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Enolboration of conjugated ketones and synthesis of β-amino alcohols and boronated α-amino acids*

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Abstract: Enolization–aldolization of conjugated ketones, enantioselective synthesis of benzofuryl β-amino alcohols, and synthesis of *p*-dihydroxyborylphenylalanine (BPA) and its analogs are described. Aldolization of benzaldehyde with lithium dienolates derived from unhindered conjugated cyclohexenones favored anti selectivity, whereas syn selectivity was favored for hindered cyclohexenones. *Anti*-aldols were preferentially formed from dienolborinates derived from conjugated cyklohexenones, however, competing aldolization at the 2-position was observed for hindered ketones. Benzofuryl β-amino alcohols were prepared using as a key step the enantioselective reduction of the corresponding α-bromoacetylbenzofurans with (–)-*B*-chlorodiisopinocampheylborane. Ionic liquids were used as solvents for the synthesis of BPA by the Suzuki cross-coupling reaction. The reaction time is short, and a solution of the catalyst in the ionic liquid can be recycled.

INTRODUCTION

Boron-mediated aldolizations play an important role in the construction of carbon–carbon bonds and are widely used in asymmetric synthesis [1,2]. Surprisingly little is known, however, on the directed aldol reactions of dienolborinates derived from conjugated ketones. The transformation is synthetically attractive since differences in stereoselectivity as compared to lithium dienolates may be expected. Consequently, we examined the enolization of representative conjugated cyclohexenones with chlorodicyclohexylborane, followed by aldolization with benzaldehyde [3], and the results are reported in the first part of this paper.

In the second part, the reduction of 2-acetyl- and 2-(bromoacetyl)benzofurans with (–)-*B*-chlorodiisopinocampheylborane is used as a key step in the enantioselective synthesis of benzofuryl alcohols and β-amino alcohols [4]. Such compounds (e.g., bufuralol [5], or 1-(3-phenethylbenzofuran-2-yl)-2-propylaminoethanol, the propafenone analog [6]) exhibit antiarrhythmic, antihypertensive, enzyme inhibitor, and β-adrenoacceptor blocking activity. Their enantiomers have been prepared by the resolution of racemates. In this study, we focused on the enantioselective synthesis of 1-(benzofuran-2-yl)-2-alkylaminoethanol, as a model compound, and on the synthesis of the propafenone analog.

In the third part, the synthesis of boronated α-amino acids for boron neutron capture therapy (BNCT), and other applications, is described. Recently, new approaches to *p*-dihydroxyborylphenylalanine (BPA) and its analogs were reported [7–9], and the field was reviewed [10]. We undertook the

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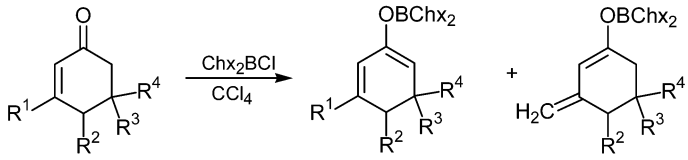
synthesis of BPA in ionic liquids, and its analogs with a quaternary carbon center, and an ether functionality.

ALDOLIZATION OF CONJUGATED KETONES

Generally, conjugated ketones may undergo aldolization at the α- or γ-position depending on the reaction employed [11–15]. Thus, enolization of 2-cyclohexenone (**1**) with LDA and aldolization with benzaldehyde affords the corresponding aldol in 81/19 anti/syn ratio. The ratio is reversed to 35/65 and 25/75, when titanium and zirconium dienolates are used, respectively [12]. Enolization of **1** with chlorodicyclohexylborane (Chx_2BCl) in carbon tetrachloride was reported to give >97 % of the dienolborinate by deprotonation at the 6-position, however, its aldolization was not studied [16]. We examined the enolization of representative conjugated cyclohexenones **1**–**5** with chlorodicyclohexylborane (Scheme 1), and LDA, followed by aldolization with benzaldehyde [3]. The ^{1}H NMR spectrum of the dienolborinate obtained from **1** showed a clean enolization at the 6-position in agreement with the earlier report [16]. However, the spectra of dienolborinates obtained from **2**–**5** showed an increasing competitive enolization at the γ-position, which may reflect the increasing steric hindrance at the 6-position.



	6	**7**
1 (R^1, R^2,R^3,R^4 = H)	> 97 %	
2 (R^1 = Me; R^2, R^3, R^4 =H)	89 %	11 %
3 (R^1, R^3 = Me; R^2, R^4 = H)	80 %	20 %
4 (R^1, R^3, R^4 = Me; R^2 = H)	50 %	50 %
5 (R^1, R^2, R^3, R^4 = Me)	30 %	70 %

Scheme 1

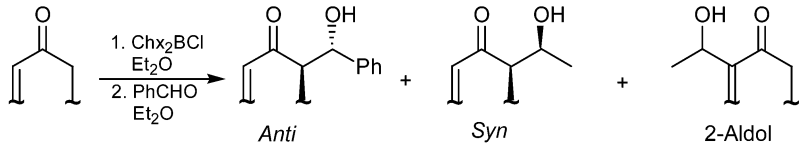
Aldolization of the dienolborinates (**6**) with benzaldehyde in diethyl ether favored consistently *anti*-aldols (Table 1). Aldolization of the dienolborinates (**7**) proceeds at the 2-position, and the double bond migration in alkaline medium accounts for the product formation (Table 1). The ratio of aldols formed by the reaction at the 6- or 2-position is higher than the **6/7** ratio. However, the amounts of **6** and **7** formed in carbon tetrachloride and in diethyl ether may not be the same.

The anti/syn ratio 81/19 obtained from **1** increased to 91/9 from **2**. The opposite was observed for the corresponding lithium dienolates producing the anti/syn ratio 91/9 from **1** and 78/22 from **2**. The dienolborinate derived from **3** produced only the *anti*-aldols, (***trans*-3a**) and (***cis*-3a**). The major one was a crystalline compound, and its X-ray analysis revealed the trans position of the methyl group at C-5. The lithium dienolate obtained from **3** reacted with lower anti/syn stereoselectivity producing ***trans*-3a** and **3s** (78/22).

The dienolborinates derived from **4** and **5** reacted with benzaldehyde to give *anti*-aldols with high anti/syn selectivity. In contrast, the reaction of lithium dienolates derived from **4** and **5** with benzaldehyde showed the opposite selectivity. The *syn*-aldols (**4s**) and (**5s**) were obtained with 94 and 95 % selectivity, respectively, and their structures were assigned by X-ray analysis [3].

Enolization of mesityl oxide (**8**) with chlorodiethylborane followed by aldolization with methyl vinyl ketone and simple hydrolysis afforded a mixture of the corresponding aldol (**9**) and its dehydration products, which was transformed into (*E*)-ocimenone (Scheme 2).

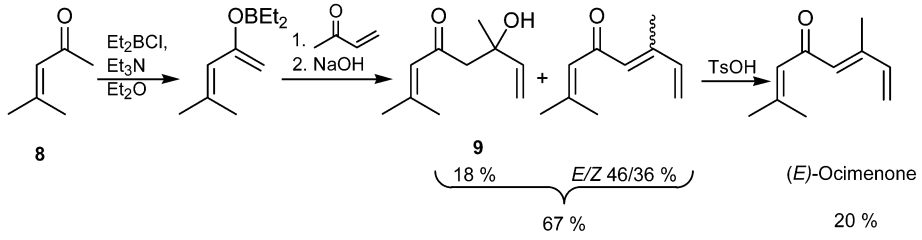
Table 1 Aldolization of dienolborinates prepared from **1**–**5** with benzaldehyde.



Ketone	Enolate	Composition, %						Yield,
		Anti		Syn		2-Aldol		%
1	C[a]	**1a**	81	**1s**	19			58[c]
	L[b]	**1a**	91	**1s**	9			73
2	C	**2a**	90	**2s**	10			72[c]
	L	**2a**	78	**2s**	22			96
3	C	***trans*-3a**	68					51[c]
		***cis*-3a**	32					
	L	***trans*-3a**	78	**3s**	22 (*cis* or *trans*)			75
4	C	**4a**	68	**4s**	10	**4b**	22	39[c]
	L	**4a**	6	**4s**	94			76
5	C	**5a**	73 (*cis/trans*)			**5b**	27	53[c]
	L	**5a**	5 (*cis/trans*)	**5s**	95			52

[a]C = enolized with Chx_2BCl.
[b]L = enolized with LDA in THF.
[c]Isolated by flash chromatography.

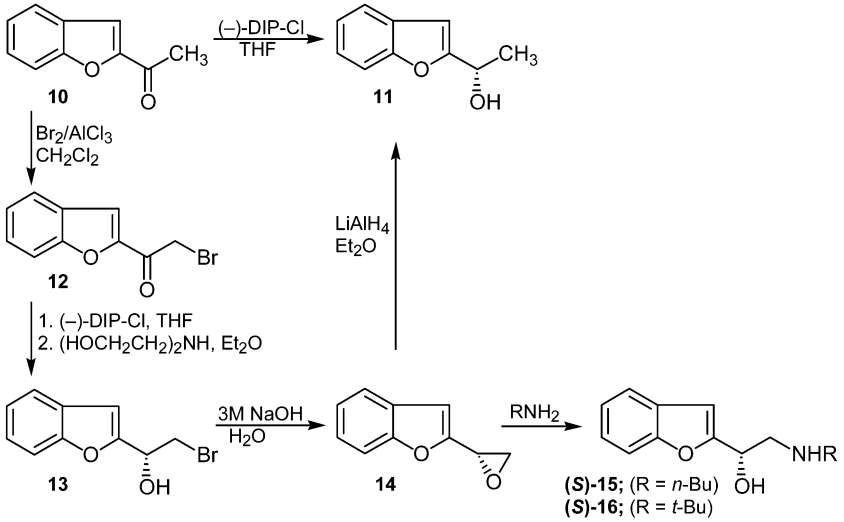
The results demonstrate preferential enolization of **1**–**5** with chlorodicyclohexylborane by the deprotonation at C-6. When this position is hindered, deprotonation at the 3-methyl group becomes competitive. Aldolization of the dienolborinates (**6**) with benzaldehyde produces the corresponding *anti*-aldols with >81 % selectivity. Aldolization of the competitively formed dienolborinates (**7**) proceeds at the 2-position. Lithium dienolates derived from the less hindered **1**–**3** react with benzaldehyde, producing preferentially *anti*-aldols, whereas syn selectivity predominates with the dienolates from the more hindered **4** and **5**. Consequently, the dienolborinates derived from conjugated cyclohexenones, often showing higher selectivity as compared to the corresponding lithium dienolates, may serve for the synthesis of *anti*-aldols. The opposite stereoselectivity of aldolization of dienolborinates and lithium dienolates derived from the more hindered ketones makes these reagents complementary.



Scheme 2

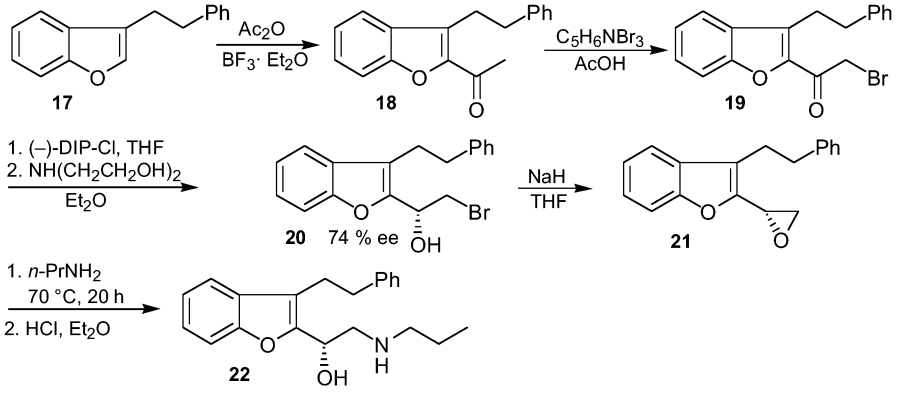
SYNTHESIS OF BENZOFURYL β-AMINO ALCOHOLS

Recently, we examined the reduction of a series of 2- and 3-acylbenzofurans with (–)-*B*-chlorodiisopinocampheylborane [(–)-(DIP-Cl)], and we found that benzofuryl alkyl and benzyl ketones were reduced with high enantioselectivity. These observations suggested an enantioselective approach to benzofuryl β-amino alcohols using as a key step the reduction of 2-(2-bromoacyl)benzofurans with (–)-DIP-Cl. To test this possibility, 1-(benzofuran-2-yl)ethanone (**10**) was used as a model starting material (Scheme 3). Its reduction with (–)-DIP-Cl afforded (*S*)-1-(benzofuran-2-yl)ethanol (**11**) of 91 % ee. The configuration was established by X-ray analysis of its *p*-nitrobenzoate. The reduction of α-bromoketone (**12**) with (–)-DIP-Cl afforded the corresponding bromohydrin (**13**), which was transformed into epoxide (**14**) of 70 % ee. Its configuration was correlated with **11** by the reduction with lithium tetrahydroaluminate. The epoxide was transformed into **(*S*)-15** and **(*S*)-16** by treatment with *n*-propylamine and *tert*-butylamine, respectively [4].



Scheme 3

The methodology described above was employed for the synthesis of the pharmacologically active propafenone analog (**22**, Scheme 4). Thus, **17** was acetylated to give **18**, which was cleanly monobrominated with pyridinium perbromide, and the reduction of bromoketone (**19**) with (–)-DIP-Cl af-

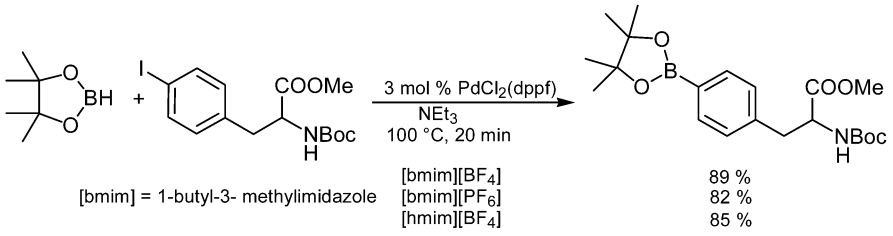


Scheme 4

forded bromohydrin (**20**) of 74 % ee. In contrast to the model compound, cyclization of **20** to **21** with aqueous sodium hydroxide was sluggish, and the labile epoxide was isolated in low yield. Fortunately, cyclization with sodium hydride in tetrahydrofuran at room temperature worked better. The crude epoxide was treated with *n*-propylamine, and **22** was obtained.

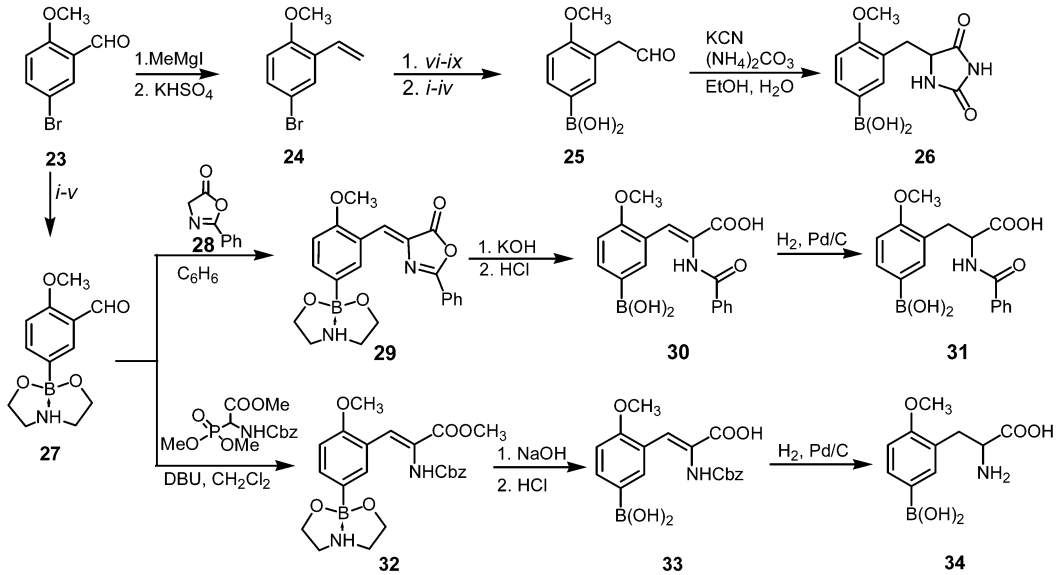
SYNTHESIS OF BORONATED α-AMINO ACIDS

In our study on the synthesis of arylboronic acids in ionic liquids, high yields of cross-coupling products from aryl iodides and bromides with the readily available pinacolborane were obtained [17]. Encouraged by these results, we used protected *p*-iodophenylalanine for the cross-coupling with pinacolborane in an ionic liquid (Scheme 5). The reaction was complete in 20 min, producing the boronated phenylalanine in good yield. The product is readily isolated by simple separation of phases, and the catalyst remains in the ionic liquid phase.



Scheme 5

In a search for new analogs of BPA, we undertook the synthesis of its alkoxy derivatives. The ether functionality provides a possibility of influencing the lipophilicity by varying the alkyl group. Starting with 2-methoxy-5-bromobenzaldehyde (**23**), two approaches were used (Scheme 6). In the first one, 2-methoxy-5-bromostyrene (**24**) was readily prepared, however, its hydroboration with borane-tetrahydrofuran produced a mixture of the corresponding primary and secondary alcohol (70:30).



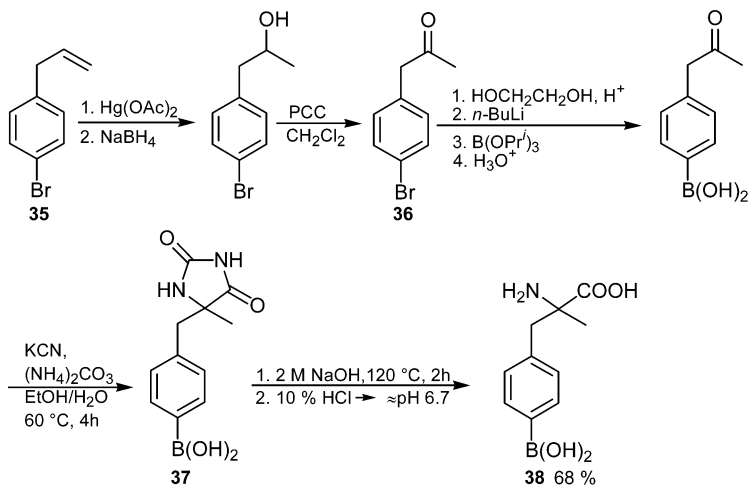
i $HOCH_2CH_2OH$, TsOH; *ii* *n*-BuLi; *iii* $B(OPr^i)_3$; *iv* H_3O^+; *v* $HN(CH_2CH_2OH)_2$; *vi* Chx_2BH; *vii* NaOH; *viii* H_2O_2, NaOH; *ix* NaOCl/TEMPO

Scheme 6

Although the regioselectivity of hydroboration with dicyclohexylborane was higher (87:13), the primary alcohol was not cleanly formed. Fortunately, hydrolysis of the intermediate organoboranes with aqueous alkali removed selectively the secondary (benzylic) group. After several unsuccessful attempts, clean oxidation of the primary alcohol to the corresponding bromoaldehyde was achieved with sodium hypochlorite/TEMPO in the presence of a phase-transfer catalyst. A similar yield of the aldehyde was also obtained by oxidation with *o*-iodoxybenzoic acid. The boronated aldehyde (**25**) was obtained by transmetalation of the protected bromoaldehyde with triisopropoxyborane. The corresponding hydantoin (**26**) was prepared under standard conditions. Unfortunately, competitive deboronation during its hydrolysis, resulting in a low yield of (2-methoxy-5-dihydroxyboryl)phenylalanine (**34**), could not be avoided.

In the second approach, the boronated 2-methoxybenzaldehyde (**27**) was used as the starting material (Scheme 6). The Erlenmeyer reaction of **27** in acetic acid-acetic anhydride resulted in deboronation under the reaction conditions. To avoid the deboronation, **27** was condensed with a preformed **28** in a neutral solvent producing **29** in good yield. The boronic acid function was deprotected, and the product was partially hydrolyzed to give **30**. Subsequent hydrogenation produced (2-methoxy-5-dihydroxyboryl)phenylalanine protected as *N*-benzoyl derivative (**31**). Attempts to remove the benzoyl group by hydrolysis under mild conditions were unsuccessful. The group could be removed by refluxing with 3 M hydrochloric acid for several hours, however, the deboronated product was obtained. Consequently, the synthetic approach was again modified, and the amino acid functionality was introduced via the Wittig reaction to give **32** (Scheme 6). Subsequent hydrolysis produced **33**, which was hydrogenated to the desired boronated amino acid (**34**).

BPA analogs with a quaternary center in the α-position were also prepared. Thus, 1-amino-3-(4-dihydroxyborylbenzyl)cyclobutanecarboxylic acid was prepared following the methodology reported for the higher homologs [18]. α-Methyl BPA was synthesized as shown on Scheme 7. Thus, oxymercuration-demercuration of 4-bromoallylbenzene (**35**) followed by oxidation with PCC afforded *p*-bromophenylacetone (**36**). The dihydroxyboryl moiety was introduced by transmetalation of the lithiated ketal and hydrolysis. Hydantoin (**37**), obtained under standard conditions, was hydrolyzed to give α-methyl BPA (**38**) using a stoichiometric amount of sodium hydroxide and the minimal reaction time and temperature.



Scheme 7

ACKNOWLEDGMENT

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