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Electron-Withdrawing, Biphenyl-2,2′-diol-Based Compounds for Asymmetric Catalysis

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Facile synthetic routes to a chiral chloro-substituted biphenyl-2,2′-diyl hydrogen phosphate and a chiral *O*,*O*-biphenyl-2,2′-diyl phosphoramidothioate are described. The performance of these compounds as catalysts for the hydrophosphonylation of imines and the Friedel–Crafts alkylation of indole was investigated. In the latter reaction, the chloro-substituted phosphoric acid derivative was found to rival the best Brønsted acid catalysts reported to date.

Introduction

The Brønsted acid catalyzed activation of carbonyl groups and imines to nucleophilic attack is one of the most ubiquitous synthetic methods used in organic chemistry; however, the use of chiral Brønsted acids to catalyze asymmetric reactions has only recently been actively investigated.[1] The application of relatively strong protic acids, such as chiral phosphoric acid derivatives, is a particularly recent development, with the majority of reports occurring within the past five years.[1]

Most chiral phosphoric acids employed to date have been binaphthol derivatives.[1–3] From this extensive body of work, two design features have emerged that effectively promote both high catalyst activity and asymmetric induction: the incorporation of bulky 3,3′-disubstitution on the binaphthol rings and the presence of electron-withdrawing substituents to lower the pK_a of the phosphoric acid derivative by inductive effects. Phosphoric acid derivatives **1b**,[4] **1c**[5] **1d**,[6] and **2**[7] (Figure 1) are representative examples of catalysts that contain these design elements. Catalysts that lack one or both of these motifs, such as **1a**, have generally been found to afford poor results.[1,4]

To investigate an alternative catalyst framework, we became intrigued with the chiral biphenyl-2,2′-diyl hydrogen phosphate **3**, originally reported by Schrock and Hoveyda as a ligand precursor in the preparation of enantioselective olefin-metathesis catalysts.[8] Acid **3** retains the desired design element of bulky 3,3′-disubstitution in the form of *tert*-butyl groups, and the parent diol possesses atropomeric chirality. Despite these desirable attributes, acid **3** lacks the electron-withdrawing substitution known to be beneficial to Brønsted acid catalyzed asymmetric catalysis. Akiyama and co-workers have previously reported the use of 3,3′-nitrophenyl-substituted biphenyl-2,2′-diyl hydrogen phosphates to effect enantioselective Mannich reactions with good yields and enantioselectivities.[3a] Seeking to investigate an alternative substitution pattern, we sought to prepare catalyst family **4** (Figure 2), where X represents electron-withdrawing moieties placed at the 5,5′-positions.

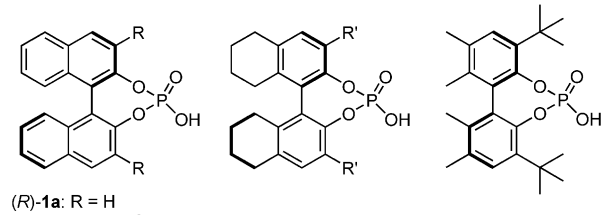

Figure 1. Examples of phosphoric acid derived catalysts.

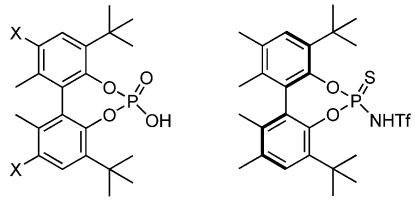

Figure 2. Target catalysts for investigation.

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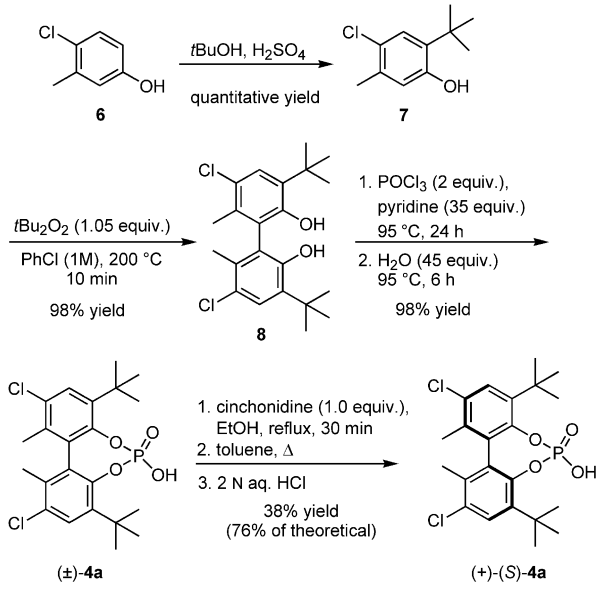
Herein, we report a facile, inexpensive synthetic route to the preparation of (*S*)-**4a**, as well as the preparation of the related biphenyl-based phosphoramidothioate catalyst (*R*)-**5**. Chiral, binaphthol-derived phosphoramidothioate catalysts were recently reported by Yamamoto and co-workers to display enhanced reaction rates and greater asymmetric induction relative to their corresponding hydrogen phosphates.[9] The relative performance of (*S*)-**4a** and (*R*)-**5** in asymmetric reactions, namely the hydrophosphonylation of imines[5,10,11] and the Friedel–Crafts alkylation of indole,[7,12] is discussed.

Results and Discussion

Prior to this article, only the racemic parent diol of **4c** had previously been reported.[13] For the others, we envisioned starting with commercially available phenols, such as **6** (Scheme 1), and generating the requisite diols by acid-catalyzed *tert*-butylation, followed by oxidative coupling to form the diol precursors to **4a**, **4b**, and **4d**, respectively. The diols could then be phosphorylated and resolved to generate the resulting chiral acid.

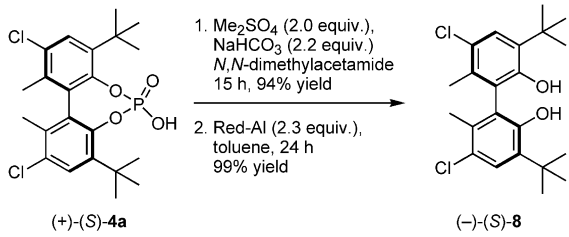


Scheme 1. Optimized route to (+)-(*S*)-**4a**.

After extensive investigation, only the preparation of **4a** proved viable according to our proposed resolution route. We found the four-step synthesis to access the diol of **4c** too low-yielding to be practicable. In the case of **4d**, the oxidative coupling afforded a negligible yield, and attempts to nitrate more readily prepared precursors were unsuccessful. In addition, we observed diol phosphorylation to be highly sensitive to the electronics of the starting phenol. Several conditions were investigated (e.g. $POCl_3$/pyridine, $POCl_3$/NaH),[2b,8] but only diol **8** was found to afford the desired product in high yield (98% yield; Scheme 1). By comparison, in the case of **4b**, only trace amounts of the desired phosphoric acid derivative were observed by mass spectrometry or ^{31}P NMR spectroscopy after heating for 24 h and aqueous workup; the starting diol was isolated with 80% recovery.

Scheme 1 shows the optimized synthetic route to (*S*)-(+)-**4a**. The *tert*-butylation of **6** proceeded smoothly to afford **7** in quantitative yield. Phenol oxidative coupling proved challenging, and numerous experimental conditions were investigated to boost product yield.[14] Ultimately, the reaction of **7** in the presence of *tert*-butyl peroxide (1.5 equiv.) in refluxing chlorobenzene (0.04 M) afforded the most consistent results; diol **8** was isolated in 40% yield. This reaction was further optimized, such that we were able to obtain higher yields (98%, following flash chromatography) using shorter reaction times (10 min) and less peroxide reagent (1.05 equiv.) by heating a solution of **7** (1 M in chlorobenzene) in a microwave reactor to form **8**.[15]

After thoroughly investigating various amine base/solvent combinations, we found optimal resolution conditions in the crystallization of the cinchonidine salt of **4a** from toluene. Subsequent decomplexation of the acid with 2 N aqueous HCl afforded analytically pure (*S*)-**4a**. Including the resolution, the preparative route to this catalyst employs five synthetic steps in 36% overall yield (73% of theoretical) and requires only a single chromatographic purification step. A suitably refined crystal structure of (–)-(*S*)-**8** in hexanes was later obtained after the methylation and reduction of (*S*)-**4a** (93% overall yield, Scheme 2),[16] providing stereochemical confirmation as well as efficient access to chiral **8** for synthetic and materials science applications.



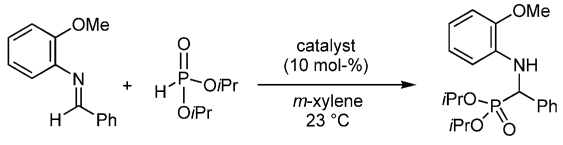
Scheme 2. Preparation of chiral diol **8**.

In addition to (*S*)-**4a**, we were able to prepare and characterize catalyst (*R*)-**5** by adapting a synthetic procedure first reported by Yamamoto and co-workers.[9] Starting from the commercially available (*R*)-diol and proceeding via a phosphorochloridothioate intermediate, (*R*)-**5** was isolated in 45% overall yield.[16]

To investigate the performance of (*S*)-**4a** and (*R*)-**5** relative to known catalysts, we first chose to screen them in the hydrophosphonylation of *N*-benzylidene-2-methoxyaniline (**9**, Table 1). In our studies, we found **9** to produce better yields and more consistent results than the more commonly used *p*-methoxyphenyl analogue with all catalysts screened. While modest, these results do highlight the better performance of (*S*)-**4a** relative to the other catalysts investigated. In addition, the positive impact of chloro versus methyl substitution on both yield and enantioselectivity (Entries 1 and 3) and the positive impact of bulky 3,3′-disubstitution (relative to Entry 5) is clearly apparent. The reaction yield

(10%) and asymmetric induction (13% *ee*) of (*R*)-**5** was found to match those of the corresponding phosphoric acid derivative (*R*)-**3**, although it should be noted that the configuration of the major isomer was inverted to favor the formation of the (*S*) enantiomer. The reactions for this study were allowed to proceed for 24 h before workup and analysis. In the case of (*S*)-**4a**, we found that the reaction did continue towards completion with additional reaction time, displaying little or no loss in enantioselectivity (Entry 2).

Table 1. Asymmetric hydrophosphonylation of **9**.



9 **10**

Entry	Catalyst	*t* [h]	Yield [%][a]	*ee*[%][b]	Configuration[c]
1	(*S*)-**4a**	24	45	38	(*S*)
2	(*S*)-**4a**	72	89	37	(*S*)
3	(*R*)-**3**	24	24	13	(*R*)
4	(*R*)-**5**	24	10	13	(*S*)
5	(*R*)-**1a**	24	10	0	–
6	(*R*)-**1b**	24	ca. 2[d]	–	–

[a] Isolated yield. [b] Determined by chiral HPLC on an OD-H column: 3% isopropyl alcohol in hexanes, 0.5 mL/min, λ = 254 nm; t_R = 17.7 and 21.0 min. [c] Absolute configuration of the major product isomer was determined by correlation of the optical rotation of deprotected **10** to that reported in ref.[17] [d] Determined by ^{1}H NMR spectroscopy.

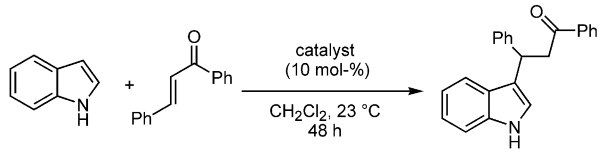
To further investigate the performance of (*S*)-**4a** and (*R*)-**5** relative to known catalysts, we next tested its ability to promote the Friedel–Crafts addition of indole to chalcone (Table 2). While several asymmetric organocatalytic examples have been developed,[11] this remains a challenging reaction for strong Brønsted acid catalysts. The best results to date using a phosphoric acid catalyst were reported by Tang and co-workers in 2008 after an extensive catalyst screen where phosphoric acid derivative **2** was found to catalyze the addition of indole to chalcone in 56% *ee*.[7] It should be noted that a slightly higher *ee* (58%) has been reported for this reaction by using a D-camphor-based sulfonic acid.[18]

When (*S*)-**4a** (10 mol-%) was employed in this model Friedel–Crafts reaction, the product indole **11** was isolated in 85% yield and 60% *ee* after 48 h. A slightly higher yield (93%) was obtained after 72 h with no loss in enantioselectivity. We found that this product readily crystallized from diethyl ether/hexanes: product **11** could be isolated in 90% *ee* and 64% overall yield after a single recrystallization step. In contrast, phosphoramidothioate (*R*)-**5** proved to be a poor catalyst in this reaction: the (*R*) enantiomer of **11** was obtained in only 39% yield and 8% *ee* after 48 h.

Conclusions

We have developed efficient routes towards the preparation of two new catalysts. In the case of chiral phosphoric acid derivative (*S*)-**4a**, the development of a new microwave synthetic protocol proved instrumental in obtaining high yields of the precursor diol. Phosphoric acid derivative (*S*)-**4a** has demonstrated itself to be a competent catalyst. In the case of the Friedel–Crafts addition of indole to chalcone, we found **4a** to possess improved asymmetric induction relative to the best acid catalysts reported to date. Beyond its use as a catalyst, we have also shown that (*S*)-**4a** can be readily converted into the corresponding (*S*)-diol in high yield. We are currently investigating these compounds as ligands in additional asymmetric reactions as well as in materials science applications, such chiral dopants in nematic liquid crystals.

Table 2. Friedel–Crafts alkylation of indole.



11

Entry	Catalyst	Yield [%][a]	*ee*[%][b]	Configuration[c]
1	(*S*)-**4a**	85	60	(*S*)
2	(*R*)-**3**	83	48	(*R*)
3	(*R*)-**5**	39	8	(*R*)
4	(*R*)-**1a**	51	6	(*R*)
5	(*R*)-**1b**	27	26	(*R*)

[a] Isolated yield. [b] Determined by chiral HPLC on a Chiralpak AD-H column: 20% isopropyl alcohol in hexanes, 1.0 mL/min, λ = 254 nm; t_R = 11.5 and 13.1 min. [c] Absolute configuration of the major product isomer was determined by correlation to the literature value.[7]

Experimental Section

2-*tert*-Butyl-4-chloro-5-methylphenol (7): A flame-dried, 500-mL flask was charged with **6** (15.0 g, 105 mmol, 1.0 equiv.). CH_2Cl_2 (50 mL) was then added with stirring. To this mixture, *tert*-butyl alcohol (10.1 mL, 105 mmol, 1.0 equiv.) was added. The reaction mixture was cooled to 0 °C for 5 min, and 95% aq. H_2SO_4 (5.9 mL, 105 mmol, 1.0 equiv.) was added. The reaction mixture was allowed to warm to ambient temperature. After 48 h, additional *tert*-butyl alcohol (10.1 mL, 105 mmol) and 95% H_2SO_4 (5.9 mL, 105 mmol) were added. After an additional 48 h, saturated aq. $NaHCO_3$ was slowly added until gas evolution ceased (ca. 100 mL). The mixture was then partitioned with EtOAc (100 mL). The organic layer was washed with saturated aq. $NaHCO_3$ (2 × 75 mL) and brine (1 × 75 mL). The organic layer was then dried with anhydrous Na_2SO_4, filtered, and concentrated to afford analytically pure product as a yellow oil in quantitative isolated yield (20.8 g). TLC (silica): R_f = 0.54 (15% EtOAc in hexanes). IR (thin film): $\tilde{\nu}$ = 3554 (w), 2958 (m), 1499 (m), 1375 (s), 1184 (s), 1169 (s), 1096 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.19 (s, 1 H, Ar*H*), 6.54 (s, 1 H, Ar*H*), 4.69 (s, 1 H, O*H*), 2.25 (s, 3 H, CH_3), 1.36 [s, 9 H, (CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 152.4, 135.4, 134.1, 127.5, 125.4, 118.8, 34.3, 29.4, 19.3 ppm. HRMS (EI): *m*/*z* = 198.0819 [M]$^+$.

3,3′-Di-*tert*-butyl-5,5′-dichloro-6,6′-dimethylbiphenyl-2,2′-diol (8): In a 250-mL flask, **7** (5.0 g, 25 mmol, 1.0 equiv.) was dissolved in

chlorobenzene (200 mL). Di-*tert*-butyl peroxide (6.9 mL, 37.8 mmol, 1.5 equiv.) was then added with stirring. The flask was capped with a reflux condenser and heated to reflux for 2 h. The reaction mixture was then allowed to slowly cool to ambient temperature. The volatiles were removed, and the resulting residue was purified by silica gel chromatography (100% hexanes) to afford the desired product as a white solid in 40% isolated yield (3.95 g). Microwave procedure: In a 0.2–5 mL microwave reaction vial, 2-*tert*-butyl-4-chloro-5-methylphenol (431 mg, 2.17 mmol, 1.0 equiv.) was dissolved in chlorobenzene (1.5 mL). Di-*tert*-butyl peroxide (416 μL, 2.28 mmol, 1.05 equiv.) was then added. The vial was capped and placed in the microwave reactor. After thoroughly mixing for 5 min, the reaction mixture was heated to 200 °C for an additional 10 min. Upon cooling, the reaction mixture was directly purified by flash chromatography on silica gel to afford the desired product in 98% isolated yield (841 mg). TLC (silica): R_f = 0.26 (100% hexanes). IR (pellet): $\tilde{\nu}$ = 3505 (s), 2969 (m), 1371 (s), 1182 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.38 (s, 2 H, Ar*H*), 4.87 (s, 2 H, O*H*), 1.96 (s, 6 H, CH_3), 1.40 [s, 18 H, (CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 150.9, 136.1, 133.5, 128.7, 126.2, 121.3, 34.9, 29.3, 16.8 ppm. HRMS (FAB): *m*/*z* = 394.1456 $[M]^+$.

3,3′-Di-*tert*-butyl-5,5′-dichloro-6,6′-dimethylbiphenyl-2,2′-diyl Hydrogen Phosphate (4a): To a 2-neck, 50-mL flame-dried flask equipped with a reflux condenser **8** (2.5 g, 6.32 mmol, 1.0 equiv.) was added under N_2. Anhydrous pyridine (18 mL, 220 mmol, 35 equiv.) was added, followed by the dropwise addition of phosphorus oxychloride (1.2 mL, 12.7 mmol, 2.0 equiv.), with stirring. The reaction mixture was heated to 95 °C under N_2 for 24 h, and then allowed to cool to ambient temperature. Deionized water (5.2 mL, 288 mmol, 45 equiv.) was added, and the mixture was reheated to 95 °C for an additional 5.5 h. Upon cooling, the reaction mixture was transferred to a separatory funnel by using CH_2Cl_2 (100 mL); 1 N aq. HCl was then slowly added until the aqueous layer was acidified to pH = 1. The layers were separated, and the organic layer was washed with 1 N aq. HCl (3 × 60 mL), dried with anhydrous Na_2SO_4, and concentrated to afford analytically pure product as a white solid in 98% yield (2.9 g). TLC (silica): R_f = 0.14 (10% CH_3OH in CH_2Cl_2). IR (pellet): $\tilde{\nu}$ = 2967 (w), 1219 (m), 1200 (m), 1098 (m), 1021 (s), 922.7 (s) cm^{-1}. ^1H NMR (300 MHz, CD_2Cl_2, 20 °C): δ = 7.50 (s, 2 H, Ar*H*), 3.23 (br., 2 H, O*H*), 1.98 (s, 6 H, CH_3), 1.44 [s, 18 H, (CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, CD_3OD, 20 °C): δ = 149.6, 141.9, 134.9, 132.5, 131.0, 129.0, 36.2, 31.9, 17.8 ppm. ^{31}P NMR (121 MHz, CD_2Cl_2, 20 °C): δ = –1.41 ppm. HRMS (FAB): *m*/*z* = 457.1100 $[M + H]^+$.

(+)-(*S*)-3,3′-Di-*tert*-butyl-5,5′-dichloro-6,6′-dimethylbiphenyl-2,2′-diyl Hydrogen Phosphate [(*S*)-4a]: In a 1-L flask racemic **4a** (7.33 g, 16.03 mmol, 1.0 equiv.) and cinchonidine (4.81 g, 16.35 mmol, 1.02 equiv.) were heated in refluxing ethanol (170 mL) until fully dissolved (ca. 5 min). After stirring for an additional 15 min, the mixture was cooled, and the volatiles were removed to afford the corresponding salt. The flask was then heated to 120 °C in an oil bath, and toluene (ca. 350 mL) was slowly added until the mixture was entirely homogeneous. The mixture was then allowed to slowly cool to ambient temperature and stand for 48 h. The flask was subsequently cooled to 0 °C for an additional 40 min before filtering to isolate the resulting white crystals. The crystals were washed with cold toluene (3 × 7 mL) and dried in vacuo to afford the (*S*)-acid/cinchonidine salt in 38% isolated yield as a single diastereomer by ^1H NMR [most notably, the peak at δ = 7.35 ppm (s, 2 H) corresponding to the biphenyl Ar*H* of the (*R*)-acid/cinchonidine salt has disappeared].[16] ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.91 (d, *J* = 4.4 Hz, 1 H, quinoline Ar*H*), 8.14 (d, *J* = 8.3 Hz, 1 H, quinoline Ar*H*), 7.83 (d, *J* = 8.2 Hz, 1 H, quinoline Ar*H*), 7.74–7.68 (m, 2 H, quinoline Ar*H*), 7.53–7.48 (m, 1 H, quinoline Ar*H*), 7.41 (s, 2 H, biphenyl Ar*H*), 6.43 (br., 1 H), 5.52–5.41 (m, 1 H, alkene C*H*), 5.03–4.95 (m, 2 H, alkene C*H*), 4.58 (br. m, 1 H, methine C*H*), 3.43–3.37 (m, 1 H, quinuclidine C*H*), 3.28–3.04 (m, 3 H, quinuclidine C*H*), 2.62 (br. m, 1 H), 2.40–1.75 (m, 4 H, quinuclidine C*H*), 1.95 (s, 6 H, ArCH_3), 1.53 [s, 18 H, Ar(CH_3)$_3$], 1.50 (m, 1 H, quinuclidine C*H*), 1.10 (br. m, 1 H, quinuclidine C*H*) ppm. To decomplex the acid salt, the solid was fully dissolved in CH_2Cl_2 (ca. 250 mL) and placed in a separation funnel. The organic layer was then washed with 2 N aq. HCl (4 × 100 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated to afford analytically pure (+)-(*S*)-**3a** (2.77 g, 38% yield). $[\alpha]_D^{23}$ = +258 (*c* = 0.017, CH_3OH). All other analytical information matches that for the racemic acid listed above.

Supporting Information (see footnote on the first page of this article): Detailed procedures and characterization data for all new compounds discussed, as well as the ^1H NMR spectra for the unresolved/resolved salts of **4a**; experimental procedures for the asymmetric hydrophosphonylation of imines and asymmetric Friedel–Crafts reaction of indole.

Acknowledgments

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