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Expanding the repertoire of cyclopropenium ion phase transfer catalysis: Benzylic fluorination

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ABSTRACT

The application of cyclopropenium ion as a phase transfer catalyst for benzylic fluorination in high yields is reported. Integral to the mechanisms of these fluorination reactions was the role of *in situ* derived cyclopropenium fluoride complexes, the existence of which was supported by ^{1}H, ^{19}F NMR and UV–Vis spectroscopy. Density functional theory calculations were applied to gain insight into the mechanism of these reactions.

1. Introduction

The influential role of phase transfer catalysis (PTC) on chemical synthesis spans decades and its impact in academia and industry continues to gain traction.[1] Contributing to this status has been a myriad of factors, including operational simplicity, general use of mild reaction conditions and inexpensive reagents/solvents, plus scalability. Catalyst mediated transport of reactive intermediates between different phases (bi- and/or tri-phasic), further adds to its utility as it reduces by-product formation arising from incompatible chemical reactivity.[1,2]

Today several classes of phase transfer catalysts exist with each having distinct advantages in terms of chemical reactivity. Classic in this respect are ammonium and phosphonium cations, which find widespread use in shuttling anionic species between phases.[3,4] Conversely, crown ethers by way of host-guest complexation enabled phase transfer of cations.[3,5] Imidazolium,[6] triazolium,[7] and tetraaminophosphonium[8] ions have also shown utility as phase transfer catalysts with the mode of action in these cases deriving from various non-covalent interactions including π-π stacking, cation-π interactions, and H-bonding.[9,10] Furthermore, our group recently pioneered the use of cyclopropenium analogues as phase transfer catalysts,[11] while in a contemporary work Lambert and co-workers reported the use of tris(dialkylamino)cyclopropenium salts as phase transfer catalyst.[12]

In terms of phase transfer catalyzed applications, C–N, C–O, and C–C bond-forming protocols are arguably the most well-established,[13] whereas, C–F bond formation remains less explored.[14] This is despite the value of fluorinated compounds in drug design, agrochemicals, material science, ^{18}F positron emission tomography (PET) imaging and pharmaceuticals.[15] In fact, it has been estimated that 20–30% of pharmaceutical molecules contain at least one fluorine, thus highlighting the importance of developing methodologies for preparing organofluorine compounds.[16] That aside, *tert*-butylammonium fluoride (TBAF) has been widely used in phase transfer catalyzed fluorination reactions,[17] however, associated with its use are drawbacks, e.g., it is hydroscopic, undergoes Hoffman E_2-elimination between 40 and 77 °C (2 Torr), has a low fluoride to total reagent mass ratio ($F^- = 7.3\%$ of total mass of NBu_4F) and stoichiometric or greater amounts are generally needed in practice. Moreover, elimination by-products are often observed when using anhydrous TBAF owing to its strong basicity.[18] Lastly, the isolation of water-soluble products, such as sugars from TBAF, can be challenging as standard work-up protocols call for aqueous acid/base washes.[19]

Recently, alternative methods for C–F bond formation have been explored using phase transfer conditions.[20] For instance, Toste and co-workers reported the use of a chiral phosphate salt together

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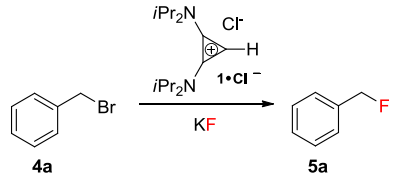
with a poorly soluble fluorinating reagent in enantioselective fluorination of allylic alcohols,[21] while in 2016 Tamamura and co-workers developed a mild fluorination method for pyrroles using a combination of Selectfluor, a lipophilic anionic phase transfer catalyst, and base.[22] Further, a series of dicarboxylic acid pre-catalysts were recently developed by Hamashima that, upon deprotonation, act as anionic phase transfer catalysts for asymmetric fluorination of alkenes.[23]

Inspired by this precedent, the prospect of employing a cyclopropenium ion (**1**) or corresponding ion pair **1**•Cl^- as a phase transfer catalyst for C–F bond forming fluorination incited our curiosity. Especially, as it would add to the rich history of cyclopropeniums,[24,25] while building upon our interest in these compounds. An interest that notably has led to the reported use of **1**•Cl^- as well as derivatives **2**•Cl^- and **3**•2 Cl^- as phase transfer catalysts by our group (Fig. 1a).[11,26,27] In building upon this precedent we disclose herein a novel cyclopropenium ion mediated phase transfer catalyzed reaction enabling benzylic fluorination.[28] One arrived at through ^1H, ^{19}F NMR and UV/Vis spectroscopic studies as well as density functional theory (DFT) calculations providing insight into the catalytic role of *in situ* derived cyclopropenium fluoride complexes such as **1**•F^- or computed DFT-**1**•F^- (Fig. 1b). Notably, this catalytic approach in comparison to protocols utilizing onium salts (e.g., TBAF) for benzylic fluorination uses lower catalyst loadings, does not require excess drying of reagents, and affords higher yields.[18]

2. Results and discussion

At the outset of this work to explore the prospect of developing our envisioned benzylic fluorination approach, benzyl bromide (**4a**) (1 equiv.) and KF (3 equiv.) were reacted under various conditions using cyclopropenium ion **1**•Cl^- as a phase transfer catalyst (Table 1, entries 1–10). These various attempts, however, afforded fluorination product **5a** in low conversions (Table 1, entries 1–10); albeit the use of propionitrile as a solvent and a catalyst loading of 15 mol % were identified as promising lead conditions (Table 1, entry 7). Reasoning the *in situ* generation of posited fluoride adducts such as **1**•F^- was unfavourable we turned to spectroscopic studies to gain insight into their formation and stability.

Table 1
Screening of the reaction conditions.



Entry	Solvent	Catalyst (mol %)	Temp. (°C)	Conversion[a]
1	CH_3CN	10	40	~5
2	CH_3CN	10	60	~5
3	CH_3CN	10	80	~5
4	CH_3CN	15	40	~5
5	CH_3CN	15	60	~5
6	CH_3CN	15	80	10
7	C_3H_5N	15	80	20
8	THF[b]	15	80	0
9	1,2-DME[c]	15	80	0
10	MTBE[d]	15	80	0

[a] Conversion based on ^1H NMR.
[b] Tetrahydrofuran.
[c] 1,2-Dimethoxyethane.
[d] Methyl *tert*-butyl ether.

To this end, ^1H NMR titration studies involving the addition of KF (0.2–0.8 equiv.) to a solution of **1**•Cl^- (CD_3CN, 0.07 M) at 298 K resulted in a very slight upfield shift of the parent cyclopropenium $C_{(sp)}^2$ –H signal ($\Delta\delta = 0.03$ ppm) suggestive of only a weak interaction between cyclopropenium (**1**) and F^- (see supporting information (SI)). Further, in a separate experiment *tetra*-butylammonium fluoride (TBAF) (0.2 equiv.) was added to a solution of **1**•Cl^- (CD_3CN, 0.07 M) at 298 K resulting in an immediate, more significant upfield shift of the signal of **1**•Cl^- at 7.75 ppm–7.71 ppm (Fig. 2a, spectra A and B). Cooling the sample to 253.9 K then resulted in splitting of the peak at 7.71 ppm into a pair of well-resolved signals at 7.69 ppm and 7.76 ppm, which from the presence of at least two or more different species can be inferred (see

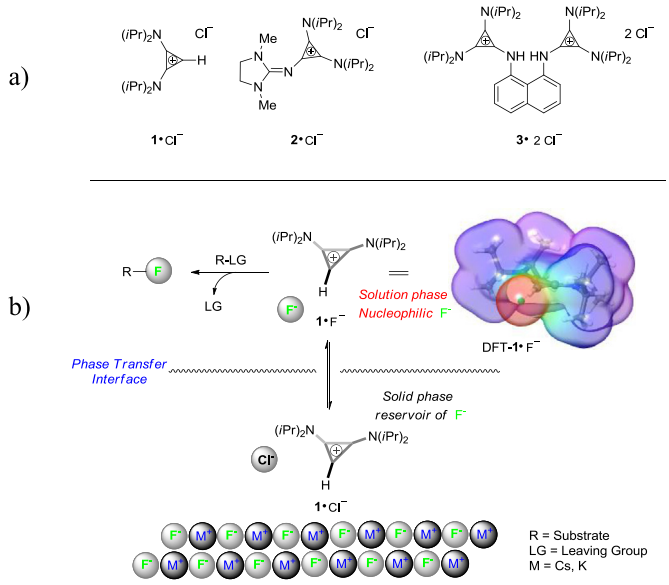


Fig. 1. (a) Previously reported cyclopropenium phase transfer catalysts **1**•Cl^-, **2**•Cl^- and **3**•2 Cl^-. (b) Structure DFT-**1**•F^- computed at the wB97XD/6-311 + G(d,p)/def2TZV level of theory.

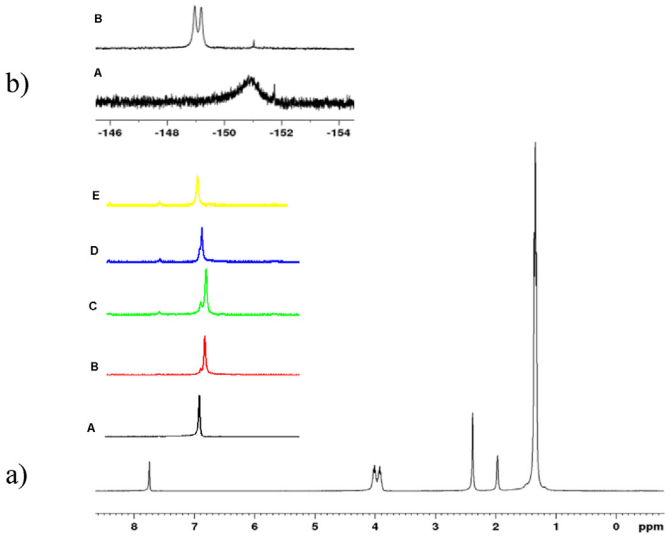


Fig. 2. (a) Comparison ^1H NMR spectra at 400 MHz of **1**•Cl^- in CD_3CN at 298 K upon titrations with TBAF- black (0.0 equiv.), red (0.2 equiv.), green (0.4 equiv.), blue (0.6 equiv.), yellow (0.8 equiv.) (b) ^{19}F NMR of **1**•F^- in CD_3CN (**A**) in presence of TBAF (0.2 equiv.) at 298.1 K (400 MHz) and (b) in presence of TBAF (0.2 equiv. at 250.3 K (600 MHz).