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Lewis acid mediated reactions of cyclopropyl aryl ketones with arylaldehydes, facile preparation of 2-(2-hydroxyethyl)-1,3-diarylpropenones

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Abstract—In the presence of Lewis acid TMSOTf, ring-opening reaction of aryl cyclopropyl ketone with arylaldehyde took place under mild conditions to give 2-(2-hydroxyethyl)-1,3-diarylpropenone in good yield. By protection of hydroxy group with triethylsilyl group (TES), the corresponding ring-opened product **7** was obtained in high yield with good geometrical selectivity.

1. Introduction

Cyclopropane derivatives, as versatile building blocks have been more than laboratory curiosities for quite some time.[1] In order to activate strained three-membered ring, electron-donating or accepting substituents are generally involved in their reactions to make polar processes more favorable. However, cyclopropane involved synthetically useful reactions frequently contains two activating groups.[2] The ring-opening reactions of monoactivated cyclopropane derivatives are in general sluggish due to their low reactivities. So far several examples have been reported under severe conditions either assisted by stronger nucleophiles such as I^- and stronger Lewis acids such as $TiCl_4$, or assisted by the β-effect of silicon atom of trimethylsilyl group (Scheme 1).[3] Therefore, it is necessary to develop a method for the ring-opening reaction of simple monoactivated cyclopropane derivatives under mild conditions.

α,β-Enones represent a common feature in many useful reactions,[3d] for example, Diels–Alder reactions,[4a] Stetter reaction,[4b] Michael additions,[4c] Baylis–Hillman reactions,[4d] Juliá-Colonna epoxidatons,[4e] and Robinson annulations.[4f] Furthermore, in addition to possessing cytotoxic activities and anticancer properties (Chalcones),[5] α,β-enones are frequently used as branching points for the creation of drug-like heterocyclic libraries (isoxazolines,[6a,b] tetrahydropyrimidines,[6a,b] dihydropyrimidiones,[6c] pyrimidines,[6c] pyridine,[6c,d] benzothiazepines,[6e] pyrazoles,[6c] pyrazolones,[6f] dihydropyran-2-ones,[6g] and pyrazolines[6h]). Olsson also achieved central cyclic or α,β-enone core products from α-substituted α,β-enone compounds through combinatorial scaffold approaches.[3h] Herein we present a Lewis acid mediated ring-opening reaction of arylcarbonyl activated cyclopropanes (monoactivated cyclopropane) with arylaldehydes under mild conditions which gives α-substituted α,β-enone compounds in good yields.

2. Results and discussion

As a first try, we searched for a protocol of the reaction of phenyl cyclopropyl ketone **1a** with 4-chlorobenzaldehyde **2a** mediated by a variety of Lewis acids in dichloromethane (DCM). We found that TfOH (1.0 equiv) or TMSOTf (1.0 equiv) can effectively promoted this reaction to give α,β-enone **3a** as mixtures of *Z*- and *E*-isomers in moderate yield along with a trace amount of [3+2] cycloaddition products **4a** and **5a** in which product **5a** was determined as a dimer of **3a** (Table 1, entries 2 and 5) by spectroscopic data and NOESY spectrum (see Supporting information). Other Lewis acids such as $BF_3 \cdot OEt_2$, $Cu(OTf)_2$, AgOTf, $Zn(OTf)_2$, $Zr(OTf)_4$ and other metal triflates did not promote this reaction. Using 1,2-dichloroethane (DCE) as solvent at higher temperature (60 °C to reflux), the yield of **3a** was raised to 66% at 60 °C and 81% under reflux in the presence of TMSOTf (1.0 equiv) (Table 1, entries 7–8). In

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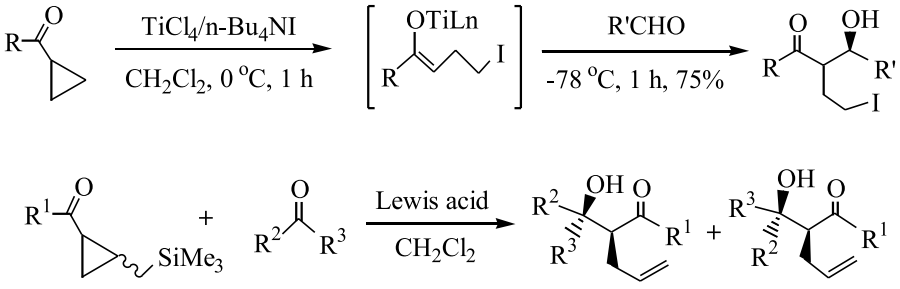
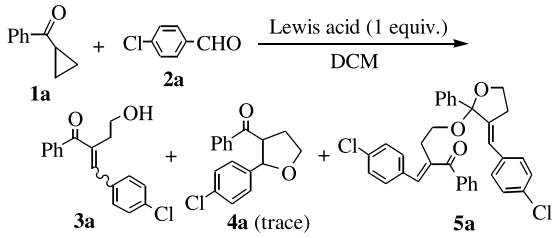


Scheme 1. Ring-opening reaction of monoactivitated cyclopropane assisted by I^- and $TiCl_4$, or assisted by the β-effect of silicon atom.

Table 1. Reaction of phenyl ketone **1a** and 4-chlorobenzaldehyde **2a** mediated by various Lewis acids



Entry	Lewis acid	Solvent	Temp.	Yield/[%][a]	Yield/[%][a]
				3a (*Z*/*E*)	**5a**
1	BF_3 OEt_2	DCM	r.t.	9 (0/100)	0
2	TfOH	DCM	r.t.	57 (15/85)	Trace
3	TfOH	DCE	60 °C	61 (16/84)	Trace
4	TfOH	DCE	Reflux	79 (45/55)	Trace
5	TMSOTf	DCM	r.t.	59 (25/75)	Trace
6[b]	TMSOTf	DCM	r.t.	10 (0/100)	0
7	TMSOTf	DCE	60 °C	66 (18/82)	Trace
8	TMSOTf	DCE	Reflux	81 (31/69)	Trace
9	TESOTf	DCE	Reflux	54 (19/81)	13

[a] Isolated yields, sterochemistry is determined by NOESY spectrum.
[b] TMSOTf (0.2 equiv).

addition, **3a** was also isolated in 61% at 60 °C and 79% under reflux in the presence of TfOH (1.0 equiv), respectively (Table 1, entries 3–4). Catalytic amounts of TMSOTf did not effectively promote this reaction (Table 1, entry 6). TESOTf was proven not as effective as TMSOTf (Table 1, entry 9).

We next carried out the reactions of a variety of aryl cyclopropyl ketones with various arylaldehydes under the optimized reaction conditions. In all of the cases we examined, α,β-enones **3** were dominantly formed along with dimers **5**.[7] The results are summarized in Table 2 which indicates that α,β-enones **3**, in some cases, were obtained in low yields because of the formation of dimers **5**, and the cleanly isolated products **3** will also immediately become mixtures of **3** and **5** due to the equilibrium shown in Scheme 2.

In order to avoid the dimerization of **3**, we decide to protect the hydroxy group. As shown in Scheme 3, after the Lewis acid mediated reaction was finished, we utilized isocyanatobenzene and TESOTf to protect the hydroxy group, respectively. The corresponding carbamate **6** was obtained in 50% yield as mixtures of *Z*- and *E*-isomers. We were delighted to find that the subsequent use of TESOTf twice could efficiently promote this reaction and trap the formed hydroxy group in the presence of lutidine to give the corresponding product **7d** in 60% yield. Interestingly, **7d** was predominantly obtained as *E*-configuration under this conditions (Scheme 3).

The reaction of a variety of aryl cyclopropyl ketones with various arylaldehydes was carried out in the presence of TESOTf. The corresponding α,β-enones **7** were obtained exclusively in good to high yields in all cases as *E*-dominated configuration. The results are summarized in Table 3. In this reaction, R^1 and R^2 could be various substituted aromatic and heterocyclic groups (Table 3, entries 1–10).

Concerning the formation of **7**-*E*, we have observed that **3**-*E* is isolated as a major product in reaction mixtures (Table 2) and compounds **3** and **5** are formed in equilibrium under ambient atmosphere as shown in Scheme 2. Interestingly, using compound **4a** as starting material, γ-hydroxy ketone **3a** was obtained in the presence of TMSOTf under reflux in DCE to give 68% isolated yield as mixtures of *Z*- and *E*-isomers (Scheme 4). This result suggests that trace amount of product **4a** is the active intermediate in this reaction. Therefore, we believe that the transformation of **3**-*Z* and **3**-*E* proceeds through intermediate **4** (Scheme 5). In any sense, **3**-*Z* suffers from severe steric interaction between