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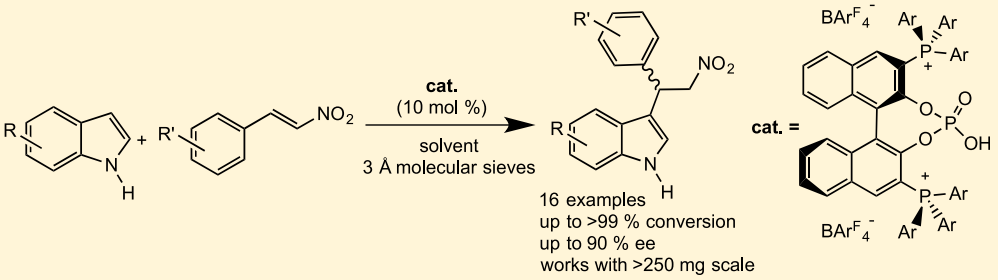
Electrostatically Enhanced Phosphoric Acids and Their Applications in Asymmetric Friedel−Crafts Alkylations

Jie Ma and Steven R. Kass*

Department of Chemistry, University of Minnesota, 207 Pleasant Street, SE, Minneapolis, Minnesota 55455, United States

Supporting Information



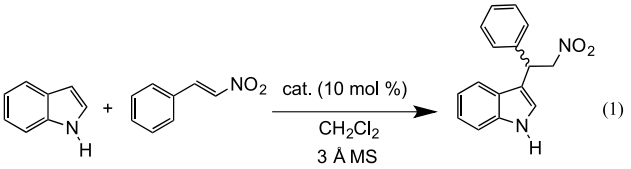
ABSTRACT: A series of electrostatically enhanced phosphoric acid catalysts were synthesized and studied. These compounds possess two positively charged *N*-octylpyridinium or triarylphosphonium ion centers at the 3,3′-positions of the (*R*)-BINOL backbone to enhance reactivity and provide needed steric bulk for enantioselective transformations. Catalytic activities for Friedel−Crafts alkylations of indoles with *trans*-*β*-nitrostyrenes were studied. Both types of catalysts accelerate reaction conversions relative to noncharged analogues, and good enantioselectivities up to 90% ee are observed with the phosphonium-ion-tagged phosphoric acids. This transformation also can be scaled up to synthetically useful amounts, affording >250 mg of product without losing any reactivity or selectivity.

INTRODUCTION

Over the past decade or so, a large body of novel Brønsted acids have emerged as effective organocatalysts for a variety of organic transformations.[1] These species are excellent alternatives to metal-containing catalysts as they typically are moisture and air tolerant and are considered to be environmentally friendlier in nature.[2] Among these Brønsted acid catalysts, phosphoric acids bearing a 1,1′-bi-2-naphthol (BINOL) backbone have been extensively investigated. Hundreds of derivatives have been prepared as they provide a means for carrying out enantioselective acid-catalyzed processes.[3] This includes asymmetric carbon−carbon bond forming transformations,[4] which are extremely valuable, but can be synthetically challenging to carry out.[5]

BINOL-derived phosphoric acids are generally more active catalysts than other chiral Brønsted acids such as BINOL derivatives,[6] thioureas,[7] and *α*,*α*,*α*,*α*-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs)[8] due to their greater acidities.[9] To broaden their scope and develop more reactive derivatives, several strategies have been employed. These include introducing electron-withdrawing groups into the catalyst backbone,[10] modifying the phosphate functional group (e.g., to phosphoramides),[11] and employing acidic achiral additives.[12]

More recently, incorporation of positively charged pyridinium ion centers without the introduction of new hydrogen-bond-donating sites was found to improve the catalytic abilities of achiral phenols,[13] thioureas,[14] and phosphoric acids[15] by orders of magnitude. In addition, several chiral charge-activated thioureas were reported and found to display excellent reactivities and good enantioselectivities in Friedel−Crafts alkylations of indoles with *trans*-*β*-nitrostyrenes.[16] Chiral phosphonium-ion-containing (*R*)-BINOL-derived phosphoric acids were also recently communicated and found to give good to excellent enantioselectivities in the reactions of indoles with 2,2,2-trifluoroacetophenones.[17] To build upon these efforts, a number of new derivatives are reported, and both charged and noncharged catalysts were investigated using the reaction illustrated in eq 1 as a well-studied test platform (Figure 1). In this regard it is worth noting that **3b** previously was used for the reaction of indole with *trans*-*β*-nitrostyrene,[18] and the PF_6^- salt of **2a** was found to be catalytically inactive for this process.[19]



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RESULTS AND DISCUSSION

Our study was initiated by synthesizing **1a** and **1b**, two (*R*)-BINOL-derived phosphoric acids with *N*-octylpyridinium groups at the 3,3′-backbone positions. A noncoordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate anion ($BAr^F{}_4^-$)

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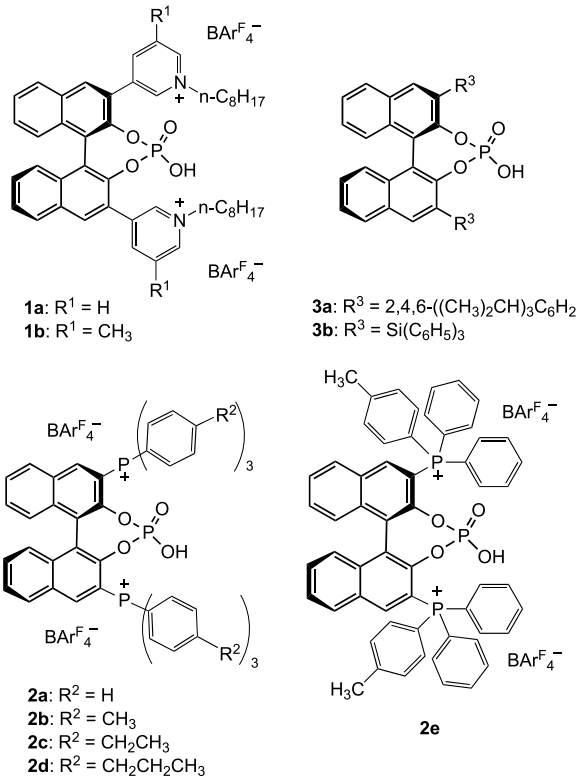

Figure 1. Catalysts used in this work. Different counteranions for **2a** were also studied.

Table 1. Optimizations of Catalysts and Reaction Conditions[a]

entry	cat.	T (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**	20	24	70	−14
2	**1a**	0	48	58	−16
3	**1a**	−30	73	26	−21
4	**1b**	20	24	70	−12
5	**1b**	0	48	64	−13
6	**1b**	−30	73	30	−16
7	**2a**	20	8	59	35
8	**2a**	0	24	50	36
9	**2a**	−30	46	38	40
10	**2b**	20	5	68	50
11	**2b**	0	24	75	59
12	**2b**	−30	46	81	70
13	**2c**	20	5	67	36
14	**2c**	0	24	71	46
15	**2c**	−30	46	83	61
16	**2d**	20	5	69	34
17	**2d**	0	24	73	46
18	**2d**	−30	46	85	61
19	**2e**	20	5	73	47
20	**2e**	0	24	63	51
21	**2e**	−30	46	60	57

[a]Reactions were performed with 0.1 mmol indole, 0.2 mmol *trans*-β-nitrostyrene, 0.01 mmol catalyst, and 10 mg of 3 Å MS in 0.5 mL of CH_2Cl_2. [b]Isolated yield. [c]Determined by chiral HPLC. Positive ee values correspond to the *S*-enantiomer being the major product.

was incorporated as the counterion because it enhances reactivity and solubility in nonpolar media.[15,20] Catalytic activities for the Friedel−Crafts alkylation of indole with *trans*-β-nitrostyrene were examined at different temperatures in CH_2Cl_2 with a 10 mol % catalyst loading and 3 Å molecular sieves (MS) to remove adventitious moisture (Table 1). Disappointingly, the enantioselectivities were poor with the best results of only 21% and 16% ee at −30 °C for **1a** and **1b**, respectively (entries 1−6). These findings led us to examine bulky triaryl phosphonium ion derivatives **2a**−**2e** as conveniently prepared alternatives.[17,19,21]

To our delight, the preliminary screening results for the phosphonium-ion-tagged phosphoric acids (entries 7−21) revealed that they are both more reactive and enantioselective than their pyridinium-ion-containing analogues. Intriguingly they also led to a reversal in the preferred enantiomer (i.e., the *S*-enantiomer is favored with catalysts **2a**−**e**),[22,23] although this type of finding has been previously noted and rationalized by steric differences in the chiral pocket.[3] The parent derivative **2a** only gave an ee of 35−40% at temperatures ranging from 20 to −30 °C (entries 7−9), but incorporation of *p*-methyl substituents on each phenyl group led to significant improvements in the reaction conversions and stereoselectivities (entries 10−12). That is, over the same time period at −30 °C, the isolated yield increased from 38% to 81% and the ee improved from 40% to 70%. A further decrease in temperature to −50 °C was not practical in that less than a 10% conversion was observed [illegible] ment of the *p*-methyl groups by larger ethyl or *n*-propyl substituents had little impact on the product yield, but [illegible]−15% lower ee values over the studied temperature range (entries 13−18).

To address whether the improvement in the stereoselectivity brought about by the *p*-methyl groups is due to steric or electronic effects, the diphenyl(*p*-tolyl)phosphonium-ion-tagged BINOL phosphoric acid **2e** was prepared and investigated. Its steric requirements should be very similar to those of the unsubstituted phosphoric acid **2a** because the Ar_3P group can rotate readily, enabling any unfavorable interactions brought about by the methyl group to be minimized. Electronically, **2e** should be intermediate in behavior to **2a** and **2b** since these compounds have 2, 0, and 6 methyl groups, respectively. The observed enantioselectivities with **2e** at 20, 0, and −30 °C (entries 19−21) are between the results for **2a** and **2b**. This indicates that the larger ee values for **2b** compared to **2a** are primarily due to the electron-donating effects of the six methyl groups in the former compound.[24] Computations are in accord with this suggestion and indicate that the *S*-enantiomer of the Friedel−Crafts alkylation product is favored as was observed. More specifically, B3LYP/6-31G(d,p) transition state structures leading to both enantiomers were located for the (*R*)-BINOL-derived phosphoric acid catalysts with H, PPh_3, P(*p*-$CH_3C_6H_4)_3$, and $SiPh_3$ at the 3- and 3′-positions. Previously reported geometries with simplified biphenyl-substituted phosphoric acid catalysts by Hirata and Yamanaka[25] and Li and You et al.[26] were used as our starting points, and subsequent M06-2X/cc-pVTZ//B3LYP/6-31G(d,p) free energy barriers were obtained. In accord with the experiment, **2b** is predicted to be more selective than **2a** or **3b** (i.e., $\Delta G^{\ddagger}$ ($R - S$) = 0.60 (**2b**), 0.35 (**2a**), and 0.32 kcal mol^{-1} (**3b**) as compared to experimental values of 0.88, 0.41,[27] and 0.51 kcal mol^{-1}, respectively). The geometries of the transition structures catalyzed by **2a** and **2b** are very similar, but the ones that lead to the *S*-enantiomer have C—H···O interactions that are not present in the geometry, leading to the *R*-enantiomer (Figure 2).

The effect of the counterion was examined next by taking the chloride anion precursor to **2a** and converting it to the BF_4^-,

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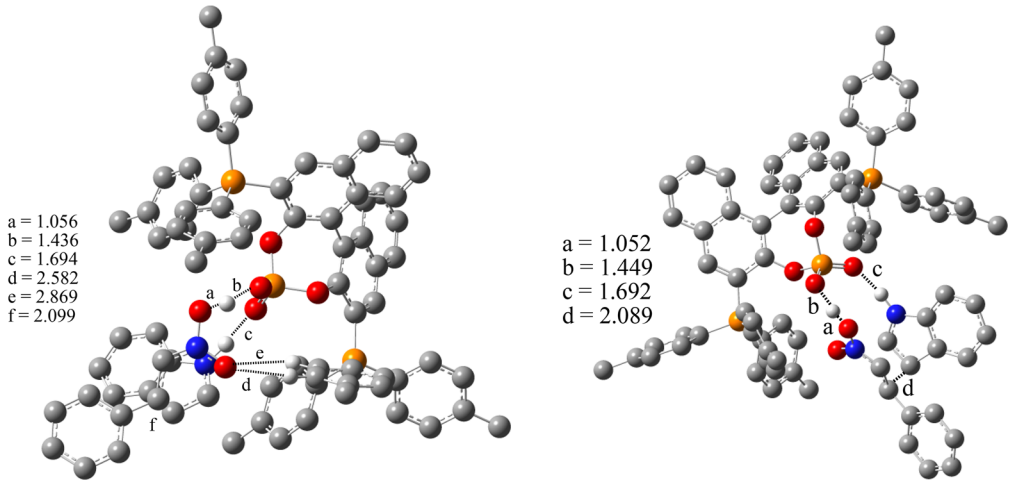


Figure 2. Computed B3LYP/6-31G(d,p) transition structures with **2b** for the *S* (left)- and *R* (right)-enantiomers. Most carbon-attached hydrogen atoms were removed for clarity.

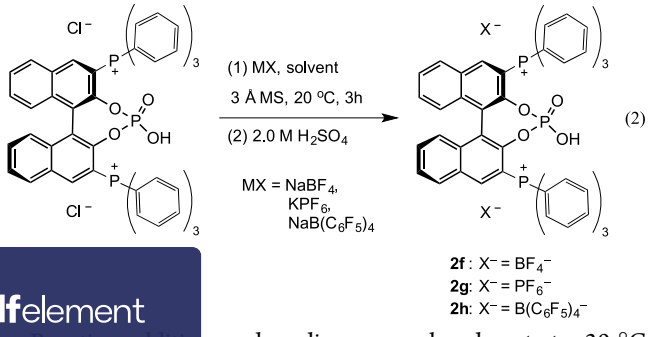
PF_6^-, and $B(C_6F_5)_4^-$ salts **2f–2h** (eq 2). These species were compared to the $BAr^F{}_4^-$ salt **2a** at −30 °C, and their reactivity order is as follows: $BF_4^- < PF_6^- < B(C_6F_5)_4^- < BAr^F{}_4^-$ (Table 2). The resulting enantioselectivities also seem to track with this

Table 2. Counteranion Screening Results[a]

entry	cat.	time (h)	yield (%)[b]	ee (%)[c]
1	**2f**	48	18	<1
2	**2g**	48	23	<1
3	**2h**	48	33	33
4	**2a**	46	38	40

[a]Reactions were performed at −30 °C with 0.1 mmol indole, 0.2 mmol *trans*-*β*-nitrostyrene, 0.01 mmol of the indicated catalyst, and 10 mg of 3 Å MS in 0.5 mL of CH_2Cl_2. [b]Isolated yield. [c]Determined by chiral HPLC.

order and is as follows: $BF_4^- \approx PF_6^- < B(C_6F_5)_4^- < BAr^F{}_4^-$. This trend follows their hydrogen bond accepting abilities,[28] and so additional experiments were carried out with $BAr^F{}_4^-$ salts. It is worth adding that **2g** was previously reported but was found to be catalytically inactive for a series of transformations including the reaction of indole with *trans*-*β*-nitrostyrene.[19] This differs from our finding and may be due to the use of a different solvent (i.e., toluene vs dichloromethane) or partially deprotonated catalyst in the previous work since the counterion exchange was done after the acidification of the phosphoric acid.



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Reaction additives and media were explored next at −30 °C as the catalyst (Table 3). Lower yields and enantioselectivities were found for the reactions carried out without MS or with additives other than 3 Å MS (entries 2–5). Of the single component solvents that were examined with 3 Å

Table 3. Reaction Medium Screening[a]

entry	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	46	81	70
2[d]	CH_2Cl_2	47	54	67
3[e]	CH_2Cl_2	48	73	57
4[f]	CH_2Cl_2	48	62	57
5[g]	CH_2Cl_2	48	61	62
6	DCE[h]	46	73	63
7	C_6H_5Cl	45	77	64
8	$CHCl_3$	45	54	41
9	EtOAc	164	trace	
10	THF	164	trace	
11	C_6H_5CN	140	43	63
12	CH_2Cl_2/C_6H_6 1:1	46	76	71
13	$CH_2Cl_2/C_6H_5CH_3$ 1:1	47	83	66
14	CH_2Cl_2/*m*-xylene 1:1	47	76	63
15	CH_2Cl_2/CCl_4 1:1	48	86	70
16	CH_2Cl_2/C_6H_6 1:2	50	88	72
17	1,2-DCE/C_6H_6 1:1	45	77	65

[a]Reactions were performed at −30 °C with 0.1 mmol indole, 0.2 mmol *trans*-*β*-nitrostyrene, 0.01 mmol of **2b**, and 10 mg of 3 Å MS (unless otherwise noted) in 0.5 mL of the specified solvent; mixtures are on a volume to volume basis. [b]Isolated yield. [c]Determined by chiral HPLC. [d]No MS was used. [e]10 mg of 4 Å MS was used. [f]10 mg of 5 Å MS was used. [g]10 mg of 13× MS was used. [h]DCE = 1,2-dichloroethane.

MS (entries 1 and 6–11), CH_2Cl_2 gave both the highest yield and ee, 81% and 70%, respectively. 1,2-Dichloroethane (DCE) and chlorobenzene are somewhat worse media for this transformation in terms of both the yield and enantioselectivity, but the results in $CHCl_3$, surprisingly are much poorer (i.e., a 54% yield and an ee of 41% were obtained; entries 1 and 6–8). Hydrogen bond accepting solvents such as EtOAc and THF completely deactivate the catalyst, shutting down product formation (entries 9 and 10). Benzonitrile, a weaker hydrogen bond acceptor than the two oxygen-containing solvents, does not retard the catalyst as strongly (entry 11) but still is a very ineffective medium, and affords the product with a 7% lower ee than in CH_2Cl_2.

In an attempt to improve these results, a number of binary solvent mixtures with a less polar component (i.e., benzene, toluene, *m*-xylene, and carbon tetrachloride) were tested

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(entries 12−17). A 1:1 (v/v) combination of CH_2Cl_2 and C_6H_6 led to a 5% reduction in yield but a 1% increase in ee relative to the former solvent (entry 12). The opposite trend was observed with a 1:1 CH_2Cl_2/toluene mixture in that the yield was 2% higher, but the ee dropped by 4% (entry 13). Unfortunately, *m*-xylene was ineffective as a cosolvent in both regards and led to a ∼6% decrease in the yield and ee (entry 14). Carbon tetrachloride and dichloromethane in a 1:1 ratio gave an improved yield (86%) without affecting the ee (entry 15). Higher proportions of benzene were also investigated since it is the only cosolvent that led to a higher observed ee. A 1:2 CH_2Cl_2/C_6H_6 mixture afforded our best result, an 88% isolated yield and a 72% ee (entry 16). A further increase in benzene to a 1:3 solvent combination is not feasible because the catalyst does not dissolve in this medium. Finally, a previously reported 1:1 DCE/C_6H_6 solvent combination was examined,[24] but it led to a reduction in both the yield and enantioselectivity (entry 17). Clearly, different solvent combinations lead to significant differences presumably due to ion pairing and poorly understood solvation effects.

Under our optimal conditions, the reactivity of charged catalyst **2b** was compared to two similar and well-established noncharged analogues, (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-BINOL phosphoric acid (TRIP, **3a**) and (*R*)-3,3′-bis-(triphenylsilyl)-BINOL phosphoric acid (**3b**, Figure 1).[29,30] The reactions of indole with *trans*-*β*-nitrostyrene were followed at the same three time points by NMR spectrsocopy, and enantioselectivies were measured by chiral HPLC. Reaction half-lifes, relative rates, and the resulting ee values are given in Table 4. Both TRIP and its 3,3′-bis(triphenylsilyl) analogue are

Table 4. Comparison of Charged and Noncharged Catalysts[a]

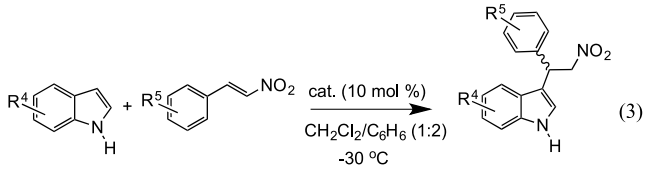
entry	cat.	$t_{1/2}$ (h)[b]	k_{rel}	ee (%)[c]
1	**3a**	74	1.3	49
2	**3b**	96	1.0	48
3	**2b**	12	7.9	72

[a]Reactions were carried out at −30 °C with 0.1 mmol indole, 0.2 mmol *trans*-*β*-nitrostyrene, 0.01 mmol of **2b**, and 10 mg of 3 Å MS in 0.5 mL of a 1:2 CH_2Cl_2/C_6H_6 mixture. [b]Reaction conversions were determined by NMR spectroscopy. [c]Measured by chiral HPLC.

similarly effective in this transformation with $t_{1/2}$ = 74 (**3a**) and 96 h (**3b**) and ee values of 49% and 48%, respectively (entries 1 and 2). The charged triarylphosphonium-ion-containing catalyst **2b** was found to be 6−8 times more reactive and significantly more selective with an ee of 72% (entry 3).

The scope of this reaction was also addressed (eq 3), and the results are summarized in Table 5. A wide range of indoles (**4a**−**4k**) and *trans*-*β*-nitrostyrenes (**5a**−**5f**) bearing electron-donating and electron-withdrawing groups are tolerated and afford high conversions (75−99%) with enantiomeric excesses ranging from 60 to 90%. Indoles **4b**−**4d** and **4f** with an electron-withdrawing halogen atom at the 5- or 6-position react more slowly than the parent compound (i.e., **4a**) and afforded ∼10% lower conversions after an ∼33% longer time period, but had little impact upon the ee (i.e., the values ranged from 69 to 73%, entries 4−6). A chlorine atom at the 7-position (**4e**) behaved differently in that it had a bigger influence on the rate of reaction and the enantioselectivity. That is, significantly more time was needed to produce the product but it also was formed with an increased ee of 83%. An electron-donating methoxy substituent at the 5- or 6-position (**4g** and **4h**)

Table 5. Substrate Scope[a]



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4a: R^4 = H
4b: R^4 = 5-F
4c: R^4 = 5-Cl
4d: R^4 = 6-Cl
4e: R^4 = 7-Cl
4f: R^4 = 5-Br
4g: R^4 = 5-MeO
4h: R^4 = 6-MeO
4i: R^4 = 6-Me
4j: R^4 = 7-Me
4k: R^4 = 7-Et

5a: R^5 = H
5b: R^5 = 4-F
5c: R^5 = 2-Cl
5d: R^5 = 3-Br
5e: R^5 = 4-Br
5f: R^5 = 4-MeO

6a: R^4 = H, R^5 = H
6b: R^4 = 5-F, R^5 = H
6c: R^4 = 5-Cl, R^5 = H
6d: R^4 = 6-Cl, R^5 = H
6e: R^4 = 7-Cl, R^5 = H
6f: R^4 = 5-Br, R^5 = H
6g: R^4 = 5-MeO, R^5 = H
6h: R^4 = 6-MeO, R^5 = H
6i: R^4 = 6-Me, R^5 = H
6j: R^4 = 7-Me, R^5 = H
6k: R^4 = 7-Et, R^5 = H
6l: R^4 = H, R^5 = 4-F
6m: R^4 = H, R^5 = 2-Cl
6n: R^4 = H, R^5 = 3-Br
6o: R^4 = H, R^5 = 4-Br
6p: R^4 = H, R^5 = 4-MeO

entry	reactants	pdt	time (h)	conv (%)[b]	ee (%)[c]
1	**4a** + **5a**	**6a**	50	88	72
2	**4b** + **5a**	**6b**	68	81	72
3	**4c** + **5a**	**6c**	66	75	73
4	**4d** + **5a**	**6d**	66	79	70
5	**4e** + **5a**	**6e**	114	88	83
6	**4f** + **5a**	**6f**	68	78	69
7	**4g** + **5a**	**6g**	40	97	68
8	**4h** + **5a**	**6h**	39	96	76
9	**4i** + **5a**	**6i**	47	92	60
10	**4j** + **5a**	**6j**	58	99	90
11	**4k** + **5a**	**6k**	58	98	85
12[d,f]	**4a** + **5b**	**6l**	64	>99	74
13	**4a** + **5c**	**6m**	39	>99	65
14	**4a** + **5d**	**6n**	39	>99	74
15[e,g]	**4a** + **5e**	**6o**	64	>99	70
16[d]	**4a** + **5f**	**6p**	68	91	79
17[h]	**4j** + **5a**	**6j**	64	>99	90

[a]Reactions were carried out at −30 °C with 0.1 mmol of the indole, 0.2 mmol of the *trans*-*β*-nitrostyrene, 0.01 mmol of **2b**, and 10 mg of 3 Å MS in 0.5 mL of a 1:2 CH_2Cl_2/C_6H_6 mixture. [b]Determined by NMR spectroscopy. [c]Measured by chiral HPLC. [d]A 1:1 CH_2Cl_2/C_6H_6 mixture was used as the solvent. [e]A 2:1 CH_2Cl_2/C_6H_6 mixture was used as the solvent. [f]This reaction was run at half of the typical concentrations. [g]This reaction was run at 2/3 of the usual concentrations in 1 mL of solvent and with 20 mg of 3 Å MS. [h]This reaction was scaled up by a factor of 10.

accelerated the transformation as expected, led to high conversions of 97 and 96%, respectively, in shorter time periods, and had little effect (±4%) on the observed ee (entries 7 and 8). Alkyl groups at the 6- and 7-positions (**4i**−**4k**) also led to very efficient transformations but had little impact on the speed of the transformation (entries 9−11). A methyl group, however, was found to have the largest influence on the enantioselectivity of all of the substituents that were studied. 6-Methylindole (**4i**) gave the smallest ee (60%) in the reaction with *trans*-*β*-nitrostyrene, whereas its 7-methyl isomer (**4j**) afforded the highest value (90% ee). 7-Ethylindole (**4k**) also displayed a good enantioselectivity (85% ee). These results indicate that subtle changes in the location and size of an indole substituent can influence the enantioselectivity of product formation and that incorporation of a chlorine, methyl, or ethyl group at the 7-

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position is particularly favorable from a stereochemical point of view. Incorporation of electron-withdrawing halogen atoms or an electron-donating methoxy group into the aromatic ring of *trans*-β-nitrostyrene led to a few solubility issues, but in all cases, excellent conversions were obtained (entries 12−16). The products were formed with a moderate ee ranging from 70 to 79% except for **5c**, which led to a lower value of 65%, presumably because of the *ortho*-chlorine atom. The reaction of **4j** with **5a** was also scaled up by a factor of 10 (entry 17) to afford >250 mg of product without any loss in the yield or ee.

1-Methylindole (**4l**) was explored to investigate the role of the N—H···O═P hydrogen bond in the reaction of indole with *trans*-β-nitrostyrene since this interaction is blocked in this case. This change resulted in a reduction in the isolated yield from 81% to 5% and in the ee from 70% to 30% under the same reaction conditions.[31] These results indicate that the hydrogen bond between indole and the phosphoryl oxygen of the phosphoric acid is important both in terms of the reaction efficiency and stereoselectivity as previously concluded with noncharged BINOL-derived phosphoric acids.[18,29a] A kinetic study with catalytic loadings of **2b** ranging from 5 to 20 mol % was also carried out. A plot of the relative rates vs the mol % of the catalyst is linear, indicating a first-order dependence on the catalyst concentration (Figure 3). Alternatively, the same

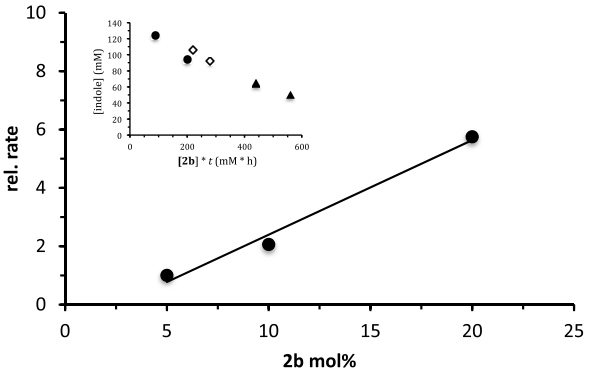

Figure 3. Linear least-squares fit of relative rates vs the catalyst (**2b**) mol %; rel. rate = 0.32 × **2b** mol % − 0.840, r^2 = 0.986. Relative rates and half-lifes follow: 1.0 and 24 h (5 mol %), 2.1 and 12 h (10 mol %), and 5.7 and 4.2 h (20 mol %). Inset is for the normalized time scale analysis.

conclusion is reached by carrying out a normalized time scale analysis.[32] Interestingly, even though the background process is not competitive, the ee was found to correlate with the catalyst loading. That is, when 5, 10, and 20 mol % of **2b**, were used, ee values of 60%, 70%, and 73% were observed. This may be due to the changes in the medium arising from differences in the catalyst concentration since it is a soluble salt. These results, nevertheless, suggest that the operating mechanism is analogous to noncharged phosphoric acid derivatives[18] and that a pair of hydrogen bond interactions play a key role in the efficiency and stereoselectivity of this transformation (Figure 4), which is consistent with previous reports of other phosphoric acid catalysts.[33] Our computations also suggest that a pair of aromatic C—H···ONO interactions are important in determining the [illegible] selectivity.

CONCLUSION

In summary, we demonstrated the successful synthesis of a series of electrostatically enhanced pyridinium-containing and phosphonium-ion-tagged phosphoric acids and studied their catalytic

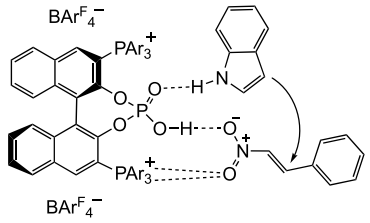

Figure 4. Proposed Friedel−Crafts alkylation transition state.

performance in the Friedel−Crafts alkylation of indoles with *trans*-β-nitrostyrenes. Unfortunately, the pyridinium-containing phosphoric acids failed to afford a high stereoselectivity. On the other hand, the phosphonium-ion-containing phosphoric acids are good catalysts for a wide range of substrates, promoting higher reactivities and enantioselectivities than their noncharged analogues. Charge-activated organocatalysts consequently continue to show promise in the development of new hydrogen bond and Brønsted acid catalysts.

EXPERIMENTAL SECTION

Materials and General Methods. All of the reagents used in this work were obtained from commercial sources and used without further purification. Reaction solvents were dried with oven-activated 3 Å molecular sieves. Proton and carbon chemical shifts are reported in ppm (δ) based upon internal reference signals from the solvent: $CDCl_3$ (7.26 and 77.0 δ) and CD_2Cl_2 (5.32 and 54.0 δ). For ^{19}F and ^{31}P, external calibrants were used as follows: CF_3COOH (−76.55 δ) and 85% aqueous H_3PO_4 (0.00 δ). High-resolution electrospray ionization mass spectra (HRMS-ESI) were obtained with a TOF instrument using methanol solutions and polyethylene glycol (PEG) or polypropylene glycol (PPG) as an internal standard. HPLC analyses were carried out on chiral 25 cm × 4.6 mm RegisCell and RegisPack columns.

*(R)-2,2′-Bis(ethoxymethoxy)-1,1′-binaphthyl (**7**).*[34] (*R*)-1,1′-Bi-2-naphthol (0.50 g, 1.75 mmol) was transferred into a 250 mL round-bottomed flask under a dry nitrogen atmosphere, and 20 mL of anhydrous THF was added via syringe. The resulting solution was stirred and cooled to −20 °C before adding 0.43 g (3.83 mmol) of potassium *tert*-butoxide in one portion. This mixture was stirred for 15 min before 0.35 mL (0.356 g, 3.83 mmol) chloromethyl ethyl ether was syringed in over 5 min. The resulting solution was allowed to warm to room temperature and stirred for 1 h, after which brine (30 mL) was added to quench the reaction and the solvent was removed under vacuum. Ethyl acetate (30 mL x 3) was used to extract the crude product and the combined organic material was washed with water (30 mL × 2) and brine (30 mL), dried over $MgSO_4$, and concentrated to give a yellow oil. Purification by MPLC was carried out using the following protocol: a hexanes wash with a flow rate of 40 mL min^{-1} was carried out for 5 min, then the eluent was switched via a linear gradient over the course of 5 min to 1:1 hexanes/CH_2Cl_2 and maintained for 20 min. The last fraction was concentrated to afford 0.47 g (67%) of the product as a colorless viscous oil. ^1H NMR (500 MHz, CD_2Cl_2): δ 8.01 (d, J = 9.0 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 9.1 Hz, 2H), 7.40 (t, J = 7.8 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 5.21 (d, J = 7.0 Hz, 2H), 5.09 (d, J = 7.0 Hz, 2H), 3.51−3.36 (m, 4H), 1.07 (t, J = 7.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.8, 134.0, 129.8, 129.3, 127.8, 126.2, 125.5, 123.9, 121.2, 117.4, 93.8, 63.9, 14.8. HRMS-ESI: calcd for $C_{26}H_{26}O_4Na^+$ $(M + Na^+)^+$ 425.1729; found, 425.1748.

*(R)-3,3′-Dibromo-2,2′-bis(ethoxymethoxy)-1,1′-binaphthyl (**8**).* (*R*)-2,2′-Bis(ethoxymethoxy)-1,1′-binaphthyl (**7**, 3.10 g, 7.70 mmol) was dissolved into 50 mL of diethyl ether in a 250 mL round-bottomed flask under a dry nitrogen atmosphere, after which *n*-butyllithium (9.25 mL, 2.5 M in hexane, 23.1 mmol) was added dropwise at room temperature. The resulting solution was stirred for 2 h before being cooled to −20 °C and slowly adding 1,2-dibromotetrachloroethane (7.52 g, 23.1 mmol) in THF (30 mL). Upon warming to room

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temperature and stirring overnight, the reaction was quenched with 30 mL of brine. Removal of the solvents with a rotary evaporator afforded a residue, which was extracted with EtOAc (30 mL × 3). The combined organic material was washed with 30 mL of water and 30 mL of brine and then dried over $MgSO_4$. Evaporation of the solvent under a vacuum gave a yellow solid, which was purified by MPLC; hexanes were used for 2 min, and then a linear gradient to a 9:1 hexanes/EtOAc mixture was applied over a 3 min period. This binary solution was maintained until the product eluted off the column. It was concentrated under reduced pressure to afford 3.88 g (90%) of a white solid (mp 107−113 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.30 (t, J = 8.2 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 4.91 (d, J = 5.9 Hz, 2H), 4.84 (d, J = 5.9 Hz, 2H), 3.08−2.98 (m, 2H), 2.72−2.62 (m, 2H), 0.60 (t, J = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 150.2, 133.0, 132.9, 131.5, 127.2, 127.0, 126.9, 126.5, 126.0, 117.5, 97.9, 64.8, 14.3. HRMS-ESI: calcd for $C_{26}H_{24}O_4Br_2Na^+$ $(M + Na^+)^+$ 582.9919; found, 582.9899.

General Procedure for the Synthesis of 9a−9b. (*R*)-3,3′-Dibromo-2,2′-bis(ethoxymethoxy)-1,1′-binaphthyl (**8**) (0.70 g, 1.25 mmol), 3-pyridinylboronic acid (0.54 g, 4.37 mmol) [or 5-methylpyridine-3-boronic acid (0.60 g, 4.37 mmol)], and tetrakis-(triphenylphosphine)palladium (0.14 g, 0.13 mmol) were mixed together in a 250 mL round-bottomed flask and then dissolved in degassed 1,2-dimethoxylethane (8 mL), after which 3.3 mL of a 2.0 M aqueous Na_2CO_3 solution was added. The resulting mixture was refluxed at 93 °C with stirring for 16 h, and upon cooling to room temperature, the volatiles were removed with a rotary evaporator. Dichloromethane (30 mL × 3) was used to extract the resulting residue, and the combined organic solutions were washed with 30 mL of saturated NH_4Cl and 30 mL of brine before being dried over Na_2SO_4. Concentration of this material under a vacuum gave a yellow oil that was purified by MPLC using EtOAc as the eluent. The resulting white solid was dissolved in 5 mL of ethanol and then 1.5 mL of 6.0 M HCl was added dropwise over 5 min with stirring. After 3 h at room temperature, a white precipitate had formed and the reaction was quenched with 30 mL of aqueous $NaHCO_3$. A rotary evaporator was used to remove the ethanol, and the remaining material was extracted with EtOAc (50 mL × 2). The combined organic layers were washed with water and brine and then dried over Na_2SO_4. Concentration of this solution afforded a viscous yellow liquid that was purified by MPLC with EtOAc as the eluent.

*(R)-3,3′-Di(3-pyridyl)-2,2′-dihydroxyl-1,1′-binaphthyl (**9a**).* This compound was obtained as a white solid (0.40 g) in a 73% yield (mp 206−212 °C). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 11.42 (s, 2H), 9.10 (s, 2H), 7.72 (d, J = 7.8 Hz, 2H), 7.58 (d, J = 7.1 Hz, 2H), 7.35−7.25 (m, 4H), 7.23−7.15 (m, 4H), 6.77 (dd, J = 5.0 and 7.6 Hz, 2H), 6.58 (d, J = 4.3 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 152.7, 150.2, 144.8, 135.7, 135.6, 134.6, 130.5, 129.6, 129.4, 128.9, 127.2, 125.1, 123.5, 123.3, 116.1. HRMS-ESI: calcd for $C_{30}H_{21}N_2O_2^+$ $(M + H^+)^+$, 441.1603; found, 441.1588.

*(R)-3,3′-Di[3-(5-methyl)pyridyl]-2,2′-dihydroxyl-1,1′-binaphthyl (**9b**).* This species was obtained as a white solid (0.42 g) in a 72% yield (mp 201−208 °C). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 11.68 (s, 2H), 8.89 (s, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.52 (s, 2H), 7.33−7.26 (m, 4H), 7.19 (d, J = 9.3 Hz, 2H), 7.17 (s, 2H), 6.30 (s, 2H), 2.03 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 152.9, 147.7, 145.2, 136.0, 135.6, 134.0, 132.7, 130.2, 129.8, 129.7, 128.5, 127.0, 125.1, 123.2, 116.0, 18.7. HRMS-ESI: calcd for $C_{32}H_{25}N_2O_2^+$ $(M + H^+)^+$, 469.1916; found, 469.1933.

General Procedure for the Synthesis of 10a−10b. Compound **9a** or **9b** (0.227 mmol) was added into a 100 mL round-bottomed flask under an atmosphere of dry nitrogen and then was dissolved in 15 mL of anhydrous acetonitrile. After the mixture was stirred for 5 min, 0.164 mL of 1-iodooctane (0.218 g, 0.908 mmol) was syringed into the flask in one portion and the solution was heated to 100 °C and refluxed overnight. Upon cooling to room temperature, the reaction mixture was concentrated under a vacuum. The crude product was dissolved in 5 mL of CH_2Cl_2 and triturated by adding it dropwise to 100 mL of hexanes. Filtration of the resulting precipitate and a subsequent wash with hexanes gave the desired product.

*(R)-3,3′-Di(3-N-octylpyridinium)-2,2′-dihydroxyl-1,1′-binaphthyl Iodide (**10a**).* A yellow solid (0.16 g) was obtained in a 77% yield (mp 278−282 °C). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 9.98 (s, 2H), 8.86−8.77 (m, 4H), 8.34 (s, 2H), 8.10−8.01 (m, 4H), 7.43 (t, J = 7.2 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 4.80−4.65 (m, 4H), 2.09−1.98 (m, 4H), 1.40−1.18 (m, 22H), 0.82 (t, J = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 149.7, 146.4, 145.6, 145.5, 142.0, 139.6, 135.0, 132.6, 130.1, 129.5, 128.9, 128.5, 125.6, 125.1, 118.6, 62.7, 32.3, 32.2, 29.50, 29.48, 26.5, 23.1, 14.4. HRMS-ESI: calcd for $C_{46}H_{53}N_2O_2^+$ $(M - H^+ - 2I^-)^+$, 665.4107; found, 665.4139.

*(R)-3,3′-Di(3-(N-octyl-5-methyl)pyridinium)-2,2′-dihy-droxyl-1,1′-binaphthyl Iodide (**10b**).* A yellow solid (0.19 g) was obtained in an 88% yield (mp 265−270 °C). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 9.86 (s, 2H), 8.71 (s, 2H), 8.65 (s, 2H), 8.30 (s, 2H), 8.04 (d, J = 7.9 Hz, 2H), 7.45 (t, J = 7.8 Hz, 2H), 7.35 (t, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 6.53 (s, 2H), 4.79−4.62 (m, 4H), 2.67 (s, 6H), 2.12−2.00 (m, 4H), 1.42−1.18 (m, 20H), 0.83 (d, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 149.5, 146.2, 144.2, 141.3, 139.8, 139.0, 135.0, 132.5, 130.2, 129.5, 128.9, 125.7, 125.3, 125.1, 118.5, 62.5, 32.3, 32.2, 29.53, 29.51, 26.5, 23.1, 19.2, 14.4. HRMS-ESI: calcd for $C_{48}H_{57}N_2O_2^+$ $(M - H^+ - 2I^-)^+$, 693.4420; found, 693.4401.

General Procedure for the Synthesis of 11a−11b. Iodide salt **10a** or **10b** (0.218 mmol) was dissolved into 20 mL of anhydrous acetonitrile under a N_2 atmosphere, and 64 μL (0.10 g, 0.654 mmol) of $POCl_3$ was added with stirring in one portion followed by 44 μL (0.044 g, 0.544 mmol) of anhydrous pyridine. The resulting solution was heated to 90 °C and refluxed for 16 h before cooling to room temperature and adding 0.5 mL of water. This material was heated back to 90 °C for 1 h and then allowed to return to room temperature. Removal of the solvent under a vacuum afforded a residue, which was dissolved in 40 mL of CH_2Cl_2, washed with 2.0 M HCl (15 mL) and 15 mL of brine, and then dried over Na_2SO_4. Rotary evaporation of this material gave a brown oil that was purified by MPLC. A linear gradient from EtOAc to a 1:1 EtOAc/MeOH mixture over 10 min followed by a 10 min wash with this solution eluted the product. This material was concentrated under reduced pressure to give the desired compound as a yellow solid.

*(R)-3,3′-(4-Hydroxy-4-oxidodinaphtho[2,1-d:1′,2′-f][1,3,2]-dioxaphosphepine-2,6-diyl)bis(1-octylpyridin-1-ium) Chloride (**11a**).* This compound (0.12 g) was generated in a 69% yield (mp 195−202 °C). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 10.38 (s, 2H), 9.11 (d, J = 5.6 Hz, 2H), 8.82 (d, J = 7.7 Hz, 2H), 8.20 (s, 2H), 8.08−7.95 (m, 4H), 7.48 (t, J = 7.3 Hz, 2H), 7.30 (t, J = 7.9 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 4.86−4.60 (m, 4H), 2.19 (bs, OH, 1H) 2.10−1.93 (m, 4H), 1.37−1.15 (m, 20H), 0.82 (t, J = 6.7 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 155.31, 155.26, 153.64, 153.58, 137.64, 137.58, 137.0, 136.7, 136.6, 129.7, 128.7, 123.9, 123.8, 121.0, 120.9, 63.0, 32.2, 32.1, 29.5, 29.4, 26.6, 23.1, 14.4. ^{31}P NMR (162 MHz, CD_2Cl_2): δ 5.64. HRMS-ESI: calcd for $C_{46}H_{52}N_2O_4P^+$ $(M - H^+ - 2Cl^-)^+$, 727.3665; found, 727.3677.

*(R)-5,5′-(4-Hydroxy-4-oxidodinaphtho[2,1-d:1′,2′-f][1,3,2]-dioxaphosphepine-2,6-diyl)bis(3-methyl-1-octylpyridin-1-ium) Chloride (**11b**).* This compound (0.15 g) was produced in an 83% yield (mp 194−200 °C). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 10.25 (s, 2H), 9.19 (s, 2H), 8.62 (s, 2H), 8.20 (s, 2H), 8.02 (d, J = 8.2 Hz, 2H), 7.47 (t, J = 7.1 Hz, 2H), 7.30 (t, J = 8.5 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H), 4.72 (t, J = 7.3 Hz, 4H), 2.63 (s, 6H), 2.54 (bs, OH, 1H), 2.15−1.95 (m, 4H), 1.45−1.14 (m, 20H), 0.82 (t, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 147.2, 146.5, 144.7, 142.6, 139.7, 138.8, 133.9, 132.5, 131.0, 129.4, 128.1, 127.6, 127.3, 126.4, 124.0, 62.6, 32.3, 32.1, 29.6, 29.5, 26.7, 23.1, 19.0, 14.4. ^{31}P NMR (162 MHz, CD_2Cl_2): δ 6.19. HRMS-ESI: calcd for $C_{48}H_{56}N_2O_4P^+$ $(M - H^+ - 2Cl^-)^+$, 755.3978; found, 755.4002.

General Procedure for the Synthesis of 1a−1b. Chloride salt **11a** or **11b** (0.0755 mmol), sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (0.141 g, 0.159 mmol), and 3 Å molecular sieves (0.10 g) were mixed in a 23 × 85 mm vial, and then 7 mL of CH_2Cl_2 was added. The resulting solution was stirred at room temperature for 3 h before being filtered through a 0.45 μm polytetrafluoroethylene (PTFE) membrane. The filtered solution was washed with 2.0 M H_2SO_4 (7 mL

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× 2) and water (7 mL × 3) and then was dried over Na_2SO_4 before being concentrated to afford the product.

*(R)-3,3′-(4-Hydroxy-4-oxidodinaphtho[2,1-d:1′,2′-f][1,3,-2]-dioxaphosphepine-2,6-diyl)bis(1-octylpyridin-1-ium)tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (**1a**).* A yellow solid (0.17 g) was formed in a 92% yield (mp 77−81 °C). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 9.54 (s, 2H), 8.90 (d, J = 7.8 Hz, 2H), 8.29 (d, J = 5.9 Hz, 2H), 8.12 (s, 2H), 8.06 (d, J = 8.3 Hz, 2H), 8.00 (dd, J = 5.9 and 7.9 Hz, 2H), 7.77 (s, 16H), 7.65−7.57 (m, 10H), 7.47 (t, J = 8.3 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 4.62−4.44 (m, 4H), 2.60 (bs, OH, 1H) 2.07−1.93 (m, 4H), 1.36−1.21 (m, 20H), 0.84 (t, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 162.4 (q, J = 48.9 Hz), 147.1, 145.7, 145.4, 141.4, 140.7, 140.5, 135.5, 134.0, 133.1, 131.3, 129.5 (qq, J = 2.92 and 31.4 Hz), 128.6, 127.9, 127.7, 127.2, 125.9, 125.2 (q, J = 270 Hz), 124.1, 118.2 (septet, J = 3.64 Hz), 63.9, 32.1, 32.0, 29.4, 29.3, 26.6, 23.0, 14.2. ^{19}F NMR (376 MHz, CD_2Cl_2): δ −62.68. ^{31}P NMR (162 MHz, CD_2Cl_2): δ 6.76. HRMS-ESI: calcd for $C_{46}H_{52}N_2O_4P^+$ (M − H^+ − 2BAr$^F{}_4^-$)$^+$, 727.3665; found, 727.3679.

*(R)-5,5′-(4-Hydroxy-4-oxidodinaphtho[2,1-d:1′,2′-f][1,3,-2]-dioxaphosphepine-2,6-diyl)bis(3-methyl-1-octylpyridin-1-ium)-tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (**1b**).* A yellow solid (0.17 g) was generated in a 91% yield (mp 54−58 °C). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 9.06 (s, 2H), 8.55 (s, 2H), 8.21 (s, 2H), 8.13 (s, 2H), 8.06 (d, J = 7.8 Hz, 2H), 7.74 (s, 16H), 7.63 (t, J = 7.1 Hz, 2H), 7.56 (s, 8H), 7.48 (t, J = 8.5 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 4.83 (bs, OH, 1H), 4.45 (t, J = 7.3 Hz, 4H), 2.55 (s, 6H), 2.07−1.90 (m, 4H), 1.36−1.17 (m, 20H), 0.82 (t, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 162.3 (q, J = 49.6 Hz), 147.6, 143.9, 142.5, 141.6, 141.3, 139.0, 135.4, 133.65, 133.63, 131.7, 129.5 (qq, J = 2.92 and 31.4 Hz), 128.4, 127.3, 125.47, 125.45, 125.2 (q, J = 270 Hz), 123.58, 123.56, 118.1 (septet, J = 3.64 Hz), 63.7, 32.1, 32.0, 29.4, 29.3, 26.6, 23.0, 19.1, 14.2. ^{19}F NMR (376 MHz, CD_2Cl_2): δ −62.76. ^{31}P NMR (162 MHz, CD_2Cl_2): δ 5.68. HRMS-ESI: calcd for $C_{48}H_{56}N_2O_4P^+$ (M − H^+ − 2BAr$^F{}_4^-$)$^+$, 755.3978; found, 755.3998

General Procedure for the Synthesis of 2f−2g. In a 23 × 85 mm vial, (*R*)-(4-hydroxy-4-oxidodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]-dioxaphosphepine-2,6-diyl)bis(triphenylphosphonium) chloride (0.188 g, 0.200 mmol), sodium tetrafluoroborate (0.046 g, 0.420 mmol) or potassium hexafluorophosphate (0.077 g, 0.420 mmol), and 3 Å molecular sieves (0.50 g) were mixed together and then 3 mL of methanol was added. After the mixture was stirred at room temperature for 2 h, 10 mL of CH_2Cl_2 was added and the reaction was stirred for an additional 1 h before filtering the solution through a 0.45 μm PTFE membrane. The solvent was removed under a vacuum, and the residue was redissolved in 8 mL of CH_2Cl_2. It was then washed twice with 8 mL of 2.0 M H_2SO_4 and three times with 8 mL of water before being dried over Na_2SO_4. Concentration of the solution under reduced pressure afforded the desired product.

*(R)-(4-Hydroxy-4-oxidodinaphtho[2,1-d:1′,2′-f][1,3,2]-dioxaphosphepine-2,6-diyl)bis(triphenyl-phosphonium)-tetrafluoroborate (**2f**).* A yellow solid (0.141 g) was afforded in a 67% yield (mp 233−236 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J = 16.3 Hz, 2H), 7.87 (d, J = 7.7 Hz, 2H), 7.83−7.72 (m, 18H), 7.68−7.62 (m, 12H), 7.57−7.48 (m, 4H), 7.28 (d, J = 8.3 Hz, 2H), 1.25 (bs, OH, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 150.7 (d, J = 9.9 Hz), 141.0 (d, J = 8.4 Hz), 136.2 (d, J = 2.4 Hz), 135.03, 134.95 (d, J = 10.5 Hz), 131.0, 130.0 (d, J = 13.1 Hz), 129.8, 129.2 (d, J = 14.3 Hz), 127.0, 126.5, 124.5 (d, J = 10.1 Hz), 118.9 (d, J = 90.4 Hz), 110.8 (d, J = 91.0 Hz). ^{19}F NMR (376 MHz, CD_2Cl_2): δ −154.11. ^{31}P NMR (162 MHz, CD_2Cl_2): δ 22.93, 0.87. HRMS- ESI: calcd for $C_{56}H_{40}O_4P_3^+$ (M − H^+ − 2BF_4^-)$^+$, 869.2134; found, 869.2103.

*(R)-(4-Hydroxy-4-oxidodinaphtho[2,1-d:1′,2′-f][1,3,2]-dioxaphosphepine-2,6-diyl)bis(triphenyl-phosphonium)-hexafluorophosphate (**2g**).* A yellow solid (0.177 g) was produced in a [illegible]30 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J [illegible] (d, J = 7.7 Hz, 2H), 7.81−7.72 (m, 18H), 7.68−7.50 (m, 4H), 7.28 (d, J = 8.3 Hz, 2H), 2.11 (bs, [illegible] NMR (100 MHz, $CDCl_3$): δ 144.7 (d, J = 8.6 Hz), [illegible], 136.2 (d, J = 2.9 Hz), 135.1, 135.0 (d, J = 10.6 Hz), 131.0, 130.1 (d, J = 13.2 Hz), 129.8, 129.2 (d, J = 14.4 Hz), 127.0, 126.5, 124.5 (d, J = 7.0 Hz), 118.9 (d, J = 90.5 Hz), 110.7 (d, J = 91.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.62 (d, J = 712 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.94, 0.77, −144.43 (septet, J = 712 Hz). HRMS-ESI: calcd for $C_{56}H_{40}O_4P_3^+$ (M − H^+ − 2PF_6^-)$^+$, 869.2134; found, 869.2155.

*(R)-(4-Hydroxy-4-oxidodinaphtho[2,1-d:1′,2′-f][1,3,2]-dioxaphosphepine-2,6-diyl)bis(triphenyl-phosphonium)tetrakis-(pentafluorophenyl)borate (**2h**).* In a 23 × 85 mm vial, (*R*)-(4-hydroxy-4-oxidodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine-2,6-diyl)bis(triphenylphosphonium) chloride (0.188 g, 0.200 mmol), potassium tetrakis(pentafluorophenyl)borate (0.302 g, 0.420 mmol), and 3 Å molecular sieves (0.50 g) were mixed together and then 8 mL of CH_2Cl_2 was added. The solution was stirred at room temperature for 3 h and then filtered through a 0.45 μm PTFE membrane. It was subsequently washed twice with 2.0 M H_2SO_4 and three times with water before being dried over Na_2SO_4. Removal of the CH_2Cl_2 gave **2h** as a yellow solid (0.337 g) in a 76% yield (mp 178−182 °C). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 8.10 (d, J = 16.5 Hz, 2H), 7.91 (d, J = 8.1 Hz, 2H), 7.84−7.77 (m, 6H), 7.77−7.69 (m, 12H), 7.69−7.59 (m, 14H), 7.54 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 2.20 (bs, OH, 1H). ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 149.7 (d, J = 9.4 Hz), 148.7 (d, J = 236.4 Hz), 142.5 (d, J = 8.5 Hz), 138.8 (d, J = 242.9 Hz), 136.9 (d, J = 231.2 Hz), 135.7 (d, J = 3.0 Hz), 136.7, 135.5 (d, J = 10.5 Hz), 132.0, 130.6 (d, J = 13.1 Hz), 130.5, 130.2 (d, J = 14.3 Hz), 128.1, 127.0, 124.7 (d, J = 6.9 Hz), 124.2 (m), 119.1 (d, J = 90.6 Hz), 110.6 (d, J = 91.2 Hz). ^{19}F NMR (376 MHz, CD_2Cl_2): δ −133.12, −163.39 (t, J = 20.4 Hz), −167.38 (t, J = 17.1 Hz). ^{31}P NMR (162 MHz, CD_2Cl_2): δ 22.81, 0.89. HRMS- ESI: calcd for $C_{56}H_{40}O_4P_3^+$ (M − H^+ − 2B(C_6F_5)$_4^-$)$^+$, 869.2134; found, 869.2116.

General Procedure for the Friedel−Crafts Alkylations. A 23 × 85 mm vial was charged with a catalyst (10 mol %) and 3 Å molecular sieves (10 mg) and then was sealed followed by a 1 min purge with dry nitrogen. After 250 μL of CH_2Cl_2 was added via syringe, the resulting solution was cooled if the reaction was being carried out at a subambient temperature. Indole (0.100 mmol) and *trans*-β-nitrostyrene (0.200 mmol) were dissolved in 250 μL of CH_2Cl_2, and this solution was then added dropwise over 10−15 s. The reaction mixture was shaken, and the transformation was allowed to proceed over the course of 5−164 h. Reaction conversions were determined by removing 1−2 drops of the reaction mixture and dissolving it in 0.5 mL of $CDCl_3$ after flowing dry nitrogen over the sample for ≤15 s to evaporate the CH_2Cl_2. Upon completion of the reaction, the solution was injected into a 4 g silica gel column followed by 0.2−0.3 mL of CH_2Cl_2 that had been used to rinse the molecular sieves. MPLC purification was carried out first with hexanes (1 min) followed by a linear gradient to 100% CH_2Cl_2 over the course of 7 min, and then this solvent was maintained until all of the components eluted off the column. Racemic reference materials were obtained in the same way using diphenylphosphate as the reaction catalyst.

Analytical Data for the Friedel−Crafts Products. *3-(2-Nitro-1-phenylethyl)-1H-indole (**6a**).*[18] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (bs, NH, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.39−7.30 (m, 5H), 7.29−7.24 (m, 1H), 7.23−7.18 (m, 1H), 7.12−7.06 (m, 1H), 7.03 (d, J = 2.5 Hz, 1H), 5.20 (t, J = 8.2 Hz, 1H), 5.07 (dd, J = 7.7 and 12.6 Hz, 1H), 4.95 (dd, J = 8.4 and 12.5 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 139.2, 136.5, 128.9, 127.7, 127.5, 126.1, 122.7, 121.6, 119.9, 118.9, 114.4, 111.4, 79.5, 41.5. HRMS-ESI: calcd for $C_{16}H_{13}N_2O_2^-$ (M − H^+)$^-$, 265.0977; found, 265.0971. Enantiomeric excess was determined with a Regiscell column (75:25 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 17.0 min, τ_{minor} = 20.1 min).

*5-Fluoro-3-(2-nitro-1-phenylethyl)-1H-indole (**6b**).*[35] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.42 (**4b**) and 4.78 (**6b**). Enantiomeric excess was measured with a Regiscell column (92:8 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 254 nm, τ_{major} = 56.1 min, τ_{minor} = 48.2 min).

*5-Chloro-3-(2-nitro-1-phenylethyl)-1H-indole (**6c**)..*[18,36] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.41 (**4c**) and 4.82 (**6c**). Enantiomeric excess was measured with a Regiscell column (80:20 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 16.8 min, τ_{minor} = 13.8 min).

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*6-Chloro-3-(2-nitro-1-phenylethyl)-1H-indole (**6d**).*[37] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.43 (**4d**) and 4.82 (**6d**). Enantiomeric excess was measured with a Regiscell column (85:15 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 21.2 min, τ_{minor} = 19.8 min).

*7-Chloro-3-(2-nitro-1-phenylethyl)-1H-indole(**6e**).* A yellow solid was isolated with a mp of 58−62 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (bs, NH, 1H), 7.37−7.29 (m, 5H), 7.29−7.26 (m, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 5.17 (t, J = 8.0 Hz, 1H), 5.06 (dd, J = 8.0 and 12.5 Hz, 1H), 4.95 (dd, J = 8.0 and 12.5 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 138.8, 133.8, 129.0, 127.71, 127.691, 127.688, 127.5, 122.1, 120.8, 117.6, 116.9, 115.6, 79.4, 41.5. HRMS-ESI: calcd for $C_{16}H_{12}N_2O_2Cl^-$ $(M - H^+)^-$, 299.0587 and 301.0558; found, 299.0577 and 301.0553. Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.60 (**4e**) and 4.95 (**6e**). Enantiomeric excess was measured with a Regiscell column (75:25 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 34.7 min, τ_{minor} = 39.6 min).

*5-Bromo-3-(2-nitro-1-phenylethyl)-1H-indole (**6f**).*[18] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.40 (**4f**) and 4.82 (**6f**). Enantiomeric excess was measured with a Regiscell column (75:25 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 12.1 min, τ_{minor} = 10.8 min).

*5-Methoxy-3-(2-nitro-1-phenylethyl)-1H-indole (**6g**).*[36] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.39 (**4g**) and 4.84 (**6g**). Enantiomeric excess was measured with a Regiscell column (75:25 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 12.9 min, τ_{minor} = 11.4 min).

*6-Methoxy-3-(2-nitro-1-phenylethyl)-1H-indole (**6h**).* A white solid was isolated with a mp of 82−85 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (bs, NH, 1H), 7.35−7.29 (m, 4H), 7.29−7.24 (m, 2H), 6.92 (dd, J = 0.8 and 2.3 Hz, 1H), 6.83 (d, J = 2.2 Hz, 1H), 6.74 (dd, J = 2.3 and 8.8 Hz, 1H), 5.14 (t, J = 8.1 Hz, 1H), 5.05 (dd, J = 7.7 and 12.4 Hz, 1H), 4.92 (dd, J = 8.3 and 12.5 Hz, 1H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 156.9, 139.2, 137.3, 128.9, 127.7, 127.5, 120.5, 120.3, 119.6, 114.4, 110.0, 94.7, 79.6, 55.6, 41.6. HRMS-ESI: calcd for $C_{17}H_{16}N_2O_3Na^+$ $(M + Na^+)^+$, 319.1059; found, 319.1074. Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.39 (**4h**) and 4.92 (**6h**). Enantiomeric excess was measured with a Regiscell column (75:25 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 20.7 min, τ_{minor} = 16.6 min).

*6-Methyl-3-(2-nitro-1-phenylethyl)-1H-indole(**6i**).* This compound was isolated as a colorless viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (bs, NH, 1H), 7.41−7.28 (m, 5H), 7.28−7.23 (m, 1H), 7.15 (s, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 5.17 (t, J = 8.0 Hz, 1H), 5.06 (dd, J = 7.7 and 12.5 Hz, 1H), 4.94 (dd, J = 8.4 and 12.5 Hz, 1H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 139.2, 136.9, 132.6, 128.9, 127.7, 127.5, 123.9, 121.7, 120.9, 118.5, 114.3, 111.3, 79.5, 41.6, 21.6. HRMS-ESI: calcd for $C_{17}H_{15}N_2O_2^-$ $(M - H^+)^-$ 279.1134; found, 279.1149. Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.51 (**4i**) and 4.94 (**6i**). Enantiomeric excess was measured with a Regiscell column (75:25 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 13.1 min, τ_{minor} = 12.0 min).

*7-Methyl-3-(2-nitro-1-phenylethyl)-1H-indole (**6j**).*[18] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.57 (**4j**) and 4.95 (**6j**). Enantiomeric excess was measured with a Regispack column (97:3 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 40.1 min, τ_{minor} = 35.6 min).

*7-Ethyl-3-(2-nitro-1-phenylethyl)-1H-indole (**6k**).*[38] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.58 (4k) and 4.96 (**6k**). Enantiomeric excess was measured with a Regispack column (97:3 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 38.3 min, τ_{minor} = 29.7 min).

*3-(1-(4-Fluorophenyl)-2-nitroethyl)-1H-indole (**6l**).*[39] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.47 (4a) and 4.79 (**6l**). Enantiomeric excess was measured with a Regiscell column (75:25 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 18.1 min, τ_{minor} = 22.8 min).

*3-(1-(2-Chlorophenyl)-2-nitroethyl)-1H-indole (**6m**).*[40] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.47 (**4a**) and 5.64 (**6m**). Enantiomeric excess was measured with a Regiscell column (75:25 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 20.5 min, τ_{minor} = 13.3 min).

*3-(1-(3-Bromophenyl)-2-nitroethyl)-1H-indole (**6n**).*[40] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.47 (**4a**) and 4.81 (**6n**). Enantiomeric excess was measured with a Regiscell column (75:25 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 20.2 min, τ_{minor} = 27.7 min).

*3-(1-(4-Bromophenyl)-2-nitroethyl)-1H-indole (**6o**).*[40] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.47 (**4a**) and 4.81 (**6o**). Enantiomeric excess was measured with a Regiscell column (75:25 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 21.7 min, τ_{minor} = 27.0 min).

*3-(1-(4-Methoxylphenyl)-2-nitroethyl)-1H-indole (**6p**).*[18] Reaction conversion was determined by relative integration of the ^{1}H NMR signals at δ 6.47 (**4a**) and 4.79 (**6p**). Enantiomeric excess was measured with a Regiscell column (80:20 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 25.3 min, τ_{minor} = 27.9 min).

*3-(2-Nitro-1-phenylethyl)-1-methylindole (**6q**).*[41] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 8.0 Hz, 1H), 7.45−7.27 (m, 7H), 7.16 (t, J = 7.0 Hz, 1H), 6.91 (s, 1H), 5.25 (t, J = 8.1 Hz, 1H), 5.09 (dd, J = 7.6 and 12.6 Hz, 1H), 4.98 (dd, J = 8.5 and 12.6 Hz, 1H), 3.75 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 139.3, 137.2, 128.8, 127.6, 127.4, 126.4, 126.2, 122.1, 119.3, 118.9, 112.6, 109.4, 79.4, 41.4, 32.6. HRMS-ESI: calcd for $C_{17}H_{16}N_2O_2Na^+$ $(M + Na^+)^+$, 303.1109; found, 303.1118. Enantiomeric excess was measured with a Regiscell column (95:5 hexanes/iPrOH, 1.0 mL min^{-1}, 20 °C, 250 nm, τ_{major} = 59.6 min, τ_{minor} = 56.6 min).

Computations. DFT calcuations were carried out with Gaussian 09[42] at the Minnesota Supercomputer Institute for Advanced Computational Research. Full B3LYP/6-31G(d,p) geometry optimizations were performed, and subsequent vibrational frequencies and M06-2X/cc-pVTZ single point energies were computed.[43,44] Stationary points that correspond to energy minima have no imaginary frequencies, while those that correspond to transition structures have one negative value.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01741.

Illustrated synthetic route for the preparation of pyridinium-ion-containing phosphoric acids **1a** and **1b**, kinetic data, NMR spectra, HPLC chromatograms, and computed geometries and energies (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kass@umn.edu.

ORCID

Steven R. Kass: 0000-0001-7007-9322

Notes

The authors declare no competing financial interest.

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J. Org. Chem. 2019, 84, 11125−11134

REFERENCES

(1) (a) Akiyama, T. Stronger Brønsted Acids. *Chem. Rev.* **2007**, *107*, 5744−5758. (b) Akiyama, T.; Mori, K. Stronger Brønsted Acids: Recent Progress. *Chem. Rev.* **2015**, *115*, 9277−9306.

(2) (a) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. Water-Compatible Iminium Activation: Organocatalytic Michael Reactions of Carbon-Centered Nucleophiles with Enals. *Angew. Chem., Int. Ed.* **2007**, *46*, 8431−8435. (b) Calogero, S.; Lanari, D.; Orru, M.; Piermatti, O.; Pizzo, F.; Vaccaro, L. Supported L-proline on Zirconium Phosphates Methyl and/or Phenyl Phosphonates as Heterogeneous Organocatalysts for Direct Asymmetric Aldol Addition. *J. Catal.* **2011**, *282*, 112−119. (c) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F. Organocatalytic Asymmetric Domino Knoevenagel/Diels-Alder Reactions: A Bioorganic Approach to the Diastereospecific and Enantioselective Construction of Highly Substituted Spiro[5,5]-undecane-1,5,9-triones. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233−4237.

(3) (a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047−9153. (b) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Addition and Correction to Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2017**, *117*, 10608−10620.

(4) (a) Terada, M. Binaphthol-Derived Phosphoric Acid as A Versatile Catalyst for Enantioselective Carbon-Carbon Bond Forming Reactions. *Chem. Commun.* **2008**, 4097−4112. (b) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. Chiral BINOL-Derived Phosphoric Acids: Privileged Brønsted Acid Organocatalysts for C-C Bond Formation Reactions. *Org. Biomol. Chem.* **2010**, *8*, 5262−5276.

(5) (a) Kaib, P. S. J.; Schreyer, L.; Lee, S.; Properzi, R.; List, B. Extremely Active Organocatalysts Enable A Highly Enantioselective Addition of Allyltrimethylsilane to Aldehydes. *Angew. Chem., Int. Ed.* **2016**, *55*, 13200−13203. (b) Bandar, J. S.; Ascic, E.; Buchwald, S. L. Enantioselective CuH-Catalyzed Reductive Coupling of Aryl Alkenes and Activated Carboxylic Acids. *J. Am. Chem. Soc.* **2016**, *138*, 5821−5824.

(6) (a) Matsui, K.; Takizawa, S.; Sasai, H. Bifunctional Organocatalysts for Enantioselective Aza-Morita-Baylis-Hillman Reaction. *J. Am. Chem. Soc.* **2005**, *127*, 3680−3681. (b) Wieting, J. M.; Fisher, T. J.; Schafer, A. G.; Visco, M. D.; Gallucci, J. C.; Mattson, A. E. Preparation and Catalytic Activity of BINOL-Derived Silanediols. *Eur. J. Org. Chem.* **2015**, *2015*, 525−533.

(7) (a) Takemoto, Y. Recognition and Activation by Ureas and Thioureas: Stereoselective Reactions Using Ureas and Thioureas as Hydrogen-Bonding Donors. *Org. Biomol. Chem.* **2005**, *3*, 4299−4306. (b) Ji, N.; Yuan, J. N.; Xue, S. S.; Zhang, J. N.; He, W. Novel Chiral Thiourea Organocatalysts for the Catalytic Asymmetric Oxaziridination. *Tetrahedron* **2016**, *72*, 512−517.

(8) (a) Seebach, D.; Beck, A. K.; Heckel, A. TADDOLs, Their Derivatives, and TADDOL Analogues: Versatile Chiral Auxiliaries. *Angew. Chem., Int. Ed.* **2001**, *40*, 92−138. (b) Rueping, M.; Sugiono, E.; Moreth, S. A. Metal-Free, Enantioselective Strecker Reactions Catalyzed by Chiral BINOL and TADDOL Catalysts. *Adv. Synth. Catal.* **2007**, *349*, 759−764.

(9) (a) Phillips, A. M. F.; Pombeiro, A. J. L. Recent advances in organocatalytic enantioselective transfer hydrogenation. *Org. Biomol. Chem.* **2017**, *15*, 2307−2340. (b) Min, C.; Seidel, D. Asymmetric Brønsted Acid Catalysis with Chiral Carboxylic Acids. *Chem. Soc. Rev.* 2017, *46*, 5889−5902.

(10) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich-Type Reaction Catalyzed by A Chiral Brønsted Acid. *Angew. Chem. Int. Ed.* 2004, *43*, 1566−1568. (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. Chiral Brønsted Acid Catalyzed Enantioselective Hydrophosphonylation of Imines: Asymmetric Synthesis of Alpha-Amino Phosphonates. *Org. Lett.* **2005**, *7*, 2583−2585. (c) Tang, H.-Y.; Lu, A.-D.; Zhou, Z.-H.; Zhao, G.-F.; He, L.-N.; Tang, C.-C. Chiral Phosphoric Acid Catalyzed Asymmetric Friedel-Crafts Alkylation of Indoles with Simple (((-Unsaturated Aromatic Ketones. *Eur. J. Org. Chem.* **2008**, *2008*, 1406−1410. (d) Sun, F. L.; Zheng, X. J.; Gu, Q.; He, Q. L.; You, S. L. Enantioselective Synthesis of Unsymmetrical Triarylmethanes by Chiral Brønsted Acids. *Eur. J. Org. Chem.* **2010**, *2010*, 47−50. (e) Yao, Y.; Shu, H.; Tang, B.; Chen, S.; Lu, Z.; Xue, W. Synthesis, Characterization and Application of Some Axially Chiral Binaphthyl Phosphoric Acids in Asymmetric Mannich Reaction. *Chin. J. Chem.* **2015**, *33*, 601−609. (f) Hatano, M.; Ishihara, H.; Goto, Y.; Ishihara, K. Remote Tris(pentafluorophenyl)borane-Assisted Chiral Phosphoric Acid Catalysts for the Enantioselective Diels-Alder Reaction. *Synlett* **2016**, *27*, 564−570.

(11) (a) Jiao, P.; Nakashima, D.; Yamamoto, H. Enantioselective 1,3-Dipolar Cycloaddition of Nitrones with Ethyl Vinyl Ether: The Difference Between Brønsted and Lewis Acid Catalysis. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411−2413. (b) Rueping, M.; Nachtsheim, B. J. Asymmetric Brønsted Acid Catalyzed Nucleophilic Addition to in situ Generated Chiral *N*-Acyliminium Ions. *Synlett* **2010**, *2010*, 119−122. (c) Vellalath, S.; Coric, I.; List, B. *N*-Phosphinyl Phosphoramide-A Chiral Brønsted Acid Motif for the Direct Asymmetric N,O-Acetalization of Aldehydes. *Angew. Chem., Int. Ed.* **2010**, *49*, 9749−9752.

(12) Li, G. L.; Antilla, J. C. Highly Enantioselective Hydrogenation of Enamides Catalyzed by Chiral Phosphoric Acids. *Org. Lett.* **2009**, *11*, 1075−1078.

(13) Samet, M.; Buhle, J.; Zhou, Y. W.; Kass, S. R. Charge-Enhanced Acidity and Catalyst Activation. *J. Am. Chem. Soc.* **2015**, *137*, 4678−4680.

(14) Fan, Y.; Kass, S. R. Electrostatically Enhanced Thioureas. *Org. Lett.* **2016**, *18*, 188−191.

(15) Ma, J.; Kass, S. R. Electrostatically Enhanced Phosphoric Acids: A Tool in Brønsted Acid Catalysis. *Org. Lett.* **2016**, *18*, 5812−5815.

(16) Fan, Y.; Kass, S. R. Enantioselective Friedel-Crafts Alkylation between Nitroalkenes and Indoles Catalyzed by Charge Activated Thiourea Organocatalysts. *J. Org. Chem.* **2017**, *82*, 13288−13296.

(17) Ma, J.; Kass, S. R. Asymmetric Arylation of 2,2,2-Trifluoroacetophenones Catalyzed by Chiral Electrostatically-Enhanced Phosphoric Acids. *Org. Lett.* **2018**, *20*, 2689−2692.

(18) Itoh, J.; Fuchibe, K.; Akiyama, T. Chiral Phosphoric Acid Catalyzed Enantioselective Friedel-Crafts Alkylation of Indoles with Nitroalkenes: Cooperative Effect of 3 Angstrom Molecular Sieves. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016−4018.

(19) Hermeke, J.; Toy, P. H. Phosphonium Ion Tagged Chiral Phosphoric Acids and Their Application in Friedel-Crafts Reactions of Indoles. *Tetrahedron* **2011**, *67*, 4103−4109.

(20) (a) Nishida, H.; Takada, N.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. Highly Lipophilic Stable Anionic Agent for Solvent-Extraction of Cations. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600−2604. (b) Blight, B. A.; Hunter, C. A.; Leigh, D. A.; Mcnab, H.; Thomson, P. I. T. An AAAA-DDDD Quadruple Hydrogen-Bond Array. *Nat. Chem.* **2011**, *3*, 244−248.

(21) Reid, J. P.; Goodman, J. M. Goldilocks Catalysts: Computational Insights into the Role of the 3,3′ Substituents on the Selectivity of BINOL-Derived Phosphoric Acid Catalysts. *J. Am. Chem. Soc.* **2016**, *138*, 7910−7917.

(22) Positive ee values [MOU2] correspond to the *S*-enantiomer being the major product, and this assignment is based upon a comparison to previously reported results. For additional details, see ref 21a.

(23) Hong, L.; Sun, W. S.; Yang, D. X.; Li, G. F.; Wang, R. Additive Effects on Asymmetric Catalysis. *Chem. Rev.* **2016**, *116*, 4006−4123.

(24) The same coupling procedure that led to **2a**−**e** did not succeed with $(p\text{-}CH_3OC_6H_4)_3P$.

(25) Hirata, T.; Yamanaka, M. DFT Study of Chiral-Phosphoric-Acid-Catalyzed Enantioselective Friedel-Crafts Reaction of Indole with Nitroalkene: Bifunctionality and Substituent Effect of Phosphoric Acid. *Chem. - Asian J.* **2011**, *6*, 510−516.

(26) Zheng, C.; Sheng, Y.-F.; Li, Y.-X.; You, S.-L. A Theoretical Investigation into Chiral Phosphoric Acid-Catalyzed Asymmetric

DOI: 10.1021/acs.joc.9b01741
J. Org. Chem. 2019, 84, 11125−11134

Friedel-Crafts Reactions of Nitroolefins and 4,7-Dihydroindoles: Reactivity and Enantioselectivity. *Tetrahedron* **2010**, *66*, 2875−2880.
(27) This value is based on the measured ee in CH_2Cl_2 as opposed to the other data, which was obtained in a 1:2 CH_2Cl_2/C_6H_6 mixture.
(28) (a) Lungwitz, R.; Spange, S. A Hydrogen Bond Accepting (HBA) Scale for Anions, Including Room Temperature Ionic Liquids. *New J. Chem.* **2008**, *32*, 392−394. (b) Claudio, A. F. M.; Swift, L.; Hallett, J. P.; Welton, T.; Coutinho, J. A. P.; Freire, M. G. Extended Scale for the Hydrogen-Bond Basicity of Ionic Liquids. *Phys. Chem. Chem. Phys.* **2014**, *16*, 6593−6601.
(29) (a) Mori, K.; Wakazawa, M.; Akiyama, T. Stereoselective Construction of All-Carbon Quaternary Center by Means of Chiral Phosphoric Acid: Highly Enantioselective Friedel-Crafts Reaction of Indoles with *β,β*-Disubstituted Nitroalkenes. *Chem. Sci.* **2014**, *5*, 1799−1803. (b) Clot-Almenara, L.; Rodriguez-Escrich, C.; Osorio-Planes, L.; Pericas, M. A. Polystyrene-Supported TRIP: A Highly Recyclable Catalyst for Batch and Flow Enantioselective Allylation of Aldehydes. *ACS Catal.* **2016**, *6*, 7647−7651. (c) Reid, J. P.; Simon, L.; Goodman, J. M. A Practical Guide for Predicting the Stereochemistry of Bifunctional Phosphoric Acid Catalyzed Reactions of Imines. *Acc. Chem. Res.* **2016**, *49*, 1029−1041.
(30) Reid, J. P.; Goodman, J. M. Selecting Chiral BINOL-derived Phosphoric Acid Catalysts: General Model to Identify Steric Features Essential For Enantioselectivity. *Chem. - Eur. J.* **2017**, *23*, 14248−14260.
(31) A low conversion due to a slow rate was observed with **4l** and is the reason for the low isolated yield.
(32) Bures, J. A Simple Graphical Method to Determine the Order in Catalyst. *Angew. Chem., Int. Ed.* **2016**, *55*, 2028−2031.
(33) (a) Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. Synthesis of TRIP and Analysis of Phosphate Salt Impurities. *Synlett* **2010**, *2010*, 2189−2192. (b) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. Enantioselective Organocatalytic Reductive Amination. *J. Am. Chem. Soc.* **2006**, *128*, 84−86.
(34) Park, Y. S.; Grove, C. I.; Gonzalez-Lopez, M.; Urgaonkar, S.; Fettinger, J. C.; Shaw, J. T. Synthesis of (−) Viriditoxin: A 6,6′ Binaphthopyran 2 one that Targets the Bacterial Cell Division Protein FtsZ. *Angew. Chem., Int. Ed.* **2011**, *50*, 3730−3733.
(35) Marques-Lopez, E.; Alcaine, A.; Tejero, T.; Herrera, R. P. Enhanced Efficiency of Thiourea Catalysts by External Brønsted Acids in the Friedel-Crafts Alkylation of Indoles. *Eur. J. Org. Chem.* **2011**, *2011*, 3700−3705.
(36) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. Catalytic Enantioselective Friedel-Crafts Alkylation of Indoles with Nitroalkenes by Using A Simple Thiourea Organocatalyst. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576−6579.
(37) Jeganathan, M.; Kanagaraj, K.; Dhakshinamoorthy, A.; Pitchumani, K. Michael Addition of Indoles to Beta-Nitrostyrenes Catalyzed by HY Zeolite under Solvent-Free Conditions. *Tetrahedron Lett.* **2014**, *55*, 2061−2064.
(38) Babu, K. S.; Rao, V. R. S.; Sunitha, P.; Babu, S. S.; Rao, J. M. Mild and Efficient Michael Addition of Activated Olefins to Indoles using TBAB as A Catalyst: Synthesis of 3-Substituted Indoles. *Synth. Commun.* **2008**, *39*, 1784−1791.
(39) Kumar, A. V.; Rao, K. R. Recyclable Graphite Oxide Catalyzed Friedel-Crafts Addition of Indoles to Alpha, beta-Unsaturated Ketones. *Tetrahedron Lett.* **2011**, *52*, 5188−5191.
(40) Ganesh, M.; Seidel, D. Catalytic Enantioselective Additions of Indoles to Nitroalkenes. *J. Am. Chem. Soc.* **2008**, *130*, 16464−16465.
(41) Lu, S. F.; Du, D. M.; Xu, J. X. Enantioselective Friedel-Crafts Alkylation of Indoles with Nitroalkenes Catalyzed by Bifunctional Bis(oxazoline)-Zn(II) Complex. *Org. Lett.* **2006**, *8*, 2115−2118.
(42) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; [illegible], et al. *Gaussian 09*; Gaussian, Inc.: Wallingford, CT, 2009.
(43) (a) Becke, A. D. Density Functional Thermochemistry. III. The Role Of Exact Exchange. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. Development Of The Colle-Salvetti Correlation-Energy Formula Into A Functional Of The Electron Density. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789.
(44) (a) Zhao, Y.; Truhlar, D. G. How Well Can New-Generation Density Functionals Describe the Energetics of Bond-Dissociation Reactions Producing Radicals? *J. Phys. Chem. A* **2008**, *112*, 1095−1099. (b) Zhao, Y.; Truhlar, D. G. The M06 Suite Of Density Functionals For Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, And Transition Elements: Two New Functionals And Systematic Testing Of Four M06-Class Functionals And 12 Other Functionals. *Theor. Chem. Acc.* **2008**, *120*, 215−241. (c) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Acc. Chem. Res.* **2008**, *41*, 157−167.

DOI: 10.1021/acs.joc.9b01741
J. Org. Chem. 2019, 84, 11125−11134