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# Cobalt(III)-Catalyzed and Dimethyl Sulfoxide-Involved Cross-Coupling of Ketones and Amides for Direct Synthesis of *β*-Amino Ketones

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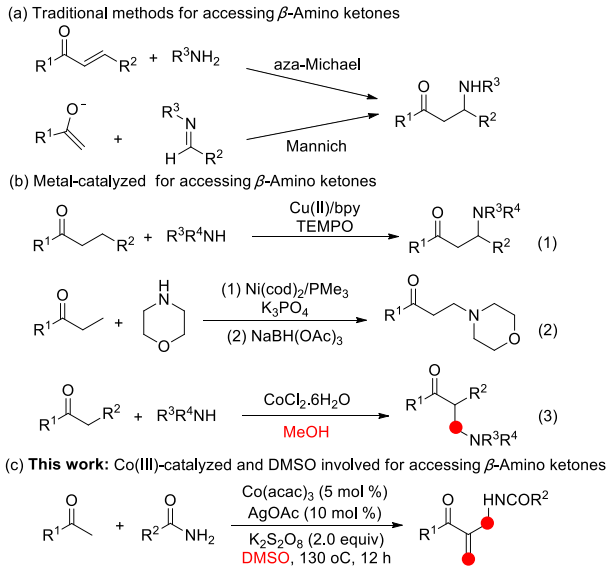
**Abstract.** A straightforward synthesis of *β*-amino ketones has been realized by employing ketones and amides as the substrates via cobalt(III)-catalyzed and dimethyl sulfoxide-involved cross-coupling reaction. Experimental investigations revealed that the *β*-methylsulfide ketone species might be involved as the active intermediate. Diverse ketones (*e.g.* acetophenone and its derivatives, heteroaryl methyl ketones and dibenzoylmethane) and amides (e.g. aromatic, aliphatic and cyclicamides) with various substitution patterns were found to be applicable to this transformation, demonstrating a broad substrate scope and excellent functional group tolerance.

**Keywords:** Cobalt(III) catalysis; Dimethyl sulfoxide; Ketones; Amides; *β*-Amino ketones.

## Introduction

*β*-Amino ketones have played an important role in organic chemistry and drug discovery owing to their unique properties and potential pharmaceutical applications.[1] Consequently, tremendous efforts have been focused on exploring the efficient methodologies toward their synthesis.[2-3] By reviewing these developments, two classic procedures for the construction of *β*-amino ketones have been stood out (Scheme 1a),[2] namely: (1) the aza-Michael reaction involving the addition of nitrogen nucleophiles on *α*,*β*-unsaturated carbonyl compounds, (2) the Mannich reaction between imines and enolates. However, the two methods usually not only require the highly functionalized starting materials, harsh conditions as well as the corrosive reagents but also give relatively poor yields or limited substrate scope.

To overcome the above mentioned disadvantages, recently developed direct C-H amination has emerged as one of the most powerful tools for the construction of *β*-amino ketones in a highly step- and atom-economic manner.[4-6] Although numerous versatile protocols have been disclosed by second-row transition metals, most of these methods mainly relied on the activation of ketones to enamines and/or enones which employed single electron




**Scheme 1.** Strategies for building the *β*-amino ketone framework.

oxidation and conjugated addition, respectively, as the key step. For example, Su and co-workers reported the copper-catalyzed direct *β*-functionalization of saturated ketones, in which the ketones were initially desaturated by stoichiometric TEMPO, followed by a catalytic conjugated addition (Scheme 1b-1).[5] A similar work was reported by Kuwano and co-workers, in which the nickel-catalyzed formation of the C-N bond at the *β*-position of propiophenone was involved and the *α*,*β*-unsaturated ketone species were employed as the active intermediate (Scheme 1b-2).[6] Moreover, the use of $PMe_3$ ligand together with an additional reduction step was inevitable for achieving the *β*-amino ketones in their work, which limited the utility potential of such reactions. Therefore, the development of more step- and atom-economic synthetic strategy to build the *β*-amino ketones is still highly desired.

Over the past decades, exploring the environmental friendly protocol for the efficient synthesis of structurally diverse and complex compounds from simple raw materials represented one of the most challenging tasks. For this topic, the cheap and commercially available polar aprotic solvents with relatively low toxicity, such as DMF,[7] DMA,[8] MeOH,[9] and DMSO,[10] have shown great potential being used as the versatile synthons in organic synthesis. Accordingly, such strategy has been applied in constructing *β*-amino ketones via cobalt(II)-catalyzed *α*-methoxymethylation and *α*-aminomethylation, in which MeOH was used as the carbon source (Scheme 1b-3). Compared to MeOH, DMSO can provide not only the methylene (-$CH_2$-) synthon, but also other functional groups including -O,[11] -SMe,[12] -$CH_2$SMe,[13] -$SO_2$Me,[14] -Me,[15] -CN[16] and -CHO.[17] Noteworthily, in view of the good leaving effect of the -SMe moiety, utilizing DMSO to install -$CH_2$SMe has selected as a powerful strategy to elongate the carbon chain through the formation of the weak C-S bond. In the course of our studies focusing on the development of earth-abundant and inexpensive cobalt-catalyzed C-H functionalization, we have developed a cobalt(III)-catalyzed C-H activation strategy for one-pot construction of the quinoline framework using DMSO as the $C_1$ source, which further highlighted the compatibility and application of DMSO-involved system in cobalt(III)-catalyzed C-N coupling reactions.[18]

On the basis of these advances, we envisaged that the easily formed *β*-methylsulfide ketones, derived from the coupling of enols/enolates and DMSO in the presence of external oxidant, could be readily converted into *β*-amino ketones via cobalt(III)-catalyzed transformation with amides to form the C-N bond. Therefore, we herein would like to disclose a novel strategy for the synthesis of *β*-amino ketones from ketones, amides and DMSO via a tandem in situ *β*-methylsulfide generation/cobalt(III)-catalyzed C-N reductive elimination process (Scheme 1c). Mechanistic studies validated that DMSO was used as the carbon source to involve the formation of the *β*-methylsulfide intermediate followed by cobalt(III)-catalyzed facile amination.

## Results and Discussion

To test the feasibility of the proposed concept, we first investigated the model reaction by choosing the simple and cheap $Co(acaac)_3$ as the catalyst. To our delight, the treatment of acetophenone (**1a**) with benzamide (**2a**) in the presence of $AgNTf_2$ and $K_2S_2O_8$ furnished the desired *β*-amination product *N*-(2-benzoylallyl)benzamide (**3a**) and *N*-(3-oxo-3-phenylpropyl)benzamide (**3aa**) in 41% and 17% yields, respectively (Table 1, entry 1). Encouraged by this promising result and considering the meaningful structure of **3a** (belong to allyl amine species) that was difficult to synthesize via conventional reactions, we further screened several parameters including peroxides, silver sources and the cobalt catalysts systemically to establish the optimized conditions for the direct synthesis of **3a**. The results revealed that other peroxides such as $(NH_4)_2S_2O_8$, $Na_2S_2O_8$ as well as TBHP were less effective (entries 2-4). After a number of trials to screen different silver salts, AgOAc was found to be superior to other candidates (entries 5-9), increasing the yield of **3a** up to 76% with excellent selectivity (no **3aa** was detected). Further investigation showed that no desired product was found in changing AgOAc to either NaOAc or CsOAc (entries 10-11), suggesting that the introduction of the AgOAc species was essential for the Co(III)-catalyzed reaction. Switching the solvent from DMSO to other reaction media also gave inferior results (entries 12-13). The control experiment demonstrated that either the cobalt(III) catalyst or $AgOAc/K_2S_2O_8$ additives was essential for this transformation (entries 14-16). Other cobalt species resulted in the sharp reduction on both the yield and the selectivity or completely inhibited the process (entries 17-20). Especially, the Cp*Co(III) species that had shown a good catalytic activity in our previous work[18] was failed to provide the desired product **3a** (entry 15), instead, 2-((methylthio)methyl)-1-phenylprop-2-en-1-one was obtained as the main products with 85% yield.[19] Taken together, the results revealed that the type and nature of the ligand attached in Co(III) metal played a decisive role in determining the reaction outcome, and in current cases, the acac ligand was optimal. Subsequently,

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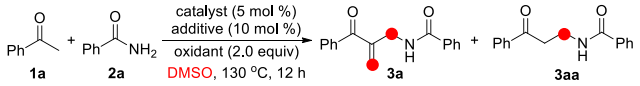
the effect of the reaction temperature was investigated. The results showed that the coupling at 130 °C gave the most satisfying result (entries 8, 21 and 22), revealing that a balance between the decomposition of the substrate and the formation of the product might exist in the reaction. In addition, lowering the loading of $K_2S_2O_8$ to 1.0 equiv led to a significant decrease in the product yield (entry 23). No distinct difference in product yield was observed when the amount of $K_2S_2O_8$ was extended to 3.0 equiv (entry 24).

**Table 1.** Optimization of reaction conditions.[a]

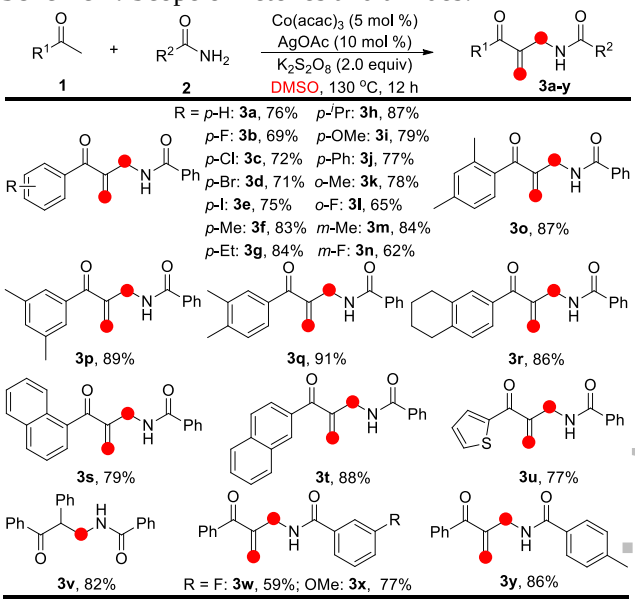



| entry | catalyst | additive | oxidant | Yield[b] (%) | |
|---|---|---|---|---|---|
| | | | | 3a | 3aa |
| 1 | $Co(acac)_3$ | $AgNTf_2$ | $K_2S_2O_8$ | 41 | 17 |
| 2 | $Co(acac)_3$ | $AgNTf_2$ | $(NH_4)_2S_2O_8$ | 0 | 0 |
| 3 | $Co(acac)_3$ | $AgNTf_2$ | $Na_2S_2O_8$ | 11 | 0 |
| 4 | $Co(acac)_3$ | $AgNTf_2$ | TBHP | 0 | 0 |
| 5 | $Co(acac)_3$ | $Ag_2SO_4$ | $K_2S_2O_8$ | 0 | 0 |
| 6 | $Co(acac)_3$ | $AgNO_3$ | $K_2S_2O_8$ | 31 | 0 |
| 7 | $Co(acac)_3$ | $Ag_2CO_3$ | $K_2S_2O_8$ | 0 | 0 |
| 8 | $Co(acac)_3$ | AgOAc | $K_2S_2O_8$ | 76 | 0 |
| 9 | $Co(acac)_3$ | AgOTf | $K_2S_2O_8$ | 51 | 0 |
| 10 | $Co(acac)_3$ | NaOAc | $K_2S_2O_8$ | 0 | 0 |
| 11 | $Co(acac)_3$ | CsOAc | $K_2S_2O_8$ | 0 | 0 |
| 12[c] | $Co(acac)_3$ | AgOAc | $K_2S_2O_8$ | 0 | 0 |
| 13[d] | $Co(acac)_3$ | AgOAc | $K_2S_2O_8$ | 0 | 0 |
| 14 | $Co(acac)_3$ | AgOAc | / | 0 | 0 |
| 15 | $Co(acac)_3$ | / | $K_2S_2O_8$ | 0 | 0 |
| 16 | / | AgOAc | $K_2S_2O_8$ | 14 | 0 |
| 17 | $Co(acac)_2$ | AgOAc | $K_2S_2O_8$ | 16 | 69 |
| 18 | $Co(OAc)_2$ | AgOAc | $K_2S_2O_8$ | 21 | 14 |
| 19[e] | $Cp^*Co(CO)I_2$ | AgOAc | $K_2S_2O_8$ | 0 | 0 |
| 20 | $CoI_2$ | AgOAc | $K_2S_2O_8$ | 0 | 0 |
| 21[f] | $Co(acac)_3$ | AgOAc | $K_2S_2O_8$ | 58 | 0 |
| 22[g] | $Co(acac)_3$ | AgOAc | $K_2S_2O_8$ | 62 | 0 |
| 23[h] | $Co(acac)_3$ | AgOAc | $K_2S_2O_8$ | 49 | 0 |
| 24[i] | $Co(acac)_3$ | AgOAc | $K_2S_2O_8$ | 78 | 0 |

[a]Reaction conditions: acetophenone **1a** (0.5 mmol), benzamide **2a** (0.6 mmol), catalyst (5 mol %), additive (10 mol %) and oxidant (2.0 equiv) in DMSO (2 mL) at 130 °C for 12 h under air.
[b]Isolated yield after chromatography.
[c]In DMF.
[d]In DMA.
[e]For details, see reference 19.
[f]At 110 °C.
[g]At 150 °C.
[h]With 1.0 equiv of $K_2S_2O_8$.
[i] With 3.0 equiv of $K_2S_2O_8$.

With the optimized conditions in hand, we proceeded to investigate the substrate scope of this transformation with respect to the use of diverse aryl ketones. As enumerated in Scheme 2, a variety of acetophenone analogues bearing either electron-donating or electron-withdrawing groups were initially evaluated. The results displayed that these substrates were fully compatible to the reaction conditions to give the desired products in moderate to good yields, revealing that the electronic and steric effects of the substituents on the aryl ring had no obvious influence on the reaction outcome. Various commonly encountered functional groups including halogens (**3b-e**), alkyl (**3f-h**), methoxy (**3i**) and phenyl (**3j**) were well tolerated regardless of the substituted position on the phenyl ring (**3k-n**). In addition, the disubstituted aryl ketones were found to be viable substrates (**3o-r**), affording the corresponding products in excellent yields (86-91%). Interestingly, this protocol could also be extended to polyaromatic naphthyl ketones, furnishing the desired *β*-amination products in 79% (**3s**) and 88% (**3t**) yields, respectively. It was worth noting that the heteroaryl methyl ketone 1-(thiophen-3-yl)ethan-1-one was also compatible to this transformation, producing the desired product **3u** in 77% yield. Gratifyingly, further examination indicated that this reaction was not limited to the methyl ketone substrates. When 1,2-diphenylethanone was subjected to the standard conditions, the corresponding product **3v** was obtained smoothly in 82% yield. Moreover, benzamides bearing different substituents on the phenyl ring also reacted efficiently with acetophenone **1a** to deliver the corresponding products in moderate to

**Scheme 2.** Scope of ketones and amides.[a]




[a]Reaction conditions: ketone **1** (0.5 mmol), amide **2** (0.6 mmol), $Co(acac)_3$ (5 mol %), AgOAc (10 mol %) and $K_2S_2O_8$ (2.0 equiv) in DMSO (2 mL) at 130 °C for 12 h under air; isolated yields were reported.

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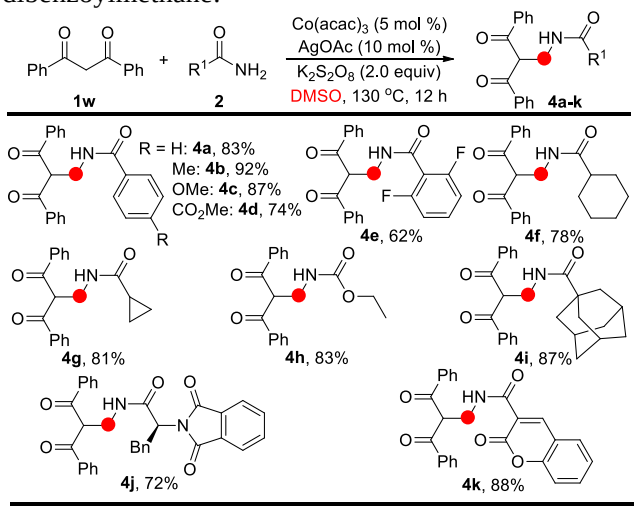
good yields (**3w-y**), illustrating the good substrate compatibility of the Co(III)-catalyzed system.

**Scheme 3.** Scope of amides with the reaction of dibenzoylmethane.[a]

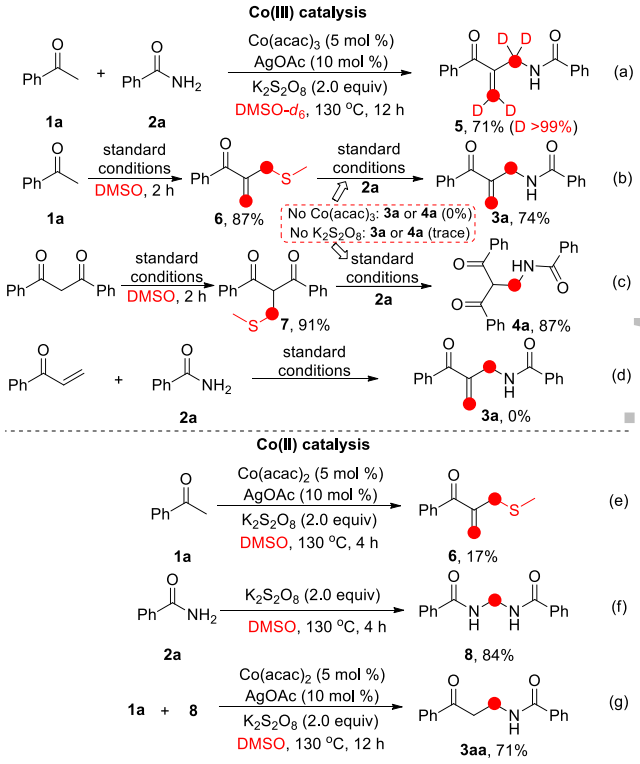



[a]Reaction conditions: ketone **1** (0.5 mmol), amide **2** (0.6 mmol), $Co(acac)_3$ (5 mol %), AgOAc (10 mol %) and $K_2S_2O_8$ (2.0 equiv) in DMSO (2 mL) at 130 °C for 12 h under air; isolated yields were reported.

Inspired by the above mentioned results, the scope of amides was further investigated with the reaction of a new diketone substrate under the optimized reaction conditions (Scheme 3). Fortunately, various benzamides bearing different electronic properties reacted smoothly with dibenzoylmethane (**1w**) to yield the corresponding products **4a-d** in high yields (74-92%). Moreover, 2,6-difluorobenzamide could be totally transformed to the desired product in a synthetically useful yield (**4e**), indicating good steric tolerance of the developed Co(III)-catalyzed system. Notably, cyclic amides and aliphatic amides could also be accommodated with the reaction conditions to give the corresponding products in good yields (**4f-h**). Remarkably, several amides derived from the natural products and biological active molecules, including adamantane-1-carboxamide, coumarin-3-carboxamide and *N*-phthaloyl-*L*-phenylalanine derivative, also reacted with **1w** smoothly to yield the desired *β*-amino ketones (**4i-k**) in good yields, which illustrated profound potentials for the rapid synthesis of novel analogs of such motifs.

Given the effective synthetic routes for the facile construction of *β*-amino ketone derivatives, we were next intrigued to conduct a series of experimental investigations to probe the reaction mechanism (Scheme 4). Firstly, deuterium-labeling experiment was carried out, which resulted in the formation of deuterated product **5** with more than 99% incorporation of deuterium at the two methylene positions in the presence of DMSO-$d_6$ (Scheme 4a), revealing that DMSO was used as both the solvent and two carbon synthons in this reaction. Subsequently, the

**Scheme 4.** Mechanistic studies.



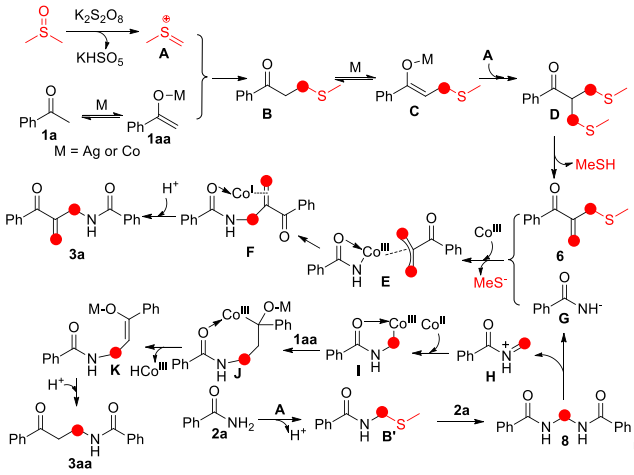

reaction was performed in the absence of benzamide under standard conditions for 2 h, generating the intermediate **6** in 87% yield. Further treatment of **6** with benzamide **2a** led to the desired *β*-amination product **3a** in 74% yield (Scheme 4b). Taken together, these results provided clear evidence that **6** should be an active intermediate involved in this transformation. Next, the reaction of dibenzoylmethane with DMSO in the absence of benzamide under the otherwise identical conditions was also carried out. As predicted, the similar *β*-methylsulfide intermediate **7** was obtained smoothly in 91% yield, which could be further converted into *β*-amino ketone **4a** in the presence of **2a** (Scheme 4c). No desired product was observed when either **6** or **7** was treated with **2a** without adding any cobalt(III) catalyst or $K_2S_2O_8$ (Schemes 4b-c), revealing that both the catalyst and the oxidant were crucial for the two reaction system. Control experiment revealed that no aza-Michael addition product was detected with 1-phenylprop-2-en-1-one substrate under the standard conditions (Scheme 4d), which further confirmed the vital role of the *β*-methylsulfide ketone species in this transformation.

To further reveal the role of the Co catalyst, several reactions were then designed in the $Co(acac)_2$-catalyzed system. Firstly, treatment of **1a** in the absence of **2a** for 4 h gave **6** in 17% yield (Schemes 4e). Moreover, the treatment of **2a** in the

presence of $K_2S_2O_8$ and DMSO provided the methylenebisamide species **8** in good yield (Schemes 4f). Finally, the cross-coupling was easily achieved by heating **1a** and **8** with $Co(acac)_2$, $K_2S_2O_8$ and AgOAc in DMSO for 12 h to deliver **3aa** as the final product in decent yield (Schemes 4g). To sum up, these results suggested that: (a) the methylenebisamide species (**8**) might act as the active intermediate to involve this transformation for the synthesis of **3aa**, and (b) two independent, side-by-side, and competitive reactions from **1a** and the generated **6** with **8** might exist in the Co(II) catalysis, thereby yielding the mixed **3a** and **3aa** as the final products, which was in consistent with our experimental observation in conditions optimization.

On the basis of our experimental results and literature precedents,[10,18,20,21] two plausible cobalt-catalyzed oxidative reaction pathways for the tunable synthesis of **3a** and **3aa** were depicted in Scheme 5. Initially, the DMSO is oxidized by $K_2S_2O_8$ to yield intermediate **A**, which is attacked by the enolate intermediate **1aa** derived from the ketone **1a**, thus giving the bisalkylsulfurized intermediate **D** via intermediates **B** and **C**. Then, **D** delivers *α*-methylene-*β*-methylsulfide ketone species **6** with the emission of MeSH. On the other hand, **A** can also be attacked by the amide substrate (**2a**) to produce the intermediate **B'**, which further reacts with an additional **2a** via a classical nucleophilic substitution to provide the methylenebisamide **8**, followed by the cleavage of the C-N bond to give **G** and **H**. The cobalt(III) species is coordinated with **G** in the presence of **6** to provide the intermediate **E** via the cleavage of the second C-S bond. Subsequent reductive elimination of the C-N bond gives the intermediate **F.** Finally, protodemetallation of **F** provides the final product **3a**. Alternatively, the reaction of **H** with the cobalt(II) catalyst gives the five-membered cobalt(III) species **I**. The insertion of **1aa** into the C-Co bond gives a seven-membered metalacycle (**J**), which undergoes *β*-hydride elimination/protonolysis to give the final product **3aa** via the intermediate **K**. However, more investigations are still needed to authenticate the above proposed mechanism.

**Scheme 5.** Proposed catalytic cycle.

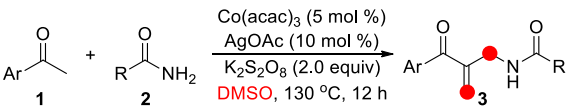



## Conclusion

In summary, we have developed, for the first time, a cobalt(III)-catalyzed and DMSO-involved cross-coupling of ketones with amides to give direct access of *β*-amino ketones, in which DMSO was employed as both the solvent and the one or two carbon building block. The remarkable features of this methodology include the simple and readily available starting materials, excellent substrate/functional group tolerance, mild reaction conditions and high efficiency, thereby rendering it as a highly versatile and atom-economical alternative to the existing protocols for building the *β*-amino ketone framework. Through a set of mechanistic investigations, the *β*-methylsulfide ketone species was identified as the active intermediate and a possible reaction pathway was rationally derived. Systematic studies on the mechanism and application of such transformation are in progress in our laboratories.

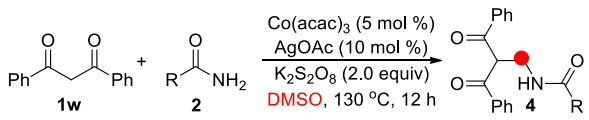
## Experimental Section

### General procedure for the synthesis of *β*-amino ketones




A reaction flask (25 mL) was charged with ketone **1** (0.5 mmol, 1.0 equiv), amide **2** (0.6 mmol, 1.2 equiv), $Co(acac)_3$ (9.0 mg, 5.0 mol %), AgOAc (8.4 mg, 10.0 mol %) and $K_2S_2O_8$ (1.0 mol, 270 mg, 2.0 equiv), then the DMSO (4 mL) was added. The mixture was stirred at 130 °C for 12 hours under an atmosphere of air. After the reaction finished, the resulted mixtures were diluted with 20 mL of dichloromethane and washed with 20 mL of $H_2O$. The aqueous layer was extracted twice with dichloromethane (10 mL) and the combined organic phase was dried over $Na_2SO_4$. After evaporation of the solvents, the residue was purified by silica gel chromatography

(hexane/AcOEt = 15 : 1 - 8 : 1) to yield the corresponding *β*-amino ketone product **3**.




A reaction flask (25 mL) was charged with diketone **1w** (0.5 mmol, 1.0 equiv), amide **2** (0.6 mmol, 1.2 equiv), $Co(acac)_3$ (9.0 mg, 5.0 mol %), AgOAc (8.4 mg, 10.0 mol %) and $K_2S_2O_8$ (1.0 mol, 270 mg), then the DMSO (4 mL) was added. The mixture was stirred at 130 °C for 12 hours under an atmosphere of air. After the reaction finished, the resulted mixtures were diluted with 20 mL of dichloromethane and washed with 20 mL of $H_2O$. The aqueous layer was extracted twice with dichloromethane (10 mL) and the combined organic phase was dried over $Na_2SO_4$. After evaporation of the solvents, the residue was purified by silica gel chromatography (hexane/AcOEt = 10 : 1 - 3 : 1) to yield the corresponding *N*-(2-benzoyl-3-oxo-3-phenylpropyl) amide derivative **4**.

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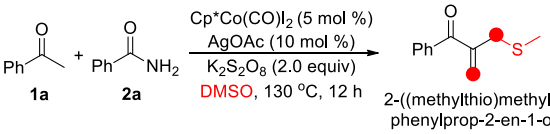


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FULL PAPER

# Cobalt(III)-Catalyzed and Dimethyl Sulfoxide-Involved Cross-Coupling of Ketones and Amides for Direct Synthesis of *β*-Amino Ketones

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