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Enantioselective Kinetic Resolution/Desymmetrization of *Para*-Quinols: A Case Study in Boronic-Acid-Directed Phosphoric Acid Catalysis

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Abstract

A chiral phosphoric acid-catalyzed kinetic resolution and desymmetrization of *para*-quinols operating via oxa-Michael addition was developed and subsequently subjected to mechanistic study. Good to excellent *s*-factors/enantioselectivities were obtained over a broad range of substrates. Kinetic studies were performed, and DFT studies favor a hydrogen bonding activation mode. The mechanistic studies provide insights to previously reported chiral anion phase transfer reactions involving chiral phosphate catalysts in combination with boronic acids.

Keywords

asymmetric catalysis; chiral phosphoric acid; reaction mechanisms; kinetics; directed reactivity; oxa-Michael addition

Chiral Anion Phase Transfer (CAPT) Catalysis has proven to be a powerful strategy for achieving asymmetric induction.[1,2] A central hypothesis in this catalytic manifold is the use of suitable H-bonding directing groups which have empirically proven crucial to obtain high selectivity in these transformations.[1h] Along these lines, our group recently reported the fluorination of allylic alcohols via the in situ generation of boronic acid-derived directing groups (Figure 1A).[3] This work was in turn inspired by a 2008 report from Falck and co-workers, in which a formal enantioselective oxa-Michael addition of hydroxide was achieved by employing a bifunctional organo-catalyst, affording cyclization of a boronic acid monoester intermediate (Figure 1B).[4]

In our own report,[3] we hypothesized that the boronic acid forms an intermediate hemiester which serves as the corresponding directing group. Because the CAPT fluorination chemistry requires the use of heterogeneous conditions, support for this hypothesis derived from the observation of hemiester formation under conditions lacking the insoluble

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components, with no test for kinetic relevance of the intermediate possible.[5] In order to gain more mechanistic insight, we sought a homogeneous model reaction to enable kinetic analysis. By examining oxa-Michael addition rather than fluorination, the insoluble reagent could be excluded. As such, we developed a chiral phosphoric acid-catalyzed kinetic resolution /desymmetrization of quinol derivatives (Figure 1C).[6–9] The homogeneity of the reaction mixtures allowed us to examine the kinetic relevance of alcohol boronic acid condensation. These studies have enabled the gathering of some new insights into the nature of reactions involving boronic acid-directed chiral phosphoric acid catalysis.

We began our investigation by examining the reaction of quinol *rac*-**1a** with phenylboronic acid (Table 1). Routine optimization identified (*R*)-TCYP as the optimal catalyst (Table 1, entry 6) (replacing (*R*)-TCYP with (*R*)-TRIP gives *s*=21)[10] and toluene as the optimal solvent for kinetic resolution.[10,11] Various arylboronic acids were examined, culminating in the identification of 1-naphthylboronic acid as the optimal boron reagent, affording a significant increase in selectivity (*s*=23). A key finding was the discovery that implementation of 1-naphthyl boroxine in place of its boronic acid analogue decreased the required reaction time and afforded an improved *s* factor of 27 in the presence of only 2 mol % catalyst at room temperature for 24 h. This trend of increased enantioselectivity and increased rate held across a variety of boronic acid/boroxine pairs, including phenylboroxine and m-tolylboroxine (Table 1).

With optimized conditions in hand, we next explored the scope of the kinetic resolution (Table 2). Various α-substitutents (R^1), β-substituents (R^2), and γ-substituents were tolerated with varying levels of selectivity, including various alkyl, unsaturated, and heteroaromatic groups. The protocol was also found to apply well in the desymmetrization of prochiral p-quinols (Table 2). Two representative substrates were examined under conditions similar to the optimized kinetic resolution protocol. Gratifyingly, the reaction proceeded smoothly to yield the corresponding diols in 88% and 85% ee, respectively.

As noted above, the homogeneity of these reactions enabled a closer examination of the mechanism. Initially, we were drawn to the observation that the boroxine hydration state affects both rate of the reaction and its enantioselectivity, suggesting that formation of boronic acid esters of the substrate may be relevant. We began our investigation by examining association between the boroxine and the substrate (**4a**) by ^{1}H-NMR spectroscopy.[12] However, no discrete observable new species were formed, and no detectable changes in the spectra were found as the concentration of each species was varied.

This lack of observable association between the substrate and boroxine was surprising given our previous observation of quantitative condensation of boroxine with primary allylic alcohols.[5] In order to gain further insight, a series of kinetic experiments were performed. Unfortunately, kinetics conducted under typical reaction stoichiometries were found at extended reaction times to deviate from simple integer-order behavior.[10,13] To simplify the analysis, the method of initial rates was employed, along with flooding conditions in one or more substrates. Under flooding in boroxine, an order in (*R*)-TRIP deviating from linearity was observed, with reasonable fits obtained to either ½ order or saturation kinetics (Figure

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2A). In order to distinguish these possibilities, the diffusion constants of both (*R*)-TRIP and the O-methylated analogue were measured by DOSY (diffusion ordered spectroscopy), affording nearly indistinguishable diffusion constants.[10] These experiments indicated that the phosphoric acid catalyst is likely monomeric under the reaction conditions, excluding the possibility of ½ order.[14]

For the remaining components, under the pseudo-zero order conditions, first-order dependence on the substrate concentration (Figure 2B) was observed. The boroxine exhibited kinetic behaviour deviating from first order which could be modelled as first-order dependence on the concentration of monomeric arylboron.[10] Taken together, this kinetic behavior indicates a preequilibrium to form boronic acid ester before the involvement of chiral phosphoric acid.

The ^{1}H-NMR spectroscopy of the mixtures of TRIP and boroxine **3e** reveals a concentration dependent shift in the resonances of the phosphoric acid, with partial decoalesence of the signals achieved upon cooling to 217 K.[10,16,17] A DFT study at the B3LYP-D3/def2-TZVPP/SMD(toluene)//B3LYP/6–31G(d) level of theory suggests that the most likely candidate for the associated complex is the mixed phosphoric/boronic anhydride (vide infra).[10] This association complex is potentially kinetically relevant.[15]

Finally, KIE experiments were conducted using **4a** labelled at the vinylic C H bonds. A separate pot experiment showed a clear inverse secondary KIE (Scheme 1), indicating that oxa-Michael addition is the rate-limiting step, either concerted with catalyst association or as a discrete second step following reversible catalyst association.[10,18,19] Initial Michael addition followed by esterification is likely inconsistent with the exclusively observed syn diastereoselectivity and the observation that methylation of the hydroxyl group of **4a** shuts down reactivity altogether, with no conversion observed over 72 h.[10]

As a whole, these data are consistent with a mechanism involving two roles for the boroxine: productive association with the substrate, and delete-rious association with the catalyst (though we cannot conclusively rule out the possibility that the mixed phosphoric boronic anhydride is on-cycle).

A DFT study conducted at the B3LYP-D3/def2-TZVPP/SMD(toluene)/ /B3LYP/6-31G(d) level of theory located four transition structures for the TRIP-catalyzed reaction. Importantly, formation of the observed major enantiomer is correctly predicted. Our proposed mechanism for the overall reaction, considering all of the collected data, is shown in Scheme 2. The lowest-energy computed transition state for oxa-Michael addition is shown, as well as the computationally suggested structure for the mixed anhydride. Based on this mechanism, we propose that the boronic acid/boroxine effect on enantioselectivity arises from a background reaction catalyzed by the boronic acid (further exacerbated by catalyst inhibition by boron), whereas the rate enhancement is a function of the equilibrium for substrate esterification.

In conclusion, a chiral phosphoric acid-catalyzed kinetic resolution (or desymmetrization) of *para*-quinols was developed. This method provides the access to enantioenriched *para*-quinols and corresponding diols. Kinetic experiments are in line with the canon of indirect

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experimental evidence we have garnered over the course of our studies on the role of H-bonding in CAPT catalysis – namely, that appropriately situated H-bonding directing groups, including *in situ* formed boronic acid esters, orient the chiral phosphate, enabling high enantiocontrol.[1h,20] Further-more, preliminary evidence supporting formation of mixed anhydrides between boronic and phosphoric acids was garnered, suggesting a potentially under-appreciated role for these species. We anticipate that new asymmetric transformations will be enabled by the knowledge garnered herein concerning the dynamics of this potent reagent pair.

Experimental Section

For details of instruments used and the general experimental procedures, see the Supporting Information.

General Procedure of Kinetic Resolution of *Para*-Quinols

The *rac*-**1** (0.20 mmol), 1-naphthylboroxine (0.04 mmol) and (*R*)-TCYP (2.0 mol%) were added to a vial containing a stir bar. The vial was twined with Teflon tape, toluene (2.0 ml) was added using a syringe, and the vial was fitted with a cap. The reaction mixture was stirred at room temperature for the indicated time. To the mixture was added MeOH/H_2O (1/1,2.0 mL), and then KHF_2 (10 eqiv.) was added and the mixture was stirred vigorously for 5–30 min until the boronic ester was removed as evident from TLC analysis. The aqueous phase was separated and collected, and the organic phase was evaporated and then re-dissolved in n-hexanes. The mixture was then washed MeOH/H_2O (1/1) twice and the aqueous phase was combined. The combined aqueous layers were then evaporated and purified by column chromatography carefully over silica gel affording the desired chiral p-quinols and diols. The products were further purified by preparative TLC as necessary.

Crystallographic Data for (*S*)-1g

CCDC-1950552 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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[12]. *m*-tolylboroxine (**3e**) and (*R*)-TRIP were employed in place of the 1-naphthyl analogue (**3f**) and (*R*)-TCYP to maintain homogeneity across a wider range of concentrations and temperatures.

[13]. We are unable to conclusively distinguish between product inhibition and catalyst deactivation due to our inability to isolate the product boronic ester without contaminating diol and/or boronic acid. In either case, initial rate kinetics obviate any confounding rate influence.

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[18]. In principle, a post-rate-determining equilibration between parent and deuterated substrate prior to the enantiodetermining step is possible, but the observation of a separate-pot KIE indicates that C O bond formation occurs before the turnover-limiting step. For a discussion on KIE interpretation, see:Simmons EM, Hartwig JF, Angew. Chem. Int. Ed 2012, 51, 3066–3072;Angew. Chem 2012, 124, 3120–3126.

[19]. These two possibilities are kinetically indistinguishable. Another possibility involves reversible oxa-Michael addition and rate-determining enolate protonation. See the Supporting information for details.

[20]. Indeed, in the limit of protonation of the carbonyl, the quinone electrophile can be seen as directly analogous to previous examples of CAPT catalysis.

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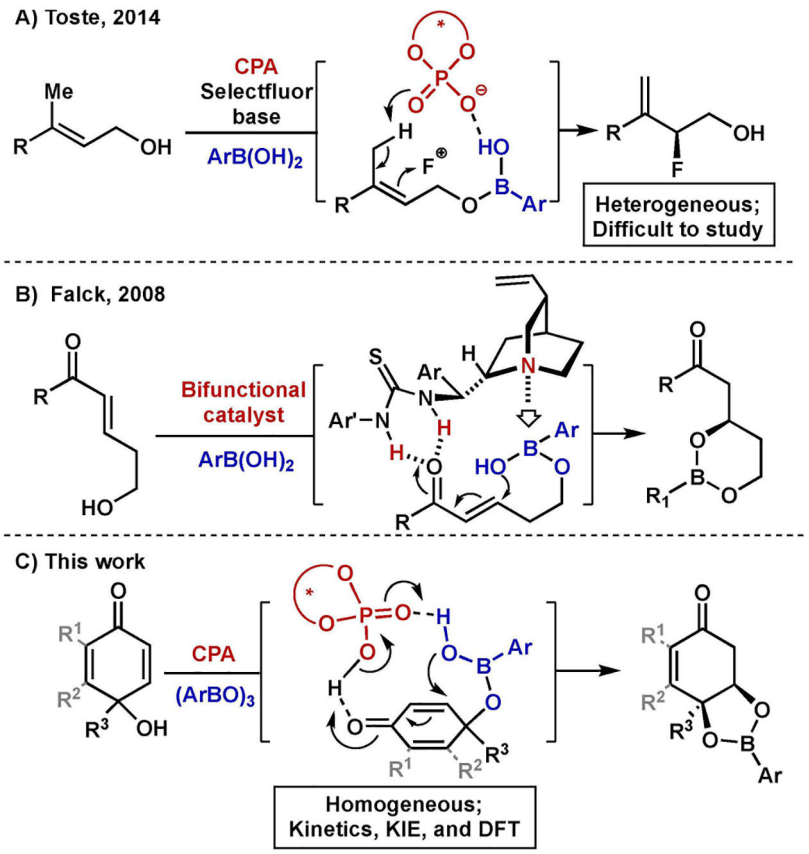

Figure 1.

A) Boronic acid monoester as an *in stiu* directing group for CAPT enantioselective fluorination of allylic alcohols (CPA=chiral phosphoric acid); B) Oxa-Michael addition of boronic acid monoester promoted by push/pull-type catalyst; C) Kinetic resolution of *para*-quinols via complexation of *in situ* directing group and phosphate.

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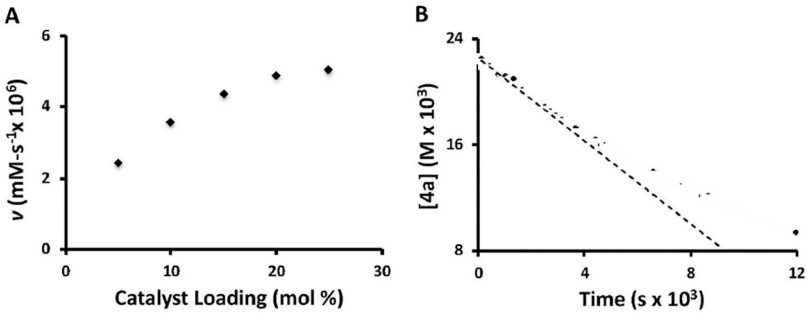

Figure 2. A)
Initial rate-*(R)*-TRIP catalyst loading plot; **B)** Reaction plot of [**4a]** under saturation of **3e**.

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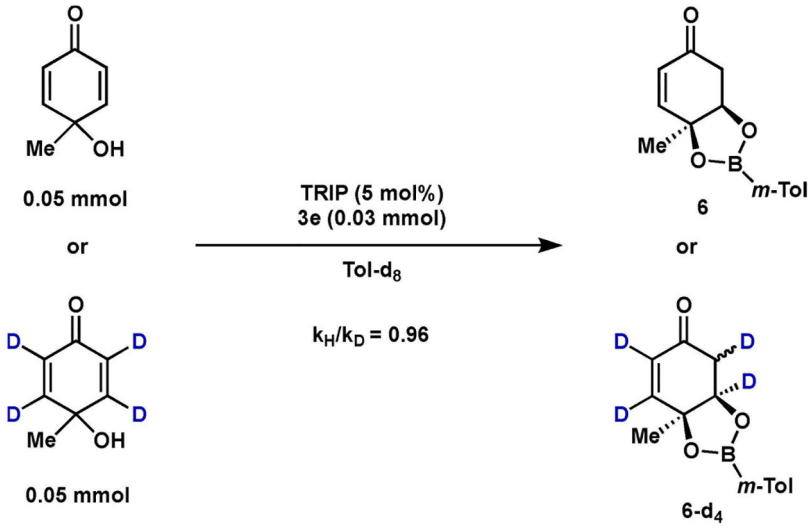

Scheme 1.
Separate-pot kinetic isotope effect.

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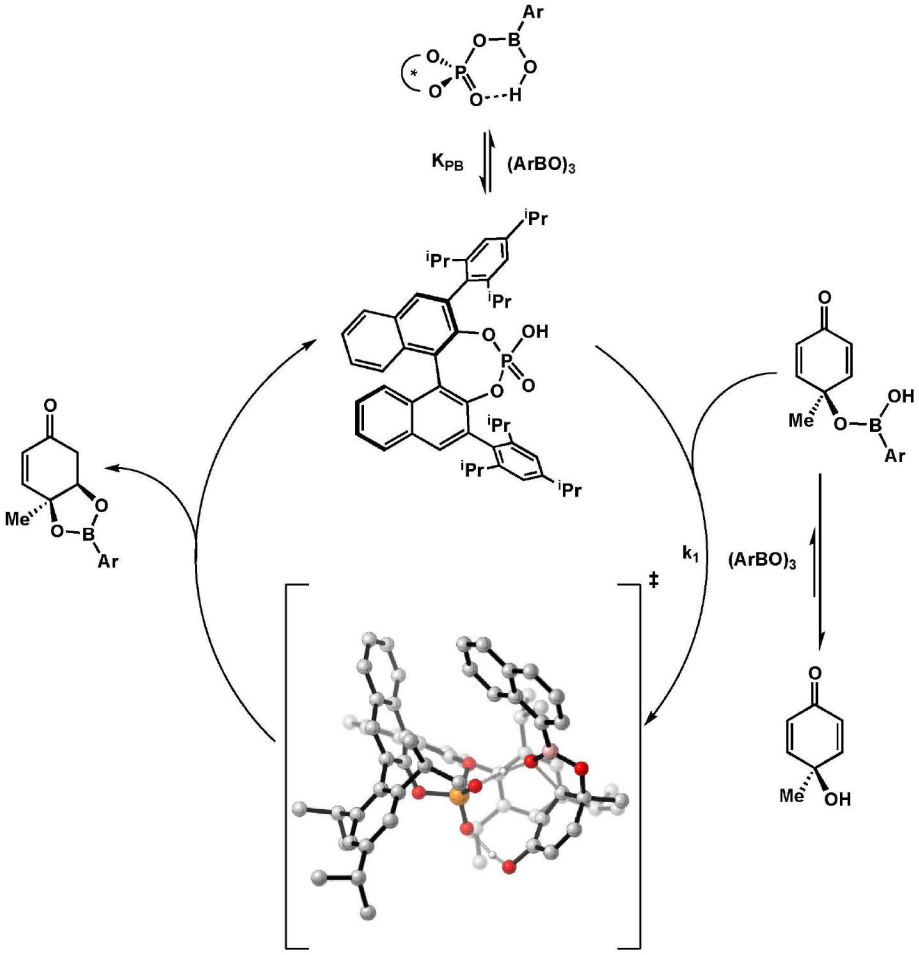

Scheme 2.
Proposed mechanism with calculated transition state.

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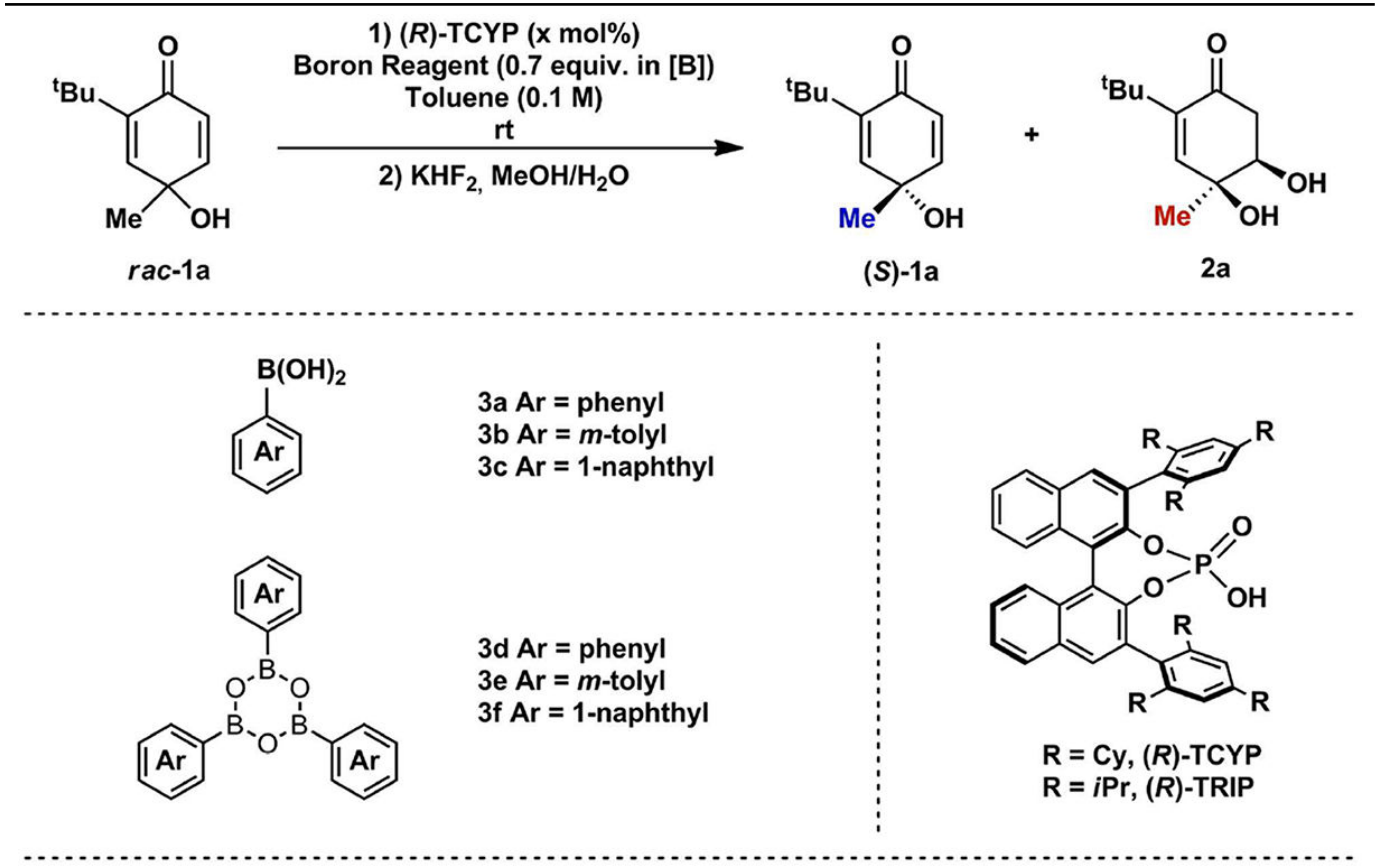
Table 1.

Key Influence of Boron Reagent Hydration State on Reaction Selectivity.[a]



Entry	Boron reagent	(*R*)-TCYP loading	Time (h)	Conversion (%)[b]	(S)-1a ee_1 (%)[c]	2a ee_2 (%)[c]	s
1	**3a**	5.0 mol%	48	58	71	54	6
2	**3b**	5.0 mol%	48	64	86	54	7
3	**3c**	5.0 mol%	48	54	90	78	23
4	**3d**	2.0 mol%	24	51	70	73	10

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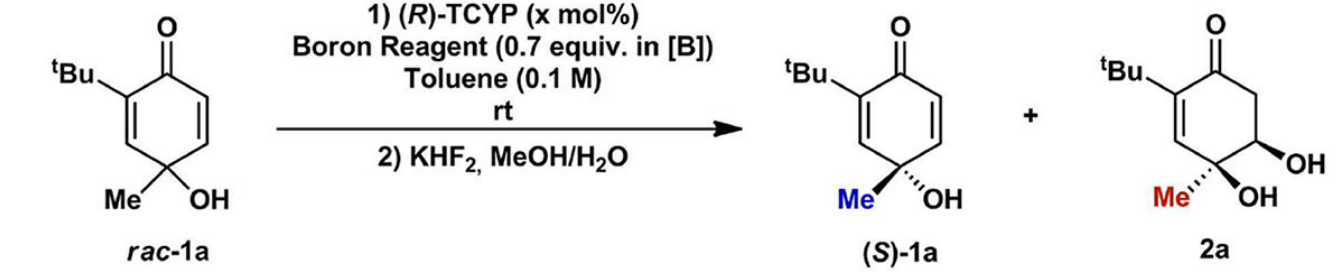

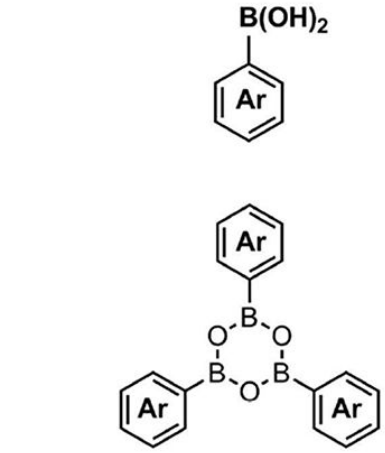

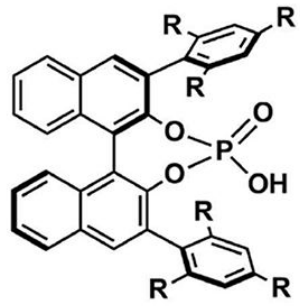

Entry	Boron reagent	(*R*)-TCYP loading	Time (h)	Conversion (%)[b]	(S)-1a ee_1 (%)[c]	2a ee_2 (%)[c]	s
5	**3e**	2.0 mol%	24	45	62	78	14
6	**3f**	2.0 mol%	24	53	90	84	27

[a] Reaction conditions: ***rac*-1a** (0.2 mmol), (*R*)-TCYP (2 or 5 mol%), Boronic acid or Boroxine (0.7 equiv.), solvent (2.0 mL), rt for 24 or 48 h;

[b] Determined by ^{1}H-NMR using internal standard;

[c] Determined by chiral phase HPLC; Selectivity factor (***s***) was calculated according $\ln[(1-C)(1\ ee_{SM})/1-C](1+ee_{SM})]$.[10]

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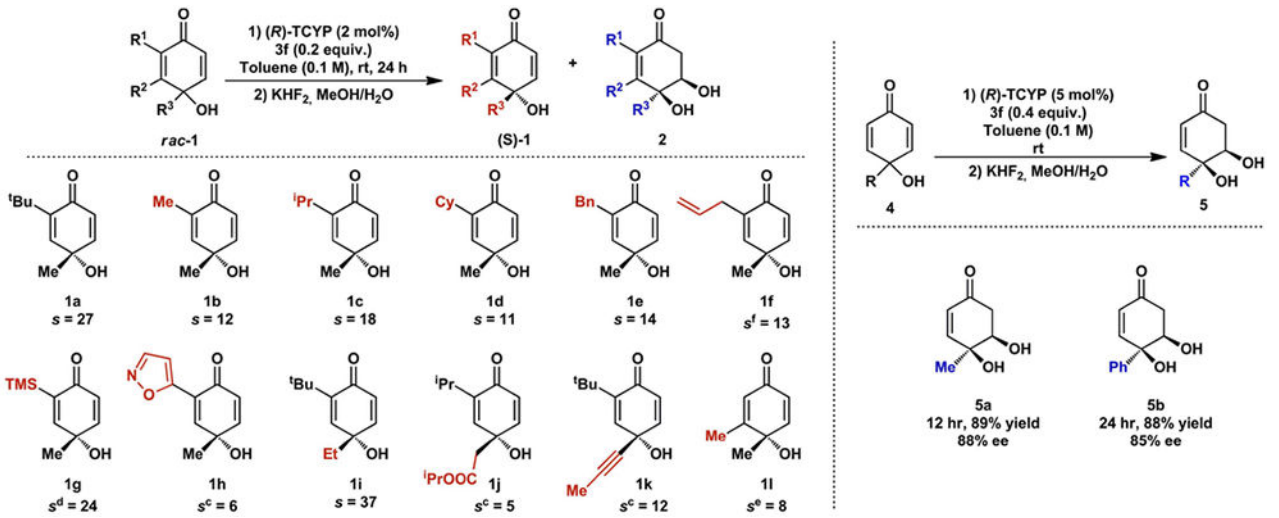
Table 2.

Scope for Kinetic Resolution and Desymmetrization.[a,b]



[a]Isolated yield. Absolute configuration assigned by analogy to that of **1g**, which was determined to be (**S**) by single-crystal X-ray diffraction.

[b]Selectivity factor (**s**) was calculated according ln[(1-C)(1 ee_{SM})/1-C](1+ee_{SM})]. For isolated yields of kinetic resolution, see Supporting Information.

[c]5.0 mol% of catalyst was used.

[d]Reaction time variation: 12 h.

[e]Reaction time variation: 18 h.

[f]Reaction time variation: 20 h.