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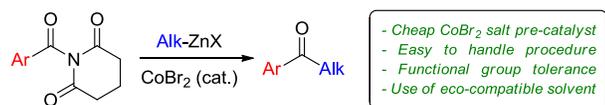
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# Cobalt bromide catalyzed Negishi-type cross-coupling of amides

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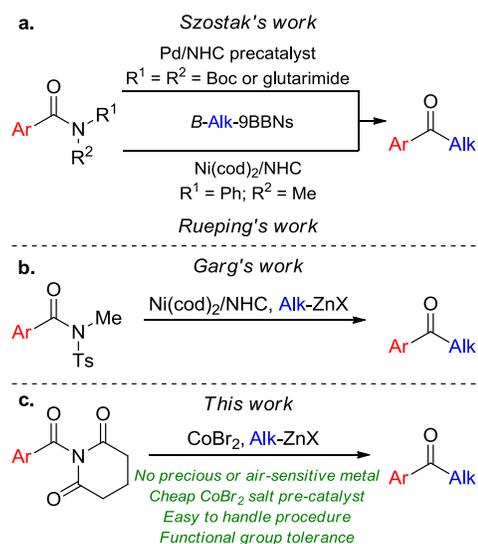
**ABSTRACT:** In this manuscript, a novel Negishi-type cross-coupling of amides was described employing only cobalt bromide salt as catalyst. This original reaction is highly tolerant toward various glutarimide amides as well as organozinc coupling partners. These conditions also allow to perform the cross-coupling reaction in an eco-compatible solvent such as ethyl acetate on a large scale.

The robustness of the amide bond makes it one of the most abundant bonds in the nature<sup>1</sup> and, probably, explains its presence in many biologically active molecules or in polymers among others.<sup>2,3</sup> This particular stability of the amide function is due to its planarity, coming from the conjugation between the nitrogen lone pair and the  $\pi$ -system of the carbonyl moiety.<sup>4</sup> However, it is possible to destabilize this planar structure through distortion of the C–N amidic bond thanks to steric and/or electronic effects on the substituents of the nitrogen.<sup>5,6</sup> These activated “distorted” amides<sup>7–10</sup> appear more reactive to many reaction conditions<sup>11</sup> and, since 2015,<sup>12–15</sup> have even shown to be efficient electrophilic coupling partners for transition metal-catalyzed transformations by direct insertion into the C–N amidic bond to create carbon–heteroatom and carbon–carbon bonds.<sup>16,17</sup> These latter include decarbonylative<sup>18</sup> as well as acyl cross-coupling reactions to form valuable ketone products.<sup>19–22</sup> If many conditions have been disclosed to achieve diarylketones,<sup>16–23</sup> the synthesis of aryl/alkyl ketones from aliphatic organometallic species<sup>24,25</sup> remains challenging, in particular due to competing decomposition of the organometallic species via  $\beta$ -hydride elimination/protodemetalation processes.<sup>26</sup> Whereas the groups of Rueping (Ni)<sup>27</sup> and Szostak (Pd)<sup>28</sup> were able to develop alkylative redox-neutral Suzuki-Miyaura reaction with alkyl boron-based coupling partners (Scheme 1a),<sup>29</sup> the group of Garg disclosed an interesting alkylative Negishi cross-coupling under nickel catalysis using low distorted *N*-,Me,Ts arylamides (Scheme 1b).<sup>30</sup> Nonetheless, those protocols are using either expensive palladium catalyst or highly air-sensitive Ni(cod)<sub>2</sub> precursor with the requirement of carbene as ligand for all methodologies. Hence, the development of a cheaper and/or easier to handle general methodology for the synthesis of aryl/alkyl ketones from amides is still greatly desirable.

Although still quite underused compared to its metal counterparts palladium and nickel, cobalt has already proven to be quite useful to catalyze cross-coupling reactions, with the advantages of necessitating very simple ligands or no ligand at all.<sup>31–34</sup> Besides, our group already showed the efficient ability of cobalt catalysts to activate the amidic bond of twisted amides to perform the thermodynamically unfavored esterifica-

tion<sup>35</sup> of *N*-Boc amides<sup>36</sup> as well as the acylating Negishi coupling of amides to achieve diarylketones.<sup>23</sup> Therefore, in the continuity of our work we report herein a very easy-to-handle alkylation of amides with aliphatic organozinc catalyzed from distorted arylglutarimides by the sole  $\text{CoBr}_2$  salt with high functional group tolerance which would complement Garg's methodology in terms of applicability (Scheme 1c).

**Scheme 1. Preparation of aryl/alkyl ketones from amides with aliphatic organometallic reagents.**



Inspired by our previous work,<sup>23</sup> we initiated our investigation reacting *N*-benzoyl glutarimide (**1a**) and *n*-pentylzinc bromide (**2a**) (2.0 equiv.) in presence of  $\text{CoBr}_2$  (20 mol%) in MeCN (0.5 M), and were delighted to observe the formation of 1-phenylhexan-1-one (**3aa**) in 77% NMR yield after one night at room temperature (Table 1, entry 1). No real influence was observed if **2a** was prepared by direct insertion of metallic zinc or by transmetalation with Grignard reagent. However, **2a** synthesized by direct insertion in DMF completely shut down the reaction probably due to the solvent nature which could deactivate the cobalt catalyst (see SI, II-3). Interestingly,

replacing **2a** by its more nucleophilic homolog dipentylzinc led to a huge drop in the selectivity of the reaction and afforded **3aa** in less than 5% yield (Table 1, entry 2). Addition of **2a** at 0 °C with further rising to room temperature resulted in a decreased yield of **3aa** (69%) (Table 1, entry 3), which might be due to a lack of reactivity of the amide partner with the active species at lower temperature and concurrent degradation processes with the alkylzinc reagent. Of note, the reactivity is compatible with many solvents especially 1,4-dioxane which afforded quantitative yield of **3aa** (Table 1, entry 4). Remarkably, more eco-compatible solvents such as AcOEt (Table 1, entry 5) or propylene carbonate (Table 1, entry 6) are also suitable for the transformation leading to **3aa** in interesting yields of 72% and 61% respectively.<sup>(Ref)</sup> However, amide polar aprotic solvents such as DMA or DMF completely shut down the reactivity (Table 1, entry 7) which was in accordance with the result observed with **2a** in DMA. Using the optimal solvent 1,4-dioxane (Table 1, entry 4), a smaller amount of both **2a** (Table 1, entry 8) and CoBr<sub>2</sub> (Table 1, entry 9) resulted in a decreased yield of **3aa**. Surprisingly, the presence of ligands such as PPh<sub>3</sub>, dppe or bipyridine decreased the efficiency of the cobalt catalyst, while the use of CoCl<sub>2</sub> led to a slight increase of the efficiency but with reproductibility problem due to its low solubility in dioxane (see SI, II-4). Finally, control experiment showed no reaction in the absence of CoBr<sub>2</sub> (Table 1, entry 10).

**Table 1. Optimization study<sup>a</sup>**



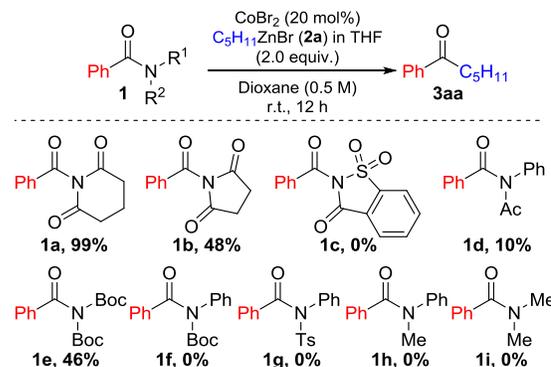
entry	variation	yield (%) <sup>b</sup>
1	none	77
2	Pent <sub>2</sub> Zn instead of PentZnBr	<5
3	0 °C to r.t. instead of r.t.	69
4	1,4-dioxane instead of MeCN	99
5	AcOEt instead of MeCN	72
6	Propylene carbonate instead of MeCN	61
7	DMA instead of MeCN	0
<b>entry 4 as new standard conditions</b>		
8	1.5 equiv. of PentZnBr	90
9	10 mol% CoBr <sub>2</sub>	84
10	No CoBr <sub>2</sub>	0

<sup>a</sup>Reactions performed on 0.25 mmol scale. See the SI for full details. <sup>b</sup>NMR yield using 1,3,5-trimethoxybenzene as internal standard.

With the optimal conditions in hand, we then evaluated the efficiency of this catalytic system on different amides showing high yield only with glutarimide derivatives while succinimide and di-Boc ones led to moderate yields. However, it appeared completely inefficient towards *N*-Boc, *N*-Ts as well as *N*-Ph amides leading to untouched starting materials which highlight

well the complementarity of this reaction with the previous methodologies described by Garg, Rueping and Szostak.

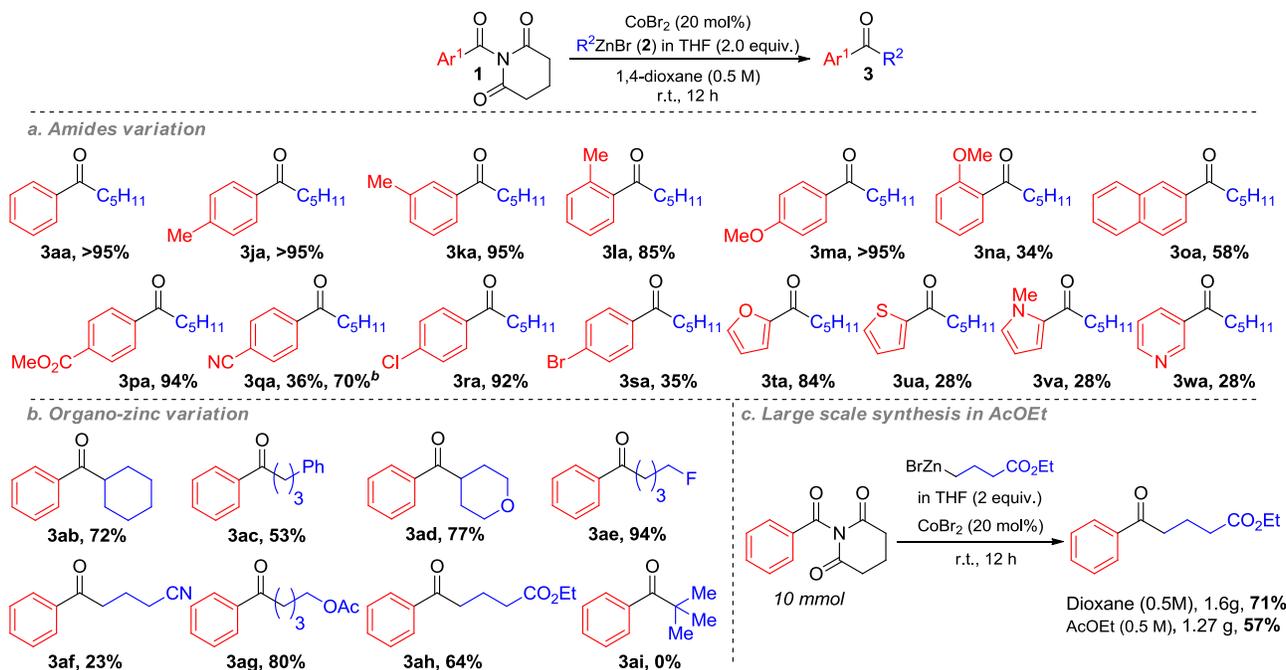
**Scheme 2. Evaluation of active amide derivatives.<sup>a</sup>**



<sup>a</sup>Reactions performed on 0.25 mmol scale. See the SI for full details. NMR yield using 1,3,5-trimethoxybenzene as internal standard.

The scope of the reaction towards functionality tolerance was then investigated. The reaction turned out to be very efficient with a large variety of aryl amide derivatives possessing methyl (**3ja-3la**), methoxy (**3ma, 3na**) or even ester groups (**3pa**) leading to the corresponding coupling products with near quantitative yields. Substituents in the *para* and *meta* positions had no influence on the efficiency of the reactivity whereas in the *ortho* position, a decreasing yield was observed in particular for hindered groups. This trend could be either due to steric hindrance between the carbonyl moiety of the amide and the catalyst or the result of a stabilization of a cobalt intermediate through chelation between the *ortho* chelating functional group and an acyl-cobalt intermediate explaining the low yield obtained for **3na**. The same phenomenon of stabilization/poisoning of the catalytic organo-cobalt intermediates was also observed when chelating functional groups, such as some hetero-aromatic substituents, were present in the substrates leading to a large decrease in the yields (**3qa, 3ua, 3va** and **3wa**). However, high conversions could be restored, in the case of **3qa** by using stoichiometric amount of cobalt salt avoiding this stabilization / poisoning problem. The reaction tolerates also chlorinated aryl moiety (**3ra**) but led to a mixture of coupling products when its brominated counterpart (**3sa**) was employed. Indeed, three different products could be identified: the target one resulting of the coupling towards the amide moiety (**3sa**), the product originated from the protodehalogenation of the bromoaryl moiety (**3aa**) and a last one where both amide and bromoarene were coupled with the pentylzinc bromide. Finally, a remarkable functional group tolerance has been noticed on the side of the alkylzinc partner. Indeed, the methodology of direct insertion of metallic zinc allows the formation of organozinc compounds bearing various functional groups which was employed in the cross-coupling and allowed the synthesis of the coupling products bearing ester (**3ah**), acetate (**3ag**) and even nitrile (**3af**) groups, even though the same chelating/stabilizing limitation effect has been observed for this later.

### Scheme 3. Scope of the reaction<sup>a</sup>.

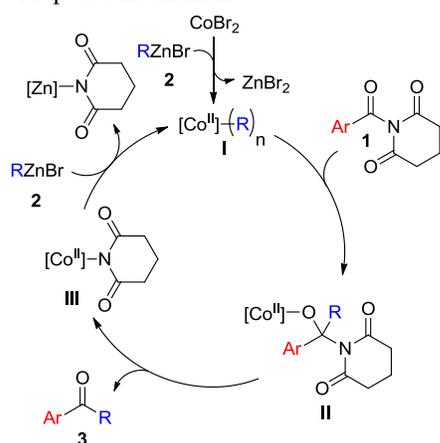


<sup>a</sup> Reactions conditions: **1** (0.5 mmol), **2** in THF (1 mmol) and CoBr<sub>2</sub> (20 mol%) in dioxane (1 mL). Isolated yields. See the SI for full details

<sup>b</sup> 1 equiv. of CoBr<sub>2</sub>

In order to demonstrate the high usefulness of this methodology, a large-scale synthesis has been performed in dioxane and in an eco-compatible solvent such as ethyl acetate leading to the isolation of coupling product in gram scale with 71% and 57% yields respectively. It is noted that a slight decrease of the yield was observed when AcOEt was used instead of dioxane which followed the same tendency observed during the screening of the reaction conditions.

#### Scheme 4. Proposed mechanism



In term of mechanism, we performed some tests in order to identify the cobalt active species involved in this reaction. Dia- or paramagnetic NMR studies did not allow to identify organocobalt intermediate probably due to the paramagnetic nature of the active species. Some experiments of crystallization and mass spectroscopy were performed in order to isolate and identify the active cobalt species formed by reaction be-

tween the organozinc coupling partner and CoBr<sub>2</sub>, but no convincing results were obtained. However, the GC analysis of the reaction between cyclohexylzinc iodide and cobalt bromide in THF allowed to titrate the amount of bicyclohexyl formed which was in direct correlation with the oxidation state of organocobalt intermediate. Only traces of bicyclohexyl compared to internal standard could be detected in GC even with different stoichiometry which tends to demonstrate that no low-valent organocobalt intermediate is involved in the reaction. Therefore, we proposed a mechanism involving an organocobalt (+II) intermediate (**I**) as active species which was formed by transmetalation between the cobalt bromide and the alkylzinc coupling partner (**2**). This organocobalt (**I**) could then activate the distorted amide through carbometallation step into the carbonyl moiety of the amide leading to the intermediate (**II**). After elimination of cobalt glutarimide **III**, the cross-coupling product was produced and the active species **I** was regenerated by a ligand exchange step on **III** with the alkylzinc coupling partner. However, we could not exclude, at this stage, a classical mechanism involving an oxidative addition step into the amidic bond, which would require deeper mechanistic investigations in particular to determine the real oxidation state of the active species.

In conclusion, this manuscript describes a really simple and straightforward methodology to perform acylating Negishi-type cross-coupling due to a cobalt catalyst involving only cobalt bromide salt. These simple conditions allow the use of eco-compatible solvents such as AcOEt and tolerate various functional groups such as ester or chlorinated compounds. However, the absence of ligand brought some limitations in particular for chelating functional groups such as pyridine, thiophene or even nitrile which probably poisoned the active

species. This main drawback could be overcome by increasing the amount of catalyst until 100 mol% in the case of nitrile compounds. The reaction is very robust and allows the synthesis of functionalized molecules in gram scale.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General experimental details, optimization of reaction, experimental procedure, characterization data, and NMR spectral data (PDF)

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### Notes

The authors declare no competing financial interest.

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