

# Asymmetric Carbamoyl Anion Additions to Chiral *N*-Phosphonyl Imines via the GAP Chemistry Process and Stereoselectivity Enrichments

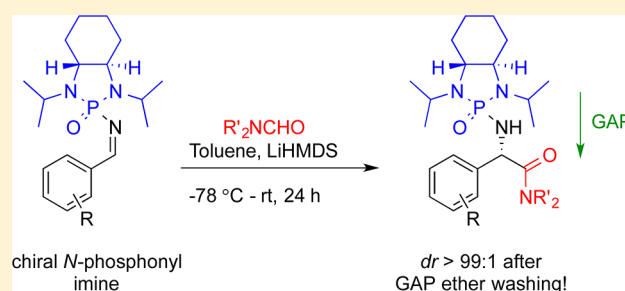
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**S** Supporting Information

**ABSTRACT:** Carbamoyl anions were found to smoothly react with chiral *N*-phosphonyl imines in toluene at  $-78\text{ }^{\circ}\text{C}$  to r.t. using LiHMDS as the base. Group-assisted purification (GAP) has been utilized to give the pure amides without using column chromatography or recrystallization. The asymmetric reaction resulted in chiral *N*-phosphonyl amino amides with good to excellent yields (71–99%) and good crude diastereoselectivities (*dr* 84:16–95:5). In this GAP procedure, the crude solids are washed with diethyl ether to afford the pure products, as revealed by  $^1\text{H}$  NMR analysis; GAP washing consistently increases the diastereopurity of the products, resulting in excellent diastereoselectivities, often with final *dr* > 99:1. Interestingly, the diastereoenriched products can be obtained either in the ether solution or as the suspended solid, depending on the substrate.



## INTRODUCTION

Chiral amines are ubiquitous throughout natural products and pharmaceuticals, and their efficient and economical synthesis is still a highly active research area.<sup>1–6</sup> The most important subclass of chiral amines are chiral  $\alpha$ -amino amides, which form the basic chemical unit of amino acids and peptides.<sup>7</sup> The synthesis of unnatural  $\alpha$ -amino amides is often carried out via a Strecker-type process.<sup>8–11</sup> This process frequently employs the cyanide ion, which requires two additional steps using harsh conditions to achieve the desired amides. Strong acids and heat are usually needed to convert the cyanide group into the carboxylic acid, followed by amide formation.<sup>12–14</sup> Phenylglycine has been shown to racemize under these conditions,<sup>15</sup> and therefore, the synthesis of phenylglycine amides would be better accomplished through other routes. One alternative for the synthesis of phenylglycine amides is through the direct addition of a carbamoyl anion to the corresponding imine. Carbamoyl anions can be easily generated from the appropriate formamide through simple deprotonation with amide bases, such as lithium diisopropyl amide.<sup>16</sup> Senanayake and co-workers recently reported the asymmetric carbamoyl anion addition to imines as a direct synthetic route to chiral  $\alpha$ -amino amides, through the use of chiral *N*-sulfinyl auxiliary chemistry.<sup>17</sup> In their report, the carbamoyl anion can directly add to the imine of choice, affording the  $\alpha$ -amino amide in one step under mild conditions.

Over the past few years, our research group has focused on the synthesis of various chiral *N*-phosphonyl and *N*-phosphinyl auxiliaries, for use in asymmetric syntheses of chiral amines

from the chiral auxiliary-protected imines.<sup>18–21</sup> This new class of chiral auxiliaries has been applied to various asymmetric reactions, such as borylation, the Umpolung reaction, the *aza*-Henry reaction, and several others.<sup>22–25</sup> In addition to their ability to effectively induce asymmetry in a variety of ways, these new auxiliaries also have the added bonus of simplifying the purification process by eliminating the need for silica column chromatography. While silica column chromatography is a standard purification method used in organic synthesis, it is often unsuitable for large-scale purification due to the high cost of silica. Also, the large amount of solvent waste generated can prove harmful to the environment. In contrast, compounds containing our phosphonyl auxiliaries can be purified by washing the crude solid products with simple solvents or solvent mixtures.<sup>22–25</sup> This cuts costs by reducing labor and by eliminating the expensive silica gel associated with column chromatography; it also greatly reduces solvent waste, creating a more environmentally friendly procedure. In some cases, this washing procedure can even increase the diastereomeric and/or enantiomeric purity of the final product.<sup>24–26</sup> This simplified and more economical purification method has been termed *GAP chemistry: A chemistry for organic synthesis that avoids traditional purification methods such as chromatography and/or recrystallization*. GAP chemistry requires considerations in regard to (1) adequate stability and chemical reactivity of functional group-attached substrates; (2) solid products that are

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