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Organocatalysis in Water at Room Temperature with *In-Flask* Catalyst Recycling

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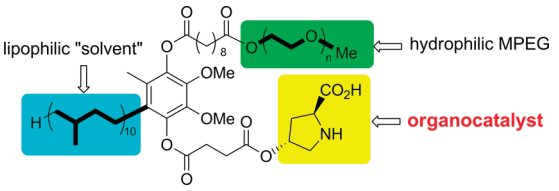
ABSTRACT



A new designer surfactant is described containing a covalently bound organocatalyst, proline. This species is water-soluble and, via spontaneous nanomicelle formation, catalyzes aldol reactions on water-soluble or -insoluble substrates in water as the only medium. Recycling the catalyst is trivial, as the amphiphile/catalyst remains in the aqueous phase in the flask.

Although organocatalysis dates back to 1971,[1] it is only over the past decade during which remarkable progress has been made.[2,3] An impressive number of reaction types can now be effected using this transition-metal-free approach, and applications abound. Reviews on this subject in 2010 alone are plentiful.[4] Included among the new directions in organocatalysis being pursued are tandem or "organocascade" reactions that combine multiple reaction partners leading to significant increases in molecular complexity in a one-pot sequence.[5] Notwithstanding these advances, the vast majority of reactions that utilize organocatalysis rely on relatively few catalyst turnovers; typically, ≥10% catalyst is needed to achieve reasonable reaction rates and ultimately, isolated yields. Under such circumstances the implications are clear: a considerable amount of organic material is lost upon workup. While economics may not enter into consideration, e.g., using an inexpensive commercially available catalyst such as proline, many second-generation catalysts require several steps to prepare.[4a,6] Moreover, the waste component due

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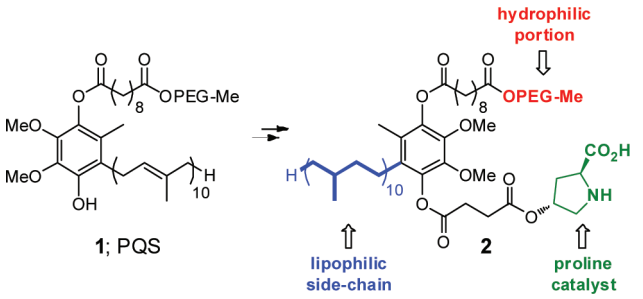
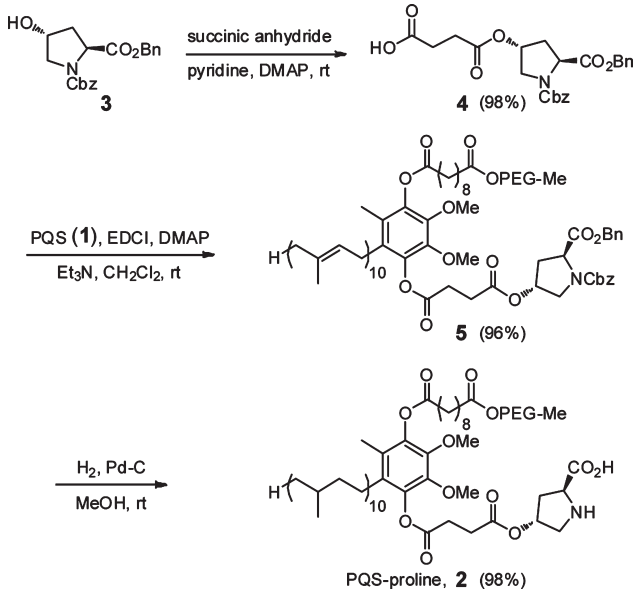


Figure 1. PQS attached proline catalyst for reactions in water.

to catalyst loss upon workup is necessarily large, detracting from even those processes amenable to use in water as solvent.[7] Those run in organic media where most substrates of interest find solubility are even less environmentally friendly. Not surprisingly, therefore, recent efforts that address catalyst recycling have come to light.[8] Those reported to date follow a similar pattern, i.e., attachment to a solid support, thereby requiring catalyst separation from a reaction mixture and, oftentimes, reactivation. Ideally, no such manipulation would be needed; i.e., in-flask processing should prevail, where the catalyst remains in the reaction vessel.[9] Use of water in place of organic solvent(s) would add a considerable element of "greenness" as well. In this communication we describe a newly designed organocatalyst-containing system that provides a solution to all of these issues: organocatalysis involving water-soluble or insoluble substrates, done in water at room temperature, with *in-flask catalyst recycling*.

As a "proof-of principle" case, 4-hydroxyproline was selected to represent the potential of the new technology developed. Covalent attachment to the water-soluble micelle-forming species "PQS" (**1**)[10] via its OH group was anticipated to arrive at species **2** (Figure 1). The synthesis of **2**

Scheme 1. Synthesis of PQS-Proline (**2**)



follows the outline shown in Scheme 1. Protected proline derivative **3**[11] was used to open succinic anhydride to arrive at acid **4** in close to quantitative yield. Esterification of coenzyme Q_{10}-derived PQS (**1**) led to ester **5** (96%), which underwent global hydrogenation to remove (1) the benzyl ester, (2) the Cbz residue, and (3) all 10 olefins present in the 50-carbon side chain found in the reduced form of CoQ_{10}, ubiquinol. Compound **2** thus functions in multiple capacities it: (a) serves as the source of the organocatalyst, in this case, proline; (b) provides the reaction solvent in the form of the 50 carbon hydrocarbon chain; (c) forms a water-soluble nanoparticle that, due to the MPEG-2000 component, remains in water upon in-flask extraction of the product. Dissolution of PQS-proline (**2**) in pure water results in formation of 79 nm micelles, as determined by Dynamic Light Scattering (DLS),[12] within which homogeneous organocatalysis can occur.

For comparison purposes, the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde was chosen for initial study (Table 1). This particular pair of reactants is described in the literature with considerable frequency for related studies in organocatalysis.[13] The closest analogy to PQS-proline **2** is Barbas' micelle-forming proline derivative **6C**,[7b] which shows considerable promise for use in industrial settings.[7c] Catalysts screened for this aldol reaction included not only PQS-proline but also the analogous mixed diester derivative **6A**[14] of 4-hydroxyproline,

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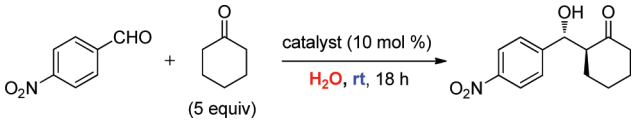
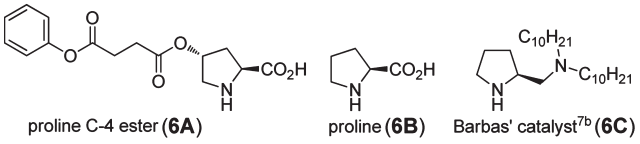
Table 1. Comparisons between Organocatalysts in an Aldol Reaction, in Water at rt



catalyst	yield[a] (%)	*anti:syn*[b]	ee[c] (%)
PQS-proline (2)	**93**	**92:8**	**96**
proline C-4 ester (**6A**)	<5	—	—
proline (**6B**)	0	—	—



proline C-4 ester (**6A**) proline (**6B**) Barbas' catalyst[7b] (**6C**)

[a] Combined yield of isolated diastereomers. [b] Determined by ^{1}H NMR of the crude product. [c] Determined by chiral-phase HPLC analysis for *anti*-product.

designed to test the importance of the micelle-forming CoQ_{10} platform and proline itself. As illustrated in Table 1, only PQS-proline (**2**) afforded the aldol product to any significant extent, the reaction being run in water at room temperature. With less ketone present (2.5 equiv), the extent of conversion was lower and the yield, therefore, dropped to 80%.

Several additional examples of aldol reactions occurring within, and mediated by, PQS-proline can be found in Table 2. Catalyst loading (10 mol %) was chosen as a compromise between maximizing the amount of **2** used (since none is lost), and the overall viscosity of the aqueous medium (typically hosting large excesses of ketone). While proline works well insofar as ee's are concerned in several cases, the goal in this study was not to maximize levels of stereoinduction. Rather, both the dr's and ee's resulting from various ketone/aldehyde combinations are all as expected based on proline as the catalyst.[15] In several cases, far better ee's can be realized using known alternative catalysts that could replace proline bonded to the PQS backbone.[16] Another feature worthy of note, given that catalysis is presumably taking place within the lipophilic core of **2** (and not in water), is that water-insoluble educts, in fact, are the preferred

(14) See Supporting Information for preparation.

(15) (a) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653–4655. (b) Kristensen, T. E.; Vestli, K.; Fredriksen, K. A.; Hansen, F. K.; Hansen, T. *Org. Lett.* **2009**, *11*, 2968–2971. (c) Lombardo, M.; Easwar, S.; Marco, A. D.; Pasi, F.; Trombini, C. *Org. Biomol. Chem.* **2008**, *6*, 4224–4229. See also refs 7b and 8a.

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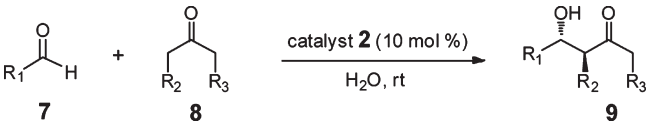
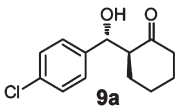
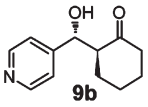
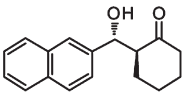
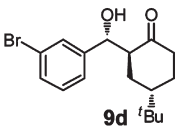
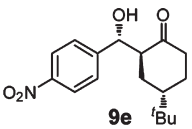
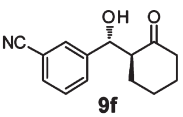
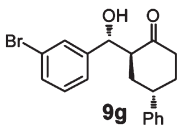
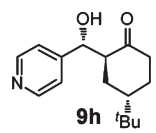
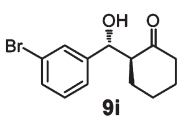
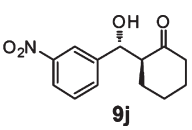
Table 2. Representative PQS-Proline (**2**)-Catalyzed Reactions[a]

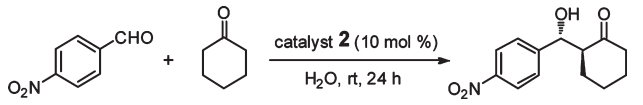


7 **8** **9**

entry	product	time (h)	yield[b] (%)	*anti:syn*[c]	ee[d] (%)
1	 **9a**	30	88	82:18	90
2	 **9b**	18	90	90:10	90
3	 **9c**	48	74	86:14	92
4	 **9d**	36	80	83:17	91
5	 **9e**	18	85	85:15	79
6	 **9f**	30	80	90:10	97
7	 **9g**	36	82	68:32	86
8	 **9h**	18	85	89:11	75
9	 **9i**	36	82	84:16	86
10	 **9j**	24	90	90:10	91

[a] The reactions were performed with aldehyde (0.1 mmol), ketone (0.5 mmol), and catalyst **2** (0.01 mmol) at rt. [b] Combined yield of isolated diastereomers. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis for *anti*-product.

Table 3. In-Flask Recycling of Catalyst **2**



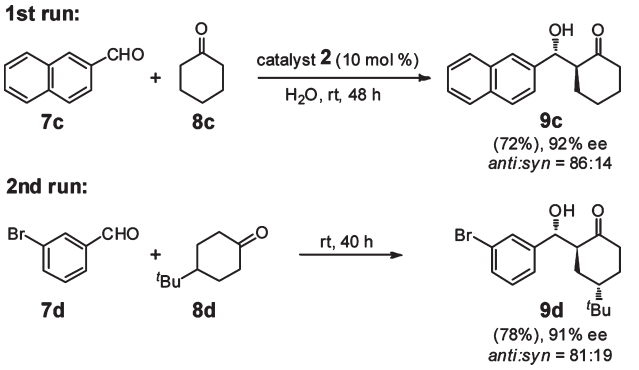
run	yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
1	94	92:8	96
2	94	94:9	96
3	93	91:9	96
4	91	90:10	96

[a] Combined yield of isolated diastereomers. [b] Determined by ^{1}H NMR of the crude product. [c] Determined by chiral-phase HPLC analysis for *anti*-product.

substrates. Thus, substituted cyclohexanones (entries 4, 5, 7, and 8) readily participate at ambient temperatures.

Key to the value of **2** as a model for organocatalytic processes is its inherent potential for in-flask recycling.[10] Thus, upon completion of the aldol event, introduction of a single organic solvent (e.g., EtOAc) allows in-flask extraction of the product. Removal of the EtOAc layer is followed by product purification and potential solvent recovery, while the residual aqueous layer *in the reaction flask* retains the proline-containing nanomicelles composed of amphiphile **2**. Reintroduction of starting materials begins the first recycle. Table 3 documents, through three recycles, that the yield, diastereomeric ratio, and ee of the process are essentially invariant.

Scheme 2. In-Flask Recycling of Catalyst **2** in Different Asymmetric Aldol Reactions



In summary, a new surfactant has been designed with the principles of green chemistry in mind to address the high levels of catalyst loading typically associated with organocatalysis. Proline, as a model catalyst, has been attached to a nanomicelle-forming amphiphile derived from the dietary supplement CoQ_{10}. In water this species self-aggregates into nanoreactors in which catalysis takes place at room temperature. Given the covalent linkage of the catalyst (that can be varied) and the high solubility in water of the amphiphile to which it is attached, typical extractive workup is avoided, and in-flask recycling of the catalyst is easily performed.[17]

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Supporting Information Available. Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) **Representative procedure** (Table 2, entry 6). 3-Cyanobenzaldehyde **7f** (13 mg, 0.10 mmol), cyclohexanone (52 μL, 0.50 mmol), and catalyst **2** (33 mg, 0.01 mmol) were sequentially added into a Teflon-coated stir-bar-containing glass vial at rt. Water (0.25 mL) was added, and the resulting solution was allowed to stir at rt for 30 h. The homogeneous reaction mixture was then diluted with EtOAc (1 mL) and filtered through a bed of silica gel layered over Celite, and the bed was further washed (3 × 4 mL) with EtOAc to collect all of the aldol product material. The volatiles were removed *in vacuo* to afford the crude product which was subsequently purified by flash chromatography on silica gel (eluting with 20% EtOAc/hexanes) to afford the product as a white solid (18 mg, 80%). Enantiomeric excess: 97%, determined by HPLC (Daicel Chiralpak AD, ^{i}PrOH/hexane = 10:90), λ = 273 nm, flow rate 0.5 mL/min, $t_{R\text{major}}$ = 46.92 min, $t_{R\text{minor}}$ = 60.28 min; *anti* isomer (2*S*,1′*R*)-**9f**: $[\alpha]^{20}_D$ = +28.0 (*c* = 0.30, $CHCl_3$); mp 69−72 °C; IR (thin film): 3498, 2941, 2864, 2229, 1704, 1483, 1449, 1434, 1311, 1229, 1130, 1042, 805 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (t, *J* = 1.2 Hz, 1H), 7.60 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.57 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 4.82 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.08 (d, *J* = 2.8 Hz, 1H), 2.61−2.54 (m, 1H), 2.53−2.48 (m, 1H), 2.41−2.33 (m, 1H), 2.15−2.09 (m, 1H), 1.85−1.80 (m, 1H), 1.67 (qt, *J* = 12.8, 4.0 Hz, 1H), 1.59−1.51 (m, 2H), 1.35 (qd, *J* = 12.8, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.1, 142.8, 131.7, 130.9, 129.4, 118.9, 112.7, 74.2, 57.3, 42.8, 30.9, 27.8, 24.9; MS (ESI): *m*/*z* 252 (M + Na); HRMS (ESI) calcd for $C_{14}H_{15}NO_2Na$ $[M + Na]^+$ = 252.1000, found 252.0993.