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Gallium-Catalyzed Scriabine Reaction

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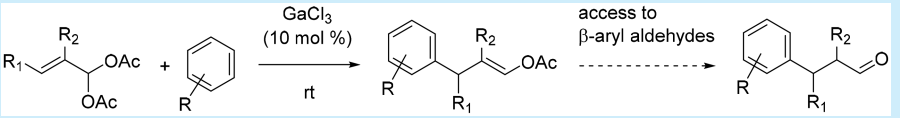
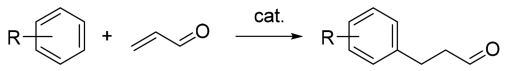
Supporting Information



ABSTRACT: γ-Aryl enol acetates are easily obtained from diacetoxy alkenes and electron-rich arenes at room temperature using $GaCl_3$ as catalyst. The products can then be converted into β-aryl aldehydes. This method represents the first broadly applicable catalytic version of the Scriabine reaction. DFT computations shed light on the mechanism of this transformation.

β-Aryl-saturated aldehydes (dihydrocinnamaldehydes) are of fundamental interest in organic chemistry, as they are used as synthons in the preparation of natural products and pharmaceuticals or as ingredients of fragrances.[1] Various strategies have been reported to synthesize such compounds, but the most obvious route, the Michael addition of arenes to α,β-unsaturated aldehydes, remains a difficult task (eq 1).[2]



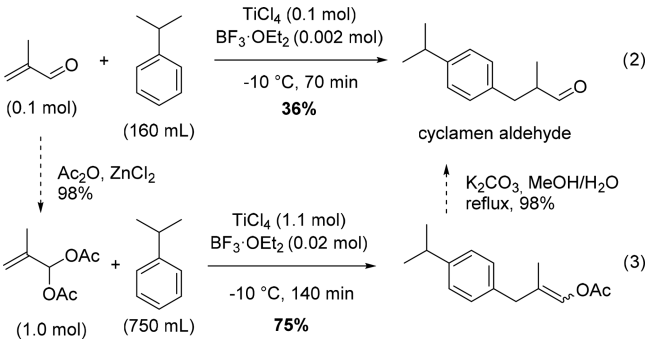
(1)

It is mostly limited to highly nucleophilic heteroarenes (indoles, pyrroles, furans), aniline derivatives, and arenes displaying directing groups for C−H activation.[3] For other arenes, efficient approaches are scarce and involve conditions that prevent the polymerization of the conjugated aldehyde such as the use of H-type zeolites as catalysts.[2] This polymerization issue has long been described. In 1961, Igor Scriabine reported that dihydrocinnamaldehydes could be obtained in low yields by condensing at low temperature (−10 °C to −40 °C) electron-rich benzenes to α,β-unsaturated aldehydes, using the arene as solvent, an equimolar amount of $TiCl_4$ compared to the aldehyde, and 2 mol % of $BF_3{\cdot}OEt_2$.[4] An example of this approach to the synthesis of cyclamen aldehyde, obtained in 36% yield, is shown in Scheme 1 (eq 2).

Interestingly, in the same paper, Scriabine demonstrated that much better yields could be obtained by replacing the α,β-unsaturated aldehyde by its diacetoxy derivative (eq 3). However, the reaction conditions remained essentially the same, with a large excess of arene used as solvent, a slight excess of $TiCl_4$ (1.1 equiv), and 2 mol % of $BF_3{\cdot}OEt_2$.

Due to the interest of the perfume industry for this reaction, which leads, for instance, to cyclamen or lily aldehydes, a number of patents have been deposited with attempts to turn this reaction catalytic, but the claims are focused on specific compounds and seem to lack generality.[5] Still in 2015, the

Scheme 1. Scriabine Synthesis of Cyclamen Aldehyde



synthesis of *para*-substituted aromatic aldehydes by condensation of substituted benzenes, used as solvent, and methacrolein diacetyl acetal, was promoted by 1.5 equiv of $TiCl_4$ at −10 °C.[6] This need for a stoichiometric or an excess amount of Lewis acid suggests that the two acetates must be activated and that their basicity precludes the regeneration of the catalyst. In this regard, we have previously reported that the use of calcium-[7] and gallium-derived Lewis acids[8] could catalyze the condensation of relatively weak nucleophiles, such as arenes, to carbon−carbon multiple bonds, even in the presence of strongly coordinating functionalities that tend to trap metal ions. Thus, we decided to turn our attention to this overlooked way of producing β-aryl-saturated aldehydes from diacetoxy alkenes. Herein, we report the first broadly applicable catalytic version of the Scriabine reaction,[9] as well as mechanistic considerations regarding the activation of such substrates obtained by DFT computations.

Proper reaction conditions were developed using diacetoxypropene **1a** and 1.5 equiv of anisole (Table 1). The use of the

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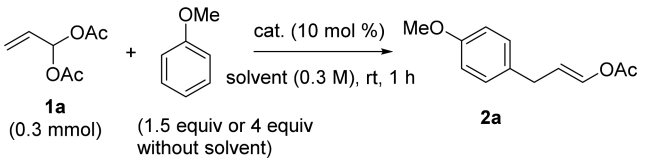
Table 1. Screening of the Reaction Conditions



entry	catalyst	solvent	conv[a] (yield) (%)
1	$Ca(NTf_2)_2/nBu_4PF_6$	toluene	63[b]
2	$Ca(NTf_2)_2/nBu_4PF_6$	HFIP	99 (24)
3	$Ga(OTf)_3$	toluene	60[b]
4	$GaCl_3$	toluene	75[b]
5	$In(OTf)_3$	toluene	60[b]
6	$InCl_3$	toluene	60[b]
7	$FeCl_3$	toluene	70[b]
8	$GaCl_3$	1,2-DCE	99 (66)
9	IPr·$GaCl_3$[c]/$AgSbF_6$	1,2-DCE	99 (35)
10	$GaCl_3$	THF	99[b]
11	$GaCl_3$	$MeNO_2$	99 (29)
12	**$GaCl_3$**	**PhF**	**99 (74)**
13	**$GaCl_3$**	-	**99 (83)**
14	$GaBr_3$	-	99 (78)
15	GaI_3	-	99 (70)
16	Ga_2Cl_4	-	99 (44)

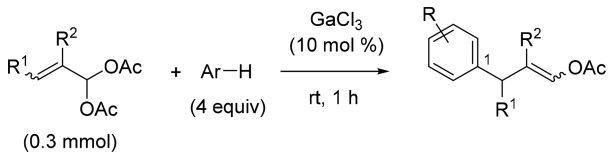
[a]GC. [b]Complex mixture. [c]IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene.

$Ca(NTf_2)_2/nBu_4PF_6$ catalytic mixture[10] led to an incomplete conversion of **1a** at rt after 1 h and to a complex mixture of products (entry 1). Full conversion was reached in hexafluoroisopropanol (HFIP),[7c] yet the desired enol acetate **2a** was isolated in a low 24% yield (entry 2). Various Lewis acids of the gallium, indium, and iron series also proved nonselective in toluene (entries 3−7). In 1,2-dichloroethane, $GaCl_3$ allowed the synthesis of **2a** in 66% yield (entry 8). The more electrophilic $[IPr{\cdot}GaCl_2][SbF_6]$ complex[11] was found to be a less selective catalyst (entry 9). Using $GaCl_3$ in THF or $MeNO_2$ was not fruitful (entries 10 and 11), but in PhF, a good 74% yield was obtained (entry 12).

In the absence of solvent, the yield could be increased to 83% provided 4 equiv of anisole was used (entry 13). Under such conditions, other gallium halides led to lower yields (entries 14−16). Thus, the reaction can be efficiently conducted using $GaCl_3$ as catalyst in PhF with 1.5 equiv of nucleophile or directly in 4 equiv of the nucleophile.

We chose to use the "solvent-free" conditions to study the scope of the $GaCl_3$-catalyzed reaction, which is shown in Table 2. The *E*/*Z* ratio of the enol acetates is indicated, but since they are meant to be converted into the corresponding aldehydes,[4,12] this point is not essential. Diacetoxypropene **1a** was first used as acceptor (entries 1−13). While no reaction was observed with deactivated aromatics[13] and benzene (entry 1), toluene led to the *para* and *ortho* isomers of the desired enol acetate in a 1.2:1 ratio (entry 2). Only the *para* isomer was obtained using cumene or anisole (entries 3 and 4). The 83% yield obtained with anisole is actually the same as the one reported by Onaka using a zeolite as catalyst.[2] The zeolite-catalyzed reaction leads to the aldehyde directly, yet as an 85:15 *para*/*ortho* mixture of regioisomers, so both approaches have their own advantages. Disubstituted benzenes (entries 5−9) and a trisubstituted one (entry 10) also furnished the expected products. With the solid nucleophiles methyl *p*-anisate, naphthalene, and biphenyl, a low amount of PhF was added to solubilize the heterogeneous mixture (250 μL) without preventing the reaction (entries 7, 11, and 12). No poisoning of the catalyst took place with thiophene, which led to the 2-thienyl isomer of the enol acetate as the major one (entry 13). Substituted diacetoxypropenes **1b−f** were next reacted with anisole (entries 14−18), and they also proved compatible with the reaction conditions. Overall, the products were isolated with good purity in 49−88% yields. These yields are comparable to those reported by Scriabine for **2a** (85%) and **2p** (88%), lower for **2c** (84%), and higher for **2b**/**2b′** (20%) and **2h** (62%).[4] The regioselectivity can be easily controlled by electronic and steric factors, except in the case of toluene (entry 2) and *o*-xylene (entry 5). It is worth noting that the proportion of arene can be lowered to 1.5 equiv when PhF is used as solvent with somewhat lower, yet appreciable, yields (entries 8−10, 77%, 69%, 67%, respectively).

Table 2. Scope of the $GaCl_3$-Catalyzed Scriabine Reaction



entry	sub.	R^1	R^2	prod.	R	yield (%)
1	**1a**	H	H	-	H	0
2	**1a**	H	H	**2b**/**2b′**	4-Me/2-Me[b]	54[e]
3	**1a**	H	H	**2c**	4-*i*Pr	63[f]
4	**1a**	H	H	**2a**	4-OMe	83[g]
5	**1a**	H	H	**2d**/**2d′**	3,4-Me_2/2,3-Me_2[c]	55[h]
6	**1a**	H	H	**2e**	2,5-Me_2	74[i]
7[a]	**1a**	H	H	**2f**	2-OMe, 5-CO_2Me	49[j]
8	**1a**	H	H	**2g**	3-Me, 4-OMe	79[g,n]
9	**1a**	H	H	**2h**	3,4-$(OMe)_2$	88[k,o]
10	**1a**	H	H	**2i**	2,4,6-Me_3	78[g,p]
11[a]	**1a**	H	H	**2j**	β-naphthyl	52[j,q]
12[a]	**1a**	H	H	**2k**	4-Ph	44[g,q]
13	**1a**	H	H	**2l**/**2l′**	2-thienyl/3-thienyl[d]	75[g,q]
14	**1b**	Me	H	**2m**	4-OMe	87[l]
15	**1c**	Et	H	**2n**	4-OMe	64[j]
16	**1d**	*n*Pr	H	**2o**	4-OMe	81[m]
17	**1e**	H	Me	**2p**	4-OMe	82[g]
18	**1f**	Et	Me	**2q**	4-OMe	89[g]

[a]When the nucleophiles are solids (entries 11 and 12), 250 μL of PhF was added. [b]Isomeric ratio: 1.2:1. [c]Isomeric ratio: 3:1. [d]Isomeric ratio 6:1. [e]*E*/*Z* ratio: 4.1:1/1.9:1. [f]*E*/*Z* ratio: 2.1/1. [g]*E*/*Z* ratio: >20:1. [h]*E*/*Z* ratio: 6:1/2.7:1. [i]*E*/*Z* ratio: 6.7:1. [j]*E*/*Z* ratio: 4:1. [k]*E*/*Z* ratio: 13:1. [l]*E*/*Z* ratio: 4.7:1. [m]*E*/*Z* ratio: 3.9:1. [n]Using 1.5 equiv of Ar−H and PhF as solvent (0.3 M): 77%. [o]Using 1.5 equiv of Ar−H and PhF as solvent (0.3 M): 69%. [p]Using 1.5 equiv of Ar−H and PhF as solvent (0.3 M): 67%. [q]A small amount of dialkylation product has been isolated as side compound.

As an application of the title reaction, we undertook the synthesis of dianethole, a natural compound found in fennel and anise,[14] the synthesis of which has not been reported in the literature (Scheme 2). Starting from 1.5 g of **1b**, compound **2m** was isolated in 66% yield. The decrease in yield compared to Table 2, entry 14, can be explained by an increase of temperature when working at such a scale. Methanolysis[12] led to the β-aryl aldehyde **3m**, which decomposes rapidly when stored at rt. It was rapidly engaged in a Horner−Wadsworth−Emmons reaction, which provided dianethole in 42% yield.

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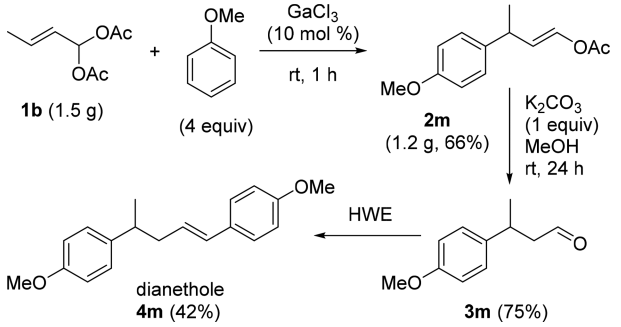
Scheme 2. Gram-Scale Reaction, Methanolysis, and Application to the Synthesis of Dianethole



To rationalize the catalytic role of $GaCl_3$ in the title reaction, DFT computations were carried out using the Gaussian 09 software package, the ωB97XD functional, and the 6-31+G** basis set for all atoms. The full energy profile is provided in the Supporting Information. The teaching of this study is that the approach of anisole to the terminal carbon of diacetoxypropene **1a** complexed to one or two $GaCl_3$ units by its carbonyl groups promotes the elimination of $GaCl_3(OAc)^-$ (Figure 1).

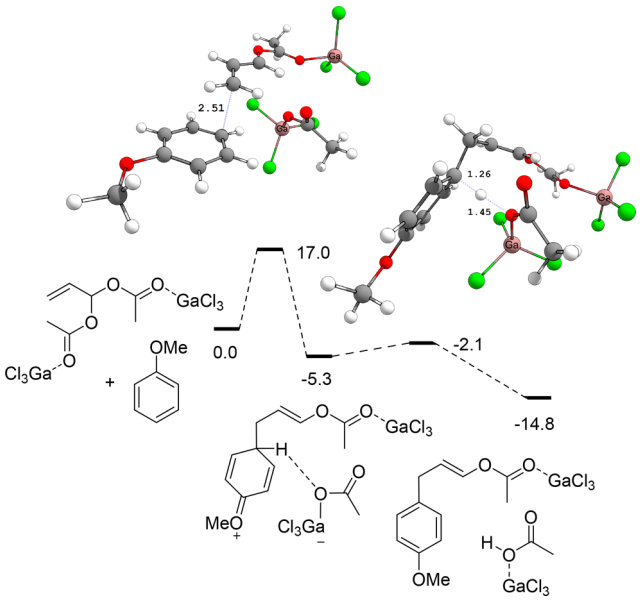


Figure 1. Computed free energy profile (ΔG_{298}, kcal/mol) and transition states (selected distances in Å).

This step is much more efficient with two $GaCl_3$ instead of one, with the barriers being 17.0 and 25.6 kcal/mol, respectively. Besides, the addition of anisole is strongly endergonic with only one $GaCl_3$ (13.3 kcal/mol instead of −5.3 kcal/mol with two $GaCl_3$). $GaCl_3(OAc)^-$ can then serve as base to deprotonate the resulting Wheland-type intermediate at a low free energy cost of 3.2 kcal/mol. From the final products complexed to $GaCl_3$, going back to **1a**·2$GaCl_3$ is exergonic by 11.9 kcal/mol (not shown), which corroborates the catalytic activity of $GaCl_3$.

In conclusion, we have developed catalytic conditions that allow the synthesis of γ-aryl enol acetates from diacetoxy alkenes and of the β-aryl-saturated aldehydes thereof. This approach avoids the use of a very large excess of nucleophile and a stoichiometric amount of $TiCl_4$. It is synthetically equivalent to a Michael addition of simple arenes to α,β-unsaturated aldehydes, which is very difficult to achieve under homogeneous conditions. DFT computations suggests that a double activation of the diacetoxy alkene by two molecules of Lewis acid would be more efficient than with just one. In spite of the strongly coordinating nature of the substrate, the use of $GaCl_3$ as catalyst allows the reaction to turn over.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03104.

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for all new compounds, coordinates, and energy of the computed species (PDF)

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Notes

The authors declare no competing financial interest.

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