Desymmetrization of Prochiral Phosphanes Using Derivatives of (−)-Cytisine

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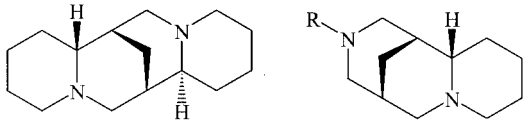
Historically, (–)-sparteine·*sec*-BuLi has been used to desymmetrize prochiral phosphanes. In this report, derivatives of an alkaloid extracted from the seeds of *Laburnum anagyroides* have been utilized to mimic (+)-sparteine, which is not readily available. In several cases, the enantioselectivities achieved with the (+)-sparteine surrogates outperformed (–)-sparteine itself in the deprotonation of alkyl-substituted (as well as aryl-substituted) prochiral phosphane derivatives. In addition, use of these surrogates allows a new methodology for a chiral switch in phosphorus chemistry.

Introduction

The development of new chiral ligands for asymmetric organometallic transformations is an important field of research within organic chemistry at present.[1] In this field, phosphanes are among the most versatile ligands, because they can coordinate to a wide range of transition metals.[2] Chiral phosphanes with the chiral centre on phosphorus (*P*-chiral or *P*-chirogenic phosphanes) are much less prevalent than phosphane ligands with axial chirality or chirality on an adjacent carbon, mainly due to the difficulties involved in preparing such ligands. However, recent developments employing the stabilizing effect of boranes coordinated to phosphorus have facilitated the preparation of *P*-chirogenic phosphanes, and several new pathways to their synthesis have been opened up.[3] An elegant approach involving the enantioselective deprotonation of prochiral dimethylphosphane−boranes with a (−)-sparteine·butyllithium complex has been developed by Evans,[4] while Livinghouse has reported a related study concerning the dynamic resolution of lithiated racemic *tert*-butylphenylphosphane−borane.[5] Imamoto has applied the enantioselective deprotonation approach both to the preparation of the BisP*[6] and MiniPHOS[7] ligands, while Zhang et al. have again shown the elegance of the (−)-sparteine·butyllithium method in their synthesis of Tangphos.[8] Palladium-catalyzed cross-coupling has been used to prepare tertiary phosphanes from enantiomerically pure secondary phosphanes[9] with retention or inversion of configuration, depending on the reaction conditions used.[10] However, none of the above mentioned methods allow for a general and convergent route to both enantiomers of a *P*-chirogenic ligand, thus halving the potential for use of those ligands. Recently, however, O'Brien reported the transformation of (−)-cytisine, isolated from the seeds of *Laburnum anagyroides* (Golden rain tree), to a diamine, (+)-**1** (Figure 1), that functions as a surrogate for (+)-sparteine in the deprotonation of *N*- and *O*-carbamates, the α-lithition and subsequent rearrangement of an epoxide, and an oxidative kinetic resolution of a racemic alcohol.[11,12] Somewhat surprisingly, reports of applications of other diamines than (−)-sparteine as the chiral ligand in the asymmetric desymmetrization of prochiral phosphane−boranes are scarce.[13]



(–)-Sparteine (+)-**1** R = Me (+)-**2** R = *i*Pr

Figure 1. Chiral diamines used in the enantioselective deprotonation of prochiral phosphane−boranes

In this report, we show that a chiral switch[14] can be used to access the other enantiomer of the phosphane−borane by using (+)-**1** or (+)-**2** (Figure 1) instead of (−)-sparteine.[15] As part of our study of (+)-**1**, we also wanted to investigate the importance of the methyl substituent on (+)-**1** and its effect on enantioselectivity. Therefore analogue (+)-**2**, containing an *isopropyl* substituent instead of the

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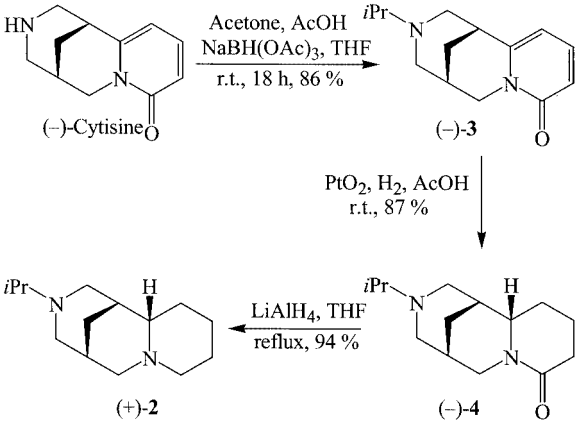
methyl group, was also prepared. The synthetic route applied in the synthesis of (+)-**2** was designed to allow the easy introduction of other R-groups at the secondary amine position.

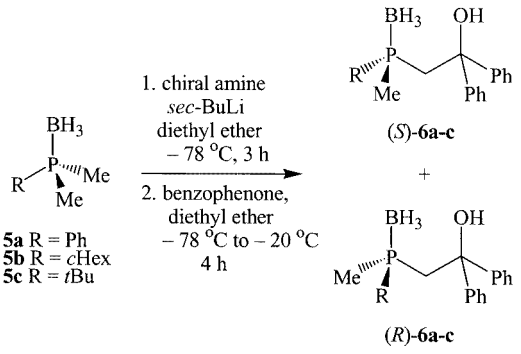
Results and Discussion

Diamine (+)-**1** was prepared from (−)-cytisine according to the procedure published by O'Brien.[11] Ligand (+)-**2** was prepared using a modified strategy, comprising an initial reductive amination followed by a platinum-oxide-catalyzed hydrogenation under acidic conditions affording lactam (−)-**4**, in good yield and with high diastereoselectivity (Scheme 1). Reduction using lithium aluminum hydride furnished diamine (+)-**2** in 70% overall yield.



Scheme 1. Synthesis of ligand (+)-**2** from (−)-cytisine

Both cytisine derivatives (+)-**1** and (+)-**2** were then applied to the asymmetric deprotonation of alkyl- and phenyl-substituted dimethylphosphane−boranes, trapping the intermediate lithium species with benzophenone (Scheme 2). Because alkyl-substituted dimethylphosphane−boranes were not included in Evans' study, we also performed the corresponding enantioselective deprotonations with (−)-sparteine for comparison.[16]



Scheme 2. Enantioselective deprotonation of dimethylphosphane−boranes using chiral amine·*sec*-BuLi complexes

To establish the reaction conditions, we first repeated the experiment of Evans, treating dimethyl(phenyl)phosphane−borane (**5a**) with (−)-sparteine·*sec*-BuLi, and subsequently quenching the intermediate lithium species with benzophenone (Table 1, entry 1). The reaction was found to be reproducible and yielded nearly exactly the same results as the published data.[17] Using (+)-**1** instead of sparteine, we found that we could indeed access the opposite enantiomer, (*R*)-**6a**, in a high yield and with an *ee* of 67% (entry 2). The bulkier diamine (+)-**2** gave similar results, although with a somewhat lower enantioselectivity (Table 1, entry 3). Subsequently, we turned to alkyl-substituted dimethylphosphane−boranes as substrates. Using cyclohexyldimethylphosphane−borane (**5b**), better results were obtained with the cytisine derivative (+)-**1** (74% *ee*, entry 5) than with (−)-sparteine (70% *ee*, entry 4), whereas (+)-**2** was somewhat less efficient (entry 6). Using *tert*-butyldimethylphosphane−borane (**5c**), we found to our delight that the enantioselectivity improved considerably, and the desired product (*R*)-**6c** was formed in 92% *ee* with (+)-**1** as the ligand (entry 8), while (+)-**2** gave approximately the same degree of enantioselectivity as (−)-sparteine (entries 9 and 7). The yields were satisfactory-to-high in all experiments and the products obtained were generally white crystalline solids. Although we have analysed the products as the phosphane−borane complexes, decomplexation to the free phosphane can be effected using amines[4,18] or treatment with acid followed by hydrolysis.[6,19]

Table 1. Enantioselectivity in the asymmetric deprotonation of prochiral phosphane−boranes using different chiral amine ligands

Entry	R	Chiral amine	*ee* [%] (config.)	yield [%]
1	Ph	(−)-Sparteine	78 (*S*)	87
2	Ph	(+)-**1**	67 (*R*)	89
3	Ph	(+)-**2**	63 (*R*)	82
4	*c*Hex	(−)-Sparteine	70 (*S*)	67
5	*c*Hex	(+)-**1**	74 (*R*)	77
6	*c*Hex	(+)-**2**	62 (*R*)	86
7	*t*Bu	(−)-Sparteine	76 (*S*)	83
8	*t*Bu	(+)-**1**	92 (*R*)	78
9	*t*Bu	(+)-**2**	75 (*R*)	72

Conclusion

In summary, we have shown that the cytisine derivatives (+)-**1** and (+)-**2** can be used in the enantioselective deprotonations of prochiral dimethylphosphane−boranes, giving access to the opposite enantiomer to that obtained with (−)-sparteine, enabling the synthesis of numerous *P*-chirogenic ligands so far only accessible in one enantiomeric form. The route developed to (+)-**2** is highly amenable towards parallel synthesis. We are currently investigating whether the enantioselectivity can be improved using other derivatives of cytisine, as well as other chiral diamines. In addition, the scope of the prochiral substrates will be examined further.

Experimental Section

General Procedure for the Asymmetric Deprotonation of 5a−c Followed by Trapping with Benzophenone: A solution of *sec*-BuLi (0.27 mmol) in cyclohexane was added dropwise to a cooled (−78 °C) solution of the chiral amine (0.30 mmol) in diethyl ether (1 mL), followed after 10 min by a solution of the dimethylphosphane−borane complex (**5a−c**, 0.27 mmol) in diethyl ether (1 mL). After 3 h at −78 °C, a solution of benzophenone (55 mg, 0.30 mmol) in diethyl ether (0.5 mL), was added dropwise. The reaction was warmed to −20 °C, stirred for 4 h and then quenched with 1 M HCl (1 mL) and diluted with ethyl acetate (4 mL). After phase separation, the aqueous layer was extracted with ethyl acetate (4 mL) and the combined organic phases washed with 1 M HCl (8 mL), H_2O (8 mL) and aqueous NaCl (8 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to afford the crude product. Purification by flash chromatography on silica gel using 5% ethyl acetate in petroleum ether (b.p. 40−60 °C) afforded the pure products **6a−c** as white crystalline solids.

Acknowledgments

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