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(S)-2-Amino-3-(2,5-dimethylphenyl)-1,1-diphenyl-1-propanol: Synthesis and Application in Enantioselective Reduction of Prochiral Ketones

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(S)-2-AMINO-3-(2,5-DIMETHYLPHENYL)-1,1-DIPHENYL-1-PROPANOL: SYNTHESIS AND APPLICATION IN ENANTIOSELECTIVE REDUCTION OF PROCHIRAL KETONES

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Abstract: The title chiral amino alcohol **6** was prepared from (s)-3-(2,5-dimethylphenyl)-alanine methyl ester hydrochloride by its reaction with phenyl magnesium bromide. In the presence of 2 mol% of **6**, the borane reduction of prochiral ketones gave optically active secondary alcohols in high yields with the ee's ranged from 40.5 to 100%.

The enantioselective borane reduction of prochiral ketones to optically active secondary alcohols catalyzed by chiral oxazaborolidines has drawn great attention for it has the advantages of high chemical and optical yield, mild reaction condations, short reaction time, easy recoverability of the catalyst precursor, and experimental simplicity. These oxazaborolidines are derived from chiral amino alcohols by either reaction with alkyl boric acid or formation in situ when treated with borane.[1,2]

In this communication, we report the synthesis of a new chiral amino alcohol **6**, (s)-2-amino-3-(2,5-dimethylphenyl)-1,1-diphenyl-1-propanol, and its use as a enantioselective catalyst in the borane reduction of prochiral ketones to form optically active secondary alcohols.

The synthesis of **6** was accomplished starting from diethyl acetamidomalonate **1** which was converted to the enolate with sodium ethoxide and alkylated with 2,5-dimethylbenzyl

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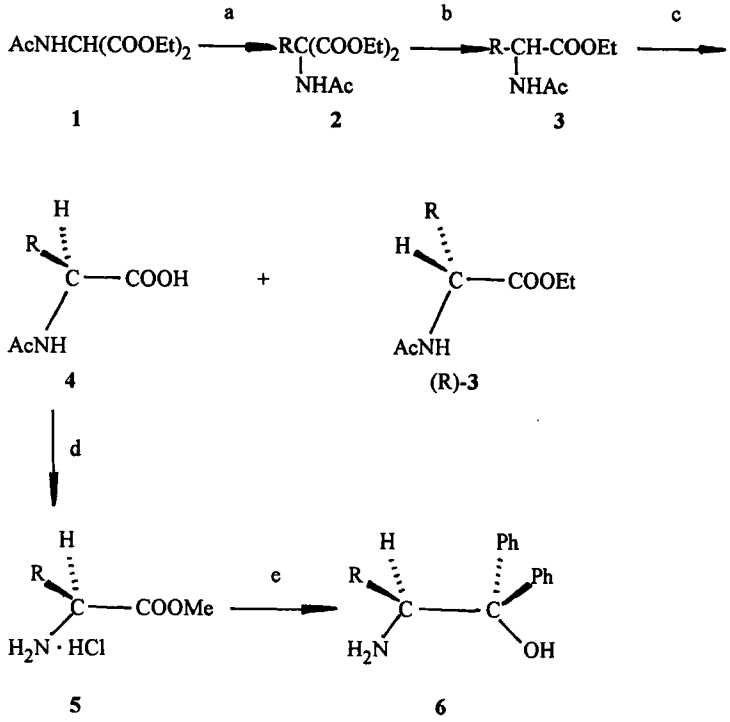
bromide to give N-acetyl-2-ethoxycarbonyl-3-(2,5-dimethylphenyl)-α-alanine ethyl ester **2**. The partial saponification of **2** followed by decarboxylation gave N-acetyl-3-(2,5-dimethylphenyl)-(±)-α-alanine ethyl ester **3**, which was then resolved by enzymic hydrolysis to yield the (S)-form acid **4** and the (R)-form ester (R)-**3**. **4** was hydrolyzed with hydrochloric acid and then convered to the amino acid methyl ester hydrochloride **5**. The treatment of **5** with phenyl magnesium bromide afforded the title chiral amino alcohol **6**. This is shown in scheme 1.

Scheme 1. The synthesis of (S)-2-amino-3-(2,5-dimethylphenyl)-1,1-diphenyl-1-propanol



R=2,5-dimethylbenzyl

a: EtONa/EtOH, RBr; b:1. NaOH, 2. HCl, 3. reflux in dioxane; c: subtilisin carlsberg, PH 7.6; d: 1. HCl, 2.$SOCl_2$/MeOH; e: PhMgBr/THF, 0℃

In the presence of catalytic ammount of **6**, prochiral ketones were reduced with excess borane to give optically active secondary alcohols. The results are listed in Table 1.

As shown by the data in Table 1, the *in-situ* formed chiral oxazaborolidine from chiral amino alcohol **6** is a good enantioselective catalyst for borane reduction of prochiral ketones. Thus, p-chloroacetophenone and ω-bromoacetophenone were reduced to (R)-1-(4-chlorophenyl)ethanol with 93.7% ee and (S)-2-bromo-1-phenylethanol with 100% ee, respectively, when 2 mol% of catalyst was used. Much better results may be obtained with increased ammount of **6**. For example, with 2 mol% of **6**, valerophenone was reduced to (R)-1-phenyl-1-pentanol with 53.8% ee, while the use of 5 mol% of **6** resulted in the formation of a product of 99% ee (entry 5).

Experimental Section

All reactions were carried out in flame-dried glassware under nitrogen atmosphere.

1. Preparation of **6**. From 15.5g of bromobenzene (98.9 mmol) and 2.2g of magnesium(91.6 mmol) was prepared phenyl magnesium bromide in dry tetrahydrofuran. To this solution was added (S)-3-(2,5-dimethylphenyl) alanine methyl ester hydrochloride **5** (2.12 g, 8.7 mmol) in portions with stirring and ice-bath cooling. The mixture was stirred at 0-5 ℃ for 6 hrs and then quenched by slow addition of 1 mol/L sulfuric acid under vigorous stirring. The mixture was made alkaline with aqueous ammonia, the resulting solid material was removed by filtration. The THF layer was separated and the aqueous layer was extracted with chloroform (40 mL, 30 mL, 30 mL). The organic phases were combined and dried over anhydrous potassium carbonate and concentrated to dryness. Recrystallization of the residue from ethanol gave 1.5g of **6** (52.0%), m.p. 120-1 ℃, $[\alpha]_D^{25}$ -114 ℃ (c=0.85,$CHCl_3$). Elemental analysis calcd. for $C_{23}H_{25}NO$: C,83.34; H,7.60; N,4.23; Found: C,83.14; H,7.85; N,4.17. ^1H NMR($CDCl_3$):δ 1.62(b, 2H), 2.51(s, 3H), 2.64(s, 3H), 2.85(m, 2H), 4.51(m, 1H), 4.90(b, 1H), 7.26-7.37(m,3H), 7.64-8.01(m, 10H).

Table 1. Enantioselective catalytic reduction of prochiral ketones with 6 and excess borane in THF at 30℃

entry	ketone	mol% of 6	chiral secondary alcohol		
			yield[a]	$[\alpha]_D$	ee%(config)[b]
1	MeCOPh	2	85.2	+17.2	40.5(R)
2	EtCOPh	2	86.8	+29.1	61.9(R)
3	n-PrCOPh	2	85.3	+28.1	62.1(R)
4	n-BuCOPh	2	91.5	+16.8	53.8(R)
5	n-BuCOPh	5	89.0	+30.9	99.0(R)
6	$BrCH_2COPh$	2	63.0	+39.0	100 (S)
7	$MeCOC_6H_4Cl$-*p*	2	90.4	+46.8	93.7(R)
8	$MeCOC_6H_4Me$-*p*	2	80.9	+31.5	57.4(R)
9	$MeCOC_6H_4OMe$-*p*	2	85.5	+33.0	63.5(R)
10	2-heptanone	2	80.2	-5.2	46 (R)
11	2-heptanone	5	85.3	-6.2	55 (R)

a. Isolated yield. b. Absolute configuration was assigned by comparison of the sign of the optical rotation with that reported and the enantiomeric excess values were calculated from specific rotations based on the following reported data: $[\alpha]_D^{25}$ +42.5° (c=5, ethanol) for (R)-1-phenyl-1-ethanol,[3] $[\alpha]_D^{25}$+47° (c=6.9,acetone) for (R)-1-phenyl-1-propanol,[4] $[\alpha]_D^{26}$-45.2° (c=4.81, benzene) for (S)-1-phenyl-1-butanol,[5] $[\alpha]_D$+27.5° (c=2.98, benzene, 88% opt. pure) for (R)-1-phenyl-1-pentanol,[6] $[\alpha]_D^{25}$ -39° (c=8, chloroform) for (R)-2-bromo-1-phenylethanol,[7] $[\alpha]_D^{21}$+49.9° (c=2, ether) for (R)-1-(4-chlorophenyl) ethanol,[8] $[\alpha]_D^{20}$+56.1° (c=1, chloroform, 85% opt. pure) for (R)-1-(4-methylphenyl) ethanol,[8] $[\alpha]_D^{25}$+44.2° (c=1, chloroform, 94% opt. pure) for (R)-1-(4-methoxyphenyl) ethanol,[8] $[\alpha]_D^{20}$+11.4° (alcohol) for (S)-2-heptanol.[9]

2.Enantioselective reduction of prochiral ketones: To the solution of **6** (66.3 mg, 0.2 mmol in 10 mL THF) was added 1 mL of BH_3-THF(1.0 mol/L, 1mmol), the mixture was stirred for 10 min at 30℃ . A solution of ketone(10 mmol in 10 mL of THF) and a solution of borane in THF(1 mmol/L, 20mL)was then added dropwise to the catalyst solution over a period of about 30 min. The stirring was continued and the temperature was kept at 30℃ for 15 min before the reaction is complete (checked by TLC). The mixture was decomposed by the addition of methanol (5 mL) with ice-bath cooling. To the resulting solution was added dry HCl/MeOH (6 mol/L, 2mL), the stirring was continued for 30 min (ice-bath cooling). The solvent was evaporated under reduced pressure. To the residue was added dry ether(30 mL) and the mixture was cooled to 0 ℃ , the crystalls of amino alcohol hydrochloride were recovered by filtration and the ether solution was washed successively with brine, saturated aqueous sodium bicarbonate, and brine, dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was distilled under reduced pressure to give the optically active secondary alcohol.

Following the procedure described above, were reduced all ketones listed in the table but *p*-methoxyacetophenone and *p*-methylacetophenone, in which, to prevent the decomposition of the acid-labile pruduct, no HCl-MeOH was added after the reaction was quenched by the addition of methanol.

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