Efficient separation of a trifluoromethyl substituted organocatalyst: just add water†

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A practical, cost-saving tagging approach is developed which takes advantage of the hydrophobicity of trifluoromethyl groups, exemplified by the application and recovery of a CBS precatalyst using tuned aqueous–organic media with minimum 50% water content.

Organocatalyst development in asymmetric synthesis is a frontier activity in modern organic chemistry.[1] This field has witnessed recent and rapid innovations which have extended the scope and repertoire in asymmetric synthesis. Although these catalysts are chemically more stable than metal based catalysts, the catalytic activity (TOF) displayed by organocatalysts remains poorer in general. In order to attain high turnover numbers for these valuable catalysts, their recovery and reuse is a current research focus of intense interest.[2] Various approaches have been explored, including soluble and insoluble supports, fluorous and ionic liquid tagging.[3] Despite promising results, the relatively high cost of the tagged catalysts and their often tedious synthesis limit their widespread utility. Herein, we report a practical, low-cost tagging and separation approach which takes advantage of trifluoromethyl groups as a hydrophobic tag. The method is applied to the well-known organocatalyst **4**[4] which as a result can be easily separated if tuned aqueous media are used.

Our laboratory has recently reported the development of an operationally straightforward and recoverable fluorous CBS methodology.[5] The fluorous tagging[6] enabled the organocatalyst **1** (Fig. 1) to function in homogeneous conditions and promoted the chiral secondary alcohol formation with high enantioselectivity. Moreover, the precatalyst **1** could be easily and efficiently recovered using fluorous solid-phase extraction. A further development of this protocol was recently reported by Curran *et al.*, who employed the hydrofluoroether HFE-7500 as a solvent.[7] The fluorous catalyst was secured in the hydrofluoroether by fluorous affinity but the organic product could be separated by washing HFE-7500 phase with a polar solvent.

Although perfluorohexyl and perfluorooctyl affinity tags have gained widespread use in fluorous catalyst immobilization, these tags retain drawbacks. Besides the elaborate nature of many of R_{f6} and R_{f8} tagged catalysts (*e.g.* catalyst **1**), their costs are high particularly for process development prospects. Furthermore, there is growing environmental concern about long-chain perfluoroalkyl compounds with uncertainty regarding their bioaccumulation and potential toxicity to populations over long term exposure.[8] These challenges provide an impetus for the development of tagging approaches which utilize alternative motifs,[9] and in our case the trifluoromethyl group,[10] the smallest perfluorinated tag, is a chemical functionality already used widely in pharmaceuticals and agrochemicals. Also there is no doubt that it is particularly attractive to achieve alternative extraction protocols without having to resort to any fluorous solid or liquid media.

To assess the possibility of trifluoromethyl tag based catalyst recovery in CBS methodology, we have synthesized three different prolinols **2–4** with an increasing number of trifluoromethyl groups (n = 0, 2, 4, Fig. 1).

Eluting these prolinols **2–4** on C-18 reversed phase TLC† using MeOH as a mobile phase, however, there was no separation. Nevertheless, by gradually increasing the water content[11] a point was reached (MeOH–H_2O, 1 : 1 vol. ratio) where prolinol **4** was retained but non-tagged prolinol **2** (representing also a "general organic molecule") eluted efficiently.[12] This observation clearly demonstrates the influence that the small "superhydrophobic" CF_3 group can exert on the chromatographic characteristics of appropriately tagged molecules, when combined with a tuned organic solvent system with relatively high water content.

After identification of the minimally decorated fluorous prolinol **4** as a recoverable catalyst precursor it was explored as a precatalyst in asymmetric CBS reductions (Table 1). Accordingly, acetophenone (**5a**) was tested as a substrate for reduction in THF at room temperature. The protocol involved

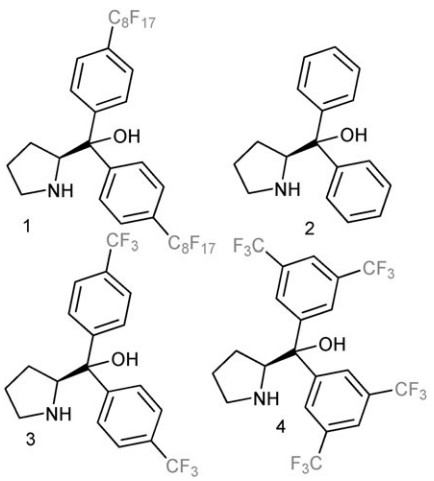

Fig. 1 Synthesized **1–4** diphenyl prolinols.

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Table 1 Asymmetric reduction of **5a–d** using phase tagged prolinol precatalyst **4**

5a-d **6a-d**

Entry	Substrate	Additive	Reducing agent	Yield[a] (%)	ee[b] (%)
1	**5a**	—	BH_3 THF	82[c]	16
2	**5a**	—	BH_3 THF	83[d]	76
3	**5a**	—	BH_3 THF	85[e]	90
4	**5a**	$B(OMe)_3$	BH_3 DMS	85[f]	94
5	**5a**	$B(OMe)_3$	BH_3 DMS	89[g]	94
6	**5b**	$B(OMe)_3$	BH_3 DMS	87[f]	95
7	**5b**	$B(OMe)_3$	BH_3 DMS	90[g]	95
8	**5c**	—	BH_3 THF	81[e]	87
9	**5c**	$B(OMe)_3$	BH_3 DMS	82[f]	94
10	**5d**	$B(OMe)_3$	BH_3 DMS	76[f]	98
11	**5d**	$B(OMe)_3$	BH_3 DMS	96[h]	98
12	**5d**	$B(OMe)_3$	BH_3 DMS	96[i]	98
13	**5d**	$B(OMe)_3$	BH_3 DMS	96[i]	98

[a] Isolated yields. [b] Determined by chiral HPLC (Chiralcel OD or OJ). [c] The substrate was added in one portion. [d] The reducing agent was added dropwise within 1 h. [e] The substrate was added dropwise within 1 h. [f] *In situ* generation of oxazaborolidine using 10 mol% additive and 2.0 mmol of **5a–d** was added dropwise within 1 h followed by solid-phase extractive work-up. [g] Performed in 25 mmol scale and isolated with U-tube method. [h] Performed in 25 mmol scale and isolated with liquid–liquid extraction. [i] Recycling experiments in 25 mmol scale with liquid–liquid extractive work-up.

the *in situ* generation of the catalyst, to circumvent the independent synthesis of the catalytically active oxazaborolidine, and thus efficient recycling of precatalyst **4** became the objective rather than the hydrolytically sensitive catalyst. Optimization of the experimental parameters revealed that both the reducing agent and the mode of addition had a pronounced effect on the resultant enantioselectivities (Table 1, entries 1–4). After optimization of reaction conditions (entry 4), a range of polar and apolar aromatic substrates were explored (entries 6, 9 and 10). The enantioselectivities were high in all cases and they were not further optimized.

Then we sought to examine the feasibility of binary separation of the tagged precatalyst **4** from the reaction products **6a–d** using solid-phase extraction (SPE) and/or liquid–liquid extractions. Since prolinol **4** can be viewed as a refinement of fluorous prolinol **1**, in the first instance fluorous silica gel was explored for solid-phase extraction (FSPE). On consumption of the acetophenone (**5a**), the reaction mixture was quenched, evaporated onto Brockman II type neutral alumina (γ-Al_2O_3) and loaded onto the FSPE cartridge. This overcame a technical difficulty of manipulating the small scale reaction and allowed reliable and reproducible data. As expected from the preceding solvent tuning experiments, minimally tagged **4** could be separated from the reaction products using water–MeOH (1 : 1) as the eluent. The reaction product **6a** eluted well after washing the loaded cartridge with the aqueous solvent, but the eluent contained 14.9% of the precatalyst **4** (Table 2, entry 1). A second-pass elution with THF then removed the retained precatalyst **4** having no detectable product contamination. In order to investigate a completely non-fluorous extraction protocol, C-18 reversed phase silica

Table 2 Leaching of prolinol **4** into products after SPE extractions

Entry	Support/SPE cartridge	**6a**[b]	**6b**[b]	**6c**[c]	**6d**[b]
1[a]	γ-Al_2O_3/FSPE	14.2	—	—	—
2[a]	γ-Al_2O_3/C-18 SPE	3.8	—	—	—
3[a]	α-Al_2O_3/C-18 SPE	3.1	1.5	<0.01	<0.01
4[a]	α-Al_2O_3/α-Al_2O_3	5.4	2.6	0.2	2.7

[a] Given in percentage, 100% was the original catalyst load. [b] MeOH–water 1 : 1 (vol. ratio) was used. [c] DMF–water 1 : 1 (vol. ratio) proved to be a better solvent for highly apolar compounds.

gel was explored. In the event, C-18 SPE cartridges efficiently (Table 2, entry 2) separated the minimally decorated **4** from non-tagged product **6a** using the same aqueous solvent system†. Interestingly, this non-fluorous protocol proved to be a better alternative for extraction in binary separation, even with the relatively high fluorine content (43%) of **4**. However, in both cases a technical problem arose from the wettability of the solid supports: the large proportion of water in the eluent increased the resistance of the loaded cartridges which resulted in a slow filtration. To reduce this effect, the less wettable corundum (α-Al_2O_3) was evaluated as a mechanical support. This modification did facilitate the filtration and it also improved the separation efficiency (Table 2, entry 3). This new separation method was then applied to work-up of CBS reductions and it proved relatively easy and efficient to separate the chemically robust catalyst precursor **4** from both apolar alcohols **6b**, **6c** and the more polar **6d**. Although it was anticipated that the alumina would function only as a mechanical support, these outcomes indicate that corundum can also enhance separation. Interestingly, the replacement of C-18 SPE with corundum resulted in only slightly higher leaching of **4** into the products (Table 2, entry 4). These observations suggest a future role for α-Al_2O_3 in work-up procedures.

Encouraged by the above results, the separation methodology was now extended to liquid–liquid extraction, which is more amenable to scale up. It was again an objective to avoid fluorous solvents.[13] Due to the unrivaled fluorophobicity of water, the partitioning of tagged **4** between a biphasic hexanes–MeOH or acetonitrile (ACN) can now be modulated by the addition of water. For example, partitioning of the quenched reaction mixture of **6d** into hexanes–aqueous ACN (4 : 1) resulted in the complete separation of two functionally similar aminols (with no requirement for pH dependent separation), **4** and **6d** after only one extraction (Table 1, entry 11). The pyridinol **6d** remained in the water–ACN phase, while the tagged precatalyst **4** was recovered ($>99.5\%$, efficiency) from the hexane phase. Furthermore, the phase tagged precatalyst **4** proved to be sufficiently robust to withstand several reaction cycles, and it could be recycled without any deleterious effect on the yield and the enantioselectivity (Table 1, entries 12 and 13).

Although the less polar reaction products **6a** and **b** were also separated by the above method, repetitive extraction of the hexane phase was necessary to obtain a full separation. For large-scale reactions this could clearly generate aqueous waste volume, which should be avoided. With this limitation in mind we have designed an apparatus to minimize the quantity of aqueous–organic blended phases for these extraction

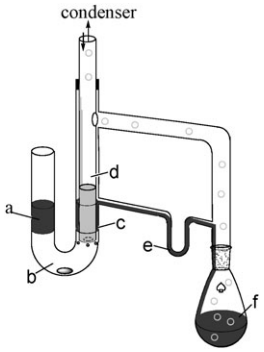

Fig. 2 Novel continuous U-tube extractor. (a) Feeding hexanes solution containing crude reaction mixture: precatalyst **4** and the products **6a** or **6b**. (b) Aqueous methanol (1 : 1 vol. ratio) liquid membrane. (c) Receiver hexanes solution. (d) Inner tube with a porous glass "frit" at the bottom. (e) Syphon. (f) Distillating pot containing hexanes.

protocols (Fig. 2).† This apparatus is a straightforward combination of a U-tube and a continuous extractor and it generates a sustainable chemical gradient of the extracted materials between the feeding and receiver arm of the U-tube. Additionally, the applied aqueous–methanol phase functions as a liquid membrane, allowing a selective passive transport of the non-tagged organic products **6a** and **b** but retains the precatalyst **4** in the feeding hexanes solution. Thus, the continuously distilled hexanes extract the reaction products **6a** and **b** from the aqueous methanol until no more product is left in the feeding arm (precatalyst **4** was recovered with >99% efficiency). Finally, the products **6a** and **b** were obtained after concentration of the distillation reservoir (Table 1, entries 5 and 7). This straightforward liquid membrane methodology offers distinct advantages over conventional liquid–liquid separation techniques. It uses less solvent and organic waste residues are substantially reduced.

In summary, CF_3 groups are shown to be a sufficient and practical design element for catalyst immobilization in combination with an optimized aqueous extraction solvent system.[14] Importantly, this approach offers an efficient alternative to the widely explored practice of appending long perfluoroalkylated C_4, C_6, C_8 segment(s) or other soluble polymers for the homogeneous recovery of organocatalysts. Also, this minimal CF_3 tagging approach results in a relatively low molecular weight immobilized catalyst which is clearly beneficial when relatively high catalyst loading is required (*e.g.* 10 mol%) as is the case currently in the field of organocatalysis.[1,2a] There are limitations and clearly the larger the organic motif in a given situation, the more CF_3 groups will be required for efficient performance. Solvent tuning is a critical and important aspect, although there is a lot of latitude and up to 50% water–co-solvent mixtures are able to dissolve organic molecules positioned across a broad polarity range (even the apolar naphthyl derivate **6c** can be separated effectively from tagged prolinol **4**). Moreover, the developed separation protocols rely on cheap traditional solvents[13] and inorganic adsorbent. Therefore, the main attractive feature of our separation methodology is its extraordinary technical and synthetic simplicity and low cost. The extension of this minimal decoration approach toward other relevant reactions (*e.g.* Wittig, Suzuki, Mitsunobu and Appel reactions) was successful and will be reported shortly.

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