Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3963–3966

TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of diarylmethylamines: preparation of selective opioid delta receptor ligands

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Received 2 October 1998; accepted 6 October 1998

Abstract

Two different methods were used for the construction of optically active diarylmethylamines. Diastereoselective alkylation on an aldimine/oxazolidine **2a/2b** derived from (*R*)/(*S*)-phenylglycinol or enantioselective reduction of 4-[η^6-chromium tricarbonylbenzoyl] bromobenzene using chiral oxazoborolidine followed by amine introduction to furnish optically active diarylmethylamines.

Diarylmethylamine moieties are part of many pharmacologically active compounds including the recently described (+)BW373U86 as a delta receptor agonist.[1] Our recent interest in developing selective non-peptidic delta receptor agonists prompted us to search for a simple and efficient methodology for the preparation of chiral diarylmethylamines. Numerous methods are available for the asymmetric synthesis of α-arylalkylamines[2] but few methods are available for the synthesis of diarylmethylamines in optically pure form.[3] Resolution using (+)- or (−)-tartaric acid salt has been previously used on diarylmethylamines.[4] We now report an efficient method for the asymmetric synthesis of diarylmethylamines in optically pure form based on diastereoselective addition of phenyllithium to aldimine/oxazolidine **2a/2b**. A second approach consists of chiral reduction of benzophenone chromium tricarbonyl complex followed by amine introduction.[5]

Chiral 1,2-amino alcohols have been extensively used as chiral auxiliaries in asymmetric synthesis.[6] Consequently, the aldimine/oxazolidine **2a/2b**[7] were prepared in quantitative yield from 4-bromobenzaldehyde **1** using either (*R*)- or (*S*)-phenylglycinol in THF in the presence of anhydrous magnesium sulfate at room temperature (Scheme 1).

Several parameters were evaluated for the alkylation reaction in order to optimize the yield (Table 1). Alkylation reactions were performed on aldimine/oxazolidine **2a/2b** prepared using (*R*)-phenylglycinol. The best addition conditions found were when phenyllithium was used as nucleophile in anhydrous THF in the presence of HMPA (10% v/v) at 0°C for 30 min to afford, after purification by flash

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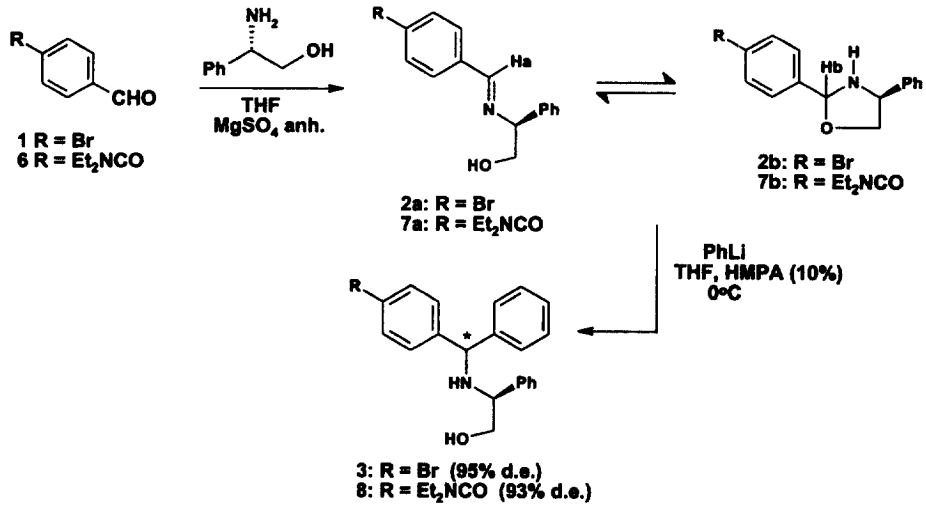
0957-4166/98/$ - see front matter
PII: S0957-4166(98)00419-4



Scheme 1.

chromatography, 71% yield of the coupling product **3**.[8] Analysis by chiral HPLC revealed that compound **3** was generated with 95% de[9] The use of lower or higher temperatures or varying the amounts of alkylating agent led to reduced yields. For example, the same reaction performed at room temperature without additives does not change the de (95% de) but lowers the yield (see Table 1). Other nucleophiles were also investigated, such as phenylmagnesium bromide or phenylcerium dichloride[10] which gave lower yields.

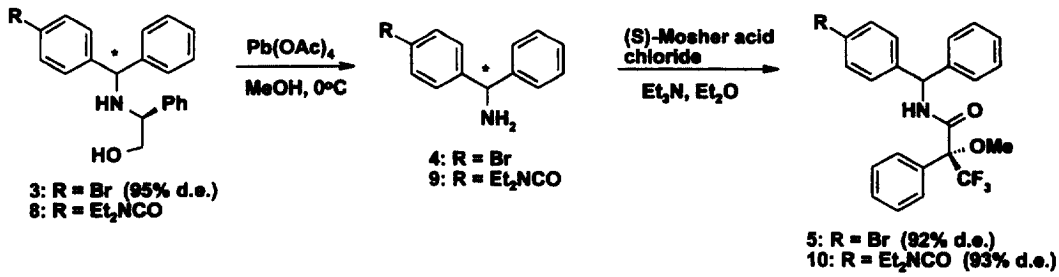
Table 1
Addition of organolithium reagent to aldimine/oxazolidine **2a/2b** in dry THF

Reagent	Additive	Temperature (Reaction Time)	Yield after purification
PhLi	10% (v/v) HMPA	0°C (30 min)	71%
PhLi		-78°C (10 min)	16%
PhLi		-40°C (10 min)	16%
PhLi		0°C (10 min)	45%
PhLi		25°C (10 min)	32%
PhMgBr		reflux (16 hrs.)	32%
PhLi	$CeCl_3$	0°C (30 min)	40%

Cleavage of the chiral auxiliary was accomplished using lead tetraacetate[11] in methanol at 0°C followed by acidic treatment (HCl conc., CH_2Cl_2) to give diarylmethylamine **4** in 60% yield[12] (Scheme 2). Oxidative cleavage of **3** using sodium metaperiodate did not improve the yield of compound **4**. The diarylmethylamine **4** was derivatized to the Mosher amide **5** and found to have 92% de after GC–MS analysis.[13] The absolute stereochemistry (*R*) in **4** is obtained by using aldimine/oxazolidine **2a/2b** derived from (*R*)-phenylglycinol.[14]

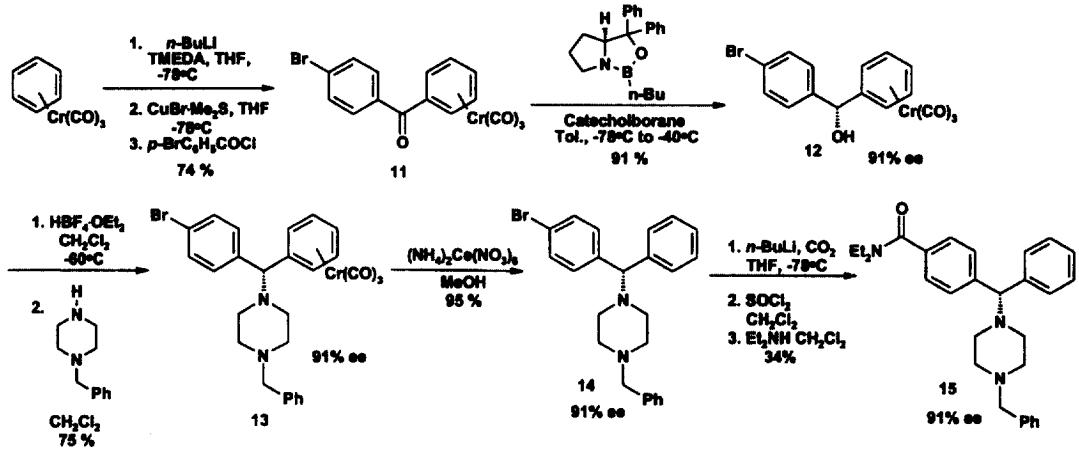
The same sequence of reaction has been effected starting from aldehyde **6**.[15] Alkylation of **7a/7b** (from (*R*)-phenylglycinol) under the same conditions as for **2a/2b** gave 40% yield of the amide **8** with 93% de. Cleavage of the chiral auxiliary and derivatization to the Mosher amide gave compound **10** with 93% de based on GC–MS analysis.[16]

The second approach uses chiral reduction of the 4-bromobenzophenone chromium tricarbonyl complex developed by Corey,[5] followed by N-benzylpiperazine introduction. Thus compound **12** (Scheme 3) obtained with 91% ee from chiral oxazaborolidine-catalyzed reduction was treated with tetrafluoroboric



Scheme 2.

acid followed by addition of N-benzyl piperazine to provide compound **13** in 91% ee.[17] Decomplexation using ammonium cerium(IV) nitrate[18] in methanol gave 95% yield of **14** without loss of enantiomeric purity.[19] Finally, the selective opioid delta receptor ligand **15** was obtained first by transmetallation in dry THF at −78°C with n-BuLi, followed by bubbling with carbon dioxide. The resulting acid was treated with thionyl chloride followed by the addition of diethylamine to give in 34% overall yield, compound **15** in 91% ee.[20]



Scheme 3.

In vitro binding assays of **15** using cloned human delta, mu and kappa opioid receptors gave an IC_{50} of 1.2 nM, 2400 nM and 5500 nM, respectively, demonstrating that optically active substituted diarylmethylamines such as **15** are highly selective delta receptor ligands. Futhermore, the enantiomer of **15** (with (*R*) stereochemistry derived from (*R*)-diphenyl-2-pyrrolidinemethanol chiral reduction) has an IC_{50} of 17 nM on human delta receptor showing a better affinity for the (*S*)-isomer.

In conclusion, we have demonstrated that two different approaches can allow the preparation of optically active substituted diarylmethylamines which are part of very active and selective delta opioid receptor ligands. Further investigations into the development of selective delta receptor agonists are underway.

Acknowledgements

C.B. is grateful to the Natural Sciences and Engineering Research Council of Canada for an Undergraduate Student Research Award.

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7. The equilibrium mixture of aldimine/oxazolidine is solvent dependent. A ratio of 9:1 in favor of the aldimine **7a** is observed in deuterated chloroform while a ratio of 20:1 is observed in THF-d_8. The ratios were obtained from ^{1}H NMR integration of the corresponding aldimine H_a and oxazoline proton H_b.
8. Typical procedure for the alkylation of aldimine/oxazolidine using phenyllithium. To a solution of imine **2** (125 mg, 0.4 mmol) in dry THF (3 ml) was added HMPA (0.3 ml) followed at 0°C with PhLi (500 μl, 0.9 mmol) under nitrogen over a period of 1 min. The reaction mixture was stirred at 0°C for 30 min then quenched with aqueous NH_4Cl. The resulting mixture was extracted with ethyl acetate (5×) and dried over $MgSO_4$. Purification using flash chromatography (hexane:ethyl acetate 7:3) afforded 71% of **3**. ^{1}H NMR (400 MHz, $CDCl_3$); δ: 2.05 (bs, 2H); 3.65 (m, 3H); 4.66 (s, 1H); 7.16–7.50 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$); δ: 61.58, 62.87, 66.99, 127.30, 127.44, 127.58, 127.79, 128.77, 128.90, 131.50.
9. Compound **3**: HPLC (Chiracel OD, 10% i-PrOH in hexanes, 1 ml/min, λ=215 nm) >95% de.
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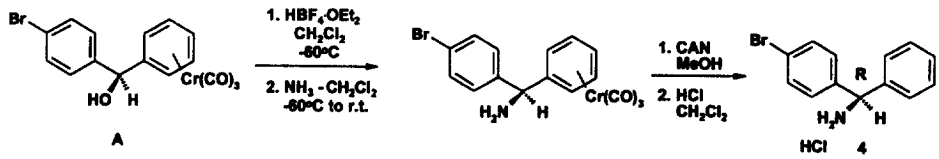
12. Compound **4** derived from (*R*)-phenylglycinol gave $[\alpha]_D^{25}$ −2.3 (c 1.0, MeOH) and compound **4** derived from (*S*)-phenylglycinol gave $[\alpha]_D^{25}$+2.3 (c 1.0, MeOH).
13. Compound **5**: GC–MS (method 200-280, column HP-5, 1 ml/min) 92% de.
14. A similar negative optical rotation value for compound **4** was obtained using compound **A**[5] and the following synthetic scheme:



15. The aldehyde **6** was prepared by heating 4-carboxybenzaldehyde with one equivalent of thionyl chloride at 50°C in a mixture of CH_2Cl_2:DMF 9:1 followed by the addition of diethylamine at 0°C. This procedure gave 90% yield of aldehyde **6**.
16. Compound **10**: GC–MS (method 200-280, column HP-5, 1 ml/min) 93% de.
17. Compound **13**: HPLC (Chiracel AD, 20% i-PrOH in hexanes, 1 ml/min, λ=215 nm) 91% de. $[\alpha]_D^{25}$ +90.8 (c 1.0, CH_2Cl_2).
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19. Compound **14**: HPLC (Chiralcel AD, 1% i-PrOH in hexanes, 1 ml/min, λ=215 nm) 91% ee. $[\alpha]_D^{25}$ +6.37 (c 1.0, CH_2Cl_2).
20. Compound **15**: HPLC (Chiralcel AD, 20% i-PrOH in hexanes, 1 ml/min, λ=215 nm) 91% ee. $[\alpha]_D^{25}$ +2.52 (c 2.02, CH_2Cl_2).