ORGANIC LETTERS

2010
Vol. 12, No. 12
2690−2693

Enantioselective Synthesis of 1-Aryltetrahydroisoquinolines

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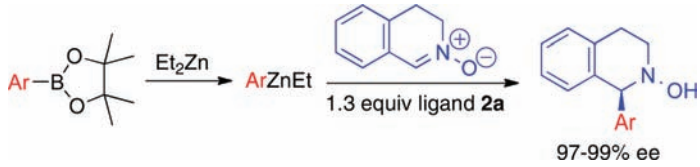
Received February 21, 2010

ABSTRACT



1-Aryltetrahydroisoquinolines (1-arylTHIQs) are important structural motifs in many alkaloids and biologically active compounds. Ligand 2a promotes the enantioselective addition of arylzinc reagents to 3,4-dihydroisoquinoline *N*-oxide to yield (*S*)-1-arylTHIQs in 97−99% ee. Pinacol arylboronic esters are the optimal precursors for the arylzinc reagents. This method is applied to the enantioselective synthesis of Solifenacin.

1,2,3,4-Tetrahydroisoquinolines (THIQ) are an important structural motif in many alkaloids, and they display significant pharmacological properties.[1] Since THIQ alkaloids often incorporate a stereocenter at the 1-position with an attached aryl substituent, this substructure has been the target for a number of asymmetric syntheses.[2] Several 1-arylTHIQs are shown in Figure 1. Compounds **1a**−**e** are antagonists of the dopamine D_1 (**1c**),[3] NMDA (**1a**, **b**, **d**),[4] and AMPA (**1e**)[5] receptors that mediate dopamine and glutamate neurotransmission in the central nervous system. Overactivation of these receptors can lead to psychiatric disorders, neuronal damage, and cell death. Antagonism of the receptors modulates excitatory synaptic neurotransmission and reduces neurotoxicity. The 1-arylTHIQ antagonists have been investigated as anticonvulsants and neuroprotective agents for the treatment of neurodegenerative diseases including ischemia, epilepsy, Huntington's, Alzheimer's, and Parkinson's diseases. Other 1-arylTHIQs possess antibacterial[6] and anti-HIV activities.[7] Compound **1f** (Solifenacin, YM-905) is a competitive antagonist that prevents binding of acetylcholine

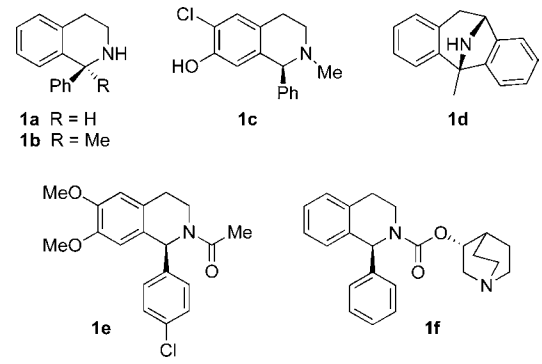


Figure 1. Bioactive 1-aryltetrahydroisoquinolines.

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10.1021/ol1004356
Published on Web 05/18/2010

to the human muscarinic acetylcholine receptor and reduces contractions of the bladder muscles.[8] The succinate salt of **1f**, marketed under the trade name Vesicare, is an FDA approved treatment for overactive bladder.

Three main strategies have been developed for the enantioselective syntheses of THIQs. The most common approach involves a Bischler−Napieralski cyclization followed by reduction of the resulting imine with a chiral hydride reducing agent or catalytic hydrogenation in the presence of a chiral catalyst.[9] A second strategy employs asymmetric Pictet−Spengler condensations.[10] Finally, chiral THIQs have been prepared by the introduction of nucleophiles or electrophiles to the 1-position of isoquinoline derivatives.[11] Herein, we report a direct and efficient method to access chiral 1-arylTHIQs by the asymmetric addition of arylzinc reagents to 3,4-dihydroisoquinoline *N*-oxide. In the optimized procedure, we use pinacol esters of boronic acids as precursors of the arylzinc reagents. Excellent enantioselectivities (97%−99% ee) are achieved with a range of arylzinc reagents using a chiral *N*-Boc ethylenediamine ligand. We demonstrate the utility of this method by performing an enantioselective synthesis of Solifenacin.

We selected arylboroxines as the precursors to arylzinc reagents since they transmetallate smoothly with Et_2Zn to give predominantly the mixed arylethylzinc species (Figure 2, eq 2).[12] In addition, a variety of boroxines can be prepared by dehydrating commercially available boronic acids. The modular, chiral ethylenediamine ligands (Figure 2, eq 1) are derived from amino acids and incorporate tertiary amine, amino acid side chain, and *N*-carbamoyl substituents that can be tuned to optimize reactivity and stereoselectivity.[11i,13]

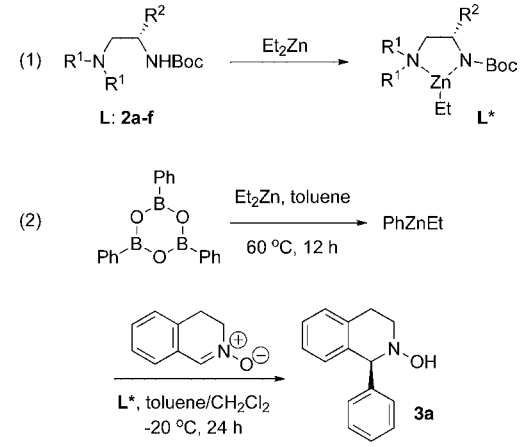

Figure 2. (1) Formation of the active catalyst **L*** by reaction of ligands **2a**−**f** with Et_2Zn. (2) **L*** promoted enantioselective addition of PhZnEt to 3,4-dihydroisoquinoline *N*-oxide.

Following deprotonation, the two nitrogen atoms provide a bidentate coordination site for zinc. Initial studies indicated that toluene was the best solvent for the arylation of 3,4-dihydroisoquinoline *N*-oxide. We settled on a mixed solvent of 2:1 toluene:CH_2Cl_2, which behaved similarly to pure toluene but gave improved solubility of the boroxines.

Table 1 shows the effect of the ligand structure on the yield and enantioselectivity of the reaction using phenylboroxine as the arylzinc precursor. All of the reactions give good yields of compound **3a**. In terms of stereoselectivity, β-branched amino acid side chains such as the *sec*-butyl group of Ile or the isopropyl group of Val are preferred over ligands with sterically demanding but non-β-branched side chains such as Cys(Trt). In addition, ligands with cyclic tertiary amines (entries 1 and 5) are preferred over noncyclic analogues (entry 6). We selected ligand **2a** for further study.

Ligand **2a** promotes the addition of a variety of arylzinc reagents, derived from the corresponding boroxines, to 3,4-dihydroisoquinoline *N*-oxide to give the chiral hydroxylamines **3a**−**h** (Table 2). Yields for the reactions range from 83% to 97%. Enantioselectivities for most of the substrates are good and range from 91% to 97% ee (entries 1−6). However, for two of the substrates (entries 7 and 8) we observed somewhat lower stereoselectivities. All of the other

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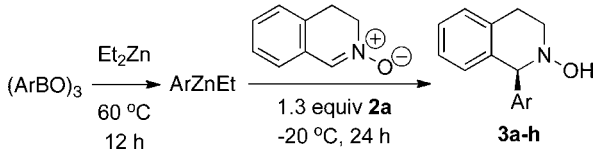
Table 1. Effect of Ligand Structure on the Addition of PhZnEt to 3,4-Dihydroisoquinoline *N*-Oxide to Yield **3a**[a]

entry	ligand	R^1	R^2 = side chain of	yield (%)[b]	ee (%)[c]
1	**2a**	$-(CH_2)_2O(CH_2)_2-$	Ile	92	92
2	**2b**	$-(CH_2)_2O(CH_2)_2-$	Val	93	90
3	**2c**	$-(CH_2)_2O(CH_2)_2-$	Chg[d]	94	86
4	**2d**	$-(CH_2)_2O(CH_2)_2-$	Cys(Trt)	95	84
5	**2e**	$-(CH_2)_5-$	Ile	90	89
6	**2f**	Et	Ile	80	73

[a] Reaction conditions: (1) $(ArBO)_3$ (0.47 molar equiv), Et_2Zn (4.2 equiv), 60 °C, 12 h; (2) **2a**−**f** (1.3 equiv), 2:1 toluene:CH_2Cl_2, −20 °C, 24 h. Syntheses of these ligands have been reported in references 11i and 13. [b] Yield of purified product. [c] Determined by chiral HPLC. [d] Cyclohexylglycine.

Table 2. Conversion of Boroxines to Arylzinc Reagents, Followed by Enantioselective Addition to 3,4-Tetrahydroisoquinoline *N*-Oxide, Promoted by Ligand **2a**[a]



entry	Ar	product	yield (%)[b]	ee (%)[c]
1	Ph	**3a**	92	92
2	4-Me-C_6H_4	**3b**	94	91
3	2-Me-C_6H_4	**3c**	85	97
4	4-F-C_6H_4	**3d**	97	93
5	4-Cl-C_6H_4	**3e**	87	93
6	4-Br-C_6H_4	**3f**	93	91
7[d]	2-Br-C_6H_4	**3g**	83	84
8[d]	2-naphthyl	**3h**	90	83

[a] Reaction conditions: (1) $(ArBO)_3$ (0.47 molar equiv), Et_2Zn (4.2 equiv), 60 °C, 12 h; (2) **2a** (1.3 equiv), 2:1 toluene:CH_2Cl_2, −20 °C, 24 h. [b] Yield of purified product. [c] Determined by chiral HPLC. [d] A small amount of precipitate formed in these reactions.

substrates gave solutions that were homogeneous at both the beginning and end of the reactions. In contrast, these two reactions contained a precipitate in the product solutions. This nonhomogeneous reaction mixture may be one factor leading to the lower enantioselectivities (84% ee and 83% ee, respectively) for entries 7 and 8.

Despite the encouraging results we obtained using arylboroxines, we encountered several difficulties that limited the scope of this procedure. First, it was difficult to prepare pure boroxines by dehydration of arylboronic acids that contained strong electron-withdrawing groups or very bulky substituents.[14] Second, a number of the arylboroxines had low solubilities in toluene and CH_2Cl_2. This solubility problem represented a significant limitation to the reaction.

These limitations prompted us to explore pinacol arylboronic esters as alternate precursors to arylzinc reagents. These derivatives are more soluble in nonpolar organic solvents than boroxines but are not commonly used to generate arylzinc species.[12a,g,h] Comparison of reactions using phenylzinc reagents derived from phenylboroxine (Table 2, entry 1) and pinacolyl phenylboronic ester (Table 3, entry 1) shows that they give the same yield of the product **3a**, but the reaction using the boronic ester gives a somewhat higher enantioselectivity (92% vs 98% ee).

Entries 1−11 in Table 3 highlight the variety of *N*-hydroxy 1-arylTHIQs that can be prepared with excellent stereoselectivities (97−99% ee) starting from boronic esters. The reaction works well with substrates that contain electron-donating (entries 2, 5, 10, and 11) or electron-withdrawing groups (entries 3 and 6). It also tolerates a larger naphthyl group (entry 4) and heteroaromatic rings that contain oxygen, sulfur, or nitrogen atoms (entries 7−9). Ether, ester, carbamate, and carbonate functional groups are all compatible with the reaction conditions.

The yield for six of the eleven substrates that we examined was 90% or better (entries 1, 3, 4, and 6−8). In contrast, substrates with electron-rich aromatic rings typically gave lower yields. For several of these reactions (entries 9−11) we isolated a significant amount of *N*-hydroxy 1-ethylTHIQ from the reaction mixture. This byproduct is formed by transfer of an ethyl group from the ArZnEt reagent or excess Et_2Zn that is present in the reaction mixture. Two potential explanations for the reduced yields we observe with electron-rich substrates are: (1) incomplete boron/zinc transmetalation caused by low reactivity of the boronic ester precursor with Et_2Zn or (2) slow transfer of the aryl group from the ArZnEt reagent to the nitrone. In either case, transfer of an ethyl group could become competitive with the desired aryl transfer and result in formation of significant amounts of *N*-hydroxy 1-ethylTHIQ.

We also examined several of the substrates using 0.2 equiv of the chiral ligand **2a**. Reducing the ligand loading resulted in modest to substantial decreases in enantioselectivity (Table 3, entries 12−16). Products **3a** and **3b** were still produced with good stereoselectivity (91% and 92% ee, respectively). However, the ee of the 4-chlorophenyl derivative **3e** was reduced to 67%. The rate of the uncatalyzed background reaction between ArZnEt and 3,4-dihydroisoquinoline *N*-oxide, which yields racemic products, can be competitive with the rate of the ligand-promoted reaction. This background reaction erodes the enantioselectivity of the transformation when the ligand is not present in stoichiometric quantities.

The absolute configuration of **3a** was determined to be (*S*) by reducing it to 1-phenyl-1,2,3,4-tetrahydroisoquinoline and comparing its specific optical rotation to a value from the literature.[15] By analogy, we believe that ligand **2a** controls addition of the other arylzinc reagents to the *Si*-face of the nitrone to give products with the (*S*)-configuration. Since the enantiomer of ligand **2a** is readily prepared from

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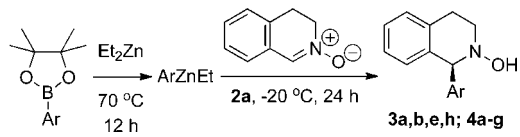
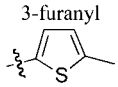
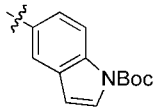
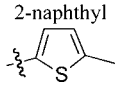
(15) Observed value for (*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline: $[\alpha]^{22}_D = +36.1°$ ($c = 0.73$, CH_2Cl_2). Literature value: $[\alpha]^{25}_D = +12.3°$ ($c = 0.57$, CH_2Cl_2). Ludwig, M.; Beer, H.; Lotter, H.; Wanner, K. T. *Tetrahedron: Asymmetry* **1997**, *8*, 2693–2695.

Table 3. Conversion of Pinacol Boronic Esters to Arylzinc Reagents, Followed by Enantioselective Addition to 3,4-Tetrahydroisoquinoline *N*-Oxide, Promoted by Ligand **2a**[a]



entry	Ar	product	equiv **2a**	yield (%)[b]	ee (%)[c]
1	Ph	**3a**	1.3	92	98
2	4-Me-C_6H_4	**3b**	1.3	79	98
3	4-Cl-C_6H_4	**3e**	1.3	95	97
4[d]	2-naphthyl	**3h**	1.3	99	97
5	4-OBn-C_6H_4	**4a**	1.3	65	99
6	3-CO_2Me-C_6H_4	**4b**	1.3	90	98
7	3-furanyl	**4c**	1.3	96	99
8		**4d**	1.3	96	97
9		**4e**	1.3	70[e]	99
10	4-BocO-C_6H_4	**4f**	1.3	35[e]	97
11	3,5-(MeO)$_2$-C_6H_3	**4g**	1.3	53[e]	99
12	Ph	**3a**	0.2	90	91
13	4-Me-C_6H_4	**3b**	0.2	81	92
14	4-Cl-C_6H_4	**3e**	0.2	89	67
15	2-naphthyl	**3h**	0.2	98	82
16		**4d**	0.2	93	77

[a] Reaction conditions: (1) Aryl pinacol boronic ester (1.4 equiv), Et_2Zn (4.2 equiv), 70 °C, 12 h; (2) **2a** (1.3 or 0.2 equiv), 2:1 toluene:CH_2Cl_2, −20 °C, 24 h. [b] Yield of purified product. [c] Determined by chiral HPLC. [d] Reaction perfomed in toluene. [e] 1-Ethyltetrahydroisoquinoline was also isolated from these reactions in the following yields: entry 9 (26%), entry 10 (37%), entry 11 (32%).

D-Ile, this method can be used to prepare either enantiomer of 1-arylTHIQs.

We applied this method to an enantioselective synthesis of Solifenacin **1f** (Figure 3). Typical syntheses of this drug require resolution of racemic 1-phenylTHIQ via its diastereomeric salt with tartaric acid or separation of the diastereomers of **1f** by chromatography.[16] Compound **3a** (98% ee) was reduced using Zn/Cu in AcOH/H_2O to give (*S*)-1-phenylTHIQ. Acylation of the amine with *p*-nitrophenyl chloroformate gave carbamate **5** in 90% yield over two steps. Finally, this carbamate was reacted with (*R*)-3-quinuclindinol, NaH, and 18-crown-6 in refluxing toluene to give Solifenacin in 74% yield.[16]

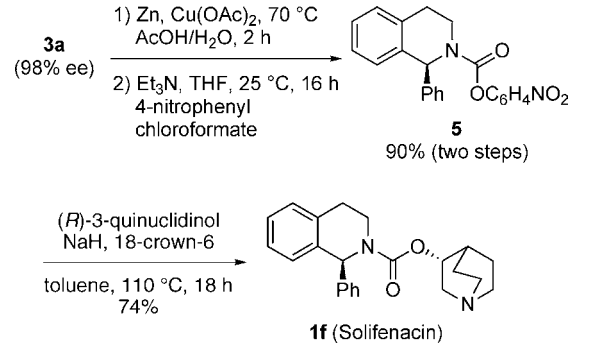


Figure 3. Synthesis of Solifenacin.

In summary, we have developed a procedure for the enantioselective addition of arylzinc reagents to 3,4-dihydroisoquinoline *N*-oxide promoted by the chiral ligand **2a**. When boronic esters are used to generate the arylzinc reagents, the reaction gives excellent enantioselectivities with a broad range of aryl and heteroaryl substrates. This method should be useful for preparing a variety of chiral 1-arylTHIQs.

Supporting Information Available: Experimental procedures, spectroscopic data, and chiral HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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