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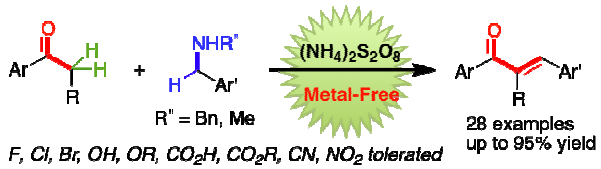

5 Metal-free synthesis of chalcone derivatives through a tandem cross-dehydrogenative-coupling/elimination reaction was achieved by treatment of ketones with benzylamines.

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ARTICLE TYPE

Practical Metal-Free Synthesis of Chalcone Derivatives via a Tandem Cross-Dehydrogenative-Coupling/Elimination Reaction

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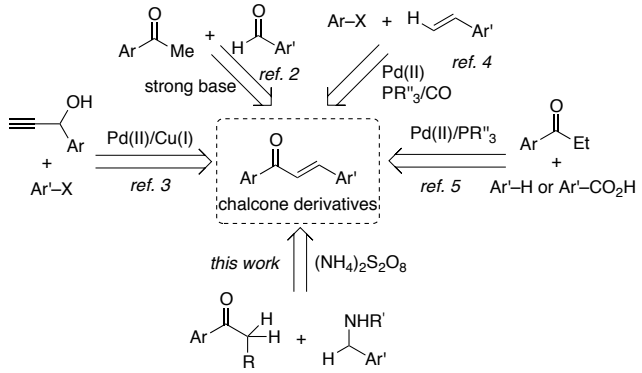
Metal-free synthesis of chalcone derivatives through a tandem cross-dehydrogenative-coupling/elimination reaction is described. A simple and inexpensive ammonium persulfate salt enables the reaction between ketones and benzylamines to proceed with high stereoselectivity and good functional group compatibility.

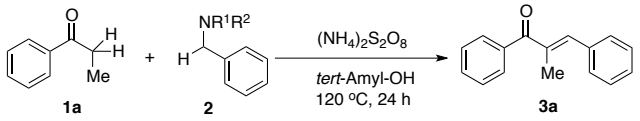
Chalcones and their derivatives are valuable synthetic targets and have been widely found in various bioactive natural products and pharmaceuticals.[1] Over the past decade, significant efforts have been addressed in developing highly efficient synthetic strategies to prepare these molecules, including strong base-promoted aldol condensation,[2] palladium-catalyzed Sonogashira coupling between aryl halides and propargyl alcohols,[3] carbonylative Heck coupling,[4] and cross-coupling of ketones with arenes or aryl carboxylic acids (Scheme 1).[5] Unfortunately, these methods typically rely on stoichiometric amounts of strong bases or toxic transition metal catalysts, and suffer from limited functional group compatibility. To overcome these drawbacks, an alternative strategy mediated on base- and metal-free environmentally benign synthetic systems is highly attractive for application in the pharmaceutical chemical industry on a large scale. In this communication, we report that a simple and inexpensive ammonium persulfate salt enables the reaction between ketones and benzylamines to proceed effectively, affording biologically interesting chalcone derivatives with high stereoselectivities via a tandem cross-dehydrogenative-coupling (CDC)/elimination transformation.[6]



Scheme 1 Synthetic Strategies to the Formation of Chalcone Derivatives.

Inspired by Li's discovery that a nonmetal oxidant allows a CDC transformation to take place smoothly,[7,8] the evaluation of oxidants was initially performed by treatment of propiophenone (**1a**) with dibenzylamine (**2d**) (See Supporting Information for pamameter optimization). The ammonium persulfate of $(NH_4)_2S_2O_8$ is superior to DDQ, $K_2S_2O_8$, $Na_2S_2O_8$ and KHS_2O_8 in the transformation, leading to *E*-conformational chalcone **3a** in excellent yield (94%). Other well-known oxidants such as the Ag_2CO_3 salt, dicumyl peroxide (DCP) and *tert*-butyl hydroperoxide (TBHP) failed to produce the desired product. Then, the influence of *N*-substituents on the benzylamines was studied (Table 1). Besides dibenzylamine, *N*-methyl-substituted partner **2b** was also proved to be suitable in the reaction, giving **3a** in satisfactory yield (entry 2). Other benzylamines, including primary, tertiary and *N*-phenyl-substituted benzylamines (entries 1, 3 and 5), afford low performance in the reaction. In contrast, triethylamine does not provide the desired product under standard conditions. It is noteworthy that the procedure was successfully applied in the gram-scale reaction, formation of chalcone **3a** in 95% yield (entry 4).

Table 1 Investigation of the Effect of *N*-Substituents on the Benzylamines (**2**) for the Synthesis of Chalcone **3a**[a,b]



1a **2** **3a**

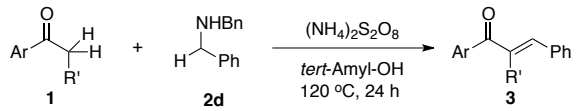
entry	**2**	R^1	R^2	**3a** (%)
1	**2a**	H	H	5
2	**2b**	H	Me	83
3	**2c**	H	Ph	7
4	**2d**	H	Bn	94 (95)[c]
5	**2e**	Me	Me	11

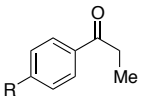
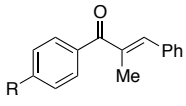
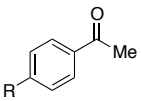
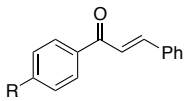
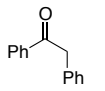
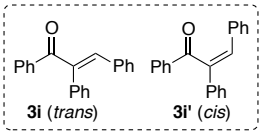
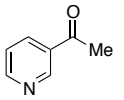
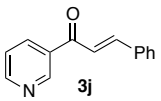
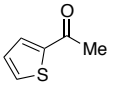
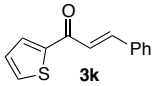
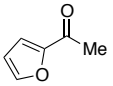
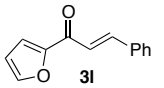
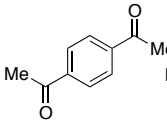
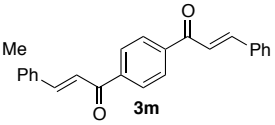
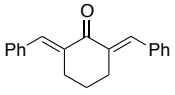
[a] Reaction conditions: propiophenone **1a** (0.5 mmol), benzylamines **2** (2.5 mmol), $(NH_4)_2S_2O_8$ (1.5 mmol) in *tert*-Amyl-OH (1.0 mL) at 120 °C for 24 h. [b] ^{1}H NMR yield using tetrachloroethane as an internal standard. [c] Isolated yield in parentheses for 1.0 g scale synthesis.

With the optimal ammonium persulfate oxidant and benzylamine sources, we next examined the scope of ketones in the reaction with dibenzylamine **2d** (Table 2). Both electron-poor and electron-rich propiophenones and acetophenones enable facilitate to react with benzylamine, giving the desired chalcone derivatives **3a**–**3h** in moderate to excellent yields (43–95%) with completely *E*-conformation (entries 1–8). To our delight, base-sensitive hydroxyl and carboxyl groups, that cannot be compatible with the classic aldol condensation, are well tolerated

by the synthetic system (entries 5 and 8). It is worthy mentioning that the α-substituents on the ketone scaffolds heavily influence the transformation. Sterically hindered 2-phenylacetophenone gives rise to a stereoisomer **3i** and **3i'** in 4:1 ratio as compared to propiophenones and acetophenones. Heterocyclic motifs such as pyridyl, thienyl and furanyl can be facility incorporated into the skeletons of chalcone derivatives (entries 10–12). The double functionalization of 1,4-diacetylbenzene works well giving rise to conjugated compound **3m** (entry 13). Even for α,α'-dialkyl-substituted cyclohexanone, the reaction also proceeds effectively leading to synthetically interesting dibenzylideneacetone **3n** in moderate yield (entry 14).[9]

Table 2 Synthesis of Chalcone Derivatives by Treatment of Dibenzylamine with Various Ketones[a]

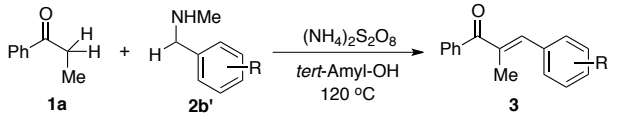


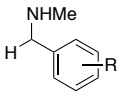
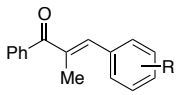
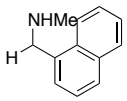
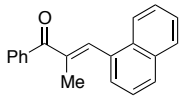
entry	substrate	product		yield[b]
1			**3a**: R = H	95%[c]
2			**3b**: R = Cl	88%
3			**3c**: R = Me	83%
4			**3d**: R = OMe	87%
5			**3e**: R = OH	75%
6			**3f**: R = H	62%
7			**3g**: R = CO_2Me	43%
8			**3h**: R = CO_2H	54%
9		 **3i** (*trans*) **3i'** (*cis*)		24% (*trans*:*cis* = 4:1)[d]
10		 **3j**		54%
11		 **3k**		74%
12		 **3l**		54%
13		 **3m**		30%[e]
14		 **3n**		52%

[a] Reaction conditions: ketone **1** (0.5 mmol), dibenzylamine **2d** (2.5 mmol), $(NH_4)_2S_2O_8$ (1.5 mmol) in *tert*-Amyl-OH (1.0 mL) at 120 °C for 24 h. [b] Isolated yield. [c] Isolated yield for 1.0 g scale synthesis. [d] The stereoisomeric ratio was determined by GC analysis using tridecane as an internal standard. [e] 36 h.

Given the commercially available and inexpensive features of *N*-methylbenzylamines, exploring the scope of substituents on the aromatic rings of *N*-methylbenzylamines was next carried out by treatment with **1a** (Table 3). A variety of functional groups such as fluoride, chloride, bromide, alkoxy, nitro and cyano can be introduced into the frameworks of the chalcone derivatives. Interestingly, the ortho steric hindrance on the aromatic rings of benzylamines slightly affects the transformation. As compared to *para*-substituted *N*-methylbenzylamines (entries 1 and 6), a low performance was observed for *ortho*-substituent-containing benzylamines (entries 2 and 7). Interestingly, the protocol can be expanded to the preparation of naphthalenyl-substituted chalcone derivative **3x**, even though the yield is moderate (entry 10).

Table 3 Substituent Effects on the Aromatic Rings of *N*-Methylbenzylamines for the Transformations[a]



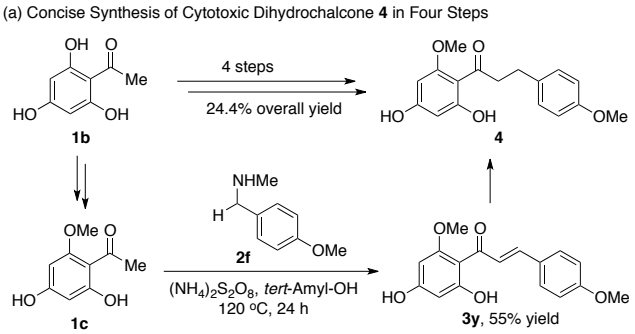
entry	substrate	product		yield[b]
1			**3o**: R = *p*-Br	89%
2			**3p**: R = *o*-Br	52%
3			**3q**: R = *o*-F	50%
4			**3r**: R = *p*-Cl	78%
5			**3s**: R = *p*-Me	75%
6			**3t**: R = *p*-OMe	67%
7			**3u**: R = *o*-OMe	56%
8			**3v**: R = *m*-NO_2	68%
9			**3w**: R = *p*-CN	89%
10		 **3x**		48%

[a] Reaction conditions: propiophenone **1a** (0.25 mmol), *N*-methylbenzylamines **2b'** (1.25 mmol), $(NH_4)_2S_2O_8$ (0.75 mmol) in *tert*-Amyl-OH (0.50 mL) at 120 °C for 24 h. [b] Isolated yield.

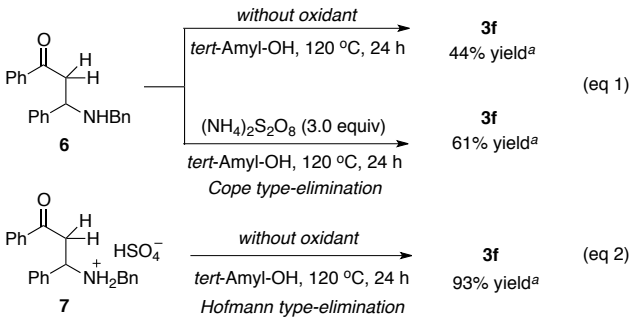
Taking advantage of its good functional group tolerance with hydroxyl group, our method was successful applied in the concise synthesis of biologically interesting anti-*Trypanosoma cruzi* active cytotoxic dihydrochalcone **4** in four steps, through a reaction pathway involving formation of chalcone derivative **3y** as a key step (Scheme 2a).[10] As compared to the known synthetic route with forming the compound **4** in six steps, the method does not require to protect the base-sensitive hydroxyl group. Given the attractive biologically activities of flavonoid derivatives,[11] the application of our procedure in one-pot synthesis of flavonoid derivative **5** is described by a sequential reaction (Scheme 2b).

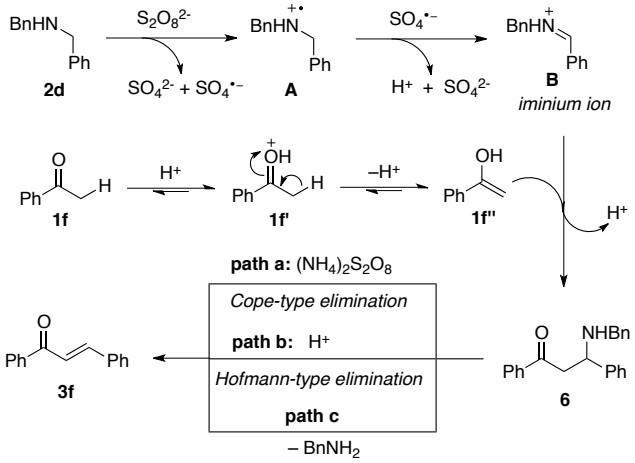
In the transformation, a critical question is regarding whether the persulfate oxidant is indispensable for the elimination step. Interestingly, starting from the corresponding CDC product **6**, the controlling experiments show that the chalcone **3f** can be formed without the oxidant, albeit with moderate yield (44%) (eq 1). In the presence of $(NH_4)_2S_2O_8$, a Cope-type elimination mechanism can be involved in the reaction pathway, giving rise to **3f** in 61% yield. Taking account of an acidity circumstance that was detected after the reaction, the ammonium salt **7** can be generated from intermediate **6**, which allows facile access to the desired product **3f** via a Hofmann type-elimination (eq 2). These results clearly demonstrate that a Cope or Hofmann type-elimination

mechanism cannot be ruled out in the elimination step.



Scheme 2 Application to the Highly Efficient Synthesis of Biologically Active Molecules.





Scheme 3 Proposed Mechanism.

Based to these preliminary study results, a viable mechanism is proposed as shown in Scheme 3. A single electron transfer (SET) from dibenzylamine **2d** to persulfate anion may initially proceed giving a radical cation **A** while generation of sulfate dianion and sulfate radical anion.[12] Subsequent the related iminium ion **B** and acidity proton can be produced from the reaction between **A** and sulfate radical anion.[13] Under the acidity circumstance, the ketone **1f** may undergo an isomerization leading to the enol compound **1f''**, which then nucleophilic attack the iminium ion **B** giving the *β*-amino ketone **6**, followed by three possible reaction pathways by mechanisms involving Cope-, Hofmann-type, and direct elimination leading to the final chalcone product **3f**. On the other hand, a mechanism involving two radical direct coupling between ketone and benzylamine cannot be ruled out for the generation of intermediate **6**.

In summary, we developed an operationally simple, metal-free tandem CDC/elimination reaction to prepare synthetically useful chalcone derivatives. A simple ammonium persulfate allows the reaction between readily available ketones and benzylamines to proceed with high chemo- and stereoselectivity. A wide range of functional groups are well tolerated by the synthetic system. Furthermore, the utility of the methodology in highly efficient synthesis of biologically interesting cytotoxic dihydrochalcone and flavonoid derivatives is demonstrated. We believe that the methodology could provide a beneficial complementarity for current synthetic strategies to the formation of chalcone derivatives. Detailed mechanistic studies are ongoing in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures and product characterization]. See DOI: 10.1039/b000000x/

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