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SHORT COMMUNICATION

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Enantioselective Synthesis of (*R*)-Homoboroproline from (*S*)-Proline Using a Borylation Approach

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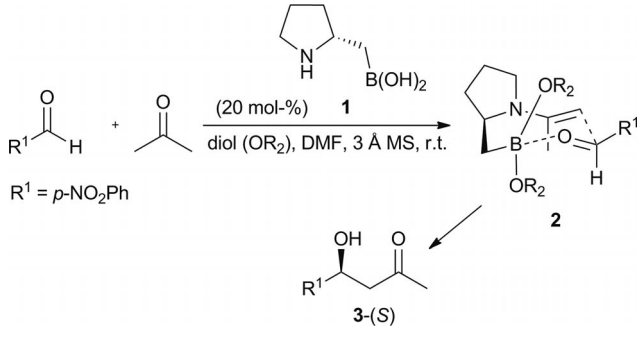
Keywords: Aldol reactions / Boron / Enantioselectivity / Amino acids / Asymmetric synthesis

(*S*)-Proline was converted through a five-step sequence into (*R*)-homoboroproline hydrochloride in 29 % overall yield with 97 % *ee* The key step was the conversion of *N*-Boc iodomethylpyrrolidine into the corresponding pinacol boronate ester by an efficient copper(I)-catalyzed borylation reaction by using bispinacolatodiboron.

Introduction

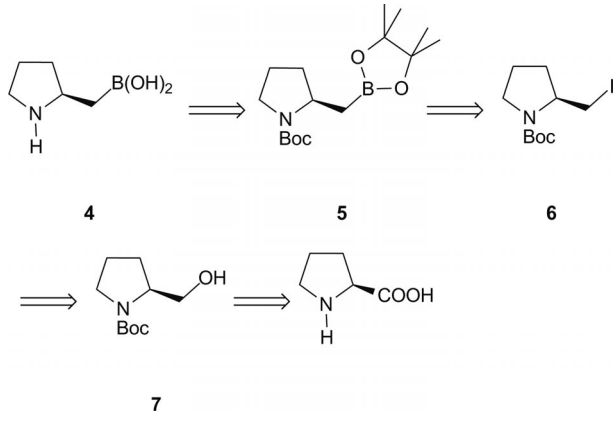
Chiral aminoboronic acids have a wide range of applications, from enzyme inhibitors and anticancer agents to molecular sensors and catalysts,[1] and hence, it has been important to develop asymmetric methods for the asymmetric synthesis of such compounds.[2] In addition, organocatalysis has emerged in recent years as a powerful tool in organic synthesis[3] with (*S*)-proline and proline derivatives becoming established as important catalysts for a number of highly enantioselective transformations.[4] For these reasons, we have also become interested in the use of bifunctional aminoboronic acid catalysts for a range of reactions,[5] and in particular, the synthesis and application of a new generation of proline-based aminoboronic acid catalysts, with the aim of both improved catalytic activity and enantioselectivity over (*S*)-proline and its derivatives.[6,7] One way to achieve this is the in situ esterification of (*S*)-homoboroproline acid (**1**) to tune the boron Lewis acidity to drive catalytic species that are capable of providing aldol products in high yield and enantiomeric excess (e.g., 89%, 95%*ee* for a 96%*ee* catalyst, Scheme 1).[7] However, catalyst **1** is currently limited by its lack of availability in both enantiomeric forms, as **1** is accessed by using a (–)-sparteine-directed metalation from *N*-Boc-pyrrolidine.[8] In this paper, we report the development of an efficient enantioselective synthesis of the antipode of **1** from cheap, readily available (*S*)-proline and involving a novel sp^3-borylation reaction.



Scheme 1. Proposed enamine transition state involving catalyst **1** and its ester derivatives as an aldol catalyst.

Results and Discussion

The synthesis of the (*R*)-enantiomer of homoboroproline (**1**), that is, **4**, could involve the use of (*S*)-proline, taking advantage of the chiral center already present and requiring a borylation transformation at an sp^3-hybridized electrophile such as iodide **6** (Scheme 2).



Scheme 2. Retrosynthetic route for the synthesis of (*R*)-homoboroproline catalyst **4** from (*S*)-proline.

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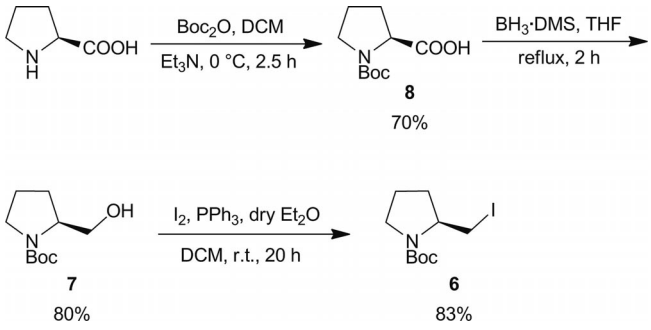
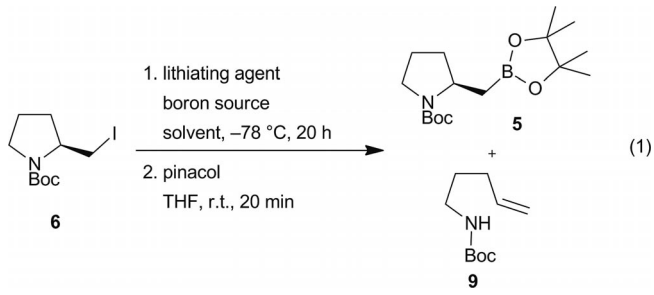
Hence, *N*-Boc protection of (*S*)-proline followed by reduction (BH_3·DMS) gave *N*-Boc-prolinol **7** in 56% overall yield (Scheme 3).[9,10] Subsequent conversion to iodide **6** was accomplished in 83% yield by using iodine, triphenylphosphane, and imidazole (Scheme 3).[10]

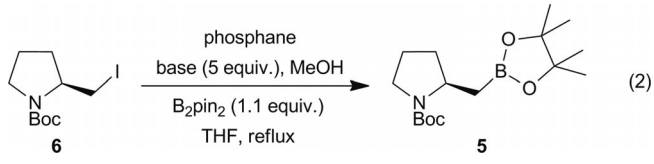


Scheme 3. Synthetic route for the formation of iodomethylpyrrolidine **6** starting from (*S*)-proline.

Having accessed iodide **6**, it was necessary to subject it to borylation to access the corresponding boronate ester **5**. Borylation of alkyl halides can theoretically be accomplished by trapping organometallic intermediates such as organolithium intermediates with a borate electrophile.[1,11] However, initial attempts to form alkylboronic acid derivative **4** were unsuccessful by using a range of lithium–halogen exchange reaction conditions.[11] For example, treatment of a mixture of iodide **6** and trimethylborate with *n*BuLi at –78 °C (Equation 1) did not give the expected boronate derivative, but rather a mixture of starting iodide **6** and its ring-opened derivative **9** in a 1:1 ratio (Table 1, entry 1). Further attempts to transform this reaction to produce a boronated derivative by increasing the amount of boron electrophile (to 3 and then 10 equiv.) did not lead to any improvements (Table 1, entries 5–7). However, quantitative conversion of iodide **6** into alkene **9** was more readily achieved by using a large excess amount of a lithiating agent and a more reactive lithiating agent (10 equiv., *t*BuLi). The exclusive formation of **9** was also reported by Tanner et al. involving analogous organozinc chemistry.[10] These results show that the intermediate organolithium reagent is extremely susceptible to β-elimination and despite the presence of the boron electrophile prior to lithiation cannot be trapped.[10,12]



Despite the variety of borylation protocols that have been developed for the synthesis of aryl- and alkenylboronates, a general and reliable method for the synthesis of alkylboronates has been elusive, apart from the trapping of organomagnesium or organolithium intermediates with borates or catalytic hydroboration of alkenes.[13] However, in 2010 metal-free boration of α,β-unsaturated compounds emerged as a new strategy for the enantioselective catalytic construction of β-borated carbonyl compounds,[14] and Fernández et al. were able to obtain β-pinacolboronated carbonyl compounds when treating α,β-unsaturated esters or ketones with B_2pin_2, Cs_2CO_3, PPh_3, and MeOH.[14] As a result, this reaction became of interest for the potential borylation of compound **6**, as outlined in Equation 2. Unfortunately, subjecting iodomethylpyrrolidine **6** to react with B_2pin_2 under the same conditions did not furnish desired product **5**, and all attempts to modify the reaction conditions (including using KO*t*Bu instead of Cs_2CO_3 or the absence of PPh_3) proved fruitless, providing full recovery of starting iodide **6**.



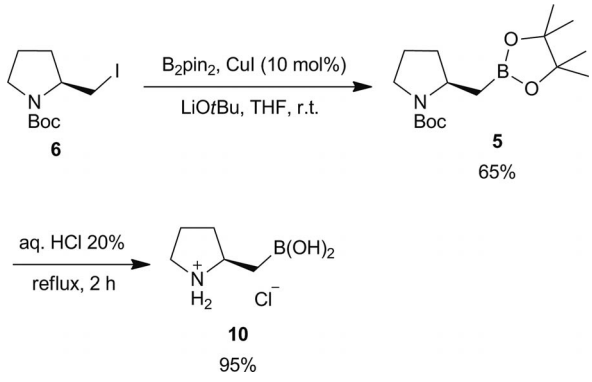
Examining alternative conditions, such as those generally used to cross-couple B_2pin_2 with aryl halides and triflates under palladium catalysis,[15] or more recently modified conditions used for the copper-catalyzed borylation of aryl halides, α,β-unsaturated carbonyl compounds and aldehydes[16] did not look promising. However, the selective borylation of primary and secondary alkyl halides using B_2pin_2 in the presence of CuI/PPh_3 was recently achieved through activation by LiO*t*Bu[17] and was thought to be ap-

Table 1. Reaction conditions for the attempted conversion of **6** into boronate ester **5** by using the lithium–halogen exchange method.

Entry	Lithium agent (equiv.)	Boron source (equiv.)	Solvent	Yield **9** [%]	Recovered **6** [%]
1[a]	*n*BuLi (1.2)	$B(OCHMe_2)_3$ (1)	THF	40	52
2[a]	*n*BuLi (2)	$B(OCHMe_2)_3$ (1)	THF	65	30
3[a]	*n*BuLi (1.2)	$B(OMe_3)_3$ (1)	THF	50	50
4[a]	*n*BuLi (1.2)	–	THF	100	0
5[b]	*n*BuLi (1)	$B(OMe_3)_3$ (1)	Et_2O	50	50
6[b]	*n*BuLi (1)	$B(OMe_3)_3$ (3)	Et_2O	23	77
7[b]	*n*BuLi (1)	$B(OMe_3)_3$ (10)	Et_2O	0	100
8[b]	*t*BuLi (1)	$B(OMe_3)_3$ (1)	Et_2O	85	15

[a] Isolated yield after SiO_2 column chromatography. [b] Estimated yield from crude product.

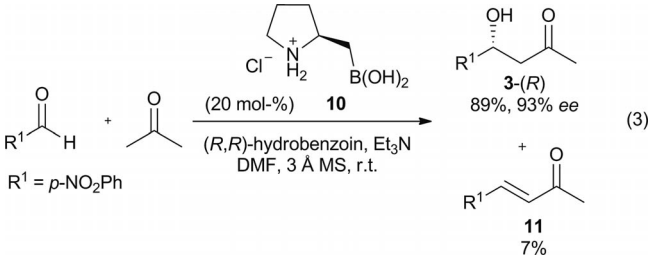
plicable in this case. Hence, under those conditions, reaction of iodide **6** with B_2pin_2, LiO*t*Bu, and catalytic CuI gratifyingly gave pinacol boronate ester **5** directly in 48% yield with, importantly, 97%*ee*. Subsequent optimization resulted in routine isolation of **5** in 65% yield by modifying the workup procedure (Scheme 4).



Scheme 4. Synthetic route towards the formation of homoboroproline catalyst **10**.

The development of this simple, high-yielding, and reproducible reaction meant that isolation of enantiomeric catalyst **4** could be easily achieved as its HCl salt **10** through this sequence from (*S*)-proline. Hence, cleavage of the Boc and pinacol protecting groups of **5** was readily conducted under the standard acidic conditions to afford deprotected **10** in near quantitative yield (Scheme 4).[4]

To demonstrate that the enantioselective aldol reaction catalyzed by the chiral boronate ester analogues of **1** arises from the chiral center present on the pyrrolidine ring of the catalyst rather than from the chirality of the diol used for the esterification of the boronic acid,[6,7] a standard aldol reaction was carried out under the optimized reaction conditions by using (*R*)-homoboroproline catalyst **10**[7] neutralized in situ. Hence, the aldol reaction between *p*-nitrobenzaldehyde and acetone in DMF was performed in the presence of (*R*,*R*)-hydrobenzoin (**10**, see Equation 3) and proceeded in full agreement with our expectations; aldol product **3** was obtained with the expected absolute stereocontrol (i.e., *R*) with 93%*ee* and in 89% yield after 7 h (Equation 3), which is opposite to that obtained from (*S*)-enantiomer **1**.



(3)

These findings indicate that the enantiomeric excess of the aldol product originates from the chiral center on the pyrrolidine ring of the catalyst, because homoboroproline catalyst **10** provides the opposite enantiomeric form of the aldol adduct compared to catalyst **1**. Taking into consideration our studies so far concerning both enantiomeric forms of the homoboroproline catalyst, our proposed catalytic cycle can be reinforced as proposed in previous reports.[6,7]

Conclusions

In summary, we have developed an efficient, novel synthetic route to amino boronic acid **4** via ammonium salt **10** by taking advantage of newly reported methodology for the sp^3-borylation of corresponding alkyl iodide **6**. Subsequent application of the boronate ester analogue of **10** in the standard aldol reaction highlighted the importance of the chiral center present on the pyrrolidine ring for the asymmetric induction of the aldol product. These studies in combination with results reported previously[6,7] have provided evidence of our understanding the mode of action of catalysts **1** and **4** through a transition state resulting from the cooperative relationship between the enamine and the boronate function.

Supporting Information (see footnote on the first page of this article): Experimental details, copies of the NMR spectra and HPLC chromatograms.

Acknowledgments

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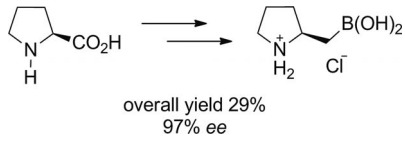
(*S*)-Proline was conveniently converted through a five-step sequence involving N-protection, reduction, iodination, borylation (using B_2Pin_2 and a Cu^I catalyst system), and deprotection into (*R*)-homoboroproline hydrochloride in 29% overall yield with 97%*ee*



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