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COMMUNICATION

Tropylium Salts as Efficient Organic Lewis Acid Catalysts for Acetalization and Transacetalization Reactions in Batch and Flow

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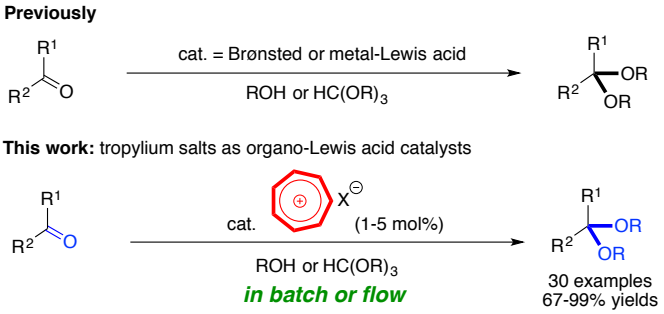
Acetalization reactions play significant roles in the synthetically important masking chemistry of carbonyl compounds. Herein we demonstrate for the first time that tropylium salts can act as organic Lewis acid catalysts to facilitate acetalization and transacetalization reactions of a wide range of aldehyde substrates. This metal-free method works efficiently in both batch and flow conditions, prompting further future applications of tropylium organocatalysts in green synthesis.

Carbonyl compounds are among the most synthetically important classes of organic substrates owing to their ubiquitous and versatile chemical reactivity in redox and nucleophilic addition or substitution reactions.[1] The highly reactive carbonyl functionality, however, requires masking or protection to survive multi-step chemical processes frequently found in modern laboratory and industrial syntheses.[1] Acetalization reaction is probably the most popular masking method for aldehydes and ketones.[1] This type of reaction typically involves condensation processes promoted by Brønsted/Lewis acids or combined Lewis/Brønsted assisted acids.[1-2] Most of the previously employed Lewis acid catalysts are metal salts,[1] which might pose significant issues in the purification process.[3] Herein, we introduce the utilization of tropylium salts as organic Lewis acids to efficiently catalyze acetalization reactions of a wide range of carbonyl compounds with orthoformates and 1,2-diols (Scheme 1). Similarly, transacetalization from acyclic to cyclic acetal systems can also be promoted by these catalysts with excellent outcomes.

The concept of using salts of stable carbocations as organic Lewis acids[4] has been reported in literature with tritylium salts as catalysts for a number of chemical transformations.[5] Applications of these methods in organic synthesis, however, are still limited due to their issues with efficiency and reaction



Scheme 1. Tropylium-catalyzed acetalization reactions

scope.[5a,5c,5f] To the best of our knowledge, salts of the aromatic tropylium ion,[6] though recognized as stable analogues of tritylium salts,[7] have never been employed as Lewis acid catalysts.[7e] Based on our previous works with tropylium-promoted chemistry[8] and carbonyl compounds,[9] we envisioned that the aromatic tropylium ion,[10] possessing one positive charge delocalized over a fully conjugated 6π-electron seven-carbon system,[7e] could serve as a soft Lewis catalyst. Thus, this work demonstrates for the first time that tropylium salts can be used in this role for acetalization and transacetalization reactions. The successful implementation of this method in a simple flow setup also pave way for further applications of tropylium catalysts in green chemistry.

Our initial investigation using 10 mol% of tropylium tetrafluoroborate to catalyze acetal formation reaction between *p*-tolualdehyde (**1a**) and triethylorthoformate (**2a**) was instantly met with very positive outcomes (entry 1, Table 1). NMR monitoring study of the reaction showed complete conversion of the aldehyde to the product within hours with high yield after chromatography isolation. Variation of reaction conditions and catalyst loading revealed that the reaction was optimal with 5 mol% $TropBF_4$ catalyst in acetonitrile (entries 5-10); the reaction however also worked effectively in other solvent systems or neat conditions at lower catalyst loadings (entries 1-4, Table 1). We did not further investigate the reaction in neat conditions as the use of a small amount of solvent facilitated the stirring of reaction mixtures. Elevated temperature reduced reaction time significantly, although

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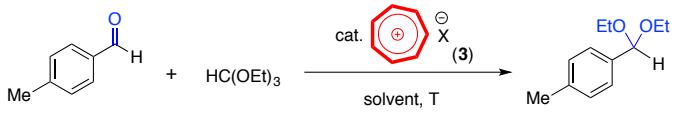
Table 1. Optimization of tropylium-promoted acetalization reaction[a]



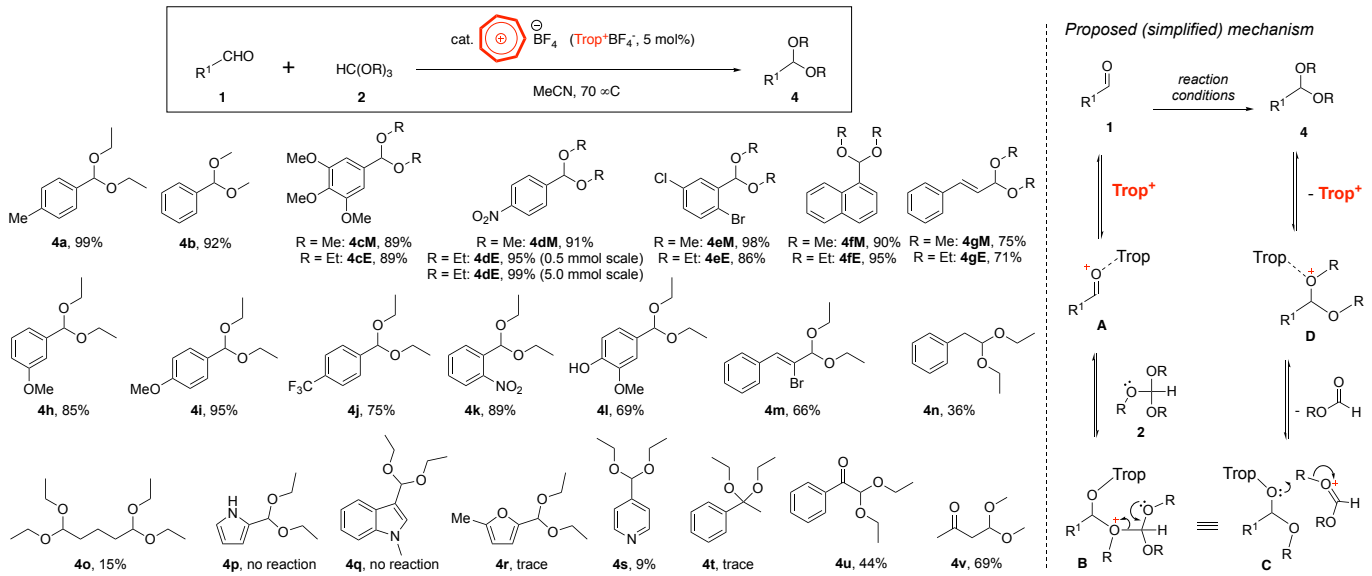
Entry	X	mol% cat.	solvent	T (°C)	time[b]	Yield[c]
1	BF_4	5	DCM	rt/70	24	83/74
2	BF_4	5	toluene	rt/70	24	56/69
3	BF_4	5	neat	70	24	46
4	BF_4	2.5	neat	70	5	80
5	BF_4	5	MeCN	rt/reflux	24/5	63/61
6	**BF_4**	**5**	**MeCN**	**70**	**5**	**99**
7[d]	BF_4	5	MeCN	70	5	89
8	BF_4	2.5	MeCN	70	5	84
9	BF_4	1	MeCN	70	5	75
10	-	0	MeCN	70	24	12
11	Br	5	MeCN	70	5	81
12	OTf	5	MeCN	70	5	88
13	BPh_4	5	MeCN	70	5	90
14[e]	BF_4	5	MeCN	70	5	96

[a] Conditions: aldehyde **1a** (0.5 mmol), triethyl orthoformate **2a** (1.0 mmol), cat. **3** in dry solvent (0.6 mL) under Ar atmosphere. [b] Reaction time (hour) for total consumption of aldehyde **1a**. [c] Yield of the isolated product. [d] Reaction flask opened to air. [e] 10 mol% of DTBMP added in extra-dry MeCN solvent.[11]

prolonged heating led to decomposition of the product (entries 1-6, Table 1). Tropylium salts with other counterions also promoted this reaction efficiently (entries 11-13, Table 1) but tropylium tetrafluoroborate was the catalyst of choice due to its superior stability and availability.[12] On the other hand, a control reaction with 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, entry 14) and extra-dry solvent confirmed that this reaction does not follow a Lewis-acid assisted Brønsted acid catalytic pathway. The reaction also seemed to tolerate aerobic environments (entries 6-7, Table 1).

Having the optimized reaction conditions in hand, we subsequently carried out a substrate scope investigation with a broad range of aldehydes (Scheme 2) and orthoesters. The reaction worked smoothly with all tested benzaldehydes to give diethyl and dimethyl acetal products in good to excellent yields. The stereoelectronic properties of substituents on the aromatic rings of benzaldehydes seemed to have little effect on reaction outcomes (**4a**-**l**, Scheme 2). Aliphatic aldehydes also reacted to give products in moderate yields (**4n**, **4o**, **4v**). Interestingly, heteroaromatic aldehydes were only either partially converted to the products or not acetalized at all under these reaction conditions (**4p-s**). Presumably, the heteroatom centres are usually more Lewis basic than the oxo moieties, thus the unwanted coordination of tropylium to these heteroatoms deactivated its catalytic efficiency. This fascinating phenomenon could be exploited in selective acetal protection of a mixture of *p*-nitrobenzaldehyde and 4-pyridine carboxaldehyde.[13] Similarly, the ketone functional group is presumably not reactive enough for this type of tropylium-catalyzed reaction, thus the ketalization did not proceed efficiently (**4t**, Scheme 2). Therefore, the aldehyde moiety could be chemoselectively protected in the presence of ketone functionality using our reaction settings (**4u-v**).

A plausible mechanism for this reaction was proposed in Scheme 2. While we believe that tropylium ion acted as a Lewis acid to activate the carbonyl moiety (**A**, Scheme 2) for nucleophilic addition reaction with trialkyl orthoformate (**B**, Scheme 2), what happened afterwards could be quite complicated with many electron-rich oxygen centres on the reactive intermediate. In a simplified hypothesis, the methyl/ethyl group could be transferred intramolecularly or intermolecularly along with elimination of the alkyl formate, which proceeded through intermediates **C**/**D** to the product with loss of the tropylium ion to another catalytic cycle. We cannot rule out the possibility that the tropylium catalyst also activates the orthoformate to promote the reaction.



Scheme 2. (left) Substrate scope of acetalization reaction; (right) proposed mechanism of the reaction. Reaction conditions: carbonyl compound **1** (0.5 mmol), triethyl or trimethyl orthoformate **2** (1.0 mmol), catalyst tropylium tetrafluoroborate (0.025 mmol, 5 mol%) in dry acetonitrile (0.6 mL) under Ar atmosphere.

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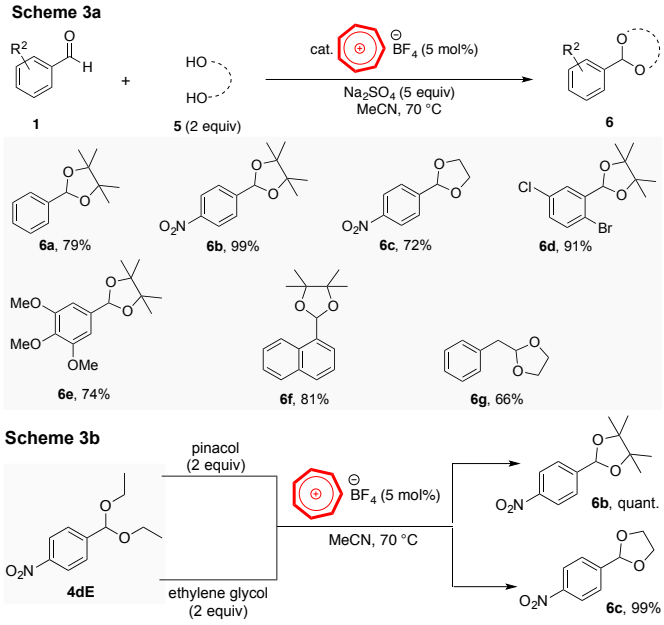
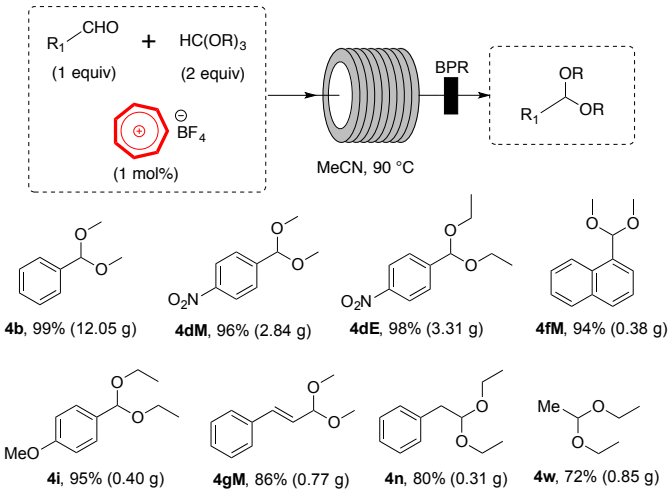


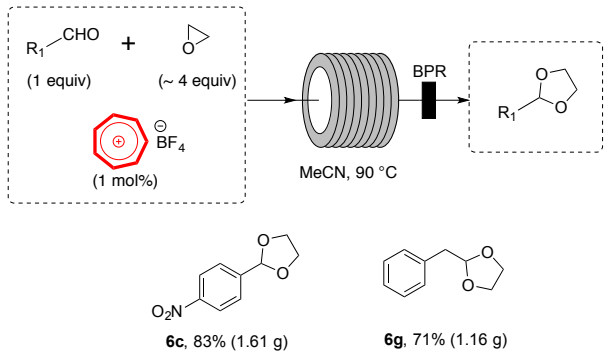
Scheme 3. (a) Cyclic acetalization and (b) transacetalization reactions.

Replacement of orthoesters with 1,2-diols and Na_2SO_4 as dehydrating agent also produced cyclic acetals in high to excellent yields (Scheme 3a). Surprisingly, the bulky pinacol proved to be more efficient than the commonly used ethylene glycol for 1,3-dioxolane formation reactions. We believe that the steric hindrance posed by four methyl substituents on pinacol helps to prevent unwanted coordination of tropylium ion to the hydroxyl groups of this diol. The transacetalization reactions from acyclic diethyl acetals to cyclic pinacol or ethylene glycol acetals also work effectively using the same catalytic conditions, offering a convenient method to switch masking groups on carbonyl functionality (Scheme 3b).

We subsequently focused on adapting this newly developed batch method to a flow chemistry approach for practical synthesis of acetal products. As outlined in Scheme 4, our simple flow system comprised of a syringe pump connected to a heated tubular reactor coil fitted with a back-pressure regulator.[14] The flow protocol mirrored batch conditions but was implemented at higher temperature to further reduce reaction/residence time. Gratifyingly, this rudimentary flow setup efficiently mediated the acetalization reactions of benzaldehyde to afford the desired products in high to excellent yields. A quick optimization study demonstrated that the tropylium tetrafluoroborate catalyst loading could be reduced to 1 mol% without affecting these remarkable reaction outcomes.[11] The tropylium catalyst remained mostly unchanged after the reaction and could be isolated for recycling purpose (see page S25 in the ESI).[11]

The optimized flow settings were subsequently employed to allow highly efficient multiple-gram synthesis of a range of acyclic acetals (Scheme 4), even with very volatile substrates such as acetaldehyde. Most interestingly, this tropylium-catalyzed flow procedure can also be applied to promote acetalization of aldehydes with ethylene epoxide,[15] which might be difficult in batch with this gaseous reagent. The simplicity and efficiency of this metal-free flow protocol offer a new practical approach to acetalization reactions of aldehyde compounds on large scales.





Scheme 4. Tropylium-promoted acetalization reactions in flow. Conditions: tropylium tetrafluoroborate (0.01 equiv, 1 mol%), aldehyde **1** (1.0 equiv), orthoester **2** (2.0 equiv) or ethylene epoxide (~ 4 equiv) in acetonitrile (0.08 M), 0.1 mL/min, T = 90 °C, PTFE tubing (0.8 mm ID) reactor volume = 4.5 mL.

Conclusions

In conclusion, we have demonstrated for the first time that tropylium salts can act as organic Lewis acid catalysts to facilitate the acetalization and transacetalization reactions on a wide range of aldehydes. This metal-free method works efficiently in both batch and flow conditions, offering a convenient protocol to mask aldehyde functional groups in organic chemistry. This work also prompts further studies to develop future applications of tropylium organocatalysts in green synthesis. Other tropylium-catalyzed chemical reactions are currently under investigation in our group and will be reported in due course.

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TOC: Tropylium salts were reported as organic-Lewis acids to efficiently catalyze acetalization reactions in batch and flow.