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Synthesis and Application of *P*-Stereogenic Phosphines as Superior Reagents in the Asymmetric Aza-Wittig Reaction

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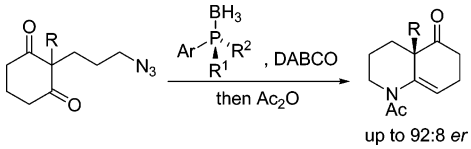

A wide variety of *P*-stereogenic aryldialkylphosphines were prepared in enantioenriched form by a systematic diversification of the (−)-sparteine-mediated dynamic kinetic resolution of racemic lithiophosphine−boranes reported by Livinghouse. Excellent asymmetric induction was observed provided that the intermediate lithiophosphine/sparteine complex precipitated from solution; more soluble derivatives returned poor ee's or racemic material. The resulting phosphine−boranes were deprotected and used as reagents in the desymmetrizing asymmetric aza-Wittig reaction of 2-alkyl-2-(3-azidopropyl)cyclohexane-1,3-diones, delivering the highest ee's yet observed in this process (up to 84% ee). Phosphines bearing bulky substituents required heating for the aza-Wittig reaction to proceed to completion, which ^{31}P NMR studies showed to be due to interception of the reaction by the formation of unreactive (*E*)-phosphazides. This was circumvented by use of methyltrioxorhenium to catalyze the formation of iminophosphoranes from the azide and phosphine, allowing reactions to take place at ambient temperature, although the ee's of the asymmetric reactions were reduced in these examples.

Introduction

Chiral monophosphines in which the phosphorus atom is an asymmetric center (*P*-stereogenic phosphines) have a long and interesting history. Initially of interest for studies of their chiroptical properties,[1] chemical applications soon followed and the application of monodentate *P*-stereogenic phosphines in the rhodium-catalyzed asymmetric hydrogenations of itaconic acid[2] and dehydroamino acids[3] by Knowles and colleagues led to the development and use of the chelating diphosphine DiPAMP in the first industrial-scale catalytic asymmetric transformation.[4] The use of chiral diphosphine-based ligands (with either C_2 or lower order symmetry) has dominated the field of asymmetric transition-metal catalysis since, but there has been a recent renaissance in the use of chiral monophosphines as ligands for transition metals.[5−7] Among these studies, *P*-stereogenic phosphines have found application not only as ligands in palladium-catalyzed allylic substitution reactions[7] but also in their own right as catalysts for asymmetric nucleophilic additions to and [3 + 2] cycloadditions of allenoates[8] as well as acyl-transfer reactions.[9] One of the limitations in the field has been the difficulties associated with the synthesis of enantioenriched *P*-stereogenic phosphines[10] and in particular the lengthy nature of resolution or chiral auxiliary-based routes has led to the recent

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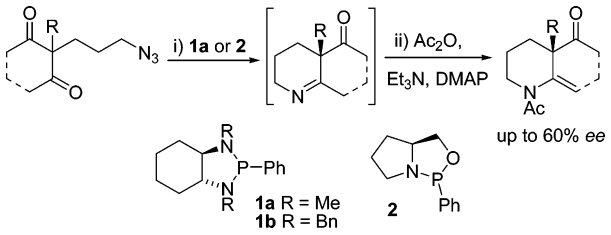
SCHEME 1. Desymmetrising Asymmetric Aza-Wittig Reactions

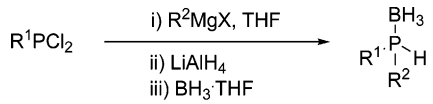


expansion in efforts toward the development of de novo asymmetric approaches to such species.[11−14]

We recently reported a new strategy for the asymmetric synthesis of chiral β-quaternary mono- and bicyclic enamides in enantioenriched form, employing a desymmetrising asymmetric aza-Wittig reaction of a prochiral azidodiketone (Scheme 1).[15,16] In this process, reaction of a chiral phosphorus(III) reagent with the azide in a Staudinger reaction leads to a chiral iminophosphorane, which undergoes preferential cyclization to one of the (now diastereotopic) carbonyl groups. In order to preserve the stereochemical integrity of the racemization-sensitive intermediates, the initially formed ketoimines were converted to configurationally stable *N*-acetylenamides before isolation. In our initial report, the chiral phosphorus(III) reagents we utilized were the known simple chiral diazaphospholidine **1a**[17] and oxazaphospholidine **2**,[18] derived from readily available 1,2-diamines and amino alcohols, respectively. We reasoned that the myriad routes available to such chiral building blocks would facilitate the rapid optimization of asymmetric induction by appropriate tuning of substituents. Such attempts, however, were stymied by the low levels of reactivity of the electron-deficient phosphorus reagents: reactions typically required extended periods of heating to reach completion, and even apparently minor substitutions (such as the alteration of the *N*-methyl substituents of **1a** to *N*-benzyl groups in **1b**) led to dramatic retardation or total shutdown of the cyclization.

A subsequent screen of a range of phosphorus(III) reagents showed that more electron-rich phosphorus reagents such as alkyl-substituted phosphines were more reactive in the Staudinger/aza-Wittig reaction sequence, in line with literature precedent.[19] Our attention therefore switched to the generation and utilization of a range of enantioenriched aryldialkylphosphines as potentially superior reagents for the asymmetric aza-Wittig reaction, and we report the results of this study herein.

TABLE 1. Synthesis of Secondary Alkyl-/Arylphosphine−Boranes



	R^1	R^2	product	yield,[a] %
1	Ph	^{t}Bu	**3**	89
2	Ph	Cy	**4**	49
3	Ph	2-Ad	**5**	33
4	^{t}Bu	*o*-tolyl	**6**	59
5	^{t}Bu	1-naphthyl	**7**	88
6	^{t}Bu	*o*-(Ph)C_6H_4	**8**	98
7	^{t}Bu	*o*-anisyl	**9**	94

[a] Isolated yield.

Results and Discussion

As a route to chiral aryldialkylphosphines, we were attracted to the method of Livinghouse,[13,20] wherein racemic *tert*-butylphenylphosphine−borane **3** undergoes deprotonation/alkylation mediated by *n*-BuLi/(−)-sparteine to yield enantioenriched aryldialkylphosphine−borane complexes by way of a dynamic kinetic resolution. Substituent variation has been achieved thus far by adaptation of the electrophilic alkylating agent utilized, with only a sole example of the use of an alternative phosphine-borane (Ph^{i}PrPH−BH_3).[20c] We felt that this method had the potential to provide access to diverse aryldialkylphosphines for our asymmetric aza-Wittig studies through systematic variation of each of the three substituents in turn and thus set about preparing a range of secondary phosphine−borane complexes for use in the dynamic kinetic resolution. Initially, the known secondary borane complex **3** was thus prepared by the method of Imamoto.[21] Selective monosubstitution of phenyldichlorophosphine with *tert*-butylmagnesium chloride was followed by reduction with lithium aluminum hydride and finally borane complexation using borane−THF complex to give **3** in 89% yield (Table 1, entry 1). Variation of the alkyl substituent in the secondary phosphine−borane complex was successfully carried out by the use of different Grignard reagents, namely cyclohexylmagnesium chloride and 2-adamantylmagnesium chloride, to yield complexes **4** and **5**, respectively. In order to systematically vary the aromatic substituents, the order of addition of substituents was changed. Thus, selective monosubstitution of *tert*-butyldichlorophosphine with a variety of aryl Grignard reagents was successfully achieved, allowing access to the secondary phosphine−borane complexes **6**−**9** following hydride reduction and borane complexation. Complexes **5**−**8**

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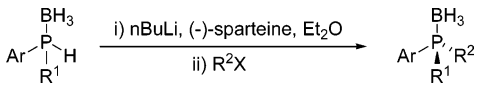
TABLE 2. Sparteine-Mediated Asymmetric Synthesis of Aryldialkylphosphine−Boranes



	Ar	R^1	R^2	product	yield,[a] %	ee, %
1	Ph	^{t}Bu	Me	**10**	83	94
2	Ph	^{t}Bu	Et	**11**	85	nd
3	Ph	^{t}Bu	Bn	**12**	70	92
4	Ph	Cy	Me	**13**	41	27
5	Ph	2-Ad	Me	**14**	99	21
6	*o*-tolyl	^{t}Bu	Me	**15**	83	92
7	1-naphthyl	^{t}Bu	Me	**16**	65	61
8	*o*-(Ph)C_6H_4	^{t}Bu	Me	**17**	83	0
9	*o*-anisyl	^{t}Bu	Me	**18**	80	0

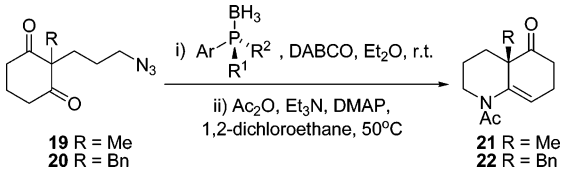
[a] Isolated yield.

are novel, and known complexes **4** and **9** have not previously been prepared by this method; the efficiency and generality of the approach highlights the synthetic utility of the Imamoto method for secondary phosphine-borane synthesis.

With the secondary phosphine−borane complexes **3**−**9** in hand, we turned our attention to their asymmetric alkylation by Livinghouse's dynamic kinetic resolution method.[13] Thus, phosphine−borane complex **3** was treated with (−)-sparteine and *n*-butyllithium at −78 °C, the mixture allowed to warm to room temperature and stirred for 1 h (with formation of a thick white precipitate), followed by re-cooling to −78 °C, addition of iodomethane, and slow warming to room temperature. We were pleased to find that tertiary phosphine-borane complex **10** was formed with comparable yield (82% vs 88%) and enantiomeric purity (94% ee vs 93%) to the reported values (Table 2, entry 1). Extension of the reaction to iodoethane and benzyl bromide as electrophiles gave comparable yields of products **11** and **12** (entries 2 and 3). While the ee of the latter was in close agreement with that for the formation of **10**, we were unable to determine a value for **11** by chiral HPLC under a range of conditions. Given the close agreement of values for **10** and **12**, which arise from the same intermediate lithiated phosphine, we presume that the value for **11** is of approximately the same magnitude, a presumption supported by the performance of the phosphines in the asymmetric aza-Wittig reactions (vide infra).

Extension of the method to the asymmetric methylation of phosphine−boranes **4**−**8** was then examined, with mixed results (entries 4−9). In all cases, the reactions yielded the desired products **13**−**18** in moderate to excellent yield, but the observed levels of asymmetric induction were variable. Methylation of **6**, the *o*-tolyl analogue of **4**, proceeded with comparable ee to the parent system, but the reactions of the other phosphines gave much reduced ee values. Notably, these more lipophilic substrates failed to give the "voluminous precipitate" observed by Livinghouse[13] and ourselves on deprotonation of **4**; presumably, the dynamic kinetic resolution is directed at least in part by this precipitation event and the failure of the more soluble analogues to form insoluble complexes is responsible for the modest to poor enantioselectivities observed. The failure to generate such a precipitate has also been observed in the metalation/alkylation of **4** using (+)-sparteine surrogates and

TABLE 3. Asymmetric Aza-Wittig with Aryldialkylphosphines



	R	reagent	method[a]	yield,[b] %	ee,[c] %
1	Me	**10**	A	50	79
2	Me	**10**	B	61	78
3	Bn	**10**	A	45	84
4	Bn	**10**	B	56	77
5	Me	**11**[d]	B	35	60[e]
6	Me	**12**[f]	A	49	44
7	Me	**13**[g]	B	52	3
8	Me	**15**	A	60	66
9	Me	**16**[g]	B	48	10
10	Me	**10**[g]	C	36	40
11	Bn	**10**[g]	C	35	46
12	Me	**12**	C	42	0

[a] Method A: two-pot. Method B. one-pot. Method C: two-pot catalyzed by methyltrioxorhenium. [b] Isolated yield, average of two runs. [c] ee corrected for phosphine, average of two runs. [d] Reactions carried out in toluene. [e] ee uncorrected. [f] Reaction carried out in toluene at 90 °C. [g] Single run only.

implicated in the resulting formation of racemic material.[22] In the case of the *o*-anisylphosphine **9**, competitive complexation of the lithium by the methoxy substituent may also interfere with sparteine coordination.

While the potential exists to promote precipitation (and hence, hopefully, improve ee values) by solvent switching, we elected to proceed first to screening of the new phosphines in the asymmetric aza-Wittig reaction, with the intention of reinvestigating the asymmetric synthesis of any reagents offering promising levels of asymmetric induction in due course. Two methods were devised for the reaction. In the first (method A), the free phosphine was prepared by decomplexation of the phosphine-borane complex with DABCO in toluene; the resulting solution was then filtered through dry neutral alumina under an inert atmosphere (to prevent aerobic oxidation) and solvent evaporated under vacuum (Schlenk line). The free phosphine was then redissolved in the solvent of choice and treated with the azide. At completion of the reaction (conveniently followed by disappearance of the azide stretch at ca. 2098 cm^{-1} in the IR spectrum) the solvent was removed on the Schlenk line and replaced by 1,2-dichloroethane, acetic anhydride, triethylamine, and catalytic DMAP and then heated to generate the configurationally stable *N*-acetylenamide. In the second approach (method B), the decomplexation and aza-Wittig reactions were carried out in the same reaction vessel by mixing phosphine−borane complex, azide, and DABCO in the appropriate solvent and monitoring for consumption of the azide; on completion of the aza-Wittig reaction the *N*-acetylenamide was prepared as for method A. As in our initial studies, the reactions were found to be highly sensitive to moisture, with material of reduced (or zero) enantiomeric purity being recovered if appropriate precautions (dry solvents, glassware, and anhydrous inert gas atmosphere) were not taken. The values for yield and ee given in Table 3 therefore represent the average of two reactions.

The phosphine from complex **10** was investigated first, using both methods A and B, with substrates **19** and **20**. Immediately

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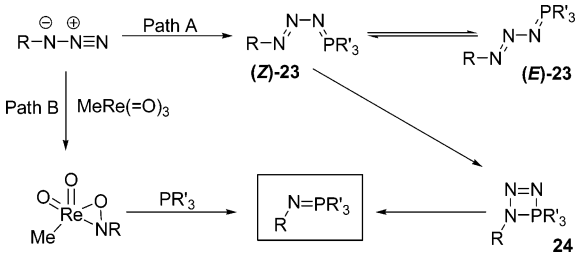
SCHEME 2. Mechanisms of Iminophosphorane Formation



we were rewarded with the highest enantiomeric excesses yet seen in the asymmetric aza-Wittig cyclization, with enamides **21** and **22** being isolated with average ee values up to 79% and 84% respectively (entries 1−4; corrected for the ee of the phosphine reagent). Although the ee values are comparable for each substrate using the different methods, we found that the one-pot process (method B) generally gave more closely reproducible results with the smallest variation in ee across different runs. The homologous phosphine from complex **11** (of unknown ee) led to material of 60% ee (uncorrected, entry 5). Assuming that the ee of **11** mirrors that of complexes **10** and **13** prepared from the same intermediate lithiated phosphine, this represents a slightly inferior level of asymmetric induction to reagent **10**. The benzyl-substituted phosphine complex **12** gave no reaction in ether at room temperature over prolonged periods; the reaction was therefore carried out in toluene at 90 °C, giving a moderate 44% ee (entry 6). Replacing the *tert*-butyl group of **10** by a cyclohexyl group (reagent **13**) gave near racemic material (entry 7). The effect of altering the aromatic substituent was also surveyed (entries 8 and 9), with the *o*-tolyl analogue **15** providing the best results with a 66% ee.

At the conclusion of this screening, it appeared that the simplest phosphine reagent **10** was optimal for the process. Conveniently, phosphine−borane **10** can be recrystallized to enantiomeric purity if required. However, we were unsatisfied with the comparison between **10** and the benzyl analogue **12**. The phosphine from the latter reagent had failed to deliver any product under conditions comparable to those for reaction of **10**, and we were concerned in particular that the requirement to operate at much higher temperatures with reagent **12** might be masking its intrinsic selectivity. Upon careful analysis of the reaction of the phosphine derived from **12** with azide **19**, we noticed that although the azide IR stretch disappeared rapidly from the reaction mixture, the signal for the desired imine did not grow in as expected. The mechanism for the Staudinger reaction between azides and phosphines is proposed to involve initial formation of *cis*-phosphazide (*Z*)-**23**, which undergoes cyclization to **24** and loss of nitrogen to give the iminophosphorane (Scheme 2, path A).[23,24] The intermediate phosphazides are not usually observed, but some have proven stable enough to be isolable; these usually have the isomeric *E*-geometry, which cannot cyclize to **24**.[23] The formation of (*E*)-**23**, which proceeds via isomerization of the initially formed (*Z*)-**23**, can be driven by a number of factors including the presence of bulky substituents at positions R and R′, as well as the presence of electron-donating substituents on phosphorus.[23] We therefore suspected that, in contrast to reagent **10**, the bulkier reagent **12** was becoming trapped as its (*E*)-phosphazide. This was supported by analysis of the ^{31}P NMR of the crude reaction mixture, which included a broad signal at ca. 24 ppm indicative of an (*E*)-phosphazide.[25] It therefore seems that the elevated temperatures are required to repopulate the reactive (*Z*)-phosphazide. A route around this dilemma was sought by catalysis of the formation of the iminophosphorane. Espenson and Zhu reported that methyltrioxorhenium (MTO) catalyzes the intermolecular formation of imines by reaction of azides, aryl aldehydes, and triphenylphosphine.[26] Although a detailed mechanism was not proposed, it was suggested that the MTO reacts with the azide via cycloaddition to an Re═O bond and subsequent loss of nitrogen. Were the resulting species to transfer a nitrenoid fragment back to the phosphine to generate an iminophosphorane, this would allow us to bypass the formation of phosphazides (Scheme 2, path B), and we therefore investigated the use of MTO in our asymmetric transformations.

In this approach (method C) the decomplexed phosphine was mixed with the appropriate azide and 5 mol % of MTO in dry ether before stirring at room temperature. In benchmarking reactions, we were pleased to find that reagent **10** did indeed form enantioenriched imine, thereby proving that the transfer of the nitrenoid to the chiral phosphine occurs prior to imine formation; however, the reactions of both **19** and **20** with **10** gave somewhat lower levels of asymmetric induction under these conditions compared with the noncatalyzed variants (Table 3, entries 10, 11; cf. entries 1, 3). Still more pleasing, we found that the benzyl-substituted reagent **12** did now react in ether at room temperature under MTO catalysis, but unfortunately, the resulting product was reproducibly found to be racemic, and further studies were abandoned.

Conclusions

In summary, we have prepared a range of racemic secondary phosphine−boranes and used them to test the scope of the Livinghouse dynamic kinetic resolution of lithiated secondary phosphine−boranes in the presence of (−)-sparteine. Several novel phosphine−boranes were prepared by this method in highly enantioenriched form, although substrates containing larger, more lipophilic substituents were not formed in high ee; this was attributed to the failure of the lithiated phosphine-sparteine complex to precipitate from solution. The phosphines derived from these complexes were examined in the desymmetrising asymmetric aza-Wittig cyclization, with several phosphines proving superior to the reagents previously studied in this transformation in terms of both reactivity and enantioselectivity (up to 84% ee). Although such enantiomeric purities are still below the 90% ee yardstick for a generally useful asymmetric transformation, the increased reactivity offers hope that application of these reagents to the desymmetrisation of other substrate classes may be possible. Additionally, the results obtained suggest that maximum differentiation between the alkyl substituents of the aryldialkylphosphines is important; this principle may be applied to the design of further reagents based on, for example, cyclic phosphine skeleta.

Experimental Section

General Procedure for Synthesis of Secondary Phosphine−Boranes: *tert*-Butyl-1-naphthylphosphine−Borane 7. This procedure was adapted from the method of Imamoto.[21] To a solution

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of $^tBuPCl_2$ (5.6 mL of a 1.25 M solution in THF, 7.0 mmol) at −78 °C was added, via cannula, a solution of 1-naphthylmagnesium bromide (30.0 mL of a 0.23 M solution in THF, 7.0 mmol). The mixture was then allowed to warm to rt over 1 h and cooled to 0 °C, and $LiAlH_4$ (7.0 mL of a 1 M solution in THF, 7.0 mmol) was added portionwise, followed by BH_3·THF (8.0 mL of a 1 M solution in THF, 8.0 mmol) and the mixture stirred at room temperature overnight. The crude mixture was added carefully via cannula to a slurry of ice, DCM, and HCl and the product extracted into DCM (3 × 30 mL). The combined organics were dried, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography eluting with 5−10% Et_2O/95−90% petroleum ether to yield the desired product as a white solid (1.4 g, 88%): mp 51−53 °C; ν_{max}/cm^{-1} 3057, 2959, 2899, 2866, 2380 (B-H), 1507, 1473, 1460; ^1H NMR ($CDCl_3$) δ 0.40−1.60 (3H, br), 1.23 (9H, d, J = 15), 5.82 (1H, dq, J = 366, 6.2), 7.52−7.65 (3H, m), 7.92 (1H, d, J = 8.0), 7.75−8.07 (2H, m), 8.30 (1H, d, J = 8.3); ^{13}C NMR ($CDCl_3$) δ 27.7 (d, J= 2.8), 30.6 (d, J = 31.9), 122.8 (d, J = 45.8), 125.4 (d, J = 12.0), 126.2 (d, J = 4.3), 126.9, 127.7, 129.7, 133.1 (d, J = 2.8), 134.0 (d, J = 6.6), 134.4 (d, J = 3.9), 136.0 (d, J = 11.4); ^{31}P NMR ($CDCl_3$) δ 15.9 (m); MS (CI, *m/z*) 248 (M + NH_4^+, 40), 217 (M − BH_3 + H^+, 100); HRMS (ES, *m/z*) found 248.1738, $C_{14}H_{24}BNP$ (M + NH_4^+) requires 248.1734.

General Procedure for Asymmetric Synthesis of Tertiary Phosphine−Boranes: (R_P)-*tert*-Butylmethyl(2-methylphenyl)-phosphine−Borane 15. This procedure was adapted from the method of Livinghouse.[13] To a solution of secondary phosphine−borane **6** (658 mg, 3.4 mmol) and (−)-sparteine (1.0 mL, 4.4 mmol) in diethyl ether (25 mL) at −78 °C was added *n*-butyllithium (1.4 M in THF, 2.7 mL, 3.8 mmol) dropwise. The mixture was then allowed to warm to rt over 1 h, and the formation of a thick precipitate was seen. The mixture was recooled to −78 °C, iodomethane (0.32 mL, 5.1 mmol) added dropwise, and the mixture allowed to warm to rt overnight. A 5% solution of H_2SO_4 (aq) was then added and the product extracted into Et_2O (3 × 20 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the crude product which was purified by flash chromatography (eluting with 5% Et_2O/95% petroleum ether) to yield the desired phosphine−borane **15** as a white solid (584 mg, 83%, 92% ee measured on a Chiralcel OD-RH column, gradient 40−51% MeCN/H_2O over 30 min, 1.0 mL/min, retention time = 24.9 min (major), 26.3 min)): $[\alpha]^{25}_D$ +28.0 (*c* 0.02, CH_2Cl_2); mp 88−90 °C; ν_{max}/cm^{-1} 3057, 2974, 2947, 2903, 2869, 2372 (B-H), 1475, 1461; ^1H NMR ($CDCl_3$) δ 0.44−1.37 (3H, br), 1.14 (9H, d, J = 14.0), 1.64 (3H, d, J = 9.2), 2.66 (3H, s), 7.22−7.27 (2H, m), 7.35−7.40 (1H, m), 7.52−7.58 (1H, m); ^{13}C NMR ($CDCl_3$) δ 9.2 (d, J = 39.0), 23.8 (d, J = 3.4), 25.8 (d, J = 2.4), 31.1 (d, J = 31.8), 125.7 (d, J = 8.2), 126.1 (d, J = 46.4), 131.5 (d, J = 2.1), 132.5 (d, J = 9.1), 134.4 (d, J = 6.3), 144.5 (d, J = 10.2); ^{31}P NMR ($CDCl_3$) δ 25.9 (q, J = 49); MS (CI, *m/z*) 226 (M + NH_4^+, 70), 195 (M − BH_3 + H^+, 45); HRMS (ES, *m/z*) found 226.1892, $C_{12}H_{26}BNP$ (M + NH_4^+) requires 226.1890.

General Procedure for Two-Pot Aza-Wittig Reaction (Method A). CAUTION: All reactions with azides were carried out behind blast shields in glassware which was kept clean of any contamination by transition metals.

To a 100 mL Schlenk tube charged with DABCO (200 mg, 1.78 mmol) was added a solution of phosphine−borane **10** (120 mg, 0.63 mmol) in degassed toluene (5 mL), and the mixture was heated at 50 °C over 16 h. On completion of the reaction, the solution was filtered into another 100 mL Schlenk tube through basic alumina and the alumina washed with 5% Et_2O/petroleum ether. The solvent was removed and the free phosphine then dried in vacuo over 4 h. To this phosphine was added via cannula a solution of azide **19** (64 mg, 0.31 mmol) in degassed Et_2O (5 mL) and the reaction stirred at room temperature and monitored by IR. On completion of the reaction, the Et_2O was removed in vacuo, and then DMAP (10 mol %) was added as a single portion and the mixture redissolved in 1,2-dichloroethane (5 mL). Triethylamine (0.17 mL, 1.22 mmol) and acetic anhydride (0.06 mL, 0.63 mmol) were then added, and the mixture was heated at 90 °C over 4 h. The mixture was then diluted with water and the product extracted into DCM (2 × 10 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (eluting with 30% acetone/petroleum ether) to yield enamide **21** as a white solid (56%, 76% ee = 84% ee corrected for the ee of the phosphine; a subsequent run gave 44% yield of material with 74% corrected ee. Measured on a Chiralpak OJ column, 10% IPA + 0.1%Et_2NH/hexanes, 1.0 mL/min, retention time = 40.0 min (major), 22.8 min). ^1H NMR data as previously reported.[15]

Alternatively, for longer reactions where the integrity of the inert gas might become an issue, the reaction can be carried out in a closed system. (**CAUTION!** These reactions were carried out behind a blast shield. Appropriate consideration must be given to the consequences of pressure build-up from the liberated nitrogen: in these examples, reaction on a 0.3 mmol scale would liberate ca. 7 mL of nitrogen gas to a head volume in the Schlenk of ca. 90 mL. Any attempt to scale this process must take account of the increased volume of gas released and hence pressure buildup.) Following addition of the solution of the azide to the phosphine, the system was isolated from the manifold and stirred at room temperature for 1 h. The reaction vessel was then briefly opened to the manifold to release the pressure buildup and then closed again. Upon completion of the reaction (IR monitoring), the reaction was progressed to the *N*-acetylenamide as before.

General Procedure for the One-Pot Aza-Wittig Reaction (Method B). To a solution of phosphine−borane **10** (65 mg, 0.34 mmol) in degassed Et_2O (2 mL) in a 100 mL Schlenk tube was added via cannula a solution of azide **20** (57 mg, 0.20 mmol) and DABCO (152 mg, 1.35 mmol) in degassed Et_2O (5 mL) and the reaction stirred at room temperature and monitored by IR. On completion of the reaction, the Et_2O was removed in vacuo, and then DMAP (10 mol %) was added as a single portion and the mixture redissolved in 1,2-dichloroethane (5 mL). Triethylamine (0.28 mL, 2.0 mmol) and acetic anhydride (94 μL, 1.0 mmol) were then added, and the mixture was heated at 90 °C over 4 h. The mixture was then diluted with water, and the product was extracted into DCM (2 × 10 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (eluting with 30% acetone/petroleum ether) to yield **22** as a white solid (53% of material with 64% ee = 77% ee corrected for the ee of the phosphine. A subsequent run gave 59% of material with 77% corrected ee. Measured on a Chiralcel OD-H column, 20% IPA/hexanes, 1.0 mL/min, retention time = 18.5 min (major), 25.0 min). ^1H NMR data as previously reported.[15]

General Procedure for Two-Pot Aza-Wittig Using MTO Catalyst (Method C). As for method A, except methyltrioxorhenium (5 mol %) was added to the phosphine solution prior to the addition of the solution of the azide. Reaction of azide **19** with phosphine−borane **10** gave **21** (36% yield of material with 33% ee = 40% ee corrected for the ee of the phosphine).

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Supporting Information Available: Characterization data for the remaining compounds, ^1H NMR spectra for compounds **3**−**18** and **21**/**22**, ^{13}C NMR spectra for all novel compounds, and ee data for the individual experiments comprising Table 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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