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Synthesis of (*R*)-(−)-1-Piperidino-3,3-dimethylbutan-2-ol: Application in the Molar Scale Asymmetric Ethylation of *trans*-Crotonaldehyde

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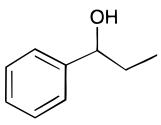
Abstract:

A simple three-step preparation of (*R*)-(−)-1-piperidino-3,3-dimethylbutan-2-ol (amino alcohol catalyst for the Noyori asymmetric alkylation of aldehydes) based on a classical resolution of the racemate is described. Use of this catalyst in a detailed study of the asymmetric ethylation of *trans*-crotonaldehyde producing *trans*-(*S*)-4-hexen-3-ol is also described. The impact of catalyst enantiopurity and loading on the product enantiopurity and yield is studied, which led to optimized conditions for reaction scale-up.

Introduction

The catalytic asymmetric addition of organozinc reagents to aldehydes is a very versatile method for preparing optically enriched secondary alcohols.[1] Pioneering work of Oguni and Omi[2] showed that (*S*)-leucinol catalyzes the addition of diethylzinc to benzaldehyde, affording (*R*)-1-phenyl-1-propanol [(*R*)-**1**] in 49% ee. This observation has given rise to many powerful methods employing bidentate catalysts for the synthesis of secondary aliphatic, benzylic, and allylic alcohols with high enantioselectivity.[1,3] Noyori was the first to achieve high asymmetric induction in the ethylation of aldehydes, showing that sterically congested amino alcohols **2** and (*R*)-**3** catalyze the formation of **1** in >98% ee for the (*S*) and (*R*) enantiomer, respectively.[4] Additionally, Noyori



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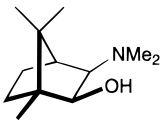

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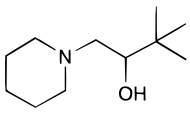

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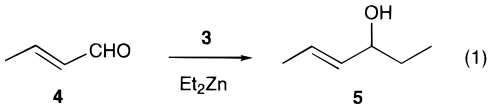
has shown catalyst (*R*)-**3** to be highly effective in the ethylation of aliphatic and α,β-unsaturated aldehydes.[3] For example, treatment of *trans*-crotonaldehyde (**4**) with Et_2Zn in the presence of 2 mol % (*R*)-**3** for 24 h at 0 °C afforded (*R*)-*trans*-4-hexen-3-ol [(*R*)-**5**] in 90% yield and 90% ee (eq 1).[3] We recently required significant quantities of (*S*)-**5**[5] and felt the Noyori method would be amenable to implementation at the requisite scale. The availability of Et_2Zn and **4**, the



4 **5** (1)

low catalyst load, and the high enantioselectivity are attractive features of this reaction.

Results and Discussion

For the preparation of (*S*)-**3**, we selected a procedure involving the asymmetric reduction of ketone **7**.[3,6] As shown in Scheme 1, ketone **7** was readily prepared upon reaction of piperidine with bromopinacolone (**6**) in the presence of K_2CO_3, a modification of Oguni's[7] conditions (benzene, triethylamine) enabling a reproducible process to give a high-quality product in excellent yield. Attempted hydrogenation of **7** under standard conditions[6] employing $Ru(OAc)_2$[(*S*)-BINAP] as the catalyst (390:1 substrate:catalyst ratio, MeOH, 1500 psi, 22 °C) failed to produce **3**. Heating the reaction mixture to 90 °C for 15 h gave only 33% conversion to product. Attempts to conduct the hydrogenation with commercially available $RuCl_2$[(*S*)-BINAP](*p*-cymene), using a high catalyst loading (50:1 substrate:catalyst ratio at 1400 psi, 60 °C, 7 h), resulted in a clean conversion to (*S*)-**3** but with low enantioselectivity (16% ee) (Scheme 1).

Since these attempts at the enantioselective reduction of **7** met with failure, a synthesis of (*S*)-**3** was chosen based on the classical resolution of alcohol (±)-**3**.[7] Reduction of unpurified **7** with lithium aluminum hydride afforded (±)-**3** in 86% yield from **6** (Scheme 1). Resolution of racemic **3** was examined by crystallization of the corresponding diastereomeric salts derived from dibenzoyl-D-tartaric acid and di-*p*-toluoyl-D-tartaric acid (DTTA). Since initial crystallization attempts from ethanol−ether mixtures revealed the DTTA salt of (±)-**3** to be a crystalline species while the corresponding dibenzoyl-D-tartrate salts were oils or tacky solids, further crystallization studies focused on **3**·DTTA. After screening a variety of solvents, it was found that 2-propanol provided efficient resolution of the diastereomeric salts. Thus, (±)-**3** was combined with 1 equiv of DTTA at 65 °C in 2-propanol, and upon cooling of the solution to room temperature, crystalline (*S*)-**3**·DTTA was furnished in 68% yield and 61% de. Three recrystallizations produced

(1) Review: Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92,* 833.
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(7) For the preparation of (*R*)-**3** via the classical resolution of (±)-**3**, see: Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110,* 7877.

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Scheme 1

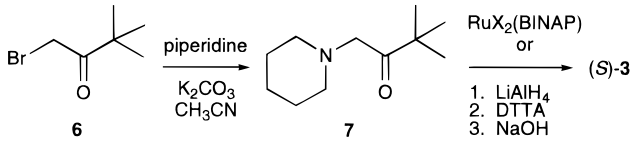

Table 1. **Asymmetric amplification in the addition of diethylzinc to 4**[a]

entry	(*S*)-**3** ee (%)[b]	(*S*)-**5** ee (%)[b]	yield (%)[c]
1[d]	98	86	
2	96	84	63
3	85	85	64
4[e]	85	84	63
5	67	83	65
6	42	84	64
7	15	80	57

[a] All reactions were carried out at 0.85 M in aldehyde using 2 mol % (*S*)-**3** and 1.18 equiv of Et_2Zn in hexane at 0 °C for 6 h. [b] Determined by capillary GC (Hydrodex β-PM or β-DEX 325 column). [c] Distilled yield. [d] Yield not determined. [e] Reaction time extended to 24 h.

(*S*)-**3**·DTTA with a diastereomeric excess greater than 98%. Although the 2-propanol crystallization often provided the desired diastereomer with a respectable diastereomeric excess and good recovery, the resolution was not always reproducible. Occasionally, the diastereomeric excess was observed to drop to less than 5% when the crystallization was performed on a 1:1 mixture of the diastereomeric salts. This problem was overcome by adding methanol to the 2-propanol, thereby increasing the solubility of the undesired salt, leading to a reproducible and efficient procedure. Thus, (±)-**3** was combined with 1 equiv of DTTA at 65 °C in 2-propanol/methanol (3:1). Cooling to ambient temperature furnished crystalline (*S*)-**3**·DTTA in 45% yield and 63% de. Finally, enantiomerically enriched (*S*)-**3** was obtained in 95% yield upon neutralization of (*S*)-**3**·DTTA with dilute NaOH.

With a suitable method in hand for the preparation of (*S*)-**3**, a study of the 1,2-addition of Et_2Zn to **4** (eq 1) was undertaken with the intent of defining the impact of catalyst loading and enantiopurity on the asymmetric induction. Initial reactions were performed following the standard protocol (hexane, 0 °C, aldehyde concentration at 0.4 M, and 2 mol % catalyst).[3] Under these conditions, Noyori obtained (*R*)-**5** in 90% ee using (*R*)-**3** of 99% ee.[3] However, in the present work we found that employing (*S*)-**3** of 96% ee gave (*S*)-**5** of 84% ee in 63% yield after distillation. Attempts to enhance the enantioselectivity by increasing the diethyl zinc stoichiometry[1,8] from 1.18 to 1.50 equiv and using toluene as the solvent were unproductive. Attention was turned toward probing the enantiopurity of (*S*)-**5** as a function of catalyst enantiopurity (Table 1). Oguni has shown that the asymmetric ethylation of benzaldehyde using (*R*)-**3** as catalyst displays significant nonlinear effects (a nonlinear correlation between the enantiopurity of the catalyst and that of the product).[7,9]

(8) Chaloner, P. A.; Langadianou, E. *Tetrahedron Lett.* **1990**, *31*, 5185.

(9) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327. (b) For a general discussion of nonlinear effects in asymmetric synthesis, see: Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc*. **1986**, *108*, 2353.

Table 2. **Reaction efficiency as a function of catalyst loading**[a]

entry	(*S*)-**3** ee (%)[b]	mol % (*S*)-**3**	(*S*)-**5** ee (%)[b]	yield (%)[c]
1	66	10	83	66
2	64	2	83	61
3	66	1	84	60
4	64	0.1	80	39
5[d]	66	0.1	83	55

[a] All reactions were carried out at 0.85 M in aldehyde using 1.18 equiv of Et_2Zn in hexane at 0 °C for 6 h. [b] Determined by capillary GC (Hydrodex β-PM or β-DEX-325 column). [c] Distilled yield. [d] Reaction time extended to 24 h.

As illustrated in Table 1, using catalyst (*S*)-**3** of 98% ee, (*S*)-**5** is afforded in 86% ee (entry 1), while catalyst of only 15% ee provides (*S*)-**5** with only slightly diminished enantiopurity (entry 7). Thus, the substantial asymmetric amplification observed in the ethylation of **4** with (*S*)-**3** allows for maximal convenience and flexibility in the catalyst preparation. Since (*S*)-**3**·DTTA of mediocre diastereomeric excess can be used for the transformation, the need to enhance optical purity through multiple crystallizations is obviated. Extending the reaction time from 6 to 24 h had no beneficial effect in terms of yield or optical purity enhancement (entry 3 vs 4).

To maximize the practicality of the asymmetric ethylation of **4**, minimal catalyst loading while maintaining good enantioselectivity and yield of (*S*)-**5** was essential. Table 2 summarizes the findings and shows that good enantiopurity is retained throughout the range of study (10 to 0.1 mol %). Unfortunately, the yield of (*S*)-**5** decreased markedly upon moving to a catalyst loading of 0.1 mol % and employing a 6-h reaction time (entry 4); however, a higher conversion was realized when the reaction time was increased to 24 h (entry 5). A catalyst loading of 1 mol % was therefore optimal in terms of practicality (low catalyst load and short reaction time) and good enantioselectivity.

Additional optimization studies revealed that the reaction concentration could be increased to 0.85 M, allowing use of the commercial[10] solution of Et_2Zn (1 M in hexane) without dilution. This increased concentration did not lower the enantiomeric excess or isolated yield of (*S*)-**5** and enabled higher throughput. Finally, the reaction has been performed on 3-L scale repeatedly without incident, clearly demonstrating the utility of this method.

Summary

An expedient, efficient preparation of amino alcohol (*S*)-**3**, a versatile ligand for the catalytic asymmetric addition of dialkylzinc reagents to aldehydes, has been described. This procedure should make the catalyst more widely available for use in organic synthesis. Furthermore, the utilization of (*S*)-**3** in the ethylation of *trans*-crotonaldehyde has been studied, resulting in a high-throughput method for generating mole quantities of (*S*)-**5**.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 or ARX-500 spectrometer. Enantiomeric

(10) 1 M diethylzinc in hexane was purchased from Aldrich Chemical Co.

excesses were determined by capillary gas chromatography on a Hewlett-Packard model 5890 instrument using a 25-m × 0.25-mm Hydrodex β-PM column or a 30-m × 0.25-mm β-DEX 325 (Supelco) column, both with FID detection. Optical rotations were measured with a Perkin-Elmer model 241 polarimeter. Elemental analyses, infrared (IR) spectra, field desorption mass spectra (FDMS), and fast-atom-bombardment high-resolution mass spectra (FAB HRMS) were performed at the Structural and Organic Chemistry Research Laboratory, Eli Lilly and Co., Indianapolis, IN. All reactions were carried out under a nitrogen atmosphere. **Warning: Extreme caution should be used when working with diethylzinc. Neat diethylzinc spontaneously combusts upon exposure to atmospheric moisture; the manipulation of diethylzinc solutions diminishes the risk of combustion.**

(*S*)-(*E*)-4-Hexen-3-ol [(*S*)-5].[5] Diethylzinc (1.0 M in hexane, 2.85 L, 2.85 mol) was combined with (*S*)-**3** (4.47 g, 24.1 mmol, 68.5% ee) and the mixture stirred for 20 min at room temperature. After the mixture was cooled to −60 °C, *trans*-crotonaldehyde (**4**) (200 mL, 2.41 mol) was added dropwise and the mixture allowed to warm to 0 °C and stir for 6 h. The reaction was quenched by carefully adding saturated NH_4Cl solution (1.5 L) and stirring the biphasic mixture for 30 min. After the mixture was filtered, the organic phase was washed with 1 M HCl (980 mL), and the combined aqueous phases were extracted with hexane (980 mL). The combined organic phases were washed with saturated aqueous NaCl (980 mL), dried ($MgSO_4$), and carefully concentrated under reduced pressure (bath temperature 20−25 °C). Distillation at atmospheric pressure afforded (*S*)-**5** (155.3 g, 64%) as a colorless liquid (bp 135 °C): $[\alpha]_D$ +12.4° (*c* 2.12, EtOH), −2.1° (*c* 1.0, $CHCl_3$); 83.0% ee by chiral GC analysis (see General); IR ($CHCl_3$, cm^{-1}) 3607 (m), 3454 (w), 3012 (s), 2969 (s), 2937 (s), 2879 (s), 2859 (m), 1453 (w), 1378 (w), 968 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 5.64 (ddq, 1H, J = 0.8, 6.4, 15.3 Hz), 5.45 (ddq, 1H, J = 1.5, 7.0, 15.3 Hz), 3.94 (ddd, 1H, J = 6.7, 6.7, 6.7 Hz), 1.67 (dd, 3H, J = 1.5, 6.4 Hz), 1.65−1.40 (m, 3H), 0.88 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.0, 126.9, 74.5, 30.1, 17.7, 9.7; FDMS (M^+) *m*/*z* 100.

(±)-1-Piperidino-3,3-dimethyl-2-butanol [(±)-3].[7] A mixture of 1-bromopinacolone (**6**) (60.9 mL, 452 mmol), piperidine (47.0 mL, 475 mmol), and K_2CO_3 (125 g, 905 mmol) in acetonitrile (1810 mL) was stirred for 22 h at 60 °C. After the mixture was cooled to room temperature, H_2O (945 mL) and EtOAc (945 mL) were added and the layers separated. The organic phase was washed with saturated aqueous NaCl (945 mL), and the combined aqueous phases were extracted with EtOAc (380 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give ketone (±)-**7** as an orange oil: ^1H NMR (300 MHz, $CDCl_3$) δ 3.33 (s, 2H), 2.41 (br t, 4H, J = 4.9 Hz), 1.60 (m, 4H), 1.43 (m, 2H), 1.14 (s, 9H). The ketone was immediately[11] dissolved in Et_2O (405 mL) and added dropwise to a solution of $LiAlH_4$ (8.59 g, 226 mmol) in Et_2O (1350 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature and quenched at 5 °C by slowly adding H_2O (34 mL), 15% NaOH solution (34 mL), and H_2O (100 mL). After the mixture was filtered, the filtrate was dried ($MgSO_4$) and concentrated to afford (±)-**3** (72.1 g, 86% yield from 1-bromopinacolone) as an orange oil: IR ($CHCl_3$, cm^{-1}) 3400 (w), 2941 (s), 2859 (m), 2805 (m), 1479 (w), 1469 (w), 1456 (w), 1443 (w), 1362 (w), 1304 (w), 1280 (w), 1252 (w), 1156 (w), 1115 (w), 1077 (m), 1016 (m), 873 (w); ^1H NMR (500 MHz, $CDCl_3$) δ 3.88−3.78 (br s, 1H), 3.26 (dd, 1H, J = 4.1, 10.5 Hz), 2.60−2.53 (br m, 2H), 2.26−2.19 (br m, 2H), 2.17 (m, 2H), 1.57−1.45 (br m, 4H), 1.43−1.35 (br m, 2H), 0.84 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 73.2, 60.1, 55.0, 33.5, 26.5, 26.0, 24.7; FAB HRMS calcd for $C_{11}H_{24}NO$ (MH^+) *m*/z 186.1858, found 186.1856.

(*S*)-1-Piperidino-3,3-dimethyl-2-butanol−Di-*p*-toluoyl-D-tartaric Acid [(*S*)-3·DTTA]. Racemic **3** (64.0 g, 345 mmol) was added to a solution of di-*p*-toluoyl-D-tartaric acid (133.4 g, 345 mmol) in *i*-PrOH/MeOH (3:1, 1250 mL) at 65 °C, and the solution was allowed to cool to room temperature for crystallization and to stir overnight. The product was collected and dried to give (*S*)-**3**·DTTA as a crystalline colorless solid (89.3 g, 45% yield of diastereomeric mixture): 62.7% de;[12] IR ($CHCl_3$, cm^{-1}) 2961 (w), 1723 (s), 1612 (m), 1367 (w), 1268 (s), 1179 (m), 1109 (m), 1021 (w); ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, 4H, J = 8.1 Hz), 7.32 (d, 4H, J = 8.1 Hz), 5.65 (s, 2H), 3.49 (d, 1H, J = 10.4 Hz), 3.20−2.87 (br m, 4H), 3.01 (d, 1H, J = 13.0 Hz), 2.81 (dd, 1H, J = 10.4, 13.0 Hz), 2.37 (s, 6H), 0.82 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.2, 165.7, 146.6, 144.6, 130.2, 130.1, 127.7, 72.7, 71.9, 59.4, 35.0, 26.3, 23.1, 22.4, 22.0. Anal. Calcd for $C_{31}H_{41}NO_9$: C, 65.13; H, 7.23; N, 2.45. Found: C, 65.15; H, 7.18; N, 2.45.

(*S*)-1-Piperidino-3,3-dimethyl-2-butanol [(*S*)-3]. Diastereomerically enriched (*S*)-**3**·DTTA (16.2 g, 28.4 mmol, 68.5% de[12]) was dissolved in Et_2O (357 mL) and treated with 1 M NaOH (357 mL, 357 mmol), and the mixture was stirred for 10 min. The layers were separated, the aqueous phase was extracted with Et_2O (97 mL), and the combined organic phases were washed with saturated aqueous NaCl (194 mL). The combined aqueous phases were extracted with Et_2O (97 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated to give (*S*)-**3** as a colorless oil (5.0 g, 95%): $[\alpha]_D$ +46.9° (*c* 1.86, $CHCl_3$); 68.5% ee by chiral GC analysis (see General).

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(11) Unpurified **7**, neat or as a solution in ethyl acetate, began to degrade upon standing overnight at −20 °C.

(12) The diastereomeric excess was determined by neutralizing (*S*)-**3**·DTTA with 1 M potassium hydroxide and analyzing the dichloromethane extract containing (*S*)-**3** by chiral capillary gas chromatography (see General).