Concise Synthesis of Conformationally Constrained Pybox Ligands

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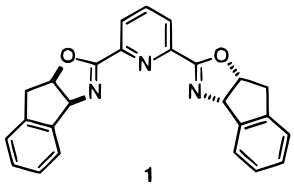
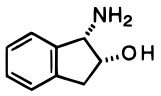
A key feature of transition metal-catalyzed processes is the ability to control the regio- and stereochemical outcome of a reaction by variation of the steric and electronic nature of the ligand. Some of the most important examples of "ligand tuning" are evident in asymmetric catalysis where ligands can have a profound influence on the enantiomeric excess of the product.[1] We have demonstrated that ligands that contain the amino-indanol motif provide very high levels of absolute and relative stereocontrol in Diels−Alder reactions in contrast to their acyclic counterparts.[2] Similar observations have now been reported by Ghosh.[3] Pyridine bis(oxazoline)—pybox—ligands were first introduced by Nishiyama for Rh-catalyzed hydrosilylation reactions,[4] and Evans has very recently demonstrated that they are very efficient ligands for Cu-catalyzed Mukiayama aldol[5] and Diels−Alder[6] reactions. Herein, we describe a concise synthesis of the conformationally constrained pybox ligand **1** derived from (1*S*,2*R*)-aminoindanol (**2**), which is amenable to the synthesis of other important pybox ligands.



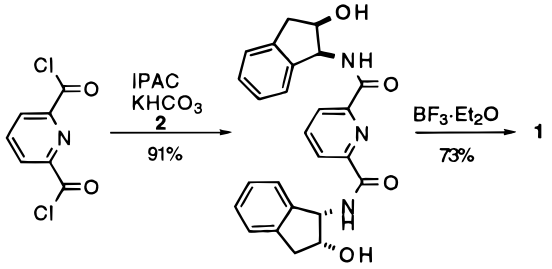
1



2

Although the Nishiyama synthesis of pybox ligands is efficient (42−70% overall yield), it involves a four-step reaction sequence and a 6-day time cycle. In addition, this approach could not guarantee the stereochemical integrity of an indan-derived amino alcohol since two sequential nucleophilic reactions are required to construct the oxazoline.[7,8] We therefore decided to prepare the pybox ligand **1** by dehydration of the bis(amide) **3**, which was prepared using Schotten Baumann conditions.[9] Addition of 2,6-pyridine dicarbonyl dichloride to an isopropyl acetate (IPAC) solution of **2** at 65 °C gave the bis(amide) **3**, which precipitated directly from the reaction mixture in 91% yield (Scheme 1). In order to induce cyclization, the amide carbonyl would first need to be activated. Singh has recently reported a MsOH-promoted dehydration of a bis(amide) to a pybox; *a priori*, it is unclear whether this reaction would tolerate a substrate that is stereogenic at the alcohol-bearing carbon.[10] In our case, reaction of the bis(amide) **3** with MsOH (toluene, 110 °C) gave 5% of the oxazoline/amide, and none of the pybox **1** was detected. This low reactivity is due in part to the insolubility of the bis(amide) **3**. The use of MsOH as solvent only led to hydrolysis affording **2** upon aqueous workup. After examination of a number of other Bronsted and Lewis acids, $BF_3{\cdot}Et_2O$ was found to be the best candidate. Reaction of the bis(amide) **3** with 4 equiv of $BF_3{\cdot}Et_2O$ in toluene at 110 °C gave a 10% yield of the in-pybox **1**. However, our best results were obtained by simply heating a 15% w/v solution of bis-(amide) **3** in $BF_3{\cdot}Et_2O$ at 120 °C. After 6 h, following an aqueous workup, the in-pybox **1** was isolated by direct crystallization in 70−73% yield (Table 1, entry 1). Significantly, similar yields were obtained when excess $BF_3{\cdot}Et_2O$ was distilled at 140 mmHg after complete reaction, making the workup easier and allowing the recovered $BF_3{\cdot}Et_2O$ to be recycled.

Scheme 1



To test the generality of this method for the preparation of other pybox ligands, we investigated the ligand derived from 1(*R*)-amino-2(*S*)-hydroxytetrahydronaphthalene.[11] The thn-pybox **5** was obtained in good yield following crystallization (Table 1, entry 2), and the expected *cis*-stereochemistry was confirmed by NOE studies. The ph-pybox **6** (mp 169−170 °C (lit.[4] mp 170−172 °C)) and tb-pybox **7** (mp 239−241 °C dec) (lit.[4] mp 242−243 °C), which are currently the most commonly used architectural features in pybox ligands, were prepared in 62 and 75% yield, respectively (Table 1, entries 3 and 4). The dm-pybox **8** (mp 139 °C (lit.[4] mp 140−141 °C) was also prepared in a similar manner (Table 1, entry 5). A limitation of this method was discovered with the bis(amide) derived from (1*S*,2*R*)-norephedrine (Table 1, entry 6). In this case, the *trans*-pybox **9** was formed exclusively (NOE), indicating that the amide acted as the

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(8) Reaction of indan-derived amides with thionyl chloride under standard conditions leads to a mixture of products including epimeric chlorides and regioisomeric indenes.

(9) Maligres, P. E.; Upadhyay, V.; Rossen, K.; Ciancosi, S. J.; Purick, R. M.; Eng, K. K.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 2195.

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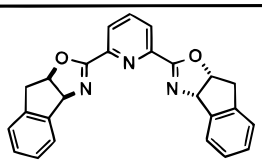
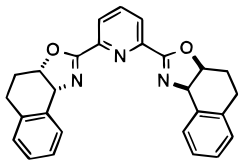
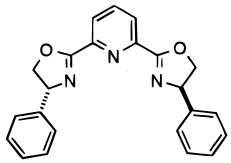
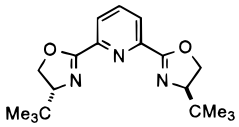
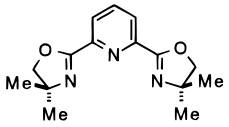
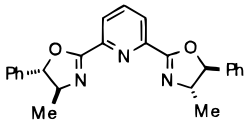
Table 1. Dehydration at 120 °C Using 15% w/v $BF_3 \cdot Et_2O$

Entry	Pybox		Time (h)	Yield (%)
1	**1**		6	73
2	**5**		2	76
3	**6**		4	62
4	**7**		2	75
5	**8**		2	61
6	**9**		1.5	70

nucleophile rather than as an electrophile, the benzylic alcohol being more susceptible to displacement than in the other examples.[12]

The pybox ligands **1**, **5**, and **6** represent a toolbox of ligands that can be used to systematically determine the role of ligand conformation in transition metal-catalyzed reactions.[13] The straightforward method described in this paper allows for rapid construction of these important new pybox ligands in two steps without a need for chromatographic purification. In addition to the pybox ligands already in use, they will find application in high-throughput screening of catalytic reactions.[14]

(12) Meyers, A. I.; Gant, T. G. *Tetrahedron* **1994**, *50*, 2297.

(13) For an example of the use of this "toolbox" of auxiliaries see: Davies, I. W.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7619.

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Experimental Section

The identities of known compounds were confirmed by comparison of melting points and spectroscopic data with the published values. All solvents and reagents were used as received from commercial sources. Melting points were determined on a Thomas Hoover apparatus and are uncorrected. *J* values are given in Hz. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Water content was determined by Karl Fischer titration on a Metrohm 737 KF Coulometer.

[3a*S*-[2(3′a*R,8′a*S**),3aα,8aα]]-2,2′-(2,6-Pyridinediyl)bis-[3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole] (1).** The procedure for the preparation of **1** is illustrative: A 15% w/v suspension of the bis(amide) **3** (0.01−0.1 mol) in $BF_3 \cdot Et_2O$ was heated to 120 °C (the mixture became homogeneous at 75 °C) for 6 h. After complete reaction (NMR), the solution was allowed to cool, diluted with dichloromethane (5×), and poured into ice-cold 2 N NaOH (5×). The phases were separated, and the dichloromethane layer was diluted with diethyl ether (1×) and treated with Darco G-60. The suspension was filtered through a pad of silica gel (1 cm) and washed with dichloromethane:diethyl ether (1:1, ×2). Concentration of this solution gave pybox **1**, which was collected by filtration and dried *in vacuo* (70−73%): mp 265−268 °C dec; $[\alpha]^{22}_D$ −364.0 (*c* 1.04, CH_2Cl_2); IR 1630, 1573 cm^{-1}; ^1H NMR ($CDCl_3$) 3.47−3.55 (4H, m), 5.60 (2H, dt, J = 8.3, 4.0), 5.79 (2H, d, J = 8.3), 7.24−7.30 (6H, m), 7.53−7.59 (2H, m), 7.78 (1H, t, J = 7.5), 8.11 (2H, d, J = 7.5); ^{13}C NMR ($CDCl_3$) 39.7, 77.0, 84.3, 125.4, 125.7, 126.0, 127.5, 128.7, 137.2, 139.9, 141.5, 146.9, 162.9. Anal. Calcd for $C_{25}H_{19}N_3O_2 \cdot 0.5(H_2O)$: C, 74.60; H, 5.00; N, 10.44. Found: C, 74.64; H, 5.06; N, 10.30.

[3a*S*-[2(3a′*R,9b′*S**),3aα,9bα]]-2,2′-(2,6-Pyridinediyl)bis-[3a,4,5,9b-tetrahydronaphth[1,2-*d*]oxazole] (5):** mp 234−235 °C; $[\alpha]^{22}_D$ +485.0 (*c* 1.00, CH_2Cl_2); IR 1643 cm^{-1}; ^1H NMR ($CDCl_3$) 1.90−2.01 (2H, m), 2.29−2.39 (2H, m), 2.59 (2H, dt, J = 15.8, 3.8), 2.80 (2H, dt, J = 15.8, 3.0), 5.33 (2H, dt, 9.8, 3.8), 5.45 (2H, d, J = 9.8), 7.12 (2H, d, J = 6.8), 7.20 (2H, t, J = 6.8), 7.29 (2H, t, J = 6.8), 7.58 (2H, d, J = 6.8), 7.78 (1H, t, J = 7.5), 8.12 (2H, d, J = 7.5); ^{13}C NMR ($CDCl_3$) 24.6, 28.1, 67.5, 79.6, 126.1, 127.0, 127.4, 128.3, 129.9, 134.3, 137.1, 138.4, 147.0, 162.7. Anal. Calcd for $C_{27}H_{23}N_3O_2$: C, 76.94; H, 5.50; N, 9.97. Found: C, 76.75; H, 5.71; N, 9.84.

[4*S*-[2(4′*R,5′*R**),4α,5*β*]]-2,2′-(2,6-Pyridinediyl)bis[4,5-dihydro-4-methyl-5-phenyloxazole] (9):** mp 138−139 °C; $[\alpha]^{22}_D$ −124.0 (*c* 0.55, CH_2Cl_2); IR 1638 cm^{-1}; ^1H NMR ($CDCl_3$) 1.50 (6H, d, J = 6.8), 4.32(2H, dq, J = 8.2, 6.8), 5.19 (2H, d, J = 8.2), 7.30 −7.40 (10H, m), 7.92 (1H, t, J = 8.2), 8.19 (2H, d, J = 8.2); ^{13}C NMR ($CDCl_3$) 21.2, 71.1, 89.3, 125.9, 126.1, 128.5, 128.8, 137.5, 139.9, 147.2, 161.6. Anal. Calcd for $C_{25}H_{23}N_3O_2 \cdot 0.4(H_2O)$: C, 74.21; H, 5.93; N, 10.38. Found: C, 74.62; H, 5.95; N, 10.23.

Acknowledgment. We thank Robert Reamer and Lisa DiMichele for key NMR assignments.

Supporting Information Available: Experimental, spectroscopic, and characterization data for amide **3** and intermediates to **5** and **9** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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