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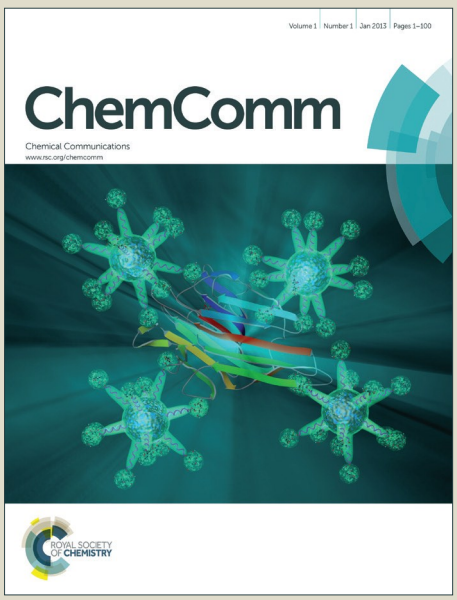

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Decarboxylative C_{sp}^3-C_{sp}^3 Coupling for Benzylation of Unstabilized Ketone Enolates: Synthesis of *p*-(Acylethyl)phenols

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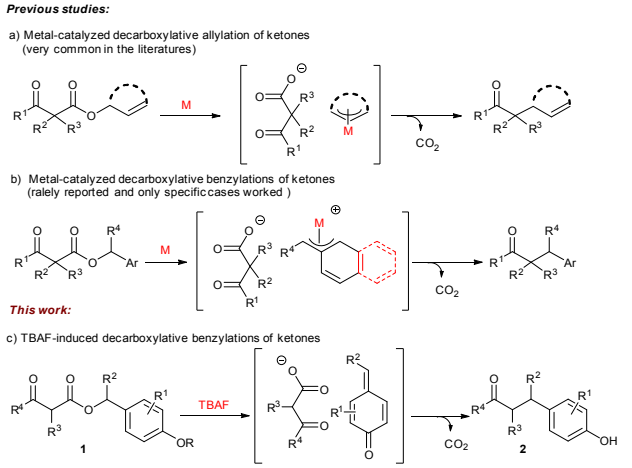
A new decarboxylative C_{sp}^3–C_{sp}^3 coupling approach for the benzylation of ketone enolates has been developed. A variety of raspberry ketone derivatives were conveniently synthesized in good to excellent yields under mild conditions. A crossover reaction shed light on the mechanism of this tandem reaction.

Decarboxylation has garnered tremendous attention as important synthetic methods for the carbon–carbon bond formation due to its high efficiency in generating a nucleophile *in situ* under mild conditions.[1] In particular, as one of the most efficient ways to capture the ketone enolates, palladium-catalyzed decarboxylative allylation of β–ketoesters[2] has attracted considerable attention since the early discoveries reported by Tsuji[3] and Saegusa[4] (Scheme 1a). Compared with a great wealth of studies on the decarboxylative allylation of ketone enolates, the corresponding benzylation reactions were much less investigated and more challenging, mainly due to transient loss of aromaticity upon π–benzyl formation.[5] Catalytic benzylation becomes more difficult for the unstabilized nucleophiles,[6] though the corresponding reactions of stabilized nucleophiles work well.[5f–i,7] Only few examples involving unstabilized ketone enolates have recently been reported (Scheme 1b).[8] In 2010, Tunge reported Pd-catalyzed decarboxylative benzylation of β–ketoesters to access a broad range of α–polyaromatic benzyl ketones. Recently, Hu developed a Cu–catalyzed decarboxylative propargylic alkylation which allowed access to a series of benzyl ketones bearing β–ethynyl. So decarboxylative benzylation reactions are still in their infancy.

Given the difficulty in generating the π–benzyl-metal species in transition-metal-catalyzed decarboxylative benzylations, we speculate that a *para*-siloxybenzyl β–ketoester might be a suitable precursor for the decarboxylative benzylation reaction (Scheme 1c). First, cleavage of the benzylic C_{sp}^3–O bond followed by decarboxylation might be initiated upon removal of the silyl group. Second, *p*-quinone methide (*p*-QMs), formed upon cleavage of the benzylic C_{sp}^3–O bond, could serve as a highly reactive electrophilic benzylating species to enable the subsequent benzylation reaction.[9] Herein, we disclose our findings regarding TBAF–induced decarboxylative benzylation of ketone enolates for the C_{sp}^3-C_{sp}^3 bond formation which provides an efficient approach to a series of synthetically useful *p*-(acylethyl)phenols such as raspberry ketone, vanillylacetone, and their derivatives under mild conditions.[10]



Scheme 1 Decarboxylative benzylation of ketone enolates

To test the feasibility of our hypothesis, *para*-siloxybenzyl β–ketoester **1a** was selected as a model substrate to evaluate the benzylation of ketone enolates (Table 1). To our excitement, the desired reaction proceeded smoothly in THF at room temperature, giving the expected ketone **2a** in 37% yield in less than 5 min (entry 1). Solvent screening revealed that toluene delivered a slightly improved yield (entries 2-8).

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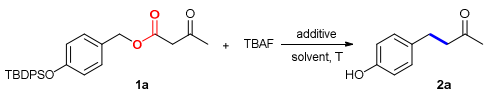
The reaction was then performed at different temperatures. It was found that increasing or decreasing the temperature did not improve the reaction (entries 9-11). Application of powdered 4 Å molecular sieves rendered the products in similar yields (entry 12). Next, the effect of acids was examined. When HOAc was added, the reaction could hardly proceed (entry 13). As for the role of Lewis acids, $Co(C_5H_7O_2)_3$, $Ni(OAc)_2{\cdot}4H_2O$, and $CuSO_4{\cdot}5H_2O$ had little impact on the product yields (entries 15, 17, and 18), and $MgCl_2$ led to a poor yield (18%), while $FeCl_3$ completely shut down the reaction (entries 14 and 16). To our delight, in the presence of $ZnCl_2$, the yield of the product was increased to 82% (entry 19). By contrast, $ZnBr_2$ and ZnI_2 did not perform as well as $ZnCl_2$ (entries 20 and 21). $ZnCl_2$ promoted the reaction presumably by its stabilization effect on the enolate generated *in situ*. It was noteworthy that one or two side-products were formed in some cases, which were determined to be 4-(hydroxymethyl)phenol and/or the corresponding desilylation product.

Table 1 Optimization of the decarboxylaive benzylation reaction conditions[a]

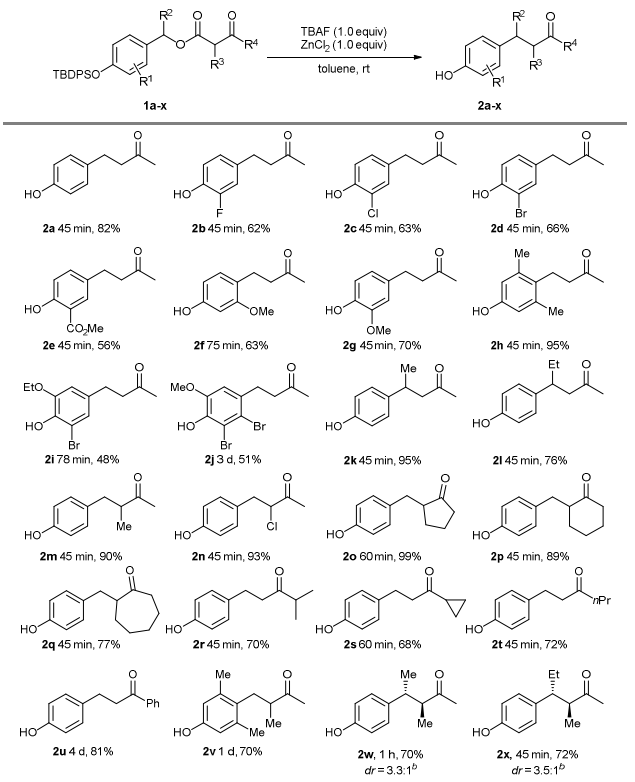


entry	solvent	T (°C)	additive[b]	time (min)	yield (%)
1	THF	rt	/	< 5	37
2	toluene	rt	/	45	57
3	ACN	rt	/	45	46
4	CH_2Cl_2	rt	/	45	48
5	1,4-dioxane	rt	/	45	54
6	xylene	rt	/	45	55
7	Et_2O	rt	/	45	55
8	*n*-hexane	rt	/	45	56
9	toluene	0	/	120	41
10	toluene	50	/	45	53
11	toluene	100	/	45	44
12[c]	toluene	rt	4 Å MS	45	56
13	toluene	rt	CH_3COOH	45	trace
14	toluene	rt	$MgCl_2$	4 d	18
15	toluene	rt	$Co(C_5H_7O_2)_3$	45	49
16	toluene	rt	$FeCl_3$	45	0
17	toluene	rt	$Ni(OAc)_2{\cdot}4H_2O$	90	62
18	toluene	rt	$CuSO_4{\cdot}5H_2O$	90	58
19	**toluene**	**rt**	**$ZnCl_2$**	**45**	**82[d]**
20	toluene	rt	$ZnBr_2$	4 d	66
21	toluene	rt	ZnI_2	45	12

[a]Determined by 1H NMR analysis of purified reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard, TBAF (*tetra-n* butylammonium fluoride, 1M in THF) is used. [b]1.0 equiv of additive was employed. [c]100 wt % of 4 Å MS was used. [d]Isolated yield.

With the optimized reaction conditions identified, we started to investigate the scope of this tandem reaction. As demonstrated in Table 2, the substituents on aromatic ring were first studied. Substrates bearing electron-deficient substituents (F, Cl, Br, CO_2Me) or electron-rich substituents (2-OMe, 3-OMe) underwent the reaction smoothly, giving the corresponding products in moderate to good yields (**2b-g**). Gratifyingly, the reaction accommodated the disubstitution pattern at the both positions ortho to the (acyloxy)methyl or the siloxy group (**2h-i**). Notably, substrate **1h** generated the desired product in a high yield of 95%. In addition, polysubstituted substrate proved to be amenable to the process as well, albeit somewhat reluctantly, furnishing the corresponding product in 51% yield after a three-day reaction (**2j**).

Table 2 Substrate scope studies[a]



[a]Reaction conditions: 1**a-x** (1 equiv), TBAF (1 equiv), $ZnCl_2$ (1 equiv) in toluene, rt; **1g** (0.2 mmol), TBAF (0.3 mmol), $ZnCl_2$ (0.2 mmol), isolated yield. [b]Ratios were determined by ^{1}H NMR analysis of the crude mixture.

The substituent effect of the *β*-keto acyl moieties was examined subsequently. Substituents at the benzyl position were compatible with the reaction conditions and the expected products were obtained in good to excellent yield (**2k** and **2l**). It is noteworthy that this method could be used to construct hindered tertiary carbon centers with high efficiency (**2m**, **2n** and **2v**). To our delight, the reaction also worked well with the substrates containing a five-, six- or seven–membered cycloalkanone ring (**2o**-**q**). Moreover, various alkyl substituents attached to the terminal residue had little effect on the reaction yields, presumably because the terminal groups were remote to the reactive site (**2r-t**). The presence of a terminal phenyl group was also well-tolerated, as demonstrated by the fact that phenyl ketone **1u** reacted to afford **2u** in 81% yield, yet taking a prolonged reaction period (**2u**). Substrates **1w** and **1x**, bearing two stereocenters, reacted to afford the expected products **2w** and **2x** in good yields with moderate diastereoselectivities.[11]

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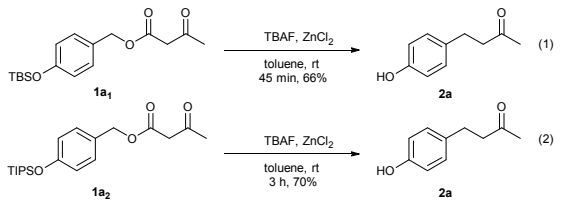
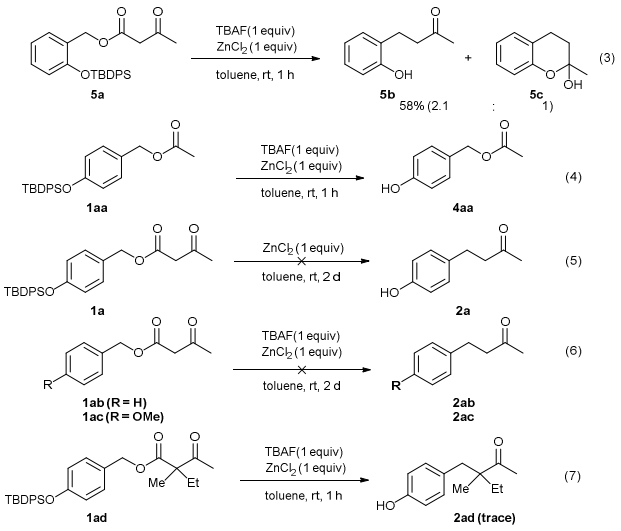
Substrates bearing different silyl groups (TBS and TIPS) led to the formation of products **2a** in the yields of 66% and 56%, respectively (Scheme 2).



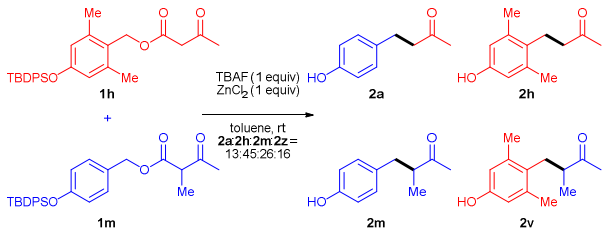
Scheme 2 Substrate scope studies: different silyl groups

Several additional substrates (**5a, 1a, 1aa**-**1ad**) were examined to gain certain insights into the reaction mechanism (Scheme 3). *ortho*-Silylated phenolic benzyl β–ketoester **5a** underwent the transformation smoothly under the optimized reaction conditions, giving a mixture of the expected ketone **5b** and the corresponding hemiacetal **5c** in a ratio of 2.1:1 (eq 3). If the substrate was lacking a β-keto moiety (e.g., in substrate **1aa**), only desilylation was effected (eq 4). A fluoride source was necessary to trigger the reaction since no reaction took place in the absence of TBAF (eq 5). Moreover, no reaction was observed with **1ab** or **1ac** (eq 6) either. Thus, the desilylation step proved to be crucial for the overall reaction outcome. Finally, treatment of the α,α-disubstituted reactant **1ad** with TBAF and $ZnCl_2$ led only to a trace amount of ketone **2ad** (eq 7).



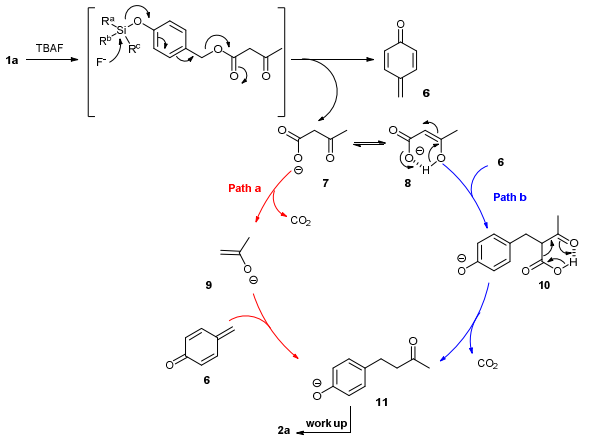
Scheme 3 Experiments of mechanistic significance

Furthermore, a crossover reaction with a 1:1 mixture of β–ketoesters **1h** and **1m** was conducted (Scheme 4). Based upon the HRMS and GC–MS analyses, two crossover products (**2a** and **2v**) were also formed in addition to **2h** and **2m**, demonstrating that the reaction involves an intermolecular process.



Scheme 4 Crossover reaction experiment

A tentative mechanism is proposed for the current decarboxylative benzylation process (Scheme 5).[2b] First, the reaction is triggered by the attack of TBAF to the silyl group to cleave the Si–O bond, resulting in the formation of the unstable *p*-QM **6** and the β–keto carboxylate **7**. In principle, both path a and path b should be possible. In path a, facile decarboxylation occurs first to give enolate **9**, 1,6–conjugated addition of which with *p*-QM **6** affords raspberry ketone **2a**. For path b, tautomerization of β–keto carboxylate **7** may generate **8**. Subsequently, 1,6–addition of **8** with *p*-QM **6** renders intermediate **10**, decarboxylation and protonation of which furnishes raspberry ketone **2a**. Since the reaction of **1ad** only produced a trace amount of **2ad** (Scheme 3, eq 7), path b might represent the dominant reaction pathway. However, the possibility of path a could not be ruled out completely at present.



Scheme 5 Proposed reaction pathways

p-(Acylethyl)phenols prepared by this current protocol could be used as versatile building blocks in synthetically useful transformations (Scheme 6). For instance, *p*-(acylethyl)phenol **2a** was converted into phenol triflate **2af**, which was reduced to deliver benzylacetone **2ag** or functionalized via Sonogashira reaction to give alkyne **2ah**. Additionally, they have been reported in the previous literatures[12] as important starting materials for the synthesis of bioactive natural products and pharmaceuticals, such as (+)-Ces-B, cephalosporolides C, E, F, and G, and tyrosinase inhibitor **2ai**. These representative applications have convincingly demonstrated the versatilities of *p*-(acylethyl)phenols in organic synthesis.

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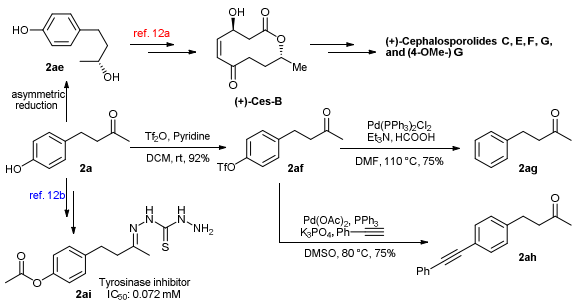

Scheme 6 Further transformations of *p*-(acylethyl)phenol **2a**

In conclusion, we have developed a novel TBAF–induced decarboxylative benzylation of unstabilized ketone enolates, which efficiently forms a C_{sp}^3-C_{sp}^3 bond. The method tolerates a broad range of substrates and functionalized raspberry ketone derivatives were obtained in good to excellent yields. This discovery represents a significant expansion of the existing decarboxylative benzylation strategies. Further development of benzylation involving other unstabilized nucleophiles is under investigation.

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