.; Lee, D.-S.; Lee, D.-Y.; Song, N.-Y.; Kim, Y.-C.; Lee, K.-T.; Chung, H.-G.; Choi, M.-S.; Jeong, T.-S.; Ahn, E.-M.; Kim, G.-S.; Baek, N.-I. *Carbohydr. Res.* **2013**, *372*, 9. (b) Disadee, W.; Mahidol, C.; Sahakitpichan, P.; Sitthimonchai, S.; Ruchirawat, S.; Kanchanapoom, T. *Phytochemistry* **2012**, *74*, 115.
- (19) For Ni-catalyzed cross-coupling of glycosyl halides, see: (a) Gong, H.; Sinisi, R.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 1908. (b) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 12177. (c) Gong, H.; Andrews, R. S.; Zuccarello, J. L.; Lee, S. J.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 879.
- (20) Recent α -selective C-glycoside synthesis, Co-catalyzed: Nicolas, L.; Angibaud, P.; Stansfield, I.; Bonnet, P.; Meerpoel, L.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11101.
- (21) Ar₂Mg to glucosyl bromide: Lemaire, S.; Houpi, I. N.; Xiao, T.; Li, J.; Digard, E.; Gozlan, C.; Liu, R.; Gavryushin, A.; Diène, C.; Wang, Y.; Farina, V.; Knochel, P. *Org. Lett.* **2012**, *14*, 1480.
- (22) For a review, see: (a) Somsak, L. *Chem. Rev.* **2001**, *101*, 81. The following glycosyl-metallics are known, but none is involved in catalytic coupling reactions. Glycosyl-Mn: (b) Deshong, P.; Slough, G. A.; Elango, V.; Trainor, G. L. *J. Am. Chem. Soc.* **1985**, *107*, 7788. Glycosyl-Pd: (c) Munro-Leighton, C.; Adduci, L. L.; Becker, J. J.; Gagné, M. R. *Organometallics* **2011**, *30*, 2646. Glycosyl-B: (d) Vasella, A.; Wenger, W.; Rajamannar, T. *Chem. Commun.* **1999**, 2215. Glycosyl-Si: (e) Pedretti, V.; Veyrières, A.; Sinaÿ, P. *Tetrahedron* **1990**, *46*, 77.
- (23) For selected examples of acyl nucleophiles: (a) Obora, Y.; Ogawa, Y.; Imai, Y.; Kawamura, T.; Tsuji, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10489. (b) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094.
- (24) Pd-catalyzed coupling of sugar-Sn with PhCOCl: Belosludtsev, Y. Y.; Bhatt, R. K.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5881.
- (25) Synthesis of β -acyl C-glycosides, from: sugar benzothiazoles (a) Dondoni, A.; Catozzi, N.; Marra, A. *J. Org. Chem.* **2005**, *70*, 9257. Sugar CN: (b) Knapp, S.; Shieh, W.-C.; Jaramillo, C.; Trilles, R. V.; Nandan, S. R. *J. Org. Chem.* **1994**, *59*, 946. Sugar acids: (c) Wolfgang Weiser, W.; Lehmann, J.; Brewer, C. F.; Hehre, E. J. *Carbohydr. Res.* **1988**, *183*, 287.
- (26) Synthesis of α -acyl C-glycosides from: sugar alkyne: (a) Álvarez-Dorta, D.; León, E. I.; Kennedy, A. R.; Riesco-Fagundo, C.; Suárez, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 8917. Sugar allene: (b) Geng, Y.; Kumar, A.; Faiddallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmidt, R. R. *Bioorg. Med. Chem.* **2013**, *21*, 4793. Sugar acyl oxazoline: (c) Jensen, C. M.; Lindsay, K. B.; Taaning, R. H.; Karaffa, J.; Mette Hansen, A.; Skrydstrup, T. *J. Am. Chem. Soc.* **2005**, *127*, 6544. Sugar alkene to α -C-glycosyl acid: (d) Wong, C.-H.; Moris-Varas, F.; Hung, S.-C.; Marron, T.-G.; Lin, C.-C.; Gong, K. W.; Weitz-Schmidt, G. *J. Am. Chem. Soc.* **1997**, *119*, 8152.
- (27) Dimerization of activated tertiary alkyl halides is known: (a) Peng, Y.; Luo, L.; Yan, C.-S.; Zhang, J.-J.; Wang, Y.-W. *J. Org. Chem.* **2013**, *78*, 10960. (b) Wada, M.; Murata, T.; Oikawa, H.; Oguri, H. *Org. Biomol. Chem.* **2014**, *12*, 298.
- (28) (a) Shukla, P.; Hsu, Y.-C.; Cheng, C.-H. *J. Org. Chem.* **2006**, *71*, 655. (b) Keh, C. C. K.; Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 4062.
- (29) See the Supporting Information for details.
- (30) Method A proved to be ineffective for **16b** giving only hydrodehalogenation product. Although **16a** generated **17a** in 90% yield, the yields for other alkyl bromides in Table 3 were generally moderate (see Table S5 in the Supporting Information). Also, extension of methods B and C to *t*-BuBr was not successful. Method B only resulted in a trace amount of **2a**. Method C though provided **2a** in 50% yield; 2-bromo-2-methylhexane did not result in **8**.
- (31) (a) Formation of acid anhydrides via reactions of acids and (Boc)₂O can be promoted by MgCl₂: Bartoli, G.; Bosco, M. *Synthesis* **2007**, *22*, 3489. (b) Suzuki: Gooßen, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3458.
- (32) Oxidative addition of alkyl acid anhydride to bipyridine-Ni⁰ is known, but with no characterization data. (a) Uhlig, E.; Bernd, N. Z.

Chem. **1981**, *21*, 451. (b) Fischer, R.; Walther, D.; Kempe, R.; Sieler, J.; Schonecker, B. *J. Organomet. Chem.* **1993**, *447*, 131.

(33) BnCONi(I) is evidenced in the electrochemical reduction process (ref 15c).

(34) Oxidative addition of alkyl halides to Ni^{I} resulting in Ni^{III} is possible: (a) Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790. (b) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Kononova, T.; Desrochers, P. J.; Pulay, P.; Vicić, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175.

(35) (a) Breitenfeld, J.; Ruiz, J.; Wodrich, M. D.; Hu, X. *J. Am. Chem. Soc.* **2013**, *135*, 12004. (b) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192. (c) Zhao, Y.; Weix, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 48. (d) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433. (e) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437. See also: (f) Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588–16593.

(36) (a) González-Bobes, R.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360. (b) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510. (c) Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. *Org. Lett.* **2011**, *13*, 2138. (d) Xu, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H. *Chem. Sci.* **2013**, *4*, 4022. (e) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012**, *338*, 647.

(37) Although a single crystal X-ray structure is not available, the formation of **I-a** (or $[\text{I-a}]_n$) was evidenced by ^1H , ^{13}C NMR and ICP studies (see the Supporting Information for details).

(38) Complexation of MgCl_2 with organometallic reagents, e.g., PhZnCl , is known to accelerate an oxidative coupling process: Jin, L.; Liu, C.; Liu, J.; Hu, F.; Lan, Y.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B.; Lei, A. *J. Am. Chem. Soc.* **2009**, *131*, 16656.

(39) Very recently, Weix reported a similar synthesis of an alkyl acyl- $\text{Ni(II)}\text{--Cl}$ complex in a THF solution with similar observation that Zn is not necessary but may enhance the reaction rate, see: Wotal, A. C.; Ribson, R. D.; Weix, D. J. *Organometallics* **2014**, *33*, 5874.

(40) MgCl_2 may also enhance the solvent dielectric: McCann, L. C.; Organ, M. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 4386.