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Asymmetric Synthesis of α-Amino-1,3-dithianes via Chiral *N*-Phosphonyl Imine-Based Umpolung Reaction Without Using Chromatography and Recrystallization

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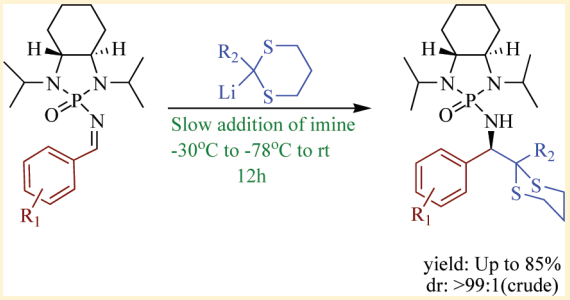
Supporting Information

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 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 a mixture of hexane−ethyl acetate.



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 effort to search 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] asymmetric synthesis of *N*-phosphonyl propargyl amines,[8] and asymmetric synthesis of *N*-phosphonyl *β*-amino Weinreb amides.[7] On the basis of the results of the above reactions, we proposed a new concept of GAP chemistry (group-assistant-purification chemistry)[5] which can avoid traditional purification 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 13 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 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 Et_2AlCN 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 enatioselectivities under convenient conditions. This reaction represented the first use of achiral *N*-phosphonyl imines and Et_2AlCN as a nonvolatile 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 reuse.

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

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Scheme 1

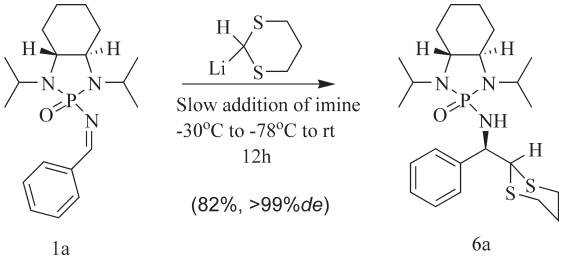
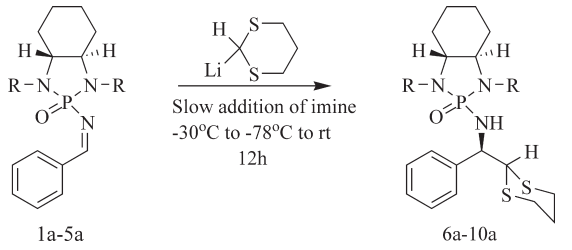


Table 1. Optimization of *N*-Protecting Groups of Phosphonyl Imines[a]

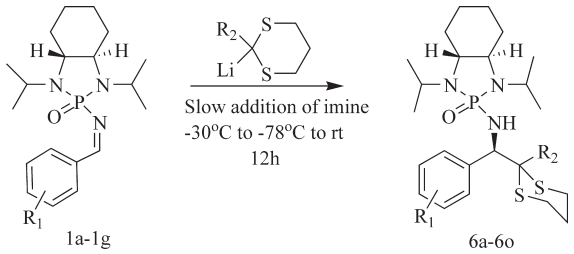


entry	substrate	R	product	yield (%)[b]	dr[c]
1	**1a**	isopropyl	**6a**	82	>99:1
2	**2a**	3-pentyl	**7a**	71	87:13
3	**3a**	cyclohexyl	**8a**	32	95:5
4	**4a**	benzyl	**9a**	81	77:23
5	**5a**	CH_2-1-naphthyl	**10a**	70	86:14

[a] Reaction conditions: 0.1 mmol of imine, 0.2 mmol of 1,3-dithiane, 0.22 mmol of base, 2 mL of solvent, −30 to −78 °C to rt. [b] Isolated yields. [c] Diastereoselectivities were determined by ^{31}P NMR analysis of crude products.

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 sulfinimines (*N*-sulfinyl imines) had 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 °C without the use of any Lewis acid promoter in yields of 70%−84% and diastereoselectivity from 92% to >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 to −25 °C) in THF in the presence of Et_2AlCl as a Lewis acid promoter.[16b] Excellent diastereoselectivities and chemical yields (64−95%) were achieved with all individual isomers readily separable via column chromatography.

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 conditions: 0.1 mmol of imine, 0.2 mmol of 1,3-dithiane, 0.22 mmol of base, 2 mL of solvent, −30 to −78 °C to rt. [b] Isolated yields. [c] Diastereoselectivities were determined by ^{31}P NMR analysis of crude products.

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 convenient to determine the 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

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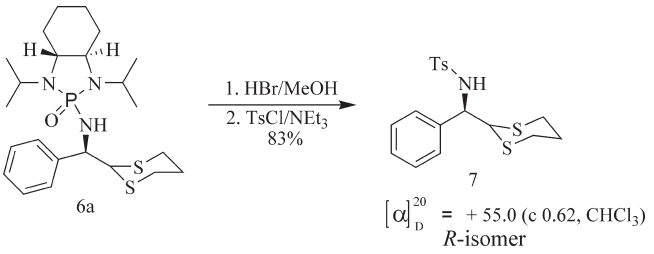
Scheme 2



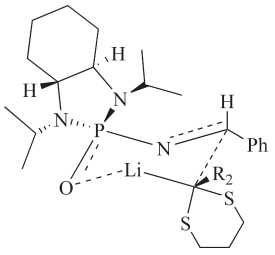


Figure 1. Proposed transition state of Umpolung reaction.

were readily obtained by washing the solid crude products with hexane or a 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 °C in THF for 12 h. Surprisingly, there was no product observed under this typical condition. The reaction temperature was then increased in a range from −25 to −20 °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 manner of addition 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 with 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).

On the basis of 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, entries 4−6 and 9−14) and electron-donating groups on the aromatic rings (Table 2, entries 7, 8, and 15) were all found suitable for this reaction with 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 (R_2 = 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 (R_2 = 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 (R_2 = 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 a 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 one-time extraction of the cleavage mixture with *n*-butanol.

On the basis of this result, a six-membered chairlike 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 with 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 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 provided 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

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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. A 30-mL, oven-dried reaction vial equipped with a magnetic stir bar and a rubber septum was charged with 1,3-dithiane (0.2 mmol) in THF (2 mL). The solution was cooled to −30 °C and *n*-butyl lithium (0.22 mmol) was added slowly. After 1 h, the temperature of the reaction mixture was brought to −78 °C and *N*-phosphonyl imine (0.1 mmol) was dissolved in 1 mL of THF and added by means of syringe pump for 1 h. The reaction mixture was stirred overnight while the temperature was slowly raised to −30 °C and consequently to rt. After confirming the completion of the reaction, satd NH_4Cl solution was added to quench the reaction. The aqueous phase was washed with EtOAc (2 × 10 mL), and 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 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***. Mp 211−213 °C; ^{1}H 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 $C_{23}H_{39}N_3OPS_2$ 468.2267, found 468.2267.

Compound ***6b***. Mp 186−188 °C; ^{1}H 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***. ^{1}H 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 $C_{29}H_{43}N_3OPS_2$ 544.2580, found 544.2590.

Compound ***6d***. Mp 200−205 °C; ^{1}H 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 $C_{23}H_{38}FN_3OPS_2$ 486.2173, found 486.2174.

Compound ***6e***. Mp 178−180 °C; ^{1}H 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 $C_{24}H_{40}FN_3OPS_2$ 500.2329, found 500.2332

Compound ***6f***. ^{1}H 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 $C_{29}H_{42}FN_3OPS_2$ 562.2486, found 562.2500.

Compound ***6g***. Mp 220−223 °C; ^{1}H 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 $C_{24}H_{40}N_3OPS_2$ 482.2424, found 482.2433.

Compound ***6h***. Mp 182−184 °C; ^{1}H 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 $C_{25}H_{42}N_3OPS_2$ 496.2580, found 496.2588.

Compound ***6i***. Mp 217−219 °C; ^{1}H 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

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(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 $C_{23}H_{38}ClN_3OPS_2$ 502.1877, found 502.1880.

Compound **6j**. Mp 197−199 °C; ^{1}H 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 $C_{24}H_{40}ClN_3OPS_2$ 516.2034, found 516.2028.

Compound **6k**. Mp 217−219 °C; ^{1}H 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 $C_{23}H_{37}BrN_3OPS_2$ 546.1372, found 546.1373.

Compound **6l**. Mp 198−200 °C; ^{1}H 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 $C_{24}H_{40}BrN_3OPS_2$ 560.1529, found 560.1523.

Compound **6m**. Mp 168−170 °C; ^{1}H 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 $C_{23}H_{38}BrN_3OPS_2$ 546.1372, found 546.1384.

Compound **6n**. Mp 180−182 °C; ^{1}H 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, 3 H), 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 $C_{24}H_{40}BrN_3OPS_2$ 560.1529, found 560.1534.

Compound **6o**. Mp 192−194 °C; ^{1}H 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, 3 H); ^{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 $C_{30}H_{45}N_3O_2PS_2$ 574.2686, found 574.2685.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra of all pure products. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Schreiber, S. L. *Science.* **2000**, *287*, 1964. (b) Frederic, L. -M.; Thierry, C.; Jean, R. *J. Am. Chem. Soc.* **2005**, *127*, 17176. (c) Trost, B. M. *Science* **1991**, *254*, 1471. (d) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 2836. (e) Snyder, S. A.; Breazzano, S. P.; Lin, R. Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753.

(2) (a) Tietze, L. F.; Brazel, C. C.; Holsken, S.; Magull, J.; Ringe, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5246. (b) Huang, Y.; Waljji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 1505. (c) Yang, J. W.; Fonseca, H. M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036.

(3) (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Ivanov, A. S. *Chem. Soc. Rev.* **2008**, *37*, 789. (c) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413.

(4) (a) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581. (b) Li, C.-J.; Trost, B. M. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 13197.

(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.

(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. (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.

(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. (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.

(8) (a) Kaur, P.; Shakya, G.; Sun, H.; Pan, Y.; Li, G. *Org. Biomol. Chem.* **2010**, *8*, 1091. (b) Ai, T.; Han, J.; Chen, Z. X.; Li, G. *Chem. Biol. Drug. Des.* **2009**, *73*, 203. (c) Kattuboina, A.; Kaur, P.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2008**, *71*, 216. (d) Ai, T.; Pindi, S.; Kattamuri, P. V.; 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) (a) Coppola, G., Schuster, H. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987. For reviews, see: (a) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121. (b) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.

(11) For reviews see:(a) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121. (b) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825. (c) Reetz, M. T. *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, M. R.; Calaza, M. I.; Sardina, F. J. *J. Org. Chem.* **1997**, *62*, 6862.

(14) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.

(15) Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron.* **2003**, *59*, 6147.

(16) (a) Davis, F. A.; Ramachandar, T.; Liu, H. *Org. Lett.* **2004**, *6*, 3393. (b) Xu, X.; Liu, J. −Y.; Chen, D. −J.; Timmons, C.; Li, G. *Eur. J. Org.* **2005**, 1805.

(17) Davis, F. A.; Ramachandar, T.; Chai, J.; Skucas, E. *Tetrahedron Lett.* **2006**, *47*, 2743.