

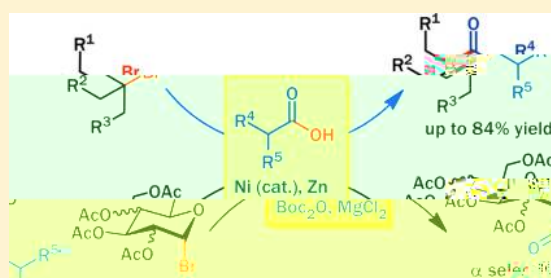
Ni-Catalyzed Reductive Coupling of Alkyl Acids with Unactivated *Tertiary* Alkyl and Glycosyl Halides

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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, α -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, *alkyl*–metallic reagents^{1,2} or *alkyl* electrophiles^{3,4} generally display pronounced difference and challenges as compared to their *aryl* and *alkyl* analogs, which require special and independent attentions. For instance, the recent development of catalytic coupling of unactivated *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 *alkyl*–metallic reagents is very rare.^{7,12} The challenge for the coupling of *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 *alkyl* and *alkyl* halides with other electrophiles including acid derivatives effectively generates $\text{C}(\text{sp}^3)\text{--}\text{C}(\text{sp}^3)$ and $\text{C}(\text{sp}^3)\text{--}\text{C}(\text{sp}^2)$ products (Figure 1),^{13–16} *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;^{16a} Hence, development of reductive ketone synthesis that allows for *alkyl* halides and alkyl acids is important.

In addition, although α -glycosides including α -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 α -aryl

previous work

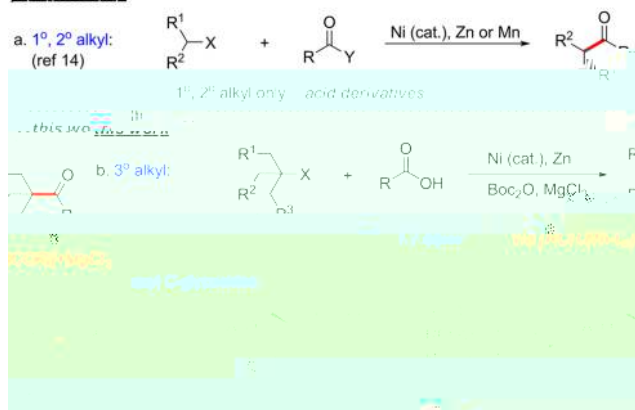


Figure 1. Ni-catalyzed ketone formation via alkyl halides.

and alkyl glycosides,^{19–21} are generally not applicable to α -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 -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 α -acyl glycosides.^{25,26} The development of a general and straightforward method to α -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 *alkyl* and glycosyl halides with alkyl acids using Zn as the reductant (Figure 1). To the best of our knowledge,

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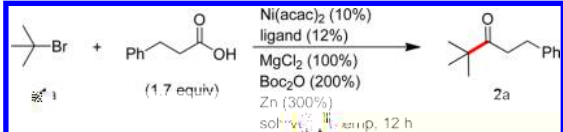
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other than Barbier-type radical addition to carbonyl or activated alkenes.^{27,28} It also represents the first reductive synthesis of α -glycosides via readily available electrophiles featuring α -selectivities. Finally, the initial mechanistic studies seem to support a radical chain mechanism, wherein MgCl_2 accelerates the reduction of the Ni^{II} complexes by Zn.

2. RESULTS AND DISCUSSIONS

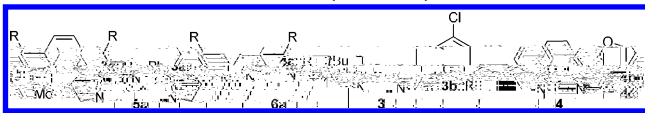
2.1. Coupling of Tertiary Alkyl Halides with Alkyl Acids. To identify whether alkyl acids and tertiary alkyl halides are competent, the coupling of BuBr (1a) with 1.7 equiv of 3-phenylpropanoic acid was intensively surveyed in the presence of $\text{Boc}_2\text{O}/\text{Zn}$ and 1.5 equiv of MgCl_2 (Table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

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



entry	ligand	solvent	Pr_2NEt (%)	MgCl_2 (%)	$^\circ\text{C}$	yield (%)
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

Reaction Conditions: 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). GC yields using dodecane as the internal standard (calibrated).

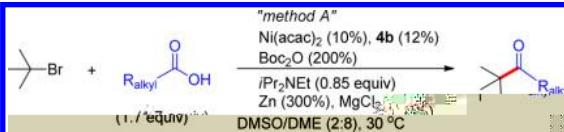


$\text{Ni}(\text{acac})_2$ being the precatalyst, ligand 4a gave the ketone 2a in 24% yield in THF, which is superior than 3a and 3b (Table 1, entries 1–3). The effects of solvents were next carefully examined. With 4a as the ligand, DME was slightly better than DMSO (entries 4–5). While a mixture of 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 Pr_2NEt 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 Pr_2NEt from 1.5 to 0.85 equiv further enhanced the yield to 79% (entries 15). Raising the temperature from 25 to 30 $^\circ\text{C}$ resulted in a slight increase of the yield to 82% (entry 16). With these conditions (entry 16), ligand 4a turned out to be much less efficient (entry 17).

With the optimized conditions (entry 16, Table 1, entry 16) in hand, a wide set of acids were able to generate good to excellent yields when coupling with BuBr 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 α -alkyl bromides was illustrated in 7–15 (Table 2). Notably, compound 14 was obtained in high α -diaseteromeric selectivity (α -4-acyl/phenyl) from its α -bromo precursor (α -4-bromo/phenyl).²⁹

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



entry	ligand	solvent	Pr_2NEt (%)	MgCl_2 (%)	$^\circ\text{C}$	yield (%)
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
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16	4b	DMSO/DME = 2:8	85	100	30	82
17	4a	DMSO/DME = 2:8	85	100	30	39

Reaction Conditions (entry 16): BuBr (0.3 mmol, 100 mol %), acid (170 mol %), $\text{Ni}(\text{acac})_2$ (10 mol %), 4b (12 mol %), MgCl_2 (100 mol %), Pr_2NEt (85 mol %), Boc_2O (200 mol %), Zn (300 mol %), DMSO/DME (0.2:0.8, v/v, 1 mL). Isolated yield after treatment of an inseparable mixture of product and butyl alkanoate (arising from Boc_2O) with TFA. Isolated yield: 15 mol % of $\text{Ni}(\text{acac})_2$ and 15 mol % of 4b were used. The 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 entry 16 (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 α -butyl benzoate or decomposed. A control experiment by exposure of equimolar mixture of 3-phenylpropanoic (0.85 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 alkyl halides in the catalytic ketone formation, and alkyl halides appear to be more reactive than the aryl ones when reacting with benzoic acid.

2.3. Coupling of **Primary** and **Secondary** Alkyl Halides

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}4jsTm.0/F9TmgC8S428(117Tm15726R269.4614Tm.015414TD0TcJII edoweed0328Tc9986.[(gended)-9(u)10Tvh

(I-c) intermediate^{29,39} with Mg^{2+} , since addition of MgCl_2 to I-c prepared from oxidative addition of PrCOCl to L-Ni(0) resulted in identical ^1H NMR spectra as that of I-a/ MgCl_2

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(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).

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