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

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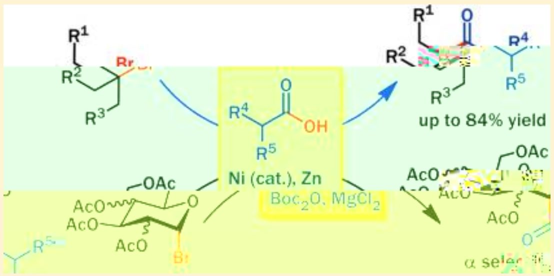
Ⓢ *Supporting Information*

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

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

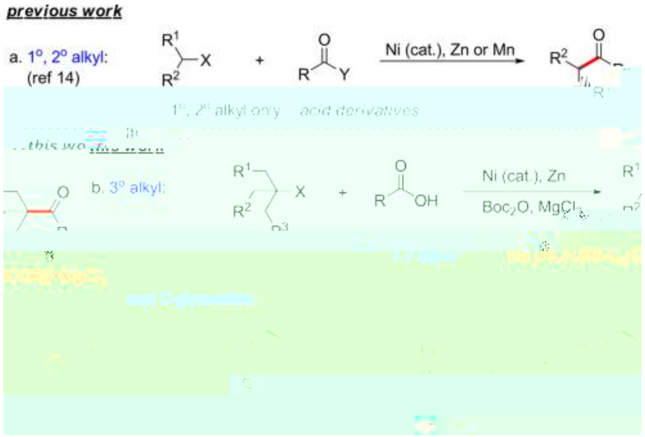


Figure 1. Ni-catalyzed ketone formation via alkyl halides.

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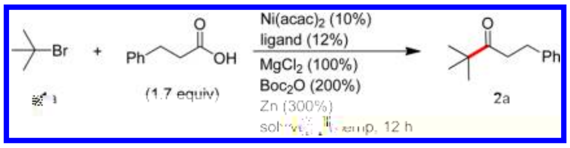
demonstrates the first construction of all carbon quaternary centers via the reductive coupling of unactivated tertiary alkyl halides with a second electrophile other than Barbier-type radical addition to carbonyl or activated alkenes.[27,28] It also represents the first reductive synthesis of C-glycosides 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 DISSCUSIONS

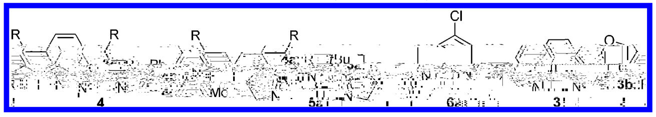
2.1. Coupling of *Tertiary* Alkyl Halides with Alkyl Acids. To identify whether alkyl acids and tertiary alkyl halides are competent, the coupling of tBuBr (1a) with 1.7 equiv of 3-phenylpropanoic acid was intensively surveyed in the presence of Boc_2O/Zn and 1.5 equiv of $MgCl_2$ (Table 1).[29] With $Ni(acac)_2$ 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 iPr_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 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 4a turned out to be much less efficient (entry 17).

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



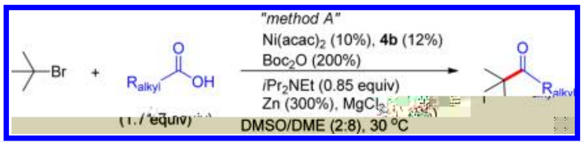
entry	ligand	solvent	iPr_2NEt (%)	$MgCl_2$ (%)	°C	yield (%)[b]
1	3a	THF	0	150	25	16
2	3b	THF	0	150	25	7
3	4a	THF	0	150	25	24
4	4a	DMSO	0	150	25	25
5	4a	DME	0	150	25	34
6	4a	DMSO/DME = 8:2	0	150	25	44
7	4a	DMSO/DME = 2:8	0	150	25	36
8	4a	DMSO/DME = 2:8	150	150	25	47
9	4b	DMSO/DME = 2:8	150	150	25	19
10	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

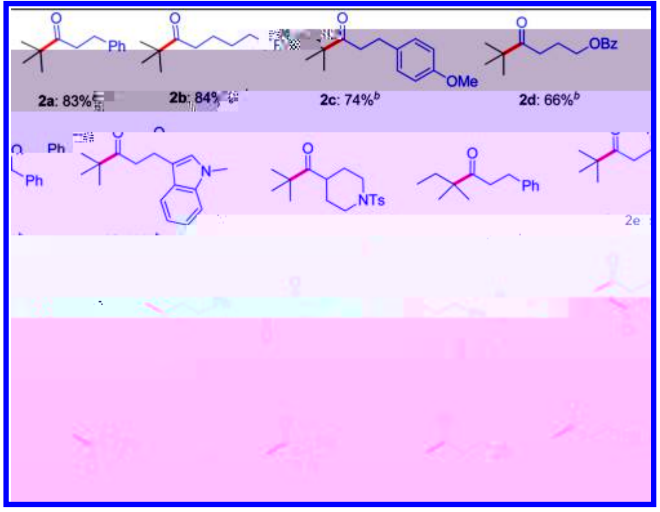
[a] Reaction Conditions: tBuBr (0.3 mmol, 100 mol %), acid (170 mol %), $Ni(acac)_2$ (10 mol %), ligand (12 mol %), Boc_2O (200 mol %), Zn (300 mol %), $MgCl_2$ (100 mol %), solvent (1 mL). [b] GC yields using dodecane as the internal standard (calibrated).



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 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-diaseteromeric selectivity (trans-4-acyl/phenyl) from its cis-bromo precursor (cis-4-bromo/phenyl).[29]

Table 2. Coupling of Unactivated *e* -Alkyl Bromides with Acids[a]





[a] Reaction Conditions (*e h d A*): tert-RBr (0.3 mmol, 100 mol %), acid (170 mol %), $Ni(acac)_2$ (10 mol %), 4b (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 4b were used. [e] 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 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 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***

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 $\mathrm{Ni^{I}}$ (III′) to give the $\mathrm{Ni^{II}}$ (IV′). Initial generation of intermediate III′ may arise from halide abstraction of R−X with complex I to give $\mathrm{R^{1}C(O)-Ni}^{\text{IIIl4jsTm.0/F9TmgC8S428(117Tm15726R269.4614Tm.015414TD0Tc)III edoweed0328Tc9986.[(gended)-9(u)10Tvih}}$

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

(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

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.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, 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-Ni(II)−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.