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A general access to 1,1-cyclopropane aminoketones and their conversion into 2-benzoyl quinolines†

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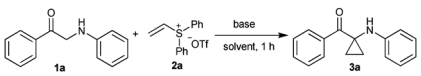
1,1-Cyclopropane aminoketones were efficiently synthesized in high yields by the tandem reaction of α-amino aryl ketones with vinyl sulfonium salts using DBU as the base in CH_2Cl_2. This methodology was utilized to synthesize 2-benzoyl quinolines.

Cyclopropanes, which play an important role in organic chemistry, occur widely as key structural units in many biologically active natural products as well as in drugs, such as ciprofloxacin.[1] In addition, they are frequently employed as versatile building blocks in organic synthesis.[2] Consequently, synthesis of cyclopropane derivatives has received much attention and general methods for cyclopropanation have been reviewed, including Simmons–Smith cyclopropanation, Michael-initiated ring closure, and the cyclopropanation of olefins with halomethyl metal reagents.[3] Although the literature on cyclopropane synthesis enjoys a rich history of versatile methodologies, new direct approaches remain highly valuable due to the continued importance of the cyclopropane derivatives in both biological and chemical fields.

As a consequence of their unique chemical and biological properties, 1,1-cyclopropane aminoketones have attracted wide interest for use in pharmaceutical products.[4] Despite their remarkable biological importance, the direct synthesis of this type of compounds remains a challenge. Inspired by the diverse reactivity of vinyl sulfonium salts which have been identified as valuable intermediates,[5] and in continuation of our current studies on tandem synthesis of cyclic compounds,[6] we herein report a simple and efficient access to 1,1-cyclopropane aminoketones with the tandem reaction of α-amino aryl ketones and vinyl sulfonium salts, and also their conversion into 2-benzoyl quinolines.

Firstly we examined the reaction between 1-phenyl-2-(phenylamino)ethanone (**1a**) and diphenyl vinyl sulfonium triflate (**2a**), which led to the formation of 1,1-cyclopropane aminoketone (**3a**) with a yield of 76% in the presence of DBU in methylene chloride solution at 25 °C for 1 h. Results of optimization are listed in Table 1. By lowering the temperature of the reaction to 0 °C, the yield of **3a** increased up to 89% (Table 1, entry 2). The choice of base played a key role in this transformation.

Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Base	T/°C	Yield[b] (%)
1	CH_2Cl_2	DBU	25	76
2	CH_2Cl_2	DBU	0	89
3	CH_2Cl_2	None	0 or 25	0
4	CH_2Cl_2	TEA	0	Trace
5	CH_2Cl_2	NaH	0	31
6	THF	DBU	0	75
7	CH_3CN	DBU	0	62
8	Toluene	DBU	0	32

[a] All the reactions were carried out using **1a** (1 mmol), **2a** (1.2 mmol), base (2.0 mmol) in 7 mL of solvent. [b] Isolated yields.

The reaction did not take place in the absence of base (Table 1, entry 3), and when the reaction was conducted in the presence of Et_3N, only trace amounts of **3a** could be detected while most of the **1a** remained (Table 1, entry 4). Low yield was observed when the reaction was conducted in the presence of NaH (Table 1, entry 5). Then, we moved on to screen the reaction solvent. It was found that methylene chloride was the most suitable solvent for this transformation among others, such as THF, acetonitrile and toluene (Table 1, entries 6–8). Thus, the most suitable reaction conditions for the formation of **3a** were established (Table 1, entry 2).

Under the optimized reaction conditions, the scope of the α-amino aryl ketones was explored. As shown in Table 2, the protocol with a variety of α-amino aryl ketones **1** gave the corresponding 1,1-cyclopropane aminoketones in good to excellent yields. Electron-donating as well as electron-withdrawing groups on aromatic rings were tolerated. Moreover, substrate **1h** with an *N*-(1-naphthyl) substituent showed excellent reaction activity in this tandem process, and afforded the corresponding product **3h** in 96% yield (Table 2, entry 8). Furthermore, the tertiary amine substrates (**1k–1m**) also reacted well in this cyclization, and smoothly afforded the desired 1,1-cyclopropane aminoketone products in 70–88% yields (Table 2, entries 11–13).

Encouraged by these results, we extended our reaction to diphenyl styryl sulfonium triflate (**2b**) as the substrate. As shown in Table 3, the substrate (**2b**) could successfully participate in the tandem reaction to afford the desired products **4** in moderate yields under the same optimized conditions. Significantly, in each

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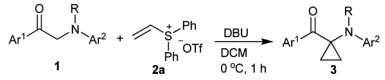
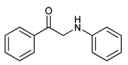
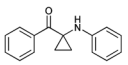
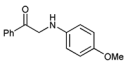
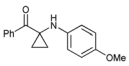
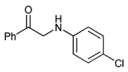
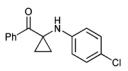
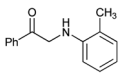
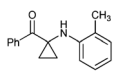
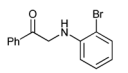
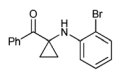
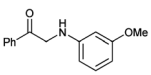
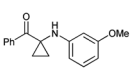
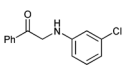
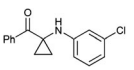
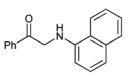
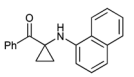
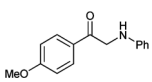
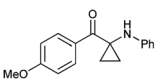
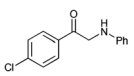
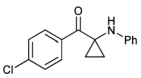
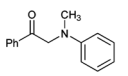
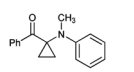
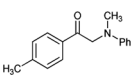
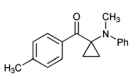
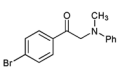
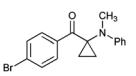
† Electronic supplementary information (ESI) available: Experimental procedure, ^1H and ^{13}C NMR spectra for all compounds. CCDC 885176. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc35235d

Table 2 Tandem reactions for the synthesis of 1,1-cyclopropane aminoketones **3**[a]



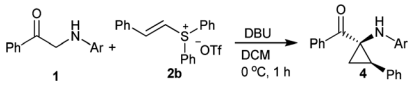
Entry	Substrate		Product		Yield[b] (%)
1		**1a**		**3a**	89
2		**1b**		**3b**	83
3		**1c**		**3c**	87
4		**1d**		**3d**	98
5		**1e**		**3e**	85
6		**1f**		**3f**	90
7		**1g**		**3g**	96
8		**1h**		**3h**	96
9		**1i**		**3i**	88
10		**1j**		**3j**	78
11		**1k**		**3k**	73
12		**1l**		**3l**	70
13		**1m**		**3m**	88

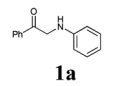
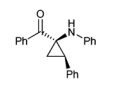
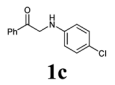
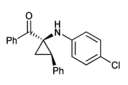
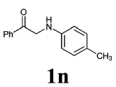
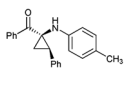
[a] All the reactions were carried out using **1** (1 mmol), **2a** (1.2 mmol) and DBU (2.0 mmol) in 7 mL of DCM. [b] Isolated yields.

case, the ratio of *Z* : *E* stereomers of **4** was determined to be higher than 97 : 3 by ^{1}H NMR. The structure of compound **4a** (Table 3, entry 1) was unambiguously confirmed by single-crystal X-ray analysis, and the configuration of the product was determined to have a *cis* relationship of the aryl amino and the phenyl group.

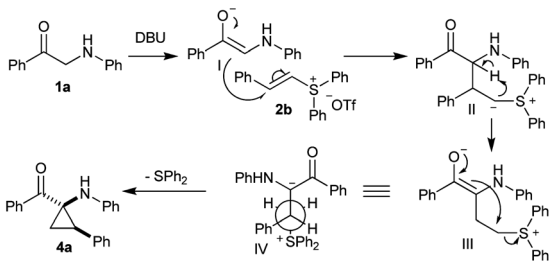
A possible mechanism for this annulation reaction is postulated in Scheme 1. Nucleophilic addition of enolate **I** to the vinyl sulfonium salt gives the ylide intermediate **II**, which forms enolate **III** after proton transfer. **IV** as shown by its Newman projection is the most stable conformation of intermediate **III**, where the less sterically hindered NHPh is *cis* to the phenyl group. Then, an intramolecular nucleophilic substitution forms the 1,1-cyclopropane aminoketone **4a**. As previously reported,[5b–d] the use of *N*-tosyl amino ketones or *N*-phenyl amino alcohols instead of *N*-aryl α-amino aryl ketones

Table 3 The tandem reaction of α-amino aryl ketones and styryl sulfonium salts[a]



Entry	Substrate	Product		Yield[b] (%)
1	 **1a**		**4a**	63
2	 **1c**		**4b**	61
3	 **1n**		**4c**	79

[a] **1a** (1 mmol), **2b** (1.2 mmol), DBU (2.0 mmol) in 7 mL of DCM. [b] Isolated yields of the *Z*-isomer.

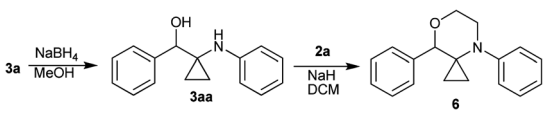


Scheme 1 Proposed mechanism.

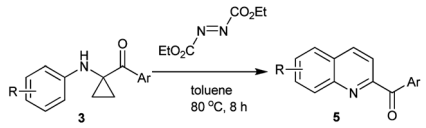
gave fused heterocyclic epoxides and morpholines, respectively, possibly due to the different deprotonation properties of these substrates.

The intensive synthetic utility is shown in Scheme 2. 1,1-Cyclopropane aminoketone **3a** was first reduced with $NaBH_4$ in MeOH to form the corresponding 1,1-cyclopropane amino alcohol **3aa** in 95% yield. Treatment of **3aa** with vinyl sulfonium salt **2a** in the presence of NaH generated 7-oxa-4-azaspiro[2.5]octane **6** as a mixture of two isomers (19 : 6) in 84% yield. The 7-oxa-4-azaspiro[2.5]octane core belongs to an underutilized class of heterocycles whose biological properties have been explored.[7]

Finally, to extend the synthetic value of our protocol, 1,1-cyclopropane aminoketones have been converted into 2-benzoyl quinolines. Quinolines and their derivatives have many important applications, not only as key structural units in many natural products and important pharmaceuticals but also as useful intermediates for various biologically active molecules and functional materials.[8] We have found that 2-benzoyl quinolines can be obtained from the prepared 1,1-cyclopropane aminoketones with diethyl azodicarboxylate (DEAD, 2.0 equiv.) in toluene at 80 °C for 8 h by oxidation, ring-opening and cyclization (Scheme 3). As shown in Table 4, we explored the protocol with a variety of the prepared 1,1-cyclopropane aminoketones

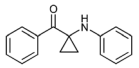
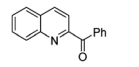
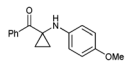
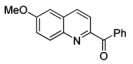
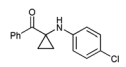
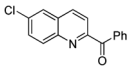
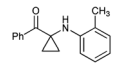
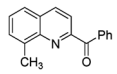
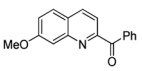
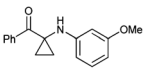
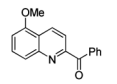
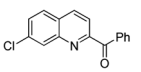
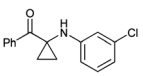
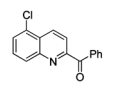
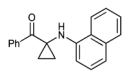
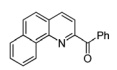
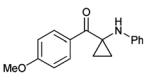
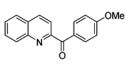
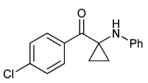
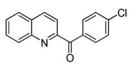


Scheme 2 Synthesis of 7-oxa-4-azaspiro[2.5]octane.



Scheme 3 Concise synthesis of 2-benzoyl quinolines.

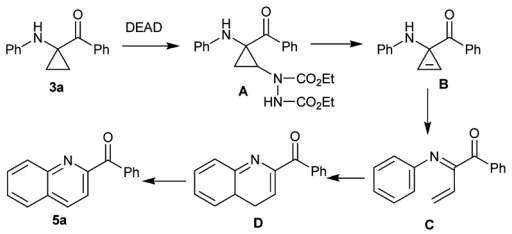
Table 4 Synthesis of 2-benzoyl quinolines **5**[a]

Entry	Substrate		Product		Yield[b] (%)
1		**3a**		**5a**	78
2		**3b**		**5b**	77
3		**3c**		**5c**	65
4		**3d**		**5d**	67
				**5e**	
5[c]		**3f**		+ **5e′**	60
				**5f**	
6[d]		**3g**		+ **5f′**	50
7		**3h**		**5g**	47
8		**3i**		**5h**	75
9		**3j**		**5i**	84

[a] **3** (0.5 mmol) and DEAD (1 mmol) in 2 mL of toluene at 80 °C for 8 h. [b] Isolated yields. [c] **5e**/**5e′** = 3 : 2. [d] **5f**/**5f′** = 7 : 3.

3 to provide the 2-benzoyl quinoline products in moderate to good yields. Electron-donating as well as electron-withdrawing groups on aromatic rings were tolerated. In the case of *meta*-substituted substrates (**3f** and **3g**), the corresponding products were observed as a mixture of two isomers which could be separated by flash chromatography on silica gel (Table 4, entries 5 and 6).

The reaction is proposed to proceed *via* a cascade procedure (Scheme 4). 1,1-Cyclopropane aminoketone **3a** is first oxidized with DEAD to give cyclopropene intermediate **B**. Then, ring-opening of **B** gives *N*-aza-diene intermediate **C**, which undergoes an intramolecular [4+2] reaction to yield the dihydroquinoline **D**.



Scheme 4 Proposed mechanism for the synthesis of 2-benzoyl quinolines.

Finally, the target product **5a** is obtained by dehydrogenation of **D**. This cascade approach to 2-benzoyl quinolines is concise and efficient, and the products are potentially useful scaffolds for the synthesis of biologically active compounds.

In conclusion, we have developed a novel direct synthesis of 1,1-cyclopropane aminoketones from a wide range of α-amino aryl ketones and vinyl sulfonium salts. Notably, the utility of this protocol has been demonstrated in the rapid access to 7-oxa-4-azaspiro[2.5]octanes and 2-benzoyl quinolines.

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