Deracemization of a Phosphine Oxide via Enantioselective Protonation

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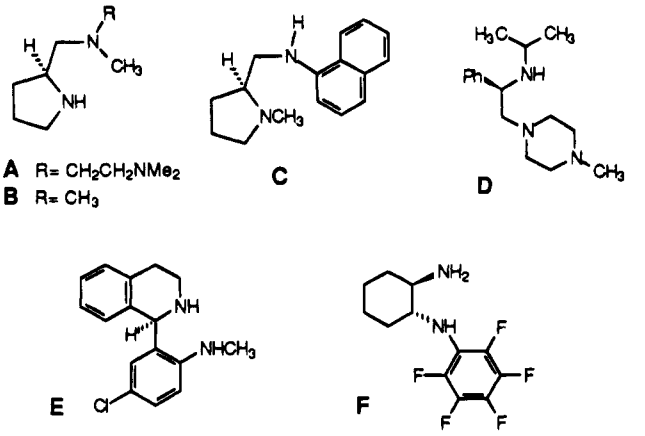
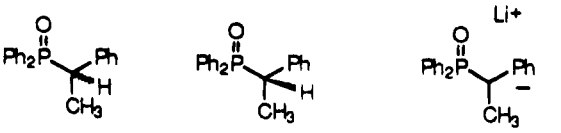
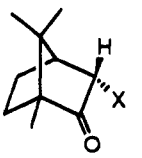
Summary: Treatment of the phosphine oxide anion **2** with the keto aniline **3c** affords (*S*)-**1** with 81–83% ee, and one crystallization upgrades the material to (*S*)-**1** with >99% ee (78% overall yield).

According to X-ray and NMR data, benzylic carbanions stabilized by a P=O substituent are planar.[1,2] Evidence from solution studies supports this generalization. Thus, Denmark and Dorow have shown that diastereomeric 2-(1-phenylethyl)-1,3,2-oxazaphosphorinane derivatives afford the same ratio of products after a deprotonation–reprotonation sequence at benzylic carbon, a result that rules out configurationally stable carbanion intermediates.[3] If these results apply to other P=O stabilized anions, then deprotonation of a chiral phosphine oxide such as **1** should afford an anion **2** that is either achiral or chiral and easily racemized. In either case, it may be possible to deracemize **1** and related phosphine oxides via protonation of the derived anions using a chiral acid or a chiral anion complexing agent, as in a number of enolate analogies.[4] We now report the first example of phosphine oxide deracemization via a phosphorus-stabilized anion, together with preliminary evidence regarding the nature of intermediates.

Deprotonation of **1** with *n*-butyllithium in toluene solution at −78 °C produced an orange solution and quenching with D_2O confirmed complete conversion to **2** as expected. Several enantiomerically pure, chiral diamines and triamines (structures **A-F**) were then evaluated under conditions known to effect enantioselective protonation of enolate substrates.[4d,e] One derivative **F**[5] was found that produced a marginal result of 29% ee for (*R*)-**1**[6] (toluene solution, −78 °C; quench with BF_3·OEt_2),[4d] but no significant (>5%) ee was obtained with any of the other di- or triamines. After these disappointing results, the survey of chiral proton donors was expanded to include a broader variety of potentially acidic structures **3** derived from camphor. The keto nitrile **3a**[7] was expected to function as a carbon acid that might be a better match for the carbon base **2**, but the reaction gave racemic **1** (toluene; −78 °C to rt). On the other hand, the related keto phosphonate **3b**[8] reacted with **2** to afford (*S*)-**1** with a significant 47% ee (generation of **2** in toluene; addition of **3b** at −78 °C (15 min), followed by warming to rt and quenching with methanolic acetic acid). Among the known 3-substituted camphor derivatives, one additional structure **3c**[9] appeared to be of potential interest. Keto aniline **3c** is the weakest acid in the series,[10] but it might resemble **3b** in the ability to coordinate lithium ion. When **2** was treated with **3c** as before, the recovered **1** after aqueous workup showed much improved ee values, depending on experimental details. The best results were obtained by adding 1.15 equiv of **3c** to **2** at −78 °C in toluene (15 min) and then adding methanol or acetic acid to quench the reaction. This produced (*S*)-**1** with 81–83% ee. One recrystallization of the crude







3a X= CN
3b X= P(O)[OEt]2
3c X= NHC6H5

4 X= NLiC6H5
5 X= NMeC6H5

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product from carbon tetrachloride afforded (*S*)-**1** with >99% ee, $[\alpha]_D = -148°$ (78% overall yield based on racemic **1**). The same enantiomer has been reported previously, although with lower enantiomeric purity.[6] Thus, Naylor and Walker prepared a sample enriched in (*S*)-**1** by treatment of (*R*)-1-phenethyl chloride with $NaPPh_2$ followed by oxidation. Judging from the reported optical rotation data ($[\alpha]_D = -48.9°$), their sample has an ee of ca. 30%, a result that indicates substantial racemization in the starting halide or in the phosphide alkylation step. The assignment of absolute configuration in all of the above experiments is based on the assumption that phosphide displacement occurs with dominant inversion of stereochemistry as proposed by Naylor and Walker.[6]

The reaction of **3c** with **2** was monitored by ^{31}P NMR to determine whether proton transfer occurs directly from **3c** as a chiral "acid", or whether carbanion protonation takes place after the addition of the protic quenching agent. In the latter case, a chiral keto aniline complex of the carbanion **2** might be activated for internal or external proton transfer, as observed in certain enolate quenching reactions.[4e,11] The phosphine oxide **1** has a characteristic absorption at δ 32 ppm in toluene, and addition of *n*-butyllithium (−70 or −13 °C) produces a new signal at δ 45 ppm due to the formation of anion **2**. When the anion solution was treated at −13 °C with a deficiency of **3c** (0.5 equiv), the orange color was observed to intensify to red, and major changes were seen in the ^{31}P spectrum. The anion signal at δ 45 ppm was replaced by a major peak at δ 34.5 ppm, together with complex absorptions from δ 35−38 ppm. The latter signals consisted of at least nine distinct maxima, suggesting the presence of a variety of mixed aggregate species containing **2**. Similar behavior has been reported for keto phosphonate anions in the presence of neutral phosphonate.[12] When a full equivalent of **3c** was added to **2** at −70 °C or at −13 °C, the signals at δ 35−38 ppm could not be detected with certainty. Only the major signal at δ 34.5 ppm was seen clearly, and no significant chemical shift changes were noted as the sample was quenched by the addition of methanol. Thus, the major product signal at δ 34.5 ppm is due to **1**. There is a small downfield shift relative to purified **1** induced by the presence of lithium ion. Keto aniline **3c** must therefore be sufficiently acidic to protonate nearly all of the anion **2** prior to the addition of protic quenching agents. In a separate experiment, **3c** was treated with *n*-butyllithium in toluene, followed by alkylation with methyl iodide. The product isolated in modest yield was **5**, derived from the *N*-lithioaniline **4**. Tentatively, this evidence suggests that the N−H bond of **3c** is kinetically more acidic than the enolizable C_3−H bond, but we do not rule out the possibility that **3c** functions as a carbon acid in the enantioselective protonation experiments.

The formation of complex species in toluene when both **1** and **2** are present raises the possibility that aggregates might contribute to (or detract from) enantioselectivity. Evidence consistent with this idea was obtained from experiments performed in toluene with 1 equiv of HMPA added (77% ee) or by using the more coordinating solvent THF in place of toluene (24% ee). Also, some evidence was obtained that enantiomerically enriched **1** can influence the enantioselective protonation step. First, the experiment was repeated by treating **2** with 0.54 equiv of (*S*)-**1** (>99% ee), but without adding **3c** or any other chiral proton source. This experiment produced **1** with 43% ee. After correcting for the amount of (*S*)-**1** added, the fraction of **1** that is formed by quenching **2** with the achiral proton donor in the workup step (methanol) would have an ee value of 13% ee. This result reveals a low, but significant, level of the "breeder" phenomenon: (*S*)-**1** acts as a chiral complexing agent for **2** and promotes the formation of additional (*S*)-**1** by a small margin over (*R*)-**1** when the *achiral* proton donor methanol is used for anion quenching. On the other hand, when a similar experiment was performed using the chiral proton donor **3c** as well as added (*S*)-**1**, the enantiomeric excess of the product **1** *decreased*. Anion **2** was generated in toluene, and 0.25 or 0.5 equiv of pure (*S*)-**1** was added, followed by the usual 1.15 equiv of **3c**. These experiments afforded **1** with ee values of 64% or 48%, respectively, after correction for the amount of (*S*)-**1** added. Initially, these results raised serious concerns because they implied that the enantiomerically enriched product might actually inhibit protonation enantioselectivity as (*S*)-**1** accumulates. However, one additional experiment was performed that argues against this undesired scenario and that somewhat clarifies the situation. Anion **2** was partially quenched using 0.25 equiv of **3c** at −78 °C. The resulting mixture of enantiomerically enriched **1**, anion **2**, amine **3c**, and the lithiated form of **3c** was then treated with excess benzaldehyde. According to a control experiment, benzaldehyde destroys **2** irreversibly under the aprotic conditions. When **1** was recovered from the partial quenching experiment, the enantiomers (*S*)-**1** and (*R*)-**1** were found in a typical 90:10 ratio (80% ee). Since the ee values at partial anion conversion and complete conversion are nearly identical, it appears that the enantioselective protonation is not affected by changes in the composition of the mixture as the proton transfer proceeds. This is consistent with the other evidence if anion protonation is fast compared to the formation of aggregated species that might interfere by acting as substrates in the proton transfer step. Apparently, such aggregates do form when excess (*S*)-**1** is deliberately added to the anion solution prior to the addition of **3c**. These are complicated experiments, and only a tentative interpretation of the decreased enantioselectivity in the presence of added (*S*)-**1** is intended. The important conclusion is that the enantiomerically enriched product does not interfere with enantioselective protonation under the optimized conditions.

In summary, we have shown that the deracemization of the phoshine oxide **1** is possible by reaction of **2** with the keto aniline **3c** as a chiral acid. These results suggest that the anion **2** has a symmetrical geometry with planar benzylic carbon or a nonplanar benzylic carbon structure that is easily inverted on the time scale of proton transfer from **3c**. The former possibility is more plausible and is consistent with evidence from other studies.[1-3] Enantiomerically pure (>99% ee) **1** can be obtained in practical yield by a combination of enantioselective protonation and crystallization steps. Further applications of this technique are under investigation.

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Supplementary Material Available: Preparation of **F**, **3c**, (*S*)-**1**, and **5** and ^1H NMR spectra of key compounds (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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