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# Dual Stereoselectivity in the Dialkylzinc Reaction Using (−)-β-Pinene Derived Amino Alcohol Chiral Auxiliaries

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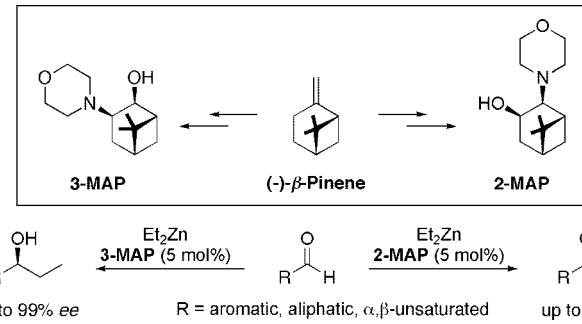


(+)-Nopinone, prepared from naturally occurring (−)-β-pinene, was converted to the two regioisomeric amino alcohols **3-MAP** and **2-MAP** in very good yield and excellent isomeric purity. Amino alcohol **3-MAP** was synthesized by converting (+)-nopinone to the corresponding α-ketooxime. This was reduced to the primary amino alcohol and was converted to the morpholino group through a simple substitution reaction. **3-MAP** was characterized by X-ray crystallography, which displayed the rigidity of the pinane framework. Amino alcohol **2-MAP** was prepared from its *trans* isomer **2**, which in turn was synthesized via hydroboration/oxidation of the morpholine enamine of (+)-nopinone. Two-dimensional NMR was used to characterize amino alcohol **2-MAP**, and NOE was used to confirm its relative stereochemistry. These amino alcohols were employed as chiral auxiliaries in the addition of diethylzinc to benzaldehyde to obtain near-quantitative asymmetric induction in the products. The use of **3-MAP** yielded (*S*)-phenylpropanol in 99% ee, and its regioisomer **2-MAP** gave the opposite enantiomer, (*R*)-phenylpropanol, also in 99% ee. Other aromatic, aliphatic, and α,β-unsaturated aldehydes were implemented in this method, affording secondary alcohols in high yield and enantiomeric excess. Amino alcohols **2-MAP** and **3-MAP** were also found to be useful in the dimethylzinc addition reaction, both catalyzing the addition to benzaldehyde with nearly quantitative ee. Regioisomeric amino alcohols **2-MAP** and **3-MAP**, even though they were prepared from one enantiomer of nopinone, provide antipodal enantiofacial selectivity in the dialkylzinc addition reaction. This circumvents the necessity to synthesize amino alcohols derived from (−)-nopinone, which in turn requires the unnatural (+)-β-pinene. Possible mechanistic insights are offered to explain the dual stereoselectivity observed in the diethylzinc addition reaction involving regioisomeric, pseudo-enantiomeric amino alcohols **3-MAP** and **2-MAP**.

## Introduction

The asymmetric addition of dialkylzinc to aldehydes is a commonly used method for synthesizing chiral secondary alcohols.[1] This is largely because organozinc reagents are mild reagents and chemoselective compared to analogous organolithium and Grignard reagents.[2] Early work in this field employed terpene-based amino alcohols, including camphor-derived DAIB and MIB ligands, to impart excellent facial selectivity in the addition of diethylzinc to aldehydes and ketones.[3] However, these methods require both enantiomers of the chiral director to access both enantiomers of the product

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alcohol. Unfortunately, (−)-camphor is over 150 times more expensive than naturally occurring (+)-camphor, the precursor for both DAIB and MIB. This is a general trend for many terpenes, amino acids, and other natural products, which are often used as chiral directors,[4] where only one enantiomer is naturally occurring and/or commercially available.

Optically active β-amino alcohols derived from pinenes have served as chiral auxiliaries in a wide variety of organic reactions, including the asymmetric reduction of ketones[5] and the asymmetric addition of organozinc reagents to aldehydes.[6] Although both enantiomers of α-pinene are readily available, (−)-β-pinene is the only natural product. However, (+)-nopinone obtained from (−)-β-pinene is an excellent precursor for amino alcohols that are promising as chiral directors in asymmetric reductions and organometallic addition reactions. Recently, amino alcohols derived from (−)-α-pinene[7] and (−)-β-pinene[5a] were used to synthesize chiral oxazaborolidines that were employed in the asymmetric reduction of ketones with excellent enantioselectivities. While *trans*-amino alcohols containing pinane framework were used with limited success as chiral auxiliaries in diethylzinc additions,[6a] the corresponding *cis*-amino alcohols have never been used for this purpose. This prompted us to synthesize *cis*-amino alcohols from (+)-nopinone and to evaluate these amino alcohols in the asymmetric dialkylzinc reaction. Even though only (+)-nopinone is easily accessible, we wanted to explore the possibility of producing dual chiral directors by synthesizing pseudo-enantiomeric amino alcohols starting from this single enantiomer of nopinone.

"Dual enantioselective control" using chiral directors derived from a single enantiomeric precursor has been sparsely reported.[8] Recently, "effective chirality switching" was reported in the diethylzinc addition reaction by simply changing the metal-to-ligand ratio in the preparation of the nickel catalyst.[9] Pseudo-enantiomeric iminolactones, derived from a single enantiomer of camphor quinone, have been reported to serve as stoichiometric, covalently bound chiral auxiliaries for diastereoselective α-alkylations of amino acids.[10] This newly growing field of dual stereoselectivity is of great interest as it has the potential to reach a myriad of applications in asymmetric catalysis utilizing amino alcohol chiral directors.[11] Herein, we report the preparation of pseudo-enantiomeric *cis*-amino alcohols from a single enantiomer of nopinone and the achievement of dual enantioselective control in the dialkylzinc reaction with aldehydes.

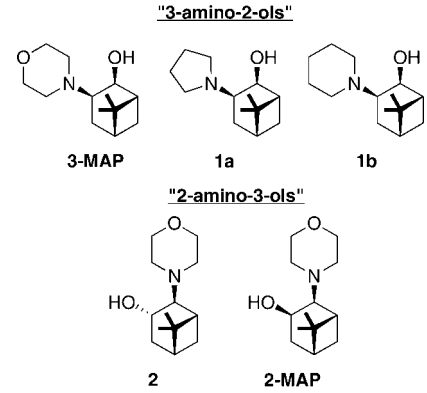


**FIGURE 1.** Amino alcohols synthesized from (−)-β-pinene.

## Results and Discussion

The dual chiral directors derived from (+)-nopinone, including (1*R*,2*S*,3*R*,5*R*)-3-dialkylamino-6,6-dimethylbicyclo[3.1.1]-heptan-2-ols **3-MAP** and **1a,b** (3-amino-2-ols), (1*R*,2*S*,3*R*,5*R*)-2-dialkylamino-6,6-dimethylbicyclo[3.1.1]heptan-3-ol **2-MAP**, and (1*R*,2*S*,3*S*,5*R*)-2-dialkylamino-6,6-dimethylbicyclo[3.1.1]-heptan-3-ol **2** (2-amino-3-ols), are shown in Figure 1.

(+)-Nopinone, needed for our work, was synthesized by ozonolysis of (−)-β-pinene in high yield.[12] Because ozonolysis is not safe to perform on a large scale, we also oxidatively cleaved (−)-β-pinene using a $RuCl_3/NaIO_4$ system.[13] (+)-Nopinone, thus obtained, was treated with a strong base and *iso*-pentyl nitrite to afford α-ketooxime **3**. Stereoselective reduction of **3** with lithium aluminum hydride ($LiAlH_4$) afforded the unsubstituted amino alcohol **4** in 60% yield over three steps (Scheme 1).[14]

Primary amino alcohol **4** was treated with a mild base and the corresponding dibromo compound to afford the morpholino, pyrrolidino, and piperidino alcohols **3-MAP**, **1a**, and **1b**, respectively (Scheme 2). X-ray crystallography was used to confirm the structure and stereochemistry of each of these novel compounds based on the known absolute configuration of the pinane ring (Figure 2).[15] The bicyclic ring provides rigidity that keeps the morpholine pseudoequatorial and the hydroxy in a pseudoaxial position, with both these groups and the *gem*-dimethyl group on the same face of the molecule (Scheme 2).

The regioisomeric amino alcohol **2-MAP** was synthesized through the intermediate formation of its *trans*-isomer **2**. This

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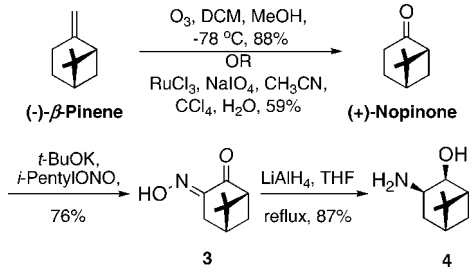
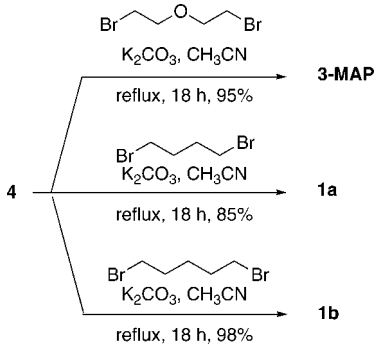
(14) Compound **4** and its regioisomer are excellent chiral auxiliaries for the asymmetric reduction of prochiral ketones, giving enantiomeric product alcohols. Krzemiński, M. P., personal communication.

**SCHEME 1. Synthesis of Primary 3-Amino-2-ol from (−)-β-Pinene**




**SCHEME 2. Synthesis of 3-Amino-2-ols**




*trans*-amino alcohol was in turn prepared from the corresponding enamine. Conversion to enamine **5** was accomplished by refluxing the common precursor (+)-nopinone with an in situ generated titanium−morpholine complex. Literature procedures for making hindered enamines reported the use of 9 equiv of secondary amine and a slight excess of $TiCl_4$ to drive the reaction to completion.[16] While only 1 equiv of amine is needed to form the enamine, the other 2 equiv are used to scavenge the HCl formed when $TiCl_4$ reacts with water produced during the reaction (eq 1).

$$RCH_2COR' + 3HNR_2'' + 0.5\ TiCl_4 \rightarrow RCH{=}C[NR_2'']R' + 2R_2''NH_2Cl + 0.5\ TiO_2 \quad (1)$$

We reasoned that some of the secondary amine could be replaced with a volatile tertiary amine, which would not complex with titanium but rather serve only to sequester HCl (eq 2).

$$RCH_2COR' + 1.5\ HNR_2'' + 1.5\ NEt_3 + 0.5\ TiCl_4 \rightarrow RCH{=}C[NR_2'']R' + 0.5\ R_2''NH_2Cl + 1.5\ NEt_3HCl + 0.5\ TiO_2 \quad (2)$$

Additionally, we were able to reduce $TiCl_4$ to a substoichiometric quantity, which is similar to other reports of $TiCl_4$-mediated enamine syntheses.[17] These adjustments not only decreased the amounts of reagents needed but also reduced the solid byproduct, allowing greater recovery of the product enamine **5**.

Enamine hydroboration followed by methanolysis and then oxidation afforded **2** in 85% isolated yield.[18] Oxidation to α-morpholino ketone **6** was accomplished with minimal epimerization via Swern oxidation.[19] We envisioned that the steric requirement of the morpholine moiety and the *gem*-dimethyl group were substantial enough to block the β-face of the molecule for stereospecific hydride delivery. However, the reduction of α-amino ketone **6** was more problematic than initially anticipated. Sodium borohydride ($NaBH_4$) reduction resulted in a 2:1 *cis*/*trans* mixture. The result using lithium diisopropylaminoborane ($Li[H_3BN(i\text{-}Pr)_2]$, LAB reagent)[20] was identical, indicating that the LAB reagent has steric requirements similar to that of $NaBH_4$. We found the addition of triethylborane ($Et_3B$) to the LAB reagent greatly improved the stereoselectivity of this reduction. It is known that the reaction of a 1:1 mixture of LAB reagent with $Et_3B$ generates lithium triethylborohydride in situ.[21] This sterically more demanding reagent preferentially adds from the α-face of the ring, resulting in a separable mixture of diastereomers, with **2-MAP** being the major product (Figure 3, Scheme 3).

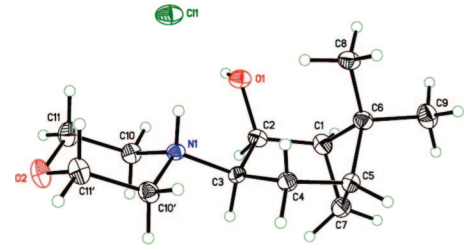


**FIGURE 2.** ORTEP diagram of **3-MAP**-HCl.

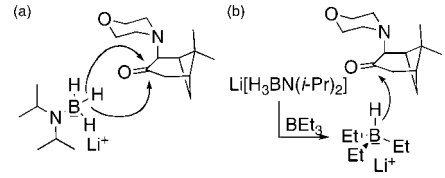
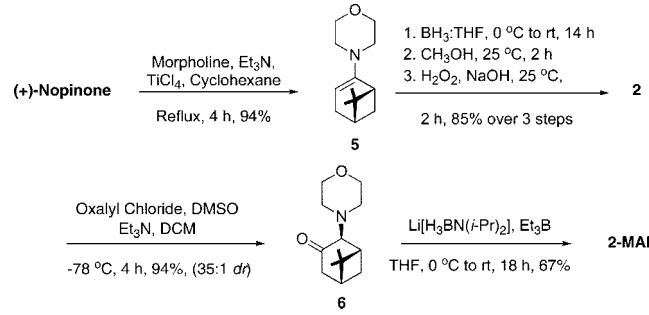



**FIGURE 3.** Proposed models for selectivity in the α-amino ketone reduction: (a) reaction of ketone **6** with LAB reagent; (b) reaction of ketone **6** with LAB reagent and $Et_3B$.

**SCHEME 3. Synthesis of Chiral Auxiliary 2-MAP**




Relative stereochemistry of **2-MAP** was determined by NOE correlations. It was possible that epimerization of the α-center

(15) (a) See Supporting Information for **1a** and **1b**. (b) Crystal data for $C_{13}H_{24}ClNO_2$: $M_r = 261.78$; monoclinic; space group $P2_1$; $a = 6.0276(10)$ Å; $b = 19.160(3)$ Å; $c = 6.0924(10)$ Å; $\alpha = 90°$; $\beta = 106.163(2)°$; $\gamma = 90°$; $V = 675.78(19)$ Å; $Z = 2$; $T = 150(2)$ K; $\lambda$(Mo Kα) = 0.71073 Å; $\mu$(Mo Kα) = 0.274 mm$^{-1}$; $d_{calc} = 1.287$g·cm$^{-1}$; 7607 reflections collected; 3302 unique ($R_{int} = 0.0307$); giving $R_1 = 0.0356$, $wR_2 = 0.0739$ for 2940 data with $[I > 2\sigma(I)]$ and $R_1 = 0.0434$, $wR_2 = 0.0769$ for all 3302 data. Residual electron density (e$^-$·Å$^{-3}$) max/min: 0.232/−0.191.

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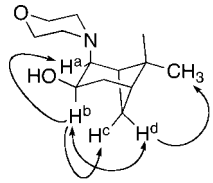
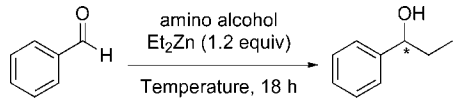



**FIGURE 4.** Key NOE correlations in **2-MAP**.[29]

**TABLE 1. Amino Alcohol Screening and Optimization of the Diethylzinc Reaction**




| entry | amino alcohol (mol %) | temp (°C) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | **1a** (10) | 0 | 99 | 84 (*S*) |
| 2[c] | **1b** (10) | 0 | 99 | 87 (*S*) |
| 3[c] | **3-MAP** (10) | 0 | 99 | 86 (*S*) |
| 4[c] | **3-MAP** (10) | −15 to 0 | 99 | 97 (*S*) |
| 5 | **3-MAP** (8) | −15 to 0 | 98 | 97 (*S*) |
| 6[c] | **3-MAP** (5) | −15 to 0 | 92 | 99 (*S*) |
| 7 | **3-MAP** (1) | −15 to 0 | 97 | 96 (*S*) |
| 8[c] | **2** (10) | 0 | 89 | 58 (*R*) |
| 9[c,d] | **2:2-MAP** (10) | −15 to 0 | 99 | 95 (*R*) |
| 10[c] | **2-MAP** (5) | −15 to 0 | 94 | 99 (*R*) |

[a] Isolated yield. [b] Determined by chiral GC, corrected for the 92% optical purity of (−)-*β*-pinene. Uncorrected values represented in Supporting Information. [c] Results reported as an average of at least 2 trials. [d] 1:2 mixture of **2**:**2-MAP**.

of ketone **6** could have occurred before reduction, yielding the diastereomeric *cis*-alcohol. We therefore found it necessary to look for through-space couplings of $H_a$ to other protons known to be on the α-face of the ring. Irradiation of the signal for proton $H_b$ showed correlation to protons $H_a$, $H_c$, and $H_d$, indicating that these protons reside on the same face of the ring. This was given further evidence by the correlation of $H_d$ to the equatorial methyl group, as well as its correlation back to $H_b$. The proximity of the fixed stereocenters of the pinane ring allowed for the confirmation of absolute configuration (Figure 4). From this data, it was clear that the Swern oxidation was mild enough to prevent epimerization.

Amino alcohols **3-MAP**, **1a,b**, **2**, and **2-MAP** were screened in the reaction of diethylzinc with benzaldehyde. Of the 3-amino-2-ols, chiral ligand **3-MAP** bearing the morpholino group provided good induction of (*S*)-phenylpropanol and was chosen for further optimization (Table 1, entries 1−3).[22] Lowering the temperature to −15 °C then gradually increasing to 0 °C drastically increased the asymmetric induction (Table 1, entry 4). It was also found that the catalyst loading could be decreased to 5 mol % and still maintain near-quantitative asymmetric induction in the product (Table 1, entries 5−7). These optimized conditions were chosen for further investigation.

We were surprised to find that the 2:1 *cis*/*trans* mixture of amino alcohols obtained from the sodium borohydride reduction of α-amino ketone **6** gave results comparable to those of pure **2-MAP** in the diethylzinc reaction (Table 1, entry 9). This suggests that diastereomeric purity of the ligand was not crucial for obtaining secondary alcohol products in high enantiomeric excess. Intrigued by this finding, we set out to further investigate the apparent asymmetric amplification in mixtures of these *cis*/*trans* diastereomers using the optimized conditions. Spiking the *trans*-amino alcohol **2** with only 19% of **2-MAP** increases the % ee from 71% to 89% (Figure 5). This significant increase in

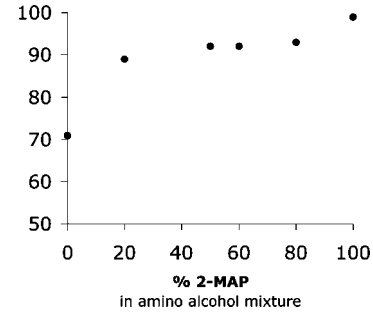



**FIGURE 5.** Correlation of % ee in the addition of diethylzinc to benzaldehyde with varying ratios of the *cis*/*trans* diastereomers **2-MAP** and **2**. Reactions carried out with 1 mmol benzaldehyde, 1.2 mmol $Et_2Zn$, and 0.05 mmol amino alcohol at −15 °C with the following results (% **2-MAP**, % ee): (0, 71), (19, 89), (45, 92), (57, 92), (80, 93), (100, 99). The yields were near-quantitative in each reaction.

ee is followed by a gradual increase from 92% to 99% ee over 45% to 100% of **2-MAP** in the *cis*/*trans* mixture.

Whereas the diastereomers **2** and **2-MAP** both favored the production of (*R*)-phenylpropanol, the latter provided far superior asymmetric induction (Table 1, entries 8 and 9). This is likely due to the chiral space of the tricoordinate alkylzinc aminoalkoxide (Figure 6).[23] This zinc complex formed with **2** is likely to occur in the plane of the ring or partially below, where influence from the sterically demanding *gem*-dimethyl group is minimal. The complexation of diethylzinc with **2-MAP**, however, is expected to take place above the plane of the ring, allowing greater interaction with the *gem*-dimethyl group and directing ethyl group delivery to the *re* face of benzaldehyde (Figure 6b and c).[24] In a 1:1 diastereomeric mixture, it is possible that the heterodimer formed between diethylzinc, **2**, and **2-MAP** could be held in a *trans* conformation, which would be more stable and less likely to catalyze an alkyl addition. On the other hand, an excess of **2-MAP** in the *cis*/*trans* mixture would create both hetero- and homodimers, the latter of which is more reactive and therefore responsible for the high induction obtained for the product alcohol.[25] However, this explanation does not account for the high asymmetric induction obtained for the *cis*/*trans* mixture containing 19% and 45% of **2-MAP**. Apparently, the rates of diethylzinc reaction catalyzed by **2** and **2-MAP** are not the same, allowing a [EtZn:**2-MAP**] homodimer to predominate the catalyst mixture. This finding makes the synthesis of **2-MAP** more practical, as the *cis*/*trans* mixture obtained from a $NaBH_4$ reduction of **6** gives results comparable to those of pure **2-MAP**.[26]

Switching the amino and alcohol positions switches the facial preference for the reaction. In the reaction of benzaldehyde with diethylzinc catalyzed by **3-MAP**, the ethyl group is situated on the *si* face of benzaldehyde (Figure 6d). Experimental observations clearly show that this pseudo-enantiomeric amino alcohol

(22) The morpholino group has been previously shown to enhance enantiomeric excess in the diethylzinc addition reaction: Steiner, D.; Sethofer, S. G.; Goralski, C. T.; Singaram, B *Tetrahedron: Asymmetry* **2002**, *13*, 1477–1483. See also ref 3b.

(23) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597.

(24) Soai, K.; Yokoyama, S.; Hayasaka, T. J. *J. Org. Chem.* **1991**, *56*, 4264–4268.

(25) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832–4842.

(26) A similar observation has been made regarding the use of diastereomeric mixtures of catalysts in the diethylzinc reaction: Bolm, C.; Muñiz, K.; Hildebrand, J. P *Org. Lett.* **1999**, *1*, 491–494.

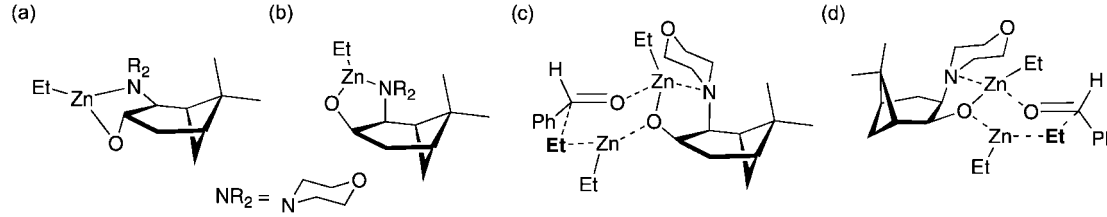
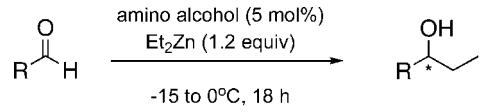
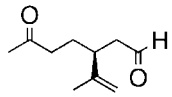



**FIGURE 6.** Proposed models for diethylzinc complexation with (a) **2** and (b) **2-MAP**; proposed transition states in the reaction of diethylzinc and benzaldehyde in the presence of (c) **2-MAP** and (d) **3-MAP**.

**TABLE 2. Addition of Diethylzinc to Aromatic and Aliphatic Aldehydes**



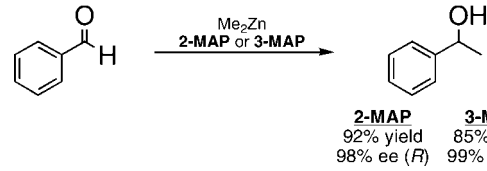

| | | 2-MAP | | 3-MAP | |
|---|---|---|---|---|---|
| Entry | Substrate | Yield (%)[a] | *ee* (%)[b] | Yield (%)[a] | *ee* (%)[b] |
| 1[c] | benzaldehyde | 100 | 99 (*R*) | 100 | 99 (*S*) |
| 2[c] | *o*-anisaldehyde | 92 | 94 (*R*) | 100 | 90 (*S*) |
| 3 | *o*-chloro benzaldehyde | 99 | 85 (*R*) | 99 | 83 (*S*) |
| 4[c] | *m*-tolualdehyde | 100 | 99 (*R*) | 100 | 97 (*S*) |
| 5[c] | *p*-anisaldehyde | 94 | 93 (*R*) | 99 | 95 (*S*) |
| 6[c] | *trans*-cinnamaldehyde | 90 | 93 (*R*) | 89 | 86 (*S*) |
| 7 | 2,2-dimethyl-4-pentenal | 94 | 99 (*R*) | 85 | 99 (*S*) |
| 8 | 2-ethyl butyraldehyde | 88 | 99 (*R*) | 85 | 99 (*S*) |
| 9[c] |  **7** | 93[d] | 82[e] | 99[f] | 89[e] |

[a] Isolated yield. [b] Determined by chiral GC, corrected for 92% optical purity of commercially available (−)-$\beta$-pinene. Absolute configuration determined by comparison of optical rotation to literature values. [c] Results are reported as an average of at least two trials [d] Product referred to as **8b** in Supporting Information. [e] de determined by integration of $^1$H NMR signals; absolute configuration not assigned. [f] Product referred to as **8a** in Supporting Information.

pair permits access to both enantiomers of the diethylzinc addition product in excellent enantiomeric excess and quantitative yields.

A substrate study was carried out to demonstrate the versatility of this reaction and compatibility with other functional groups. The two chiral auxiliaries **3-MAP** and **2-MAP** consistently provided good induction in the diethylzinc addition to aromatic aldehydes (Table 2, entries 1−5). In addition, we demonstrated the ability to alkylate $\alpha,\beta$-unsaturated as well as aliphatic aldehydes with good ee (Table 2, entries 6−10). As expected, a higher degree of substitution at the $\alpha$-center increased asymmetric induction in the aliphatic substrates. This is exemplified by the nearly quantitative asymmetric induction

**SCHEME 4. Asymmetric Dimethylzinc Addition with 2-MAP and 3-MAP[a]**




[a] Reactions were carried out using 1 mmol benzaldehyde, 1.5 equiv of $Me_2Zn$ (2M in toluene), and 0.05 mmol amino alcohol at −15 °C for 18 h.

observed in the reactions of 2,2-dimethyl-4-pentenal and 2-ethylbutyraldehyde (Table 2, entries 7 and 8).

We were delighted to find that the oxidative cleavage product of (−)-limonene oxide **7**[27] was converted to the secondary alcohol in high diastereomeric excess while leaving the methyl ketone intact. This demonstrates reaction chemoselectivity as well as the ability to deliver an ethyl group with high facial selectivity, distinguishing between a proton and a $\beta$-branched group. Additionally, amino alcohols **2-MAP** and **3-MAP** were equally effective as chiral directors in the essentially quantitative asymmetric addition of the less reactive dimethylzinc to benzaldehyde (Scheme 4).

## Conclusion

A pseudo-enantiomeric pair of amino alcohols was synthesized from naturally occurring (−)-$\beta$-pinene through the common intermediate (+)-nopinone. These bicyclic amino alcohols were used as chiral directors in the addition of dimethyl- and diethylzinc to various aldehydes. By virtue of the position of the amino and alcohol groups, ligands **3-MAP** and **2-MAP** promote opposite enantiofacial selectivity in the ethyl group delivery to the aldehyde. This circumvents the problem with using the more expensive and unnatural (+)-$\beta$-pinene for the synthesis of the enantiomer of **3-MAP**. To the best of our knowledge, this is the first report of regioisomeric, noncovalently bound chiral directors promoting dual stereoselectivity. The apparent complementarity with which amino alcohols **3-MAP** and **2-MAP** bind to the metal center suggests that these directors have potential applications toward other organozinc or perhaps other organometallic addition reactions.

## Experimental Section

The following experimental details and characterizations are for compounds that are not previously reported in the literature. For experimental details and characterization of all other compounds, see Supporting Information.

**(1*R*,2*S*,3*R*,5*R*)-6,6-Dimethyl-3-morpholinobicyclo[3.1.1]heptan-2-ol (3-MAP).** To a 50-mL round-bottom flask were added **4** (310

(27) Binder, C. M.; Dixon, D. D.; Almaraz, E.; Tius, M. A.; Singaram, B. *Tetrahedron Lett.* **2008**, *49*, 2764–2767.

mg, 2 mmol), $K_2CO_3$ (558 mg, 4 mmol), bis(2-bromoethyl)ether (0.3 mL, 2.4 mmol), and $CH_3CN$ (16 mL). The flask was fitted with a water-cooled reflux condenser and drying tube ($CaCl_2$) and the reaction mixture was heated to reflux for 18 h. After the mixture had cooled to room temperature, the solids were filtered off and rinsed with $CH_3CN$. The organic liquid was concentrated in vacuo. The remaining oil was acidified with concd HCl (0.4 mL) and extracted with $Et_2O$ (3 × 10 mL). The remaining white solid was dissolved in water (1 mL) and 2:1 $Et_2O$/THF (15 mL) and then neutralized with solid NaOH (200 mg). The aqueous layer was extracted with 2:1 $Et_2O$/THF (3 × 15 mL). The combined organic layers were concentrated in vacuo, leaving 420 mg of **3-MAP** as a white solid (95% yield). $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ (ppm): 4.23 (dd, $J$ = 6.6 Hz, $J$ = 7.2 Hz, 1H), 3.77 (ddd, $J$ = 15.0 Hz, $J$ = 11.4 Hz, $J$ = 3.0 Hz, 2H), 3.75 (ddd, $J$ = 15.0 Hz, $J$ = 11.4 Hz, $J$ = 3.0 Hz, 2H), 2.76 (td, $J$ = 8.4 Hz, $J$ = 7.2 Hz, 1H), 2.67 (brs, 2H), 2.58 (brs, 2H), 2.35 (q, $J$ = 5.4 Hz, 1H), 2.10 (dt, $J$ = 10.8 Hz, $J$ = 5.4 Hz, 1H), 1.98 (qd, $J$ = 5.4 Hz, $J$ = 0.6 Hz, 1H), 1.94 (dt, $J$ = 12.6 Hz, $J$ = 5.4 Hz, 1H), 1.89 (td, $J$ = 12.6 Hz, $J$ = 10.8 Hz, 1H), 1.57 (brs, OH, 1H), 1.35 (d, $J$ = 10.8 Hz), 1.22 (s, 3H), 1.03 (s, 3H). $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm): 69.8, 67.3, 58.4, 45.9, 40.5, 38.9, 30.4, 27.5, 27.1, 23.5, 22.7. Mp 78 °C, $[\alpha]^{20}_D$ −5.9 (*c* 4, MeOH), IR (DCM, HCl salt) 3400, 3255 cm$^{-1}$. ESITOFMS *m*/*z* $[M + H]^+$ 226.1821 (calcd for $C_{13}H_{24}NO_2$ 226.1802).

**4-[(1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl]morpholine (5).** An oven-dried 250-mL flask with sidearm was equipped with a stir bar and water-cooled condenser fitted with a rubber septum connected to an argon bubbler. The assembly was cooled under argon and the flask was charged with cyclohexane (50 mL), morpholine (4.7 mL, 54 mmol), and $Et_3N$ (7.3 mL, 54 mmol) and then cooled to 0 °C in an ice bath. The rubber septum was replaced with a drying tube ($CaCl_2$). A 1 M solution of $TiCl_4$ in toluene (13.4 mmol) was added dropwise over 45 min, creating large amounts of a dark green precipitate. (+)-Nopinone (2.5 g, 18 mmol) was added in one portion and the solution was refluxed for 4 h, during which time the flask contents changed from dark green to dark red to light brown. The contents were cooled to room temperature and filtered through celite under Schlenk conditions. The solids were washed with 200 mL of cyclohexane and the organic extracts were concentrated in vacuo, yielding the desired product (3.5 g, 16.8 mmol, 94% yield) as an orange oil. $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ (ppm): 4.43 (dd, $J$ = 1.0 Hz, 1H), 3.72 (t, $J$ = 4.8 Hz, 4H), 2.74 (m, 4H), 2.39 (m, 1H), 2.24 (m, 1H), 2.21 (td, $J$ = 5.0 Hz, $J$ = 2.0 Hz, 1H), 2.08 (septet, d, $J$ = 3.0 Hz, $J$ = 1.2 Hz, 1H), 1.29 (s, 3H), 1.24 (d, $J$ = 8.4 Hz, 1H), 0.87 (s, 3H). $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm): 156.1, 95.9, 66.9, 49.3, 43.9, 41.0, 38.3, 31.5, 29.5, 26.4, 21.4. Bp 124−126 °C (10 mmHg), IR (neat) 1635 cm$^{-1}$.

**(1*R*,2*S*,5*R*)-6,6-Dimethyl-2-morpholinobicyclo[3.1.1]heptan-3-one (6).** An oven-dried 25-mL round-bottom flask with a magnetic stir bar was fitted with a rubber septum and cooled under argon. The flask was charged with freshly distilled DCM (4 mL) followed by oxalyl chloride (1.2 mmol, 0.1 mL) and cooled to −78 °C. DMSO (2.1 mmol, 0.15 mL) was then added dropwise followed by the dropwise addition of **2** (0.98 mmol, 200 mg) as a 1 M solution in anhydrous DCM. $Et_3N$ (5 mmol, 0.7 mL) was added and the reaction was stirred at −78 °C for 4 h. The crude reaction mixture was immediately poured over crushed ice into a separatory funnel containing 3 M HCl (15 mmol) and the organic layer was extracted with 1 M HCl (3 × 5 mL). The combined acidic aqueous portions were cooled to 0 °C and solid NaOH (25 mmol, 1 g) was added. The basic aqueous layer was extracted with $Et_2O$ (4 × 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the product as a yellow oil (205 mg, 94% yield). Diastereomeric ratio (>35:1) was measured by integration of $^1$H NMR signals. The product was immediately taken onto the next step, as storing overnight at 0 °C resulted in epimerization at the α-center. $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ (ppm): 3.69 (tdd, $J$ = 11.0 Hz, $J$ = 6.0 Hz, $J$ = 3.0 Hz, 2H), 3.66 (tdd, $J$ = 11.0 Hz, $J$ = 6.0 Hz, $J$ = 3.0 Hz, 2H), 2.87 (brs, 1H), 2.81 (brs, 2H), 2.74 (dt, $J$ = 19.0 Hz, $J$ = 3.0 Hz, 1H), 2.63 (dtd, $J$ = 11.0 Hz, $J$ = 6.5 Hz, $J$ = 3.5 Hz, 1H), 2.49 (m, 4H), 2.09 (septet, $J$ = 3.0 Hz, 1H), 1.31 (s, 3H), 1.08 (d, $J$ = 11.0 Hz, 1H), 1.06 (s, 3H). $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm): 218.3, 71.9, 67.3, 50.6, 44.4, 39.9, 37.9, 29.7, 29.4, 26.6, 19.9. Bp 126 °C (10 mmHg), IR (neat) 1716 cm$^{-1}$. ESITOFMS *m*/*z* $[M + H]^+$ 224.1644 (calcd for $C_{13}H_{22}NO_2$ 224.1645).

**(1*R*,2*S*,3*R*,5*R*)-6,6-Dimethyl-2-morpholinobicyclo[3.1.1]heptan-3-ol (2-MAP).** To a 25-mL round-bottom flask containing **6** (226 mg, 1 mmol) was added a stir bar and THF (1 mL), which was then cooled to 0 °C. A 1 M solution of $Et_3B$ in THF (1 mmol) was added followed by the dropwise addition of Li[$H_3BN(i\text{-}Pr)_2$] reagent (1 M in THF, 1.25 mmol), which was synthesized by literature procedures.[28] This solution was allowed to stir overnight (18 h) while gradually warming to room temperature. The reaction was quenched at 0 °C by the slow addition of water (1 mL), followed by 3 M HCl (2 mL). The aqueous fraction was washed with $Et_2O$ (2 × 25 mL) and then treated with solid NaOH (25 mmol, 1 g). The aqueous fraction was extracted with $Et_2O$ (3 × 15 mL). The combined organic extracts were washed with water (2 × 5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a clear oil (220 mg). The oil was loaded onto a silica gel column (10 mL $SiO_2$) and the desired product was eluted with 0.5% MeOH in DCM to give a clear oil, which solidified upon standing (121 mg, 67% yield). $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ (ppm): 4.13 (ddd, $J$ = 9.0 Hz, $J$ = 2.4 Hz, 1H), 3.77 (brs, 2H), 2.93 (dd, $J$ = 9.0 Hz, $J$ = 3.0 Hz, 1H), 2.64 (brs, 2H), 2.46 (ddd, $J$ = 14.4 Hz, $J$ = 9.6 Hz, $J$ = 4.0 Hz, 1H), 2.42 (brs, 2H), 2.37 (dtd, $J$ = 9.6 Hz, $J$ = 6.0 Hz, $J$ = 2.4 Hz, 1H), 2.32 (ddd, $J$ = 9.0 Hz, $J$ = 6.0 Hz, $J$ = 3.0 Hz, 1H), 1.99 (dq, $J$ = 14.4 Hz, $J$ = 2.4 Hz, 1H), 1.89 (dddd, $J$ = 9.0 Hz, $J$ = 6.0 Hz, $J$ = 4.0 Hz, $J$ = 2.4 Hz, 1H), 1.19 (s, 3H), 1.034 (s, 3H), 0.89 (d, $J$ = 9.6 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm): 68.8, 67.1, 59.3, 53.0, 42.6, 41.0, 38.4, 36.2, 30.8, 27.4, 21.9. Mp 42−44 °C, $[\alpha]^{20}_D$ +28.7 (*c* 4, MeOH), IR (DCM) 3254 cm$^{-1}$. ESITOFMS *m*/*z* $[M + H]^+$ 226.1808 (calcd for $C_{13}H_{24}NO_2$ 226.1802).

**General Procedure for Dimethyl- and Diethylzinc Addition to Aldehydes.** A 25-mL round-bottom flask and magnetic stir bar were oven-dried, fitted with a rubber septum, and cooled under argon. Amino alcohol (0.05 mmol, 11.3 mg) was added and the flask was purged with argon for 5 min. $Et_2Zn$ (1.2 mmol, 1 M in hexane) or $Me_2Zn$ (1.5 mmol, 2 M in toluene) was added to the flask and the mixture was stirred at −15 °C for 15 min. Aldehyde (1 mmol) was added dropwise (neat or as a 10 M solution in anhydrous DCM) and a bright yellow color was observed for aromatic substrates. The reaction was allowed to stir at −15 °C for 1 h and then kept at 0 °C. The reaction was quenched with satd $NH_4Cl$ (2 mL) and diluted with $Et_2O$ (5 mL). The aqueous layer was separated and the organic fraction was washed with 3 M HCl (5 mL) followed by 1 M HCl (5 mL). The combined acidic aqueous portions were extracted with $Et_2O$ (3 × 10 mL) and then set aside for recovery of amino alcohol. The combined organic fractions were washed with water (2 × 5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the product alcohol. The amino alcohol was recovered by treating the acidic aqueous portions with 3 M NaOH, extracting with $Et_2O$ (3 × 10 mL), drying ($MgSO_4$), filtering, and evaporating the solvent under reduced pressure.

**(*S*)-4,4-Dimethyl-1-hepten-5-ol.** $[\alpha]^{20}_D$ +4.1 (*c* 1.3, MeOH, 92% ee uncorrected, >99% ee corrected), GC (80 °C, 20 min, ramp at 8 °C/min to 90 °C) $t_R$ 31.23 min. **(*R*)-4,4-dimethyl-1-hepten-5-ol.** $[\alpha]_D^{20}$ −5.2 (*c* 4.0, MeOH, 91% ee uncorrected, 99% ee corrected),

(28) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378–6385.

(29) The structure is shown in the chair conformation for simplicity; however, X-ray crystal structures of related compounds show that this is not the case. Thus, relative stereochemical assignments could not be assigned by calculating coupling constants and NOE correlations were used to make these assignments.

GC (80 °C, 20 min, ramp at 8 °C/min to 90 °C) $t_R$ 30.13 min. Absolute configuration assignments made by analogy to other substrates reacted with **2-MAP** and **3-MAP**, all of which gave *R* and *S* products, respectively. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm): 5.87 (m, 1H), 5.06 (dd, $J$ = 2.5 Hz, $J$ = 1.0 Hz, 1H), 5.03 (d, $J$ = 1.0 Hz, 1H), 3.17 (dd, $J$ = 10.5 Hz, $J$ = 2.0 Hz, 1H), 2.13 (dd, $J$ = 13.0 Hz, $J$ = 8.0 Hz, 1H), 1.99 (tdt, $J$ = 13.0 Hz, $J$ = 8.0 Hz, $J$ = 1.0 Hz, 1H), 1.59 (tdd, $J$ = 15.0 Hz, $J$ = 7.5 Hz, $J$ = 2.0 Hz, 1H) 1.47 (bs, OH, 1H), 1.26 (ddq, $J$ = 15.0 Hz, $J$ = 10.5 Hz, $J$ = 7.5 Hz, 1H), 0.99 (t, $J$ = 7.5 Hz, 3H), 0.874 (s, 3H), 0.865 (s, 3H). $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm): 135.8, 117.1, 80.3, 43.8, 37.9, 24.0, 23.3, 22.7, 11.6. ESITOFMS *m*/*z* $[M + H]^+$ 143.1408 (calcd for $C_9H_{19}O$ 143.1436).

**(5*R*)-5-Isoprenylnon-7-ol-2-one (8a).** $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm): 4.82 (dq, $J$ = 2.5 Hz, $J$ = 1.0 Hz, 1H), 4.76 (d, $J$ = 2.5 Hz, 1H), 3.44 (dtd, $J$ = 9.0 Hz, $J$ = 6.0 Hz, $J$ = 2.5 Hz, 1H), 2.36 (t, $J$ = 7.0 Hz, 2H), 2.33 (m, 1H), 2.11 (s, 3H), 1.63 (m, 2H), 1.58 (q, $J$ = 1.0 Hz, 3H), 1.57 (m, 1H), 1.51 (ddd, $J$ = 14.0 Hz, $J$ = 11.0 Hz, $J$ = 2.5 Hz, 1H), 1.45 (td, $J$ = 7.0 Hz, $J$ = 6.0 Hz, 1H), 1.44 (td, $J$ = 7.0 Hz, $J$ = 6.0 Hz, 2H), 1.37 (ddd, $J$ = 14.0 Hz, $J$ = 9.0 Hz, $J$ = 4.0 Hz, 1H), 0.91 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm): 209.2, 146.5, 113.2, 70.9, 43.3, 41.6, 40.3, 30.7, 29.9, 27.2, 17.3, 9.9. $[\alpha]^{20}_D$ +12.2 (*c* 4, MeOH), IR (neat) 3423, 1714, 1644 cm$^{-1}$. ESITOFMS *m*/*z* $[M + H]^+$ 199.1665 (calcd for $C_{12}H_{23}O_2$ 199.1693). dr 15:1 (**8a**:**8b**, via integration of signals at 3.44 and 3.59); 81% de uncorrected, 89% de corrected.

**(5*R*)-5-Isoprenylnon-7-ol-2-one (8b).** $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm): 4.80 (dq, $J$ = 3.0 Hz, $J$ = 1.5 Hz, 1H), 4.77 (dd, $J$ = 1.5 Hz, $J$ = 1.0 Hz, 1H), 3.59 (tt, $J$ = 8.0 Hz, $J$ = 4.5 Hz, 1H), 2.36 (t, $J$ = 8.0 Hz, 2H), 2.20 (m, 1H), 2.12 (s, 3H), 1.73 (dtd, $J$ = 15.5 Hz, $J$ = 6.0 Hz, $J$ = 4.5 Hz, 2H), 1.64 (dd, $J$ = 1.5 Hz, $J$ = 1.0 Hz, 3H), 1.49 (m, 4H), 0.94 (t, $J$ = 7.0 Hz, 3H).$^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ (ppm): 209.3, 148.0, 112.6, 71.9, 44.2, 41.1, 40.9, 30.0, 29.9, 26.0, 17.7, 9.7. $[\alpha]^{20}_D$ −5.8 (*c* 4, MeOH), IR (neat) 3423, 1714, 1644 cm$^{-1}$. ESITOFMS *m*/*z* $[M + H]^+$ 199.1659 (calcd for $C_{12}H_{23}O_2$ 199.1693). dr 1:10 (**8a**:**8b**, via integration of signals at 3.44 and 3.59); 74% de uncorrected, 82% de corrected.

**Acknowledgment.** We would like to thank Jinsoo Kim, Max Mahoney, and Rushia Turner for helpful discussions. The single-crystal X-ray diffraction data in this work were recorded on an instrument supported by the National Science Foundation, Major Research Instrumentation (MRI) Program under Grant CHE-0521569.

**Supporting Information Available:** Experimental procedures and characterization of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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