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Lewis Acid-Mediated Transformations of *trans*-2-Aroyl-3-aryl-cyclopropane-1,1-dicarboxylates into 2-Pyrones and 1-Indanones

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Abstract: *trans*-2-Aroyl-3-arylcyclopropane-1,1-dicarboxylates upon treatment with aluminium(III) chloride ($AlCl_3$) underwent ring-opening, fragmentation, recombination and lactonization to give highly substituted 2-pyrones. Alternatively, when treated with titanium(IV) chloride ($TiCl_4$), the cyclopropane diesters underwent a Nazarov cyclization to afford 1-indanones with high diastereoselectivity.

Keywords: carbocycles; heterocycles; ring expansion; small ring systems; synthetic methods

2-Pyrone and 1-indanone cores are frequently encountered in many bioactive natural products and pharmaceuticals (Figure 1).[1,2] Some representative examples for 2-pyrone-containing natural products include (−)-citreoviridine, which displays excellent inhibitory activity against HIV-1 protease,[1a] arisugacin A, which shows potential for the treatment of Alzheimer's and other dementia diseases,[1b,c] and neurymenolide A, which exhibits significant antibiotic activities.[1d] Examples for 1-indanone-containing natural products include monachosorin A, which shows mast cell stabilization activity,[2a] and pterosines, which possess cytotoxic properties,[2b] and for pharmaceuticals, the antihypertensive drug (+)-indacrinone[2c,d] and the anti-Alzheimer drug donepezil.[2c,d] Many synthetic 2-pyrone and 1-indanone derivatives also exhibit remarkable biological activities[3] and, in addition, they act as valuable synthons for various target compounds.[4] Consequently, many promising methods have been developed for the synthesis of 2-pyrones[5] and 1-indanones.[6] Most of the methods reported for the synthesis of 2-pyrones involve generation of unsaturated δ-keto esters or equivalent compounds through various routes and subsequent lactonization, which echo the biosynthesis of the 2-pyrone motif from a polyketide.[7] Of the various methods available for the synthesis of 1-indanones, the most straightforward and widely used strategy is the Nazarov cyclization of aryl vinyl ketones.[8]

Donor–acceptor (D-A) cyclopropanes are versatile building blocks in organic synthesis.[9] They undergo facile ring cleavage upon treatment with Lewis acids to yield 1,3-dipoles (zwitterions), which undergo various transformations affording a plethora of cyclic and acyclic compounds. Recently, we reported a convenient procedure for the preparation of the doubly activated D-A cyclopropanes **1** and explored their utility

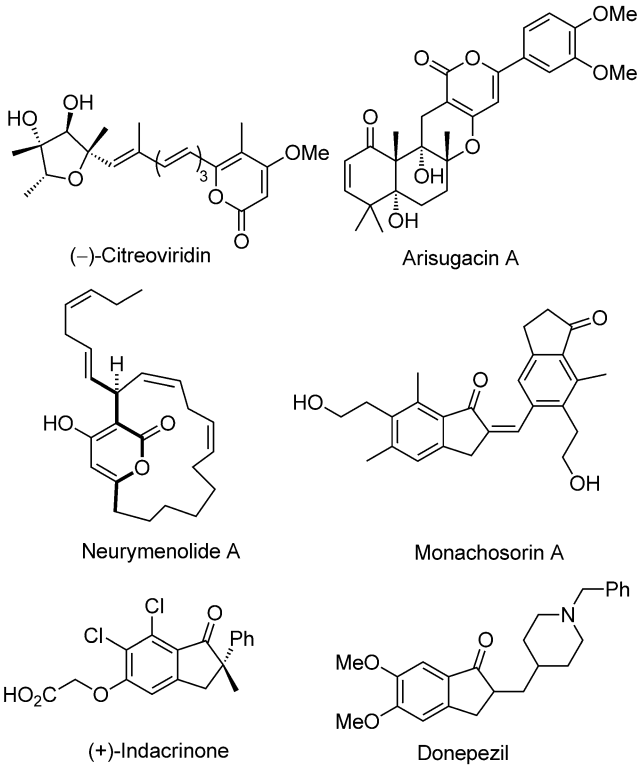
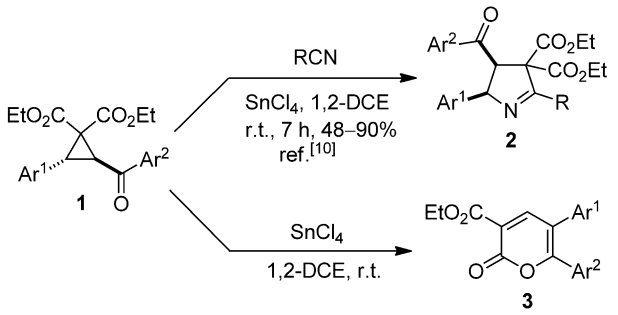
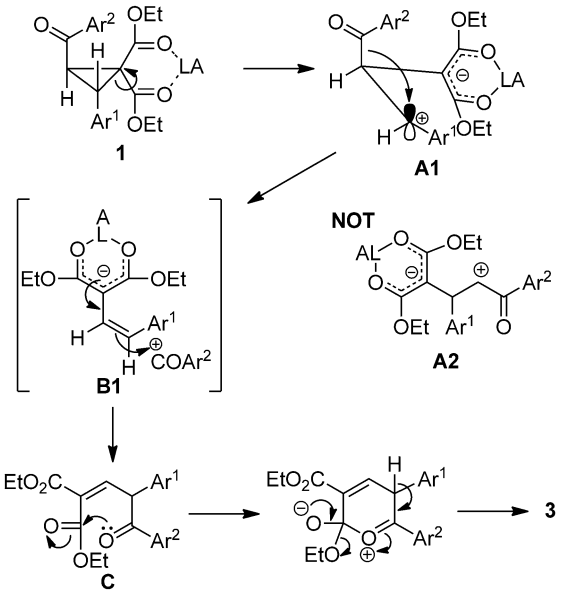


Figure 1. Examples for natural products and pharmaceuticals containing 2-pyrone and 1-indanone cores.



Scheme 1. $SnCl_4$-mediated reactions of D-A cyclopropanes **1** in the presence and absence of nitriles.



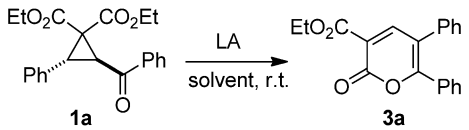
Scheme 2. Plausible reaction mechanism for the formation of 2-pyrones **3**.

for the diastereoselective synthesis of 1-pyrrolines through $SnCl_4$-promoted formal [3+2]cycloaddition with nitriles (Scheme 1).[10] During the course of the work, we were surprised to observe that in the absence of nitriles in the reactions, 2-pyrones **3** were produced in good yields. It may be noted that there are only two reports which describe the conversion of cyclopropyl ketones into 2-pyrones or dihydro-2-pyrones. Smith and co-workers have reported the conversion of nitrocyclopropyl ketones into 2-pyrones under the action of sodio malonate esters.[11] Recently, You et al. disclosed the N-heterocyclic carbene-catalyzed ring expansion of formylcyclopropyl ketones into 3,4-dihydro-2-pyrones.[12]

A plausible mechanism for the formation of 2-pyrones **3** from the D-A cyclopropanes **1** is depicted in Scheme 2. The Lewis acid upon coordination to the malonyl unit of **1** opens up the ring to give zwitterion **A1**.[10,13] An alternate mode of ring opening to form zwitterion **A2** is ruled out because it would place a positive charge on the carbon attached to aroyl group. Since a 1,2-aroyl anion shift in **A1** (to give **C** directly) is not feasible, we presume that **A1** may fragment to form the ion pair **B1**. The fragmentation takes place *via* sideways overlap of the σ C–$COAr^2$ orbital (HOMO) with the LUMO of the cation. The ion pair **B1** undergoes recombination to generate α,β-unsaturated δ-keto ester **C**, which eventually undergoes lactonization under the reaction conditions to give 2-pyrone **3**.

The above observation prompted us to investigate the optimum reaction conditions for the facile transformation of D-A cyclopropanes **1** into 2-pyrones **3**. The cyclopropane **1a** was chosen as a model substrate for the optimization study. When **1a** was treated with a stoichiometric amount of $SnCl_4$ in 1,2-dichloroethane at room temperature, it afforded pyrone **3a** in 79% isolated yield (Table 1, entry 1). The yield improved slightly when the solvent was changed to dichloromethane (entry 2). Switching the Lewis acid to $AlCl_3$ increased the yield a little more (entry 3). When the stoichiometry of $AlCl_3$ was reduced to 0.5 equiv., the reaction did not go to completion even after 24 h and, thus, gave a lower yield (entry 4). On the other hand, when 1.5 equiv. of $AlCl_3$ were used, there was no significant change in the yield (entry 5). However, when 2 equiv. of $AlCl_3$ were used, there

Table 1. Optimization of reaction conditions for the formation of **3a** from **1a**.[a]



Entry	Lewis acid (equiv.)	Solvent	Time [h]	Yield [%][b]
1	$SnCl_4$ (1.0)	1,2-DCE	14	79
2	$SnCl_4$ (1.0)	DCM	12	82
3	$AlCl_3$ (1.0)	DCM	10	86
4	$AlCl_3$ (0.5)	DCM	24	54
5	$AlCl_3$ (1.5)	DCM	10	85
6	$AlCl_3$ (2.0)	DCM	10	78
7	$InCl_3$ (1.0)	DCM	24	trace[c]
8	$ZnCl_2$ (1.0)	DCM	24	NR[d]
9	MgI_2 (1.0)	DCM	24	NR[d]
10	$Ni(ClO_4)_2$ (1.0)	DCM	24	NR[d]
11	$Sc(OTf)_3$ (1.0)	DCM	24	NR[d]
12	$Cu(OTf)_2$ (1.0)	DCM	24	NR[d]
13	$In(OTf)_3$ (1.0)	DCM	24	NR[d]
14	$Yb(OTf)_3$ (1.0)	DCM	24	NR[d]
15	*p*-TsOH (1.0)	DCM	24	NR[d]

[a] The reaction was conducted with **1a** (1 mmol), Lewis acid (x equiv.), and solvent (5 mL).
[b] Isolated yield.
[c] Only a trace of **3a** was formed.
[d] No reaction.

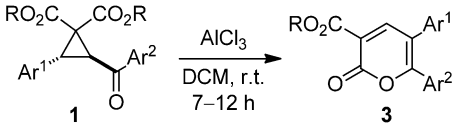
was a small decrease in the yield (entry 6). The use of $InCl_3$ as the Lewis acid afforded only a trace of the product (entry 7). We also screened other Lewis acids such as $ZnCl_2$, MgI_2, $Sc(OTf)_3$, $Cu(OTf)_2$, $In(OTf)_3$, $Yb(OTf)_3$ and $Ni(ClO_4)_2{\cdot}6H_2O$ and a Brønsted acid, *p*-TsOH, which were known to cause ring cleavage in other types of D-A cyclopropanes.[9] Unfortunately, none of them was found to promote the reaction (entries 8–15). Thus, the optimal conditions for the reaction were identified as stirring the substrate with 1 equiv. of $AlCl_3$ in dichloromethane at room temperature.

Having optimized the reaction conditions, we next examined the generality of the reaction for a variety of other D-A cyclopropanes (Table 2). Generally, the presence of various substituents at different positions of the two aryl rings (Ar^1 and Ar^2) was well tolerated and the respective 2-pyrones **3a–m** were produced in high yields ranging from 63–93% (entries 1–13). The substrate **1e** which possesses a *para*-nitrophenyl group as Ar^1 remained inert under the reaction conditions owing to its low reactivity[10] (entry 5). The yield was low for **3g** due to the formation of unidentifiable byproducts in the reaction (entry 7). Even though 2-furyl and 2-pyridyl rings were not compatible, the reaction was successful with a 2-thienyl ring-containing cyclopropane and the corresponding pyrone **3n** was produced in 74% yield (entry 14). The reaction could also work equally well with methyl esters of the cyclopropanes, as it was exemplified by the formation of pyrone **3o** in 80% yield from the cyclopropane **1o** (entry 15). All the products were thoroughly characterized by ^1H and ^{13}C NMR spectroscopy and HR-MS and for one of the products, **3c**, the structure was further confirmed by single-crystal XRD studies[14] (Figure 2).

To ascertain whether the recombination step proposed in the reaction mechanism (Scheme 2) is inter- or intramolecular, we performed a cross-over experiment using the substrates **1g** in which $Ar^1 = Ph$ and $Ar^2 = p\text{-}MeOC_6H_4$ and **1k** in which $Ar^1 = p\text{-}MeC_6H_4$ and $Ar^2 = p\text{-}ClC_6H_4$. The absence of any cross-over products in the reaction revealed that the recombination step is intramolecular in nature.

Next, we prepared cyclopropane substrates **4a–c** in which a vinyl unit is inserted between the aryl ring and the keto group and evaluated their utility for pyrone formation (Scheme 3). These substrates are interesting because they could also give rise to cyclohexenones through a homo-Nazarov cyclization.[8] However, these substrates too furnished the corresponding vinyl pyrones **5a–c** in 70–80% yields. The ^1H NMR data and XRD studies of one of the products, **5c**[15] (Figure 3) indicated that the *trans*-configu-

Table 2. $AlCl_3$-promoted transformation of D-A cyclopropanes **1** into pyrones **3**.[a]



1 3

Entry	Ar^1, Ar^2, R	Time [h]	Product, Yield[b]
1	Ph, Ph, Et (**1a**)	10	**3a**, 86%
2	4-MeC_6H_4, Ph, Et (**1b**)	10	**3b**, 88%
3	4-$MeOC_6H_4$, Ph, Et (**1c**)	8	**3c**, 77%
4	4-ClC_6H_4, Ph, Et (**1d**)	10	**3d**, 75%
5	4-$NO_2C_6H_4$, Ph, Et (**1e**)	24	**3e**, –[c]
6	Ph, 4-MeC_6H_4, Et (**1f**)	10	**3f**, 84%
7	Ph, 4-$MeOC_6H_4$, Et (**1g**)	7	**3g**, 63%
8	Ph, 4-ClC_6H_4, Et (**1h**)	10	**3h**, 86%
9	Ph, 4-$NO_2C_6H_4$, Et (**1i**)	10	**3i**, 93%
10	Ph, 3,4-$Cl_2C_6H_3$, Et (**1j**)	10	**3j**, 84%
11	4-MeC_6H_4, 4-ClC_6H_4, Et (**1k**)	10	**3k**, 89%
12	4-$MeOC_6H_4$, 4-$MeOC_6H_4$, Et (**1l**)	9	**3l**, 80%
13	4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, Et (**1m**)	8	**3m**, 82%
14	4-ClC_6H_4, 2-thienyl, Et (**1n**)	7	**3n**, 74%
15	Ph, Ph, Me (**1o**)	12	**3o**, 80%

[a] The reaction was conducted with **1** (1 mmol), $AlCl_3$ (1 mmol) and DCM (5 mL).
[b] Isolated yield.
[c] Not formed.

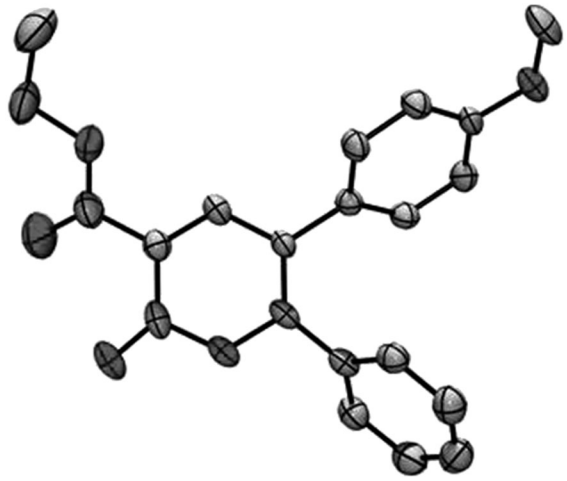
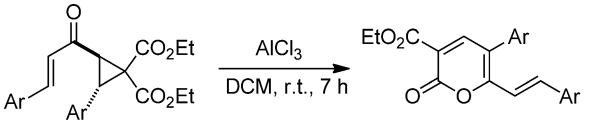


Figure 2. X-ray structure of **3c**.



4a: Ar = Ph
4b: Ar = 4-MeC_6H_4
4c: Ar = 4-$MeOC_6H_4$

5a: Ar = Ph, 70%
5b: Ar = 4-MeC_6H_4, 71%
5c: Ar = 4-$MeOC_6H_4$, 80%

Scheme 3. $AlCl_3$-promoted transformation of vinyl-incorporated D-A cyclopropanes **4** into pyrones **5**.

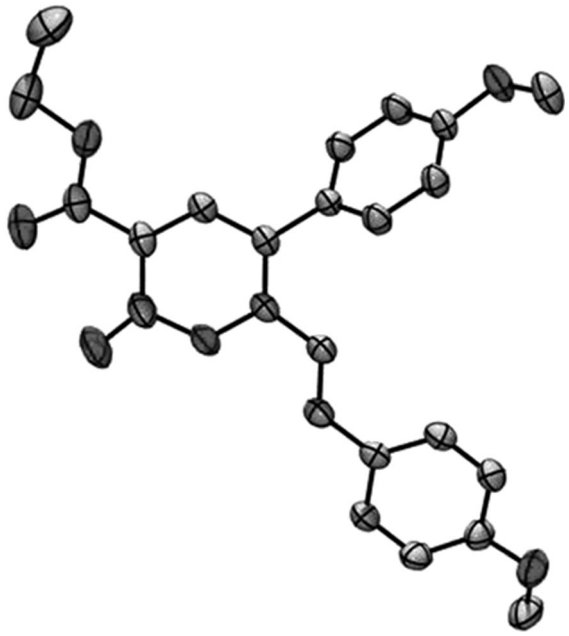
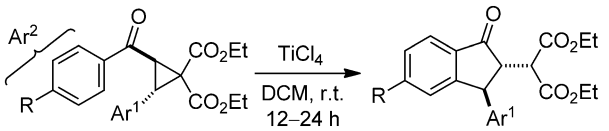


Figure 3. X-ray structure of **5c**.

ration of the double bond was preserved in the products.

We made an interesting observation during the optimization of the reaction conditions for the conversion of cyclopropane **1a** into pyrone **3a**. When a stoichiometric amount of $TiCl_4$ was used as the Lewis acid in the reaction, an entirely different product, 1-indanone **6a** was produced in 38% yield and, the yield rose to 78% when the amount of $TiCl_4$ was increased to 1.5 equiv. (Table 3, entry 1). Impressed by this result, we examined the scope of the reaction for different cyclopropanes **1c–f**, **1h** and **1i** (entries 2–7). Except for **1i** (Ar^1 = Ph; Ar^2 = *p*-$NO_2C_6H_4$) which produced a complicated mixture of products (entry 7), all other substrates furnished the corresponding 1-indanones **6b–f** in 60–82% yields. Surprisingly, cyclopropane **1e** (Ar^1 = *p*-$NO_2C_6H_4$; Ar^2 = Ph) which was inert under the action of $AlCl_3$, now afforded the respective indanone **6d** (entry 4). However, the yield of **6d** was low probably due to the difficulty in the development of a positive charge on the respective benzylic carbon during the course of the reaction (see intermediate **A3** in the mechanism in Scheme 4). In all the cases, the products are formed as single diastereomers with substituents at C-2 and C-3 in a *trans*-relationship as evidenced from ^{1}H NMR coupling constants and the X-ray structure of one of the products, **6a**[16] (Figure 4).

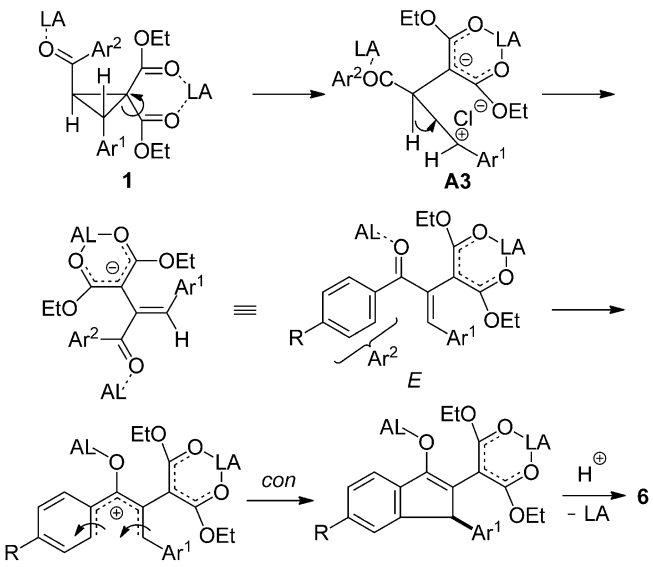
Table 3. $TiCl_4$-promoted transformation of D-A cyclopropanes **1** into 1-indanones **6**.[a]



1 **6**

Entry	Ar^1, R	Time [h]	Product, Yield [%][b]
1	Ph, H (**1a**)	12	**6a**, 78
2	4-$MeOC_6H_4$, H (**1c**)	12	**6b**, 72
3	4-ClC_6H_4, H (**1d**)	14	**6c**, 74
4	4-$NO_2C_6H_4$, H (**1e**)	24	**6d**, 60
5	Ph, Me (**1f**)	14	**6e**, 82
6	Ph, Cl (**1h**)	14	**6f**, 65
7	Ph, NO_2 (**1i**)	24	–[c]

[a] The reaction was conducted with **1** (1 mmol), $TiCl_4$ (1.5 mmol) and DCM (5 mL).
[b] Isolated yield.
[c] Complicated mixture.



Scheme 4. Plausible mechanism for the formation of indanones **6**.

We propose a Nazarov cyclization mechanism as depicted in Scheme 4 for the formation of indanones **6**. A part of the Lewis acid coordinates to the malonyl unit of **1** and the remaining part to the carbonyl group, which results in ring opening to form the intermediate **A3**. Even though Cl^- from the Lewis acid does not assist in the ring opening (as evidenced by the stereochemistry of the product alkene), it may still interact with the carbocation (in the form of intimate ion pair by exchange with malonate anion[17]) as shown in **A3**. As a result, the elimination of a proton takes place in a concerted manner (E2-like pathway) in **A3** and the corresponding *E*-alkene is selectively produced. The *E*-alkene undergoes a standard Nazarov cyclization promoted by the Lewis acid to give the indanone **6**. Only the thermodynamically more

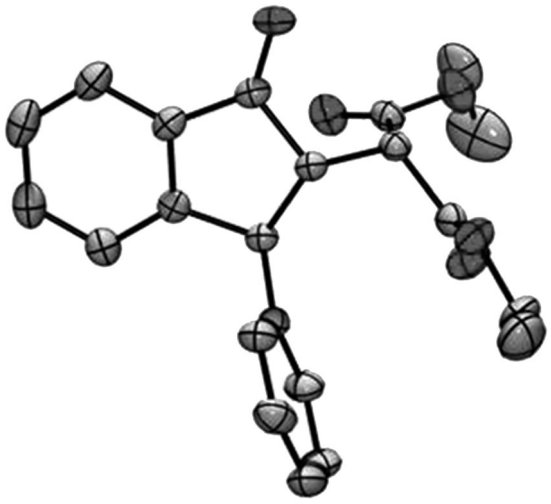
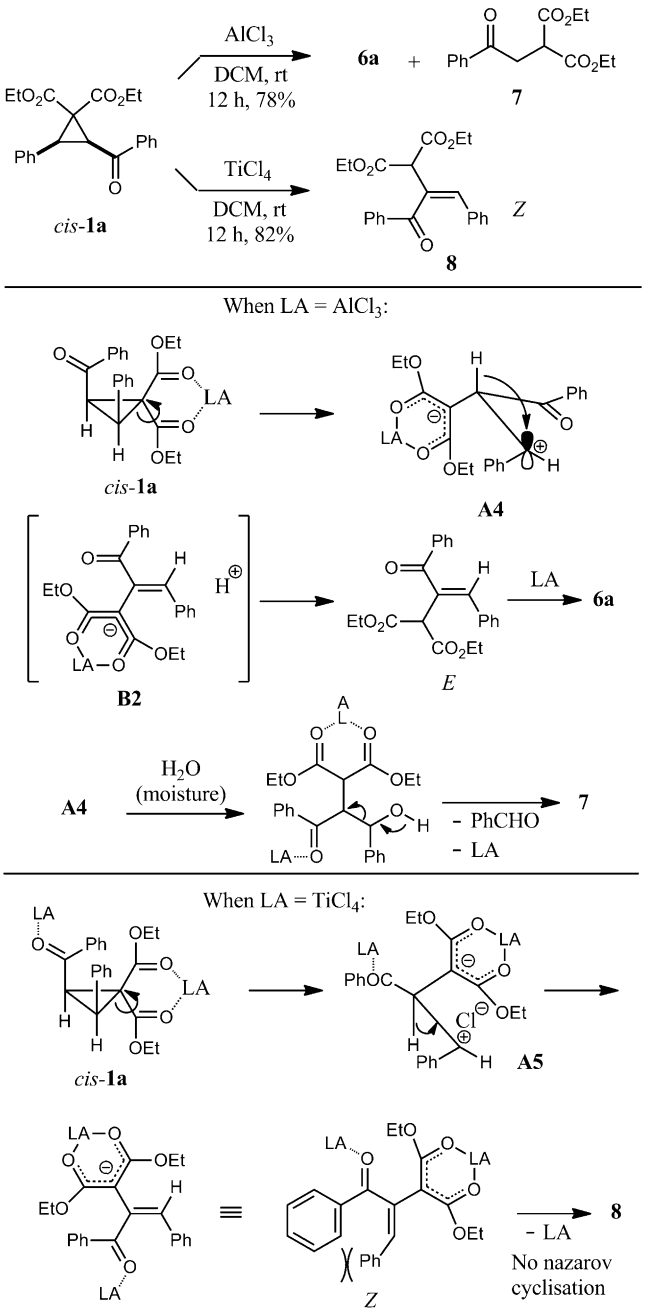


Figure 4. X-ray structure of **6a**.

stable *trans*-diastereomers are formed in all the reactions as observed with many Nazarov cyclizations.[18] The literature reveals that aryl cyclopropyl ketones undergo homo-Nazarov cyclization in the presence of Lewis/Brønsted acids to give the corresponding aryl ring-fused cyclohexanone derivatives.[8,19] In contrast to these reports, we observed only aryl ring-fused cyclopentanone derivatives (1-indanones) in our reactions.

To get more insight into the mechanism proposed for the formation of pyrones and indanones from **1**, we studied the ring opening reactions of diethyl *cis*-2-benzoyl-3-phenylcyclopropane-1,1-dicarboxylate[20] (*cis*-**1a**) in the presence of $AlCl_3$ and $TiCl_4$ (Scheme 5). Surprisingly, when treated with $AlCl_3$, *cis*-**1a** gave a 3:1 mixture[21] of indanone **6a** and phenacylmalonate (**7**) in 78% isolated total yield. On the other hand, upon treatment with $TiCl_4$, it gave the *Z*-alkene **8** in 80% yield. We rationalize the formation of these products as follows. Similar to the mechanism proposed in Scheme 2, *cis*-**1a**, under the action of $AlCl_3$, undergoes ring opening to form zwitterion **A4.** The fragmentation of **A4** gives ion pair **B2** which collapses to furnish an *E*-alkene. The Nazarov cyclization of this *E*-alkene affords **6a**. The zwitterion **A4** may also combine with H_2O (moisture) to give an intermediate alcohol which upon fragmentation gives **7**. The formation the products **6a** and **7** clearly indicates the mode of ring opening in **1** and the formation of zwitterion **A1** (and not **A2**) in *trans*-cyclopropanes (Scheme 2). In the case of the $TiCl_4$-promoted reaction of *cis*-**1a**, the ring opening and elimination of a proton take place similar to the mechanism proposed in Scheme 4 to give *Z*-alkene **8**. Since this alkene is not suitable for Nazarov cyclization due to steric interaction between the phenyl rings[22] and also $TiCl_4$ is not capable of isomerizing it into the *E*-alkene, it did not undergo further change. It may be



Scheme 5. $AlCl_3$ and $TiCl_4$-mediated ring-opening reactions of *cis*-**1a**.

interesting to note that when treated with $AlCl_3$, the isolated *Z*-alkene **8** does not undergo Nazarov cyclization and remained inert. Thus the reaction supports the proposed mechanism (Scheme 4) for the formation of indanones **6** from **1**.

In conclusion, we have developed an efficient procedure for the transformation of *trans*-2-aroyl-3-arylcyclopropane-1,1-dicarboxylates into highly substituted 2-pyrones (heterocycles) and 1-indanones (carbocycles). Upon treatment with $AlCl_3$, the cyclopropanes underwent ring opening followed by fragmenta-

tion and recombination to give α,β-unsaturated δ-keto esters which lactonized to produce 2-pyrones. Switching the Lewis acid to $TiCl_4$ in the reactions generated 1-indanones with a *trans*-configuration of substituents at C-2 and C-3 *via* a Nazarov cyclization. Both reactions are of wide scope and a variety of 2-pyrones and 1-indanones could be conveniently synthesized using the protocols.

Experimental Section

General Procedure for the Synthesis of 2-Pyrones 3, 5 and 1-Indanones 6

To a solution of cyclopropane diesters **1** or **4** (1.0 mmol) in dichloromethane (5 mL) was added $AlCl_3$ (1.0 mmol) or $TiCl_4$ (1.5 mmol) at room temperature. The reaction mixture was stirred at room temperature and monitored by TLC. After the reaction was complete, the reaction mixture was quenched with ice-water and extracted with dichloromethane (3×). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (10:1) as the eluent to give the pure product.

Spectral data, copies of ^1H and ^{13}C NMR spectra and X-ray structural information of **3c**, **5c** and **6a** are available in the Supporting Information.

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