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# Asymmetric Rhodium-Catalyzed 1,4- and 1,2-Additions of Arylboronic Acids to Activated Ketones in Water at Room Temperature Using a Mixed Sulfur-Olefin Ligand

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**Abstract:** Performing catalytic enantioselective reactions, especially enantioselective carbon-carbon bond forming reactions, in water without using any organic solvents is one of the important goals in modern asymmetric synthesis. Herein, we report an efficient enantioselective micellar catalytic approach for the 1,4-addition of arylboronic acids to cyclic ketones. Noteworthy, applying the same catalytic system we have also developed the first addition of boronic acids to the more challenging α-keto carbonyl compounds in water, affording tertiary carbinols with high yields and high enantioselectivities. Beside the mild conditions used, the reported processes use as catalyst precursor the robust sulfinamido-olefin mixed ligand **1** obtained on a multigram scale and in one step from a sugar-derived sulfinate ester.

**Keywords:** enantiopure tertiary carbinols; enantioselective catalysis in water; green chemistry; micellar catalysis; mixed sulfur-olefin ligand

The utilization of water as a cheap, safe and green solvent in organic transformations is receiving an increasing attention in academia and in chemical industries.[1] Among these transformations, those allowing the preparation of optically pure compounds, ubiquitous in pharmaceuticals, are of particular interest.[2] Therefore, performing catalytic enantioselective reactions, especially enantioselective carbon-carbon bond forming reactions, in water without using any organic solvents is a central goal in modern asymmetric synthesis.[3] Nevertheless, despite the great efforts to conduct aqueous asymmetric processes, achieving high enantiosectivities has proved to be extremely challenging. In addition to solubility constraint reasons, many transition metal-based catalysts and intermediates are highly instable in water. A practical solution to these drawbacks is the creation of a hydrophobic nanoenvironment within the water phase able to solubilize and stabilize both the catalyst and the substrate. This has been usually achieved by the use of amphiphiles which, above their critical micellar concentration (CMC), self-organize into micelles with a hydrophobic inner core and hydrophilic outer phase that are able to host hydrophobic molecules.[4] On the other hand, within C–C bond formation reactions, the Rh(I)-catalyzed addition of boronic acids to activated ketones is one of the most salient approaches.[5] Although many attempts have been made to carry out these transformations in water, only two successful cases have been reported for the special case of the asymmetric 1,4-addition of boronic acids to cyclic ketones,[6] using an amphiphilic resin-supported BINAP ligand at 100 °C,[7a] and a hydrophilic bicyclo-[3.3.0]diene ligand.[7b] In the case of the more challenging 1,2-addition, and as far as we know, no aqueous approach has been reported yet. Herein, we disclose a highly efficient and enantioselective protocol

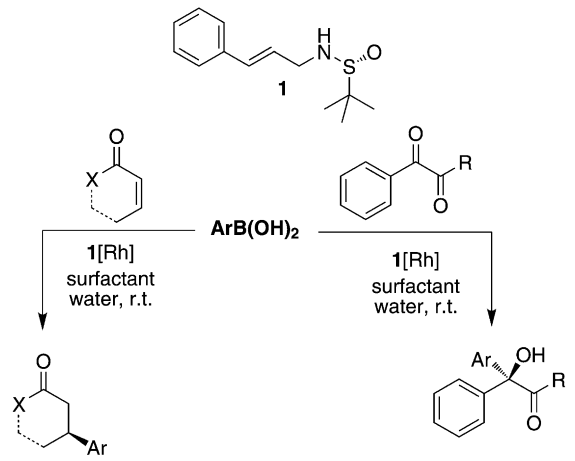


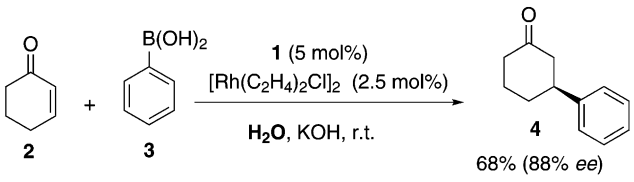

**Figure 1.** Enantioselective 1,4- and 1,2-addition of arylboronic acids to activated ketones using sulfolefin ligand **1**.

for the 1,4- and 1,2-addition of boronic acid to alkenones, α-keto esters and α-diketones in water at room temperature (Figure 1).

Within our interest in the synthesis and applications of chiral sulfur derivatives in organic and metal-promoted catalysis,[8] we have recently reported that mixed sulfinamido-olefin ligands, "sulfolefins", are highly efficient in the 1,4-addition of boronic acids to cyclic ketones.[9] Inspired by the high efficiency of the simple cinnamylsulfinamide **1**, as catalyst precursor, we decided to assay the system in pure water. Using the addition of phenylboronic acid **3** to cyclohexenone **2** as model reaction,[10] we were pleased to find that the reaction takes place and affords the desired compound **4** with 68% yield and an interesting 88% *ee* (Scheme 1).

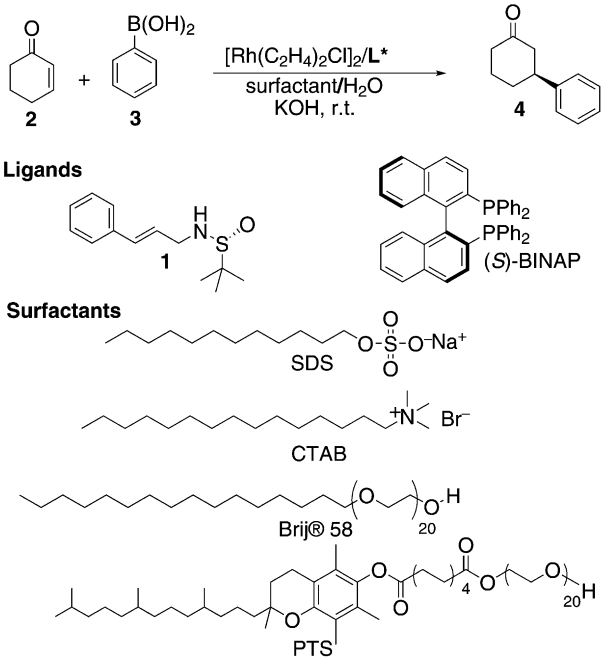
Encouraged by this positive result, we decided to enhance the yield and the enantioselectivity of the process through the application of micellar catalysis. A number of commercially available amphiphiles including a cationic (CTAB), anionic (SDS), and two neutral ones (Brij® 58, and PTS), known to self-organize in nanometer-size micelles, were screened in the model reaction (Table 1).

Catalytic activity proved to be highly dependent on the nature of the surfactant used, affording in most cases the desired product **4** with better yield and




**Scheme 1.** Enantioselective 1,4-addition of phenylboronic acid **3** to cyclohexenone **2** in pure water.

**Table 1.** Effect of surfactants on the Rh-catalyzed 1,4-addition of phenylboronic acid **3** on cyclohexenone **2** in water.[a]




| Entry | Ligand | [Conc.] [mol%] | Surfactant [Surfactant/water] (wt%) | Yield[b] [%] | *ee*[c] [%] |
|---|---|---|---|---|---|
| 1 | **1** | 5 | none | 68 | 88 |
| 2 | **1** | 5 | CTAB (0.03) | 90 | 84 |
| 3 | **1** | 5 | SDS (0.3) | quant | 99 |
| 4 | **1** | 2.5 | SDS (0.3) | 68 | 88 |
| 5 | **1** | 5 | Brij®58 (0.01) | quant | 99 |
| 6 | **1** | 5 | PTS (2) | quant | 92 |
| 7 | **1** | 5 | PTS (5) | quant | 99 |
| 8 | **1** | 2.5 | PTS (2) | quant | 99 |
| 9 | **1** | 1.25 | PTS (2) | 72 | 94 |
| 10 | (*S*)-BINAP | 5 | PTS (2) | 11 | 22 |

[a] All reactions were conducted by mixing the ligand together with $[Rh(C_2H_4)_2Cl]_2$ in surfactant/water solution at room temperature.
[b] Isolated product.
[c] Determined by chiral stationary phase HPLC

enantioselectivity than in water alone. The cationic micellar medium formed by CTAB afforded the product **4***S* with 90% yield and 84% *ee* (entry 2), similar to the result obtained in water alone. In contrast, the use of anionic surfactant SDS leads to the formation of the desired compound **4***S* in excellent yield and enantioselectivity (entries 3 and 4). The same result was obtained with the neutral amphiphile Brij® 58

(entry 5), and the vitamin E-derived amphiphile PTS[11] (entries 7 and 8), where the product was obtained in quantitative yield and mostly as a single enantiomer. Efforts to reduce the catalyst loading show that use of 2.5 mol% of the sulfolefin **1** {1.25 mol% of $[Rh(C_2H_4)_2Cl]_2$}, in the presence of SDS afforded the product with moderate yield (68%) and moderate enantioselectivity (Table 1, entry 4).

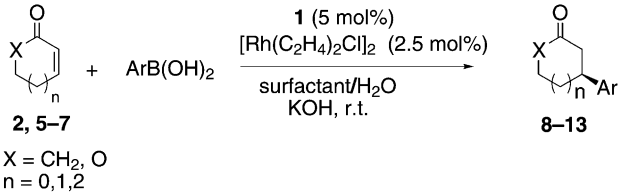
Interestingly enough, in PTS/water solution, lowering the ligand concentration to 1.25 mol% {0.65 mol% of $[Rh(C_2H_4)_2Cl]_2$} still affords the product with acceptable yield (72%) and an interesting 94% *ee* (Table 1, entry 9). It is worthy of mention that under the best conditions, the Rh(I) catalyst derived from (*S*)-BINAP (5 mol%) gave product **4** with very low yield (11%) and a disappointing 22% *ee* (Table 1, entry 10), highlighting the efficiency of sulfolefin ligand **1**.

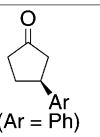
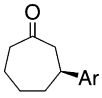
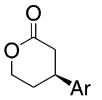
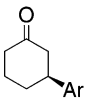
Based on these results, we can conclude that both neutral and anionic amphiphiles are able to form an adequate milieu for the reaction to take place with complete enantioselectivity and quantitative yield. In this sense, a TEM analyses of the reaction media showed the formation of spherical nanomicelles both in the case of SDS/water and in the case of PTS/water (see the Supporting Information for TEM images), which support the hypothesis that the reactions are taking place within the micelles.

Next, and in order to determine the reaction scope, we conducted a study using different cyclic ketones and different boronic acids in the presence of either SDS or PTS as surfactants (Table 2).

Excluding the case of cyclic lactone **7** (entries 5 and 6), where the product **10***S* was obtained as a single enantiomer in SDS and PTS micellar media, the later was better both in terms of reactivity and enantioselectivity (compare entry 1 with entry 2, entry 3 with entry 4, and entry 5 with entry 6). Indeed the product **8***S*, resulting from the addition of phenyl boronic acid on cyclopentenone **5** (entry 2), and the product **9***S*, deriving from the addition of phenylboronic acid on cycloheptenone **6** (entry 4), were obtained as single enantiomers in quantitative yields when PTS was used as amphiphile. The same trend was observed in the case of addition of other arylboronic acids to cyclohexenone, where SDS was less efficient than PTS (compare entry 7 with entry 8, entry 9 with entry 10, and entry 11 with entry 12). Additionally, at this point of our research we have found that the addition of NaCl to the PTS solution ameliorates substantially the results.[12] Using the optimal conditions (PTS with 3 M NaCl), various phenylboronic acids with different steric and electronic characters were added to cyclohexenone affording the corresponding adducts **11**–**13** with excellent yields and enantioselectivities (entries 8, 10, and 12).

**Table 2.** Substrate scope of the Rh-catalyzed 1,4-addition of boronic acids to cycloalkenones in water/surfactant media.[a]



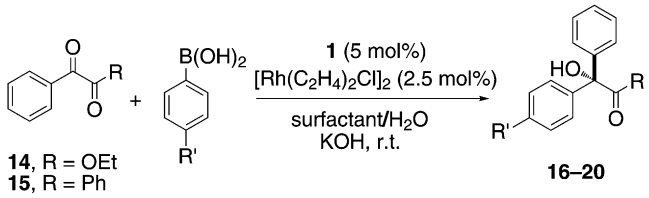

| Entry | Enone | Product | Surfactant | Yield[b] [%] | *ee*[c] [%] |
|---|---|---|---|---|---|
| 1 |  |  | SDS | 87 | 76 |
| 2 | **5** | **8** (Ar = Ph) | PTS | 100 | 99 |
| 3 |  |  | SDS | 82 | 79 |
| 4 | **6** | **9** (Ar = Ph) | PTS | 100 | 99 |
| 5 |  |  | SDS | 85 | 99 |
| 6 | **7** | **10** (Ar = Ph) | PTS | 100 | 99 |
| 7 |  |  | SDS | 85 | 76 |
| 8 | **2** | **11** (Ar = 4-MeC$_6$H$_4$) | PTS[d] | 94 | 98 |
| 9 |  |  | SDS | 57 | 90 |
| 10 | **2** | **12** (Ar = 3-MeC$_6$H$_4$) | PTS[d] | 84 | 94 |
| 11 |  |  | SDS | 99 | 92 |
| 12 | **2** | **13** (Ar = 2-MeOC$_6$H$_4$) | PTS[d] | 99 | 94 |

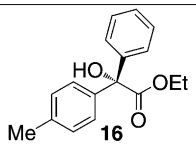
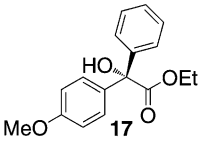
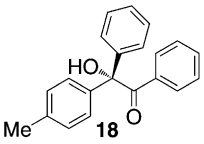
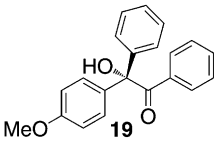
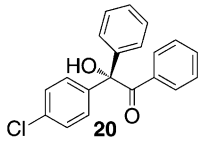
[a] All reactions were conducted using 5 mol% of the ligand together with 2.5 mol% of $[Rh(C_2H_4)_2Cl]_2$ in water at room temperature, in the presence of SDS or PTS.
[b] Chromatographically isolated product.
[c] Determined by chiral stationary phase HPLC.
[d] The reaction was conducted in 3 M NaCl, PTS/water.

Inspired by the success obtained in the 1,4-addition of boronic acids to cyclic alkenones, we decided to see whether this approach could be extended to the more challenging 1,2-addition to α-keto-carbonyl compounds. Tetrasubstituted carbon stereocenters in general, and chiral β-hydroxy carbonyl compounds in particular, are commonly found in numerous classes of natural products and pharmaceutical intermediates.[13] Although a number of methods have been developed to selectively access this versatile structural motif, the preparation of compounds containing these centers with high enantioselectivity is fairly limited.[14] Additionally, and as far as we know, there is no aque-

**Table 3.** Substrate scope of the Rh-catalyzed 1,2-addition of boronic acids to α-keto carbonyl compounds in water/surfactant media.[a]




| Entry | Enone | Surfactant | Yield[b] [%] | *ee*[c] [%] |
|---|---|---|---|---|
| 1 |  | SDS | 46 | 76 |
| 2 | | PTS | 63 | 86 |
| 3 |  | SDS | 76 | 86 |
| 4 | | PTS | 72 | 92 |
| 5 |  | PTS | 87 | 99 |
| 6 |  | SDS | 83 | 92 |
| 7 | | PTS | 73 | 96 |
| 8 |  | SDS | 59 | 98 |
| 9 | | PTS | 56 | 98 |

[a] All reactions were conducted using 5 mol% of the ligand together with 2.5 mol% of $[Rh(C_2H_4)_2Cl]_2$ in water at room temperature, in the presence of SDS or 3 M NaCl/PTS.
[b] Chromatographically isolated product.
[c] Determined by chiral stationary phase HPLC.

ous catalytic approach for the enantioselective preparation of these important intermediates, making this an excellent goal to test the effectiveness of our method. We firstly assayed our system, in the addition of arylboronic acids to α-keto esters for the asymmetric synthesis of α-hydroxy esters and the results are summarized in Table 3. Using ethyl phenylglyoxylate **14** as electrophilic partner, we were pleased to find that the additions take place at room temperature affording the desired products in moderate to good enantioselectivities depending on the surfactant used (entries 1–4). In this case, the use of PTS in the presence of 3 M NaCl also afforded the products of addition with better enantioselectivity than obtained with SDS. Using the optimized conditions, products **16** (entry 2) and **17** (entry 4), derived from the addition of *p*-tolyl- and *p*-methoxyphenylboronic acids, were obtained with 86% and with 92% *ee* respectively. Next, we turned our attention to the addition of boronic acids to the more challenging α-diketone substrates in order to obtain tertiary α-hydroxy ketones (entries 5–9). Pleasingly, the addition of *p*-tolylboronic acid to benzil **15** afforded the tertiary hydroxy ketone **18** with the *S* absolute configuration in 87% yield and 99% *ee* (entry 5). Addition of other boronic acids such as *p*-methoxy- and *p*-chlorophenylboronic acids led to the formation of the corresponding tertiary alcohols **19** (entry 7) and **20** (entry 9) with moderate to good yields and with excellent enantioselectivities (96 and 98% *ee*, respectively).

In summary, we have developed a green,[15] and efficient micellar catalytic approach for the 1,4-addition of arylboronic acids to cyclic ketones which permits the synthesis of chiral ketones in high yields and high enantioselectivities. Noteworthy, applying the same catalytic system we have also developed the first addition of boronic acids to the more challenging α-keto carbonyl compounds in water, affording tertiary carbinols with high yields and high enantioselectivities. The reactions take place under very mild conditions using water as solvent and at room temperature, in contrast to the conditions generally required for such transformations in organic solvents. Additionally, the processes use the robust sulfolefin ligand **1** with a sulfinyl sulfur as sole chiral center as catalyst precursor, which can be obtained on a multigram scale and in one step from a sugar-derived sulfinate ester.[9,16] The applications of the present system in other organic and metal-promoted enantioselective processes, are being actively investigated in our laboratories, and will be reported in due course.

## Experimental Section

### Typical Procedure for the Rhodium-Catalyzed 1,4- and 1,2-Addition of Boronic Acids to Activated Ketones

A Schlenk tube, equipped with a magnetic stirring bar, was charged with $[\{Rh(CH_2CH_2)_2Cl\}_2]$ (6.0 mg, 5 mol%), sulfolefin **1** (7.1 mg, 2.5 mol%) and water (1.4 mL) containing the surfactant at or over its critical micellar concentration was added and the mixture was stirred for 15 min at room temperature. Then, the arylboronic acid (1.2 mmol, 2 equiv.), the α,β-unsaturated substrate or dicarbonyl substrate (0.6 mmol, 1 equiv.) and 2.5 M KOH aqueous solution were added. The reaction mixture was stirred for 24 h, and then

extracted with AcOEt (2 mL). The solvent was removed under vacuum to afford the crude product which was subsequently purified by flash chromatography on silica gel.

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