A Highly Enantioselective Phosphabicyclooctane Catalyst for the Kinetic Resolution of Benzylic Alcohols

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Abstract: A new class of chiral phosphines belonging to the *P*-aryl-2-phosphabicyclo[3.3.0]octane family (PBO) has been prepared by enantioselective synthesis starting from lactate esters and 2,2-dimethylcyclopentanone enolate **5**. A selective enolate alkylation method has been developed for preparation of **9** and **10** using a chelating ester substituent in the triflate alkylating agent **11**. Subsequent conversion to the PBO catalysts **2** and **39** relies on a diastereoselective cyclization from the cyclic sulfate **17** and LiPHAr to afford the more hindered *endo*-aryl phosphines. These phosphines function as efficient catalysts for the kinetic resolutions of aryl alkyl carbinols by benzoylation (**16**, **21**, **22**) or *iso*-butyroylation in the case of the less hindered aryl alkyl carbinol substrates. With *o*-substituted aryl alkyl carbinols, the enantioselectivities exceed 100, and $s = 380 \pm 10$ has been demonstrated in the case of methyl mesityl carbinol. The PBO-catalyzed acylations probably involve a *P*-acylphosphonium carboxylate intermediate and a tightly ion paired transition state.

In 1996, we reported the first examples of enantioselective acyl transfer reactions catalyzed by a chiral phosphine. These experiments demonstrated that 1-phenyl-*trans*-2,5-dimethylphospholane activates *m*-chlorobenzoic anhydride for the chlorobenzoylation of alcohols with significant enantioselectivity ($s = k_{FAST}/k_{SLOW} = 13-15$).[1] There had been many prior attempts to develop chiral nucleophilic acylation catalysts,[2] but this was the first case where a nonenzymatic catalyst was shown to react with $s > 10$.[3] However, the reaction was very slow, so a search for more reactive catalysts was initiated. While our study was in progress, reports from other groups began to appear describing chiral nitrogen nucleophiles that have reached impressive levels of enantioselectivity.[4,5]

Between 1996 and 1999, work in our laboratory encountered a variety of mono- and disubstituted phospholanes that were not significantly better than the original lead structure.[6] On the other hand, bicyclic derivatives based on the 2-phosphabicyclo-[3.3.0]octane (PBO) skeleton proved to be remarkably more reactive even though they are more hindered than their monocyclic analogues.[7-10] The phosphine-catalyzed acylations involve *P*-acyl phosphonium carboxylate intermediates,[11] and the high reactivity of **1** appears to be due to a preference for *P*-phenyl rotamers that allow easy access to the unshared electron pair at phosphorus.

The *gem*-dimethyl catalyst **1** was exceptionally promising in terms of reactivity and also gave encouraging enantioselectivity results in acylations, but the racemic catalyst-borane complex had to be laboriously separated into enantiomers by HPLC.[10] Clearly, an enantioselective synthesis was needed before extensive effort to optimize variables would be worthwhile. Modifications of the scheme developed for preparation of **1** from 1,1-dimethylcyclopentanone were therefore considered that

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Scheme 1

R= Et; 10-15 : 1 **9 : 10**

R= (CH₂)₂O(CH₂)₂OCH₃
6-10 : 1 **10 : 9**
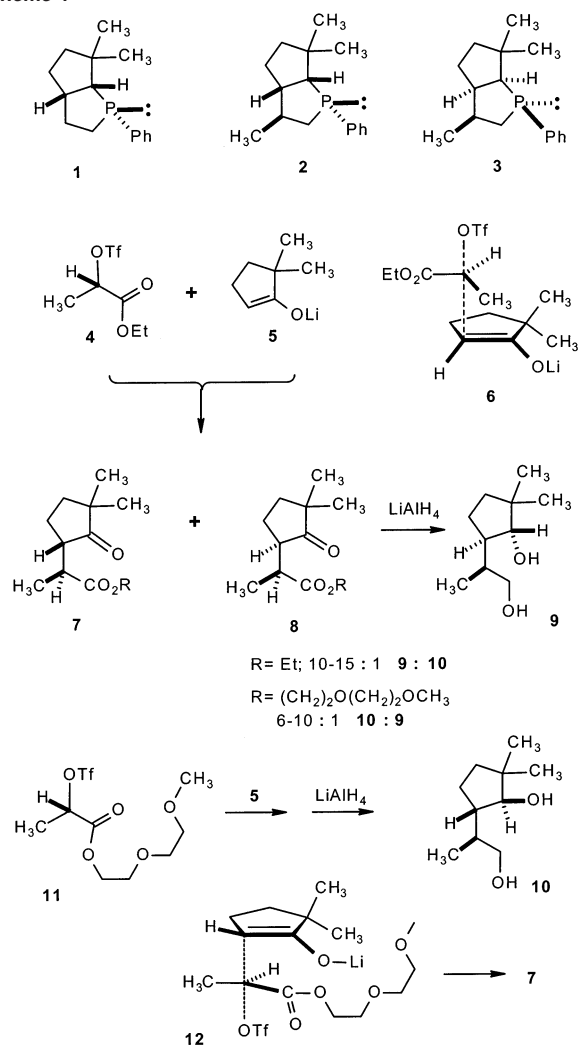
might allow the synthesis of analogues such as **2** (Ph-PBO) or **3** in single enantiomer form. In principle, the only change needed would be to use a chiral lactate triflate **4** in place of the achiral ethyl glycolate triflate alkylating agent in the reaction with the lithium enolate (**5**) of 2,2-dimethylcyclopentanone.[12a−c] Depending on the degree of stereoselectivity in the enolate alkylation step, this approach was expected to provide access to either or both of the diastereomeric phosphines via ketoesters **7** or **8** and diols **9** or **10** (Scheme 1).

Enolate Alkylations Studies Using Lactate Triflates

The alkylation experiments involving **4** and **5** were challenging due to the ease of product equilibration. After considerable experimentation, the following reaction conditions were found to be optimal. Thus, **5** was reacted with **4** from −55 to −60 °C in THF followed by immediate reduction of the crude ketoesters **7** and **8** with LiAlH₄ at −70 °C to give **9** and **10** in ratios as high as 10−15:1. If the intermediate ketoester mixture (presumably 10−15:1 **8**:**7**) was isolated and then subjected to reduction, then a 1:1 mixture of **9**:**10** was obtained. Most likely, equilibra-

(12) β-Keto ester lithium enolates[12a,b] and acyloxazolidinone lithium enolates[12c] have been alkylated with lactate triflates. We could find no case of the use of lactate triflates for alkylation of simple ketone enolates. (a) Hoffman, R. V.; Kim, H.-O. *Tetrahedron Lett.* **1993**, *34*, 2051. (b) Hoffman, R. V.; Kim, H.-O. *J. Org. Chem.* **1995**, *60*, 5107. (c) Decicco, C. P.; Nelson, D. J.; Corbett, R. L.; Dreabit, J. C. *J. Org. Chem.* **1995**, *60*, 4782.

tion had occurred via enolization of **8** during the time that the alkylation product was warmed to room temperature. However, this complication could be avoided by taking care to control the temperature prior to and during the reduction step, resulting in good selectivity for **9**. The stereochemistry of the major product was assigned on the basis of X-ray crystallography of intermediates later in the synthesis.

The next problem was to access the diastereomeric diol **10** by inverting enolate facial selectivity in the alkylation step. An analysis of possible transition states for alkylation of enolate **5** by the ethyl lactate triflate **4** suggested that the major diastereomer **8** may be formed by attack from the top face of enolate **5** as shown in the proposed transition state **6**. This model assumes that the triflate leaving group is displaced with inversion of configuration and places the smallest substituent (hydrogen) of the alkylating agent over the cyclopentene ring. Given these constraints, structure **8** is the expected product if the ester group is positioned to avoid the enolate oxygen (**6**). Presumably, this arrangement minimizes unfavorable electronic interactions as well as nonbonded steric interactions.

By the same logic, access to the other enolate face (attack from below) would be expected if the apparent tendency of the ethyl ester to avoid enolate oxygen could be reversed by modifying the ester alkoxy group. The triflate **11** suggests a possible solution, based on the notion that the methoxyethoxy-ethyl ester group might have an affinity for lithium ion. To test this possibility, **11** was prepared from methyl (*S*)-lactate by a sequence involving transesterification with methoxyethoxyethanol followed by triflic anhydride/pyridine. The triflate was formed as a somewhat unstable liquid which had to be used on the same day due to decomposition.
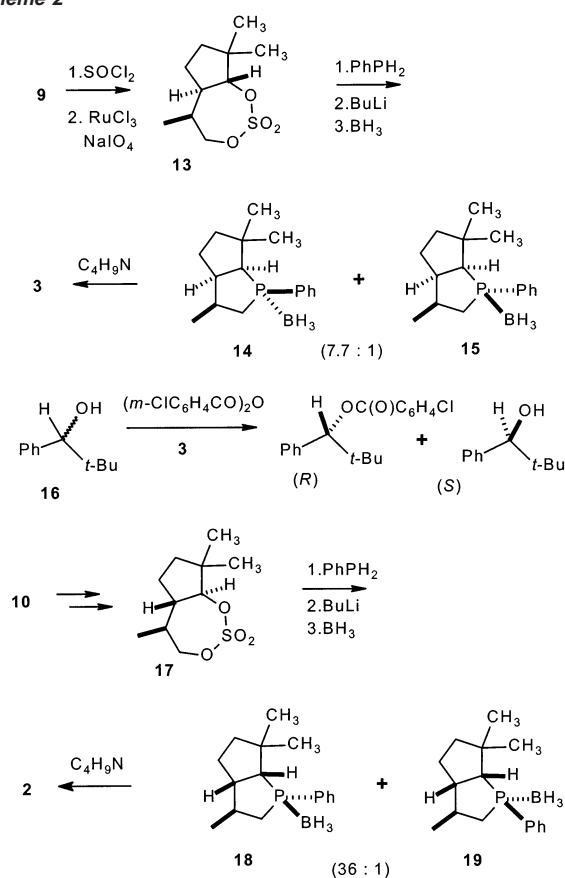
The alkylation of enolate **5** with **11** was explored in solvents of varying lithium coordination ability. Generation of the enolate in toluene using LDA followed by addition of **11** and immediate reduction as in the ethyl ester case gave the desired, inverted product ratio. The best result was obtained from −55 to −60 °C (ca. 10:1 **10:9**), although the yield was in the 30−40% range. Better yields could be achieved at higher temperatures, but at the expense of a decreased diastereomer ratio. When the experiment was repeated in the more coordinating THF as a solvent, the opposite ratio (1:10 **10:9**) was obtained in low yield (10−15%), supporting the involvement of lithium coordination in the toluene experiment. While the yield in toluene was modest, the possibility of alkylating either face of the enolate by using an ester group that is capable of lithium coordination was successfully demonstrated. Subsequent experiments established that the alkylation proceeds with clean inversion of configuration at the triflate-bearing carbon, and without detectable racemization.

A proposed transition state for the alkylation using **11** is illustrated by structure **12**. The enolate lithium ion may be coordinated to all three oxygens of the methoxyethoxyethyl carboxylate. With hydrogen placed beneath the cyclopentane ring to minimize steric interactions, the result is to position the electrophile for alkylation of the desired face of the enolate. Complexation involving the lithium ion is presumably broken up in THF, resulting in the same sense of diastereoselectivity as with the ethyl lactate triflate reagent via the geometry **6**.

We could find no prior examples where enolate facial selectivity in analogous alkylations has been inverted by modifying

Scheme 2

the lithium coordination ability in the ester alkoxy substituent. Possibly related examples of inverted facial selectivity have been reported in alkylations of sulfoxide anions (MeI gave opposite facial selectivity as compared to the alkylation with trimethyl phosphate)[13a] and amide enolates[13b,c] (opposite facial selectivities for alkylations with alkyl halides versus epoxides).[13b] Lithium interactions with the different leaving groups have been invoked in these examples.

With both diastereomers **10** and **9** available in enantiomerically enriched form, attention was turned to the synthesis of **2** and **3** (Scheme 2). The precedented[14] synthesis of cyclic sulfate **13** from diol **9** was uneventful, and reaction of **13** with LiPHPh followed by BH$_3$−THF afforded the epimeric borane complexes **14** and **15** in a ratio of 7.7:1. The diastereomers were separated by column chromatography, and the *endo*-phenyl phosphine **3** was liberated by brief warming with pyrrolidine.[15] This isomer has the less hindered *exo* orientation for the unshared electron pair at phosphorus and is expected to be the most reactive nucleophilic catalyst.[10] The enantiomeric excess of **3** was checked at the stage of **14** and was found to be >99.9% after a single recrystallization, even though the starting lactate was no better than 97% ee. The relative and absolute configuration of **14** was then confirmed by X-ray crystallography, confirming that the reaction of the 2,2-dimethylcyclopentanone enolate **5** with ethyl (*S*)-lactate triflate **4** had occurred with inversion.

Phosphine **3** is the less stable diastereomer in terms of phosphorus configuration and proved to be somewhat sensitive to epimerization at phosphorus.[16] Thus, deprotection of **14** with pyrrolidine at 50 °C always gave a trace of an isomeric phosphine, presumably having the *exo-P*-phenyl orientation. Reaction times in the deprotection experiments had to be carefully controlled to minimize this complication.

Preliminary evaluations of phosphine **3** as an acylation catalyst indicated somewhat lower reactivity and enantioselectivity compared to **1**. Thus, a value of $s = 8.9$ was found for the *m*-chlorobenzoylation of **16** using **3** as the catalyst compared to $s = 14$ using **1** in the corresponding reaction. Further attention was therefore focused on the diastereomer **2** (Scheme 2).

The synthesis of **2** (Ph-PBO) from the crude diol **10** used the same treatment with SOCl$_2$ followed by oxidation to afford the cyclic sulfate **17** (21% yield overall from 2,2-dimethylcyclopentanone). Subsequent reaction of **17** with LiPHPh and complexation using BH$_3$−THF allowed the isolation of a borane complex with a remarkable 36:1 diastereomer ratio of **18**:**19** in favor of the desired *endo*-phenyl epimer. In the corresponding cyclization step in the synthesis of **1**, a 16:1 ratio of diastereomers had been obtained in favor of the *endo* phenyl isomer.[10] The diastereomers **18** and **19** were separated by column chromatography, and phosphine **2** was liberated by briefly warming **18** with pyrrolidine. The absolute and relative configuration of **2** was confirmed at the stage of **18** by X-ray crystallography. In contrast to the borane complex of **1**,[10] the crystal lattice of **18** contains only one conformer. The ee of **18** was 96−98% if nonrecrystallized cyclic sulfate **17** was used in the synthesis, or 99.7% ee if **17** was recrystallized prior to use. Alternatively, a single recrystallization of **18** with ≥96% ee raised the ee to >99.9%.

In anticipation of a lengthy optimization study for catalyst **2**, a qualitative method was sought that would allow a rapid estimate of enantioselectivity by NMR assay of a mixture containing ^{13}CH$_3$-labeled **20** and the enantiomeric ^{12}CH$_3$ alcohol (Scheme 3). Thus, (*S*)-^{13}CH$_3$-**20** was prepared from the labeled 2-acetonaphthone with (−)-DIP chloride,[17] while unlabeled (*R*)-**20** was made by reduction of unlabeled 2-acetonaphthone using (+)-DIP chloride. The two quasi-enantiomers were easily distinguished because of the large ^{13}C−CH coupling, resulting in a doublet of doublets for the ^{13}CH$_3$ group of (*S*)-^{13}CH$_3$-**20**, spaced symmetrically on both sides of the simple doublet due to the ^{12}CH$_3$ group of unlabeled (*R*)-^{12}CH$_3$-**20**.[18a] The NMR sample of the quasi-racemate **20** was then partially benzoylated using benzoic anhydride and catalyst **2**, and the resulting mixture of benzoate ester and alcohol was monitored over time by ^{1}H NMR integration. The methyl region was well resolved, and separate signals due to the quasi-enantiomeric benzoate esters and unreacted quasi-enantiomeric alcohols were observed, allowing assay for conversion as well as % ee of starting material and product from a single ^{1}H NMR spectrum by

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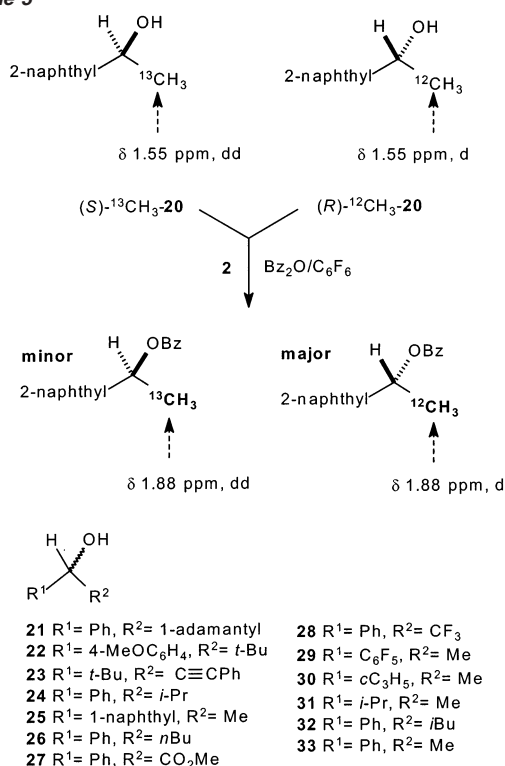(15) Wolfe, B.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 5116.

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Scheme 3

Table 1. Solvent Effects in Benzoylation of (S)-$^{13}CH_3$-**20**/(R)-$^{12}CH_3$-**20** by NMR Assay (Room Temperature)

solvent	enantioselectivity
C_6D_6	$s = 8-9$
toluene-d_8	$s = 8-9$ (7)[a]
CD_3CN	$s = 5$
CD_2Cl_2	$s = 6-7$ (5.5)[a]
EtOAc	$s = 7.5$
C_6F_6	$s = 8-9$
acetone-d_6	$s = 6-7$
3-methyl-3-pentanol	$s = 7$
THF-d_8	$s = 7-9$
DMF-d_7	$s = 5-6$

[a] Value of s determined by HPLC assay.

comparison of integral intensities. The results are summarized in Table 1. Enantioselectivities were somewhat overestimated using NMR, judging from standard HPLC methods applied to the toluene and dichloromethane entries (s values in parentheses). The source of the discrepancy is a combination of errors in integration, alcohol ee values, and relative proportions of the quasi-enantiomers, but the trends were clear. The reactions were faster and more enantioselective in the nonpolar, aromatic solvents (toluene, benzene). Saturated hydrocarbon solvents could not be monitored conveniently by NMR due to solubility problems with the benzoic anhydride.

The effort needed to prepare the isotopically enriched, quasi-racemic mixture for NMR assay was worthwhile as long as s values were modest, and numerous data points were required for the same substrate–anhydride combination. Mass spectroscopy provides an alternative for the rapid assay of isotopically labeled mixtures using an automated approach,[18b] but the NMR technique was convenient for our purposes even though it is imprecise. However, optimization studies soon revealed conditions resulting in much higher s values that required the precision of HPLC assay.

Table 2. Acylation of Alcohols R^1R^2CHOH with $(RCO)_2O$ Using Catalyst **2**[a]

entry	alcohol	anhydride R	R^1	R^2	relative rate[b]	s
1	**16**	Ph	Ph	t-Bu	1	24
2	**16**	Ph	Ph	t-Bu	1 (heptane)	21
3	**16**	Ph	Ph	t-Bu	0.1 (−40 °C)	67
4	**16**	m-ClC$_6$H$_4$	Ph	t-Bu	0.1 (CH$_2$Cl$_2$)	14
5	**16**	1-naphthyl[c]	Ph	t-Bu	0.02	25
6	**16**	Me	Ph	t-Bu	0.6	16
7	**16**	i-Pr	Ph	t-Bu	0.01	4.9
8	**21**	Ph	Ph	1-adamantyl	0.6	23
9	**22**	Ph	4-MeOC$_6$H$_4$	t-Bu	0.8	22
10	**23**	Ph	Ph-ethynyl	t-Bu	8	3.7
11	**24**	Ph	Ph	i-Pr	12	15
12	**24**	i-Pr	Ph	i-Pr	0.1	13
13	**20**	Ph	2-naphthyl	Me	24	7
14	**20**	1-naphthyl[c]	2-naphthyl	Me	2	13
15	**20**	2-naphthyl[c]	2-naphthyl	Me	10	5.8
16	**20**	phthalic	2-naphthyl	Me	NR	
17	**20**	i-Pr	2-naphthyl	Me	3	12
18	**20**	t-Bu	2-naphthyl	Me	0.04	6.9
19	**25**	i-Pr	1-naphthyl	Me	2	21
20	**26**	Ph	Ph	n-Bu	17	9.8
21	**26**	i-Pr	Ph	n-Bu	5	11
22	**27**	i-Pr	Ph	CO$_2$Me	3	3.0
23	**28**	i-Pr	Ph	CF$_3$	8	5.9
24	**29**	i-Pr	C$_6$F$_5$	Me	4	3.9
25	**30**	i-Pr	c-C$_3$H$_5$	Me	6	1
26	**31**	i-Pr	i-Pr	Me	0.1	1

[a] All reactions used 0.13 M substrate in toluene with 2.5 equiv of anhydride at room temperature unless noted. [b] The relative rate (as compared to entry 1) was estimated by calculating rate constants from individual % conversion and time data points, and assuming pseudo-first-order conditions and linear behavior with respect to the catalyst. The (R) alcohol was the faster-reacting enantiomer for entries 1−21. Assignments were not made for the less selective reactions (entries 22−26). [c] The naphthoic anhydride was used as a stirred suspension.

Acylations of representative aryl alkylcarbinols catalyzed by **2** were investigated in the optimal hydrocarbon solvents, as summarized in Table 2. The hindered substrate **16** was used for the initial optimization studies, and several anhydrides were evaluated. The highest enantioselectivity at room temperature was obtained using 1-naphthoic anhydride (entry 5), but the reagent was inconvenient because of limited solubility, lack of a commercial source, and low reactivity requiring many hours at room temperature. Benzoic anhydride was far more reactive, and nearly as enantioselective as 1-naphthoic anhydride, while *iso*-butyric anhydride (entry 7) was the least reactive anhydride tested with **16**. Enantioselectivity was considerably lower with *iso*-butyric anhydride ($s = 4.9$) and intermediate with acetic anhydride ($s = 16$; entry 6). The benzoic anhydride procedure was briefly evaluated with other hindered aryl t-alkyl carbinol substrates at room temperature, and comparable results were obtained with **21**[19a] and **22**[19b] as with **16**. On the other hand, an alkynyl *tert*-butyl alcohol **23**[19c] reacted with low selectivity (entry 10), suggesting that the aryl substituent plays a large role in recognition of the enantiomers.

The best kinetic resolution result with **16** was obtained with benzoic anhydride in toluene solution at −40 °C ($s = 67$). Although the optimized experiment involves a temperature drop of 60 °C from the room temperature conditions, the benzoylation rate decreased by only ca. 8-fold. Similar behavior had been

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observed for the simpler PBO catalyst **1**,[10] resulting from an unusual combination of low activation enthalpy and large, negative activation entropy. This pattern has proven to be general for all of the PBO catalysts encountered in this study.

A number of other aryl alkyl carbinols were resolved with good selectivity using catalyst **2** in toluene (Table 2, entries 11–21). However, the optimum match of the anhydride reactant with catalyst **2** for these substrates proved to be different as compared to the substrates containing a tertiary alkyl substituent. In the representative example of 2-naphthyl(-1-ethanol), **20**, the enantioselectivity of kinetic resolution using *iso*-butyric anhydride (entry 17; *s* = 12) was higher than that with benzoic anhydride (entry 13), and almost as high as in the reaction with 1-naphthoic anhydride (entry 14; *s* = 13). Because the benzoylations were considerably faster, the benzoic anhydride method was used with a number of other substrates. Temperature optimization was not explored because a better catalyst was discovered by varying the *P*-aryl group, as described below. However, the reactions using **2** at room temperature helped to establish qualitative enantioselectivity and reactivity trends that have proven to be general.

Rates of acylation were estimated from % conversion versus time data by assuming pseudo-first-order kinetics[10] and are tabulated in Table 2 relative to the benzoylation of **16** (entry 1). The relative rate numbers are approximate,[20] but they are close enough to provide a qualitative ordering of substrate and anhydride reactivity. Thus, the reactions using benzoic anhydride were at least an order of magnitude faster than the *iso*-butyroylations, an effect that was also seen with the simpler catalyst **1**. Increasing electron withdrawal in the substrate (entries 22–24) increased rates, while steric hindrance in the alcohol or in the anhydride reagent resulted in considerably slower reactions. Good enantioselectivity was observed if an aromatic ring was attached to the hydroxyl-bearing carbon, but simple steric differentiation of the alcohol substituents was not sufficient for enantioselectivity, as shown in entries 25 and 26.
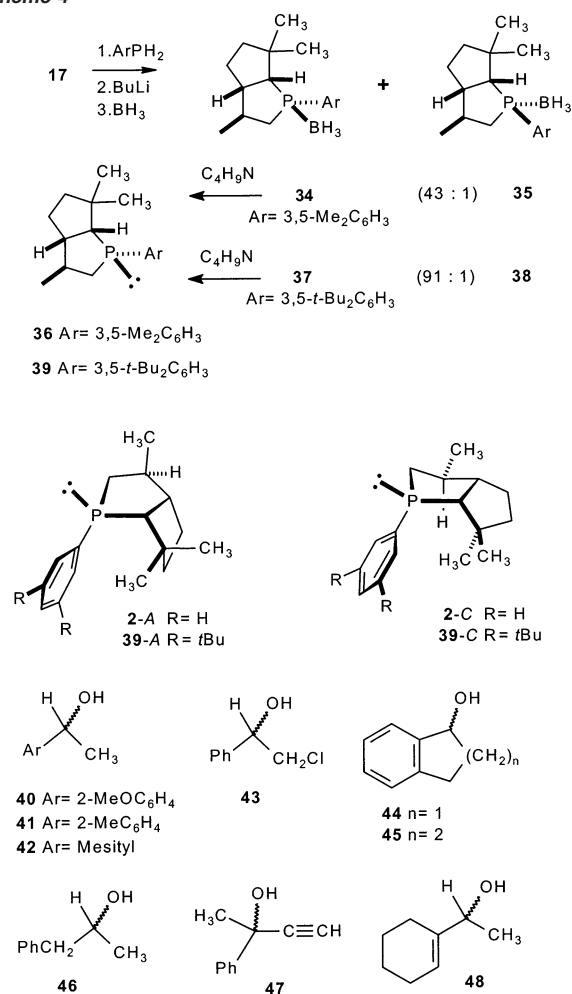
The Synthesis and Evaluation of Me₂Ph-PBO (36)

The phenyl group in Ph-PBO (**2**) was replaced by 3,5-dimethylphenyl to evaluate acylation selectivity. The synthesis was uneventful and followed the earlier precedent (Scheme 4), although the diastereoselectivity in the cyclization from **17** was somewhat improved compared to the Ph-PBO series (dr 43:1 **34**:**35** versus 36:1 **18**:**19**). Deprotection of **34** in the usual way with pyrrolidine provided the new catalyst **36**. Acylations catalyzed by **36** were somewhat faster compared to those using **2**, but there was no significant advantage in enantioselectivity in several examples at room temperature: benzoylation of **16**, *s* = 8.1, toluene; *iso*-butyroylations of **20**, *s* = 14, toluene; **24**, *s* = 14, heptane; and **32** (1-phenylethanol), *s* = 12, heptane. The exploration of this series was terminated, and no optimization was attempted because a superior catalyst was discovered as described in the next section.

The Synthesis and Evaluation of *t*-Bu₂Ph-PBO (39)

The synthesis of **39** (*t*-Bu₂Ph-PBO) was carried out by the usual method from **17** (Scheme 4), and the corresponding borane

(20) Reference 10 shows that pseudo-first-order conditions are satisfied using 6 equiv of the anhydride, while 2.5 equiv was used in experiments for enantioselectivity determination.

Scheme 4

complex was isolated in 85% yield. The key cyclization step was incredibly selective and gave a 91:1 ratio in favor of the desired diastereomer **37**, ca. 20% overall from 2,2-dimethylcyclopentanone. The ee of **37** could not be measured with high precision due to HPLC overlap of trace impurities with the minor enantiomer, but the ee of the recrystallized precursor sulfate **17** could be assayed by conversion to **18** (99.7% ee for the batch of **17** used for most of the work described below), so the same ee value was assumed for **39**. Phosphine **39** was then tested in acylations, as summarized in Table 3. It became apparent that the new catalyst is superior to all of the PBO derivatives described earlier, except for the case of the highly hindered alcohol **16** where the combination of catalyst **2** and benzoic anhydride gave better results (Table 2, entry 3). Aryl alkyl carbinols that contain *n*-alkyl or *sec*-alkyl substituents are resolved more efficiently using **39**, and *iso*-butyric anhydride was the best match for this catalyst. In all cases where direct comparisons were made (see Supporting Information), the sense of enantioselection was the same. Thus, the catalyst configuration shown for **39** results in the preferential acylation of the (*R*)-alcohol for the entries of Table 3.

Enantioselectivities were improved in heptane compared to toluene, so the toluene conditions were used only where necessary due to alcohol solubility. In the case of 1-phenyl-1-pentanol (**26**, entries 16, 17), alcohol solubility in heptane was sufficient to vary the concentration over a reasonable range. This example was used to confirm that *s* at −40 °C is not

Table 3. Acylation of Alcohols R^1R^2CHOH with $(RCO)_2O$ Using Catalyst **39**[a]

		anhydride				
entry	alcohol	R	R^1	R^2	solv/temp[b]	s
1	**16**	Ph	Ph	t-Bu	tol/RT	10
2	**16**	i-Pr	Ph	t-Bu	tol/RT	9.8
3	**24**	Ph	Ph	i-Pr	tol/RT	6.9
4	**24**	i-Pr	Ph	i-Pr	tol/RT	18
5	**24**	i-Pr	Ph	i-Pr	hept/RT	20
6	**24**	i-Pr	Ph	i-Pr	hept/−40 °C	99 (117)[c]
7	**20**	n-Pr	2-naphthyl	Me	tol/RT	9.2
8	**20**	i-Pr	2-naphthyl	Me	tol/RT	17
9	**20**	t-Bu	2-naphthyl	Me	tol/RT	12
10	**33**	i-Pr	Ph	Me	tol/RT	18
11	**33**	i-Pr	Ph	Me	hept/RT	22
12	**33**[d]	i-Pr	Ph	Me	hept/−20 °C	42 (45)[c]
13	**33**[e]	Me	Ph	Me	tol/−40 °C	11
14	**43**	i-Pr	Ph	CH₂Cl	hept/RT	12
15	**43**	i-Pr	Ph	CH₂Cl	hept/−20 °C	19
16	**26**	i-Pr	Ph	n-Bu	hept/RT	18
17	**26**	i-Pr	Ph	n-Bu	hept/−40 °C	55 (60)[c]
18	**32**	i-Pr	Ph	i-Bu	hept/RT	14
19	**32**[f]	i-Pr	Ph	i-Bu	hept/−40 °C	31
20	**28**	i-Pr	Ph	CF₃	hept/RT	7.5
21	**28**[f]	i-Pr	Ph	CF₃	hept/−20 °C	12
22	**25**	Ph	1-naphthyl	Me	tol/RT	6.0
23	**25**	i-Pr	1-naphthyl	Me	tol/RT	35
24	**25**	i-Pr	1-naphthyl	Me	hept/RT	42 (44)[c]
25	**25**	i-Pr	1-naphthyl	Me	tol/−40 °C	99 (116)[c]
26	**40**	i-Pr	2-MeOC₆H₄	Me	hept/RT	38
27	**40**	i-Pr	2-MeOC₆H₄	Me	tol/−40 °C	82 (94)[c]
28	**41**	i-Pr	2-MeC₆H₄	Me	hept/RT	39 (41)[c]
29	**41**	i-Pr	2-MeC₆H₄	Me	hept/−40 °C	145 (185)[c]
30	**41**[g]	i-Pr	2-MeC₆H₄	Me	hept/−40 °C	142 (180)[c]
31	**41**[h]	i-Pr	2-MeC₆H₄	Me	hept/−40 °C	188[h]
32	**42**	i-Pr	2,4,6-Me₃C₆H₂	Me	hept/RT	22
33	**42**	i-Pr	2,4,6-Me₃C₆H₂	Me	tol/RT	15
34	**42**	i-Pr	2,4,6-Me₃C₆H₂	Me	tol/−10 °C	87 (100)[c]
35	**42**	i-Pr	2,4,6-Me₃C₆H₂	Me	tol/−40 °C	220 (328)[c]
36	**42**[h]	i-Pr	2,4,6-Me₃C₆H₂	Me	tol/−40 °C	390[h]
37	**42**[h]	i-Pr	2,4,6-Me₃C₆H₂	Me	tol/−40 °C	370[h]
38	**42**[e,h]	Me	2,4,6-Me₃C₆H₂	Me	tol/−40 °C	112[h]

[a] All reactions used 0.13 M substrate, 2.5 equiv of anhydride, and **38** with 99.7% ee unless noted. The (R) alcohol was the more reactive enantiomer in all of the secondary alkyl aryl carbinols, and recoveries of alcohol and ester were routinely >90%. [b] Solvents tol = toluene; hept = heptane; RT = room temperature. [c] Selectivity corrected[21] to 99.7% ee of catalyst (the correction becomes significant at s > 40). [d] Concentration 0.033 M due to solubility limitation. [e] 0.6 equiv of anhydride was used. [f] Concentration 0.05 M. [g] Experiment using **41** on 7.5 mmol scale. [h] Recrystallized catalyst **39**, >99.9% ee.

affected by changes in concentration (over the range from 0.033 to 0.2 M) or % conversion (from 36 to 51%), and consistent values of $s = 55 \pm 2$ were obtained in several experiments. These findings support the kinetic assumptions mentioned earlier.

As before, benzoylations were at least 10-fold faster than the *iso*-butyroylations, but the latter were considerably more enantioselective. Overall, the reactivity trends for the examples of Table 3 were similar to those of Table 2. Thus, the effect of temperature on the reaction rate was relatively small, and a 60 °C drop in temperature was tolerated with a rate decrease of severalfold in typical examples. For example, the *iso*-butyroylation of **41** in heptane at −40 °C was 5 times slower compared to the room-temperature experiment (entries 28, 29).

In the most dramatic advantage for catalyst **39**, the enantioselectivity increased substantially as the temperature was lowered. Alcohols such as **25**, **40**, **41**, containing an *o*-substituted phenyl group, showed the largest temperature dependence on enantioselectivity and were among the best substrates for catalyst

39. At −40 °C, these alcohols were resolved with s in the range of 100 or above.

Early experiments with **41** gave an empirical $s = 39$ at room temperature or $s = 142-145$ at −40 °C, but the catalyst **39** had been made from a batch of cyclic sulfate **17** known to have 99.7% ee as described earlier. With such high selectivity, we wondered how s would be affected by the enantiomeric contaminant (*ent*-**39**). Ismagilov's mathematical treatment for correcting s to the value expected for the pure catalyst (100% ee) became available as these experiments were conducted,[21] and the calculation indicated a corrected $s = 180-185$. To test the calculation, the catalyst **39** was recrystallized, and the experiment was repeated. In this case, an empirical (uncorrected) value of $s = 188$ was determined, in excellent agreement with the calculation if the recrystallized catalyst has >99.9% ee.

The correction is very sensitive to the precision of ee assay for the impure catalyst. For example, if the empirical $s = 145$ had resulted using a catalyst sample having 99.6% ee, then the calculated enantioselectivity corrected to 100% catalyst ee increases to $s = 204$ versus $s = 185$ for the assumption that the catalyst has 99.7% ee. There is less sensitivity to catalyst ee, and a smaller calculated correction to s, as the enantioselectivity decreases. Below $s = $ ca. 40, the difference between the empirical and the corrected s values becomes insignificant for catalyst having 99.7% ee.

The *o,o*-disubstituted substrate 2,4,6-trimethylphenyl methyl carbinol (**42**) also proved to be interesting. The room-temperature experiments were not exceptional, and good selectivity was observed in toluene ($s = 15$) as well as in heptane ($s = 22$). Because of solubility limitations, the more promising heptane conditions could not be used at lower temperatures, so the toluene conditions were explored. This resulted in the largest temperature effect seen for any of the alcohol substrates, as well as the highest enantioselectivity. Starting with catalyst believed to be 99.7% enantiomerically pure, an empirical enantioselectivity $s = 220$ was measured. Assuming $ee_{cat} = 99.7\%$, the corrected[21] value for 100% ee catalyst would be $s = 328$. However, if catalyst ee is taken as a slightly lower number (99.6% ee), then the corrected enantioselectivity increases to $s = 392$. Because the effect of catalyst purity is so large, the experiment was repeated using the same batch of recrystallized catalyst demonstrated to have >99.9% ee in the acylation of **41**. In two experiments, enantioselectivities were determined as $s = 370$ and $s = 390$ at −40 °C in toluene (Table 3, entries 36, 37). The calculated numbers are highly sensitive to error in the measured ee values, but good agreement in s was possible because the enantiomers of **42** are well separated by HPLC on a chiral support and can be assayed with high precision. The enantioselectivity with **42** is the highest value known to date for a nonenzymatic acyl transfer reaction.

In view of the high enantioselectivity in the *iso*-butyroylation of **42**, a similar experiment was carried out using acetic anhydride. As shown in Table 3, entry 38, reasonably high enantioselectivity was observed ($s = 112$), in contrast to less hindered alkyl aryl carbinols. For example, the acetylation of 1-phenyl-1-ethanol (**33**, entry 13) under similar conditions was far less selective ($s = 11$).

The other entries in Table 3 show that typical aryl alkyl carbinols are resolved with good to excellent enantioselectivity

(21) Ismagilov, R. F. *J. Org. Chem.* **1998**, *63*, 3772.

using *t*-Bu$_2$Ph-PBO (**39**). Almost any alkyl group is tolerated (entries 4–19), with the best selectivity for R = *i*-Pr. As mentioned earlier, the R = *t*-Bu example (entries 1, 2) is unusual because better results are obtained with the *P*-phenyl catalyst **2**. For primary or secondary alkyl groups, **39** is the more effective catalyst. However, cyclic aryl alkyl carbinols such as 1-indanol (**44**) or 1-tetrahydronaphthol (**45**) are not resolved (*s* < 1.5). Furthermore, the homoallylic alcohol **46** is not a good substrate for acylation (*s* = 1), nor is the tertiary alcohol **47** (*s* = 1.3).

One other substrate category does react with useful enantioselectivity. In a preliminary experiment, the allylic alcohol **48** reacted with *s* = 52 at −40 °C. This topic has been discussed in another publication from our laboratory, and kinetic resolutions of a number of other allylic alcohols have been demonstrated.[9a] These findings underscore the importance of a double bond attached to the hydroxyl-bearing carbon for enantioselection in the acyl transfer process.

Discussion

A new class of chiral phosphines belonging to the *P*-aryl-2-phosphabicyclo[3.3.0]octane family (PBO) has been prepared by enantioselective synthesis starting from methyl lactate and 2,2-dimethylcyclopentanone. In the course of the synthesis, an enolate alkylation method has been developed that allows reversal of the alkylation facial selectivity by introducing a chelating ester substituent in the electrophile. Subsequent conversion to the PBO catalysts **2**, **3**, and **39** relies on a diastereoselective cyclization from the cyclic sulfates and LiPHAr reagents to afford the more hindered *endo*-aryl phosphines. These phosphines have proven to be efficient catalysts for the kinetic resolutions of aryl alkyl carbinols and allylic alcohols[9a] by benzoylation (**16**, **21**, **22**) or *iso*-butyroylation in the case of the less hindered aryl alkyl carbinol substrates. With *o*-substituted aryl alkyl carbinols, the enantioselectivities exceed 100, and *s* = 370–390 has been measured in the case of methyl mesityl carbinol. For the best substrates, the enantioselectivities using PBO catalysts have reached the levels usually associated with enzymatic acyl transfer reactions.[3] Several other nonenzymatic acyl transfer kinetic resolution catalysts have recently been reported that function with potentially useful enantioselectivity for the best substrates.[4,5]

As discussed elsewhere,[10] the PBO-catalyzed acylations are believed to involve a tight ion pair transition state, derived from a *P*-acylphosphonium carboxylate intermediate. Additional evidence consistent with this proposal is provided by a number of examples tabulated using the new catalysts **2**, **3**, and **39** where the fastest reactions are observed in the least interactive solvent (heptane). This finding suggests that tight ion pairing in the acylation transition states allows the most effective participation by carboxylate anion in the eventual proton transfer that must occur as the alcohol is recognized, deprotonated, and acylated. However, we cannot specify the geometric details of the transition state, nor is it clear whether the reaction involves a cyclic transition state, a conventional tetrahedral intermediate,[22–24] or a concerted displacement of the phosphonium leaving group by the alcohol oxygen acting as the nucleophile.

We cannot comment in detail on the origins of enantioselectivity without knowing other important details of transition state geometry. In particular, a knowledge of carboxylate placement and orientation would be important. Without evidence bearing on this issue, specific proposals regarding the geometry for acyl transfer would not be justified. We do know that cyclic benzylic alcohols such as **44** and **45** are constrained to geometries that do not fit the preferences of the PBO catalyst **39**, judging from the negligible enantioselectivity in these examples. High enantioselectivity requires a flexible, unconstrained π-system adjacent to the hydroxyl group. This could be taken to imply that a π-stacking interaction is important between the aryl rings of the substrate and the catalyst,[25] but several arrangements are possible where such effects could be invoked. These geometries cannot be distinguished from the evidence available at this time.

The lactate-based enantioselective synthesis of the new PBO catalysts introduces an additional methyl substituent on the pholane ring compared to the original lead compound **1**. Modeling studies suggest that two distinct conformations of **1** are likely (designated as conformers *A* and *C* in ref 10) and that they have similar energies, but rather different environments near phosphorus.[10] The corresponding conformers of **2** or **39** are shown in Scheme 4 as the structures **2**-*A* or **2**-*C*, and **39**-*A* or **39**-*C*. Conformers in the *C*-series (**2**-*C* or **39**-*C*) accept the pseudoequatorial methyl substituent in the pholane ring with no significant change in geometry along the bicyclic (PBO) framework. This geometry corresponds closely to the conformation of **18** determined by X-ray crystallography and is regarded as the most likely ground-state geometry for **2** and **39**. A similar PBO geometry is plausible in the transition state for catalytic anhydride activation because structures such as **2**-*C* or **39**-*C* maintain an easily accessible unshared electron pair at phosphorus.

Conformers similar to **2**-*A* or **39**-*A* are less likely to serve as the reactive catalysts because the pholane methyl group would be closer to the unshared electron pair at phosphorus. Furthermore, the *P*-aryl substituent is closer to the plane of maximum unshared electron pair density in the *A*-series of conformers. However, a small (ca. 10–15°) change in the *P*-aryl dihedral angles would be enough to obscure this difference between the *A* and *C* conformers, while a modification of pholane twist envelope conformations would accommodate the methyl substituent in a more nearly pseudoequatorial orientation. Such geometries may be accessible and cannot be ruled out as participants in the acyl transfer process. More rigid structures will need to be investigated to further clarify transition state preferences.

A substantial effort was invested to probe the relationship between catalyst purity and enantioselectivity.[21,26] The magnitude of the correction for the most selective reactions (Table 3; entries 29–31, 34–37) initially surprised us, but the explanation is simple enough. Samples of **39** having 99.7% ee contain 0.15% of *ent*-**39**, a contaminant that is the best match for catalytic conversion of the (*S*)-carbinols in Table 3 (the slower reacting substrates for **39**). The competing pathway resulting from catalysis by the contaminant lowers the enantiomeric purity of

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the ester product as well as the unreacted alcohol relative to the values expected for pure catalyst. The result is to lower the uncorrected value calculated for *s*. The difference between empirical and corrected values of *s* becomes especially striking as the inherent enantioselectivity becomes exceptionally high. When reactions are so selective that even the impure catalyst affords products with an apparent value of *s* = 220 (entry 35), the use of purified catalyst is not so important in the practical context because the enantioselectivity is already good enough for most purposes. We emphasize the corrected *s* values primarily because this allows a more meaningful comparison with the analogous enzymatic acyl transfer reactions. Presumably, natural acyl transfer catalysts have ≫99.9% ee. Optimized, highly selective synthetic catalysts would be at a disadvantage in the comparisons unless they are used as enantiomerically pure substances.

Supporting Information Available: Experimental procedures and tabulated data for kinetic resolutions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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