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C A A Tertiary A

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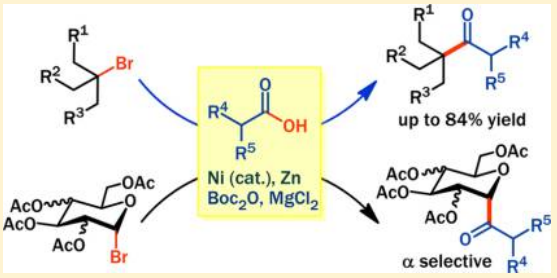
Supporting Information

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.

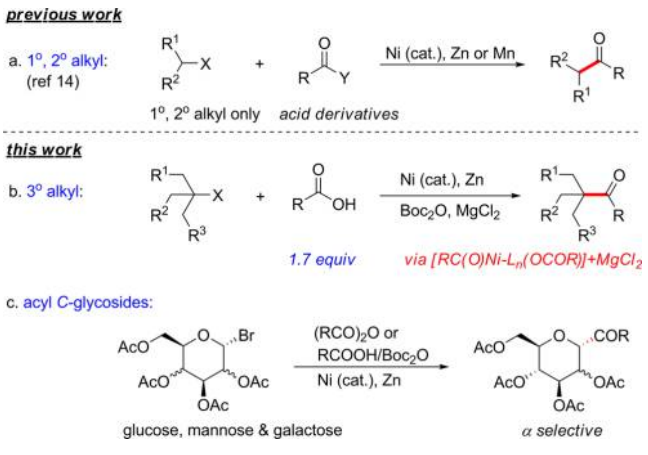


1. D C

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 $C(sp^3)-C(sp^3)$ and $C(sp^3)-C(sp^2)$ 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 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.



. Ni-catalyzed ketone formation via alkyl halides.

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. E A D

2.1. C . Tertiary A A

A . To identify whether alkyl acids and tertiary alkyl halides are competent, the coupling of tBuBr ( ) with 1.7 equiv of 3-phenylpropanoic acid was intensively surveyed in the presence of Boc_2O/Zn and 1.5 equiv of $MgCl_2$ (Table 1).[29] With

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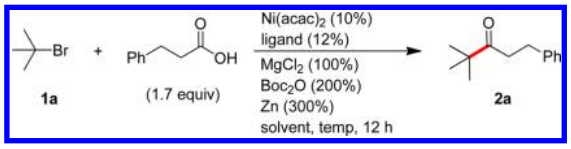
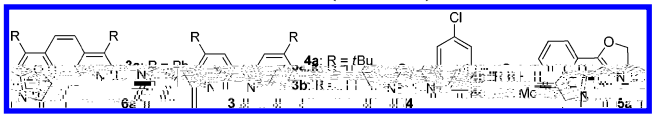


entry	ligand	solvent	iPr_2NEt (%)	$MgCl_2$ (%)	°C	yield (%)[b]
1		THF	0	150	25	16
2		THF	0	150	25	7
3		THF	0	150	25	24
4		DMSO	0	150	25	25
5		DME	0	150	25	34
6		DMSO/DME = 8:2	0	150	25	44
7		DMSO/DME = 2:8	0	150	25	36
8		DMSO/DME = 2:8	150	150	25	47
9		DMSO/DME = 2:8	150	150	25	19
10		DMSO/DME = 2:8	150	150	25	46
11		DMSO/DME = 2:8	150	150	25	<10
12		DMSO/DME = 2:8	150	150	25	<10
13		DMSO/DME = 2:8	150	100	25	39
14		DMSO/DME = 2:8	150	100	25	65
15		DMSO/DME = 2:8	85	100	25	79
		/		//	/	
17		DMSO/DME = 2:8	85	100	30	39

[a]Reaction Conditions: tBuBr (0.3 mmol, 100 mol %), acid (170 mol %), $Ni(acac)_2$ (10 mol %), ligand (12 mol %), Boc_2O (200 mol %), Zn (300 mol %), $MgCl_2$ (100 mol %), solvent (1 mL). [b]GC yields using dodecane as the internal standard (calibrated).



$Ni(acac)_2$ being the precatalyst, ligand gave the ketone in 24% yield in THF, which is superior than and (Table 1, entries 1–3). The effects of solvents were next carefully examined. With 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 iPr_2NEt to the latter conditions increased the yield to 47% (entry 8). Other ligands, e.g., , , and 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 (entries 8 vs 13), the yield was boosted to 65% from 19% when ligand was employed (entries 9 vs 14). Decrease of iPr_2NEt 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 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 tBu-Br as evident in , except that a low yield was obtained for using a secondary acid. The excellent compatibility of sterically more hindered tert-alkyl bromides was illustrated in (Table 2). Notably, compound was obtained in high trans-diaseteromeric selectivity (trans-4-acyl/phenyl) from its cis-bromo precursor (cis-4-bromo/phenyl).[29]

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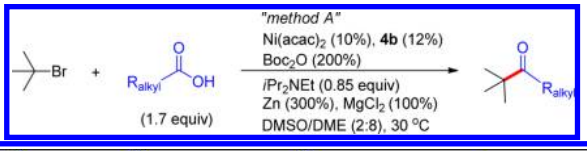

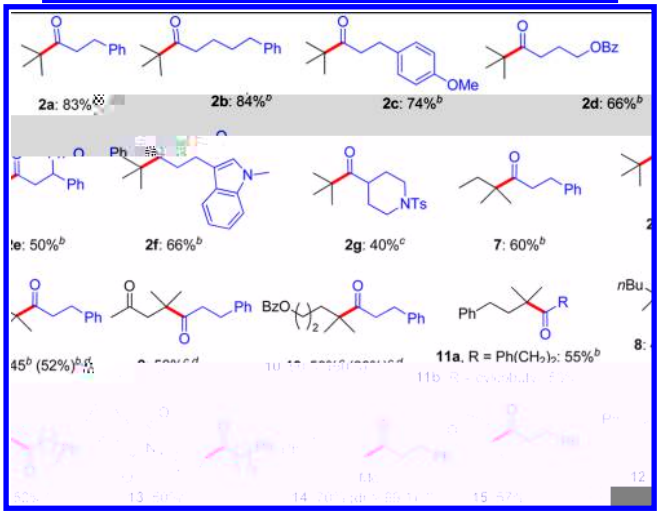

[a]Reaction Conditions (*e h d A*): tert-RBr (0.3 mmol, 100 mol %), acid (170 mol %), $Ni(acac)_2$ (10 mol %), (12 mol %), $MgCl_2$ (100 mol %), iPr_2NEt (85 mol %), Boc_2O (200 mol %), Zn (300 mol %), DMSO/DME (0.2:0.8, v/v, 1 mL). [b]Isolated yield after treatment of an inseparable mixture of product and t-butyl alkanoate (arising from Boc_2O) with TFA. [c]Isolated yield. [d]15 mol % of $Ni(acac)_2$ and 15 mol % of were used. [e]The dr for isolated was determined by GC-MS analysis which is different from the crude reaction mixture (dr = 19:1); the relative stereochemistry of was determined by single crystal X-ray diffraction analysis (see Supporting Information).

2.2. C . Tertiary A A

With method A (Table 1, entry 16), coupling of benzoic acid (1.7 equiv) with (3-bromo-3-methylbutyl)benzene did not generate ketone , 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 gave ketones in 60% yield, while was not detected (eq 1). In addition, reaction of equimolar mixture of and 4-bromo-1-tosylpiperidine ( ) with

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benzoic acid only generated 10% yield of the acylation product from the secondary halide, wherein most of was recovered and 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. C ***Primary*** ***Secondary* A**

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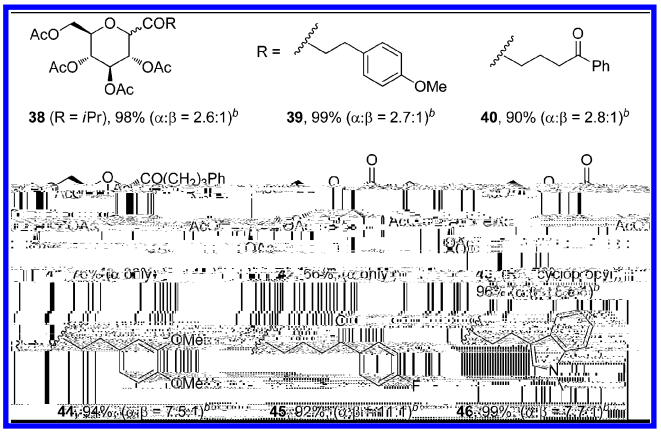

[a]Isolated yields (α/β ratio was determined by ^{1}H NMR). [b]Method C1: Same as method C except DMF/CH_3CN = 1:4. [c]Method B.

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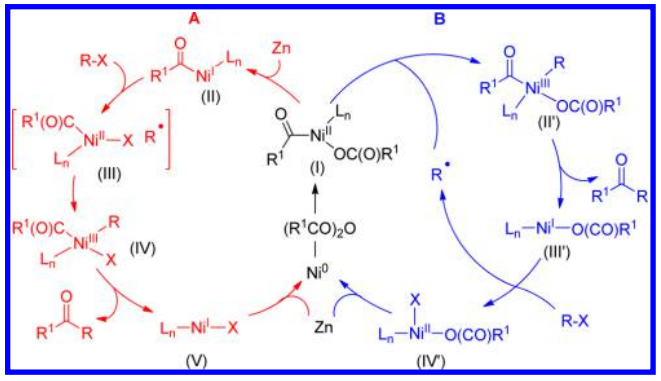
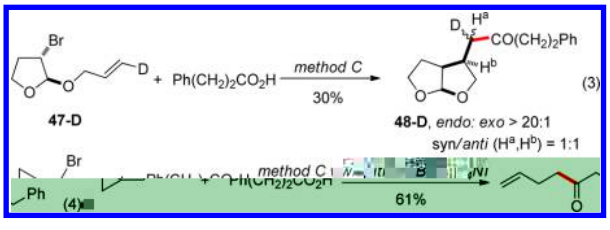
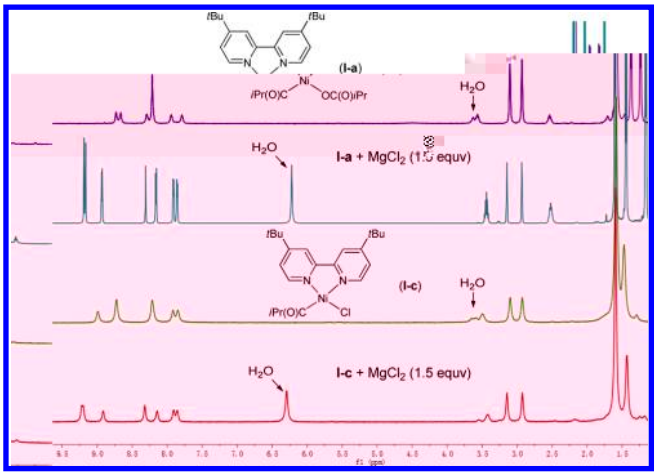


process is possible via combination of an alkyl radical with intermediate , similar to the recent Hu's Ni-catalyzed alkyl Kumada, Weix's reductive arylation and Fu's Negishi mechanisms (Scheme 1, cycle B).[35] The alkyl radical can be generated by reaction of alkyl halide with the Ni^I (′) to give the Ni^{II} (′). Initial generation of intermediate ′ may arise from halide abstraction of R−X with complex to give $R^1C(O)-Ni^{III}(OC(O)R)-X$ (′), 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 , - with 3-phenylpropanoic acid giving endo- 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-phenylpropanic acid (eq 4).[36]

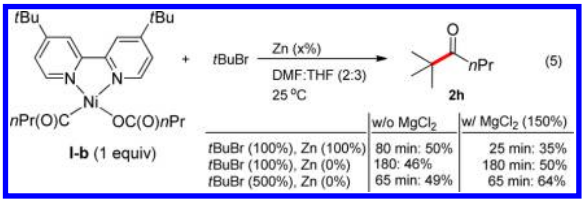


2.5.3. Radical Chain versus Double Oxidative Addition Mechanism. Treatment of $Ni(COD)_2$ with , and $(iPrCO)_2O$ or $(nPrCO)_2O$ in Et_2O gave isolatable - (Figure 2) and -



. ^{1}H NMR spectra of - in DMF without (top) and with $MgCl_2$, and - without and with (bottom) $MgCl_2$.

(eq 5),[32,37] which are stable in DMF and DMSO, respectively. Without Zn and $MgCl_2$, tracking the equimolar reaction of



	w/o $MgCl_2$	w/ $MgCl_2$ (150%)
tBuBr (100%), Zn (100%)	80 min: 50%	25 min: 35%
tBuBr (100%), Zn (0%)	180: 46%	180 min: 50%
tBuBr (500%), Zn (0%)	65 min: 49%	65 min: 64%

tBuBr with - in DMSO/DME indicated that the reaction went to completion within 180 min, giving in 46% yield (Supporting Information Figure S7). With 5 equiv of tBuBr, the reaction completed much faster, delivering in 50% yield after 65 min.[29] Similar results were also detected for the reactions of - with (see Supporting Information Table S4), albeit much slower. The observations that Zn was not needed for the stoichiometric reactions of 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 .[35b] Cycle A is less likely as it would require reduction of by Zn to be a key step. When Zn was introduced, the equimolar reactions of - with tBuBr 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 - with tBuBr except reduction of Ni^{II} complex (IV′) to Ni^I or Ni^0. Generation of R_{alkyl} radicals by these low-valence Ni species is possible, which may in turn accelerate the reaction.[36c]

Addition of $MgCl_2$ to the stoichiometric reactions of - with tBuBr without Zn did not seem to affect the yields and completion time as much as those with Zn (eq 5). In contrast, $MgCl_2$ appears to be indispensable for the catalytic conditions as evident in the coupling of (3-bromo-3-methylbutyl)benzene ( ) with $Ph(CH_2)_2CO_2H$, without which no - formed. One of its key roles seems to be to significantly accelerate the reduction rate of the Ni(II) complexes. Without $MgCl_2$, most of - remained untouched after 3 h in the presence of excess Zn in DMF (Supporting Information Figure S2).[29] With it, ~80% and ~100% of - were consumed in DMF and DMF/THF (2:3, v/v) after 1 h, respectively (Supporting Information Figures S3 and S4).[29] ^{1}H NMR studies indicated that a different complex may form upon addition of $MgCl_2$ to - in DMF (Figure 2).[29,38] This may involve $Cl^-/[iPr\ C(O)O]^-$ anion metathesis and interaction of the resultant $iPrC(O)-Ni(L_n)Cl$

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(-) intermediate[29,39] with Mg^{2+}, since addition of $MgCl_2$ to - prepared from oxidative addition of iPrCOCl to L_n-Ni(0) resulted in identical ^1H NMR spectra as that of - /$MgCl_2$ (Figure 2).[37,40] It should be noted that reduction of - is much faster than - in the absence of $MgCl_2$ (Supporting Information Figure S5), indicating anion metathesis plays an important role in reduction of - /$MgCl_2$. However, the role of Mg^{2+} cannot be eliminated, as we also observed that $MgCl_2$ can markedly enhance the rate of reduction of L_n-$NiBr_2$ (L_n = ,) by Zn. Without $MgCl_2$, most of L_n-$NiBr_2$ 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 tBuBr with 3-phenylpropanoic acid, the yield of - was comparable to the optimized one (Table 1). Equimolar mixture of $ZnCl_2$ with - in DMSO showed that - 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 proceses,[35a,b]

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