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Studies directed towards asymmetric synthesis of levobupivacaine

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Abstract—We report herein the first catalytic asymmetric synthesis of levobupivacaine. The key step involves the asymmetric alkylation of *N*-benzylimine glycinamide (**2b**).

Bupivacaine is currently the most widely used, long acting local anaesthetic agent in both surgery and obstetrics. Though it has a good safety record, it can result in fatal cardiotoxicity if given intravenously by mistake or if used in excessive dose by other routes.[1] Bupivacaine exhibits stereoisomerism and recent studies comparing the two enantiomers have shown that *R*-(+)-bupivacaine is 3–4 times more likely to cause cardiovascular toxicity than *S*-(−)-bupivacaine in rabbit hearts.[2] While the *S*-enantiomer of bupivacaine, also known as levobupivacaine (**1**), retains the anaesthetic activity of the racemate, it produces less CNS side-effects. It also has wider application as it has FDA approval for post operative pain management.[3]

Levobupivacaine is obtained mainly by diastereomeric resolution of bupivacaine or its synthetic intermediates like pipecolic acid using D-tartaric acid[4] and/or D-dibenzoyl tartaric acid.[5] An alternative method uses (*S*)-lysine as a synthon.[6] Herein we report a novel and efficient catalytic route to levobupivacaine.

Retrosynthetic analysis of levobupivacaine indicates that it could be synthesized from benzophenone imine glycinamide **2a** (Scheme 1).

Our laboratory has been studying asymmetric alkylation of various imine glycinamides using chiral phase-transfer catalysis.[7] Earlier we found that alkylation of imine glycinamide **2a** using chiral phase-transfer catalysts *O*(9)-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**3**, Fig. 1), gave very low enantioselectivty (20%, Table 1, entry 1).

We explained, through molecular modeling studies, that the reason for this low enantioselectivity was the hydrogen bonding possibility between the NH group of the glycinamide **2a** enolate and the nitrogen atom of the

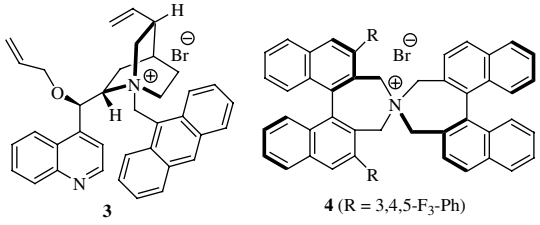
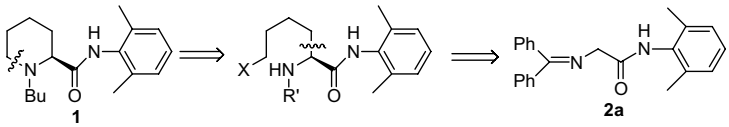


Figure 1.



Scheme 1. Retrosynthetic analysis of levobupivacaine.

Keywords: Chiral phase-transfer catalysts; Asymmetric synthesis; Alkylations.
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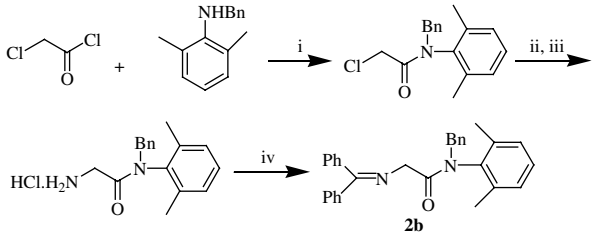
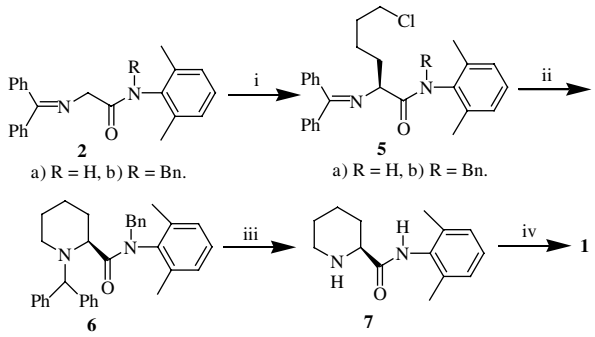
Table 1. Alkylation with 1-chloro-4-iodobutane catalyzed by **3** or **4**

Entry	Substrate (R)	Base[a]	Catalyst	Solvent	Temp (°C)	Time (h)	% ee[b]	Yield[c] (%)
1	**2a** (H)	$CsOH{\cdot}H_2O$	**3** (10 mol%)	CH_2Cl_2	−50	18	20	60, **5a**
2	**2b** (Bn)	$CsOH{\cdot}H_2O$	**3** (10 mol%)	Toluene:CH_2Cl_2 (7:3)	−40	19	64	58, **5b**
3	**2b** (Bn)	$CsOH{\cdot}H_2O$:K_2CO_3 (2:10)	**3** (10 mol%)	Toluene:CH_2Cl_2 (7:3)	−40	25	64	78, **5b**
4	**2a** (H)	$CsOH{\cdot}H_2O$	**4** (1 mol%)	Toluene:CH_2Cl_2 (7:3)	−40	20	43	63, **5a**
5	**2b** (Bn)	$CsOH{\cdot}H_2O$	**4** (1 mol%)	Toluene:CH_2Cl_2 (7:3)	−40	18	86	57, **5b**
6	**2b** (Bn)	$CsOH{\cdot}H_2O$:K_2CO_3 (2:10)	**4** (1 mol%)	Toluene	−40	22	96	85, **5b**

[a] 12 equiv.
[b] Determined using a Chiralcel OD-H column.
[c] Isolated products.



Scheme 2. Reagents and conditions: (i) 0–30 °C, toluene, 4 h, 92%; (ii) NaN_3, acetone, 20 h, 93%; (iii) (a) H_2, Pd–C; (b) Et_2O, HCl (dry), 98%; (iv) $Ph_2C{=}NH$, CH_2Cl_2, rt, 93%.



Scheme 3. Reagents and conditions: (i) $I(CH_2)_4Cl$, **3** or **4**, base, solvent; (ii) (a) $NaCNBH_3$, THF; (b) $NaHCO_3$, NaI, CH_3CN, 92%; (iii) $PdCl_2$, EtOAc–AcOH (4/1), 40 psi, rt, 6 h, 95%; (iv) BuBr, K_2CO_3, 94%.

quinoline nucleus of the catalyst **3**, which stabilized the ion pair leading to formation of the unwanted isomer.[7]

To circumvent the possibility of hydrogen bonding, we modified the substrate by introducing a benzyl group onto the amide nitrogen making it a tertiary amide as shown in Scheme 2. As anticipated, reaction with this substrate **2b** while using the catalyst *O*(9)-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**3**), resulted in an increase in the enantioselectivity of the alkylated product **5b** to 64% (Table 1, entry 2).[8]

We next used (*R*,*R*)-3,4,5-trifluorophenyl-NAS bromide (**4**, Fig. 1),[9] which has a different structural motif, as the chiral phase-transfer catalyst for the asymmetric alkylation of the imine glycinamide **2a**.

Binaphthyl derived catalysts such as (*R*,*R*)-3,4,5-trifluorophenyl-NAS bromide (4) were reported by Maruoka's group.[10] The advantages of using the above catalysts is their higher stability, high asymmetric inductions and the use of only 1 mol% of the catalyst. With the catalyst **4** the asymmetric alkylation of imine glycinamide **2a** gave the alkylated product **5a** in moderately good enantioselectivity (43%) as compared to 20% ee with catalyst **3** (Table 1, entries 1 and 4).

When *N*-benzylated imine glycinamide **2b** was alkylated in the presence of catalyst **4** and $CsOH{\cdot}H_2O$ at −40 °C, the enantiomeric excess of the alkylated product increased steeply to 86% (Table 1). Thus even here, the *N*-benzylated imine glycinamide was found to be more suitable as a substrate for asymmetric alkylation. The use of toluene as solvent gave higher selectivity (98:2), compared to a mixture of solvents such as toluene–dichloromethane (7/3). This indicates that the catalyst **4** exhibits greater asymmetric induction in nonpolar medium. Further, we found that a combination of $CsOH{\cdot}H_2O$ and K_2CO_3 increased the yield of the product from 57% to 85%. Thus the conditions for the synthesis of **5b**, were optimized to obtain a high yield and excellent stereoselectivity.

Next, the alkylated intermediate **5b** was reduced with sodium cyanoborohydride in tetrahydrofuran at 0 °C, followed by cyclization at 60 °C in the presence of $NaHCO_3$ and a catalytic amount of NaI in acetonitrile to afford **6** in 92% yield. Amine deprotection and amide debenzylation was achieved in one-pot by hydrogenolysis using $PdCl_2$ in EtOAc–AcOH (4/1)[11] to give **7** in 95% yield. This was finally alkylated with *n*-butyl bromide to complete the asymmetric synthesis of levobupivacaine (Scheme 3).[12]

In conclusion, we have achieved the first asymmetric synthesis of levobupivacaine in high yield and enantiopurity through a novel catalytic route.

Acknowledgements

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8. Formation of **5b**: under argon, to a cooled (−40 °C) and stirred solution of imine glycinamide **2b** (0.500 g, 1.15 mmol), catalyst **4** (0.011 mmol), $CsOH{\cdot}H_2O$ (0.388 g, 2.31 mmol) and potassium carbonate (1.59 g, 11.5 mmol) in toluene (10 mL) was added 1-chloro-4-iodobutane (0.424 mL, 3.46 mmol) dropwise via a syringe pump. The contents were stirred for 22 h. The reaction mixture was diluted with water (5 mL) and the contents were allowed to warm to rt. The aqueous phase was extracted with dichloromethane (3×25 mL) and the combined organics dried over $MgSO_4$. The extract was concentrated in vacuo and the residue was passed through a short pad of silica gel to afford **5b** as an oil (0.513 g, 85%). $[\alpha]_D^{25}$: +56.53 (*c* 0.5, $CHCl_3$); ee 96%; IR (KBr): 3053, 2958, 2932, 2854, 1655, 1444, 1400, 1312, 1286, 1254, 1233, 1188, 1079, 772; ^{1}H NMR δ ($CDCl_3$, 300 MHz): 1.02–1.07 (m, 2H), 1.31 (m, 1H), 1.49 (s, 3H), 1.48 (m, 2H), 1.92 (s, 3H), 2.3 (m, 1H), 3.34 (t, $J = 6.61$ Hz, 2H), 3.64 (dd, $J = 2.79$ Hz, 7.02, 1H), 4.22 (d, $J = 13.49$ Hz, 1H), 5.34 (d, $J = 13.49$ Hz, 1H), 6.18 (d, $J = 6.93$ Hz, 2H), 6.98 (t, $J = 6.69$ Hz, 2H), 7.12–7.55 (m, 14H); ^{13}C NMR δ ($CDCl_3$, 75 MHz): 17.8, 18.2, 23.7, 32.2, 32.5, 44.5, 52.6, 63.4, 127.1, 127.5, 127.8, 128.0, 128.2, 128.4, 128.6, 129.3, 130.1, 130.2, 135.2, 137.1, 137.0, 137.6, 138.9, 139.1, 169.1, 172.0; MS (APCI): *m/z* (%) 525 (M^+ +2, 42), 523 (100). HPLC conditions [Chiralcel OD-H, R_T 8.9 min for the *S*-enantiomer, 11.40 for the *R*-enantiomer isopropanol–hexane (15/85), flow rate: 0.5 mL/min, $\lambda = 254$ nm].
9. [(*R*)-3,3′-di(3″,4″,5″-trifluorophenyl)-1,1′-binaphthyl-2,2′-dimethylammonium]spiro[(*R*)-1,1′-binaphthyl-2,2′-dimethyl amine]bromide.
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