## **Rhodium-Catalyzed Asymmetric 1,4-Additions, in Water at Room Temperature, with In-Flask Catalyst Recycling**

Bruce H. Lipshutz,<sup>a,\*</sup> Nicholas A. Isley,<sup>a</sup> Ralph Moser,<sup>a</sup> Subir Ghorai,<sup>a</sup> Helena Leuser,<sup>a</sup> and Benjamin R. Taft<sup>a</sup>

<sup>a</sup> Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106, USA Fax: (+1)-805-893-8265; e-mail: lipshutz@chem.ucsb.edu

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**Abstract:** Using the newly introduced designer surfactant polyethylene glycol ubiquinol sebacate (PQS), as the platform for micellar catalysis, non-racemic BINAP has been covalently attached and rhodium(I) inserted to form PQS-BINAP-Rh. This species, the first example of a non-racemically-ligated transition metal catalyst-tethered amphiphile, can be utilized for Rh-catalyzed asymmetric conjugate addition reactions of arylboronic acids to acyclic and cyclic enones. These are performed in water at room temperature, while the catalyst can be recycled without its removal from water in the reaction vessel.

**Keywords:** 1,4-additions; catalyst recycling; chemistry in water; green chemistry; homogeneous catalysis; in-flask recycling; micellar catalysis; polyethylene glycol ubiquinol sebacate (PQS); rhodium-catalyzed 1,4-additions

The chemical enterprise is rapidly gaining an awareness of, and an appreciation for, the 12 Principles of Green Chemistry<sup>[1]</sup> as guidelines in the design of new chemical processes. One component highlights catalysis, and implied in this context is the highly desirable feature of catalyst recycling.<sup>[2a]</sup> Another important component of green chemistry is the use of "safer solvents", ideally being "innocuous when used." Thirdly, "safer chemicals" of minimal toxicity should be utilized, while maintaining functionality. Based on these key teachings, a new amphiphile, polyethylene glycol ubiquinol sebacate (PQS, 2; Scheme 1), was constructed<sup>[3]</sup> derived from the reduced form of readily available coenzyme Q<sub>10</sub>; i.e., ubiquinol.<sup>[4]</sup> This species undergoes spontaneous self-aggregation in water, with the resulting nanomicelles enabling homogeneous catalysis within their lipophilic hydrocarbon cores.<sup>[2b]</sup>

Since this platform is derived from a hydroquinone, one hydroxy moiety remains available for further derivatization. Previously, we have described opportunities to covalently attach both Grubbs-Hoveyda-1<sup>[5]</sup> and  $-2^{[6]}$  ruthenium carbene catalysts, thereby leading to olefin metathesis reactions within these aqueous nanomicelles. Likewise, we recently disclosed a strategy for effecting organocatalysis in water at room temperature using the related POS-containing proline,<sup>[7]</sup> which serves as both the reaction medium and catalyst. In each type of chemistry, the amphiphile was designed to remain in the water; extraction with minimal organic solvent (e.g., EtOAc) leads to subsequent product isolation without loss of catalyst from the reaction vessel; i.e., the catalyst remains in the aqueous phase within the flask ready for recycling.

An important, alternative application of PQS technology yet to be documented focuses on asymmetric catalysis. In this regard, we are now pleased to report the first example of a recyclable, amphiphile-bound, non-racemic transition metal catalyst that functions in water at room temperature. Given the rich history of BINAP in asymmetric catalysis,<sup>[8]</sup> this ligand was selected as a "proof of principle" example for covalent attachment to the PQS skeleton 2 in the form of catalyst 1. Complexation of non-racemic BINAP to rhodium(I) is well known from the work of Miyaura,<sup>[9]</sup> Hayashi,<sup>[10]</sup> and Carreira<sup>[11]</sup> to mediate 1,4-addition reactions of arylboronic acids to enones with high levels of enantiocontrol.<sup>[12,13]</sup> Catalyst 1 was prepared via (R)-BINAP derivative 4 by esterification of PQS with known BINAP acid 3 (Scheme 1).<sup>[14]</sup> Subsequent addition of  $[Rh(nbd)_2]BF_4$  to 4 leads to complex 1, which readily dissolves and self-assembles in water forming 43 nm nanomicelles as shown by dynamic light scattering.<sup>[15]</sup> As illustrated in Figure 1, water-soluble, highly colored catalyst 1 is untouched upon attempted extraction into solvents such as Et<sub>2</sub>O.

Conditions most amenable to micellar catalysis using the model system 2-cyclohexenone and

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Scheme 1. Synthesis of PQS-BINAP-Rh (1).



Figure 1. Aqueous solution of PQS-BINAP-Rh complex 1 in water in the presence of  $Et_2O$ .

 $PhB(OH)_2$  focused on the selection of the base, which can be a major factor in such Rh-catalyzed conjugate additions.<sup>[16]</sup> On the one hand, use of KOH would be expected to accelerate both the transmetalation event from an ate salt of the boronic acid, as well as arrive at a more reactive RhOH-containing species.<sup>[17]</sup> Unfortunately, given the diester nature of the PQS platform, presumed saponification of PQS led to little-tonone of the desired 1,4-adduct (Table 1, entry 1). While Hünig's base was far more effective (entry 2),  $Et_3N$  (3.0 equiv.) provided the best balance of basicity and lipophilicity, leading to the product of 1,4-addition in 95% yield and >99% ee (entry 3), results that compare quite favorably with those using alternative ligand and catalyst arrays.<sup>[18,19]</sup> Only three mole percent of the catalyst PQS-BINAP-Rh (1) is needed, and that only 1.2 equivalents of boronic acid suffice may reflect the high concentrations of reactants normally present within the limited amounts of surfactant in the aqueous medium.<sup>[20b]</sup> Less base (entry 4) led to essentially no reaction. While dilution of the reaction by an equal volume had little impact (entry 5), drop-

$ \underbrace{\begin{array}{c} O \\ H \\$			
Entry	Base	Yield <sup>[b]</sup> [%]	ee <sup>[c]</sup> [%]
1	КОН	<5	-
2	DIPEA	61	98 ( <i>R</i> )
3	NEt <sub>3</sub>	95	99 ( <i>R</i> )
4 <sup>[d]</sup>	NEt <sub>3</sub>	<5	-
5 <sup>[e]</sup>	NEt <sub>3</sub>	92	99 ( <i>R</i> )
6 <sup>[f]</sup>	NEt <sub>3</sub>	58	99 (R)

Table 1. Screening for the optimal base.<sup>[a]</sup>

- <sup>[a]</sup> General procedure: 0.20 mmol cyclohexenone, 0.24 mmol PhB(OH)<sub>2</sub>, 0.006 mmol PQS-BINAP-Rh, 0.60 mmol base, and 0.4 mL H<sub>2</sub>O (0.5 M).
- <sup>[b]</sup> Yield of isolated product.
- <sup>[c]</sup> Determined by HPLC on a chiral stationary phase.
- <sup>[d]</sup> 0.5 equiv. of base.
- <sup>[e]</sup> Reaction run in  $0.8 \text{ mL H}_2\text{O}$  (0.25 M).
- <sup>[f]</sup> 1 mol% of PQS-BINAP-Rh.

ping the catalyst loading from three to one percent slowed the 1,4-addition considerably (entry 6).

Representative examples of both cyclic and acyclic enones are illustrated in Scheme 2. Arylboronic acids bearing either electron-donating or electron-withdrawing groups participated in good to high yields with excellent enantioselectivities. The more hindered



<sup>[a]</sup> General procedure: 0.20 mmol enone, 0.24 mmol ArB(OH)<sub>2</sub>, 0.006 mmol PQS-BINAP-Rh, 0.60 mmol Et<sub>3</sub>N, 0.4 mL H<sub>2</sub>O (0.5 M).

**Scheme 2.** Representative examples using PQS-BINAP-Rh as the catalyst for 1,4-addition reactions.





Figure 2. Comparisons with literature results.

case of *ortho*-methylboronic acid reacted smoothly as well, affording the conjugate adduct in close to 98% *ee.* Furthermore, asymmetric additions of phenylboronic acid to five- and seven-membered cyclic enones were both quite successful, affording good yields with excellent levels of asymmetric induction.

Comparison cases with literature examples using the identical catalyst, albeit in organic media, document the potential improvements that may be realized, perhaps in a general sense, based on the hydrophobic effect.<sup>[20]</sup> Thus, examples in both the 2-cyclohexenone and 2-cycloheptenone series afford yields and *ees* of conjugate adducts that are comparable to, or better than, those previously described (Figure 2).

The inherent water solubility of PQS-BINAP-Rh is conducive to in-flask catalyst recycling. Hence, upon completion of the 1,4-addition, the product was extracted from the reaction mixture with a single, suitable organic solvent (e.g., EtOAc). Re-introduction of fresh substrate, base, and boronic acid only (i.e., no additional catalyst, solvent, or co-solvent) resulted in product, likewise, of excellent enantioselectivity, as well as in good isolated yield (Scheme 3). Different substrates could be used, added to the same reaction mixture sequentially, and in each case the anticipated product was obtained. While the integrity of the PQS-BINAP-Rh system appears to remain intact judging from the consistently high ees obtained, the extent of conversion, and hence, isolated yield from cycle 4 was only 50%. This suggests that the POS-BINAP-Rh catalyst may have a fundamentally limited lifetime under such conditions, or perhaps eventual oxidation of the phosphines is responsible for this drop in activity. Since the starting enone could be easily recovered from the reaction mixture, it was initially thought that potential build-up of boronic acid(s) might be hindering reactivity. However, a control experiment conducted in the presence of three equivalents of boronic acid (rather than the usual 1.2 equivalents) had no influence on reaction rate.

Tests for loss of metal from catalyst **1** were conducted to assess the level of anticipated bleed under our micellar catalysis conditions, an important factor for future applications to the potential syntheses of phar-

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Scheme 3. In-flask recycling of aqueous PQS-BINAP-Rh (1).

macologically active targets. Analysis of the toluene/ Et<sub>2</sub>O extract containing the desired 1,4-addition adduct by induced coupled plasma mass spectrometry (ICP-MS) revealed that each extract contained rhodium in a range of 1–40 ppb, with an average of 17 ppb (see Supporting Information). Thus, over four recycles essentially none of the metal was lost in work-up, sugesting that the decrease in catalyst activity is due to factors other than removal of **1** from the reaction mixture (e.g., ligand oxidation).

In summary, a new catalyst system, PQS-BINAP-Rh, has been constructed that enables homogeneous catalysis in the form of asymmetric conjugate additions of arylboronic acids to enones to be conducted in water at ambient temperatures. Yields are high given the mild reaction conditions, and the extent of enantiocontrol is found to be comparable to that previously seen for related methodologies. No organic solvents are needed as reaction media, and neither heating nor cooling is required, a phenomenon that takes advantage of the high concentrations associated with the micellar effect.<sup>[20b]</sup> Most noteworthy is the opportunity to recycle the water-soluble, covalently bound catalyst without its removal from the reaction flask. Finally, this study should highlight the many alternatives available for attaching and thereby recycling other ligand arrays to the PQS platform, especially those that are lengthy to prepare, and that ultimately involve an investment in precious metals.

## **Experimental Section**

# **Representative Procedure for 1,4-Addition Reactions** (Scheme 2)

Under an atmosphere of argon a 1-mL screwcap vial was charged with PQS-BINAP-Rh precatalyst (30 mg, 0.006 mmol), boronic acid (0.24 mmol), and removed from the glovebox. Water (0.4 mL) and Et<sub>3</sub>N (84  $\mu$ L,

0.6 mmol) were added to the vial and stirred for 15 min. When the solution became homogeneous, enone (0.2 mmol) was added *via* syringe and the mixture was stirred at room temperature for 12 h. The homogeneous reaction mixture was then diluted with EtOAc (0.5 mL), filtered through a bed of silica gel, and the bed further washed  $(3 \times 2 \text{ mL})$  with EtOAc to collect all of the coupled material. The volatiles were removed under vacuum to afford the crude product which was subsequently purified by flash chromatography on silica gel using EtOAc/hexanes.

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