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Enantioselective acyl-transfer catalysis by fluoride ions†

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The asymmetric nucleophilic catalysis by fluoride ions at a carbon-based electrophile has been demonstrated for the first time. Using a library of *ad hoc* designed bifunctional phase-transfer catalysts in which both the anion and the cation are directly involved in the reaction, the desymmetrisation of *meso*-succinic and -glutaric anhydrides is possible. ^{19}F NMR spectroscopic studies support the intermediacy of an acyl fluoride intermediate.

Tetraalkylammonium fluorides have a long history of utility in the field of catalysis, where, due to the hard nature of fluoride, they are almost invariably used (*inter alia*) as either a base[1] (catalytic or stoichiometric) or a desilylating agent.[1,2] Chiral ammonium fluorides for applications in asymmetric synthesis are less common but also known.[3] It is remarkable that the use of fluoride as a nucleophilic catalyst has received almost no attention. In 1967, Bunton and Fender reported that fluoride ions catalysed the hydrolysis of acetic anhydride (**1**) in both water and aqueous media (Fig. 1A). Reaction kinetics indicated that the rate of consumption of the starting material outstripped the rate of product formation in a clean reaction, indicating the build-up of a stable intermediate. Aspiration experiments allowed the identification of acetyl fluoride (**2**) as the intermediate, indicating that acyl transfer proceeded predominantly *via* nucleophilic catalysis.[4,5]

The idea that fluoride can be used as an acyl transfer catalyst has gained little currency since. Superstoichiometric fluoride has been used to catalyse the hydrolysis of nucleotide phosphotriesters,[6] and the cleavage of activated amino-acid esters[7] and carbamates (*e.g.* Boc-cleavage, 10 equiv. tetrabutylammonium fluoride (TBAF), THF, reflux, 8 h).[8] The mechanism of these transformations was not elucidated but nucleophilic catalysis has been implicated in the latter study. More recently, Chan, Hendrick *et al.*[9] rationalised the fluoride-catalysed of transesterification of aryl ester **5** to furnish **6** in the presence of (for example) benzyl alcohol *via* nucleophilic catalysis (Fig. 1B), however no mechanistic evidence was provided. In such scenarios, the possibility of the basicity of fluoride dominating catalysis is a potential issue: for instance Edgar *et al.*[10] demonstrated that the TBAF-mediated deacetylation of cellulose-derivative **7** occurs *via* general base catalysis at C-6 and specific-base catalysis (*i.e.* E1cB) at C-2/C-3 (Fig. 1B).

We have been interested in the development of the first asymmetric nucleophilic catalysis reactions promoted by fluoride. We were prompted to report our results by a very recent disclosure by Gouverneur *et al.* detailing the development of an elegant urea-catalysed enantioselective nucleophilic fluoridation reaction involving stoichiometric fluoride, alkyl bromides such as **8** and catalyst **9** (Fig. 1C).[11]

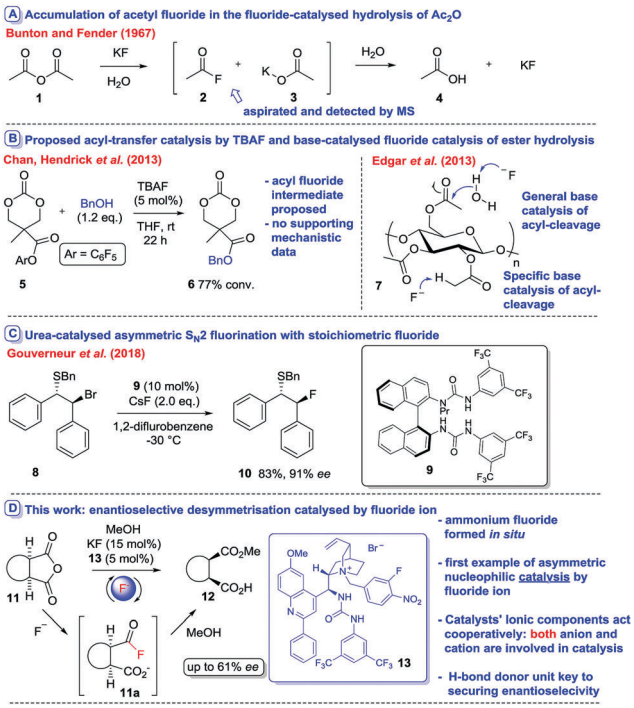

Fig. 1 Nucleophilic catalysis by fluoride.

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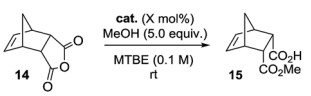
Herein we report the design of a system that utilises fluoride as an asymmetric nucleophilic catalyst in the desymmetrisation of *meso*-anhydrides of general type **11** by alcoholysis[12–15] (Fig. 1D) to form hemiesters **12** *via* the putative intermediate **11a** – with the generation of 4 stereocentres. Ring-opening is mediated by an ionic Phase-Transfer Catalyst (PTC) **13** designed to maximise the potential for delivery of fluoride ion to a catalyst-bound electrophile using cooperation between a hydrogen-bond donating urea moiety (located on the cation) and an alkaloid-derived ammonium bromide unit which forms a nucleophilic chiral ammonium fluoride *in situ*. To the best of our knowledge it represents the first example of asymmetric nucleophilic catalysis by fluoride ion at a carbon centre.

Our study began with preliminary experiments to investigate the potential of TBAF as an acyl-transfer catalyst compared to diisopropylethylamine (DIPEA) in the addition of MeOH to *meso*-anhydride **14** in MTBE solvent[16] at ambient temperature (Table 1). In the absence of catalyst no desymmetrisation occurs under the reaction conditions (entry 1). DIPEA (5 mol%) is able to mediate the formation of low levels of **15** after 3 days reaction time (entry 2), however, use of an equivalent loading of TBAF led to quantitative conversion, with smooth generation of **15** (entry 3). Further experiments demonstrated that TBAF could promote the reaction to quantitative conversion in a time frame where use of DIPEA could provide only trace amounts of product (entries 4 and 5). 1 mol% appears to be the lower loading limit under these conditions – providing over 50% conversion in 12 h (entry 6). Consistent with the activity of TBAF emanating from fluoride anion rather than the ammonium cation, a control reaction using TBAB (5 mol%) exhibited no conversion (entry 7).

We have shown previously that (thio)urea-modified cinchona alkaloids can catalyse anhydride desymmetrisation by alcoholysis[16a] – where the hydrogen bond donor presumably stabilises developing negative charge as the alcohol (under the influence of general base catalysis) adds to the anhydride. We therefore reasoned that if such alkaloids were alkylated at the quinuclidine moiety,[17] that they could serve as materials capable of both phase-transfer catalysis involving fluoride ion and electrophile activation. Alternatively, they could serve as PTCs capable of binding fluoride ion *via* the hydrogen bond donating unit and delivering it to the anhydride.

Table 1 TBAF as an acyl-transfer catalyst



Entry	Catalyst	Loading (*X*)	Time (h)	Conv. (%)[a]
1	—	—	72	0
2	**DIPEA**	5	72	20
3[b]	**TBAF**	5	72	>98
4	**DIPEA**	5	24	6
5[b]	**TBAF**	5	12	>98
6[b]	**TBAF**	1	12	53
7	**TBAB**	5	24	0

[a] Determined by ^{1}H NMR spectroscopy. [b] TBAF as a 1.0 mol solution in THF.

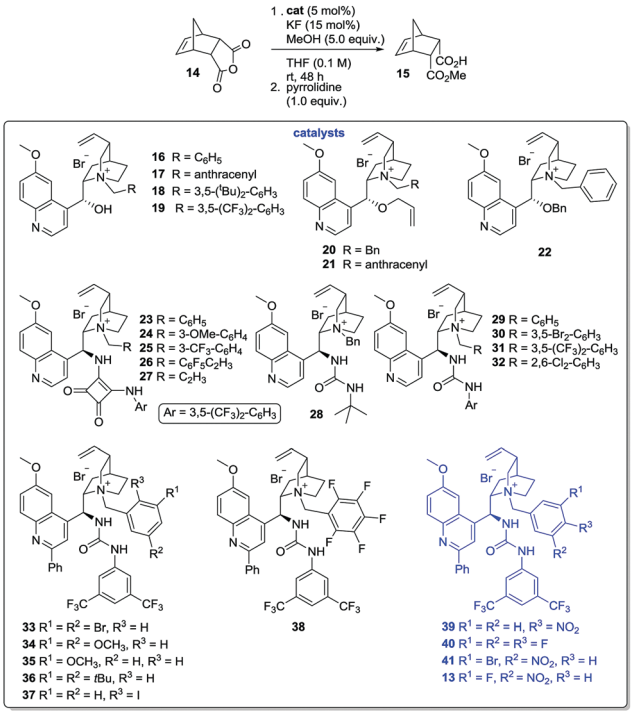
Initial attempts to generate such catalysts produced mixed results. Formation of the ammonium fluorides was possible in solution, but decomposition and/or loss of HF on attempted isolation from solution for characterisation were problematic. It was therefore decided to generate the ammonium fluorides from the corresponding (stable) bromides *in situ via* anion metathesis. The bromides were expected to be catalytically inert (Table 1, entry 7), so provided that the rates of halide ion exchange were not prohibitively slow, it held promise as an operationally practical methodology. After considerable experimentation, it was found that anhydride **14** underwent methanolysis to **15** in the presence of KF (15 mol%) and ammonium bromides (5 mol%) in THF (0.1 M) at ambient temperature, but no conversion occurred if either the fluoride catalyst or the PTC were absent. These conditions were selected to evaluate a library of alkaloid-based PTCs equipped with hydrogen bond donating moieties and *N*-alkyl ammonium ions substituents of variable steric/electronic characteristics (Table 2).

N-Alkyl quinines **16–19** promoted the methanolysis in poor-moderate conversion; with the formation of **15** as a near racemate (entries 1–4).[18] Bulky *N*-alkyl substituents slowed the reaction rate considerably. Deletion of the hydrogen bonding capabilities of these materials *via* alkylation of the hydroxyl unit (*i.e.* **20–22**, entries 5–7) failed to improve selectivity appreciably. Exchange of the C-9 substituent (with concomitant inversion of configuration) with the strongly hydrogen bond donating squaramide moiety[17e] was advantageous: use of the simple *N*-benzyl catalyst **23** provided **15** with the highest enantiomeric excess observed up to that point (23%, entry 8), and while the installation of either a single electron donating- or electron withdrawing-group at the *N*-benzyl moiety led to little change in product ee (*i.e.* **24–25**, entries 9 and 10), the pentafluorobenzyl ammonium ion **26** could mediate the desymmetrisation with a greatly improved 44% ee (entry 11). These findings, together with the relative failure of the *N*-propargyl catalyst **27** (entry 12), underscore the role both the hydrogen bond donating unit and the *N*-alkyl substituent play in bringing about selective methanolysis of **14**.

Accordingly, we next evaluated the use of urea-substituted PTCs – a class of catalyst which recently performed well in the asymmetric alkylation of 3-substituted oxindole derivatives.[17f] These experiments got off to an inauspicious start: both the bulky *tert*-butyl urea **28** and the archetypal *N*-benzyl catalyst **29** accelerated the formation of near optically inactive products (entries 13 and 14). However, variants of **29** characterised by the presence of electron withdrawing groups at the *m*-positions of the benzyl substituent promoted reactions with >50% ee and improved conversion relative to squaramide-based systems (*i.e.* catalysts **30–31**, entries 15 and 16). *o*-Substitution (*i.e.* PTC **32**) is less well tolerated (entry 17).

We had previously shown that installation of an aryl substituent at C-2 of the catalyst's quinoline ring can improve the performance of related PTCs,[17f] and thus prepared a small library of C-2 arylated catalysts **33–38** (entries 18–23). The influence of this modification on efficacy can be divined by comparing catalyst **30** (entry 15) with the superior, substituted analogue **33** (entry 18), which could promote the reaction with 60% ee.

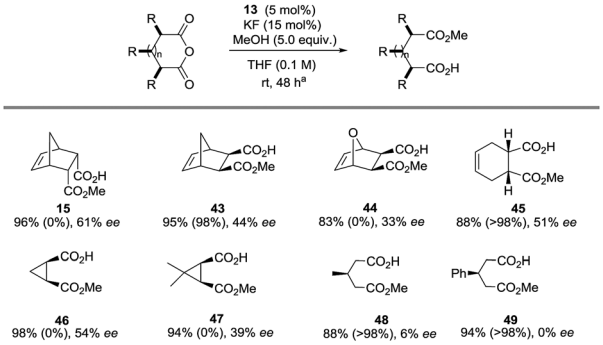
Table 2 Catalyst screening



Entry	Catalyst	T (°C)	Conv.[a] (%)	ee[b] (%)
1	**16**	rt	58	−3
2	**17**	rt	49	−2
3	**18**	rt	38	3
4	**19**	rt	34	10
5	**20**	rt	80	−11
6	**21**	rt	17	0
7	**22**	rt	30	−4
8	**23**	rt	47	−23
9	**24**	rt	46	−21
10	**25**	rt	45	−25
11	**26**	rt	43	−44
12	**27**	rt	43	−17
13	**28**	rt	45	−6
14	**29**	rt	70	0
15	**30**	rt	79	53
16	**31**	rt	66	51
17	**32**	rt	48	25
18	**33**	rt	66	60
19	**34**	rt	57	46
20	**35**	rt	70	43
21	**36**	rt	44	40
22	**37**	rt	55	23
23	**38**	rt	61	51
24	**39**	rt	66	60
25	**39**	−15	11	n.d.
26	**39**	50	93	44
27[c]	**39**	rt	70	61.5
28	**40**	rt	72	61
29	**41**	rt	77	61
30	**13**	rt	79	61

[a] Determined by ^{1}H NMR spectroscopy. [b] Enantiomeric excess determined by ^{1}H NMR spectroscopic analysis after derivatisation of the appropriate hemiester. [c] 0.2 M, 50 h.

Table 3 Substrate scope: the anhydride component



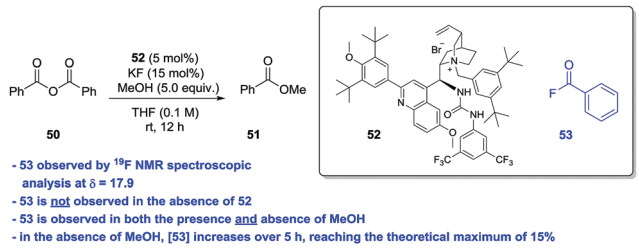
[a] Yields are isolated. The value in parenthesis refers to the conversion of a repeat reaction in the absence of **13** under otherwise identical conditions after 48 h. Enantiomeric excess determined by ^{1}H NMR spectroscopic analysis after derivatisation of the appropriate hemiester.

The same structural trends were observed as before: *N*-benzyl moieties containing electron-withdrawing groups lead to better stereocontrol than either electron-rich or bulky analogues, while *o*-substitution is detrimental. The *p*-nitro substituted variant **39** proved equal to the hitherto best catalyst in the library (entry 24), although either lowering or raising the reaction temperature failed to improve the process (entries 25 and 26). The difluorobenzyl-PTC **40** (entry 27) promoted the reaction with similar ee and higher conversion, while the incorporation of a bromine atom *o*- to the nitro functionality of catalyst **39** (*i.e.* **41**, entry 29) led to further marginal improvement. Finally, exchange of the bromine atom for the more electronegative fluorine atom (*i.e.* **13**, entry 30) provided a catalyst in which the hydrogen-bond donating unit, the *N*-benzyl moiety and the C-2 quinoline substituent had been modified in near optimal fashion.

In terms of substrate scope, a range of *meso*-anhydrides could be converted to the corresponding methyl hemiesters **15** and **43–49** in good-excellent yields at ambient temperature in the presence of methanol, KF and **13** at 5 eq., **15**- and 5 mol% levels respectively (Table 3). Enantiomeric excess ranged from trace levels for the glutaric anhydride-derived **47–48** to 33–61% ee for the bicyclic succinic anhydride-derived esters **15** and **43–47**. In the case of **43**, **45**, and **48–49**, product optical purity is modulated by competing (occasionally rapid) background methanolysis of the less sterically demanding anhydrides by potassium fluoride alone. No background reaction was observed in the other cases. The fact that (for instance) **45** can be formed in 51% ee despite stiff competition from a racemic pathway is remarkable.

Bunton and Fender (Fig. 1A)[4] could not isolate or detect the build-up of acyl fluoride intermediate in the fluoride-catalysed hydrolysis of succinic anhydride – most likely due to either a rapid equilibrium involving ring closure by the carboxylate or general base catalysis of the hydrolysis of the acyl fluoride by the neighbouring carboxylate. Accordingly, we deemed it unlikely that we could isolate or trap an acyl fluoride in the current system. In order to circumvent the problem of interference from a tethered carboxylate ion, we carried out a study on fluoride-catalysed methanolysis of benzoic anhydride (**50**) in the presence of a PTC (Scheme 1).

Under conditions identical to those in the desymmetrisation experiments outlined above using PTC **52**,[17f] during the formation



Scheme 1 Observation of an acyl fluoride intermediate.

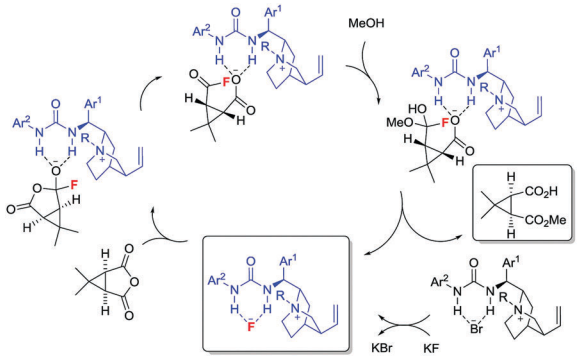


Fig. 2 Proposed catalytic cycle.

of **51** we could detect the presence of **53** by ^{19}F NMR spectroscopy. In the absence of the PTC, **53** is not formed; while the levels of **53** detected were higher in the absence of MeOH than in its presence. In the absence of methanol, we could (using the catalyst's CF_3 resonances as an internal standard) track the increase in concentration of **53** over time. After 5 h, all KF is converted to **53**. These observations do not exclude a competing general base catalysed pathway, however, it is seems likely that nucleophilic catalysis (Fig. 2) is responsible for much of the observed activity.

In summary, the first asymmetric reaction involving nucleophilic catalysis by fluoride ion has been developed. A library of quinine-derived PTCs capable of forming ammonium fluorides *in situ* were evaluated in the desymmetrisation of a *meso*-anhydride by methanolysis. The presence of a strong H-bond donating unit at C-9 is essential from an enantioselectivity standpoint. The optimum catalyst designed was capable of promoting the desymmetrisation of **14** with 61% ee. Experiments involving the fluoride-catalysed methanolysis of benzoic anhydride unambiguously demonstrated the formation of the corresponding acyl fluoride, and in the absence of methanol, quantitative formation of **53** was observed.

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Conflicts of interest

There are no conflicts to declare.

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