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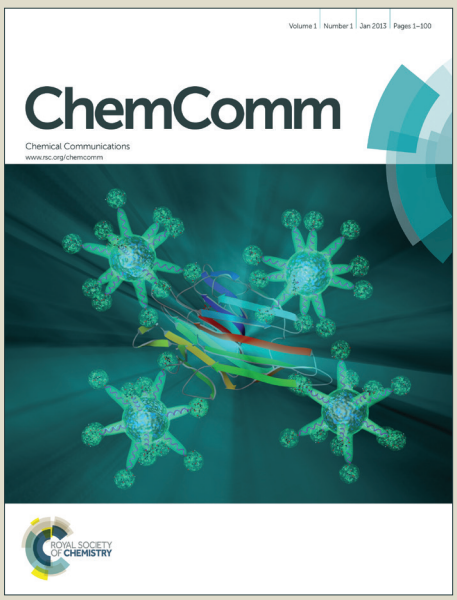

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Alkyl-Aryl Ketone Synthesis via Nickel-Catalyzed Reductive Coupling of Alkyl Halides with Aryl Acids and Anhydrides†

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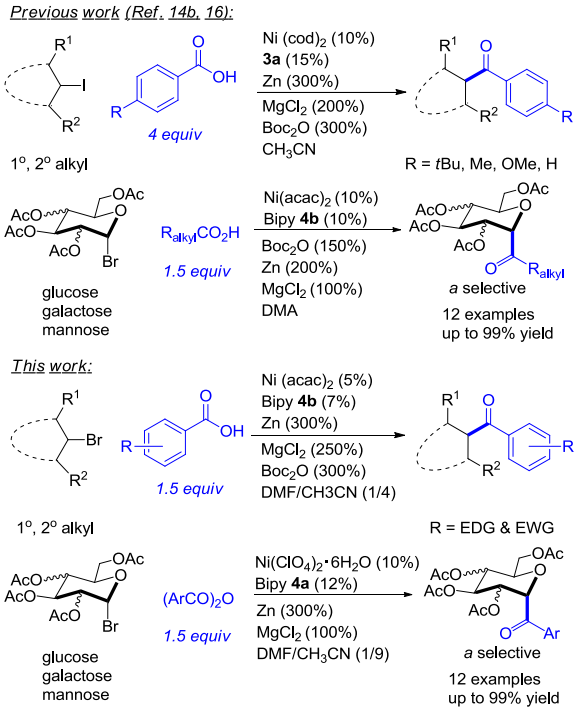
The present work disclosed a much improved method for the construction of alkyl–aryl ketones by direct coupling of unactivated alkyl bromides with 1.5 equiv of acids. In addition, the synthesis of aroyl C-glycosides was first achieved by reductive coupling of 1-glycosyl bromides with acid derivatives, which may otherwise require multi-step synthesis.

Construction of ketones is conventionally achieved by addition of organo nucleophiles to acid derivatives.[1] However, over addition of the organo nucleophiles to the resultant ketones can be problematic, and hence requires special conditions e.g., low temperature, or special acid derivatives.[2] To avoid this issue, mild catalytic ketone synthesis has been well-established which generally involves the coupling of organometallic reagents with acid derivatives.[3-6] However, preparation of alkyl organometallics, particularly those bearing β-functional groups often suffers β-elimination issues.[7-8]

Reductive coupling of alkyl halides with a variety of other electrophiles has led to facile construction of a number of C(sp^3)–C(sp^3) and C(sp^3)–C(sp^2) bonds.[9-16] The formation of alkyl ketones, for example, can now be efficiently achieved when coupling of alkyl halides with acid chlorides, anhydrides and in situ activated acids in the presence of $MgCl_2$ and Boc_2O.[14, 15b, 16] Direct coupling of alkyl halides with acids is particularly intriguing as both electrophiles are readily available, which avoids pre-preparation of alkyl nucleophiles and acid derivatives. Recently, we have demonstrated that the most challenging tertiary alkyl bromides can effectively couple with in situ activated alkyl acids.[16] Extension of this protocol to the α-selective synthesis of alkanoyl *C*-glycosides is also satisfactory (Figure 1).[16] However, the previous conditions for alkyl acids or their anhydrides were not applicable to aryl acids and their derivatives, possibly due to unmatched reactivities of alkyl halides with in situ formed aryl acid anhydrides.[16]



Scheme 1. Methods to ketones by the coupling of alkyl halides with acids

Although our early studies disclosed that the coupling of unactivated primary and secondary alkyl iodides react with 4 equiv of aryl acids with a narrow range of substrate scope,[14b] in general low to moderate yields were obtained except for 4-H- and 4-*t*Bu-substituted benzoic acids. In the present work, we describe a much improved process for the coupling of unactivated alkyl bromides with in situ activated acids by formation of acid anhydrides in the presence of Boc_2O and $MgCl_2$. The reaction conditions allow use of 1.5 equiv of acids in excess. In addition, the coupling strategy can be extended to efficient coupling of glycosyl bromides with aryl acid derivatives, particularly anhydrides to generate α-selective aroyl C-glycosides, which may require multistep synthesis due to the challenges of coupling with classic glycosyl and acyl nucleophiles.[17-19]

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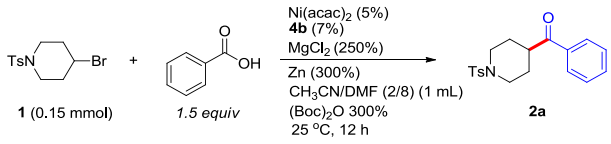
At the outset, we chose 4-bromo-1-tosylpiperidine **1a** and 1.5 equiv of benzoic acid as the model substrates. Under the previously developed reaction conditions for the coupling of alkyl halides with alkyl acids,[16] and alkyl iodides with 4 equiv of aryl acids,[14b] the ketone product **2** was obtained in very low yields. With significant amount of optimization efforts, we eventually identified that a combination of $Ni(acac)_2$/**4b**/DMF in the presence of $MgCl_2$ and Boc_2O in CH_3CN/DMF (1/4) enabled the reaction to generate **2** in 88% yield at ambient temperature (Table 1, entry 1). The amount of Ni precatalyst loading was reduced to only 5% as opposed to 10% in the previous conditions for the coupling of alkyl iodides with aryl acids using air sensitive $Ni(COD)_2$.[14b] Other ligands (entries 2–10), nickel sources (entries 11–14) and solvents (15–19) were inferior. A mixture of CH_3CN and DMF in a ratio of 2/8 proved to be optimal which is more efficient than any of the single solvent (entries 16 and 18). In general, the major side reaction comprised of hydrodehalogenation reduction of **1**.

With the optimized conditions in hand, a wide set of alkyl bromides and aryl acids was examined (Figure 2). The coupling of variety of para-substituted aryl acids with **1** disclosed that the electron-rich aryl rings were generally more effective than electron-poor ones, as evident in **2b–k**. While acids containing alkyl, chloro, fluoro and methoxyl groups generated ketones in good to high yields, the electron deficient acids bearing CF_3 and CO_2Me produced the ketones **2f** and **2g** in low yields. Under the present method the yield for **2k** was 58%, which is enhanced from 40% under the previous method for the coupling of 4-iodo-1-tosylpiperidine **1b** with 4 equiv of aryl acid. Other secondary alkyl bromides bearing functional groups such as ester, ether, amide and silyl ethers proved to be effective as evident in **8–17**. More sterically demanding TBS group in the neighboring positions also gave the ketone products **16** and **17** in excellent yields with high diasteroselectivities. The alkyl bromides without functionality such as cyclohexyl bromide and isopropyl bromide produced the ketones **18** and **19** in low yields which is much less effective than the previous methods using iodo alkanes with 4 equiv of acids.[14b] However, under the conditions developed for 1-glycosyl bromides (Figure 3, vide infra), the unfunctionalized iodo substrates effectively coupled with 1.5 equiv of aryl acids.

Table 1. Optimization for the cyclization of 1a



1 (0.15 mmol) 1.5 equiv 2a

entr[a]	variation from the "standard" conditions	Yield (%)[b]
1	none	88
2	**3a**, instead of **4b**	22
3	**3b**, instead of **4b**	27
4	**3c**, instead of **4b**	23
5	**4a**, instead of **4b**	47
6	**4c**, instead of **4b**	53
7	**5a**, instead of**4b**	71
8	**5b**, instead of **4b**	14
9	**5c**,instead of **4b**	23
10	**6**, instead of **4b**	17
11	$Ni(cod)_2$, instead of $Ni(acac)_2$	70
12	$NiBr_2$, instead of $Ni(acac)_2$	62
13	$NiCl_2$, instead of $Ni(acac)_2$	ND[c]
14	NiI_2, instead of $Ni(acac)_2$	59
15	DMF, instead of CH_3CN/DMF 0.2/0.8	63
16	DMA, instead of CH_3CN/DMF 0.2/0.8	38
17	THF, instead of CH_3CN/DMF 0.2/0.8	20
18	CH_3CN, instead of CH_3CN/DMF 0.2/0.8	16
19	DME/DMF 0.2/0.8 , instead of CH_3CN/DMF 0.2/0.8	77

[a] Reaction Conditions: 1a (0.15 mmol), $Ni(acac)_2$ (5 mol %), Zn (300 mol %), $MgCl_2$ (250 mol %) Ligand (7 mol %), CH_3CN/DMF 1/4 (1 mL), 25 °C. [b] Isolated yields. [c] Not detected.

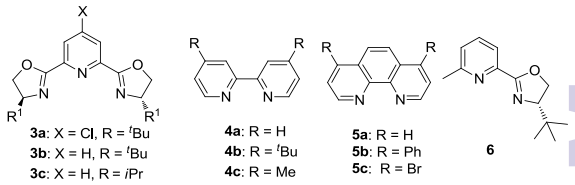


Figure 1. Structures of ligands

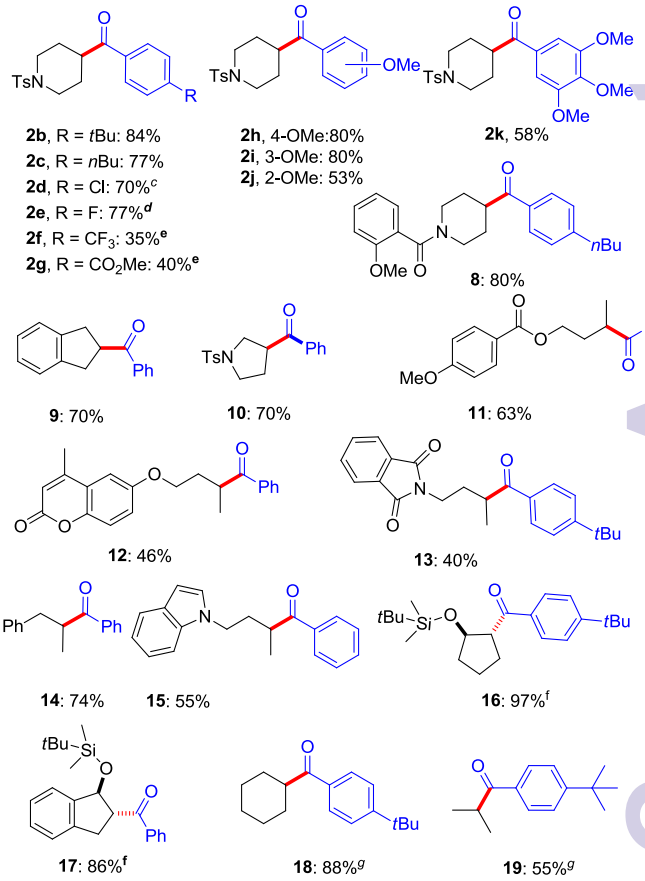


Figure 2. (a) Same as Table 1, entry 1. (b) Isolated yields. (c) DME/DMF = 1/9 (1 mL). (d) CN_3CN/DMF (4/1, 0.5 mL). (e) 10% $Ni(acac)_2$ and 15% **4b** were used. (f) dr > 20:1 (g) Alkyl iodide (0.3 mmol) was used under the reaction conditions in Table 2, entry 1 except CN_3CN/DMF (4/1, 1 mL).

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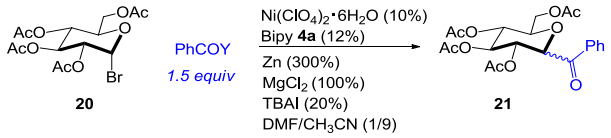
Encouraged by the success in the efficient coupling of aryl acids with alkyl bromides, we then extended the optimized reaction conditions to the coupling of glucosyl bromide with benzoic acid. However, even with 10% $Ni(acac)_2$, only trace amount of the desired ketone was obtained (Table 2, entry 1 and Table S3, entry 1).[20] By addition of 20% of Bu_4NI (TBAI), the ketone product **21** was obtained in 47% with an α/β ratio of 2.8:1 (entry 2). While changes of ligands or the acid derivative to PhCOCl did not yield better results (Table 2, entries 3–5), optimization using benzoic acid anhydride in CH_3CN with ligand **5a** was able to generate **21** in 62% yield, although the α selectivity slightly dropped (Table 2, entries 6–8). Use of a mixture of solvent CH_3CN/DMF in a ratio of 4:1 with ligand 4a increased the yield to 68% (Table 2, entries 9–10). Replacement of $Ni(acac)_2$ with $Ni(ClO_4)_2{\cdot}6H_2O$ further enhance the yield to 74%. Finally, CH_3CN/DMF in a ratio of 9:1 gave the product in a highest 92% yield with an α/β ratio of 2.7:1.

The scope and limitation of acyl C-glycoside formation was next examined. When coupling with glucosyl bromides, the electron-rich aryl acid anhydrides generally gave ketones in high yields with moderate α selectivities as evident in **22–26**. The reaction conditions also tolerate 2-furyl acid chloride, although a low coupling yield for was observed.[21] The formation of acyl galactosides displayed high coupling efficiency as evident in **27–31** with higher α selectivities than glucosides. Finally, mannoside **32** with only α anomer was also successfully obtained. The low yield for **32** was due to rapid E-2 elimination during silica column chromatography.

Table 2. Optimization for benzoylation of glucosyl bromides



entry[a]	PhCOY	Ni/ligand/additive	CH_3CN /DMF	yield% (α:β)[b]
1[c]	PhCOOH	$Ni(acac)_2$/**4b**/none	4:1	trace (NA)
2[c]	PhCOOH	$Ni(acac)_2$/**4b**/TBAI	4:1	47 (2.8:1)
3[c]	PhCOOH	$Ni(acac)_2$/**4a**/TBAI	4:1	28 (2.1:1)
4	PhCOCl	$NiBr_2$·diglyme/**4a**/ TBAI	CH_3CN	33 (3.6:1)
5	PhCOCl	$NiBr_2$·diglyme/**3c**/ TBAI	CH_3CN	45 (2.8:1)
6	$(PhCO)_2O$	$Ni(acac)_2$/**4b**/TBAI	CH_3CN	25 (7:1)
7	$(PhCO)_2O$	$Ni(acac)_2$/**4a**/TBAI	CH_3CN	37 (4.3:1)
8	$(PhCO)_2O$	$Ni(acac)_2$/**5a**/TBAI	CH_3CN	62 (2.4:1)
9	$(PhCO)_2O$	$Ni(acac)_2$/**5a**/TBAI	4:1	59 (2.5:1)
10	$(PhCO)_2O$	$Ni(acac)_2$/**4a**/TBAI	4:1	68 (3.2:1)
11	$(PhCO)_2O$	$Ni(ClO_4)_2{\cdot}6H_2O$/**4a** /TBAI	4:1	74 **(3.1:1)**
12	**$(PhCO)_2O$**	**$Ni(ClO_4)_2{\cdot}6H_2O$/4a /TBAI**	**9:1**	**92(2.7:1)[d]**

[a] Reaction Conditions: **20** (0.3 mmol), $Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol %), Zn (300 mol %), ligand (12 mol %), TBAI (20 mol %), CN_3CN/DMF (9/1,1 mL), 25 °C. [b] NMR yield using trimethyl(phenyl)silane as the internal standard. [c] Boc_2O (300% was added. [d] Isolated yields.

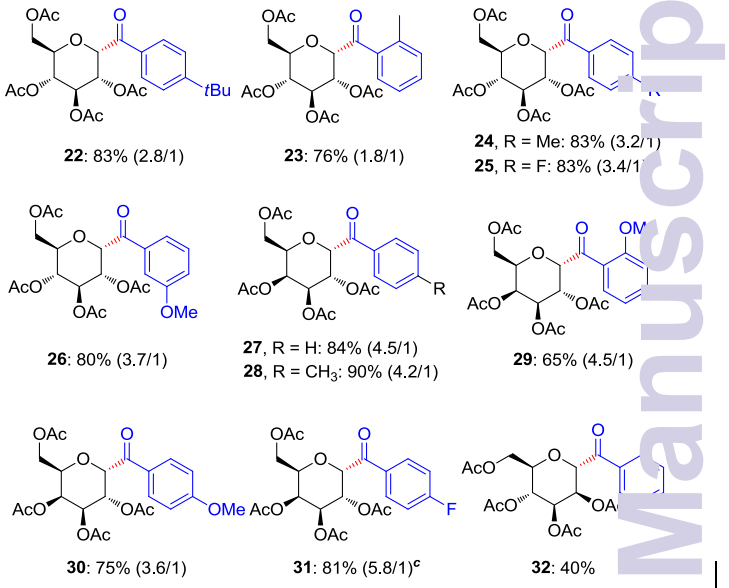


Figure 3. (a) Reaction conditions: same as Table 2, entry 12. (b) Isolated yields. (c) $Ni(acac)_2$ (10 mol %), Ligand (**4b**, 12 mol %), CH_3CN/DMF 4/1 (1 mL).

In conclusion, we have described the coupling of aryl acids with unactivated alkyl bromides which displayed much higher coupling efficiency than the previous conditions for the coupling with alkyl iodides by significantly reducing the catalyst and acid loading. The use of easy-to-handle $Ni(acac)_2$ renders this method more practical for the synthesis of secondary alkyl aryl ketones. The first efficient synthesis of aroyl *C*-glycosides by direct reductive coupling of glycosyl bromides with acid derivatives provided a rapid access to the construction of C-C bonds on carbohydrates, which may find applications to the synthesis of bioactivally relevant compounds.

Acknowledgement

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20 See the Supporting Information for details.

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