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A Comparison of Monocyclic and Bicyclic Phospholanes as Acyl-Transfer Catalysts

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The synthesis and evaluation of chiral phosphines **11**, **15a**, **19a**, **24a**, and **28a** as nucleophilic catalysts for anhydride activation and kinetic resolution of alcohols is described. The relative reactivity follows the order **11a** > **11b** > **15a** > **1** in the monocyclic series, and **24a** > **19a** > **28a** in the bicyclic series, with an overall rate advantage of ca. 2 orders of magnitude for the bicyclic phospholanes over the monocyclic analogues. The increased reactivity of the bicyclic phospholanes for the acylation of alcohols is attributed to conformational effects and ground-state destabilization in a highly associative mechanism. Kinetic resolution data demonstrate promising enantioselectivities for **24a**.

In 1993, a report from our laboratory demonstrated that tributylphosphine is comparable to *p*-(dimethylamino)pyridine as a nucleophilic catalyst for the acylation of alcohols by anhydrides.[1,2] The *P*-arylphosphines were less effective than is Bu_3P, but dialkylarylphosphines retained sufficient reactivity to activate anhydrides at room temperature. These observations stimulated a survey of chiral dialkylarylphosphines as potential enantioselective acylation catalysts, and initial screening identified 2,5-dimethylphospholane **1**[3] as a promising nucleophilic catalyst (Scheme 1). Phospholane **1** activated *m*-chlorobenzoic anhydride for chlorobenzoylation of alcohols via the transient ion pair intermediate **2**. In the case of racemic phenyl-*tert*-butylcarbinol (**3**), the chlorobenzoylation occurred with significant enantioselectivity ($s = k_{fast}/k_{slow} = 13-15$).[4] However, the reaction was very slow and required ca. two weeks to reach 25% conversion to **4** at room temperature using 15% of the catalyst. Furthermore, other dialkylphenylphosphines such as **5**[5] and **6**[6] were unreactive under the same room temperature conditions, while **7** and **8**[5] were marginally reactive but less selective compared to **1**.

The initial results were encouraging because the enantioselectivity for the conversion from **3** to **4** was relatively high. After a long history of work in many

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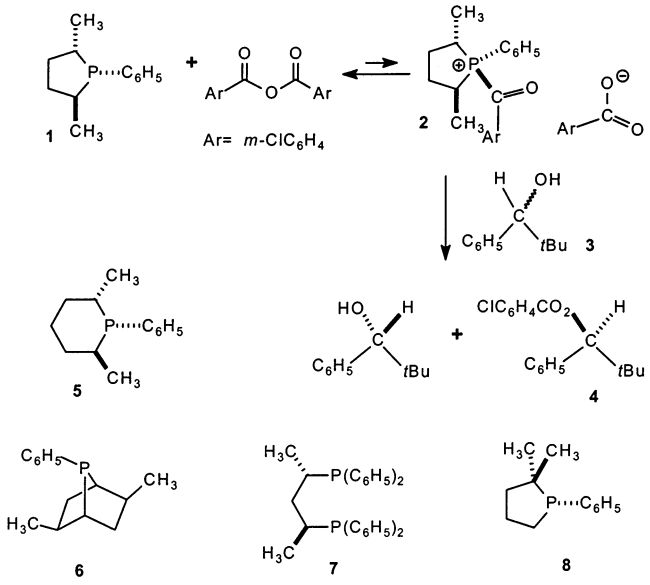

laboratories,[7] this was the first example to demonstrate $s > 10$ for a kinetic resolution based on acyl transfer using a nonenzymatic catalyst.[8] On the other hand, catalyst reactivity was a major concern, and a large effort had to be initiated to define the factors that might

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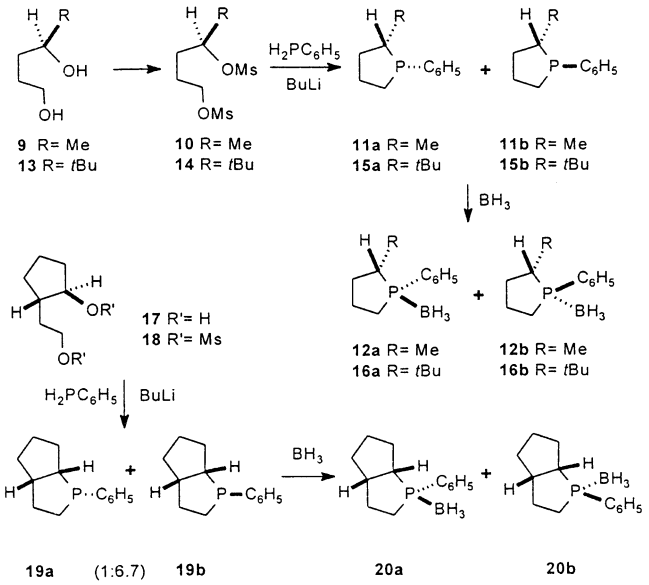

increase the rate of acylation. During this search, important advances from other groups began to appear,[9] and several intriguing nitrogen-based esterification catalysts for acyl-transfer reactions are now known that are capable of potentially practical levels of enantioselectivity with $s > 30$, depending on the alcohol substitution pattern.[10]

Synthesis and Reactivity of Phospholane Derivatives

In an effort to improve catalyst reactivity in the chiral phosphine series, modifications of the lead structure **1** were considered that would improve access to the unshared electron pair at phosphorus. Removal of one of the adjacent methyl substituents was the logical first step, and our optimization studies began with the investigation of 2-monosubstituted phospholanes (Scheme 2). Diastereomeric 2-methyl-1-phenylphospholanes **11a** and **11b** (previously reported as a mixture of isomers)[11] were prepared from the diol **9** via the known bismesylate **10**[12] by treatment with $PhPH_2$/BuLi, and were isolated as the phosphine boranes **12a** and **12b** (7.3:1 ratio). The borane complexes were stable to chromatography, and the diastereomers as well as the enantiomers could be separated by HPLC. Enantiomerically enriched samples of the phosphines **11a** and **11b** were then obtained by brief warming with pyrrolidine or Et_2NH. The major isomer **11a** was confirmed to have the *cis* stereochemistry by X-ray crystallographic analysis of the derived methiodide salt.

TABLE 1. *m*-Chlorobenzoylation of 3 Catalyzed by Monocyclic Phospholanes[a]

entry	catalyst	rel rate	**s**
1	**1**	1	13[b]
2	**11a**	36	5
3	**11b**	4	5.1
4	**15a**	2	5.6

[a] All experiments at room temperature in dichloromethane using 2.5 equiv of *m*-chlorobenzoic anhydride. [b] Ref 3a.

With diastereomers **11a** and **11b** available, qualitative reactivity comparisons were carried out using the *m*-chlorobenzoylation of **3** as the test reaction. Significant rate improvement was observed with both diastereomers compared to **1** (*trans*-isomer **11b**, 6-fold faster; *cis*-isomer **11a**, ca. 36-fold faster according to comparisons of initial rates), but enantioselectivity was decreased ($s = 5-5.1$). Furthermore, an attempt to improve enantioselectivity by introducing additional steric constraints quickly encountered reactivity limitations. Thus, 2-*tert*-butylphospholane **15a**, available via a similar sequence from diol **13**,[13] gave a small increase in enantioselectivity (Table 1, entry 4; $s = 5.6$). However, reactivity dropped considerably compared to that of **11a**.

Related structures were considered that might retain the promising reactivity of **11a** while allowing at least some potential for structural modification. The bicyclic phospholane **19a** was one attractive possibility. The electron pair at phosphorus would be more accessible because the fused cyclopentane ring should increase the $P-CH-CH_2$ bond angle in **19a** compared to the corresponding $P-CH-CH_3$ bond angle in **11a**. Nucleophilic reactivity might also be influenced by conformational preferences resulting from repulsive interactions between the fused cyclopentane ring and the *P*-phenyl substituent in **19a**. Compared to the situation in **11a**, the additional bulk on the lower face of **19a** should favor *P*-phenyl rotamers where the phenyl group is turned more toward the adjacent bridgehead C−H bond and away from the ring CH_2 groups. This effect might destabilize the ground state relative to the transition state for nucleophilic catalysis, and could increase the reaction rate.

The bicyclic phosphines **19a** and **19b** were made in the usual way from the known diol **17**[14] via the bismesylate **18**.[14] However, in contrast to the behavior of the simpler bismesylate **10**, the ring-fused analogue **18** reacted with $PhPH_2$/BuLi to give a 1:6.7 mixture in favor of the undesired *exo*-phenyl diastereomer **19b** over **19a**. The diastereomers of the corresponding borane complexes **20a**

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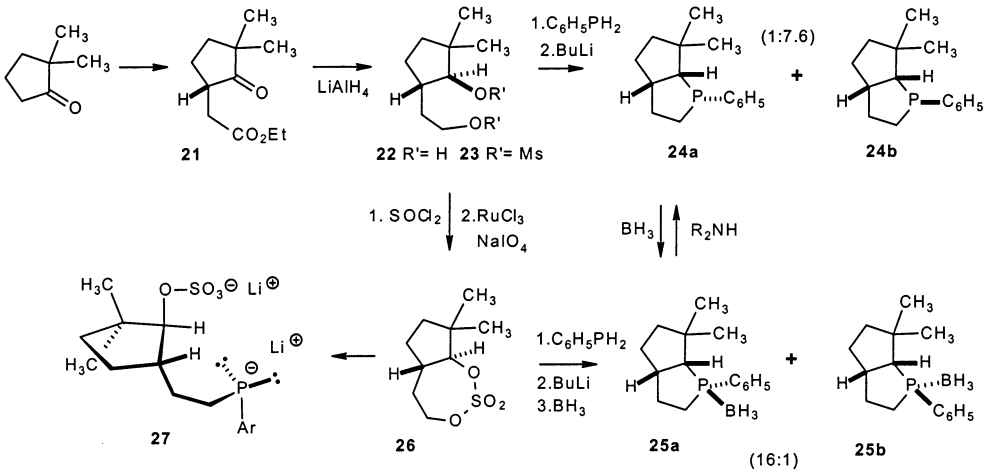
SCHEME 3



and **20b** were difficult to separate, and only 4% of racemic **20a** was recovered from the mixture. Fortunately, this provided sufficient material for deprotection to the phosphine **19a** by brief warming with pyrrolidine, and allowed evaluation of the rate of *m*-chlorobenzoylation of **3** using racemic **19a**. Remarkably, **19a** was more reactive than **11a** by at least 10-fold in the qualitative comparison. Indeed, the reactivity was so much better in the case of less hindered alcohols that it became difficult to make comparisons under the usual room temperature conditions with *m*-chlorobenzoic anhydride and the procedures had to be modified as discussed later. On the other hand, the synthesis and purification of **20a** were difficult and the HPLC separation of enantiomers was challenging in the initial studies. The accumulation of preparative obstacles raised concerns about pursuing this series of structures. We therefore elected to investigate the more highly hindered bicyclic analogue **24a** in the hope that reactivity would be retained and that the synthesis and purification might be easier (Scheme 3).

The first attempts[5] to prepare **24a** from keto ester **21**[15] by the usual sequence via **22**[16] and the bismesylate **23** encountered the same problems as with **19a**. Thus, reaction of **23** with $PhPH_2$/BuLi gave an unfavorable 1:7.6 mixture of **24a**/**24b**. Fortunately, much better results were obtained by changing the leaving groups. The key improvement was to use a cyclic sulfate, **26**, in place of the bismesylate **23**. Conversion of diol **22** into **26** was performed following a 1,4-diol analogy by Burk et al. ($SOCl_2$, $NaIO_4$/$RuCl_3$),[17] and the sequence afforded an 80% yield of crystalline **26**. The subsequent reaction with $PhPH_2$/BuLi gave a mixture of **24a** and **24b**, and conversion to the corresponding borane complexes resulted in a 16:1 ratio of isomers **25a**/**25b**. The desired major isomer was isolated in 64% yield as a crystalline solid. Enantiomerically enriched **25a** was then obtained after HPLC on a chiral support, and the relative stereochemistry and the absolute configuration were established by X-ray crystallography (Figure 1).

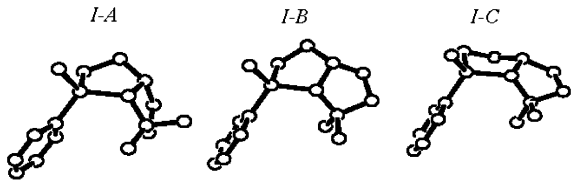


FIGURE 1. Conformers of **25a** in the crystal lattice.

Compared to the analogous reaction of the bismesylate **23**, the conversion from cyclic sulfate **26** to **24** occurred with considerably higher selectivity (16:1), and with an inverted preference for the formation of the more hindered *endo*-phenyl diastereomer **24a**. Even higher selectivity has been encountered recently in a closely related cyclization reaction using 3,5-disubstituted aryl phosphide reagents, as described in another paper from our laboratory.[18] The mechanistic details of this reaction are poorly understood, but the initial event is likely to be the S_N2 displacement at the less hindered primary carbon of **26**. The dramatic change in diastereoselectivity at phosphorus starting from the cyclic sulfate **26** compared to the bismesylate **23** is therefore due to the behavior of a monoalkylated phosphide intermediate, **27**, in the subsequent cyclization step. Formation of the *endo*-phenyl diastereomer **24a** probably requires intramolecular backside attack on the sulfate leaving group (OSO_3Li) in **27**. On the basis of this assumption, the stereochemistry of **27** can be deduced from that of the product **24a**. However, we cannot explain why the difference in leaving groups (MsOLi from **23**, $LiOSO_3Li$ from **26**) results in the indicated phosphorus configurations. Presumably, simple steric effects dominate transition-state preferences starting from **23**, and lead to the less hindered (undesired) *exo*-phenyl diastereomer **24b**. By implication, interactions among the phosphorus unshared electron pairs, monoalkyl sulfate oxygens, and two lithium ions are responsible for the predominant formation of the *endo*-phenyl diastereomer in the conversion from **26** to **27** to **24a**, but the nature of the interactions is not understood in detail. In any event, the much improved diastereoselectivity profile in the cyclization reaction starting from the cyclic sulfate **26** greatly simplifies the

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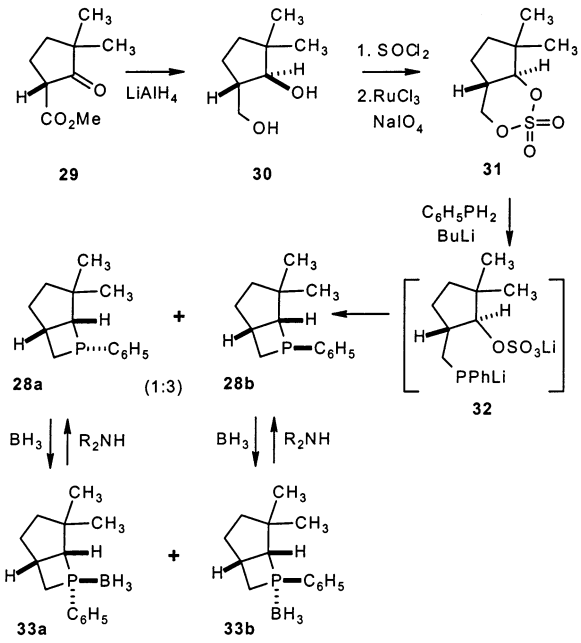
SCHEME 4



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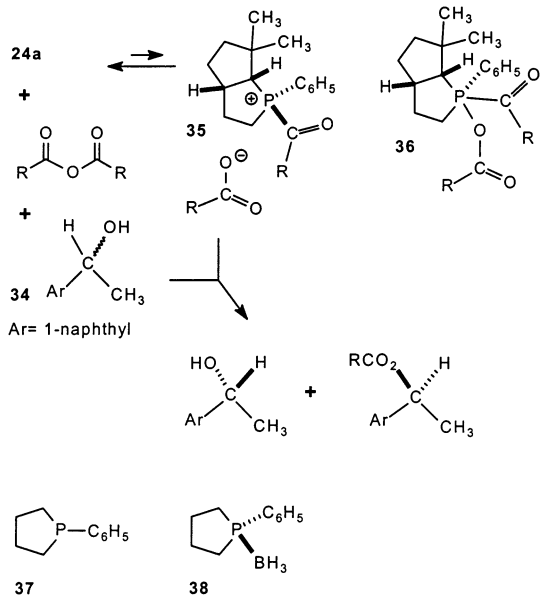

synthesis of **24a**, and allows preparation of sufficient material to evaluate the new phosphine.

Enantiomer separation of the borane complex **25a** using HPLC on a chiral support gave the individual enantiomers with 63−85% ee, and crystallization of **25a** provided a further upgrade to afford a small amount of material with >99% ee. The stereochemistry and the absolute configuration of the crystallized sample were established unambiguously using X-ray crystallography (see the Supporting Information). The relative HPLC retention time behavior of the individual enantiomers on a chiral support was then used to develop an empirical correlation with the enantiomers of the analogous phosphine **20a** and of related phosphines to be discussed shortly. Together with the enantioselectivity profiles of the related bicyclic phosphines, this empirical data allowed tentative assignments of absolute configuration in all of the bicyclic phosphines.

Preliminary experiments demonstrated that **25a** is decomplexed by brief warming with pyrrolidine and that the resulting **24a** is more reactive than **19a** in the *m*-chlorobenzoylation of **3**. We therefore carried out the synthesis of one additional analogue in the bicyclic series in the hope that further insight might be obtained regarding the relationship between phosphine geometry and catalytic reactivity. If the improved reactivity of 2-phosphabicyclo[3.3.0]octane derivative **19a** or **24a** compared to the monocyclic phospholanes results from improved access to phosphorus resulting from a small increase in the P−CH−CH_2 bond angle compared to the situation in **11a** or **15a**, then a substantially faster rate should be seen with the phosphetane analogue **28a** where the corresponding angle would be larger. To test this proposal, the synthesis of **28a** was carried out as described in Scheme 4, using a small variation of the approach that was successful for the preparation of **24a**. Conversion from the known keto ester **29**[19] to the cyclic sulfate **31** was routine, but the subsequent phosphide cyclization procedure gave a diastereomer ratio of only 3:1 according to NMR assay of the phosphine borane complexes **33** obtained after treatment with THF−borane. Furthermore, the phosphine derived from the major borane complex proved to be unreactive as a catalyst for anhydride activation under the standard conditions, while the minor phosphine was reactive. In all of the other bicyclic phosphines, the more reactive diastereomer has proven to be the *endo*-phenyl isomer. By that argument, the desired phosphine **28a** must be the *minor* cyclization product from the reaction of **31** with $PhPH_2$/BuLi, while the major isomer is the relatively unreactive **28b**. The cyclization diastereoselectivity favoring the *exo*-phenyl isomer is therefore opposite by comparison with the reaction of the analogous cyclic sulfate **26** with $PhPH_2$/BuLi, apparently due to differing intramolecular interactions in the phosphide intermediate **32** compared to **27**. Despite the disappointing diastereoselectivity, the phosphine borane complexes **33a** and **33b** could be separated, purified, and subjected to HPLC on a chiral support for resolution of enantiomers. Decomplexation by brief warming with pyrrolidine was then conducted in the usual way, and provided sufficient enantiomerically enriched **28a** to evaluate reactivity and enantioselectivity.

Relative Reactivity Studies with the Bicyclic Phospholane Catalysts

As already mentioned, the reactivity of the bicyclic catalysts was too high for convenient evaluation using the prior conditions with *m*-chlorobenzoic anhydride, especially for relatively nonhindered substrates such as 1-(1-naphthyl)ethanol (**34**) (Scheme 5). In principle, the rate could be adjusted as needed by limiting the amount of catalyst, but that approach gave less reproducible reactivity data, perhaps due to competing oxidation of the catalyst by residual oxygen in reagents or solvents. More consistent rates were obtained by decreasing the reactivity of the anhydrides, by maintaining relatively

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TABLE 2. Acylations Catalyzed by Bicyclic Phospholanes[a]

entry	catalyst	alcohol	$(RCO)_2O$	rel rate	s
1	**1**	**34**	R = Ph	1	3.3
2	**19a**	**3**	R = Ph	11	5.5
3	**19a**	**34**	R = *i*Pr	76	1.5
4	**19a**	**34**	R = Ph	300	2.8
5	**24a**	**3**	R = Ph	18	14
6	**24a**	**34**	R = *i*Pr	110	9, 15[b]
7	**24a**	**34**	R = Ph	1200	10,[c] 28[b]
8	**28a**	**34**	R = *i*Pr	80	1.2
9	**28a**	**34**	R = Ph	130	4.8

[a] 2.5 equiv of anhydride, toluene solution, room temperature unless noted; *s* values corrected for catalyst ee according to ref 24. [b] −25 °C. [c] 35 °C.

high catalyst loading in the range of 10−20 mol % relative to the alcohol, and by using the less hindered alcohol **34** as the substrate for the comparisons. The latter substrate is more representative of the arylalkylcarbinols featured in a related series of acylations using an optimized catalyst,[18] and was therefore employed for most of the remaining experiments designed to probe reactivity. However, the original substrate **3** was also studied with two of the bicyclic catalysts using benzoic anhydride as the acyl donor. In all cases, the phosphines were generated by cleavage of the purified borane complexes with pyrrolidine, and were used directly after rapid filtration chromatography. Rate comparisons were then performed under marginal pseudo-first-order conditions using 2.5 equiv of the anhydride relative to the alcohol reactant so that reactions could be monitored over 10−40% conversion, the range where NMR integration was adequate for the purpose of determining the extent of reaction. This qualitative technique allowed a ranking of catalyst reactivity (Table 2) and demonstrated that the more highly substituted bicyclic phospholane **24a** is more reactive than the phospholane **19a** or the phosphetane **28a**, and that benzoic anhydride is significantly more reactive than isobutyric anhydride.

The rate comparisons involving the phosphetane catalyst **28a** were complicated by 15−20% catalyst decomposition over the course of the acyl-transfer experiment, as evidenced by the gradual appearance of four new downfield signals in the ^{31}P NMR spectrum (ca. 60−130 ppm). Because the extent of catalyst decomposition was too small to explain the observed decrease in reactivity compared to **24a**, the details of the decomposition pathways have not been investigated. Furthermore, no such complications were observed in any of the phospholane experiments where the only side reaction detected was oxidation to afford minor amounts of the phosphine oxide. No ^{31}P evidence was found to indicate the formation of a detectable concentration of the *P*-acylphosphonium intermediate **35**,[20] or a pentavalent phosphorus species such as **36**, although the ^{31}P signal characteristic of the bicyclic phosphine catalysts was easily observed in the range of 0 to −5 ppm throughout the experiments. According to earlier work, **35** is likely to be formed as a transient intermediate, but the concentration must be too low for NMR detection under acyl-transfer conditions. In principle, an equilibrium between **35** and **36** is also plausible, although the *P*-acylphosphorane subunit of **36** lacks direct precedent.

A surprisingly small (less than 5-fold) decrease in acylation rates was observed in representative examples as the reaction temperature was lowered by 50−60 °C using the bicyclic phospholane catalysts. This result implies that activation enthalpy is relatively small, and that the activation barrier is dominated by entropic factors.[21−23] Rates were therefore determined over a broad temperature range to establish the activation parameters for acylation of **34** using the most reactive bicyclic catalyst **24a**. A modified procedure was developed to improve reproducibility and to maintain pseudo-first-order conditions, including a larger excess of anhydride (6 equiv over the alcohol), deoxygenation of solvents, preparation and storage of catalyst solutions in an inert atmosphere drybox, GLPC assay for percent conversion, and quenching the anhydride as well as the catalyst prior to assay. The latter precaution proved to be important for the experiments monitored by GLPC assay.

Enantioselectivity data were also obtained (HPLC assay on a chiral support, *s* corrected for catalyst ee[24]). This allowed the determination of pseudo-first-order rate constants for the competing acylations of both alcohol enantiomers and calculation of the corresponding activation parameters (Table 3). As expected from the minimal temperature dependence on acylation rates, the enthalpies of activation are small (1.4−4.5 kcal/mol), and the activation entropies are large and negative (−64 to −74 eu). In each case, the less reactive alcohol enantiomer is acylated via a pathway having significantly larger activation enthalpy, and marginally larger (less negative) activation entropy. Therefore, the $\Delta\Delta G^{*}$ term that reflects enantiomer discrimination is dominated by differences in activation enthalpy, resulting in a significant temperature effect on enantioselectivity. The most dramatic example in this context is the benzoylation of **34** catalyzed by **24a**, with $s = 10$ at 35 °C and $s = 28$ at −25 °C.

Catalyst Conformation

The X-ray crystal structure of borane complex **25a** provided an unexpected opportunity to explore conformational preferences. Three distinct conformers of **25a** (*I-A*, *I-B*, *I-C*, Figure 1) were present in the unit cell, suggesting that these geometries may be similar in energy. Although this unusual situation undoubtedly reflects crystal lattice packing effects, it provides three convenient starting geometries for the identification of the most likely solution-phase energy minima. More importantly, it also offers a means to calibrate compu-

(20) The adduct of acetyl chloride with tributylphosphine is characterized by a ^{31}P chemical shift in the region typical of phosphonium salts, δ 28.8 ppm; see ref 1a, footnote 10.

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TABLE 3. Activation Parameters for Kinetic Resolution of 34 Catalyzed by 24a

entry	solvent	$(RCO)_2O$	ΔG^*_{fast}[a,b]	ΔH^*_{fast}[b]	ΔS^*_{fast}[c]	ΔG^*_{slow}[b]	ΔH^*_{slow}[b]	ΔS^*_{slow}[c]
1	toluene	R = Ph	20.8	1.90	−68.0	22.3	4.51	−64.1
2	MeCN	R = Ph	20.8	1.72	−68.7	22.1	3.65	−66.3
3	toluene	R = *i*Pr	22.1	1.39	−74.4	23.4	2.99	−73.3

[a] Fast and slow refer to the two competing kinetic resolution pathways from fast-reacting and slow-reacting substrate enantiomers. The ΔG values are calculated at 5 °C, the midpoint of the temperature range for entries 1 and 2 (−25 to +35 °C). Entry 3 was monitored over the range from −25 to +22 °C, and enantioselectivities were determined as **s** = 15 and **s** = 9, respectively. [b] Kilocalories per mole. [c] Entropy units.

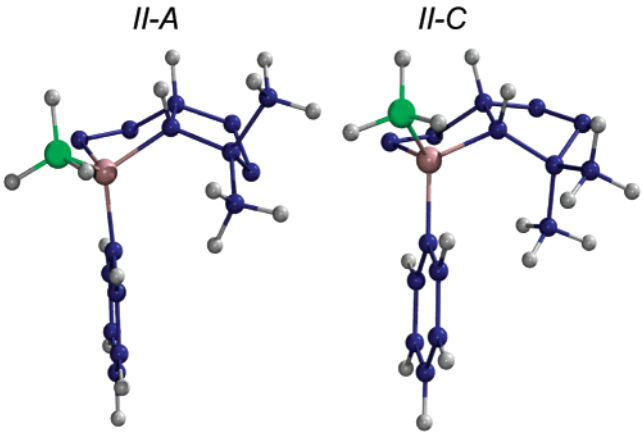

FIGURE 2. Energy minima for **25a** (3-21G*).

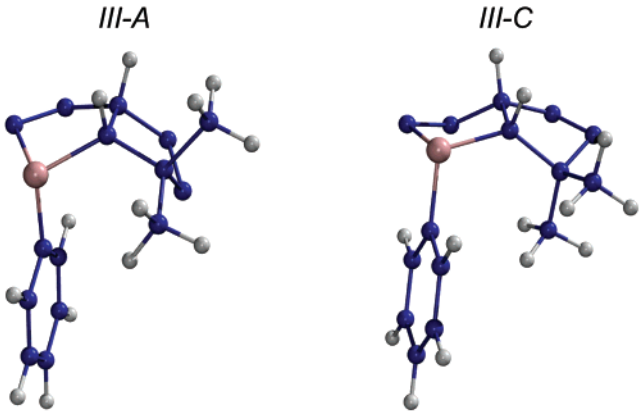

FIGURE 3. Energy minima for **24a** (3-21G*).

tational methods that might be useful for modeling ground-state structures and for evaluating individual geometric features that could be important in the transition state. This might help to understand why the bicyclic phospholanes are 2 orders of magnitude more reactive than the monocyclic analogues.

Initial modeling attempts focused on semiempirical methods (AM1, PM3) as implemented in Spartan. Local energy minima were identified by systematically varying *P*-phenyl dihedral angles and ring conformations. Neither AM1 nor PM3 identified any of the three structures *I-A*, *I-B*, and *I-C* as an energy minimum for **25a**, suggesting that these methods are unlikely to provide meaningful relative energy information in the phospholane environment. However, the semiempirical study did provide a broad range of ring conformers that could be optimized using more sophisticated methods.

The next conformational search was carried out at the 3-21G* (ab initio) level, starting from a variety of ring conformations and varying the *P*-phenyl dihedral angle in 3° increments. This search was far more time-intensive as expected, but the results were more in accord with the notion that crystal lattice conformers may resemble energy minima in solution.

Two energy minima were found in the 3-21G* search. One of these geometries (*II-C*, Figure 2) is nearly identical to *I-C*, while the other (*II-A*) closely resembles *I-A*. The differences in the latter case involve subtle modifications between envelope and twist envelope geometries in the five-membered rings. The former energy mimimum (structure *II-C*) has the same bicyclic ring conformation as the solid-state conformer *I-C*, but there is a small difference in *P*-phenyl dihedral angles relative to the BH_3 group (*II-C*, −31 ± 3°; *I-C*, −38.6°). The corresponding dihedral angles differ somewhat more in the alternative minimum energy conformers (*II-A*, −13 ± 3°; *I-A*, −25.0°), but both conformers experience a significant twist of the *P*-phenyl group away from the C−B bond. The effect is greater in the *C*-series of conformers (*I-C* and *II-C*), presumably due to a larger steric effect from the pseudoaxial *endo*-methyl group.

No energy minima were found that resemble the solid-state conformer *I-B*. Conformers having the same combination of phospholane and cyclopentane envelope or twist envelope forms were processed, but could not be evaluated without imposing artificial constraints on the geometry. Unconstrained geometries invariably relaxed to one of the other conformer series related to *II-A* and *II-C*, suggesting that there is no energy minimum corresponding to *I-B*, and that the latter structure may be the result of crystal lattice effects. Assuming that specific solvation does not alter this picture, conformers *II-A* and *II-C* are likely to be the principal equilibrium species in solution. According to the 3-21G* comparison, these conformers have essentially identical energies (within 0.1 kcal/mol!). Although the precision of calculated energy values is certainly not this high, the qualitative picture fits well with the presence of both solid-state conformers *I-A* and *I-C* in the unit cell, as well as with *II-A* and *II-C* in solution, and suggests that the 3-21G* level is satisfactory for modeling other phospholanes.

The same computational approach was therefore extended to the parent phosphine **24a**. Results similar to those of the borane complex series were obtained. Two families of conformers were identified, and two energy minima were found (*III-A* and *III-C*, Figure 3). Conformer *III-C* is virtually identical to *II-C*, while *III-A* resembles *II-A*, but has a more nearly planar phospholane subunit. As in the borane complexes, the energies of the two conformers are essentially identical (0.3 kcal/mol in favor of *III-A*), and the phenyl ring in *III-C* is twisted more from the plane of maximum unshared electron pair

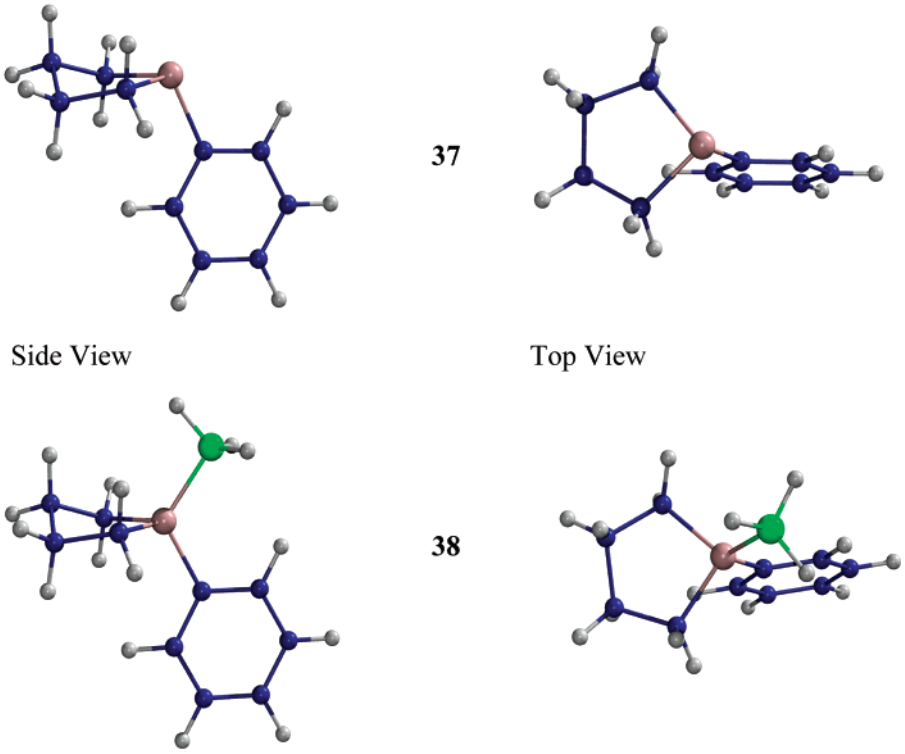

FIGURE 4. Energy minima for **37** and **38** (3-21G*).

density at phosphorus (ca. 42°) compared to that in *III-A* (ca. 29°).

To gain further insight regarding conformational preferences of *P*-phenylphospholane structures, the parent monocyclic derivative **37**[25] was evaluated (3-21G*). The most stable conformer found in this case was quite different from any of the bicyclic phospholane minima. The phenyl ring orientation is within 2° of bisecting the C−P−C ring bond angle, and eclipsing the unshared electron pair at phosphorus (Figure 4). The same minimum energy geometry was found for the corresponding borane complex **38**. These results are consistent with the conclusion stated earlier that the bicyclic ring system enforces geometries having the *P*-phenyl ring turned 10−30° toward the bridgehead hydrogens, and away from the hindered *endo* face. They also suggest a possible explanation for the exceptional reactivity of the bicyclic phospholanes based on a simple steric effect related to *P*-phenyl conformer preferences. Thus, geometries similar to *III-C* have a more accessible unshared electron pair at phosphorus compared to eclipsed conformers such as that found in the monocyclic phospholane **37**. If the *P*-phenyl orientation is important as proposed, then **37** should be less reactive than the more highly substituted bicyclic phospholane **24a**. This proposition was tested by using **37** as the catalyst for the isobutyroylation of **34** under the standard conditions used for Table 2. Monocyclic **37** was found to be less reactive than any of the bicyclic phospholanes, and 13-fold less reactive than **24a**.

Discussion

The reactivity of the phospholane family of nucleophilic catalysts reveals surprising differences between the monocyclic and bicyclic phospholanes. Simple steric considerations are sufficient to account for relative reactivity in the monocyclic series, and increased access to the unshared electron pair at phosphorus correlates with the observed reactivity trends (**11a** > **11b** > **15a** > **1**, Table 1). Matters are not so simple in the bicyclic series (Table 2). Here, the trend appears to connect increased reactivity with increased hindrance (for example, **24a** > **19a** > **37**), but this is probably a coincidence. We believe that the real factor is the role of unsymmetrical substitution on phospholane conformer and *P*-phenyl rotamer preferences.

Our findings suggest that the bicyclic phospholanes **19a** and **24a** are more reactive than their monocyclic analogues because the *P*-phenyl geometry corresponds more closely to the preferred geometry of the transition state for acyl transfer. The presence of a fused five-membered carbocyclic ring probably destabilizes the ground state relative to the transition state by favoring geometries where the *P*-phenyl group is twisted to minimize eclipsing interactions with the bond from phosphorus to the carbonyl carbon derived from the anhydride. This effect increases with increasing substitution next to the bridgehead, as in **24a**.

The extrapolation from preferred phosphine borane or phosphine geometries to the transition state for acyl transfer is a large one. Pending further investigation of more rigid structures, we cannot be certain which of the two conformers (*II-A* or *II-C*) is the most reactive geometry for nucleophilic catalysis with the catalyst **24a**. Since the energies of structures corresponding to the two conformers *II-A* and *II-C* do not differ significantly in either the phosphine **24a** or the borane complex **25b**, the transition-state geometry for acyl transfer would be controlled by new interactions between the catalyst and

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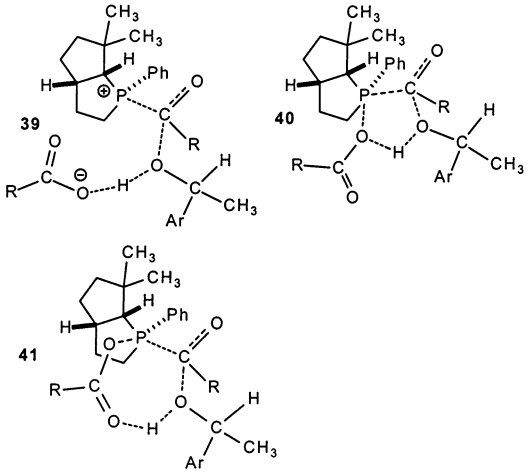

FIGURE 5. Transition-state bonding options.

the anhydride and alcohol reactants. Several other critical features remain undefined, and a detailed discussion of the acyl-transfer process would not be justified. However, a qualitative discussion of some key features in the more plausible scenarios is possible.

From the large, negative activation entropy, a highly associative mechanism can be proposed, having all three components (anhydride, alcohol, catalyst) present in the transition state. The lack of a significant solvent dielectric effect on the activation parameters from toluene to acetonitrile (Table 3; compare entries 1 and 2) suggests that there is little change in charge separation in the transition state compared to the reactants. If the reaction proceeds via **35** and not the phosphorane **36**, then the transition state would have to involve tightly ion paired phosphonium and carboxylate subunits interacting with the alcohol, as shown in **39** (Figure 5). This option maintains the mechanistic analogy with DMAP-catalyzed acyl transfer, to the extent that the latter process is understood.[26]

The alternative transition-state descriptions **40** and **41** represent pathways that might be accessible from the ion pair **35**, or from a transient phosphorane, **36**. There is no direct precedent for a *P*-acylphosphorane such as **36** to help evaluate its role as a potential intermediate. However, if **36** were formed reversibly as a higher energy intermediate from **35**, then the analogy with simpler alkoxyphosphoranes would suggest that pseudorotation would result in facile epimerization at phosphorus[27] and interconversion of **24a** and **24b**. Because interconversion does not occur (<3%) on the time scale of the catalytic experiments, the formation of **36** as an intermediate appears unlikely. On the other hand, transition states such as **40** or **41** might also be formed directly from the acylphosphonium salt **35**. There would be little formal charge separation in either of these phosphorane-like structures (**40**, **41**), a feature that is in better accord with the striking similarity of activation parameters in the acetonitrile and toluene experiments (Table 3). However, caution is appropriate in the interpretation of our data in the context of any of these structures. The geometric differences among **39**, **40**, and **41** need not be large, depending on the orientation of the carboxylate subunit and the relative distances between phosphorus and oxygen. Furthermore, we have no basis to assign the configuration of the transient tetrahedral (formally asymmetric) carbon in **39**, **40**, or **41**, nor do we know the placement or the exact role of the carboxylate anion. Another problem is that activation parameters for the analogous DMAP-catalyzed acyl transfer have not been reported. Pending comparisons based on that information, it will be difficult to evaluate a mechanism via a tight ion pair variant of transition state **39**.

The activation parameters determined for the acylations catalyzed by **24a** are qualitatively consistent with a highly associative nucleophilic catalysis mechanism via **39**, **40**, or **41**. Prior studies have shown that activation entropy for a variety of nucleophile-assisted acyl-transfer reactions is usually in the range of −10 to −40 eu for reactions in hydroxylic solvents.[21] Acyl transfer in acetonitrile has also been studied (catalyzed aminolysis of ethyl aryl carbonates), and was found to have very large, negative values for the entropy of activation (−65 to −67 eu) and minimal activation enthalpy (1.8−1.9 kcal/mol).[22] As already mentioned, the activation parameters for DMAP-catalyzed esterification of alcohols have not been reported. However, DMAP-catalyzed phosphorylations have been investigated, and the kinetic parameters feature a similar combination of large, negative activation entropy, and minimal activation enthalpy.[23]

In terms of the potential for applications of chiral phosphines as nucleophilic catalysts, the results presented above reveal that bicyclic *P*-arylphospholanes have excellent reactivity as well as promising enantioselectivity. Optimized phosphabicyclo[3.3.0]octane (PBO) analogues having exceptional enantioselectivy for the kinetic resolution of alcohols have been prepared in our laboratory using similar methods, as described elsewhere.[18] These catalysts are useful for the enantioselective acylations of allylic as well as benzylic alcohols.[18,28]

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Supporting Information Available: Experimental procedures, characterization data, and X-ray data tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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