Letter

Kumada Arylation of Secondary Amides Enabled by Chromium Catalysis for Unsymmetrical Ketone Synthesis Under Mild Conditions

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Kumada Arylation of Secondary Amides Enabled by Chromium Catalysis for Unsymmetrical Ketone Synthesis Under Mild Conditions

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ABSTRACT: The synthesis of aromatic ketones by chromium-catalyzed Kumada arylation of secondary amides with organomagnesium reagents is described. This reaction was enabled by using low-cost chromium(III) salt as precatalyst combined with trimethylsilyl chloride as additive, and presents a rare example of catalytic transformation of secondary amides to ketones at room temperature. It was shown that catalytically active low-valent chromium species might be responsible for the amide–ketone exchange by mechanism involving the activation of benzimidate intermediate.

KEYWORDS: *chromium, homogeneous catalysis, Kumada reaction, amides, ketones*

Transition metal-catalyzed coupling reactions are one of the most powerful tools in synthetic chemistry.[1,2] Among the numerous named reactions, Kumada coupling reaction has emerged as a useful strategy to form ubiquitous C–C bonds by catalytic assembly of two molecule fragments.[3,4] Conventional methods for Kumada reaction include the use of electrophiles such as organic halides and pseudohalides to couple with organomagnesium reagents.[5–10] In contrast, other electrophilic reagents such as commercially available amides have rarely not been used as reactants for transition metal-catalyzed Kumada-type reaction by treatment with Grignard reagents.[11] This reaction would form acylative C–C bonds in providing access to ketone compounds that are important structural motifs found in pharmaceuticals, fragrances, bioactive molecules, and organic materials.[12–16] Because of the competitive over-addition of Grignard reagents to ketones in facilely giving alcohol byproducts,[17] selectivity in the construction of ketone motifs by Kumada-type reaction of amides remains an issue.[18] To overcome the over-addition obstacle, we questioned whether it's possible to develop new catalytic protocol using amide to react with organomagnesium reagent in the formation of a masked intermediate, which may provide access to the ketone product upon work up with hydrolysis.

Recently, the transformation of amides to ketones by transition metal catalysis has been described with cross-coupling reactions.[19] Garg and Szostak achieved the Suzuki-Miyaura cross-coupling,[20,21] Mizoroki-Heck cyclizations,[22] and Negishi reactions[23] of amides with nickel catalysis (Figure 1a).[24] The palladium-catalyzed examples have been disclosed by the groups of Szostak[25–28] and Zou.[29] These conversion usually used tertiary amides containing substituent of *N*-Boc or Ts group to react with organoboron and organozinc reagents. To our knowledge, there have no report of the catalytic synthesis of ketones by using relatively simple, widely accessible secondary amides as substrates, despite that Charette demonstrated that secondary amides could be converted to

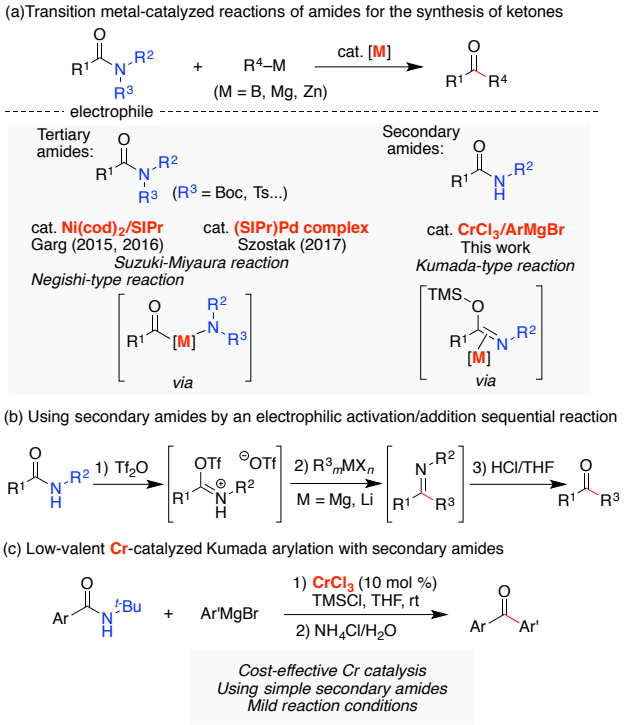


Figure 1. (a) Transition-metal-catalyzed reactions of amides for ketone synthesis. (b) Using secondary amides as reactants. (c) Chromium-catalyzed Kumada arylation with secondary amides.

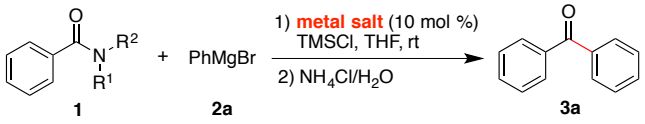
ketone compounds by an activation/addition sequential reaction with three-step operation (Figure 1b).[30] Herein, we report a chromium-catalyzed Kumada arylation using secondary amides for the construction of arylative C–C bonds at room temperature (Figure 1c).[31–42] This reaction was promoted by low-cost chromium salt combined with trimethylsilyl chloride (TMSCl) as additive, allowing for the catalytic synthesis of unsymmetrical aromatic ketone motifs upon hy-

drolysis in the work-up procedure, without giving the adducts of Grignard reagents to ketones.

We commenced our investigation by exploring the effect of *N*-substituent of benzamide (**1**) on the reaction with PhMgBr (Table 1). In the presence of 10 mol % of $CrCl_3$ and 2 equivalents of TMSCl, the arylative C–C bond formation reaction using *N*-methylbenzamide did not take place (entry 1). Gratifyingly, variation of methyl to phenyl in the nitrogen substituent of benzamide allowed the reaction proceeding smoothly, giving the benzophenone product **3a** in 37% yield upon hydrolysis (entry 2). The conversion was largely increased when incorporation of bulky *tert*-butyl group into the nitrogen scaffold of secondary amide, the formation of **3a** in 91% yield was observed (entry 4). Similar result was obtained using $CrCl_2$ salt in the reaction (entry 6). In the absence of chromium salt, the Kumada arylation did not take place (entry 7). Other transition metal catalysts, including $NiCl_2$, $CoCl_2$, $CuCl_2$ and $PdCl_2$, cannot promote the transformation of secondary amide to ketone (entries 8–11). In addition, common Lewis acid catalysts such as $FeCl_3$ and $AlCl_3$ also showed no efficiency in the reaction (entries 12 and 13). It was found that TMSCl is required for the Cr-catalyzed C–C bond formation reaction of secondary amide with phenyl Grignard reagent. Decreasing the amount of TMSCl resulted in low conversion of *N*-(*tert*-butyl)benzamide (entry 14). Whereas the reaction was completely inhibited in the absence of TMSCl (entry 15).

Having establishing the optimal conditions, the substrate scope of secondary amides in the chromium-catalyzed reaction with phenyl Grignard reagent was evaluated. As shown in Scheme 1, the introduction of either electron-donating or electron-withdrawing substituents into the meta position of *N*-(*tert*-butyl)benzamides did not largely impact on the transformation, providing access to unsymmetrical benzophenone derivatives **3b**–**3f** in good to excellent yields (79–92%). *Para*-substituted benzamides was suitable reactants for the formation of arylative C–C bonds at room temperature (**3g**–**3k**). Aromatic ketones containing di- or tri-substituents on the arenes could be accessed by the Cr-catalyzed protocol (**3l**–**3p**). In addition, the Kumada-type reaction using secondary amides containing naphthyl scaffold, heterocycles of 1,3-benzodioxole and 1,4-benzodioxine also proceeded smoothly, forming the desired ketone compounds **3q**–**3s** in preparatively useful yields. Synthetically valuable functionalities of alkoxy, fluoride, chloride, trifluoromethyl can be compatible with the catalytic system. Notably, the bis(amide) scaffolds on arene can be synchronously arylated by the Cr-catalyzed reaction with excess of PhMgBr. It provides a concise route to the preparation of bis(carbonyl)-containing phenylenebis(phenylmethanone) derivatives **3t** and **3u**.

Table 1. Probing the Effect of *N*-Substituents and Transition Metal Salts on Reaction of Benzamides with PhMgBr[a,c]

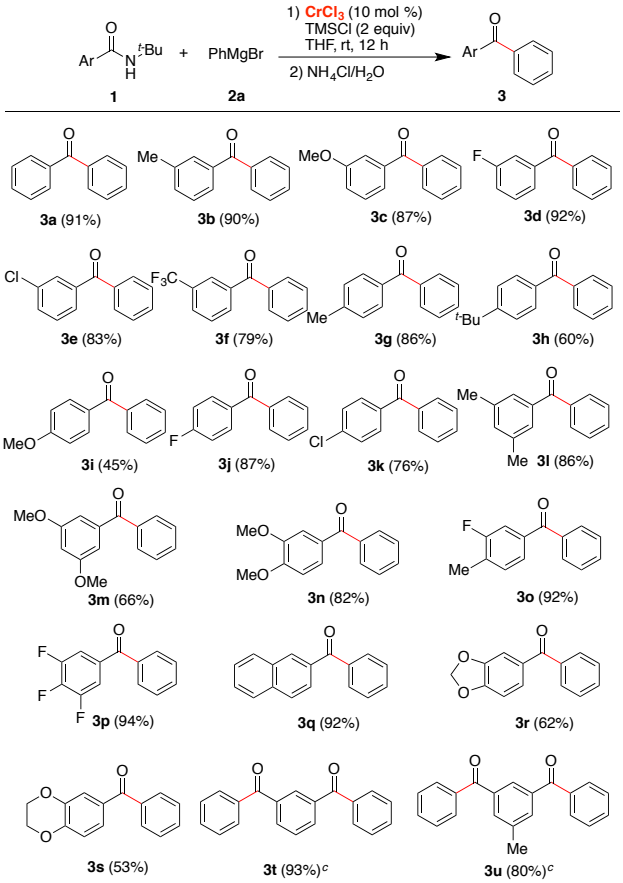


1 2a 3a

entry	–NR¹R²	metal salt	TMSCl (X equiv)	yield (3a)
1	–NHMe	$CrCl_3$	2	nd[b]
2	–NHPh	$CrCl_3$	2	37%
3	–NH*i*-Pr	$CrCl_3$	2	51%
4	–NH*t*-Bu	$CrCl_3$	2	91%
5	$-NMe_2$	$CrCl_3$	2	43%
6	–NH*t*-Bu	$CrCl_2$	2	91%
7	–NH*t*-Bu	–	2	nd[b]
8	–NH*t*-Bu	$NiCl_2$	2	nd[b]
9	–NH*t*-Bu	$CoCl_2$	2	nd[b]
10	–NH*t*-Bu	$CuCl_2$	2	nd[b]
11	–NH*t*-Bu	$PdCl_2$	2	nd[b]
12	–NH*t*-Bu	$FeCl_3$	2	nd[b]
13	–NH*t*-Bu	$AlCl_3$	2	nd[b]
14	–NH*t*-Bu	$CrCl_3$	1	46%
15	–NH*t*-Bu	$CrCl_3$	–	nd[b]

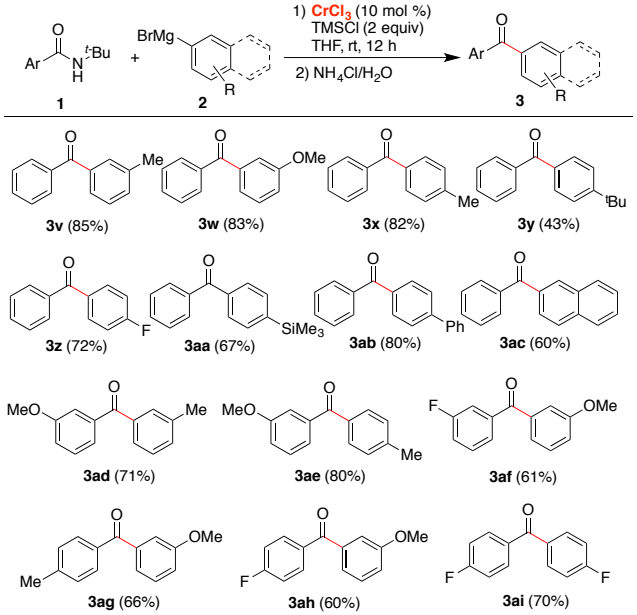
[a]Reaction conditions: **1** (0.2 mmol), PhMgBr (0.8 mmol). Metal salt (0.02 mmol), TMS, THF, rt, 12 h; then NH_4Cl/H_2O. Isolated yields are given. [b]Not detected. [c]The purities of metal salts: $CrCl_2$ (99.99%), $CrCl_3$ (99.99%), and $CoCl_2$ (99.9%).

Scheme 1. Chromium-Catalyzed Synthesis of Ketones by Reaction with Secondary Amides[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.8 mmol), $CrCl_3$ (0.02 mmol), TMSCl (0.4 mmol), THF, rt, 12 h; then NH_4Cl/H_2O. [b]Isolated yields are given. [c]PhMgBr(1.6 mmol) was employed.

Scheme 2. Cr-Catalyzed Reaction of Secondary Amides with Arylmagnesium Bromides[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), $CrCl_3$ (0.02 mmol), TMSCl (0.4 mmol), rt, 12 h; then NH_4Cl/H_2O. [b]Isolated yields are given.

We then examined the scope of organomagnesium reagents in the Cr-catalyzed arylative C–C bond formation reaction with aromatic amides (Scheme 2). Phenyl Grignard reagents containing alkyl, alkoxy, fluoride and phenyl scaffolds underwent the amide–ketone exchange smoothly, leading to the desired products **3v**–**3ab** in good yields. 2-Naphthyl Grignard reagent was amenable to the transformation in the production of naphthalen-2-yl(phenyl)methanone **3ac**. Furthermore, this methodology can be applied to access to unsymmetrical diaryl ketones **3ad**–**3ah** by the reaction between substituted benzamides with aryl Grignard reagents. Whereas the arylation with aliphatic amides or alkyl Grignard reagents failed to give the related ketone compounds.

The chromium-catalyzed reaction between secondary amide with phenylmagnesium bromide is scalable, and can be performed on gram-scale without loss of the efficiency (Figure 2, eq 1). Interestingly, the arylation using *para*-bromo-substituted benzamide furnished bisarylated product **3ab** by synchronously functionalization of the amide and bromide scaffolds (eq 2). The success of the arylative C–C bond formation with secondary amides stimulated us to probe the possible mechanism for the conversion. According to our previous studies, reactive low-valent chromium species can be formed by the treatment of simple chromium salt with phenyl Grignard reagent.[37,41,43] It was found that the in-situ generated low-valent chromium species shows high catalytically active for the amide–ketone exchange reaction, leading to the desired ketone in 79% yield (eq 3). Interestingly, the reaction of trimethylsilyl (*Z*)-*N*-phenylbenzimidate (**4**) with phenyl Grignard reagent was able to afford the benzophenone **3a** in the presence of $CrCl_3$ and TMSCl, albeit with low yield (eq 4). However, without chromium salt or TMSCl, the transformation cannot occur (eqs 5 and 6). These results

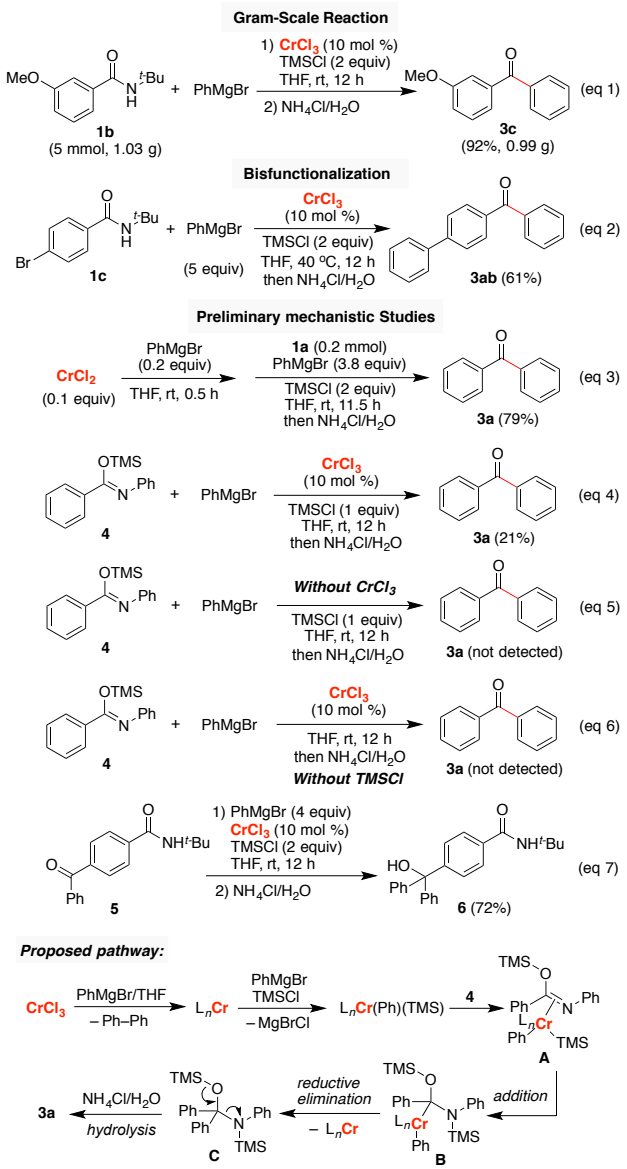


Figure 2. Gram-scale reaction, bisfunctionalization, preliminary mechanistic studies and possible pathway.

suggest that chromium plays an important role in the formation of arylative C–C bond with TMSCl. We envisioned that the relevant alkyl imidate intermediate, probably being formed by treating aliphatic amides with TMSCl and PhMgBr, may not be stable enough under present catalysis conditions, resulting in the unsuccessful reaction of aliphatic amides. The reaction using 4-benzoyl-substituted benzamide **5** did not form the related Kumada arylation product (eq 7). Notably, the addition of phenyl Grignard to carbonyl group occurred to give the related alcohol compound **6** in 72% yield. This suggests that carbonyl group cannot be compatible with the reaction system, indicating that the ketone product might be formed upon hydrolysis in the final work-up procedure, thereby avoiding the addition of Grignard reagent to carbonyl group. We hypothesized that the in-situ generated low-valent chromium may react with PhMgBr and TMSCl to give organochromium species, which can coordinate and activate the benzimidate intermediate, followed by the processes of addition/reductive elimination to form the masked

terminal state **C**. The desired ketone compound is probably produced upon hydrolysis in the work up procedure.

In summary, we have developed a Kumada arylation of secondary amides for the synthesis of unsymmetrical aryl ketones with cost-effective chromium catalysis. This reaction was enabled by the use of low-cost chromium salt as precatalyst combined with trimethylsilyl chloride as additive to give ketone products upon work up. The ketone is probably protected in the reaction cycle, thereby without forming the adduct of Grignard reagent to ketone. It presents a rare example of the use of readily available secondary amides as reactants for the arylative C–C bond formation reaction by catalytic activation of benzimidate intermediate with chromium at room temperature. Further studies on understanding the mechanism and application of the Cr-catalyzed protocol in synthesis are under way.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data for all products, detailed optimized geometries, and free energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interests.

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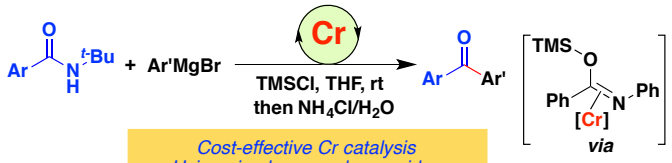

Cost-effective Cr catalysis
Using simple secondary amides
Mild reaction conditions
Without addition of Grignard to ketone