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Asymmetric Synthesis of α -Amino 1,3-Dithianes *via* Chiral *N*-Phosphonyl Imine-based Umpolung Reaction

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Abstract

A series of α -amino-1,3-dithianes have been synthesized *via* the asymmetric Umpolung reaction of 2-lithio-1,3-dithianes with chiral *N*-phosphonyl imines in good chemical yields (up to 82%) and good to excellent diastereoselectivities (>99:1). The addition manner by which chiral *N*-phosphonyl imines are slowly added into the solution of 2-lithio-1,3-dithiane was found to be crucial for achieving excellent diastereoselectivity. The current synthesis was proven to follow the GAP chemistry (Group-Assistant-Purification chemistry) process which avoids traditional purification techniques of chromatography or recrystallization, *i.e.*, the pure chiral α -amino-1,3-dithianes attached with the chiral *N*-phosphonyl group were readily obtained by washing the solid crude products with hexane or the mixture of hexane-ethyl acetate.

Keywords

N-Phosphonyl Imine; Asymmetric Umpolung Reaction; α -Amino 1; 3-Dithianes; GAP chemistry

Introduction

The development of economic, greener and environmentally friendly synthetic methodologies has been a great challenge in modern organic chemistry.^{1–4} So far, general reagents, particularly chiral reagents that enable organic synthesis to be performed without the use of traditional purifications *via* chromatography or recrystallization, have not been established.⁵ However, this concept would encourage the synthetic community to make more efforts on searching for greener reagents and related reactions to better serve academia and the pharmaceutical industry. It would substantially minimize the use of energy, starting materials and manpower as to save nature's resources.

In the past several years, we have established new chiral reagents of *N*-phosphonyl and *N*-phosphinyl amides and imines and have successfully applied them to various asymmetric reactions,^{5–9} such as asymmetric aza-Darzen reaction,^{6a} asymmetric aza-Henry reaction,^{6b} asymmetric Mannich reaction,^{6d,7b} asymmetric additions of allylmagnesium bromides,^{6c}

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asymmetric synthesis of *N*-phosphonyl propargyl amines,⁸ and asymmetric synthesis of *N*-phosphonyl β -amino Weinreb amides.⁷ Based on the results of the above reactions, we proposed a new concept of GAP chemistry (Group-Assistant-Purification chemistry)⁵ which can avoid traditional purification of using chromatography and recrystallization, *i.e.*, the pure chiral amino products attached with the chiral *N*-phosphonyl groups can be readily obtained by washing their solid crude products with hexane or a mixture of hexane-ethyl acetate. After this concept was generated, we re-examined and confirmed that all thirteen chiral *N*-phosphonyl and *N*-phosphinyl imine-based asymmetric reactions^{5–9} can be performed by following the GAP chemistry process. Furthermore, the asymmetric catalysis by using achiral *N*-phosphonyl imines as electrophiles has also been proven to undergo the GAP chemistry process, which was shown by the asymmetric catalytic Strecker reaction.⁵ In this GAP Strecker reaction, achiral *N*-phosphonyl imines were subjected to react with Et₂AlCN in the presence of three types of catalysts: free amino alcohols,^{5b} primary free natural amino acids^{5a} and BINOLs^{5b}; all of these catalysis processes resulted in excellent chemical yields and enantioselectivities under convenient conditions. This reaction represented the first use of achiral *N*-phosphonyl imines and Et₂AlCN as a non-volatile and inexpensive cyanide source in asymmetric catalysis. The GAP chemistry process has also been proven to be effective for this catalysis. The achiral *N*-phosphonyl auxiliary can be readily cleaved under mild acidic conditions and recycled *via* extraction with *n*-butanol to afford a quantitative recovery of *N,N'*-bis(naphthalen-1-ylmethyl)ethane-1,2-diamine for future re-use.

In the meanwhile, the asymmetric synthesis of enantiomerically pure α -amino aldehydes and α -amino ketones have become an active topic in synthetic chemistry as they serve as valuable versatile building blocks for organic and medicinal research.^{10–13} It is well known that α -amino carbonyl compounds are relatively sensitive to racemization and self-condensation conditions even when the amino group is protected by various protecting groups.¹⁴ These problems are usually avoided or minimized by protecting their carbonyl groups with 1,3-dithioacetal to give α -amino-1,3-dithianes that can be selectively deprotected for further functional manipulations.¹⁵ A few years ago, the asymmetric addition of 2-lithio-1,3-dithianes to sulfonimines (*N*-sulfinyl imines) has been successfully conducted by Davis and our group.¹⁶ In the former,^{16a} three examples were studied by reacting 2-lithio-2-alkyl-1,3-dithiane with *N*-sulfinyl imine nucleophiles at $-78\text{ }^{\circ}\text{C}$ without the use of any Lewis acid promoter in yields of 70%–84% and diastereoselectivity of 92%–>97% *de*.^{7a} This reaction has been successfully utilized for the asymmetric synthesis of polyoxypeptin amino acid (2*S*,3*R*)-(-)-3-hydroxy-3-methylproline. In the latter,^{16b} *N*-sulfinyl imine nucleophiles were subjected to the reaction with 2-lithio-2-phenyl-1,3-dithiane, a less reactive nucleophile than 2-lithio-2-alkyl-1,3-dithianes; this decrease in reactivity was attributed to the electronic delocalization effect from the aromatic phenyl ring of 2-lithio-2-phenyl-1,3-dithianes. The reaction has to be performed at a higher temperature ($-20\text{ }^{\circ}\text{C}$ to $-25\text{ }^{\circ}\text{C}$) in THF in the presence of Et₂AlCl as a Lewis acid promoter.^{16b} Excellent diastereoselectivities and chemical yields (64–95%) were achieved with all individual isomers readily separable *via* column chromatography.

Results and Discussion

To continue our projects on chiral *N*-phosphonyl imine chemistry and on searching for more practical GAP synthesis of a series of amino compounds, we investigated the Umpolung reaction of chiral *N*-phosphonyl imines with three types of nucleophilic species: 2-lithio-1,3-dithiane, 2-lithio-2-alkyl-1,3-dithianes and 2-lithio-2-phenyl-1,3-dithianes; we found that this asymmetric Umpolung reaction proceeded smoothly and efficiently under new conditions. In this paper, we would like to report our results as represented in Scheme 1 and summarized in Table 1.

As compared with *N*-sulfinyl imine chemistry, our chiral *N*-phosphonyl imines show some unique merits: (1) chiral *N*-phosphonamide and *N*-phosphonyl imines have a higher thermolytic stability; (2) multiple sites of their structures can be readily modified; (3) the *N*-phosphonyl group in the resulting amino compounds are inert to oxidative conditions; (4) the *N*-phosphonyl group is readily cleavable and the chiral auxiliary precursor recyclable; (5) it is a convenient method to determine diastereoselectivity by ^{31}P -NMR measurement; (6) the *N*-phosphonyl imine-based reactions follow the GAP chemistry process in which traditional purifications of using chromatography or recrystallization can be avoided, *i.e.*, the pure chiral α -amino-1,3-dithianes attached with chiral *N*-phosphonyl group were readily obtained by washing the solid crude products with hexane or the mixture of hexane-ethyl acetate.

For this asymmetric Umpolung reaction, the *N*-phosphonyl imine was first subjected to the reaction with 2-lithio-1,3-dithiane at $-78\text{ }^{\circ}\text{C}$ in THF for 12 hours. Surprisingly, there was no product observed under this typical condition. The reaction temperature was then increased in a range of -25 to $-20\text{ }^{\circ}\text{C}$; only a trace amount of the anticipated Umpolung adduct was observed. Previously, Et_2AlCl has been successfully utilized to promote the chiral sulfinimine-based asymmetric Umpolung reaction,^{16b} thus, it was utilized in this system. Interestingly, no obvious improvement was observed after Et_2AlCl and Et_2AlI were added into the reaction mixture. We found that the addition manner of the *N*-phosphonyl imine is very important for this reaction to occur. Slow addition of *N*-phosphonyl imine into 2-lithio-1,3-dithiane solution *via* a syringe pump was proven to be an efficient way to consume all imine starting material in good chemical yield (82%) and excellent diastereoselectivity ($>99:1$). In fact, only one isomer was detected by ^{31}P -NMR analysis of the crude product.

Next, *N*-phosphonyl imines with different *N*-protecting group were examined (Table 1) for comparison. Among the five protecting groups, the isopropyl group (Table 1, entry 1) was found to be the best in regard to both chemical yield and diastereoselectivity. The cyclohexyl protected *N*-phosphonyl imine (Table 1, entry 3) produced a fairly good diastereoselectivity (100:5) but the chemical yield was substantially decreased to 32%. Interestingly, the CH_2 -1-naphthyl protected imine (Table 1, entry 5), which was proven to be efficient in some of our previous asymmetric additions of ester and ketone derived enolates, only produced a moderate yield (70%) and diastereoselectivity (100:16).

Based on the above optimal conditions, the substrate scope of this Umpolung reaction was examined by using several *N*-phosphonyl imines and lithio-1,3-dithianes. *N*-Phosphonyl imines containing both electron withdrawing groups (Table 2, entry 4–6, 9–14) and electron donating groups on the aromatic rings (Table 2, entry 7,8 and 15) were all found suitable for this reaction in regard to both chemical yield and diastereoselectivity. Good yields (74–85%) and good to excellent diastereoselectivities ranging from 100:24 to $>99:1$ were observed. The substituents on 2-lithio-1,3-dithianes also showed different effects on the diastereoselectivities of the reactions. Increasing the bulkiness of R_2 of 2-lithio-1,3-dithianes (2-lithio-2-methyl-1,3-dithianes) resulted in lower diastereoselectivities. For 2-lithio-1,3-dithiane ($\text{R}_2 = \text{H}$), excellent diastereoselectivities of $>99:1$ were obtained with the exception of the 3-Br substituted *N*-phosphonyl imine (Table 2, entry 13). 2-Lithio-2-methyl-1,3-dithiane ($\text{R}_2 = \text{Me}$) gave good diastereoselectivities of 100:5 to 100:10 for all the substrates that were examined (entries 2, 5, 8, 10, 12 and 14 in Table 2). For 2-lithio-2-phenyl-1,3-dithiane ($\text{R}_2 = \text{Ph}$), moderate diastereoselectivities of 100:20 to 100:24 were obtained (entries 3 and 6, Table 2). As compared with the former two aliphatic 1-lithio-1,3-dithiane nucleophiles, 2-lithio-2-phenyl-1,3-dithiane showed lower reactivity due to the electron delocalization effect of the aromatic ring as mentioned above.

The absolute configuration of the resulting Umpolung adducts was determined by converting an product (**6a**) into an authentic sample.^{16,17} In this procedure, the *N*-phosphonyl group was cleaved by treating with HBr/MeOH at room temperature followed by protection of the free amino group using TsCl in the presence of triethylamine to give a known derivative **7**. (Scheme 2). The optical rotation of **7** was consistent with that of a known sample with *R* configuration. The known compound **7** was obtained with a chemical yield of 83%. In the meanwhile, *N,N*-diisopropyl diamine chiral auxiliary was recovered in quantitative yield by onetime extraction of the cleavage mixture with *n*-butanol.

Based on this result, a six-membered chair like transition state was proposed to explain the resulting stereoselectivity (Figure 1); this model is similar to that of the previous two asymmetric Umpolung reaction processes. Interestingly, the *R* configuration of the final product was in discordance to the stereochemistry of other enolate addition reactions that were studied before.^{5–9} This is the first example in which the (*R,R*)-1,2-cyclohexanediamine auxiliary resulted in the opposite control of forming chiral *N*-phosphonyl amine products. This observation is probably due to the fact that in nearly all previous asymmetric reactions, the lithium cation is coordinated unto the nitrogen of the *N*-phosphonyl amine reactant. However, in this reaction, the metal lithium is connected unto the oxygen atom of *N*-phosphonyl imine.

Conclusion

Chiral *N*-phosphonyl imines have been found to react with 2-lithio-1,3-dithiane, 2-lithio-2-methyl-1,3-dithiane and 2-lithio-2-phenyl-1,3-dithiane without the use of any Lewis acid promoters to produce α -amino 1,3-dithianes in good yields and good to excellent diastereoselectivities. The addition manner by which chiral *N*-phosphonyl imines are added into the solution of 2-lithio-1,3-dithiane was found to be crucial for this asymmetric Umpolung reaction. This reaction provide an easy access to α -amino-1,3-dithianes as versatile synthetic building blocks. The current synthesis was proven to follow the GAP chemistry (Group-Assistant-Purification chemistry) process by avoiding the use of traditional purifications *via* chromatography and recrystallization, *i.e.*, the pure chiral α -amino-1,3-dithianes attached with the chiral *N*-phosphonyl group were readily obtained by washing the solid crude products with hexane or a mixture of hexane-ethyl acetate.

Experimental Section

Typical procedure for the asymmetric synthesis of α -amino 1,3-dithianes *via* chiral *N*-phosphonyl imines

In a 30-ml, oven-dried reaction vial equipped with a magnetic stir bar, and a rubber septum, 1,3-dithiane was taken (0.2mmol) in THF (2ml). The solution was cooled to $-30\text{ }^{\circ}\text{C}$ and *n*-butyl lithium (0.22mmol) was added slowly. After 1 hour, the temperature of the reaction mixture was brought to $-78\text{ }^{\circ}\text{C}$ and *N*-phosphonyl imine (0.1mmol) was dissolved in 1ml THF and added by means of syringe pump for 1 hour. The reaction mixture was stirred overnight while the temperature was slowly raised to -30 and consequently to r.t. After confirming the completion of the reaction, sat. NH_4Cl solution was added to quench the reaction. The aqueous phase was washed with EtOAc ($2 \times 10\text{ml}$), the organic layer was collected, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. Purification of the crude product was done by simple washing with hexanes or, in some instances, with a mixture of hexane and ethyl acetate, which is defined as GAP chemistry (GAP: Group-Assistant purification) by our group.¹³ The final product was obtained as a white solid. When the final products are oily liquids, purification by flash column chromatography (solvent system: EtOAc-Hexanes 1:1 to Acetone-Hexanes 1:1) was performed.

Compound 6a—m.p 211 °C-213 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.43-7.30 (m, 5H), 4.66 (td, $J=4.5$ Hz, $J=10.2$ Hz, 1H), 4.36 (d, $J=4.5$ Hz, 1H), 3.59-3.34 (m, 3H), 3.10-2.90 (m, 1H), 2.79-2.68 (m, 4H), 2.12-1.95 (m, 4H), 1.77 (bs, 3H), 1.41-1.29 (m, 4H), 1.25 (d, $J=6.6$ Hz, 3H), 1.19 (d, $J=6.9$ Hz, 3H), 1.07 (d, $J=6.9$ Hz, 3H), 0.93 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.4 (d, $J=2.5$ Hz), 128.0, 127.5, 59.9 (d, $J=11.3$ Hz), 59.4, 59.0 (d, $J=9.9$ Hz), 55.5 (d, $J=5.9$ Hz), 44.1 (d, $J=3.5$ Hz), 43.8 (d, $J=4.9$ Hz), 31.5 (d, $J=11.9$ Hz), 31.1 (d, $J=9.0$ Hz), 30.3, 30.0, 25.6, 24.4 (d, $J=11.9$ Hz), 24.0 (d, $J=8.4$ Hz), 23.6 (d, $J=3.5$ Hz), 19.5, 19.3 (d, $J=2.4$ Hz); ^{31}P NMR (202 MHz; CDCl_3) δ 23.71; HRMS(ESI) m/z calcd for $\text{C}_{23}\text{H}_{39}\text{N}_3\text{OPS}_2$ 468.2267, found 468.2267.

Compound 6b—m.p 186 °C-188 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.48-7.44 (m, 2H), 7.34-7.23 (m, 3H), 4.72 (t, $J=9.3$ Hz, 1H), 3.76-3.67 (m, 1H), 3.22 (t, $J=8.4$ Hz, 1H), 2.77-2.66 (m, 3H), 2.06-1.84 (m, 4H), 1.74-1.69 (m, 2H), 1.67 (s, 3H), 1.37-1.24 (m, 4H), 1.22 (d, $J=6.9$ Hz, 3H), 1.08-1.03 (m, 6H), 0.84 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.0, 128.8, 127.6, 127.5, 63.8, 59.4 (d, $J=11.9$ Hz), 58.9 (d, $J=9.8$ Hz), 54.3 (d, $J=9.4$ Hz), 43.8 (d, $J=3.0$ Hz), 43.7 (d, $J=4.5$ Hz), 31.9 (d, $J=11.9$ Hz), 31.4 (d, $J=9.9$ Hz), 29.6, 26.9, 26.7, 26.2, 24.7, 24.4, 24.3, 24.1 (d, $J=4.5$ Hz), 19.6 (d, $J=1.5$ Hz), 19.0; ^{31}P NMR (202 MHz; CDCl_3) δ 24.66, 24.03.

Compound 6c— ^1H NMR (300 MHz, CDCl_3) δ 7.72-7.68 (m, 2H), 7.30-7.26 (m, 3H), 7.16-7.10 (m, 3H), 6.84-6.81 (m, 2H), 4.89-4.81 (m, 1H), 3.70-3.60 (m, 1H), 3.19-3.05 (m, 2H), 2.93-2.88 (m, 1H), 2.68-2.55 (m, 4H), 2.04-2.00 (m, 2H), 1.89-1.86 (m, 2H), 1.73-1.69 (m, 2H), 1.32-1.26 (m, 5H), 1.20 (d, $J=6.6$ Hz, 3H), 1.09-1.06 (m, 3H), 0.98-0.95 (m, 3H), 0.91-0.89 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.5, 138.2, 130.8, 129.0, 128.1, 127.3, 127.2, 126.9, 65.9, 59.4 (d, $J=12.4$ Hz), 58.9 (d, $J=9.8$ Hz), 43.9 (d, $J=3.0$ Hz), 43.7 (d, $J=4.5$ Hz), 32.0 (d, $J=12.4$ Hz), 31.6 (d, $J=9.4$ Hz), 29.7, 27.6, 27.4, 24.8, 24.4 (d, $J=6.0$ Hz), 19.6, 19.0; ^{31}P NMR (202 MHz; CDCl_3) δ 24.19, 23.56; HRMS (ESI) m/z calcd for $\text{C}_{29}\text{H}_{43}\text{N}_3\text{OPS}_2$ 544.2580, found 544.2590.

Compound 6d—m.p 200 °C-205 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.41-7.37 (m, 2H), 7.08-7.02 (m, 2H), 4.67 (td, $J=4.2$ Hz, $J=10.2$ Hz, 1H), 4.34 (d, $J=4.2$ Hz, 1H), 3.53-3.32 (m, 3H), 3.00-2.94 (m, 1H), 2.83-2.70 (m, 5H), 2.10-1.99 (m, 4H), 1.82-1.73 (m, 3H), 1.36-1.30 (m, 3H), 1.23 (d, $J=6.9$ Hz, 3H), 1.18 (d, $J=6.9$ Hz, 3H), 1.09 (d, $J=6.6$ Hz, 3H), 0.98 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.3, 161.3, 136.2, 129.1 (d, $J=8.0$ Hz), 115.0, 114.8, 59.9 (d, $J=11.4$ Hz), 59.0 (d, $J=9.9$ Hz), 58.8, 55.7, 44.1, 43.8 (d, $J=4.5$ Hz), 31.5 (d, $J=11.4$ Hz), 31.0 (d, $J=9.4$ Hz), 30.4, 30.0, 25.5, 24.3 (d, $J=13.3$ Hz), 23.9 (d, $J=7.9$ Hz), 23.6 (d, $J=3.0$ Hz), 19.5, 19.3 (d, $J=2.0$ Hz); ^{31}P NMR (202 MHz; CDCl_3) δ 23.55; ^{19}F NMR (282.34 MHz; CDCl_3) δ -114.97; HRMS(ESI) m/z calcd for $\text{C}_{23}\text{H}_{38}\text{FN}_3\text{OPS}_2$ 486.2173, found 486.2174.

Compound 6e—m.p 178 °C-180 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.44-7.40 (m, 2H), 7.04-6.96 (m, 2H), 4.69-4.62 (m, 1H), 3.72-3.60 (m, 2H), 3.20-3.14 (m, 1H), 2.89-2.70 (m, 5H), 2.06-1.97 (m, 4H), 1.71-1.64 (m, 5H), 1.34-1.28 (m, 5H), 1.19 (d, $J=6.9$ Hz, 3H), 1.09 (d, $J=6.9$ Hz, 3H), 1.04 (d, $J=6.9$ Hz, 3H), 0.86 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.2, 161.2, 137.1, 130.4 (d, $J=7.9$ Hz), 114.5, 114.4, 63.4, 59.5 (d, $J=11.9$ Hz), 58.9 (d, $J=9.9$ Hz), 54.4 (d, $J=9.9$ Hz), 53.8, 43.9 (d, $J=3.0$ Hz), 43.8 (d, $J=3.9$ Hz), 32.0 (d, $J=12.4$ Hz), 31.4 (d, $J=9.9$ Hz), 30.2 (d, $J=9.9$ Hz), 29.7, 29.3, 26.9 (d, $J=6.5$ Hz), 26.2, 24.7, 24.3, 23.1 (d, $J=4.0$ Hz), 20.7 (d, $J=13.8$ Hz), 19.7, 19.1; ^{31}P NMR (202 MHz; CDCl_3) δ 24.44, 24.06; HRMS(ESI) m/z calcd for $\text{C}_{24}\text{H}_{40}\text{FN}_3\text{OPS}_2$ 500.2329, found 500.2332.

Compound 6f— ^1H NMR (300 MHz, CDCl_3) δ 7.68-7.65 (m, 2H), 7.29-7.26 (m, 3H), 6.79-6.74 (m, 4H), 4.86-4.78 (m, 1H), 3.69-3.61 (m, 1H), 3.20-3.11 (m, 1H), 3.05-2.85 (m, 2H), 2.69-2.54 (m, 5H), 2.05-1.98 (m, 2H), 1.88-1.85 (m, 2H), 1.72-1.69 (m, 2H), 1.35-1.34 (m, 5H), 1.20-1.18 (m, 3H), 1.07-1.01 (m, 5H), 0.95-0.85 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.0, 161.0, 138.1, 135.5 (d, $J = 3.0$ Hz), 130.5, 128.2, 127.3, 113.7, 113.6, 65.7 (d, $J = 9.4$ Hz), 65.3, 59.4 (d, $J = 3.4$ Hz), 59.3 (d, $J = 4.5$ Hz), 58.9, 58.8, 54.7, 53.8, 44.1 (d, $J = 3.0$ Hz), 43.8 (d, $J = 2.9$ Hz), 43.7 (d, $J = 4.5$ Hz), 43.3 (d, $J = 4.9$ Hz), 36.7, 32.0 (d, $J = 12.3$ Hz), 31.5, (d, $J = 13.3$ Hz) 29.2, 28.4, 27.5, 27.3, 24.7, 24.4 (d, $J = 3.9$ Hz), 24.3 (d, $J = 3.5$ Hz), 24.0 (d, $J = 5.0$ Hz), 19.7 (d, $J = 2.4$ Hz), 19.5 (d, $J = 1.9$ Hz), 19.3, 18.9; ^{31}P NMR (202 MHz; CDCl_3) δ 24.01, 23.57; ^{19}F NMR (282.34 MHz; CDCl_3) δ -115.60; HRMS(ESI) m/z calcd for $\text{C}_{29}\text{H}_{42}\text{FN}_3\text{OPS}_2$ 562.2486, found 562.2500.

Compound 6g—m.p 220 °C-223 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.29-7.26 (m, 2H), 7.16-7.14 (m, 2H), 4.61 (td, $J = 4.5$ Hz, $J = 10.5$ Hz, 1H), 4.35 (d, $J = 4.2$ Hz, 1H), 3.55-3.35 (m, 3H), 3.01-2.93 (m, 1H), 2.85-2.67 (m, 5H), 2.34 (s, 3H), 2.11-1.96 (m, 3H), 1.76 (bs, 3H), 1.36-1.30 (m, 4H), 1.25 (d, $J = 6.9$ Hz, 3H), 1.20 (d, $J = 6.9$ Hz, 3H), 1.07 (d, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.4, 137.1, (d, $J = 3.0$ Hz), 128.7, 127.2, 59.9 (d, $J = 11.4$ Hz), 59.1, 59.0 (d, $J = 9.9$ Hz), 56.0 (d, $J = 6.0$ Hz), 44.1 (d, $J = 3.4$ Hz), 43.7 (d, $J = 4.9$ Hz), 31.5 (d, $J = 11.9$ Hz), 31.1 (d, $J = 8.9$ Hz), 30.5, 30.1, 25.6, 24.3 (d, $J = 14.3$ Hz), 24.0 (d, $J = 8.5$ Hz), 23.6 (d, $J = 3.5$ Hz), 21.2, 19.5, 19.2 (d, $J = 2.4$ Hz); ^{31}P NMR (202 MHz; CDCl_3) δ 23.75; HRMS(ESI) m/z calcd for $\text{C}_{24}\text{H}_{40}\text{N}_3\text{OPS}_2$ 482.2424, found 482.2433.

Compound 6h—m.p 182 °C-184 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.31 (m, 2H), 7.12-7.10 (m, 2H), 4.68 (t, $J = 9.6$ Hz, 1H), 3.77-3.63 (m, 1H), 3.22-3.12 (m, 1H), 3.06-2.97 (m, 1H), 2.92-2.79 (m, 3H), 2.77-2.64 (m, 3H), 2.32 (s, 3H), 2.05-1.88 (m, 4H), 1.73-1.69 (m, 2H), 1.66 (s, 3H), 1.35-1.24 (m, 4H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.06-1.04 (m, 6H), 0.85 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.8, 137.0, 128.6, 128.2, 63.4, 59.3 (d, $J = 11.8$ Hz), 58.8 (d, $J = 9.9$ Hz), 54.5, (d, $J = 9.9$ Hz), 43.7, 31.9 (d, $J = 12.4$ Hz), 31.4 (d, $J = 9.9$ Hz), 29.6, 26.8, 26.4, 26.2, 24.8, 24.2, 24.1 (d, $J = 3.9$ Hz), 21.0, 19.5 (d, $J = 1.9$ Hz), 19.0; ^{31}P NMR (202 MHz; CDCl_3) δ 24.76, 24.11; HRMS(ESI) m/z calcd for $\text{C}_{25}\text{H}_{42}\text{N}_3\text{OPS}_2$ 496.2580, found 496.2588.

Compound 6i—m.p 217 °C-219 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.31 (m, 4H), 4.66 (td, $J = 4.2$ Hz, $J = 10.5$ Hz, 1H), 4.34 (d, $J = 4.5$ Hz, 1H), 3.54-3.32 (m, 3H), 3.00-2.90 (m, 1H), 2.83-2.69 (m, 5H), 2.11-1.99 (m, 4H), 1.85-1.71 (m, 3H), 1.36-1.30 (m, 3H), 1.23 (d, $J = 6.9$ Hz, 3H), 1.19 (d, $J = 6.6$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H), 0.99 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.9, 133.6, 128.8, 128.2, 59.9 (d, $J = 11.3$ Hz), 59.0, 58.9 (d, $J = 6.5$ Hz), 55.5 (d, $J = 6.4$ Hz), 44.1 (d, $J = 3.0$ Hz), 43.8 (d, $J = 4.5$ Hz), 31.5 (d, $J = 11.9$ Hz), 31.0 (d, $J = 8.9$ Hz), 30.4, 30.1, 29.7, 25.5, 24.3 (d, $J = 10.9$ Hz), 24.0 (d, $J = 8.9$ Hz), 23.6 (d, $J = 3.4$ Hz), 19.5, 19.4 (d, $J = 2.0$ Hz); ^{31}P NMR (202 MHz; CDCl_3) δ 23.53; HRMS(ESI) m/z calcd for $\text{C}_{23}\text{H}_{38}\text{ClN}_3\text{OPS}_2$ 502.1877, found 502.1880.

Compound 6j—m.p 197 °C-199 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.39-7.38 (m, 1H), 7.37-7.36 (m, 1H), 7.28-7.23 (m, 2H), 4.68 (t, $J = 9.6$ Hz, 1H), 3.74 (m, 1H), 3.14-3.08 (m, 1H), 2.97-2.61 (m, 7H), 2.04-1.83 (m, 4H), 1.72-1.67 (m, 2H), 1.62 (s, 3H), 1.34-1.23 (m, 4H), 1.19 (d, $J = 6.9$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.03 (d, $J = 6.9$ Hz, 3H), 0.84 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.8, 133.2, 130.2, 127.7, 63.4, 59.4 (d, $J = 11.8$ Hz), 58.9 (d, $J = 9.8$ Hz), 54.2 (d, $J = 9.4$ Hz), 43.8 (d, $J = 3.5$ Hz), 43.7 (d, $J = 4.5$ Hz), 31.9 (d, $J = 11.9$ Hz), 31.4 (d, $J = 9.9$ Hz), 29.2, 26.9, 26.8, 26.2, 24.7, 24.4, 24.3, 24.3, 24.0 (d, $J = 3.9$ Hz), 19.7 (d, $J = 2.0$ Hz), 19.0; ^{31}P NMR (202 MHz; CDCl_3) δ 24.36, 24.03; HRMS(ESI) m/z calcd for $\text{C}_{24}\text{H}_{40}\text{ClN}_3\text{OPS}_2$ 516.2034, found 516.2028.

Compound 6k—m.p 217 °C-219 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.46-7.42(m, 2H), 7.27-7.25 (m, 2H), 4.60 (td, $J = 4.5$ Hz, $J = 10.5$ Hz, 1H), 4.30 (d, $J = 4.5$ Hz, 1H), 3.50-3.25 (m, 3H), 2.96-2.89 (m, 1H), 2.78-2.65 (m, 5H), 2.07-1.98 (m, 4H), 1.78-1.73 (m, 3H), 1.29-1.26 (m, 3H), 1.19 (d, $J = 6.6$ Hz, 3H), 1.14 (d, $J = 6.6$ Hz, 3H), 1.05 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.5, (d, $J = 2.9$ Hz), 131.1, 129.2, 121.8, 59.9 (d, $J = 11.3$ Hz), 59.0, 59.0, 58.9, 55.4 (d, $J = 6.4$ Hz), 44.1 (d, $J = 3.0$ Hz), 43.8 (d, $J = 4.5$ Hz), 31.5 (d, $J = 11.9$ Hz), 31.0 (d, $J = 9.4$ Hz), 30.4, 30.1, 25.5, 24.3 (d, $J = 9.9$ Hz), 23.9 (d, $J = 8.4$ Hz), 23.5 (d, $J = 3.5$ Hz), 19.5, 19.4 (d, $J = 2.0$ Hz); ^{31}P NMR (202 MHz; CDCl_3) δ 23.49; HRMS(ESI) m/z calcd for $\text{C}_{23}\text{H}_{37}\text{BrN}_3\text{OPS}_2$ 546.1372, found 546.1373.

Compound 6l—m.p 198 °C-200 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.44-7.39(m, 2H), 7.34-7.30 (m, 2H), 4.67 (t, $J = 9.3$ Hz, 1H), 3.74-3.61 (m, 1H), 3.15 (t, $J = 9.3$ Hz, 1H), 2.97-2.79 (m, 4H), 2.74-2.64 (m, 3H), 2.04-1.81 (m, 4H), 1.72-1.67 (m, 2H), 1.62 (s, 3H), 1.33-1.21 (m, 4H), 1.19 (d, $J = 6.9$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.03 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.3, 130.6, 121.4, 63.4, 59.4 (d, $J = 11.9$ Hz), 58.9 (d, $J = 9.9$ Hz), 54.2 (d, $J = 9.4$ Hz), 43.8 (d, $J = 3.5$ Hz), 43.7 (d, $J = 4.5$ Hz), 31.9 (d, $J = 12.4$ Hz), 31.4 (d, $J = 9.9$ Hz), 26.9, 26.7, 26.2, 24.7, 24.4 (d, $J = 9.4$ Hz), 24.3, 24.1 (d, $J = 4.4$ Hz), 19.7 (d, $J = 1.4$ Hz), 19.0; ^{31}P NMR (202 MHz; CDCl_3) δ 24.40, 24.08; HRMS(ESI) m/z calcd for $\text{C}_{24}\text{H}_{40}\text{BrN}_3\text{OPS}_2$ 560.1529, found 560.1523.

Compound 6m—m.p 168 °C-170 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.59 (bs, 1H), 7.46-7.43 (m, 1H), 7.38-7.35 (m, 1H), 7.27-7.21 (m, 1H), 4.69 (td, $J = 4.5$ Hz, $J = 10.5$ Hz, 1H), 4.33 (d, $J = 4.2$ Hz, 1H), 3.55-3.29 (m, 3H), 3.12-2.91 (m, 1H), 2.81-2.71 (m, 4H), 2.11-1.94 (m, 3H), 1.78 (bs, 4H), 1.43-1.29 (m, 4H), 1.22-1.17 (m, 6H), 1.13 (d, $J = 6.6$ Hz, 3H), 1.03 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.1, 130.9, 130.4, 129.5, 126.3, 122.2, 59.9 (d, $J = 11.9$ Hz), 59.2, 59.0 (d, $J = 9.9$ Hz), 55.1 (d, $J = 7.0$ Hz), 44.1 (d, $J = 3.0$ Hz), 43.8 (d, $J = 5.0$ Hz), 31.6, 24.1 (d, $J = 8.5$ Hz), 23.6 (d, $J = 4.0$ Hz), 19.5, 19.5, 19.5; ^{31}P NMR (202 MHz; CDCl_3) δ 23.46, 23.64; HRMS(ESI) m/z calcd for $\text{C}_{23}\text{H}_{38}\text{BrN}_3\text{OPS}_2$ 546.1372, found 546.1384.

Compound 6n—m.p 180 °C-182 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.45-7.40 (m, 2H), 7.27-7.21 (m, 1H), 7.23-7.17 (m, 1H), 4.71 (t, $J = 9.6$ Hz, 1H), 3.76-3.67 (m, 1H), 3.22-3.16 (m, 1H), 2.95-2.66 (m, 6H), 2.07-2.00 (m, 3H), 1.98-1.88 (m, 2H), 1.72 (bs, 2H), 1.67 (s, 3H), 1.32-1.28 (m, 4H), 1.24 (d, $J = 6.9$ Hz, 3H), 1.15 (d, $J = 6.6$ Hz, 3H), 1.08 (d, $J = 6.9$ Hz, 3H), 0.93 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.6, 131.6, 130.5, 129.1, 127.9, 121.8, 63.6, 59.4 (d, $J = 12.4$ Hz), 59.9, (d, $J = 9.9$ Hz), 54.0 (d, $J = 9.9$ Hz), 43.9 (d, $J = 3.5$ Hz), 43.8 (d, $J = 4.4$ Hz), 32.0 (d, $J = 11.9$ Hz), 31.4 (d, $J = 9.9$ Hz), 26.9, 26.8, 26.2, 24.6, 24.5 (d, $J = 8.9$ Hz), 24.3, 24.1 (d, $J = 4.0$ Hz), 19.8 (d, $J = 2.0$ Hz), 19.1; ^{31}P NMR (202 MHz; CDCl_3) δ 24.35, 24.19; HRMS(ESI) m/z calcd for $\text{C}_{24}\text{H}_{40}\text{BrN}_3\text{OPS}_2$ 560.1529, found 560.1534.

Compound 6o—m.p 192 °C-194 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.47-7.32 (m, 7H), 6.99-6.95 (m, 2H), 5.08 (s, 2H), 4.62 (td, $J = 4.2$ Hz, $J = 10.8$ Hz, 1H), 4.35 (d, $J = 4.5$ Hz, 1H), 3.55-3.38 (m, 3H), 3.00-2.95 (m, 1H), 2.81-2.67 (m, 5H), 2.12-2.02 (m, 3H), 1.82-1.77 (m, 3H), 1.37-1.29 (m, 4H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.20 (d, $J = 6.9$ Hz, 3H), 1.08 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 158.4, 136.9, 132.8 (d, $J = 2.4$ Hz), 128.7, 128.5, 127.9, 127.5, 114.3, 69.9, 60.0 (d, $J = 11.9$ Hz), 59.1 (d, $J = 9.9$ Hz), 58.9, 55.9 (d, $J = 6.9$ Hz), 44.2 (d, $J = 2.9$ Hz), 43.8 (d, $J = 4.9$ Hz), 31.5 (d, $J = 11.9$ Hz), 31.1 (d, $J = 9.4$ Hz), 30.3, 30.0, 25.6, 24.4, 24.3, 24.0 (d, $J = 8.4$ Hz), 23.7 (d, $J = 2.9$ Hz), 19.6, 19.4 (d, $J = 2.0$ Hz); ^{31}P NMR (202 MHz; CDCl_3) δ 23.68; HRMS(ESI) m/z calcd for $\text{C}_{30}\text{H}_{45}\text{N}_3\text{O}_2\text{PS}_2$ 574.2686, found 574.2685.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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NOTES and REFERENCES

1. (a) Schreiber SL. *Science*. 2000; 287:1964. [PubMed: 10720315] (b) Frederic L-M, Thierry C, Jean R. *J Am Chem Soc*. 2005; 127:17176. [PubMed: 16332052] (c) Trost BM. *Science*. 1991; 254:1471. [PubMed: 1962206] (d) Wender PA, Gamber GG, Hubbard RD, Pham SM, Zhang L. *J Am Chem Soc*. 2005; 127:2836. [PubMed: 15740103] (e) Snyder SA, Breazzano SP, Ross Lin Y, Zografos AL. *J Am Chem Soc*. 2009; 131:1753. [PubMed: 19143488]
2. (a) Tietze LF, Brazel CC, Holsken S, Magull J, Ringe A. *Angew Chem, Int Ed*. 2008; 47:5246.(b) Huang Y, Waljji AM, Larsen CH, MacMillan DWC. *J Am Chem Soc*. 2005; 127:1505.(c) Yang JW, Fonseca HMT, List B. *J Am Chem Soc*. 2005; 127:15036. [PubMed: 16248637]
3. (a) Tietze, LF.; Brasche, G.; Gericke, KM. *Domino Reactions in Organic Synthesis*. Wiley-VCH; Weinheim: 2006. (b) Ivanov AS. *Chem Soc Rev*. 2008; 37:789. [PubMed: 18362984] (c) de Meijere A, von Zezschwitz P, Bräse S. *Acc Chem Res*. 2005; 38:413. [PubMed: 15895979]
4. (a) Li CJ. *Acc Chem Res*. 2010; 43:581. [PubMed: 20095650] (b) Li CJ, Trost BM. *Proc Natl Acad Sci*. 2008; 105:13197. [PubMed: 18768813]
5. (a) Kaur P, Pindi S, Wever W, Rajale T, Li G. *Chem Commun*. 2010; 46:4330.(b) Kaur P, Pindi S, Wever W, Rajale T, Li G. *J Org Chem*. 2010; 75:5144. [PubMed: 20597482]
6. (a) Kattuboina A, Li G. *Tetrahedron Lett*. 2008; 49:1573.(b) Kattuboina A, Kaur P, Ai T, Li G. *Chem Biol Drug Des*. 2008; 71:216. [PubMed: 18251775] (c) Kattuboina A, Kaur P, Nguyen T, Li G. *Tetrahedron Lett*. 2008; 49:3722.(d) Han J, Ai T, Nguyen T, Li G. *Chem Biol Drug Des*. 2008; 72:120. [PubMed: 18631372]
7. (a) Kaur P, Nguyen T, Li G. *Eur J Org Chem*. 2009:912.(b) Han J, Ai T, Li G. *Synthesis*. 2008; 16:2519.(c) Han J, Chen Z-X, Ai T, Li G. *Chem Biol Drug Des*. 2009; 73:203. [PubMed: 19207422] (d) Chen Z-X, Ai T, Kaur P, Li G. *Tetrahedron Lett*. 2009; 50:1079.(e) Ai T, Li G. *Bioorg Med Chem Lett*. 2009; 19:3967. [PubMed: 19297153]
8. (a) Kaur P, Shakya G, Sun H, Pan Y, Li G. *Org Biomol Chem*. 2010; 8:1091. [PubMed: 20165799] (b) Ai T, Han J, Chen ZX, Li G. *Chem Biol Drug Des*. 2009; 73:203. [PubMed: 19207422] (c) Kattuboina A, Kaur P, Ai T, Li G. *Chem Biol Drug Design*. 2008; 71:216.(d) Ai T, Pindi S, Kattamuri PV, Li G. *Sci China Series B: Chem*. 2010; 53:125.
9. (a) For chiral N-phosphinyl imine chemistry see: Pindi S, Kaur P, Shakya G, Li G. *Chem Biol Drug Design*. 2011; 75:20.(b) For chiral N-phosphoryl imine chemistry see: Sun H, Rajale T, Pan Y, Li G. *Tetrahedron Lett*. 2010; 51:4403.
10. Coppola G, Schuster H. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*. WileyNew York1987. For reviews see: (a) Reetz MT. *Chem Rev*. 1999; 99:1121. [PubMed: 11749442] (b) Sardina FJ, Rapoport H. *Chem Rev*. 1996; 96:1825. [PubMed: 11848813] (c) Reetz MT. *Angew Chem, Int Ed Engl*. 1991; 30:1531.
11. For reviews see: (a) Reetz MT. *Chem Rev*. 1999; 99:1121. [PubMed: 11749442] (b) Sardina FJ, Rapoport H. *Chem Rev*. 1996; 96:1825. [PubMed: 11848813] (c) Reetz MT. *Angew Chem, Int Ed Engl*. 1991; 30:1531.
12. Gryko D, Chalko J, Jurczak J. *Chirality*. 2003; 15:514.
13. For references leading to the asymmetric synthesis of α -amino ketones, see: Paleo MR, Calaza MI, Sardina FJ. *J Org Chem*. 1997; 62:6862.
14. Lubell WD, Rapoport H. *J Am Chem Soc*. 1987; 109:236.
15. Yus M, Najera C, Foubelo F. *Tetrahedron*. 2003; 59:6147.

16. (a) Davis FA, Ramachandar T, Liu H. *Org Lett.* 2004; 6:3393. [PubMed: 15355060] (b) Xu X, Liu J-Y, Chen D-J, Timmons C, Li G. *Eur J Org.* 2005:1805.
17. Davis FA, Ramachandar T, Chai J, Skucas E. *Tetrahedron Lett.* 2006; 47:2743.

Figure 1.
Proposed transition state of Umpolung reaction.

Scheme 1.

Scheme 2.
(Lit.:¹⁴ -61.2, c 0.52, CHCl₃, *S*-isomer)

Table 1

Optimization of *N*-protecting groups of phosphonyl imines^a

Entry	Substrate	R	Product	Yield(%) ^b	dr ^c
1	1a	<i>iso</i> -propyl	6a	82	>99:1
2	2a	3-pentyl	7a	71	87:13
3	3a	cyclohexyl	8a	32	95:5
4	4a	benzyl	9a	81	77:23
5	5a	CH ₂ -1-naphthyl	10a	70	86:14

^a Reaction condition: 0.1mmol imine, 0.2mmol 1,3-dithiane, 0.22mmol, base 2ml solvent, -30 °C to -78 °C to r.t.;^b Isolated yields;^c Diastereoselectivities were determined by ³¹P-NMR analysis of crude products.

Table 2

Asymmetric addition of lithio-1,3-dithianes to *N*-phosphonyl imines^a

Entry	Imine	R ₁	R ₂	Product	Yield(%) ^b	dr ^c
1	1a	H	H	6a	82	>99:1
2	1a	H	Me	6b	78	94:6
3	1a	H	Ph	6c	75	81:19
4	1b	4-F	H	6d	80	>99:1
5	1b	4-F	Me	6e	77	90:10
6	1b	4-F	Ph	6f	73	81:19
7	1c	4-Me	H	6g	75	>99:1
8	1c	4-Me	Me	6h	70	92:8
9	1d	4-Cl	H	6i	79	>99:1
10	1d	4-Cl	Me	6j	80	91:9
11	1e	4-Br	H	6k	77	>99:1
12	1e	4-Br	Me	6l	74	92:8
13	1f	3-Br	H	6m	75	92:8
14	1f	3-Br	Me	6n	74	91:9
15	1g	4-OBn	H	6o	85	>99:1

^a Reaction condition: 0.1mmol imine, 0.2mmol 1,3-dithiane, 0.22mmol, base 2ml solvent, -30 °C to -78 °C to rt.;^b Isolated yields;^c Diastereoselectivities were determined by ³¹P-NMR analysis of crude products.