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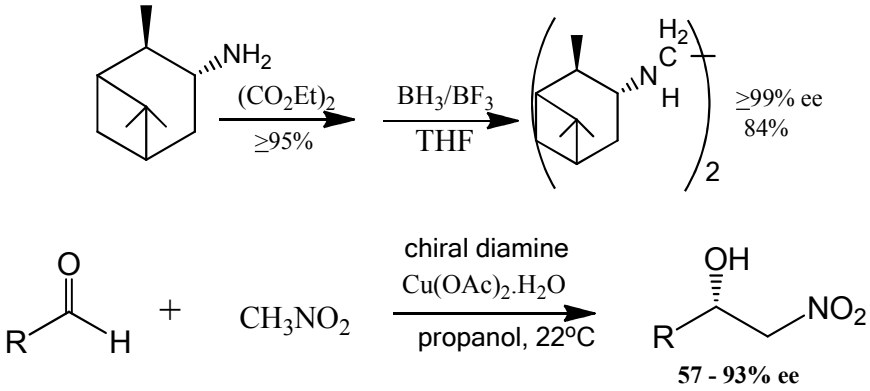
Terpene based novel chiral C_2-Symmetric diamines are synthesized and their utility in enantioselective C-C bond formation has been demonstrated.



C_2-Symmetric N, N'-bis(terpenyl)ethylenediamines—Synthesis and Application in the Enantioselective Nitroaldol Reaction[†]

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Abstract: Optically pure C_2-symmetric chiral diamines, have been synthesized by the reaction of terpenylamines with diethyloxalate, followed by the reduction of diamide with BH_3/BF_3. The methodology has been successfully applied and high yields achieved in the synthesis of chiral diamines derived from terpenes such as α-pinene, β-pinene, and 2-iso- and 4-carenes. These chiral diamines are found to be to be highly effective in inducing chirality in the nitroaldol reaction.

Key words: N, N' bis(terpenyl)ethylenediamine, enantioselective, C_2-symmetric, nitroaldol

INTRODUCTION

The vicinal diamines with their biological activity,[2] metal chelation[3] and potential as starting materials in heterocyclic chemistry,[4] are an important class of molecules in organic synthesis and medicinal chemistry.[5] Enantiomeric 1,2-diamines are known to be efficient chiral auxiliaries in various asymmetric transformations, such as aldol reactions,[6] Michael additions,[7] Sharpless dihydroxylation,[8] chiral Lewis acid-based reactions,[9] acylation of alcohols,[10] protonation of enolates,[11] conjugate addition,[12] desymmetrization of *meso*- ketones[13] and epoxides.[14] Given these applications of chiral 1,2-diamines several efforts have been made to develop synthetic routes that will enanble preparation of efficient diastereo- and enantioselective products.[15] Despite availability of several chiral 1,2-diamines, the design of new and improved enantiomerically enriched compounds is still an attractive research endeavor. Towards this goal pinenes are attractive chiral source due to their easy availability in enantiomerically pure forms, and therefore, terpene derivatives have been used as common building blocks for a broad range of asymmetric syntheses.[16a,b] There are number of literature reports describing the synthesis of diamines with two different substituents. However, these methods are relatively lengthy and give low yields.[17a,b,c] With these facts in mind; we have been interested in designing pinene-based C_2 symmetric diamines and explore their potential in asymmetric transformations.

Our experience in asymmetric synthesis via organoborane using terpenes as chiral auxiliaries has shown that terpenes such as Δ^2- and Δ^3carene and 2-alkyl apopinene provide superior results in asymmetric hydroboration,[18] asymmetric reduction[19] and asymmetric allylboration.[20] The success achieved with terpene-based reagent and also the utility of C_2-symmetric chiraldiamines in organic transition metal chemistry[21-23] prompted us to develop methodology to synthesize terpene-based

diamines. Herein, we report a simple and practical method for the synthesis of C_2-symmetrical 1,2-ethylenediamines (Table 1, **1c-5c**) derived from commercially available terpene-based primary amines **1a-5a** (Figure 1), and demonstrate their utility in enantioselective C-C bond formation, i.e. the nitroaldol reaction.

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† Dedicated to the memory of my mentor, Nobel Laureate (late) Professor Herbert C. Brown.

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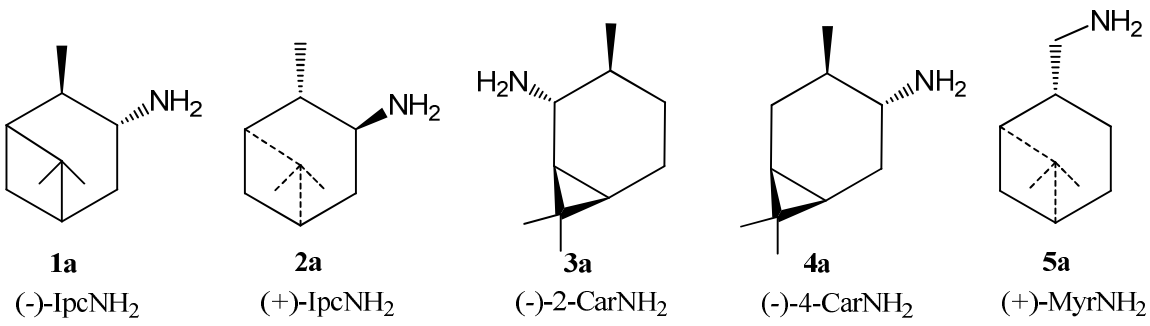


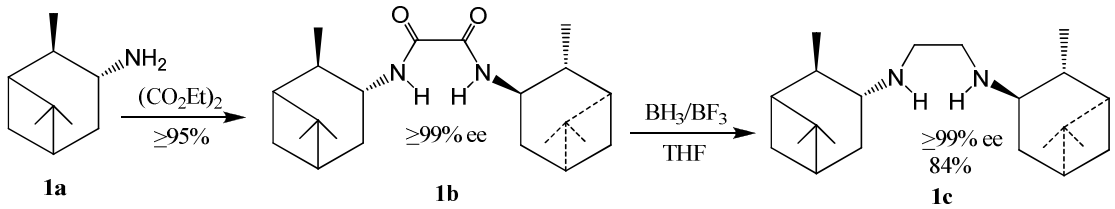
1a (-)-IpcNH$_2$ **2a** (+)-IpcNH$_2$ **3a** (-)-2-CarNH$_2$ **4a** (-)-4-CarNH$_2$ **5a** (+)-MyrNH$_2$

Figure 1: Primary amines

Results and Discussion

A simple procedure for the generation of the 1,2-diamino units is the aminolysis of the corresponding vicinal dihalides. However, this method mainly yielded elimination products in more complex systems.[24] Therefore, we devised a simpler and more efficient methodology for the synthesis of C_2-symmetric ethylenediamines from the respective primary amine. A representative procedure is shown n in Scheme 1. The primary amines were obtained through

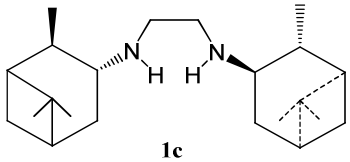
previously reported procedure.[18] We reacted isopinocampheylamine (^{d}IpcNH$_2$, **la**) with diethyloxalate at room temperature which gave a white solid product diisopinocampheyldiamide (**lb**) in a quantitative yield. Subsequent treatment of the diamide with a BH_3/BF_3 mixture[25] readily provided the desired product N, N'-bis(isopinocampheyl)ethylenediamine (**1c**). As an alternative method, the reduction of diamide **1b** and **5b** was also carried out with $LiAlH_4$. In this case, yields of the diamines (**1c, 5c**) obtained were 75% and 78%, respectively, which are lower than those obtained with the BH_3/BF_3 mixture. Therefore, in the synthesis of all other diamines the BH_3/BF_3 mixture was used for the reduction of diamides.

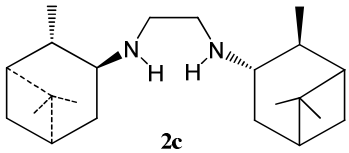


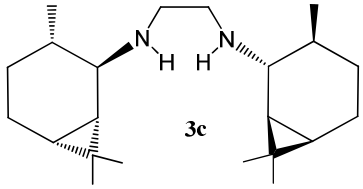
Scheme 1: Synthesis of N, N'-bis (isopinocampheyl) ethylenediamine

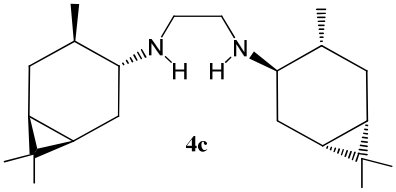
This procedure was successful employed in the synthesis of C_2-symmetric N, N'-bis(terpenyl)ethylenediamines (**1c-5c**) from their respective primary amines (**1a-5a**). Irrespective of the structural complexity of starting terpene, all diamines were obtained in very high yields (77-85%). The enantiopurity of products were determined by first converting each diamine to its respective methyl (trifluoromethyl) phenylacetamide (MTPA amide) derivative[26] and measuring the enantiomeric excess (ee) by gas chromatographic analysis using an SPB-5 capillary column. Results are summarized in Table 1.

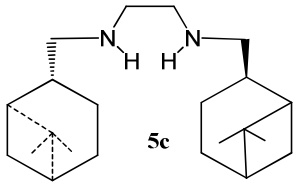
Table 1: Synthesis of N, N'-bis(terpenyl)ethylenediamines.











Terpene	Primary amine	Diamide yield[a] (%)	Diamide m.p. °C	product	Diamine yield[a] (%)	Diamine ee[b] (%)	$[\alpha]_D^{23}$ (neat)
(+)-α–pinene	**1a**	**97**	**186-189**	**1c**	**84(75)[c]**	**≥ 99**	**-28.71**
(-)-α–pinene	**2a**	**98**	**186-189**	**2c**	**79**	**≥ 99**	**+26.73**
(+)-2–carene	**3a**	**92**	**181-183**	**3c**	**81**	**≥ 99**	**-6.20**
(+)-3–carene	**4a**	**89**	**179-180**	**4c**	**77**	**≥ 99**	**-15.16**
(-)-β–pinene	**5a**	**92**	**181-183**	**5c**	**85(78)[c]**	**≥ 99**	**-14.98**

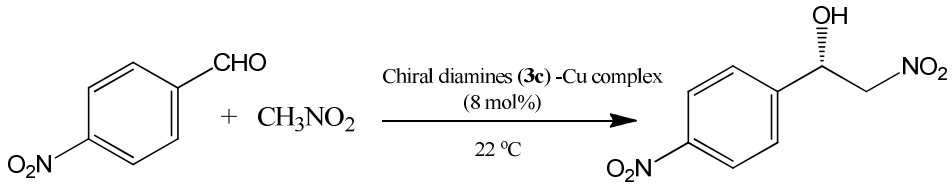
[a]Isolated yield. [b]Determined as the MTPA amide on a SPB-5 capillary column. [c]by reduction with $LiAlH_4$ in THF under reflux for 12 h.

Application of pinene-based vicinal C_2-symmetric diamines

Several catalytic approaches for asymmetric nitroaldol reactions have been reported in the literature, for example using lanthanide–BINOL complexes,[27] copper-based bisoxazoline complexes,[28] chiral dinuclear zinc complexes,[29] guanidine-derived Brønsted bases,[30] cinchona alkaloids[31] and other chiral metal complexes.[32] However, these catalytic systems have limitations such as a lower substrate scope, being restricted to aromatic or aliphatic aldehydes, need for low reaction temperatures, need for additives like organic bases and molecular sieves, and relatively high catalyst loading. Given these limitations of existing methods, there remains tremendous interest in developing new catalytic systems for an enantioselective nitroaldol reaction. This reaction provides the atom economic advantages in C-C bond formation and has applications in the preparation of

valuable building blocks. Attracted by these merits, we sought to explore the utility of our newly synthesized diamines (**1c-5c)** in the asymmetric nitroaldol reaction. As a first step of acquiring suitable conditions, a model system of reaction between p-nitrobenzaldehyde and nitro-methane using chiral diamine **3c**.

Table 2: Screening of reaction conditions

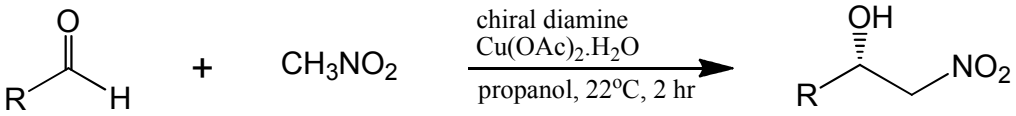


Entry	Metal catalyst	Solvent	Time(h)	Yield	ee %
1	$Zn(OAc)_2.2H_2O$	CH_2Cl_2	16	50	47
		EtOH	1.5	77	60
		Propanol	1.5	80	62
		Toluene	12	61	58
		THF	12	65	57
2	$Ni(OAc)_2.4H_2O$	CH_2Cl_2	16	59	45
		EtOH	2	68	57
		Propanol	1.5	78	52
		Toluene	20	60	49
		THF	12	65	39
3	$Cu(OAc)_2.H_2O$	CH_2Cl_2	16	65	51
		EtOH	2	85	62
		Propanol	1.5	79	74
		Toluene	20	67	63
		THF	12	80	58
4	$Cu(OTf)_2$	CH_2Cl_2	16	63	45
		EtOH	2	79	56
		Propanol	1.5	81	61
		Toluene	20	57	46
		THF	12	70	55

A series of divalent Lewis acids and solvents were screened in combination with chiral bidentate ligand **3c** as catalyst for our model reaction.. The results of these investigations are listed in Table **2**. In general, reactions proceeded rapidly in polar solvents, i.e. EtOH and propanol, compared to the less polar solvents THF, toluene and CH_2Cl_2. Though all catalysts were

effective in influencing the reaction, the best results were obtained with $Cu(OAc)_2.H_2O$ in propanol. Therefore, we settled with these conditions for further studies. he scope of this transformation and potential utility of diamines were further examined with several substrates and the results are summarized in Table 3. We found that the aldehydes containing either electron-withdrawing or electron-donating substituents, even at different positions on the aromatic ring of aryl aldehydes, gave products in moderate to good yields (44-89%) and ee values ranging from 57% to 93% (Table **3**). Also, α-pinene–based diamines were found to be the most effective in this group of chiral catalysts. In some cases small amounts (< 10%) of the corresponding elimination product were also obtained, along with the expected nitroaldol product.

Table 3: Enantioselective nitroaldol reaction



R =	Product[a] yield[b](%)/ee[c](%)				
	Diamine	**1c**	**2c**	**3c**	**4c**	**5c**
Ph-	**74/87**	**69/89**	**70/66**	**64/65**	**59/72**
o-MeO-C_6H_4	**77/82**	**64/70**	**64/59**	**59/61**	**74/75**
m-MeO-C_6H_4	**70/78**	**78/80**	**69/70**	**44/65**	**66/73**
p-MeO-C_6H_4	**80/84**	**85/89**	**70/75**	**74/67**	**78/77**
p-Cl-C_6H_4	**68/77**	**72/70**	**58/57**	**62/65**	**73/82**
p-Br-C_6H_4	**74/84**	**73/85**	**62/68**	**58/69**	**75/83**
p-F-C_6H_4	**84/92**	**81/87**	**73/83**	**76/79**	**80/83**
1-naphthyl	**71/77**	**74/80**	**63/68**	**65/71**	**76/78**
p-NO_2-C_6H_4	**87/90**	**84/85**	**79/74**	**76/70**	**80/72**
Cyclohexyl	**85/80**	**81/77**	**80/65**	**79/69**	**82/85**
butyl-	**89/83**	**86/81**	**82/73**	**84/77**	**87/84**

[a]Product characterization is based on comparison with literature;[33] [b]Isolated yield; [c]Determined as the MTPA amide on a SPB-5 capillary column.

These results can be rationalized by considering that the reaction involves Cu-mediated dual activation of the nitronate and the aldehyde substrates. In a favorable transition state (as proposed in figure 2), the nucleophilic carbon of the nitronate ion formed in situ by deprotonation of nitromethane with an acetate ion approaches the aldehyde from the Si face to give the (S)-isomer as the major product. The Re face attack is not favored due to severe non-bonding interactions between the aromatic group or the longer chain of the corresponding aldehyde with the methyl substituents of the C_2-symmetric N,N'-bis(terpenyl)ethylenediamine ligand.

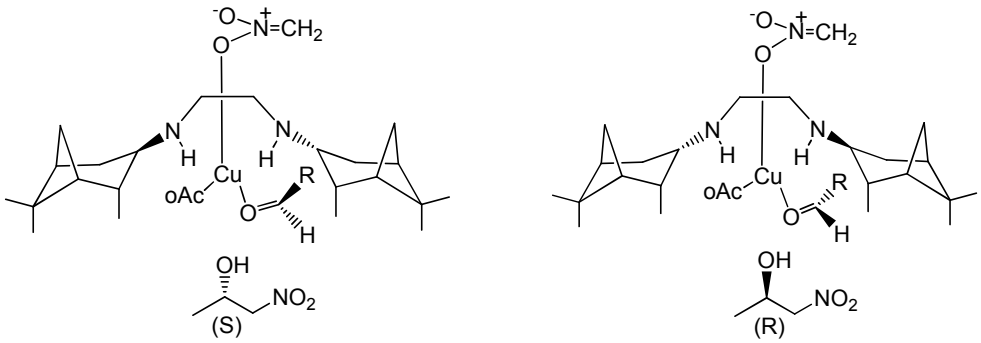


Figure 2: Proposed transition state

These results have prompted us to explore the potential utility of new chiral diamines in other organic transformations. The outcomes of such investigations will be presented in due course.

Conclusions

We have developed methodology for synthesise of optically pure C_2-symmetric N,N'-bis(terpenyl)ethylenediamines in very high yields from readily available terpenes. Also, their potential to induce high chirality has been demonstrated through the nitroaldol reaction. Ease of synthesis and ready availability of highly enantiopure, terpene-based chiral diamines will enrich the pool of chiral auxiliaries available to organic chemists.

EXPERIMENTAL

General methods. All operations were carried out under inert atmosphere.[32] The ^{1}H NMR spectra were plotted on a Varian Gemini-300 spectrometer with a Nalorac-Quad probe. The infrared spectra were recorded on a Perkin-Elmer 1420 ratio recording spectrophotometer. The mass spectra were obtained on a Finnigan Model 4000 gas chromatograph–mass spectrometer. Analysis of the MTPA amide of **1c-5c**, was performed on a Hewlett-Packard 890A gas chromatograph using a SPB-5 capillary column (30 m), and integrated using a Hewlett-Packard

3904 integrator. Optical rotations were measured on a Rudolph Autopol III polarimeter. The melting point was measured with a Thomas Scientific Model SP11 melting point apparatus.

Materials. Anhydrous ethyl ether purchased from Mallinckrodt, Inc., was used as received. THF was distilled from sodium benzophenone. The $LiAlH_4$, diethyloxalate, $BH_3.SMe_2$ and $BF_3.OEt_2$, and the metal catalysts, were all obtained from Aldrich Chemical Co.

Synthesis of Chiral Terpene-Based Chiral Diamine

Representative procedure: preparation of N^1-((*1R,2R,3R,5S*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-N^2-((*2R,3R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)ethane-1,2-diamine (1c). An oven-dried 50-mL round-bottom flask was charged with isopinocapheyalmine (^{d}IpcNH$_2$, **1a**, 7.7g, 50 mmol). Diethyloxalate (2.659g, 25 mmol) was added slowly with continuous stirring at room temperature. As a result, the reaction mixture became viscous (~25 min) and a white solid product, N, N'-bis(terpenyl)ethylenediamide, formed in a 95% yield. This diamide (20 mmol, 7.2g) was dried, powdered and mixed with THF (4 mL). The boron trifluoride-etherate (5.0 mL, 40 mmol) was added, the mixture was heated under reflux and, as a result, a clear solution formed in 20 min. To this solution, borondimethylsulfide (3.0 mL, 30 mmol, or 90 mmol in THF) was added drop wise over a period of 15 min. The liberated dimethyl sulfide and ether were distilled off as formed and collected. After 20 min, the solvents were removed under suction. Ethyl ether (EE, 20 ml) was added, followed by tetramethylethylenediamide (3.7 5 mL, 25 mmol). The reaction mixture was stirred for 90 min at room temperature. The solid was separated, washed with ethyl ether (2 x 15 mL). The combined EE layers were dried over anhydrous $MgSO_4$. Purification by flash chromatography and removal of the solvent gave the diamine, N, N'-bis(isopinocampheyl)ethylenediamine (^{d}IpcNHCH$_2$CH$_2$NH ^{d}Ipc) in 84% isolate yield, as an oily

mass. $[\alpha]_D^{23}$ = -28.7I. MS m/z 332 (M^+); IR: 2960, 2780, 1475,1 035; ^{1}H NMR ($CDC1_3$): δ 0.96 (s, 6H, -2CH_3); 0.99 (2s, 12H, -4CH_3); 1.41 (dd, 2H, -CH, cyclohexane); 1.42 (dd, 2H, -CH, cyclohexane); 1.49 (dd, 2H, -CH_2, cyclohexane); 1.53 (dd, 2H, -CH_2, cyclohexane); 1.82 (m, 2H, -CH, cyclohexane); 1.83 (m, 2H, -CH, cyclohexane); 2.00 (s, -2H, 2NH); 2.56 (2H, cyclohexane-2H); 2.67 (tt, 4H, -2CH_2-N).

(2) N^1-((*1S,2S,3S,5R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-N^2-((*2S,3S*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)ethane-1,2-diamine (**2c**)

MS m/z 332 (M^+); IR: 2970,2780,1470, 1035; ^{1}H NMR: δ0.96 (s, 6H, -2CH_3); 0.99 (2s, 12H, -4CH_3); 1.41 (dd, 2H, -CH, cyclohexane); 1.42 (dd, 2H, -CH, cyclohexane); 1.24 (dd, 2H, -CH_2, cyclohexane); 1.53 (dd, 2H, -CH_2, cyclohexane); 1.82 (m, 2H, -CH, cyclohexane); 1.83 (m, 2H, -CH, cyclohexane); 2.01 (s, -2H, 2NH); 2.56 (2H, cyclohexane-2H); 2.67 (t, 4H, -2CH_2-N).

(3) N^1,N^2-bis((*1S,2R,3S,6R*)-3,7,7-trimethylbicyclo[4.1.0]heptan-2-yl)ethane-1,2-diamine (3c)

MS m/z 332 (M^+); IR: 2920,1440,1300, 780; ^{1}H NMR: δ0.96 (s, 6H, -2CH_3); 0.99 (2s, 12H, -4CH_3); 1.41 (t, 2H, -2CH, cyclohexane); 1.64 (t, 2H, -2CH, cyclohexane); 1.27 (dd, 2H, -CH_2, cyclohexane); 1.52 (dd, 2H, -CH_2, cyclohexane); 1.83 (m, H, -CH, cyclohexane); 1.84 (m, H, -CH, cyclohexane); 2.01 (s, -2H, 2NH); 2.55 (2H, cyclohexane-2H); 2.67 (t, 4H, -2CH_2-N).

(4) N^1,N^2-bis((*1R,3R,4R,6S*)-4,7,7-trimethylbicyclo[4.1.0]heptan-3-yl)ethane-1,2-diamine (4c)

MS m/z 332 (M^+); IR: 2940,1460,1050, 735; ^{1}H NMR: δ0.96 (s, 6H, -2CH_3); 0.99 (2s, 12H, -4CH_3); 1.41 (t, 4H, -4CH, cyclohexane); 1.64 (t, 2H, -2CH, cyclohexane); 1.24 (dd, 2H, -CH_2, cyclohexane); 1.49 (dd, 2H, -CH_2, cyclohexane); 1.36 (dd, 2H, -CH_2, cyclohexane); 1.61 (dd, 2H, -CH_2, cyclohexane); 1.84 (m, 2H, -2CH, cyclohexane); 1.84 (m, H, -CH, cyclohexane); 2.00 (s, -2H, 2NH); 2.56 (2H, cyclohexane-2H); 2.67 (t, 4H, -2CH_2-N)

(5) N^1-(((*1S,2R,5S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-N^2-(((*2R*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)ethane-1,2-diamine (5c)

MS m/z 332 (M^+); IR: 2930,1515,1275, 740; ^{1}H NMR: δ 0.99 (2s, 12H, -4CH_3); 1.41 (dd, 2H, -2CH, cyclohexane); 1.42 (dd, 2H, -2CH, cyclohexane); 1.24 (dd, 2H, -2CH_2, cyclohexane); 1.49 (dd, 2H, -2CH_2, cyclohexane); 1.35 (dd, 2H, -2CH_2, cyclohexane); 1.45 (dd, 2H, -2CH_2, cyclohexane);); 1.27 (m, 2H, -2CH_2, cyclohexane); 1.52 (m, 2H, -2CH_2, cylohexane); 1.66 (m, 2H, -2CH, cyclohexane); 2.38 (d, 2H, -CH_2-N-cyclohexane); 2.63 (d, 2H, -CH_2-N-cyclohexane); 2.67 (t, 4H, -2CH_2-N); 2.00 (s, -2H, 2NH);

Preparation and analysis of diastereomeric amides

General procedure. The racemic carboxylic acid (0.1 mmol) was added to a vial containing 0.016 g (0.1 mmol) of 1, 1'-Carbonyldiimidazole CDI in 3 mL of dry THF. To this solution, 0.015 g (0.1 mmol) of (-)-4e was added and stirred for 1 h. In those cases where the acid was a solid, the acid (0.1mmol) and CDI (0.1 mmol) were weighed into a vial and dissolved in 3 mL of THF, followed by the addition of (-)-4e. One µL of the THF solution of the resulting diastereomeric amides was injected directly into a gas chromatograph fitted with an appropriate capillary column maintained isothermally at the required temperature. The diastereomeric amides revealed a 1:1 correspondence with the corresponding retention times.

General procedure for the enantioselective nitroaldol reaction. The procedure followed was from the literature.[34] To an oven-dried 10-mL round-bottomed flask, a solution of ligand **3c** (39.0 mg, 0.12 mmol) and $Cu(OAc)_2 \bullet H_2O$ (20.0 mg, 0.10 mmol) in the CH_2Cl_2 solvent (1 mL) was stirred for 6 h at 22 °C. A clear, deep blue solution resulted. The CH_2Cl_2 was removed under reduced pressure, and then propanol (1 mL) and nitromethane (10 mmol) were added and stirred for 30 min. The aldehyde (1mmol) was added and the reaction mixture was stirred at 22 °C until the reaction was complete (upon disappearance of aldehyde by TLC). After evaporation of the solvent, the residue was purified by column chromatography on silica gel (10-15% EtOAc–hexane) to afford the nitroaldol product.

ACKNOWLEDGMENTS

Financial support from the United States Army Research Office, Grant No. (DAAH-94-G-O3L3), is gratefully acknowledged.

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