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A Practical and Efficient Route for the Highly Enantioselective Synthesis of Mexiletine Analogues and Novel β-Thiophenoxy and Pyridyl Ethers

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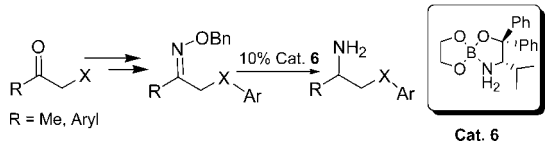
Received June 3, 2008



A practical and efficient procedure for the enantioselective synthesis of mexiletine analogues with use of 10% of spiroborate ester **6** as chirality transfer agent is presented. A variety of mexiletine analogues were prepared in good yield with excellent enantioselectivities (91−97% ee) from readily available starting materials. The developed methodology was also successfully applied for the synthesis of novel β-amino ethers containing thiophenyl and pyridyl fragments.

Mexiletine (Figure 1) is an effective sodium channel blocker used as an antiarrhythmic and analgesic oral drug.[1,2] Structure−activity studies in vivo[3] and in vitro[4] of pharmacologically active mexiletine indicate that its (−)-(*R*) enantiomer binds preferentially to the cardiac sodium channels. In addition, (−)-(*R*)-mexiletine is also more active than (+)-(*S*)-mexiletine on native skeletal muscular fibers.[1b,5] The use of mexiletine as a racemate in the treatment of neuromuscular disorders is limited due to its possible side effects.[6] The optically active mexiletine analogue (*R*)-**2** (Figure 1) is 27-fold more potent than (*R*)-

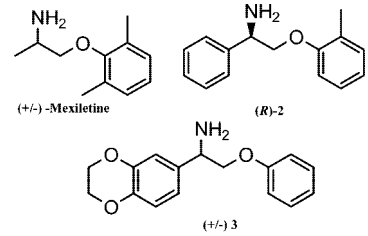


FIGURE 1. Mexiletine and examples of its more potent analogues.

mexiletine in producing a tonic block and 23-fold more potent in condition of high frequency of stimulation (phasic block).[6] Recently, racemate **3** was established as a novel potent blocker of voltage-gated K^+ channels by using structure-based virtual screening in conjunction with electrophysiological assays in rat hippocampal neurons.[7]

The preparation of mexiletine enantiomers has been reported previously by several groups. Generally, the methods involved resolution of racemic intermediates,[8] enzymatic hydrolysis of an *N*-acyl derivative,[9] or using a stereospecific, four-step procedure, in 7.2% overall yield.[8b] Flippin and co-workers[10] reported a convenient procedure for the preparation of stereoisomers of mexiletine, but the scope of products was limited by the availability of chiral substrates and expensive chromium tricarbonyl complexes of aryl halides: hence, some amines were provided in the racemate form. Although Franchini's group[6] synthesized the stereoisomers of mexiletine analogues, the use of 2-phenyloxirane as chiral source restricted the range of mexiletine analogues. Furthermore, the procedure is also controlled by the regiospecificity of the ring-opening reaction,[11] and the possible racemization of the benzylic carbon by the substitution of the alkoxy group by the amine.[12] Hence, a practical and efficient route for the synthesis of highly enantiopure mexiletine analogues is highly desirable.

The asymmetric reduction of oxime ethers with borane-based catalysts offers a facile and direct approach to obtain enantioenriched primary amines; however, more than an stoichiometric amount of in situ prepared oxazaborolidine has been employed to obtain a high degree of enantioselectivity.[13a–n] Our recent success in the borane-mediated asymmetric reduction of *O*-benzyl oximes, using a truly catalytic amount of the air and moisture stable spiroborate esters indicated in Figure 2,[13o,p]

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10.1021/jo801181d CCC: $40.75
Published on Web 08/09/2008

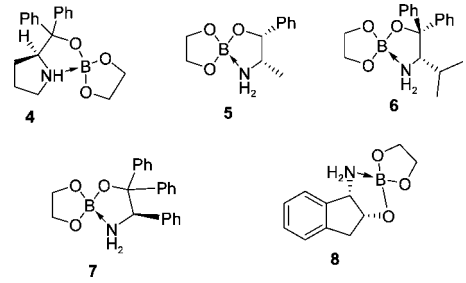
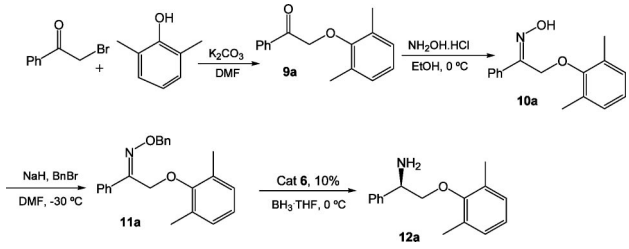


FIGURE 2. Spiroborate esters derived from nonracemic aminoalcohols and ethylene glycol.

SCHEME 1. Synthetic Route to 12a

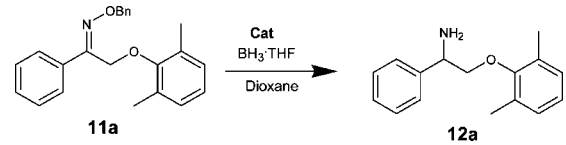


prompted us to investigate their application for the enantioselective synthesis of β-amino ethers of biological interest.

The synthesis of **12a**, as outlined in Scheme 1, was selected as a model protocol. The aryloxy acetophenone **9a** was prepared from the 2-chloro- or 2-bromoacetophenone with different bases (NaOH, NaH, and K_2CO_3). After optimization, it was found that treatment of 2-bromoacetophenone with K_2CO_3 (1.5 equiv) and 2,6-dimethylphenol (1.5 equiv) in DMF at room temperature for 24 h gave the desired ketone in 81% yield. The oxime was then prepared by addition of $NH_2OH\cdot HCl$ and pyridine at 0 °C.[14] Since the enantiofacial selectivity in the reduction of C=N bonds depends not only on the chirality's transfer agent but also on the *E*/*Z* isomeric purity,[13] the main (*Z*) isomer was easily obtained by simple recrystallization. The pure (*Z*)-benzyl oxime ether **11a** was obtained in high yield from (*Z*)-oxime with use of NaH and benzyl bromide in DMF at −30 °C.

Initially, we screened the spiroborates presented in Figure 2 for the reduction of *O*-benzyl oxime **11a.** The reactivity of catalysts **5**, **7**, and **8** was rather low at 0 °C. The complete conversion was achieved at room temperature (22 °C) affording 57%, 81%, and 82% ee, respectively, (entries 2, 5, and 6, Table 1). Spiroborate ester **6** provided the best enantioselectivities (Table 1, entries 3 and 4).

TABLE 1. Screening of Different Catalysts for the Reduction of 11a



entry	cat.	temp (°C)	cat. (equiv)	yield (%)	ee (%)[a]
1	**4**	0	0.10	87	70(*R*)
2	**5**	22	0.10	40	57(*R*)
3	**6**	0	0.10	84	97(*R*)
4	**6**	0	0.25	92	99(*R*)
5	**7**	22	0.10	80	81(*S*)
6	**8**	22	0.10	76	82(*S*)

[a] Determined by chiral HPLC (Chiralcel OD-H column) of acetyl derivatives.

Under the optimized conditions, a variety of *O*-benzyl oximes were prepared and reduced in dioxane employing 10% spiroborate ester **6** and 4 equiv of $BH_3\cdot$THF at 0 °C. Table 2 illustrates the results for various *O*-benzyl oximes that were reduced to the enantiopure amines in 91−97% ee in good to excellent isolated yield. Noteworthy, (*S*)-mexiletine was prepared in 94% ee and 84% chemical yield (entry 2), illustrating, clearly, the catalyst ability to differentiate between the methyl and the alkoxy moiety in the borane reduction. Generally, substituents on each aryl group influenced slightly the enantioselectivities (entries 3−11). For example, *O*-benzyl oximes bearing both electron-withdrawing and electron-donating aryl groups provided higher enantioselectivities (entry 3 and 6). The absolute configuration of products was determined by comparing the optical rotations with the corresponding known compounds.

Our current efforts in the design of novel neuronal nicotinic acetylcholine receptors (nAChRs) agonists led us to target enantiopure arylamino ethers as therapeutic agents for the treatment of CNS and peripheral nervous system disorders.[15,16] Within the past ten years, a series of selective agonist of human neuronal nAChRs, such as Epibatidine (**13**),[17] A-85380 (**14**),[18] ABT-594 (**15**),[19] A-84543 (**16**),[20] and SIB-1553A (**17**)[21] (Figure

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(16) Karlin, A. *Nat. Rev. Neurosci.* **2002**, *3*, 102–114.

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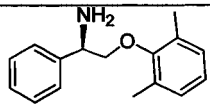
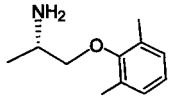
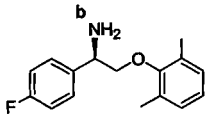
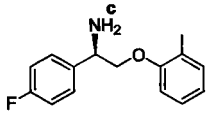
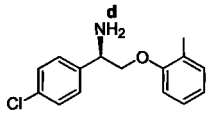
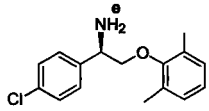
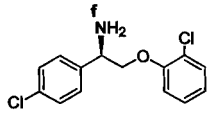
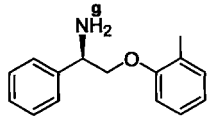
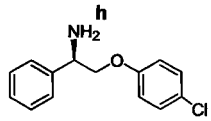
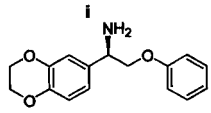
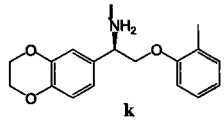
TABLE 2. Asymmetric Reduction of Representative Oxime Benzyl Ethers with 0.1 equiv of Catalyst 6[a,b,c,d]

entry	12	$[\alpha]^{20}_D$ [a]	yield (%)	ee (%)[b]
1	 **a**	-28 (1.2)	84	97[c]
2		-4 (1.6)	83	94[d]
3	 **b**	-19 (1.9)	89	97
4	 **c**	-47 (1.5)	82	92
5	 **d**	-36 (1.2)	73	94
6	 **e**	-17 (1.0)	85	95[c]
7	 **f**	-43 (1.2)	74	92
8	 **g**	-47 (2.4)	91	93[c]
9	 **h**	-38 (1.2)	89	93
10	 **i**	-36 (1.0)	83	94
11	 **k**	-25 (1.2)	86	91

[a] $CHCl_3$ as solvent. [b] Determined by amine on chiral HPLC (Chiralcel OD-H column). [c] Determined by acetyl derivative on Chiralcel OD-H column. [d] Determined by GC of acetyl derivative on Chiral column (CP-Chirasil-DexCB).

3), has been found. Additionally, compounds containing fluorine are widely applied in the fields of agricultural, medicinal, and material chemistry,[22] especially fluorinated aromatics which are widely found in many modern drugs.

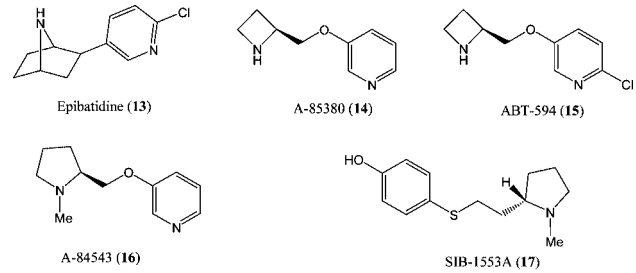
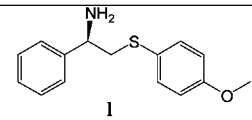
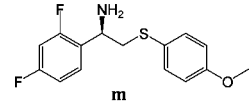
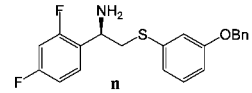
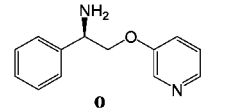
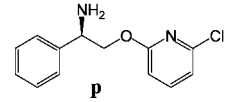


FIGURE 3. Neuronal nicotinic acetylcholine receptors agonist.

TABLE 3. Asymmetric Synthesis of Novel Amines with 0.1 equiv of Catalyst 6[a,b,c]

entry	12	$[\alpha]^{20}_D$ [a]	yield (%)	ee (%)[b]
1	 **l**	+35 (1.3)	86	96
2	 **m**	+26 (1.2)	72	94
3	 **n**	+28 (1.5)	72	97
4		-36 (2.1)	83	97[c]
5	 **o** **p**	-23 (3.5)	84	96

[a] $CHCl_3$ as solvent. [b] Determined by chiral HPLC (Chiralcel OD-H column). [c] Determined by ^{31}P NMR analysis of the phosphonate derivative.[23]

On the basis of related structural features present in nAChRs agonists, highly enantiopure benzylic primary amines or fluorinated aryl groups with β-thiophenoxy or pyridyloxy groups of biological significance were prepared by using the previous procedure in good yield with excellent enantioselectivity (94−97% ee), as shown in Table 3.

In summary, the preparation of chiral mexiletine analogues, in addition to novel β-thiophenoxy and pyridyl ethers, was achieved by a facile four-step synthesis in good yield and

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excellent enantioselectivities. The highly enantioselective reduction of benzyloxime α-ethers, efficiently catalyzed by 10% of the novel spiroborate ester **6**, is applicable for a wide range of other bioactive compounds. Considering the convenience and efficiency of this route, this methodology should open new avenues for further research.

Experimental Section

General Procedure for the Preparation of Ketones: 2-(2, 6-Dimethylphenoxy)-1-phenylethanone[3] (9a). To a 100 mL round-bottomed flask charged with a magnetic stirrer, 2-bromoacetophenone (1.99 g, 10 mmol), 2,6-dimethylphenol (15 mmol), and K_2CO_3 (15 mmol) was added 20 mL of DMF and the resulting mixture was stirred for 24 h at room temperature. The reaction was quenched with 50 mL of H_2O and the aqueous phase was extracted with diethyl ether (3 × 40 mL). The combined organic phases were washed with 2 N NaOH (2 × 20 mL) to remove the excess of phenol, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel/hexane:ethyl acetate (5:1), as a yellow solid: mp 57−59 °C (lit.[6] mp 60−61 °C); yield 81% (1.94 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 6H), 5.02 (s, 2H), 6.89 (m, 1H), 6.97 (m, 2H), 7.41 (m, 2H), 7.52 (m, 1H), 7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 74.5, 124.5, 127.9, 128.8, 129.0, 130.8, 133.7, 134.7, 155.7, 194.1; GC-MS *m*/*z* 240.2 (M^+).

General Procedure for the Asymmetric Reduction of *O*-Benzyl Oximes: (*R*)-2-(2,6-Dimethylphenoxy)-1-phenylethylamine (12a). To a 50 mL reaction tube with catalyst **6** (33 mg, 0.1 mmol) under N_2 was added 10 mL of anhydrous dioxane and 4 mL of BH_3·THF (1 M in THF) in one portion. After the mixture was stirred for 1 h at room temperature, the clear solution was cooled at 0 °C and the benzyl oxime (1 mmol) in 5 mL of dioxane was added dropwise during 1 h with a syringe pump. The resulting mixture was stirred at 0 °C until the conversion was complete in about 48 h. The reaction was quenched with 6 N HCl and basified with 6 N NaOH. The reaction mixture was extracted with ether and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography and purified by silica gel/hexane:ethyl acetate (2:1) column chromatography as a colorless oil: yield 84% (101 mg); 97% ee; $[\alpha]_D^{20}$ −28.5 (*c* 1.2, $CHCl_3$) [lit[6] −14 (*c* 2, MeOH)], % ee not given; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (s, 2H), 2.33 (s, 6H), 3.93 (m, 2H), 4.51 (m, 1H), 6.99 (m, 1H), 7.07 (m, 2H), 7.35−7.44 (m, 3H), 7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 56.4, 77.8, 124.0, 126.0, 127.6, 128.5, 128.9, 130.9, 142.3, 155.5; GC-MS *m*/*z* 241.1 (M^+). The Enantiomeric excess was determined by HPLC for the acetyl derivative with use of a Chiralcel OD-H column (9:1 hexane:2-propanol), 0.8 mL/min, 254 nm, minor enantiomer t_R = 11.3 min, major enantiomer t_R = 16.2 min.

Acknowledgment. Financial support by the National Institutes of Health through their MBRS (GM 08216) and INBRE (NC P20 RR-016470) grants is greatly appreciated. We express our special gratitude to the NSF-MRI (01-07) and NIH-MBRS programs to have made possible the acquisition of a 400 MHz NMR spectrometer.

Supporting Information Available: Experimental procedures, analytical data, and all spectra for **9a**−**p**, **10a**−**p**, **11a**−**p**, **12a**−**p**,and derivatives and enantiomeric determination for **12a**−**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801181D