Decarboxylative Coupling

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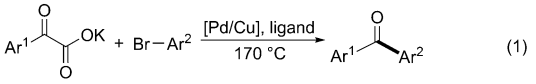
Transition-Metal-Free Formal Decarboxylative Coupling of α-Oxocarboxylates with α-Bromoketones under Neutral Conditions: A Simple Access to 1,3-Diketones**

Zhen He, Xiaotian Qi, Shiqing Li, Yinsong Zhao, Ge Gao, Yu Lan,* Yiwei Wu, Jingbo Lan, and Jingsong You**

Abstract: *A transition-metal-free formal decarboxylative coupling reaction between α-oxocarboxylates and α-bromoketones to synthesize 1,3-diketone derivatives is presented. In this reaction, a broad scope of substrates can be employed, and neither a metal-based reagent nor an additional base is required. DFT calculations reveal that this reaction proceeds through a coupling followed by decarboxylation mechanism and the α-bromoketone unprecedentedly serves as a nucleophile under neutral conditions. The rate-determining step is an unusual hydrogen-bond-assisted enolate formation by thermolysis.*

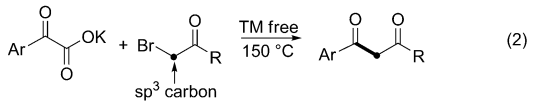
Transition-metal-catalyzed decarboxylative coupling reactions have recently attracted much attention for their use in C–C bond formation reactions.[1] Among them, α-oxocarboxylic acids have emerged as a new acyl anion reagent.[2] The acyl anions[3] are generated in situ by extrusion of carbon dioxide facilitated by the use of transition metals (TM). Compared to the masked acyl reagents, such as dithianes,[4] protected cyanohydrins,[5] and hydrazones,[6] where the carbonyl functionality must be unmasked after the reaction, α-oxocarboxylic acids are stable, easy to prepare,[7] and need no post-reaction treatment. These advantages make them convenient and clean acyl anion equivalents, which complement the traditional acyl cation equivalents, such as acyl chlorides and anhydrides. In 2008, Goossen et al. reported the synthesis of diarylketones through the Pd/Cu-catalyzed decarboxylative coupling of α-oxocarboxylates with aryl bromides [Eq. (1)].[2a] After this seminal work, various sp^2-hybridized carbon derivatives, including allyls,[2d,e] (hetero)-arenes,[2f–j] enamides,[2k] and formamides,[2l] have been successfully acylated using this strategy. However, no example involving sp^3-hybridized carbon centers has been reported.

Goossen et al.: TM-catalyzed decarboxylative coupling with sp^2 carbon



(1)

This work: TM-free decarboxylative coupling with sp^3 carbon



(2)

α-Bromoketones are commonly used C(sp^3) electrophiles in organic synthesis.[8] We envisioned that the decarboxylative coupling of α-oxocarboxylate salts with α-bromoketones should afford 1,3-diketone derivatives, which are an important class of organic compounds. 1,3-Diketone derivatives are starting materials in Knoevenagel reactions and as intermediates for the synthesis of heterocycles. Many naturally occurring 1,3-diketones exhibit antimicrobial, antiviral, and antifungal activities.[9] They also serve as bidentate ligands in metal complexes for catalysis and luminescent materials.[10] The main strategy to construct this useful scaffold is the well-established enolate chemistry. The typical example is the classical Claisen condensation reaction between an ester and a ketone, in which a hard enolate[11] is generated by the deprotonation of the α-hydrogen atom on the ketone using a strong base. The rigorous reaction conditions required and hence limited substrate scope are major drawbacks for this reaction. Recent improvements include the use of soft enolates in the presence of a Lewis acid and a weak base,[12] tin enolates[13] through a radical process, and kinetic zinc enolates using bis(iodozincio)methane.[14] The decarboxylative coupling strategy would certainly provide an attractive alternative route to 1,3-diketone compounds. Herein, we report that α-oxocarboxylates undergo reaction with α-bromoketones to afford 1,3-diketones in the absence of a transition-metal catalyst [Eq. (2)]. DFT calculations suggested a unique mechanism involving coupling followed by decarboxylation.

Our investigation started with the cross-coupling reaction between potassium 2-oxo-2-phenylacetate (**1a**) and 2-bromo-1-phenylethanone (**2a**) in the presence of $PdCl_2$ (2 mol%),

[*] Z. He, S. Li, Y. Zhao, Prof. Dr. G. Gao, Y. Wu, Prof. Dr. J. Lan, Prof. Dr. J. You
Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Medical School, Sichuan University
29 Wangjiang Road, Chengdu 610064 (P. R. China)
E-mail: gg2b@scu.edu.cn
jsyou@scu.edu.cn
X. Qi, Prof. Dr. Y. Lan
School of Chemistry and Chemical Engineering
Chongqing University, Chongqing 400030 (P. R. China)
E-mail: lanyu@cqu.edu.cn

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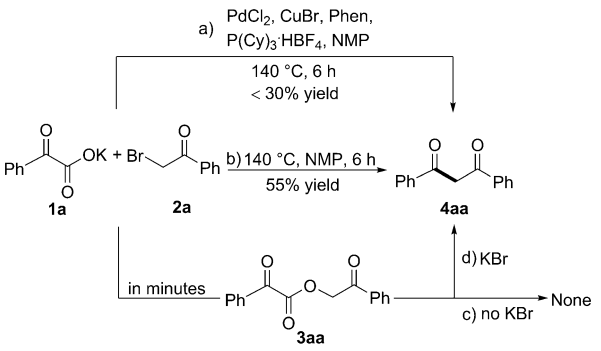


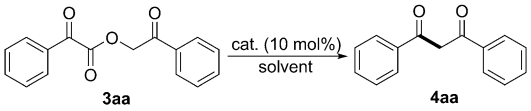
Scheme 1. Initial investigations of the reaction. NMP = *N*-methyl-2-pyrrolidone; Phen = phenanthroline; Cy = cyclohexyl.

CuBr (15 mol %), and $P(Cy)_3 \cdot HBF_4$ (6 mol %) in *N*-methyl-2-pyrrolidone (NMP; Scheme 1).[2a] After heating at 140 °C for 6 h, the desired 1,3-diphenylpropane-1,3-dione (**4aa**) was obtained in a low yield (< 30 %, Scheme 1 a). Surprisingly, the control experiment without Pd, Cu, and ligand gave an even better yield of 55 % (Scheme 1 b). Meanwhile, the formation of compound 2-oxo-2-phenylethyl 2-oxo-2-phenylacetate (**3aa**) was detected within minutes of the start of the reaction.

To gain a better understanding of this decarboxylative coupling reaction, the ester **3aa** was then separately synthesized[15] as the starting material for further investigations. However, heating **3aa** in NMP alone did not result in the formation of **4aa** (Scheme 1 c). When KBr, the inorganic product of the metathesis of **1a** and **2a**, was added, **4aa** was again obtained (Scheme 1 d). It suggested that KBr catalyzed the intramolecular decarboxylation of **3aa** to give the 1,3-diketone product **4aa**. The ICP–AES analysis (inductively coupled plasma atomic emission spectroscopy) showed that the concentrations of transition metals, such as Pd, Ag, Rh, Ru, and Cu, in the reaction system were lower than the detection limits of the machine, confirming that no transition metal was involved. Thus, this reaction was quite attractive because it was not only a decarboxylative coupling reaction of an α-oxocarboxylate with an sp^3-hybridized carbon, but also a TM-free version. A radical pathway[16] was also precluded since the reaction was not affected significantly in the presence of a radical scavenger, such as 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO) or 3,5-di-*tert*-4-butylhydroxytoluene (BHT; see Supporting Information).

We then set out to optimize the reaction conditions (Table 1). **4aa** was isolated in 65 % yield in the decarboxylation of **3aa** in the presence of KBr (10 mol %; entry 1). Using KCl as the catalyst only gave 38 % yield of **4aa** and the majority of the **3aa** reagent was recovered (entry 2). The use of KI resulted in a complicated mixture and only a trace amount of **4aa** (entry 3). When different cations were used, tetrabutylammonium bromide (TBAB) resulted in an enhanced yield of 82 %, whereas NaBr gave a similar result as KBr (entries 4 and 5). The use of 1.0 equivalent of TBAB further increased the yield to 86 % (entry 6). These results suggested that the bromide anion might be the actual catalyst and the TBA cation probably served as the phase-transfer reagent and the intermediate stabilizer.[17] It was also noted

Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst	Solvent	*T* [°C]	*t* [h]	Yield[b] [%]
1	KBr	NMP	140	6	65
2	KCl	NMP	140	6	38
3	KI	NMP	140	6	trace
4	NaBr	NMP	140	6	63
5	TBAB	NMP	140	6	82
6[c]	TBAB	NMP	140	6	86
7	TBAB	DMF	140	6	69
8	TBAB	DMA	140	6	73
9	TBAB	toluene	140	6	66
10	TBAB	DMSO	140	6	N.D.
11	TBAB	NMP	120	6	54
12	TBAB	NMP	160	6	88
13	TBAB	NMP	140	8	**92**
14[d]	TBAB	NMP	140	8	88
15[e]	TBAB	NMP	150	6	**73**

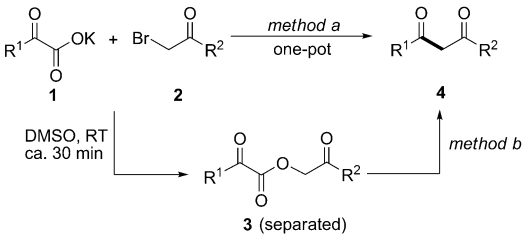
[a] The reactions were carried out with **3aa** (0.50 mmol) in solvent (1 mL) at 140 °C in the present of a catalyst (10 mol %, unless otherwise stated) under N_2. [b] Yield of isolated product. [c] TBAB (1.0 equiv; tetrabutylammonium bromide) was used. [d] NMP was used as purchased. [e] One-pot reactions between **1a** and **2a** in stoichiometric amounts. N.D.: not detected. Trace: detected by GC–MS. DMA = dimethylacetamide. DMF = dimethylformamide.

that using less potassium ion was beneficial, comparing entry 1 with the direct coupling of **1a** with **2a** (Scheme 1 b). Other aprotic solvents were also tested in the reaction but gave rise to lower yields (entries 7–9), but no product was detected in dimethylsulfoxide (DMSO; entry 10). Only a small improvement of the yield was found at 160 °C whereas a significantly decreased yield was obtained at 120 °C (entries 11 and 12). Finally, extending the reaction time to 8 hours resulted in an optimal yield of **4aa** of 92 % (entry 13). The use of unpurified NMP only slightly influenced the reaction (entry 14). More practically, the yield of the direct-coupling reaction of **1a** with **2a** could be improved to 73 % in the presence of TBAB (10 mol %) at 150 °C for 6 h (entry 15).

With the optimized conditions in hand, a series of potassium α-oxocarboxylates **1** and α-bromoketones **2** were subjected to the TBAB-catalyzed decarboxylative reaction (Table 2, method a). In general, the one-pot procedure delivered **4** in yields ranging from 52 % to 81 %. The aryl α-oxocarboxylates **1** (R^1 = aryl) with an electron-withdrawing substituent on the phenyl ring gave satisfactory yields (entries 2–6) except for the reaction employing **1** with an *ortho*-bromo substituent (entry 4). **1g** with an electron-donating methoxy group required 18-crown-6 (1.0 equiv) to achieve comparable yields (entries 7, 23, and 24). The heteroaryl α-oxocarboxylate containing a thienyl ring produced the desired 1,3-diketone **4ha** in 53 % yield (entry 8). The alkyl α-oxocarboxylate derivatives **1** (R^1 = alkyl) gave complicated mixtures and very low yields (entries 9 and 10).

For α-bromoketones **2**, both aryl and alkyl groups were suitable (R^2 = aryl and alkyl). The *para*- and *meta*-methoxy substrates afforded products **4ag** and **4ak** in 72 % and 81 %

Table 2: Substrate scope of the decarboxylative reaction.[a]



Entry	R^1	R^2	4	Yield[b] [%]
1	Ph	Ph	**4aa**	73 (92)
2	*p*-BrPh	Ph	**4ba**	66 (87)
3	*m*-BrPh	Ph	**4ca**	73 (82)
4	*o*-BrPh	Ph	**4da**	54 (58)
5	*p*-ClPh	Ph	**4ea**	78
6	*p*-CF_3Ph	Ph	**4fa**	62 (81)
7	*p*-MeOPh	Ph	**4ga**	74[c] (86)
8	2-thienyl	Ph	**4ha**	53
9	Me	Ph	**4ia**	– (52)
10	*i*Pr	Ph	**4ja**	– (49)
11	Ph	*p*-MeOPh	**4ag**	72 (74)
12	Ph	*m*-MeOPh	**4ak**	81 (91)
13	Ph	*o*-MeOPh	**4al**	56 (54)
14	Ph	1-naphthyl	**4am**	75 (76)
15	Ph	benzo[*d*][1,3]dioxole	**4an**	75 (91)
16	Ph	*p*-MeOC(O)Ph	**4ao**	64 (67)
17	Ph	*p*-NO_2Ph	**4ap**	69 (71)
18	Ph	*p*-CNPh	**4aq**	64
19	Ph	*p*-HOPh	**4ar**	58
20	Ph	PhCH=CH-	**4as**	73 (72)
21	Ph	*t*Bu	**4at**	74 (62, 81[d])
22	*p*-BrPh	*p*-BrPh	**4bb**	58 (79)
23	*p*-MeOPh	*p*-MeOPh	**4gg**	57[c] (61)
24	*p*-MeOPh	*p*-BrPh	**4gb**	69[c] (66)
25	*p*-ClPh	*p*-MeOPh	**4eg**	70
26	2-thienyl	2-thienyl	**4hh**	52 (50)

[a] Method a: reagents **1** (0.50 mmol) and **2** (0.50 mmol) in NMP (2 mL) in the presence of TBAB (10 mol%) at 150°C for 6 h under N_2. Method b: reagent **3** (0.50 mmol) in NMP (1 mL) at 140°C for 8 h in the presence of TBAB (10 mol%) under N_2. [b] Yields obtained using method a given outside parentheses, yields obtained using method b given inside parentheses. [c] 18-crown-6 (0.50 mmol) was added. [d] 170°C.

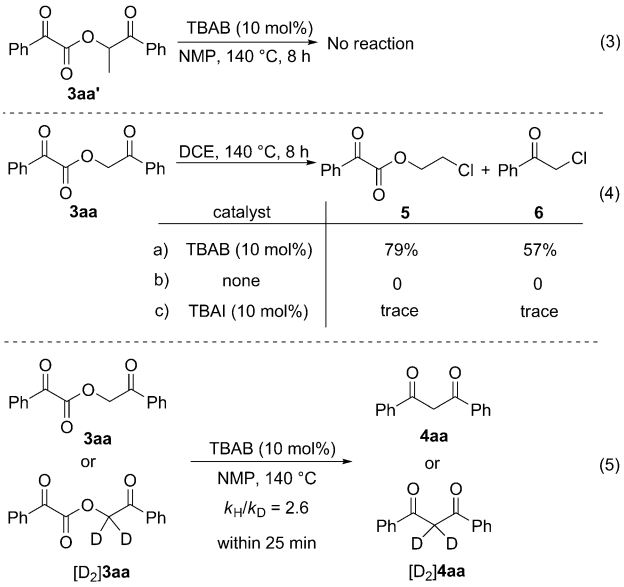
yields, respectively, whereas the *ortho*-methoxy substrate gave **4al** in 56% yield (entries 11–13). When R^2 was the bulky 1-naphthyl group, the yield of **4am** reached 75% (entry 14). The sensitive functionalities, such as benzo[*d*][1,3]dioxole, *para*-MeOC(O)Ph, *para*-NO_2Ph, and *para*-CNPh, were all tolerated (entries 15–18). Strikingly, phenol was also well-tolerated, and the phenol-containing 1,3-diketone **4ar** was achieved in 58% yield (entry 19). Additionally, the α,β-unsaturated 1,3-diketone **4as** was synthesized in 73% yield (entry 20). When alkyl α-bromoketone **2t** was used, 1-*tert*-butyl-3-phenylpropane-1,3-dione (**4at**) was obtained in 74% yield (entry 21). As well as the monofunctional 1,3-diketones, the bifunctional 1,3-diketones could also be accessed conveniently. The symmetrical and unsymmetrical 1,3-diketones with electron-withdrawing and electron-donating phenyl were obtained in 57–70% yields (entries 22–25).The diheteroaryl-functionalized 1,3-diketone derivative **4hh** was isolated in 52% yield (entry 26).

Reactions starting from the ester derivatives **3** were also conducted (Table 2, method b). The corresponding yields were generally higher than the one-pot processes, probably because of the absence of the deleterious potassium ion. Additionally, the reactions of **3ia** and **3ja** (R^1 = Me and *i*Pr, R^2 = phenyl) afforded the 1,3-diketones **4ia** and **4ja** in 52% and 49% yields, respectively (entries 9 and 10). It should also be mentioned that the yield of **4at** could be improved to 81% using method b by elevating the reaction temperature to 170°C (entry 21), but limited yield improvements were found for other substrates after increasing the reaction temperature.

The preliminary mechanistic study showed that the reaction was triggered by the S_N2 attack of a bromide anion toward the methylene carbon of the ester **3** to cleave its C–O bond. When a hydrogen atom on the methylene carbon was substituted by a methyl group (**3aa′**), which hindered the bromide attack, no reaction occurred [Eq. (3)]. When **3aa** was heated together with TBAB (10 mol%) in 1,2-dichloroethane (DCE), compounds 2-chloroethyl 2-oxo-2-phenylacetate (**5**) and 2-chloro-1-phenylethanone (**6**) were obtained in 79% and 57% yields, respectively [Eq. (4), a]. Without TBAB, however, only the starting material **3aa** was recovered [Eq. (4), b]. These results indicated that bromide first attacked the methylene carbon of **3aa** to generate 2-bromo-1-phenylethanone (**2a**) and the α-oxocarboxylate anion. Then esterification of the α-oxocarboxylate anion with DCE formed the ester **5** and released a chloride anion. Finally, halide exchange between the chloride anion and **2a** gave product **6**. Interestingly, the reaction in the presence of tetrabutylammonium iodide (TBAI) afforded only trace amounts of **5** and **6**, and **3aa** was almost fully recovered [Eq. (4), c].[18] However, the use of KI as the catalyst led to a complicated reaction mixture in NMP, in which the more nucleophilic iodide probably preferred to attack the carbonyl carbon rather than the methylene carbon of **3aa** (Table 1, entry 3). Other nucleophiles, such as Et_3N and PPh_3, were not effective. Therefore, it is assumed that the nucleophilicity of bromide should be key to this reaction. The kinetic isotopic effect (KIE) experiment gave a k_H/k_D value of 2.6, indicating that the cleavage of the methylene C–H bond was involved in the rate-determining step [Eq. (5); see also the Supporting Information].

The next decarboxylation step was elusive as the spontaneous decarboxylation of an α-oxocarboxylate anion seemed unlikely to occur without the help of any other reagent under the current conditions.[1b,d] To shed light on this process, the density functional theory (DFT) method B3LYP with a standard 6-31 + G(d) basis set was employed. The calculation suggested that the reaction was a two-stage process as shown in Figure 1. In the first stage, the C–O bond of the ester **3aa** was cleaved by the S_N2 attack of the bromide anion to form α-bromoketone **2a** and α-oxocarboxylate anion **8** through the transition state **7-TS** with an energy barrier of 11.2 kcal mol^{-1} (path I).

In the second stage, the keto–enol tautomerization of **2a** tended to form enol **2a′** as a result of the stabilization by the formation of an eight-membered ring **9** through two hydrogen



bonds, which was 3.2 kcal mol^{-1} lower in energy. Next, an unusual thermolytic dissociation of the complex **9** generated the naked enolate anion **10** and the α-oxocarboxylic acid **11** with an energy barrier of 23.5 kcal mol^{-1}. The nucleophilic attack of **10** toward the carbonyl carbon in **11** took place immediately via the transition state **12-TS** to form the intermediate **13** through an energy barrier of only 0.6 kcal mol^{-1}. Next, a synergetic decarboxylation and bromide leaving process via the transition state **14-TS** (5.4 kcal mol^{-1} higher in energy) formed the C=C double bond to give **15**, which was the more stable isomer of 1,3-diketone **4aa**. An alternative potential route, denoted path II, was also determined by DFT calculations. Path II involves the direct nucleophilic attack of α-bromoketone **2a** towards α-oxocarboxylate anion **8** via the transition state **16-TS**. The relative free energy of **16-TS** turned out to be 33.9 kcal mol^{-1}, which was 6.2 kcal mol^{-1} higher than that of **12-TS**. Therefore, path II was thermodynamically disfavored as compared with path I.[19] Based on the DFT calculations, a proposed mechanism is shown in Scheme 2.

Several key points should be made regarding these proposed pathways. First, the crucial step was the dissociation of complex **9**, which resulted in an unusual proton transfer from enol **2a′** to α-oxocarboxylate **8** to generate the more basic naked enolate **10** and the more acidic α-oxocarboxylic acid **11**. The process was believed to be a thermolysis facilitated by hydrogen bonding. Second, the nucleophilic attack via transition state **12-TS** was the rate-determining step, which had the highest energy of 27.7 kcal mol^{-1} relative to **3aa**. Third, the effect of the TBA cation was to stabilize the as-generated naked enolate anion.[20] Finally, the nucleophilic addition of the α-bromoketone to the carbonyl carbon of the α-oxocarboxylate gave the intermediate **13**, which had an α-hydroxycarboxylate structure with an α-bromoketone substituent. It had a significantly lower energy barrier of only 5.4 kcal mol^{-1} to achieve decarboxylation, compared with transition-metal-assisted decarboxylation.[2a,b] A comparable reported example is the thiazolium-substituted α-hydroxycarboxylate intermediate reported by Scheidt and co-workers.[21] CO_2 was easily extruded from this intermediate under mild conditions to generate the active Breslow intermediate, which subsequently underwent addition to the α,β-unsaturated 2-acyl imidazoles to afford 1,4-dicarbonyl compounds.

In summary, we report herein a transition-metal-free decarboxylative coupling of α-oxocarboxylates with α-bromoketones to synthesize 1,3-diketone compounds. The reaction was self-catalyzed by the bromide anion but performed better in the presence of a catalytic amount of TBAB. It featured mild and neutral conditions without any metal or extra base, and also tolerated a broad spectrum of functional groups. This reaction is unique in two aspects: a) the transition-metal-free formal decarboxylative coupling of a C(sp^3)-hybridized substrate proceeded through a coupling followed by decarboxylation pathway, and b) α-bromoketone, a common electrophile, acted as a nucleophile through its enolate form by thermolysis. Note, the mechanism of coupling followed by decarboxylation significantly lowers the energy barrier for decarboxylation and may serve as a new strategy to conduct metal-free decarboxylative coupling reactions. Other applications using this strategy are currently under investigation in our laboratory.

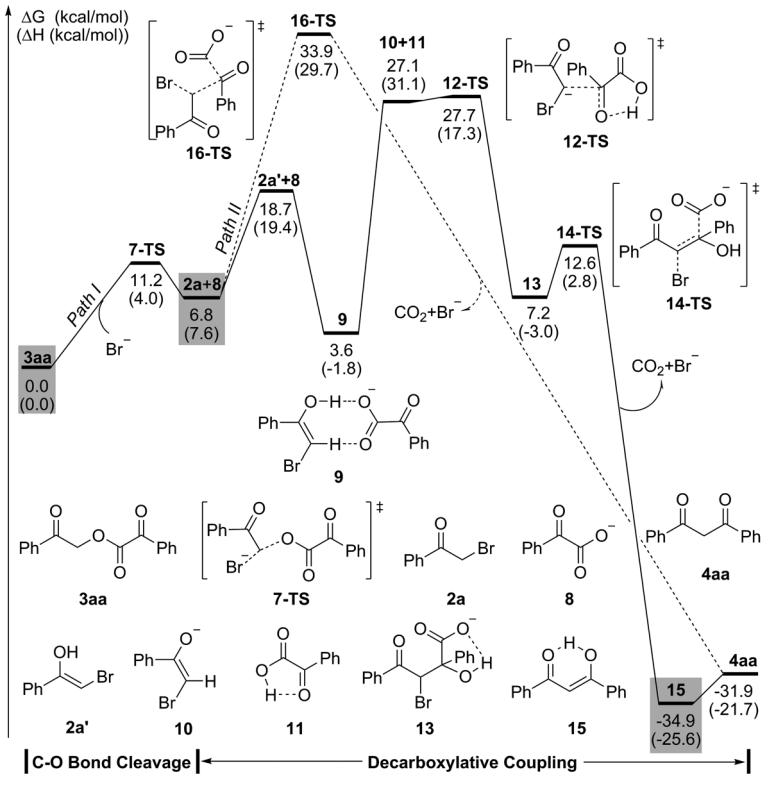
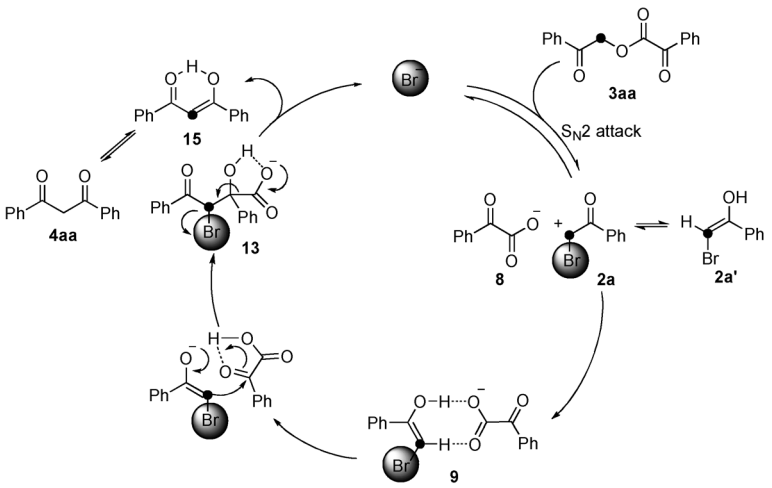


Figure 1. Free energy profile of the decarboxylative coupling reaction.



Scheme 2. Proposed mechanism for the bromide-catalyzed formation of **4aa**.

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