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Modular Asymmetric Synthesis of P-Chirogenic β-Amino Phosphine Boranes

Magnus J. Johansson,* Kristian H. O. Andersson, and Nina Kann*

Organic Chemistry, Department of Chemical and Biological Engineering, Chalmers University of Technology, SE-41296 Göteborg, Sweden

magjo@chembio.chalmers.se; kann@chalmers.se

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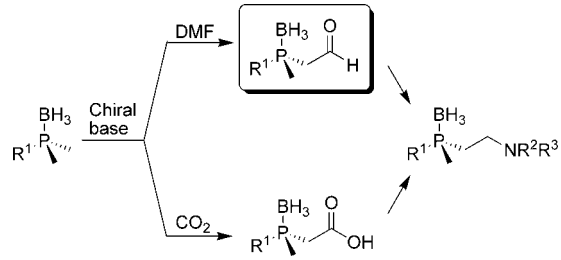

A short concise route to β-aminophosphine boranes is presented via the desymmetrization of prochiral phosphine boranes, forming P-chirogenic aldehydes that are rapidly transformed to the target compounds employing reductive amination under microwave irradiation. This sequence provides a modular route to P-chirogenic P,N ligands, and in addition, the intermediate aldehydes are versatile P-chiral building blocks for ligand design in general. An alternative pathway via the corresponding α-carboxyphosphines is also described. The ligands were subsequently evalutated in the asymmetric conjugate addition of diethylzinc to *trans*-β-nitrostyrene.

Introduction

In recent years, P-chirogenic ligands have become an important alternative to phosphorus ligands with the chirality residing on the surrounding carbon skeleton.[1] Presumably, it would be interesting to investigate P-chirogenic ligands in more detail as the chiral center is moved closer toward the metal upon coordination, and the electronic properties of the phosphorus part of the ligand can be altered more freely. However, practical methods for attaining chirality on phosphorus without traditional resolution are limited. The most commonly employed techniques are the diastereoselective opening of oxazaphospholidine boranes, a methodology developed by Genêt and Jugé,[2] and the asymmetric deprotonation of prochiral aryl dimethyl phosphine boranes as described by Evans and co-workers.[3] More recently, catalytic methods allowing the direct enantioselective synthesis of tertiary phosphine boranes have been developed, metal-mediated as well as biocatalytic.[4]

The pharmaceutical and fine chemicals industry are reliant on both enantiomers of chiral ligands for use in asymmetric catalysis. Therefore, it is surprising to see that many ligands are still only available in one enantiomeric form. To overcome this obstacle, we have recently reported on the use of (+)-sparteine surrogates to achieve the synthesis of both enantiomers of P-chirogenic phosphine boranes independently via enantioselective deprotonation.[5] By extending this methodology to the preparation of mixed bidentate ligands, one would get access to ligands where the coordinating atoms have different binding properties to the metal.

To achieve this target, we thus embarked upon the preparation of a diverse set of P-chirogenic β-aminophosphine boranes. Although numerous exmples of chiral P,N-ligands have been

(1) For reviews on P-chirogenic phosphines, see: (a) Ohff, M.; Holz, J.; Quirmbach, M.; Börner, A. *Synthesis* **1998**, 1391–1415. (b) Crépy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79–101. (c) Crépy, K. V. L. Imamoto, T. *Top. Curr. Chem.* **2003**, *229*, 1–40. (d) Johansson, M. J.; Kann, N. C. *Mini-Rev. Org. Chem.* **2004**, *1*, 233–247. (e) Grabulosa, A.; Granell, J.; Muller, G. *Coord. Chem. Rev.* **2007**, *251*, 25–90.

(2) Jugé, S.; Stephan, M.; Laffitte, J. A.; Genêt, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357–6360.

(3) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075–9076. ^{1}H NMR data were in accordance to published data for this compound.

(4) (a) Chan, V. S.; Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 2786–2787. (b) Scriban, C.; Glueck, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 2788–2789. (c) Wiktelius, D.; Johansson, M. J.; Luthman, K.; Kann, N. *Org. Lett.* **2005**, *7*, 4991–4994. (d) Kiełbasiński, P.; Albrycht, M.; Żurawiński, R.; Mikołajczyk, M. *J. Mol. Catal. B-Enzym.* **2006**, *39*, 45–49.

(5) (a) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. C. *Eur. J. Org. Chem.* **2004**, 1894–1896. (b) Johansson, M. J.; Schwartz, L.; Amedjkouh, M.; Kann, N. *Tetrahedron: Asymmetry* **2004**, *15*, 3531–3538. (c) McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378–16379.

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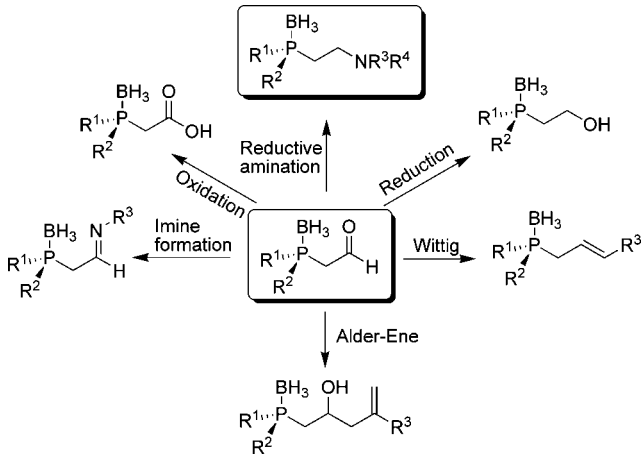
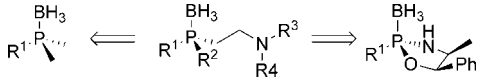
SCHEME 1. Versatile α-Formyl Phosphine Intermediate



SCHEME 2. Precursors to P-Chirogenic Aminophosphines

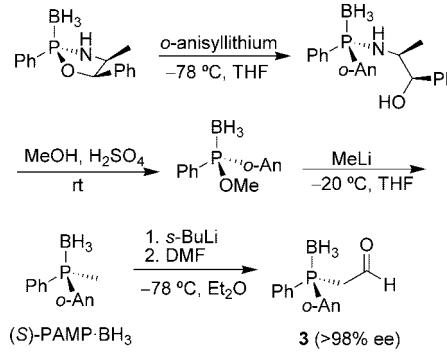


reported,[6] only a very limited number of these have the chirality residing on the phosphorus atom.[7] Also, the methodologies described do not allow for facile variation of the substitution pattern on *both* phosphorus and nitrogen, allowing fine-tuning of the electronic and steric properties of the ligands. The most appealing route would preferably render P-chirogenic phosphine boranes functionalized with an α-formyl moiety, a useful building block for reductive amination, but also for other types of diversifying transformations (Scheme 1).[8]

We envisioned that an asymmetric deprotonation of a prochiral phosphine borane or a diastereoselective opening of an oxazaphospholidine borane would give access to P-chirogenic ligands with the desired modular structural properties (Scheme 2). The asymmetric deprotonation gives easy access to both enantiomers of the desired phosphine borane using either (−)-sparteine or a (+)-sparteine surrogate. In the diastereselective opening of the oxazaphospholidine, both enantiomers of the desired phosphine borane can also be accessed by reversing the order of addition of the aryl/alkyl lithium.[2]

Both of the above-mentioned routes will provide methyl substituted phosphine boranes that can be further elaborated into aldehydes by asymmetric deprotonation and subsequent trapping

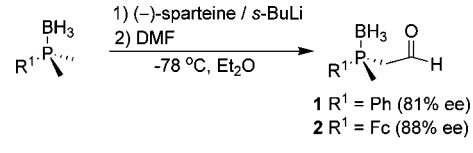
SCHEME 3. Synthesis of a PAMP-Derived α-Formylphosphine Borane



using a formyl source like DMF or formyl-piperidine, using a modified Beak procedure.[9]

Results and Discussion

A diverse set of prochiral phosphine boranes, containing phenyl-, ferrocenyl- or *tert*-butyl- as substituents on phosphorus, were selected for the study. Both ferrocenyl dimethylphosphine borane as well as phenyldimethylphosphine borane were subjected to asymmetric deprotonation using (−)-sparteine/*sec*-BuLi. We were delighted to find that *N*,*N*-dimethylformamide was a very effective electrophile in the desymmetrization of prochiral phosphine boranes, affording the corresponding chiral aldehydes in good yields (eq 1).



(1)

Because P,P-diaryl substituted α-formylphosphines cannot be synthesized via asymmetric deprotonation, the stereoselective ring-opening of an oxazaphospholidine borane complex proved to be the best alternative route to introduce two different aryl-substituent onto phosphorus. Borane-protected PAMP (*o*-anisyl methyl phenyl phosphine) was synthesized in three steps,[2] followed by deprotonation with *sec*-BuLi. The lithiated PAMP·BH_3 was subsequently quenched with DMF to give the P-diaryl α-formylphosphine borane in good yield and excellent optical purity (Scheme 3). It should be emphasized that this route can be used to introduce a variety of substituents other than anisyl, although it is somewhat longer than the asymmetric deprotonation sequence.

The P-chirogenic aldehydes synthesized were then subjected to a reductive amination, treating the aldehyde with sodium triacetoxyborohydride and different amines in dichloroethane, following a protocol reported by Abdel-Magid and co-workers.[10] The amines chosen for the study were anisidine, morpholine, as well as both enantiomers of α-methylbenzyl amine, selected to provide a diverse set of amines with different binding properties to a potential metal center (Figure 1).

Initial attempts were carried out on the crude aldehydes at room temperature. Reaction progress was slow, and the desired

(6) For a recent review on P,N-ligands, see: Guiry, P. J.; Saunders, C. P. *Adv. Synth. Cat.* **2004**, *346*, 497–537.

(7) (a) Bianchini, C.; Cicci, S.; Peruzzini, M.; Pietrusiewicz, K. M.; Brandi, A. *J. Chem. Soc., Chem. Commun.* **1995**, 833–834. (b) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547–7583. (c) Yang, H.; Lugan, N.; Mathieu, R. *Organometallics* **1997**, *16*, 2089–2095. (d) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 3047–3050. (e) Gilbertson, S. R.; Genov, D. G.; Rheingold, A. L. *Org. Lett.* **2000**, *2*, 2885–2888. (f) Maj, A. M.; Pietrusiewicz, K. M.; Suisse, I.; Agbossou, F.; Mortreux, A. *J. Organomet. Chem.* **2001**, *626*, 157–160. (g) Camus, J.-M.; Andrieu, J.; Richard, P.; Poli, R.; Darcel, C.; Jugé, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2061–2065. (h) Cheng, X. H.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *Tetrahedron: Asymmetry* **2004**, *15*, 2241–2246. (i) Lam, H.; Horton, P. N.; Hursthouse, M. B.; Aldous, D. J.; Hi, K. K. *Tetrahedron Lett.* **2005**, *46*, 8145–8148. (j) Sun, X.-M.; Koizumi, M.; Manabe, K.; Kobayashi, S. *Adv. Synth. Cat.* **2005**, *347*, 1893–1898. (k) Oliana, M.; King, F.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Org. Chem.* **2006**, *71*, 2472–2479.

(8) For examples of non-chiral/racemic α-formylphosphines and phosphine boranes, see: (a) Pellon, P. *Tetrahedron Lett.* **1992**, *33*, 4451–4452. (b) Mathey, F.; Mercier, F. *J. Organomet. Chem.* **1979**, *177*, 255–263. The latter reference indicates an alternative method for the preparation of P-chirogenic α-formylphosphines via the corresponding phosphine sulfide, although this was not carried out in practice for the α-formyl example.

(9) Beak, P.; Kerrick, S. T.; Wu, S. D.; Chu, J. X. *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239.

(10) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.

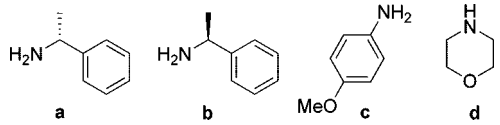
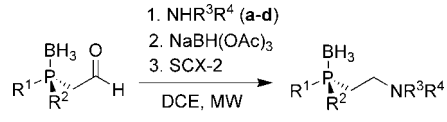


FIGURE 1. Set of amines used for the reductive amination.

TABLE 1. Microwave-Assisted Reductive Amination



1, **2** or **3** — **4, 5** or **6**

entry	R^1	R^2	product[a]	yield[b]
1	Ph	Me	**4a**	88
2	Ph	Me	**4b**	88
3	Ph	Me	**4c**	98
4	Ph	Me	**4d**	90
5	Fc	Me	**5a**	95
6	Fc	Me	**5b**	71
7	Fc	Me	**5c**	88
8	Fc	Me	**5d**	83
9	Ph	*o*-An	**6a**	84
10	Ph	*o*-An	**6b**	89
11	Ph	*o*-An	**6c**	96
12	Ph	*o*-An	**6d**	90

[a] See Figure 1 for amino-structures **a**−**d**. [b] Isolated yields after SCX-2 purification, eluting with NH_3 in MeOH.

product amines were difficult to purify, affording isolated product in general in yields of 6−22%. Purification of the precursor aldehydes in conjunction with the use of microwave heating gave substantially better results.[11] After 6 min under microwave irradiation at 120 °C, the desired amino-substituted phosphine boranes could be isolated in high purity and good yields by simple cation exchange chromatography, eluting the product with NH_3 in MeOH (Table 1).

Attempted preparation of *tert*-butyldimethylphosphine borane derivatives using the desymmetrization strategy afforded only small amounts of product upon quenching and isolation, although the crude material contained substantial quantities of the desired compound. Purification by chromatography on either deactivated silica gel or neutral/basic alumina resulted in degradation of the product. Reductive amination of the crude aldehyde gave desired products but in low yields. These derivatives were thus prepared via an alternative route involving the formation of α-carboxyphosphine-boranes using (−)-sparteine/*sec*-BuLi and carbon dioxide, followed by amide bond formation using 1-(3-dimethylaminpropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole hydrate (HOBt) (Scheme 4).

The resulting amides **7** were then reduced with BH_3·THF at elevated temperature to furnish the β-aminophosphines **8** in respectable yields (Table 2). After BH_3 mediated reduction, the β-aminophosphines were protected with borane on phosphorus and partially on nitrogen. Selective deprotection has earlier been reported using 1 equivalent of 1,4-diazabicyclo[2.2.2]octane (DABCO). However, we instead applied a strong cationic ion-exchange resin (SCX-2) to selectively remove borane from nitrogen.

(11) For some other examples of microwave-assisted reductive amination, using slightly different reaction conditions, see: (a) Bailey, H. V.; Heaton, W.; Vicker, N.; Potter, B. V. L. *Synlett* **2006**, 2444–2448. (b) Anderluh, M. *Tetrahedron Lett.* **2006**, *47*, 9203–9206. (c) Varma, R. S.; Dahiya, R. *Tetrahedron* **1998**, *54*, 6293–6298.

SCHEME 4. Alternative Strategy for the Synthesis of Alkyl-Substitued β-Aminophosphines

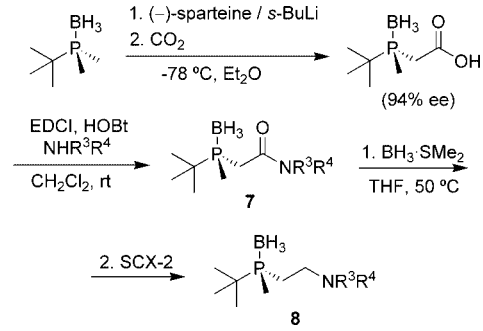
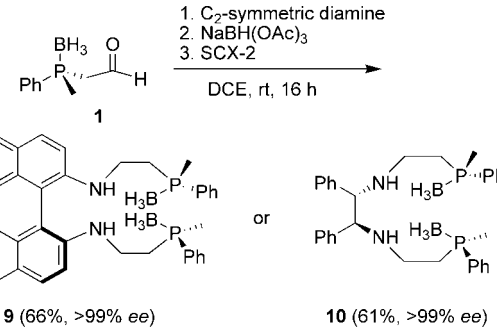


TABLE 2. Preparation of Dialkyl-Substituted Aminophosphines

entry	prod.[a]	yield[c]	entry	prod.[b]	yield[d]
1	**7a**	92	5	**8a**	87
2	**7b**	89	6	**8b**	95
3	**7c**	88	7	**8c**	71
4	**7d**	71	8	**8d**	77

[a] See Scheme 5. [b] See Figure 1 for amino-structures **a**−**d**. [c] Crude yield. [d] Yield of pure product.

SCHEME 5. Preparation of Tetradentate P,N-Ligands



Two tetradentate C_2-symmetric P,N,N,P-ligands were also prepared starting from the chiral diamines 2,2′-diaminobinaphthalene and 1,2-diphenylethylenediamine respectively (Scheme 5).[12]

Reductive amination with α-formyl phosphine borane **1** at ambient temperature afforded, after preparative HPLC, the desired tetradentate ligands **9** and **10** in moderate yields but excellent optical purity.

To evaluate the ligands in catalytic asymmetric synthesis, they were applied in the copper-catalyzed conjugate addition of diethylzinc to *trans*-β-nitrostyrene.[13–15] Jugé and co-workers have shown that borane-protected phosphines can be applied directly in several types of metal-catalyzed transformations

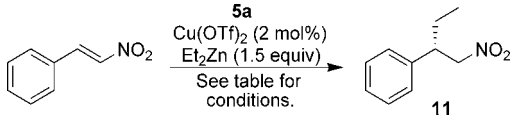
(12) See: Widhalm, M.; Wimmer, P.; Klintschar, G. *J. Organomet. Chem.* **1996**, *523*, 167–178, for a related macrocyclic ligand.

(13) For the first example of the conjugate addition of diethylzinc to a nitroolefin, see: (a) Alexakis, A.; Vastra, J.; Mangeney, P. *Tetrahedron Lett.* **1997**, *38*, 7745–7748. For a review on asymmetric copper-catalyzed conjugate addition, see: (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236.

(14) For other examples of asymmetric conjugate addition to nitroolefins, see: (a) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579–2581. (phosphoramidite ligands). (b) Ongeri, S.; Piarulli, U.; Jackson, R. F. W.; Gennari, C. *Eur. J. Org. Chem.* **2001**, 803–807. (sulfonamide-based ligands)

(15) For other examples of the use of P-chirogenic ligands in the copper-catalyzed asymmetric conjugate addition reaction, see: (a) Takahashi, Y.; Yamamoto, Y.; Katagiri, K.; Danjo, H.; Yamaguchi, K.; Imamoto, T. *J. Org. Chem.* **2005**, *70*, 9009–9012. (b) Duncan, A. P.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4117–4119.

TABLE 3. Optimization of Conditions for the Asymmetric Copper-Catalyzed Conjugate Addition of Diethylzinc to *trans*-β-Nitrostyrene, Using Ligand 5a



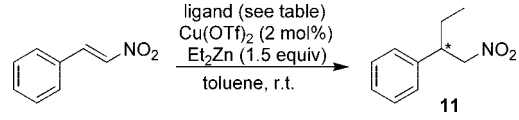
entry	[Cu]:L	temp. (°C)	solvent	time (h)	yield (%)	ee[a] (%)
1	1:2	0	toluene	12	35	19
2	1:2	−78	toluene	24	35	14
3	1:2	25	toluene	12	70	17
4	1:1	25	toluene	12	45	16
5[b]	1:1	25	toluene	18	n.r.	n.a.
6	1:2	25	CH_2Cl_2	20	69	16
7[c]	1:2	0	Et_2O	24	15	5
8[d]	1:2	25	CH_2Cl_2	20	30	10
9[e]	1:2	25	CH_2Cl_2	20	10	20
10[f]	1:2	0	toluene	12	33	14
11[f]	1:2	25	CH_2Cl_2	20	47	13

[a] Measured by chiral HPLC, see Experimental Section for details. [b] Trimethylsilyl iodide added. [c] Deprotection step performed in toluene. [d] CuOTf used. Deprotection with HBF_4. [e] Cu(acac) used. Deprotection with HBF_4. [f] **5b** used instead of **5a**.

without the need for prior deprotection of the phosphine.[16,17] The metal salt is reduced by borane and the phosphine ligand is simultaneously deprotected, thus affording a practical and direct method for the formation of the phosphine-metal complex. To ascertain that this method could be applied in our case, ligand **5a** was treated with $Cu(OTf)_2$ in a 1:1 ratio in different solvents (CH_2Cl_2, THF, toluene) at room temperature and at 50 °C. No deprotection occurred at ambient temperature, whereas full conversion of the **5a** to the corresponding free phosphine could be achieved in dichloromethane and in toluene at the higher temperature. We then focused on the conditions for the conjugate addition reaction. As monodentate, bidentate, and also bridging structures could be envisaged with the P-chirogenic aminophosphine ligands, a metal to ligand ratio of both 1:2 and 1:1 was tested. Results of the trial reactions, including variation of the solvent, reaction temperature, and decomplexation method, are shown in Table 3.

Reaction in toluene using two equivalents of ligand to metal (entries 1−3) gave slightly higher enantioselectivity and better yield when performed at room temperature than at −78 °C. The use of a 1:1 metal to ligand ratio (entry 4) gave only a slight decrease in enantioselectivity, but a markedly lower yield as compared to the corresponding reaction with more ligand added (entry 3). Addition of trimethylsilyl iodide was found to be detrimental to the reaction and no product was isolated in this case (entry 5). Performing the reaction in dichloromethane instead gave nearly identical results in terms of yield and enantioselectivity as compared to reaction in toluene (entry 6), whereas the use of diethyl ether (deprotection step performed in toluene) gave poor results (entry 7). The use of copper(I) triflate, with prior deprotection of the ligand with HBF_4,[18] did not offer any improvement (entry 8). The latter reaction was also performed using copper(I) acetylacetonate (entry 9). Although the enantioselectivity was somewhat improved (20% ee), the yield was low in this case. To see if the modest enantioselectivities were due to a mismatched situation, considering that ligand **5a** contains two chiral centers, two reactions were also performed with ligand **5b**, with the opposite stereochemistry on the amine moiety. A slightly lower enantioselectivity was obtained, but no great difference could be seen.

TABLE 4. Results from the Asymmetric Copper-Catalyzed Conjugate Addition of Diethylzinc to *trans*-β-Nitrostyrene Using the P-Chirogenic Ligands



entry	ligand[a]	yield	ee (%)[b]
1	**4a**	39	16 (*S*)
2	**4b**	47	21 (*S*)
3	**4c**	47	0
4	**4d**	22	0
5	**5a**	70	17 (*R*)
6	**5b**	56	10 (*R*)
7	**5c**	22	10 (*R*)
8	**5d**	59	12 (*R*)
9	**6a**	58	0
10	**6b**	18	37 (*S*)
11	**6c**	20	9 (*S*)
12	**6d**	49	14 (*S*)
13	**8a**	57	6 (*S*)
14	**8b**	56	14 (*S*)
15	**8c**	63	5 (*S*)
16	**8d**	53	28 (*S*)
17	**9**	30	2 (*R*)
18	**10**	44	16 (*S*)

[a] [Cu]:L ratio 1:2. [b] Measured by chiral HPLC, see Experimental Section for details.

We then turned to the screening of the ligand library to study the effect of different substituents on phosphorus (Table 4). Following the optimization studies described earlier, a metal to ligand ratio of 1:2 was selected together with toluene as the solvent. The reactions were performed at room temperature with 2 mol% copper(II) triflate as the catalyst. Methyl phenyl ligands **4a**−**b** gave enantioselectivities of 16 and 21% respectively, both affording the same enantiomer of the product (*S*), indicating that the phosphine part of the ligand determines the stereochemical outcome (entries 1 and 2). Ligands **4c** and **4d** somewhat surprisingly afforded racemic product (entries 3 and 4). Ferrocenyl methyl phosphine ligands **5a**−**d** all gave enantioselectivities in the range of 10−17% and product with *R*-configuration (entries 5−8). Ligands **6a**−**d**, based on a PAMP-structure, gave more interesting results. Ligand **6a** afforded racemic product, while switching to the opposite enantiomer of the amine component of the ligand gave an enantiomeric excess of 37%, indicating a mismatched situation in the first case (entries 9 and 10). Ligands **6c** and **6d** gave more modest selectivities (entries 11 and 12). For the *tert*-butyl methyl phosphine ligands **8a**−**d** (entries 13−16), the morpholine substituted ligands gave best results (28% ee). Tetradentate ligands **9** and **10** were also investigated. Ligand **9**, based on a binaphthyl-diamine skeleton, gave nearly racemic product (entry 17), while the more flexible ligand **10** gave an enantioselectivity more in line with the earlier results (entry 18). Widhalm and co-workers have studied similar ligands in other asymmetric

(16) Darcel, C.; Kaloun, E. B.; Merdès, R.; Moulin, D.; Riegel, N.; Thorimberg, S.; Genêt, J. P.; Jugé, S. *J. Organomet. Chem.* **2001**, *624*, 333343.

(17) For other examples of application of this methodology, see: (a) Vasse, J.-L.; Stranne, R.; Zalubovskis, R.; Gayet, C.; Moberg, C. *J. Org. Chem.* **2003**, *68*, 3258–3270. (b) Dolhem, F.; Johansson, M. J.; Antonsson, T.; Kann, N. *J. Comb. Chem* **2007**, *9*, 477–486.

(18) (a) McKinstry, L.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 7655–7666. (b) McKinstry, L.; Overberg, J. J.; Soubra-Ghaouli, C.; Walsh, D. S.; Robins, K. A.; Tangredi Toto, T.; Toto, J. L. *J. Org. Chem.* **2000**, *65*, 2261–2263.

(19) The corresponding racemic compound has been prepared earlier, see ref 8b.

carbon−carbon bond forming reactions such as asymmetric allylic substitution and nickel-catalyzed cross-coupling reactions,[12] and it may be that these are more suitable test reactions for these two ligands.

Conclusion

In conclusion, we have shown that α-formyl phosphine boranes can be produced in enantio-enriched form by either asymmetric deprotonation of prochiral phosphine boranes or by deprotonation of PAMP·BH_3. This methodology gives access to a new type of P-chirogenic compounds that are highly versatile building blocks for the design and construction of new chiral phosphine ligands. These complementary routes allow for alkyl,alkyl; aryl,alkyl; and aryl,aryl substituents on phosphorus. P,N-ligands are becoming increasingly popular and the reported approach allows a facile, modular, and efficient synthesis of such compounds. In addition, a selective *N*-deprotection of the diboronated P,N-ligands is reported, employing a strong cation exchange resin. The ligands were evaluated in the copper-catalyzed asymmetric conjugate addition of diethyl zinc to nitrostyrene, employing in situ deprotection of the ligands by the metal. Noteworthy is the reversal in absolute configuration going from *P*-phenyl or *P*-anisyl to *P*-ferrocenyl. Although the enantioselectivities were modest, the concept of in situ deprotection and concomitant complexation to a metal has proven to be a viable alternative to isolation of the free phosphine followed by complexation. This allows for easy screening of ligands in their protected form relying on the metal, in its higher oxidation state, to cleave the P−B bond. Further studies in exploring the utility of the obtained α-formyl phosphine boranes both as ligands in different processes and as building blocks for ligand development are in progress.

Experimental Section

(S_p)-(α-Formylmethyl)-methylphenylphosphine Borane (1).[19] To a cooled (−78 °C) solution of (−)-sparteine (1.70 g, 7.24 mmol) in 30 mL of diethyl ether was added *sec*-BuLi (7.24 mmol) *via cannula*. After stirring for 30 min, a solution of dimethylphenylphosphine borane[3] (1.00 g, 6.58 mmol) in 20 mL of diethyl ether was added dropwise *via cannula*. The reaction was left to stir for 3 h after which dry *N*,*N*-dimethylformamide (0.96 g, 13.2 mmol) was added dropwise *via cannula*. The reaction was left to stir for 1 h. The reaction was quenched with sat. NH_4Cl (aq). The aqueous layer was extracted three times with diethyl ether. The combined organic phases were washed three times with $KHSO_4$ (aq) and once with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (25% ethyl acetate, 75% petroleum ether) yielded the product as a pale-yellow oil (1.12 g, 93%). Data for **1**: $[\alpha]_D^{20} = +22.3$ (*c* 1.03 in $CHCl_3$, 81% ee); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.68 (dt, $J = 3.2$, 1.6 Hz, 1H), 7.80−7.70 (m, 2H), 7.60−7.44 (m, 3H), 3.10 (dq, $J = 12.0$, 1.2 Hz, 2H), 1.71 (d, $J = 10.0$ Hz, 3H), 1.87 (br q, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 195.2 (d, $J = 12.4$ Hz), 131.9 (d, $J = 3.1$ Hz), 131.2 (d, $J = 13.1$ Hz), 128.9 (d, $J = 9.9$ Hz), 42.4 (d, $J = 26.6$ Hz), 10.5 (d, $J = 25.7$ Hz); two signals in the aromatic area overlap. Anal. Calcd for $C_9H_{14}BOP$: C 60.06, H 7.84; Found: C 59.93, H 7.81. The enantioselectivity was determined by reduction to the corresponding alcohol and HPLC analysis on a Daicel Chiralcel OD-H column (*n*-hexane-*i*-PrOH).

(S_p)-Ferrocenyl-(α-formylmethyl)-methylphosphine Borane (2). To a cooled (−78 °C) solution of (−)-sparteine (0.30 g, 1.27 mmol) in 5 mL of ether was added *sec*-BuLi (1.27 mmol) *via cannula*. After stirring for 30 min, a solution of dimethylferrocenyl phosphine borane[20] (0.30 g, 1.15 mmol) in 5 mL of toluene was added dropwise *via cannula*. The reaction was left to stir for 4 h after which dry *N*,*N*-dimethylformamide (0.17 g, 2.30 mmol) was added dropwise *via cannula*. The solution was then heated to 50 °C for 1 h and subsequently allowed to cool to rt. The reaction was quenched with sat. NH_4Cl (aq). The aqueous layer was extracted three times with diethyl ether. The combined organic phases were washed three times with sat. $KHSO_4$ (aq) and once with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (30% ethyl acetate, 70% petroleum ether) yielded the product as a thick brown oil (0.27 g, 82%). Data for **2**: $[\alpha]_D^{20} = +22.4$ (*c* 1.19 in $CHCl_3$, 88% ee); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.61 (t, $J = 12.5$ Hz, 1H), 4.58−4.56 (m, 1H), 4.54−4.51 (m, 1H), 4.50−4.48 (m, 1H), 4.31 (s, 5H), 4.30−4.27 (m, 1H), 3.00−2.93 (m, 2H), 1.66 (d, $J = 10.4$ Hz), 0.83 (br q, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 195.3 (d, $J = 4.5$ Hz), 72.4 (d, $J = 39.2$ Hz), 72.2 (d, $J = 33.2$ Hz), 71.9 (d, $J = 6.8$ Hz), 69.9 (d, $J = 5.4$ Hz), 69.7, 44.3 (d, $J = 25.7$ Hz), 10.5 (d, $J = 37.9$ Hz); some signals in the aromatic area overlap. Anal. Calcd for $C_{13}H_{18}BFeOP$: C 54.23, H 6.30; Found: C 54.29, H 6.18. The enantioselectivity was determined by reduction to the corresponding alcohol and HPLC analysis on a Daicel Chiralcel OD-H column (*n*-hexane-*i*-PrOH).

(S_p)-(α-Formylmethyl)-(2-methoxyphenyl)-phenylphosphine Borane (3). To a cooled (−78 °C) solution of (*S*)-PAMP·BH_3[2] (5.14 mmol, 1.25 g, >98% ee) in 30 mL THF was added *sec*-BuLi (6.17 mmol) *via cannula*. The reaction was left to stir for 2 h after which dry *N*,*N*-dimethylformamide (10.28 mmol, 0.75 g) was added dropwise *via cannula*. The reaction was stirred for 1 h and then quenched with sat. NH_4Cl (aq). The aqueous layer was extracted three times with diethyl ether. The combined organic phases were washed three times with saturated $KHSO_4$ (aq) and once with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (15% ethyl acetate, 85% petroleum ether) yielded the product as colorless oil (1.18 g, 84%). The product degraded rapidly upon storage, even when stored under argon at −18 °C. Freshly prepared compound and immediate use in the next step are thus recommended. Data for **3**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.70 (t, $J = 3.2$ Hz, 1H), 7.82 (ddd, $J = 14.8$ Hz, $J = 8.0$ Hz, $J = 2.0$ Hz, 1H), 7.67−7.62, (m, 2H), 7.57−7.52 (m, 1H), 7.47−7.39 (m, 3H), 7.10−7.06 (m, 1H), 6.93 (dd. $J = 8.4$ Hz, $J = 3.6$ Hz, 1H), 3.75 (s, 3H), 3.62−3.45 (m, 2H), 1.60−0.60 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.5, 161.0, 135.9 (d, $J = 15.2$ Hz), 134.5 (d, $J = 1.5$ Hz), 131.4 (d, $J = 10.6$ Hz), 131.1 (d, $J = 2.3$ Hz), 128.6 (d, $J = 58.4$ Hz), 128.6 (d, $J = 10.6$ Hz), 121.4 (d, $J = 12.9$ Hz), 114.5 (d, $J = 53.1$ Hz), 111.2 (d, $J = 3.8$ Hz), 55.4, 40.4 (d, $J = 30.3$ Hz).

General Procedure for the Microwave-Assisted Reductive Amination (4a−d, 5a−d, 6a−d). P-chirogenic aldehyde **1**, **2**, or **3** (1.2 equiv) was solubilized at room temperature in 5 mL of dichloroethane into a 5 mL microwave vial with a magnetic stirrer. To this was added an amine (**a**−**d**, 1 equiv) followed by sodium triacetoxyborohydride (1.3 equiv) in one portion. The vial was then sealed and evacuated before being filled with N_2. The microwave reaction was performed at 130 °C for 6 min in a Biotage Series 60 Initiator, where the reaction temperature was monitored with an IR sensor. Purification was performed using a cationic ion-exchange resin (IST SCX-2) and washed with eight column volumes of DCM and eight column volumes of methanol. The product was eluted with NH_3/methanol and concentrated *in vacuo*.

(20) Oohara, N.; Katagiri, K.; Imamoto, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2171–2175. ^{1}H NMR data were in accordance to published data for this compound.

Data for Compounds 4a, 5a, and 6a. (S_P)-Methylphenyl-[*β*-{(1R)-1-phenethyl}amino]-phosphine Borane (4a).[21] Transparent oil (88%). $[\alpha]_D^{20} = +25.7$ (*c* 0.79 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.71−7.65 (m, 2H), 7.52−7.40 (m, 3H), 7.32−7.20 (m, 4H), 3.77−3.70 (m, 1H), 2.72−2.62 (m, 2H), 2.12−2.01 (m, 2H), 1.89 (br s, 1H), 1.56 (d, $J = 10.2$ Hz, 3H), 1.32 (d, $J = 6.6$ Hz, 3H), 1.20−0.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 144.9 (d, $J = 6.1$ Hz), 131.5 (dd, $J = 9.2$, 3,1 Hz), 129.7, 129.2, 128.7 (d, $J = 9.8$ Hz), 128.3, 126.9, 126.4, 57.9, 41.7, 28.0 (d, $J = 35.1$ Hz), 24.0, 11.3 (d, $J = 38.7$ Hz). Anal. Calcd for $C_{17}H_{25}BNP$: C 71.60, H 8.84; Found: C 71.46, H 8.71.

(S_P)-Ferrocenyl-[*β*-{(1R)-1-phenethyl}amino]-phenylphosphine Borane (5a). Brown oil (95%). $[\alpha]_D^{20} = +2.95$ (c 0.61 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.19 (m, 5H), 4.44−4.39 (m, 4H), 4.27 (s, 5H), 4.26−4.25 (m, 1H), 3.69 (q, $J =$ 6.6 Hz, 1H), 2.71−2.55 (m, 2H), 1.91−1.83 (m, 2H), 1.49 (d, $J =$ 10.3 Hz, 3H), 1.29 (d, $J = 6.6$ Hz, 3H), 1.10−0.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 128.4, 126.9, 126.5, 72.2 (d, $J = 13.9$ Hz), 71.3 (d, $J = 7.6$ Hz), 71.2 (d, $J = 6.2$ Hz), 69.7 (d, $J = 6.0$ Hz), 69.5, 69.5, 69.4, 58.0, 41.9, 29.3 (d, $J = 36.2$ Hz), 24.0, 11.4 (d, $J = 40.2$ Hz). Anal. Calcd for $C_{21}H_{29}BFeNP$: C 64.16, H 7.44; Found: 63.86, H 7.58.

(S_P)-(2-Methoxyphenyl)-[*β*-{(1R)-1-phenethyl}amino]-phenylphosphine Borane (6a). Pale-yellow solid (84%). $[\alpha]_D^{20} =$ +14.5 (*c* 0.83 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84 (dd, $J = 14.0$ Hz, 7.6, 1H), 7.59 (app. t, $J = 9.6$ Hz, 2H), 7.48−7.19 (m, 9H), 7.02 (t, $J = 7.2$ Hz, 1H), 6.81 (dd, $J = 8.0$ Hz, 3.2, 1H), 3.85−3.70 (m, 1H), 3.62 (s, 3H), 2.90−2.73 (m, 2H), 2.72−2.48 (m, 2H), 1.33 (d, $J = 6.8$ Hz, 3H), 1.30−0.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.2, 136.2 (d, $J = 14.4$ Hz), 133.8, 131.4 (d, $J = 9.1$ Hz), 130.4 (d, $J = 3$ Hz), 129.7, 128.4, 128.2 (d, $J =$ 9.9 Hz), 126.7, 121.1 (d, $J = 12.1$ Hz), 115.9, 115.4, 110.9 (d, $J =$ 4.5 Hz), 57.9, 55.3, 41.8, 24.0 (d, $J = 38$ Hz), 23.6. Anal. Calcd for $C_{23}H_{29}BNOP$: C, 73.22; H 7.75. Found: C, 73.08; H, 7.70.

General Procedure for the Amidation of 2-(S_P)-(tert-butyl-(methyl)phosphino)acetic Acid Borane (Formation of 7a−d). 2-(S_P)-(*tert*-Butyl(methyl)phosphino)-acetic acid borane[22] (1.0 mmol, 94% ee) was dissolved in THF (10 mL) under N_2. HOBt (2.0 mmol) and EDCI (1.2 mmol) was added in one portion at 0 °C, then the mixture was stirred at room temperature for 30 min. An amine (**a-d**, 1.2 mmol) was added at 0 °C, and the solution was stirred at ambient temperature. The reaction was quenched after 16 h by the addition of 1 M HCl (30 mL) and diluted with $CHCl_3$ (10 mL). The layers were separated. Then the combined organic layers were washed with saturated $NaHCO_3$, 2 M NaOH, 2 M HCl and brine. The organic phase was then dried over Na_2SO_4. Filtration and evaporation of the solvent gave crude phosphineamide boranes **7**, of sufficient purity to be used directly in the next step.

Data for 7a: (R_c,S_P)-2-(tert-Butyl(methyl)phosphanyl)-N-(1-phenylethyl)-acetamide borane (7a). White solid (92%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.26 (m, 5H), 6.45 (d, $J = 6.8$ Hz, 1H), 5.07 (q, $J = 6.8$ Hz, 1H), 2.58 (d, $J = 11.6$ Hz, 2H), 1.52 (d, $J = 6.8$ Hz, 3H), 1.33 (d, $J = 9.6$ Hz, 3H), 1.13 ($J = 14.4$ Hz, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 142.6, 128.6, 127.4, 126.3, 49.8, 30.9 (d, $J = 23.5$ Hz), 27.8 ($J = 32.6$ Hz), 5.2 (d, $J =$ 33.3 Hz). Anal. Calcd for $C_{15}H_{27}BNOP$: C, 64.54; H, 9.75. Found: C, 64.63; H, 9.71.

General procedure for the borane reduction of phosphine amides 7a-d (formation of 8a-d). Phosphine amide borane **7a−d** respectively (1.0 mmol) were dissolved in THF (5 mL) under N_2. Then BH_3-DMS (5.0 mmol) was added dropwise at 0 °C, and then the mixture was stirred at 50 °C for 6 h. The crude mixture was poured directly onto a cationic ion-exchange resin (IST SCX-2). The column was washed thoroughly with 8 × 20 mL DCM and 8 × 20 mL MeOH. Finally the product was eluted using methanol saturated with ammonia. Evaporation of the solvent gave the corresponding analytically pure *β*-aminophosphine boranes **8a−d**.

Data for 8a: (S_P)-tert-Butyl-methyl-[*β*-{(1R)-1-phenethyl}amino]-phosphine borane (8a). White solid (87%). $[\alpha]_D^{20} = +23.4$ (*c* 1.29 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.21 (m, 5H), 3.77 (q, $J = 6.8$ Hz, 1H), 2.80 (m, 1H), 2.75 (m, 1H), 2.0 (broad s, 1H), 1.82−1.62 (m, 2H), 1.35 (d, $J = 6.8$ Hz, 3H), 1.14−1.05 (m, 12H), 0.90−0.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 128.4, 127.0, 126.5, 58.4, 42.2 (d, $J = 1.5$ Hz), 27.2 (d, $J = 34.2$ Hz), 24.8 (d, $J = 2.2$ Hz), 24.2, 21.9 (d, $J = 31.1$ Hz) 5.6 (d, $J =$ 34.2 Hz). Anal. Calcd for $C_{15}H_{29}BNP$: C, 67.94; H, 11.02. Found: C, 67.82; H, 10.96.

General Procedure for the Asymmetric Conjugate Addition of Diethyl Zinc to *trans*-*β*-Nitrostyrene (Formation of 11). The desired ligand (8.2 μmol, 4 mol%) was placed in a 5 mL round-bottom flask together with $Cu(OTf)_2$ (4.1 μmol, 3 mg, 2 mol%) and dry toluene (1.5 mL) under an argon atmosphere. The mixture was heated to 50 °C, and the deprotection was monitored by TLC. When no phosphine borane complex could be detected, *trans*-*β*-nitrostyrene (0.2 mmol, 30 mg) in 0.5 mL toluene was added. After 20 min, the reaction was cooled to 0 °C, and a 1 M solution of diethylzinc in hexane (0.3 mmol, 0.3 mL) was added. The reaction was allowed to warm up to room temperature and stirred until no substrate could be detected by TLC (12−24 h). Quenching with saturated ammonium chloride was followed by extraction with ether and washing with saturated sodium bicarbonate and brine. The combined organic phases were filtered through a short plug of silica gel, dried with sodium sulfate, and concentrated *in vacuo*, affording essentially pure 1-nitro-2-phenylbutane (**11**). The enantioselectivity was determined by HPLC analysis on a Daicel Chiralcel OD-H column (*n*-hexane-*i*-PrOH 95:5, 0.5 mL/min, 230 nm). 1-Nitro-2-phenylbutane: t_R/min = 17.8 (*R*), 23.5 (*S*).[23] ^1H NMR data were in accordance to published data for this compound.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The corresponding free phosphine has been prepared earlier, see ref 7c.

(22) Ohashi, A.; Kikuchi, S.-I.; Yasutake, M.; Imamoto, T. *Eur. J. Org. Chem.* **2002**, 2535–2546. ^1H NMR data were in accordance to published data for this compound.

(23) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *52*, 2305–2324.