Tropolonate Salts as Acyl Transfer Catalysts for Esterification Reactions under Thermal and Photochemical Conditions

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Dedication ((optional))

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Abstract: Acyl transfer catalysis is a frequently used tool to promote the formation of carboxylic acid derivatives, which are important synthetic precursors and target compounds in organic synthesis. However, there have been only a few structural motifs known to efficiently catalyze the acyl transfer reaction. Herein we introduce a new acyl transfer catalytic paradigm based on the tropolone framework. We show that tropolonate salts, due to their strong nucleophilicity and photochemical activity, can promote the coupling reaction between alcohols and carboxylic acid anhydrides or chlorides to give the products with excellent efficiency under thermal or blue light-photochemical conditions. Kinetic studies and density functional theory (DFT) calculations suggest interesting mechanistic insights for reactions promoted by this new acyl transfer catalytic system.

Introduction

Esters of carboxylic acids are ubiquitous not only as useful synthetic precursors in organic synthesis but also as important building blocks in pharmaceuticals and agrochemicals.[1] The synthesis of these derivatives directly from carboxylic acids and alcohols in Fischer esterification processes normally suffers from incomplete conversion due to the condensation/hydrolysis equilibrium.[1] Thus, reactive acylation reagents such as acid chlorides or acid anhydrides are typically the reagents of choice to couple with alcohols or phenols in esterification reactions.[2] Nevertheless, when the alcohol or phenol substrates are non-reactive due to electronic or steric hindrance, these reactions become sluggish and inefficient.[2a, 2b] A number of acyl transfer catalysts have therefore been used to promote these reactions.[3] Most of these acyl transfer systems include a 4-aminopyridine motif,[2a, 2b, 4] developed based on the well-known catalytic activity of DMAP[5] in the Steglich esterification reaction discovered by Steglich, Hassner and other researchers.[6] The structural properties of the planar and symmetric 4-aminopyridine system lead to several limitations in its catalytic scope, such as in asymmetric synthesis or peptide coupling reactions.[1-2, 3q] Therefore, it is of significant importance to develop other structural motifs to broaden acyl transfer catalysis. Herein we introduce a new acyl transfer paradigm based on the tropolone scaffold, which can promote the coupling reaction between alcohols and carboxylic acid anhydrides or chlorides to give the ester products with excellent efficiency under thermal or photochemical conditions.

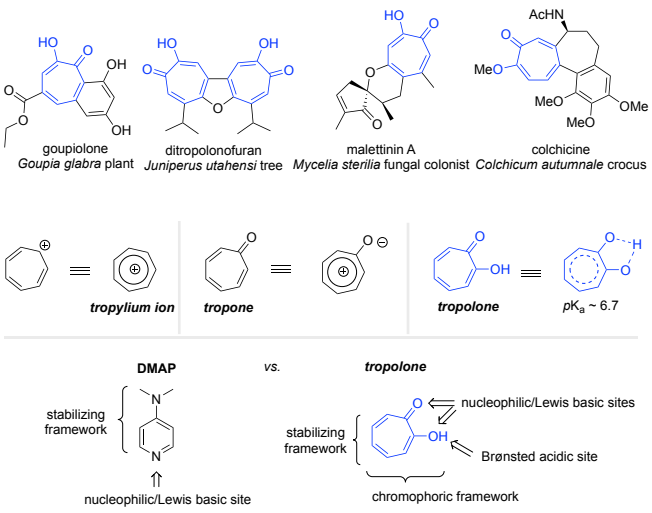


Figure 1. Tropylium, tropone, and tropolones.

We had previously developed several methods to use tropone as a stoichiometric or catalytic system in esterification and amidation reactions of carboxylic acids.[7] Presumably, tropone possesses these types of reactivities due to its ability to partially aromatize[7-8] to the tropylium oxide form (Figure 1), which displays Lewis base characteristics.[9] Its 2-hydroxy derivative, tropolone, has been frequently used as model systems to study intramolecular

proton transfer and tunneling processes.[10] The tautomerism between the carbonyl moiety and the adjacent hydroxyl group through the seven-membered non-benzenoid aromatic ring renders it relatively Brønsted acidic with a pK_a value of ~6.7 (Figure 1).[11] In its deprotonated tropolonate form, this species is even more nucleophilic such that it has been used as a powerful bidentate chelating agent for *d*-block and *f*-block organometallic complexes.[12] Many of these are interesting photo-active materials thanks to the chromophoric contributions from tropolone chelation.[12-13] Furthermore, tropolone has also been used as a luminogen to enhance fluorescence and recognition of biological systems such as amino acids, proteins or DNAs.[14]

Although tropolone is a commonly found framework in biologically valuable natural products,[15] little has been explored on its synthetic applications except as precursors in the synthesis of azulenes in the seminal works by Nozoe.[16] With such interesting structural features discussed above, we envisioned enormous potential for tropolone in organic synthesis. There are common electronic properties and reactivity between tropolone and DMAP, as depicted in Figure 1, that triggered our interest in exploring the acyl transfer catalytic activity of tropolone.

Results and Discussion

In order to establish if tropolone would be a suitable motif for acyl-transfer catalysis, we investigated its nucleophilicity index ($\mathbf{N}_{(Nu)}$)[17] using DFT calculations.[18] The nucleophilicity index values of tropone, tropolonate ion, and DMAP are calculated to be 2.74, 4.29, and 3.22 eV, respectively (Figure 2).[19] While tropolone can be considered a weak nucleophile, the nucleophilicity of tropolonate (estimated $N_{parameter}$ ~ 17.9 from $\mathbf{N}_{(Nu)}$ = 4.29 eV) is much higher than DMAP (~15.5 according to Mayr's nucleophilicity scale).[20] This study provides a promising theoretical standpoint for our hypothesis on the acyl transfer catalytic activity of tropolone. It also suggests that the tropolonate salt might be better for this purpose, which is in line with typical catalytic acylation reactions, where a basic additive, which can easily convert tropolone to tropolonate, would normally be used to facilitate the reaction.

We started the investigations using an unreactive and slightly sterically challenging phenol 2,4,6-trichlorophenol (**1a**) as the

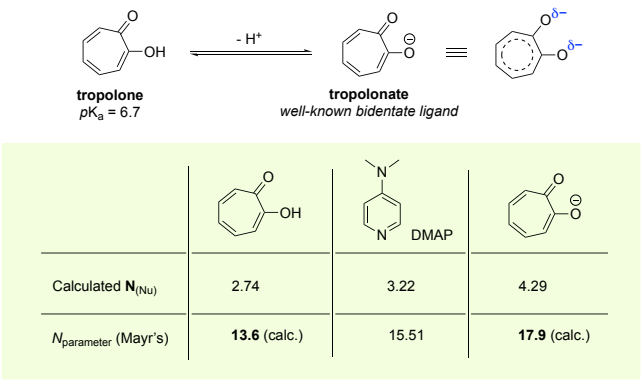


Figure 1. Calculated nucleophilicity of tropolone and tropolonate at M06-2X/6-311+G(2d,2p)-SMD(MeCN)//M06-2X/6-31+G(d,p)-SMD(MeCN).

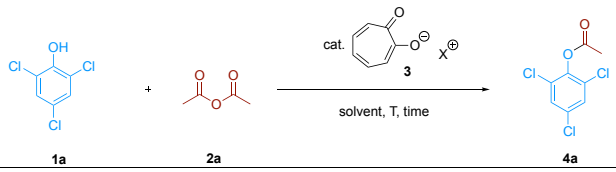
model substrate in the reaction with acetic anhydride (**2a**) using tropolone or tropolonate salts (**3**) as reaction promoters. Interestingly, all tropolonate salts outperformed the parent tropolone and gave much better outcomes than the control experiments without catalysts (Table 1).[19] Contrary to DMAP and other pyridine-based acyl transfer agents,[1b, 2a, 4c, 5] we found that the use of a stoichiometric amount of base such as NEt_3 is not necessary for our reactions with tropolonate. The presence of base slightly sped up the reaction, but we set forth without it to optimize the atom economy. A range of commonly used organic solvents were tested for the reaction and acetonitrile seemed to be optimal, presumably with the best tropolonate solubility. In most solvents, potassium tropolonate (**3-K**) gave higher efficiency than the lithium, sodium, or tetrabutylammonium analogues.

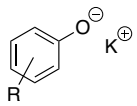
Catalyst loading was optimal at 5 mol% (entries 23-25) and increasing the temperature reduced the reaction time from two days to just four hours (entry 26). Without the catalyst, the reaction was sluggish and inefficient (entry 27, Table 1, also see Scheme 3d), with starting materials remained unreacted. With potassium benzoate or acetate as weak Brønsted base catalysts, the reaction outcomes were not much better (entries 28-29). Similarly, the use of potassium phenoxides with a range of aromatic substituents did not lead to any satisfactory results either (entries 30-31). It should be noted that the parent carboxylic acids or phenols of the potassium salts in entries 28-31 (Table 1) have pK_a ranges similar to that of tropolones. Salicyladehyde (the last entry of 31, Table 1) can also be considered a structural analogue of tropolone. The negative results of these control experiments further highlight the intriguing catalytic activity of tropolonate salts in acyl transfer reactions and hint that the tropolonate salt did not merely act as a Brønsted base catalyst in these reactions.

Having the optimal conditions in hand, a range of unactivated alcohols and phenols were subjected to the reaction to produce their corresponding esters with acetic and benzoic anhydride (Scheme 1). High to excellent yields were obtained for a majority of the acylated substrates, with the benzoic anhydride generally yielding slightly lower than the acetic anhydride, probably due to the somewhat more sterically demanding and less electrophilic nature of the benzoyl group. The most obvious examples to demonstrate this difference was with 2,4-di(*tert*-butyl)phenol, which showed a significant drop in yield when it reacted with benzoic anhydride (46% of **5e**) in comparison to the reaction with acetic anhydride (89% of **4e**). 1-Adamantol was acylated with poor yields of ester products **4m** and **5m**, perhaps due to the sterically hindered position of the alcohol group. Biologically relevant alcohols and phenols such as menthol, cinchonine, quinidine and estrogen reacted smoothly with acid anhydrides under the optimal conditions to produce the corresponding products in good to high yields (**4n**-**4q** and **5n**-**5p**). Several mercaptans could also be subjected to the same tropolonate-catalyzed acyl transfer reactions with similarly good efficiency (**4s**, **4t**, **5x**).

A similar optimization study was carried out for the tropolonate salt catalyzed reaction between alcohols or phenols with acid chlorides.[19] It identified a parallel set of optimal reaction conditions to the reaction with acid anhydrides, except that the best solvent was dichloromethane instead of acetonitrile. It should be noted that control reactions without a catalyst revealed significantly worse reaction outcomes, confirming the essential

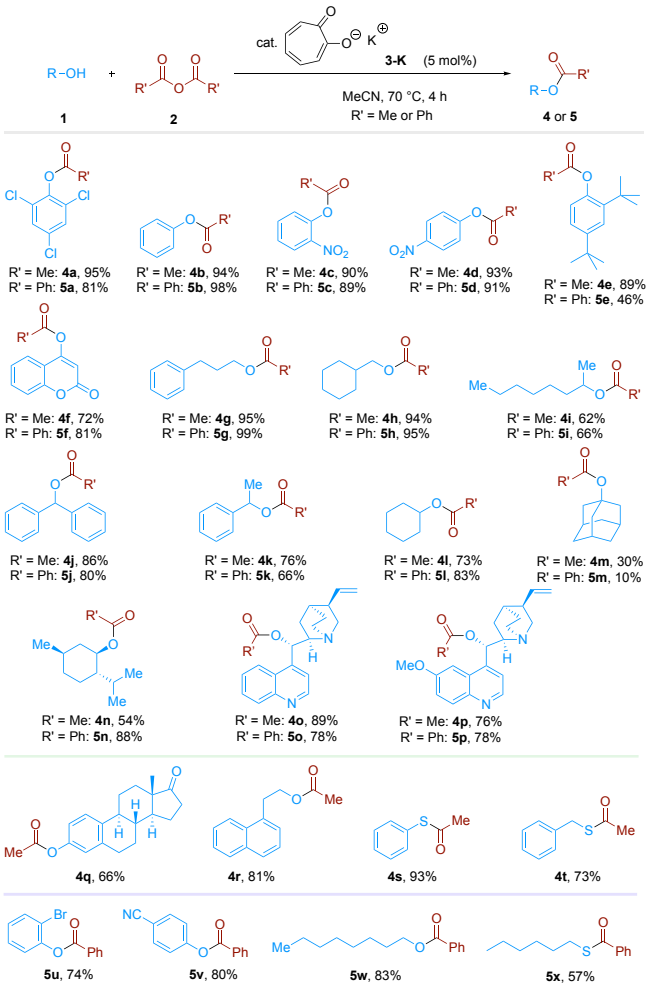
Table 1. Optimization of tropolonate-promoted acylation reaction[a]



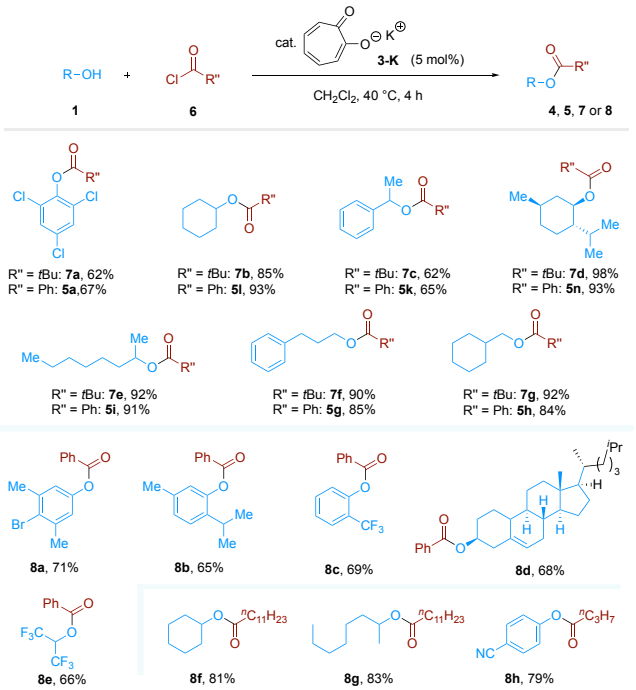
Entry	X	mol% cat.	Solvent	T (°C)	Time[b]	Yield (%)[c]
1	no catalyst	-	Toluene	rt	12 d	37
2	no catalyst	-	CH_2Cl_2	rt	12 d	28
3	no catalyst	-	MeCN	rt	12 d	29
4	H	5	Toluene	rt	12 d	46
5	H	5	CH_2Cl_2	rt	12 d	49
6	H	5	MeCN	rt	12 d	55
7	Li	5	Toluene	rt	12 d	74
8	Na	5	Toluene	rt	12 d	80
9	K	5	Toluene	rt	12 d	68
10	^{n}Bu$_4$N (TBA)	5	Toluene	rt	12 d	59
11	Li	5	CH_2Cl_2	rt	48 h	68
12	Na	5	CH_2Cl_2	rt	48 h	77
13	K	5	CH_2Cl_2	rt	48 h	84
14	TBA	5	CH_2Cl_2	rt	48 h	61
15	Li	5	MeCN	rt	48 h	56
16	Na	5	MeCN	rt	48 h	80
17	K	5	MeCN	rt	48 h	94
18	TBA	5	MeCN	rt	48 h	85
19	K	5	EtOAc	rt	48 h	88
20	K	5	DMSO	rt	48 h	67
21	K	5	DMF	rt	48 h	80
22	K	5	NMP	rt	48 h	82
23	**K**	**5**	**MeCN**	**rt**	**24 h**	**94**
24	K	2.5	MeCN	rt	24 h	91
25	K	1	MeCN	rt	24 h	89
26	**K**	**5**	**MeCN**	**70**	**4 h**	**95**
27	no catalyst	-	MeCN	70	4 h	25
28	KOBz	5	MeCN	70	4 h	30
29	KOAc	5	MeCN	70	4 h	25
30	KOPh	5	MeCN	70	4 h	32
31		5	MeCN	70	4 h	R = *p*-OMe: 34 R = *p*-CO_2Me: 27 R = *p*-NO_2: 19 R = *o*-NO_2: 29 R = *o*-CHO: 36

[a] Conditions: phenol **1a** (0.5 mmol), acetic anhydride **2a** (0.55 mmol) and catalyst **3** in solvent (0.5 mL) under normal atmospheric conditions. [b] Reaction time for total consumption of **1a**. [c] Yield of the isolated product.

role of the tropolonate catalyst for esterification reactions with acid chlorides. Again, it was observed that a stoichiometric amount of base such as NEt_3 sped up the reaction but was not essential for it to be effective. Using the optimal conditions, high to excellent yields were generally obtained for the acylation reactions of a range of alcohols and phenols with pivaloyl and benzoyl chlorides (Scheme 2). The reaction also worked well for the benzoylation of cholesterol (**8d**, Scheme 2) and HFIP (**8e**). The latter is a useful precursor in organic synthesis as its ester functionality is known to be activated by the perfluorinated alkyl moiety to undergo



Scheme 1. Substrate scope with acid anhydrides.



Scheme 2. Substrate scope with acid chlorides.

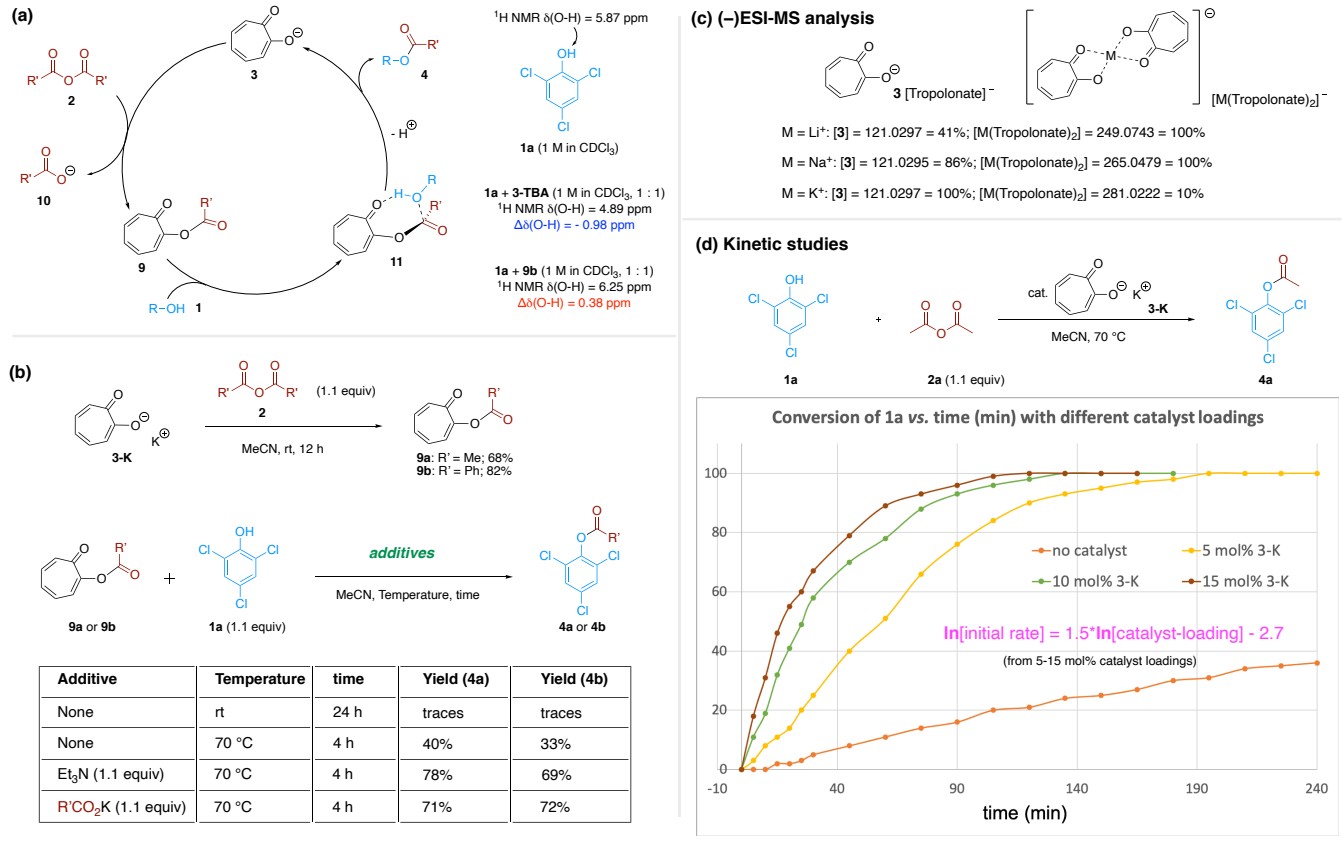
interesting nucleophilic substitution reactions.[21] A few other acid chlorides also proved to work smoothly under the reaction conditions (**8f-8h**, Scheme 2).

Thus, we have developed a robust synthetic method to use tropolonate salts as an acyl transfer catalyst for esterification reactions of inactive alcohols and phenols with acid anhydrides or chlorides. At this stage in the project, it was clear that the tropolone framework brought the 2-hydroxyl group within the suitable pK_a and nucleophilicity ranges to promote the reaction. However, the contribution of the aromatic cycloheptatrienone moiety in the tropolonate salts and its role in the catalytic cycle remained unknown to us. The mechanism of the tropolonate-promoted acyl transfer reaction is especially interesting given that such reactivity is not observed with analogous carboxylate or phenolate Brønsted bases, as discussed earlier in Table 1.

Mechanistic Studies

We initially hypothesized that the acyl transfer reaction with tropolonate salts occurred via a similar mechanistic pathway to what has been widely accepted for DMAP (Figure 3a). In that, the tropolonate ion **3** acted as a nucleophile to react with acid anhydrides or chlorides **2** to form acyl tropolonate ester intermediates **9**. These intermediates subsequently underwent nucleophilic acyl transfer reactions with alcohols or phenols **1** via **11** to afford the products and release the tropolonate ion back to the catalytic cycle. We indeed observed evidence of H-bonding complexation, hinting at **11**, between pre-formed benzoyl tropolonate ester **9b**[19] and phenol **1a** in a preliminary ^{1}H NMR study (Figure 3a and also page S46 in the experimental SI). However, attempts to detect the acyl tropolonate ester intermediates **9** by GC-MS or NMR spectroscopy during the course of the reaction were unsuccessful. On the other hand, control experiments with stoichiometric amounts of pre-formed acyl tropolonate ester intermediates **9**[19] and phenol **1a** did lead to the formation of products (Figure 3b), confirming the 'acyl transfer' role of the tropolonate moiety. However, the efficiency of such direct reactions was unsatisfactory compared to the tropolonate-promoted acylation reactions (Schemes 1 and 2). These experimental results suggest that the simple hypothesis in Figure 3a cannot accurately describe the mechanism of the reaction under investigation.

A deeper analysis of our experimental results revealed that the tropolonate ion likely did not operate alone in the reaction mixture. As mentioned in the introduction, tropolonate is a strong bidentate chelating agent. Our negative electron-spray ionization (–ESI) high-resolution mass spectrometric analyses of tropolonate salts used in this study showed obvious evidence for cluster formation between tropolonate and all alkali-metal counterions (Li^+, Na^+, and K^+, Figure 3c and also page S6 in the experimental SI). These results are consistent with literature reports on the complexation of tropolonate with metal ions in different stoichiometric ratios.[12-13, 22] Given the concentrated nature of our catalytic reaction mixtures and the low solubility of tropolonate salts, in the optimal setting being potassium salt (**3-K**), it is most likely that the catalyst exists and promotes the



Additive	Temperature	time	Yield (4a)	Yield (4b)
None	rt	24 h	traces	traces
None	70 °C	4 h	40%	33%
Et_3N (1.1 equiv)	70 °C	4 h	78%	69%
$R'CO_2K$ (1.1 equiv)	70 °C	4 h	71%	72%

Figure 3. (a) The first mechanistic hypothesis; (b) Control studies; (c) ESI-MS analysis of metal tropolonate salts; (d) kinetic studies of reaction between **1a** and **2a** with different catalyst loadings.

reaction in cluster form. The analysis with different catalyst loadings indicated that the reaction rate is not first-order with respect to tropolonate salt **3-K** (reaction order ~ 1.5, Figure 3d and also page S47 in the experimental SI),[19] which further makes us believe that more than one tropolonate ion was involved in the promotion of the reaction. It should also be noted here that the outcomes of the direct acyl transfer reactions between tropolonate ester intermediates **9** and phenol **1a** improved significantly in the presence of a base such as Et_3N (Figure 3b). Similar results were observed with the potassium carboxylate salt as an additive, despite the fact that the carboxylate salt is less Brønsted basic than Et_3N. This hinted that we probably should not too soon be dismissive of the role of the carboxylate salt by-product (**10** in Figure 3a) in this acyl-transfer reaction.

We therefore turned our focus to DFT calculations to seek better insights into the tropolonate-catalyzed acylation of benzoic anhydride (**2b**) and benzoyl chloride (**6b**) with cyclohexanol (**1l**) as model substrates. After exploring several possible reaction pathways, we came up with a possible explanation. The calculated free energy profile for the acylation of benzoic anhydride **2b** is shown in Figure 4a. The reaction starts with the nucleophilic attack of solvated potassium tropolonate **3-K-MeCN** to benzoic anhydride via **TS-1** to form intermediate **12**, which is a chelating potassium complex. The activation barrier for the first step is calculated to be 20.2 kcal/mol relative to **3-K-MeCN**. The nucleophilic attack of cyclohexanol **1l** to the benzoyl moiety of **12** takes place via **TS-2**, which involves another potassium tropolonate, to generate product **5l** and potassium complexes **13** and **14**. **TS-2** is calculated to be 15.3 kcal/mol higher in energy than **3-K-MeCN**. Finally, a proton transfer step from **14** to **13** occurs to produce benzoic acid, regenerate **3-K-MeCN**, and close the catalytic cycle. It is important to mention that in the second step, the participation of another potassium tropolonate as a base catalyst is necessary in order to abstract proton from cyclohexanol and, thus, enhance the nucleophilicity of cyclohexanol. We have also considered the possibility that the benzoate ion acts as a base catalyst instead of potassium tropolonate (**TS-2'**). This reaction pathway is also viable, however, the activation barrier of **TS-2'** is calculated to be 4.3 kcal/mol higher in energy than **TS-2**. Thus, it agrees well with our earlier belief that the presence of benzoate ion (Figures 3a and 3b) assists the reaction, but is not the driving factor for it to happen like the tropolonate ion.

Our DFT calculations suggest that, in this reaction, potassium tropolonate acts as nucleophilic and base catalysts and the nucleophilic attack of potassium tropolonate to benzoic anhydride is the rate-determining step (Figure 4a). Our proposed mechanism is consistent with previous calculations for the acylation of DMAP derivatives.[2a, 4d] Overall, this mechanism also agrees well with experimental results we collected, as depicted and discussed earlier in Scheme 3.

Obviously, this acylation reaction can also take place via a single-step mechanism with the direct nucleophilic attack of cyclohexanol to benzoic anhydride (see Figure S1 – page S4 in the computational SI for optimized structure).[19] In this

mechanistic pathway, potassium tropolonate only participates as a base catalyst. However, the activation barrier for this step is calculated to be 7.7 kcal/mol higher in energy than **TS-1** and can, therefore, be ruled out as a feasible or competitive mechanism.

The calculated free energy profile for the acylation of benzoyl chloride **6b** is shown in Figure 4b. It is likely that this reaction also occurs via a two-step mechanism, i.e. the first step is the nucleophilic attack of potassium tropolonate, solvated by cyclohexanol instead of the non-coordinating dichloromethane, to benzoyl chloride, which is followed by the nucleophilic attack of cyclohexanol to generate the product. It is interesting to note that potassium complex cluster (**16 + 17**) is calculated to be the most stable species. This result suggests that (**16 + 17**) is a possible resting state of the reaction, i.e. after the first cycle, the reaction starts from (**16 + 17**), which is followed by a proton transfer from **17** to **16** and a ligand exchange giving **3-K-CyOH**; after that, two subsequent nucleophilic additions can then take place giving the product. The nucleophilic attack of potassium tropolonate to benzoyl chloride is the rate-determining step with an overall activation barrier of 22.3 kcal/mol (from (**16 + 17**) to **TS-3**, see Figure 4b). This barrier, although higher than that of the reaction with benzoic anhydride, is still quite feasible and consistent with the experimental conditions of this reaction. It should also be noted here that computational exploration of a possible role of HCl, such as protonating the carbonyl of **6a'** hence activating it, did not lead to any feasible pathways that need to be taken into account.

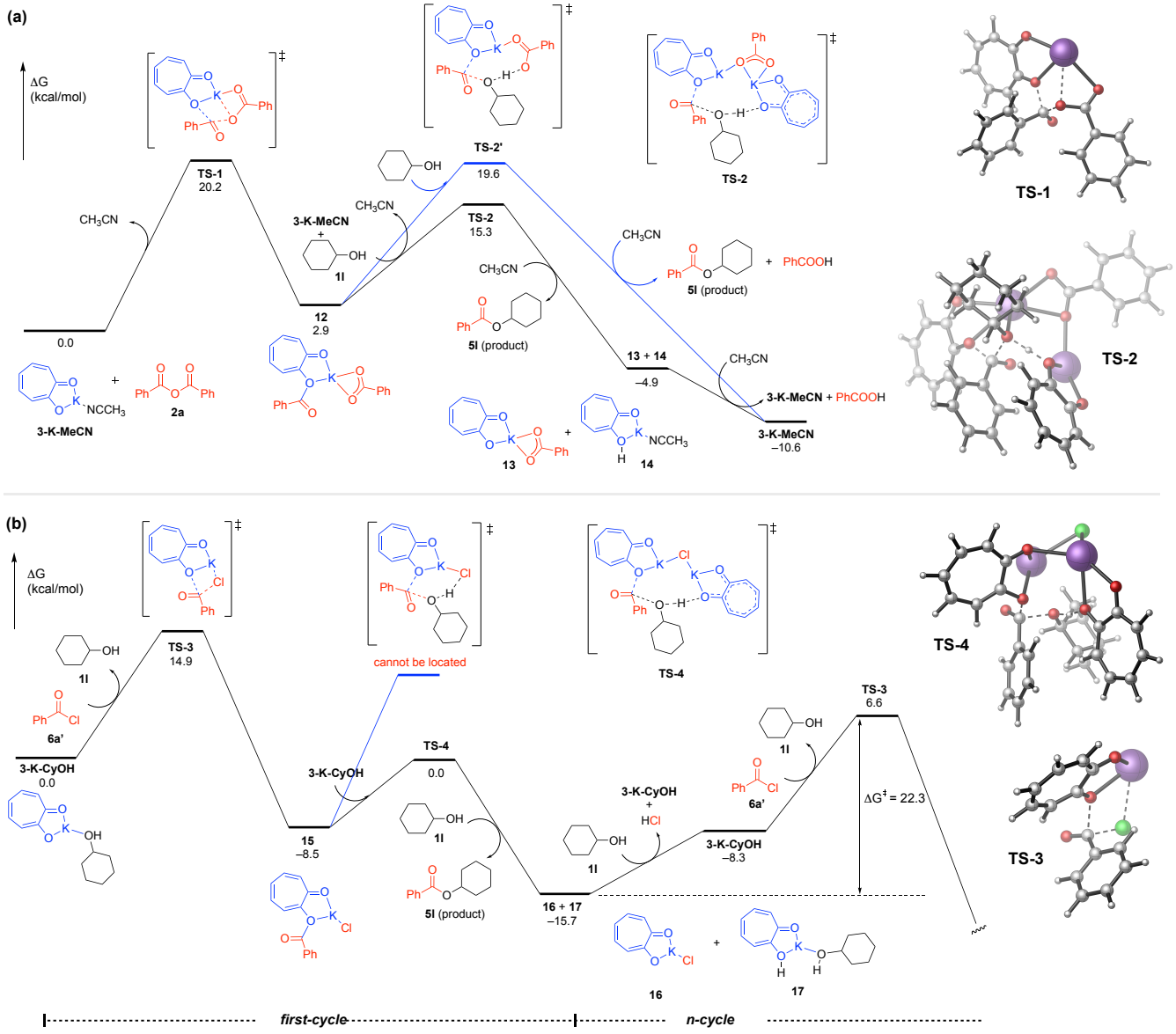


Figure 4. (a) Calculated free energy profile (kcal/mol, M06-2X/6-311+G(2d,2p)-SMD(MeCN)//M06-2X/6-31+G(d,p)-SMD(MeCN)) and optimized structures of transition states for the tropolonate-catalyzed acylation of benzoic anhydride. (b) Calculated free energy profile (kcal/mol, M06-2X/6-311+G(2d,2p)-SMD(CH_2Cl_2)//M06-2X/6-31+G(d,p)-SMD(CH_2Cl_2)) and optimized structures of transition states for the tropolonate-catalyzed acylation of benzoyl chloride.

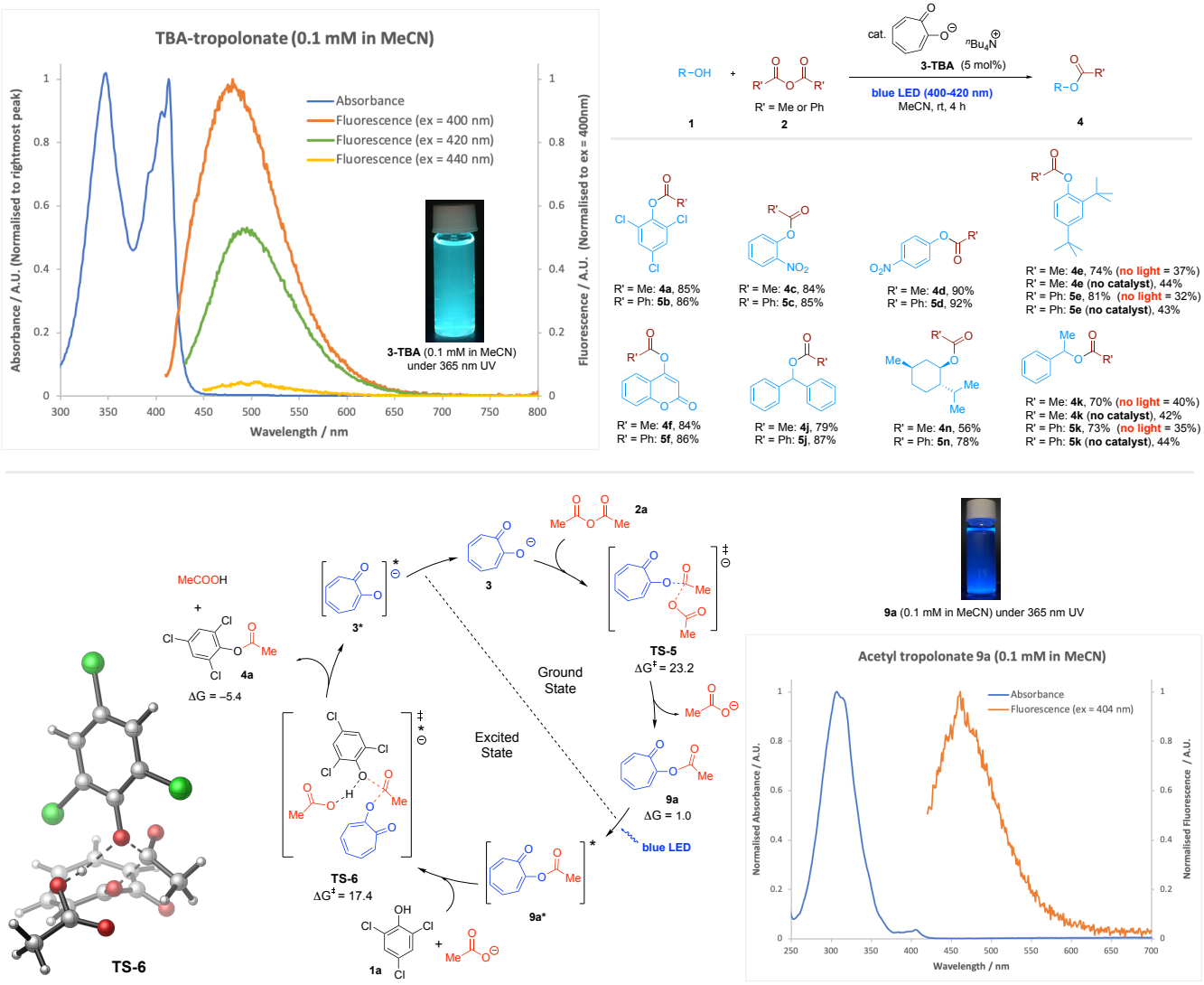


Figure 5. Blue light mediated esterification reactions.

Photochemical Studies

As mentioned in our introduction, tropolonate ion is known to be a good chromophoric chelating agent for transition metals[12-13] or sensing probe for biological systems by enhancing their fluorescent properties.[14] Thus, we also wanted to explore if this photo-activity can also be exploited in the promotion of acyl-transfer reactions. We started the investigation by looking at the UV-vis absorption and photoluminescent spectra of tetrabutylammonium tropolonate (**3-TBA**) in acetonitrile. This tropolonate salt was used in preference over potassium tropolonate (**3-K**) due to its superior solubility in acetonitrile and some other organic solvents. **3-TBA** displayed two absorption maxima in acetonitrile at ~350 nm and ~410 nm (Figure 5, top-left). Excitations at 400 nm or 420 nm both gave weak luminescence with emission peaks at ~460-470 nm.

We envisioned that such photochemical properties would enable tetrabutylammonium tropolonate to act as a photosensitizer to promote the acyl-transfer reaction under investigation in this work.

Indeed, under otherwise identical conditions, **3-TBA** could efficiently catalyse the esterification of a range of alcohols and phenols under blue light irradiation at ambient temperature instead of 70 °C (400-420 nm blue LED, Figure 5, top-right). At the same ambient temperature but without light, the reaction outcomes were rather unsatisfactory, indicating that blue-light indeed promoted the reaction (Figure 5, top-right, **4e**-**5e** and **4k**-**5k**). Without **3-TBA** catalyst, poor efficiency was also observed (Figure 5, top-right, **4e**-**5e** and **4k**-**5k**). Therefore, it can be concluded that **3-TBA** can act as a photosensitizer or -catalyst for the acyl-transfer reaction between alcohols or phenols with acid anhydrides.

We again resorted to TD-DFT calculations to elucidate the reaction mechanism for the photochemical tropolonate-catalyzed acylation reaction with **1a** and **2a** as model substrates (Figure 5, bottom). Interestingly, we found that this reaction occurs in both ground and excited states. The first step of this reaction is the nucleophilic attack of tropolonate ion **3** to acetic anhydride via **TS-5** giving tropolone acetate **9a** in the ground state. It should be noted here that in the absence of potassium counterion, the activation pathways seen in Figure 4 might not occur at all. The

activation barrier of **TS-5** is calculated to be 23.2 kcal/mol relative to **3**. To proceed, tropolone acetate **9a** is excited by blue LED to form **9a***. **9a** was confirmed to absorb weakly at ~404 nm (Figure 5, bottom). The nucleophilic attack of 2,4,6-trichlorophenol **1a** to **9a*** can then take place via **TS-6**, providing product and regenerating tropolonate ion **3** via the relaxation of **3***. The second step of this reaction occurs in the excited state with the calculated activation barrier of 17.4 kcal/mol relative to **9a***. It is important to also note that we could not locate any feasible mechanism for this reaction if it only occurs in the ground or excited state. Due to the weak luminescence of the **3-TBA** catalyst and its tropolonate esters **9**, we did not pursue its catalytic capability further at this stage but instead focused on developing novel tropolone-based photo-sensitizers for better catalytic efficiency. This work is underway in our laboratories and will be reported in due course.

Conclusion

We have established a new acyl transfer catalytic motif based on the interesting structural properties of the non-benzenoid aromatic tropolone. We showed that tropolonate salts, due to their strong nucleophilicity and photochemical activity, can promote the coupling reaction between alcohols and carboxylic acid anhydrides or chlorides to give the products with excellent efficiency under thermal or blue light-irradiated conditions. A combination of experimental studies and computational calculations suggest interesting mechanistic insights and warrant further works to fully explore the potential of this new acyl transfer catalytic system.

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Keywords: acylation • acyl transfer • tropolone • esterification • catalysis

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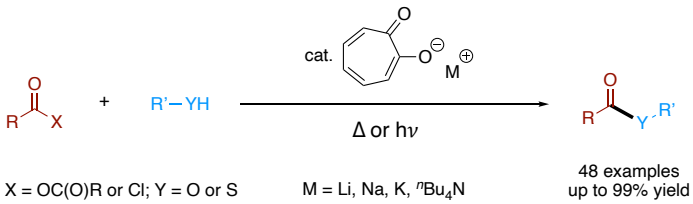
Entry for the Table of Contents



X = OC(O)R or Cl; Y = O or S

M = Li, Na, K, $^{n}Bu_4N$

48 examples
up to 99% yield

Acyl transfer: Tropolonate ion, a novel motif in acyl transfer catalysis, proved to be an efficient catalyst for the esterification of acid anhydrides or chloride with unactivated alcohols or phenols under thermal or photochemical conditions.