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Reactions of β-styrylmalonates with aromatic aldehydes: the development of a catalytic version using gallium trichloride

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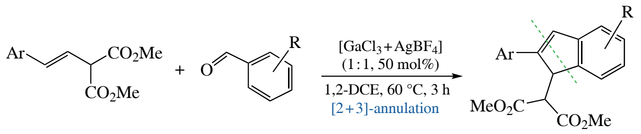
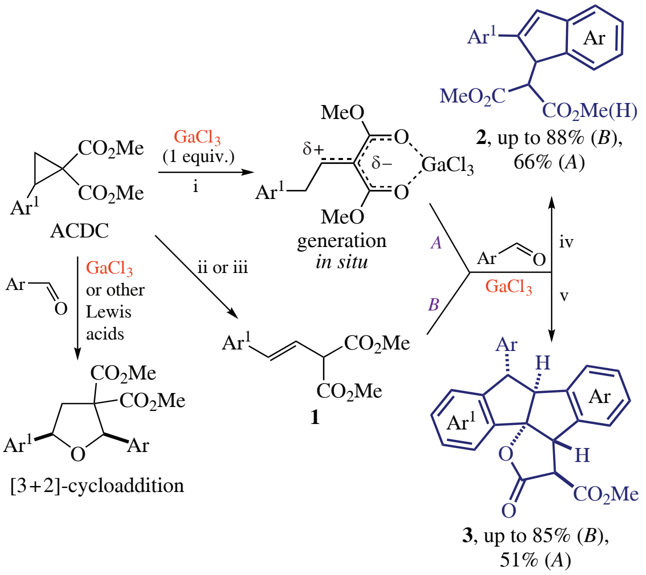
A catalytic system based on gallium trichloride and silver tetrafluoroborate was successfully tested in the [2+3]-annulation reaction of β-styrylmalonates with aromatic aldehydes leading to 2-arylinden-1-ylmalonates. This allows to reduce the amount of gallium compound and to halve the amount of aldehyde used while maintaining the optimal yields of the resulting indenylmalonates previously achieved using 2 equiv. of $GaCl_3$ and 4–6 equiv. of aldehyde. Under these conditions, aldehydes previously non-reactive were also involved into the transformation.



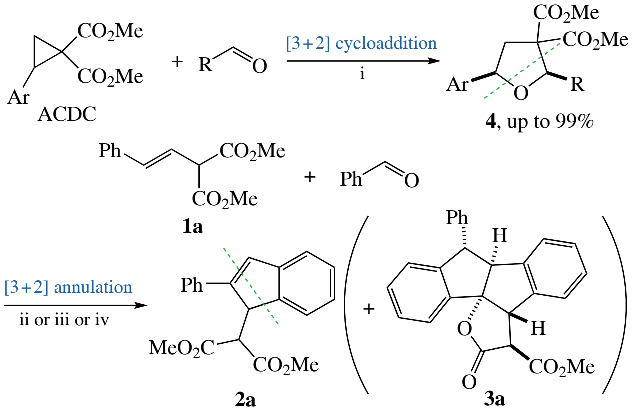
Keywords: styrylmalonates, aromatic aldehydes, inden-1-ylmalonates, gallium trichloride, silver tetrafluoroborate.

Donor–acceptor cyclopropanes (DACs), and 2-arylcyclopropane-1,1-dicarboxylates (ACDCs) in particular, are popular substrates for the introduction of three-carbon moiety into the target molecules.[1–7] Recently, isomeric to ACDCs β-styrylmalonates **1** have been suggested as alternative sources of this moiety. Under Lewis acid catalysis, these compounds are involved into various cycloaddition and/or annulation processes,[8] often reacting more efficiently as compared to ACDC. For instance, the formation of indenylmalonates **2** or pentacyclic lactones **3** using gallium trichloride was particularly more successful with styrylmalonates than with ACDCs (Scheme 1), with the nature of Lewis acids demonstrating significant influence on the reaction outcome. In some cases, these 'Ga-specific' processes required at least equimolar amounts of anhydrous $GaCl_3$.[9–11] The thus accessed indene-based and pentacyclic lactone scaffolds are found in various natural and biological active compounds.[12–14] Additionally, indenes are used as ligands or as precursors for functional materials.[15,16] Therefore, the development of approaches utilizing lower amounts of $GaCl_3$ (up to catalytic) is of great interest.

Recently, catalytic system based on cationic gallium phthalocyanines (^{R}PcGa$^+$) with weakly coordinating anions was successfully used in reactions of donor–acceptor substrates with



Scheme 1 *Reagents and conditions*: i, 0 °C, 10–15 min; ii, TMSOTf, PhCl, Δ; iii, $GaCl_3$, then MeOH and HCl/H_2O; iv, DCE, 60–80 °C, 0.3–1 h; v, 60–80 °C, 3–6 h.



Scheme 2 *Reagents and conditions*: i, R^t_nPcGa$^+$ SbF$_6^-$, CH_2Cl_2, 40 °C (ref. 18); ii, Bu$^t_4$PcGa$^+$ SbF$_6^-$, PhCl, 130 °C (60% of **2a**, ref. 17); iii, Bu$^t_4$PcGa$^+$ Sb$_2$F$_{11}^-$, $Cl(CH_2)_2Cl$, 83 °C (80% of **2a**, ref. 17); iv, this work, see Table 1.

aldehydes. We demonstrated that $Bu^t_4PcGa^+ SbF_6^-$ was applicable in [3 + 2]-cycloaddition between ACDCs and aldehydes leading to substituted tetrahydrofurans **4** (Scheme 2). In addition, we demonstrated the possibility of using $Bu^t_4PcGa^+ Sb_2F_{11}^-$ in the reaction between β-styrylmalonate **1a** and benzaldehyde resulting in indenylmalonate **2a**.[17,18] Unlike ACDCs, β-styrylmalonates demanded additional activation, which was achieved through the replacement of SbF_6^- with $Sb_2F_{11}^-$, giving a more active Ga-center in phthalocyanines, or through increasing the reaction temperature. In this article, we present an alternative catalytic system of gallium activation of β-styrylmalonates of type **1** in [3 + 2]-annulations with aromatic aldehydes, based on the anion exchange reaction between anhydrous gallium chloride and silver tetrafluoroborate, the latter being quite common as an activator of organometallic catalysts (see Scheme 2).[19–21]

In our first report[9] on the synthesis of indenylmalonates **2** from the reaction between styrylmalonates and aromatic aldehydes we have shown that the reaction required the use of two equivalents of anhydrous $GaCl_3$ and 4–6-fold molar excess of aldehyde (we will refer to them as previous conditions). Decreasing the loading of $GaCl_3$ to 1.0, 0.5 or 0.1 equiv. leads to the reduction in yield of indene **2a** (Scheme 2, Table 1, entries 3–5).[9] The situation changes significantly when we add $AgBF_4$ to activate the catalyst. It should be noted that $AgBF_4$ itself does not catalyze the process (entry 6), however its use with $GaCl_3$ increases the yield of indenylmalonate **2a** up to 55–84% (entries 8–10). Meantime, the transition from 0.5 equiv. of a 1 : 1 mixture to 0.2 equiv. afforded a slightly lower conversion of starting **1a** and significantly lower yield of **2a**. Raising the temperature from 60 to 80 °C provided high conversion but decreased the yield of **2a** to 15% (entries 11 and 12) which is apparently due to dimerization of **1a**.[11]

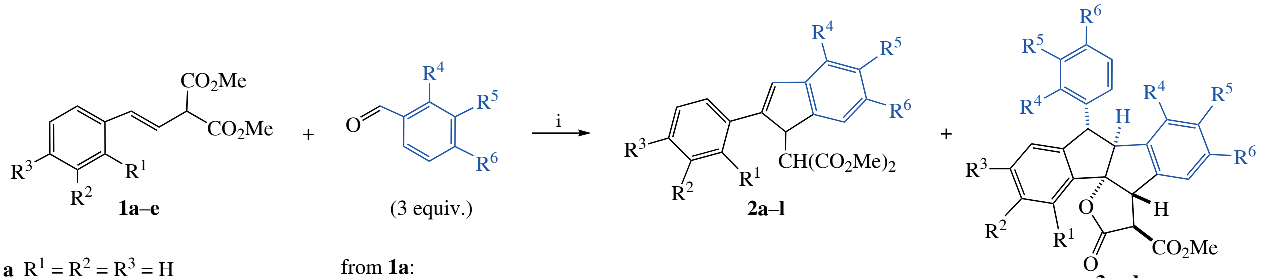
Table 1 Screening of catalysts in [3 + 2]-annulation of styrylmalonate with benzaldehyde.

Entry	Catalyst	Loading (equiv.)	*T*/°C	*t*/h	Conversion of **1a** (%)	Yield of **2a** (%)
1	none	–	60	3	0	–
2[a]	$GaCl_3$	2	60	0.25	>90	up to 71
3[a]	$GaCl_3$	1	60	3	100	26
4	$GaCl_3$	0.5	60	3	96	29
5	$GaCl_3$	0.1	60	3	21	5
6	$AgBF_4$	0.5	60	3	<5	–
7	$GaCl_3$ + $AgSbF_6$	0.5 + 0.5	60	3	100	(43[b])
8	**$GaCl_3$ + $AgBF_4$**	**0.5 + 0.5**	**60**	**3**	**99**	**77**
9	$GaCl_3$ + 2$AgBF_4$	0.5 + 1	60	3	97	55
10	$GaCl_3$ + 3$AgBF_4$	0.5 + 1.5	60	3	87	84
11	$GaCl_3$ + $AgBF_4$	0.2	60	3	65	29
12	$GaCl_3$ + $AgBF_4$	0.2	80	3	96	15

[a] Data from ref. 9. [b] Yield for lactone **3a** as main identified product.

We suppose that the most catalytically active particle generated in the initial stage of the proposed anion exchange reaction is $Ga_2Cl_5^+ BF^-_{4(solv.)}$ formed when AgCl precipitates. However, the anion exchange does not stop at this step with the use of 2–3 equiv. of $AgBF_4$, and further anion exchange proceeds with lower selectivity. Subsequent replacement of the chloride anion with the tetrafluoroborate anion leads to an increase in the electrophilicity of the gallium atom, which, in turn, results in the gradual abstraction of the fluorine anion from the tetrafluoroborate anion and the formation of the Ga–F bond. This process partially deactivates the complex, reduces its solubility and as a result it precipitates together with AgCl and $AgGaCl_4$. Thus, gallium is partially removed from the reaction, and the actually working quantity of catalytically active mixture is no more than 50%. The partial precipitation of gallium from mixtures along with silver chloride was confirmed by electron microscopy data.

During the optimization of the reaction of styrylmalonate **1a** with benzaldehyde, we found a reasonable balance between good yields and economic loading of gallium chloride and silver tetrafluoroborate (see Table 1, entry 8), and the reaction conditions of choice were 1,2-dichloroethane, 50 mol% of equimolar mixture $GaCl_3$ and $AgBF_4$, 2.5–3 equiv. of aldehyde, 60 °C, 3 h. With these conditions, we tested our catalytic system on a wide range of aromatic aldehydes and β-styrylmalonates **1a–e** (Scheme 3). The reaction between styrylmalonate **1a** and 2-bromo-, 4-methoxy- and 4-nitrobenzaldehydes afforded indenylmalonates **2b–d** with good yields (conversion of **1a** was 95–100%), which are comparable to yields of corresponding indenes obtained under previous conditions (~2 equiv. of $GaCl_3$). Unreactive under previous conditions, 2,4-dichlorobenzaldehyde was successfully transformed into product **2e** with 79% yield. It is worth noting that the reactions of **1a** with 2-naphthaldehyde and 4-methylbenzaldehyde led to the formation of both indenylmalonates **2f,g** and pentacyclic lactones **3b,c** in approximately equal proportions. In case of 1-naphthylstyrylmalonate **1d**, the $GaCl_3$ + $AgBF_4$ provided the yield of indenylmalonate **2j** of 36% (which was 10% better than with the previous catalyst[9]); the formation of the corresponding polycyclic lactone of type **3** was not observed. In contrast, the lactonization of 4-methylstyrylmalonate **1e** with benzaldehyde proceeded very effectively and led to lactone **3d** with 60% yield. In all cases, the conversions of styrylmalonates **1a–e** were not less



1a–e

(3 equiv.)

2a–l

3a–d

a $R^1 = R^2 = R^3 = H$
b $R^1 = R^3 = H, R^2 = Br$
c $R^1 = R^2 = H, R^3 = Cl$
d $R^1 + R^2 = (CH{=}CH)_2, R^3 = H$
e $R^1 = R^2 = H, R^3 = Me$

from **1a**:
2a 77%, **3a** 13%, $R^4 = R^5 = R^6 = H$
2b 69%, $R^4 = Br, R^5 = R^6 = H$
2c 45%, $R^4 = R^5 = H, R^6 = OMe$
2d 62%, $R^4 = R^5 = H, R^6 = NO_2$
2e 79%, $R^5 = H, R^4 = R^6 = Cl$
2f 47%, **3b** 47%, $R^4 = H, R^5 + R^6 = (CH{=}CH)_2$
2g 44%, **3c** 49%, $R^4 = R^5 = H, R^6 = Me$

from **1b–e**:
2h 80%, $R^1 = R^3 = R^4 = R^5 = R^6 = H, R^2 = Br$
2i 71%, $R^1 = R^2 = R^4 = R^5 = R^6 = H, R^3 = Cl$
2j 36%, $R^1 + R^2 = (CH{=}CH)_2, R^3 = R^4 = R^5 = R^6 = H$
2k 68%, $R^1 = R^3 = R^4 = R^5 = H, R^2 = Br, R^6 = Me$
2l 86%, $R^1 = R^3 = R^5 = R^6 = H, R^2 = R^4 = Br$
3d 60%, $R^1 = R^2 = R^4 = R^5 = R^6 = H, R^3 = Me$

Scheme 3 *Reagents and conditions*: i, $GaCl_3$ (0.5 equiv.), $AgBF_4$ (0.5 equiv.), 1,2-dichloroethane, 60 °C, 3 h. For compounds **2f,g** and **3a** NMR yields are given.

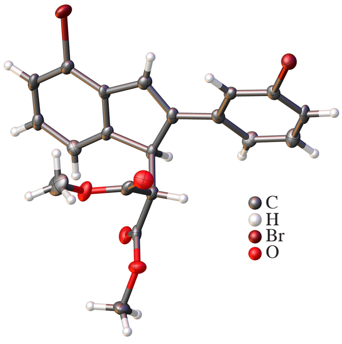
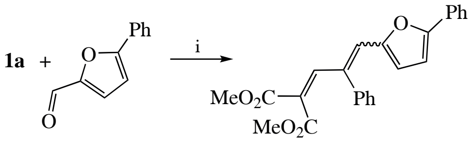


Figure 1 Single-crystal X-ray analysis data of **2l**.



5, 66%, *E*/*Z* ~ 1.1 : 1

Scheme 4 *Reagents and conditions*: i, $GaCl_3$ (0.5 equiv.), $AgBF_4$ (0.5 equiv.), 1,2-dichloroethane, 60 °C, 3 h.

than 95%. The structure of indenylmalonate **2l** was confirmed by X-ray structural analysis of its single crystal (Figure 1).[†]

The reaction between styrylmalonate **1a** and 5-phenyl-2-furaldehyde proceeds unusually resulting in 3-(furan-2-yl)-allylidenemalonate **5** (Scheme 4).

To sum up, a novel catalytic system based on anion exchange reaction between equimolar amounts of gallium chloride and silver tetrafluoroborate, with loading of 50 mol% each, was developed and successfully tested in [3 + 2]-annulation reaction of β-styrylmalonates with aromatic aldehydes. This catalytic system enabled the efficient synthesis of the corresponding indenylmalonates and/or pentacyclic lactones with yields comparable to those obtained using two equivalents of $GaCl_3$.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7594.

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[†] *Crystal data for* **2l**. $C_{20}H_{16}Br_2O_4$ (M = 480.15), T = 100 K, monoclinic, space group $P2_1/c$, a = 13.546(2), b = 8.0371(14) and c = 17.920(3) Å, $\alpha = \gamma = 90°$, β = 107.182(7)°, V = 1863.9(6) Å^3, Z = 4, μ(MoKα) = 4.372 mm^{-1}. At the angles $4.758 < \theta < 51.992°$, total of 14198 reflections were measured, including 3634 unique reflections (R_{int} = 0.1248). The final R_1 = 0.0723, wR_2 = 0.1634 (all data) and R_1 = 0.0600, wR_2 = 0.1553 [$I > 2\sigma(I)$], GOOF = 1.028. Largest diff. peak/hole 0.66 and –1.01 eÅ^{-3}. X-ray crystallographic data were obtained on a Bruker Apex II diffractometer equipped with CCD detector, MoKα radiation tube and graphite monochromator (ω-scans). A semi-empirical absorption correction using the SADABS program was applied.[22] Using Olex2, the structure was solved with a ShelXS structure solution program using Direct Methods and refined using a ShelXL refinement package with the Least Squares minimization in anisotropic approximation for nonhydrogen atoms.[23,24] The H-atoms were added in the calculated positions and refined using the riding model in isotropic approximation. The main crystallography data and refinement details are given in Table S1.

CCDC 2360163 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.