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Potassium fluoride: A convenient, non-covalent support for the immobilization of organocatalysts through strong hydrogen bonds

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ABSTRACT

The development of potassium fluoride as a practical non-covalent support for a carboxylic acid containing a pyrrolidine substituent with organocatalytic activity in the asymmetric Michael addition is described. The immobilization is carried out by simply treating the catalytic ligand in dichloromethane (DCM) solution with non-anhydrous potassium fluoride (KF). XRD and FTIR results suggest that the organocatalyst is efficiently loaded onto KF through strong hydrogen bond (SHB) formation, affording the KF-supported catalyst (*KF-supCAT*, **8**) for the direct asymmetric Michael addition of carbonyl compounds to trans-β-nitrostyrenes. Good yields, excellent diastereoselectivities (up to 99:1 *syn:anti*) and excellent enantioselectivities (up to 97% *ee* for the *syn* diastereomer) are recorded in the Michael additions of cyclohexanone to trans-β-nitrostyrenes, considerably improving previous results obtained with a closely related catalyst covalently immobilized onto polystyrene. The *KF-supCAT* could be recovered and recycled three times by increasing the supersaturation degree of the solution.

1. Introduction

Asymmetric organocatalysis is a powerful tool for the manufacture of enantiomerically pure organic compounds [1,2]. Organocatalytic methods are especially attractive for the preparation of compounds that do not tolerate metal contamination, e.g. pharmaceutical intermediates and natural products [3]. The development of asymmetric organocatalysts and their immobilization onto solid supports has attracted the attention of the synthetic community as a valuable tool to simplify product isolation and catalyst recycling, which in turn decreases the effective catalyst loading [4–7]. For immobilization, the organocatalyst is usually supported onto a polymer, dendrimer or inorganic nanoparticle that can be reused by recovering it after centrifugation, magnetic decantation or filtration [8–15]. In most of the cases, a covalent bond is chosen to attach the organocatalysts onto the solid phase. This bond gives robustness to the system, allowing a high number of recyclings [9,16–19]. However, this robustness may induce to a partial loss of effectiveness due to a lower mobility of the catalyst [20]. In addition, laborious synthetic manipulations are required to achieve a covalent immobilization, and significant structural perturbations to the catalyst core are usually not avoidable. For the latter reasons, an alternative for anchoring catalysts onto supports that solves most of these problems, i.e. the non-covalent bonding, has been explored in recent years. Accordingly, some organocatalysts have been successfully supported onto polyoxometalates (POMs), polymers, clays, cyclodextrines or graphene oxide [21,22]. In all these cases, the immobilization is achieved *via* electrostatic interactions. Minimal synthetic modifications of the catalyst are needed, thus resulting in minimal structural perturbation. Last but not least, these supports are usually commercially available and no functionalization of the support is needed before immobilization of the catalyst.

An example of the versatility and advantages of non-covalent supporting is the immobilization of chiral amines by utilizing solid acids reported by Luo and Cheng [23–25]. In this case, the support has a dual function, first, acting as an anchor for the chiral diamines and second acting as a critical modulator for the catalytic activity and stereoselectivity.

Among other non-covalent interactions, strong hydrogen bond is an important subclass of hydrogen bonds that is clearly distinguishable from normal hydrogen bonding [26]. SHBs are postulated to be important in biological catalysis, and under adequate circumstances, they can act as strong and reversible locks in encapsulating structures [27,28]. SHBs are usually formed between carboxylates and carboxylic acids [29], carboxylates and imidazoles [30], phenoxide and phenols [31] or KF and carboxylic acids.

Emsley and co-workers, while studying the behaviour of solutions of KF in glacial acetic acid, reported the latter type of SHB

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[32]. In this particular case, the solubility of KF in acetic acid was possibly due to the fact that fluoride anion is also capable of forming SHB to the hydroxyl group of carboxylic acids. In fact, calorimetric, spectroscopic and theoretical studies suggested very strong H-bond energies of 110–120 kJ mol^{-1} [33,34]. Further studies showed the ability of KF to form SHB in light carboxylic acids, diols, some fluorinated alcohols, formamide and N-methylformamide [35]. In these media, the fluorides are solubilized by formation of H-bonds between fluoride anions and the solvent molecules, this resulting in the transfer of electron density from the anion to the solvent, with enhancement of the nucleophilicity of the solvent and reduction of the nucleophilicity of dissolved fluoride. Thus, none of these KF–carboxylic acid and KF–solvent systems are suitable as nucleophilic fluoride sources but, in turn, they are very useful sources of carboxylate anion and appropriate media for reactions involving the solvent as a reactant [36]. In order to avoid solvent interference, polar aprotic solvents have generally been used in studies on reactions promoted by KF [37,38].

Although the use of potassium fluoride in organic synthesis has been widely reported and its ability to form SHB has been studied, its potential use as non-covalent support has been poorly explored to date. To the best of our knowledge, only its use as an excellent support for *m*-chloroperbenzoic acid (*m*-CPBA) has been described. Thus, an insoluble KF–*m*-CPBA system allowed the performance of Baeyer Villiger oxidations and epoxidation reactions of olefins with greatly facilitated work-up [39,40].

Based on the ability of fluoride to form strong hydrogen bonds with carboxylic acids and on our previous experience in developing reusable organocatalytic systems, we report the possibility of using KF as a support for the development of recyclable organocatalysts with high efficiency. To bring this approach into practice, we designed a supportable catalyst by attaching its active centre (a α-triazolylmethylpyrrolidine) to a benzoic acid unit *via* a 1,4-triazolediyl moiety. While the pyrrolidine moiety is designed act as a rather unperturbed catalytic site, the carboxylic acid moiety has to serve as the anchoring site to solid potassium fluoride (see Fig. 1).

The present contribution addresses the preparation and characterization of the functionalized pyrrolidine, its coordination to KF and the catalytic behaviour and reusability of the final system in asymmetric Michael addition reactions [41,42].

2. Experimental

2.1. Materials and methods

All reagents were purchased from Aldrich and used as received. All reactions were carried out directly under open air. All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H, or at 100 MHz and 125 MHz for ^{13}C, respectively. TMS was used as internal standard for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR. Chemical shifts are reported in ppm referred to TMS. FT-IR measurements were carried out on a Bruker Optics FTIR Alpha spectrometer equipped with a DTGS detector. Elemental analyses were performed at the MEDAC Ltd. Laboratories, United Kingdom, using a Metrohm761 Compact Ion Chromatograph. The analysis of metals was performed using the Varian VistaMPX CCD Simultaneous axial ICP-OES micro-analyzer. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier Instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Specific optical rotation measurements were carried out on a Jasco P-1030 model polarimeter equipped with a PMT detector using the sodium line at 589 nm. The experiments under microwave irradiation were carried out in a CEM Discover microwave reactor. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Series 1100 and 1200), using Chiralpak IA and AD-H columns and guard columns. Racemic standard products were prepared using DL-proline as catalyst in order to establish HPLC conditions. TEM images were collected using a JEOL 1011 Transmission Electron Microscope operating at 100 kV and magnification values of 12–60 k. The dried samples were placed onto carbon coated-copper grids. The same equipment was applied to make Selected Area Electron Diffraction (SAED). SEM images were recorded using a JEOL JSM-6400 scanning microscope. The same equipment was applied to measure energy-dispersive X-ray spectroscopy (EDX). The PXRD samples were prepared by placing the powders between two foils without background. PXRD data were acquired on a Bruker D8 Advance.

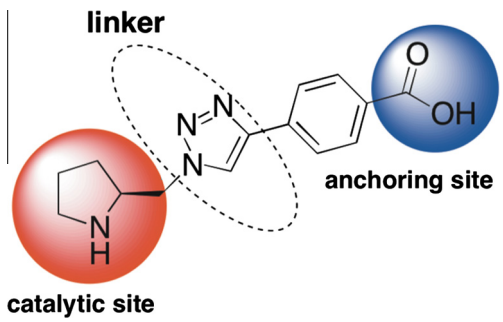

Fig. 1. Proposed catalyst design.

2.2. Synthesis of the KF-supported catalyst (KF-supCAT)

2.2.1. (S)-tert-butyl-2-((4-(4-(ethoxycarbonyl)phenyl)-1H-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate **3**

A mixture of alkyne **1** (1 g, 4.06 mmol), CuBr (116 mg, 0.81 mmol), azide **2** [42] (918 mg, 4.06 mmol), water (0.14 mL, 8.12 mmol) and triethylamine (0.56 mL, 4.06 mmol) in DMF (20 mL) was stirred at 100 °C for 16 h. Then, the reaction mixture was cooled to room temperature, and a saturated aqueous solution of ammonium chloride was added (10 mL) and extracted with ethyl acetate (3 × 40 mL). The organic layer was washed with water, dried over sodium sulphate, filtered and concentrated under reduced pressure. Purification by flash chromatography using the system Hex:EtOAc (6:4) afforded the triazole as a pale brown solid (1.12 g, 69%).

mp 154–156 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.43 (t, J = 7.2 Hz, 3H), 1.52 (s, 9H), 1.79 (brs, 2H), 2.01 (brs, 2H), 3.31 (m, 2H), 4.15 (brs, 1H), 4.41 (dd, J = 14.3 and 7.2 Hz, 2H), 4.65 (m, 2H), 7.77 (brs, 1H), 7.90 (d, J = 8.0 Hz, 2H), 8.13 (d, J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3 (CH_3), 23.4 (CH_2), 28.4 ($3CH_3$), 47.1 (CH_2), 51.7 (CH_2), 52.9 (CH), 57.3 (CH_2), 61.0 (CH_2), 80.4 (C), 121.4 (C), 125.3 (CH), 129.8 (CH), 130.2 (3CH), 134.8 (C), 146.8 (C), 154.8 (C=O), 166.3 (C=O).

IR (ATR): ν·2976, 2881, 1703, 1682, 1394, 1275, 1172 cm^{-1}.

HRMS (ESI+): m/z = 400.2111, calcd. for $C_{21}H_{28}N_4NaO_4$ $[M+Na]^+$: 423.2003.

$[\alpha]_D^{25}$ = −31.6 (c 0.84 in $CHCl_3$).

2.2.2. (S)-4-(1-((1-(tert-butoxycarbonyl)pyrrolidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)benzoic acid **4**

The triazole **3** (1.12 g, 2.8 mmol) was dissolved in ethanol and sodium hydroxide (1 M solution, 14 mL) was added. The reaction was stirred at room temperature for 2 h. Then, it was extracted with diethyl ether (3 × 20 mL), and the aqueous layer was acidified