Synthesis of a Chiral Receptor Molecule with Converging Amidinium and Hydroxy Groups

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Abstract: The axially chiral amidinium ion **1** was synthesized by Suzuki cross coupling and by base induced cyclization of an amino nitrile intermediate. Receptor **1** may interact with guest molecules by three converging H-bond donors.

Key words: chiral axis, guanidine, hydrogen bond, molecular recognition, Suzuki reaction

Amidinium and guanidinium ions have been successfully applied to the construction of anion receptors[1] which cleave RNA[2] and undergo rapid transphosphorylation chemistry.[3] Chiral anion receptors are used for enantioselective complexation of guest molecules. In addition, since they can stabilize anionic transition states, the catalysis of many useful reactions by such receptors may be envisioned. In consequence, several syntheses of chiral guanidines appeared in the literature.[4] We have developed a general method for the preparation of chiral amidines (e.g. **2**) based on a diastereoselective cyclization of amino nitriles.[5] We reasoned that additional hydrogen bonds between host and guest should further improve complex stability and stereoselectivity of guest recognition (Figure 2).

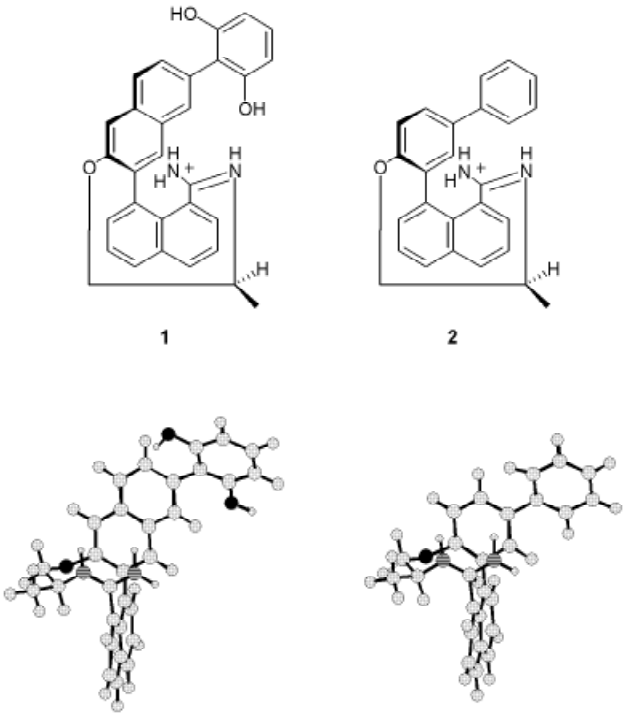


Figure 1 Molecular models of amidinium ions **1** and **2**

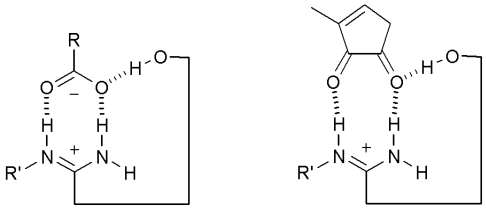
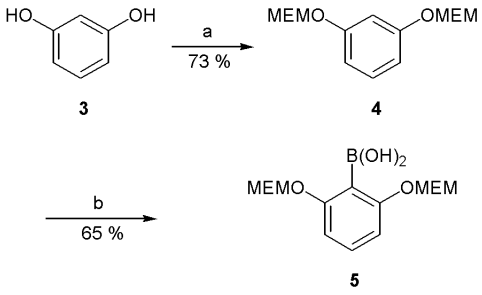


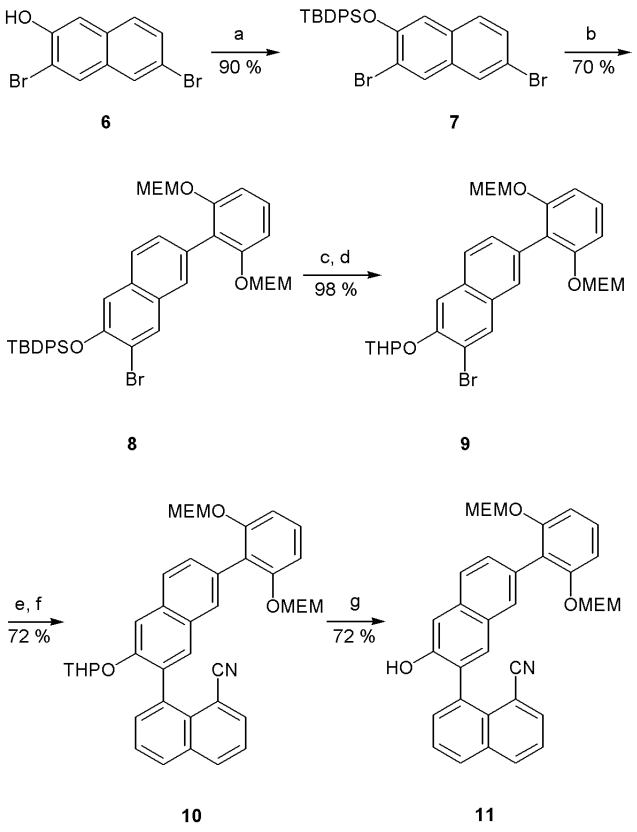
Figure 2 Recognition of anionic and neutral guests by three converging hydrogen bond donors

Inspection of molecular models finally led to the target structure **1**. Due to the symmetric resorcinol subunit, rotation around the biaryl axis of compound **1** cannot remove the hydroxy group from the binding site. This motion will only allow a fine tuning in host-guest structures of the receptor molecule which is completely rigid in the remaining parts.

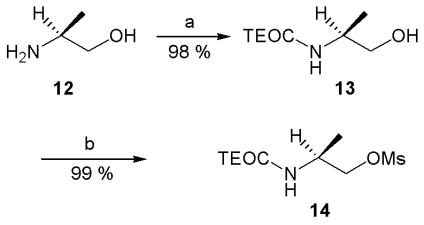


Scheme 1. *Reagents and conditions*: a) MEMCl, DIPEA, CH_2Cl_2, r.t., 24 h; b) 1. *n*-BuLi, THF, -10 °C, 2. $B(OMe)_3$, 3. H^+

The terarylic skeleton of **1** was established by palladium catalyzed cross coupling. In the first Suzuki reaction,[6] we employed boronic acid **5** which could be prepared from MEM protected resorcinol **4** in 65 % yield (Scheme 1). Naphthalene building block **7** was accessible *via* perbromination of 2-hydroxynaphthalene and reduction (**6**),[7] followed by silylation of the hydroxyl group (90 %, Scheme 2). The sterically demanding TBDPS group proved to be essential for the selectivity of the Suzuki coupling. Using standard conditions, a clean reaction was observed leading to 70 % of biaryl **8**. In contrast, THP protected analogues of **7** produced mixtures in the coupling step. After conversion of **8** into the tetrahydropyranyl ether (**9**, 98 %), a boronic acid was prepared from the



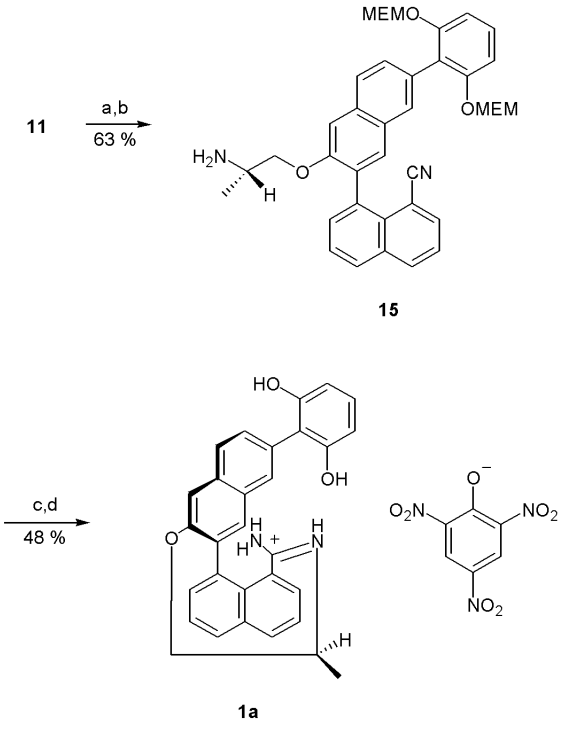
Scheme 2. *Reagents and conditions*: a) TBDPSCl, imidazole, DMF, r.t., 1 d; b) **5**, $Pd(PPh_3)_4$ (5 mol %), Na_2CO_3, toluene, 80 °C, 2 h; c) HF∗pyridine, THF, r.t., 4 h; d) DHP, PPTS, r.t., 3 d; e) 1. *n*-BuLi, THF, -90 °C, 2. $B(OMe)_3$, 3. H_2O; f) 8-Iodonaphthalene-1-carbonitrile, $Pd(PPh_3)_4$ (10 mol %), Na_2CO_3, toluene, 90 °C, 18 h; g) $(HO_2C)_2$, MeOH, r.t., 12 h



Scheme 3. *Reagents and conditions*: a) 2-Trimethylsilylethyl-p-nitrophenylcarbonate, Na_2CO_3, dioxane, r.t., 1 d; b) MsCl, pyridine, r.t., 15 min

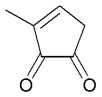
bromo naphthalene **9**. Cross coupling of the non-purified reagent with 8-iodonaphthalene-1-carbonitrile [8] then led to 72 % of teraryl **10**. Treatment with oxalic acid in methanol allowed a selective deprotection of the naphthol moiety (**11**, 72 %).

As shown in Scheme 3, the side chain was prepared from *(S)*-2-amino-1-propanol **12** by *N*-protection with TEOC (2-trimethylsilylethyl carbamate; **13**, 98 %) and activation as a mesylate (**14**, 99 %). Alkylation of naphthol **11** by mesylate **14** in the presence of Cs_2CO_3 and selective cleavage of TEOC led to amino nitrile **15** (63 %, Scheme 4). Since the final cyclization was blocked by hydroxy groups, it was of critical importance not to remove MEM from compound **15**. When BOC was used instead of TEOC, selective *N*-deprotection could not be achieved. In the base induced cyclization of amino nitrile **15**, preorganization of the aromatic skeleton favors the formation of the ten-membered ring. For steric reasons, ring closure can only occur when the methyl group adopts an equatorial position in the product (see Figure 1). By this mechanism, the chirality is efficiently transferred from the amino side chain to the chiral axes of the amidine.[9] Finally, acid induced removal of MEM and crystallization of the picrate salt **1a** completed the synthesis of receptor molecule **1** (48 % from **15**).[10] The corresponding chloride **1b** and tetrakis(3,5-bistrifluoromethylphenyl)-borate salts **1c** were prepared by ion exchange.



Scheme 4. *Reagents and conditions*: a) **14**, Cs_2CO_3, DMF, 60 °C, 1 d; b)TBAF, THF, 50 °C, 3 h; c) LiHMDS, dioxane, 80 °C, 2 h; d) 1. AcCl, MeOH, r.t., 2 h, 2. Picric acid

Preliminary complexation experiments were carried out with the yellow diketone **16**. According to its achiral structure, the CD spectra of **16** did not show any bands. However, upon addition of amidinium salt **1c**, the yellow color became more intense and a broad CD band around 400 nm was induced: coordination of **16** to the receptor resulted in a chiral perturbation of its chromophore (room temperature; CH_2Cl_2; [**1c**] = 10 mM, [**16**] = 12 mM). When cyclic phosphate **17** was added in slight excess, both effects were completely reversed. Phosphate **17** is a better ligand for amidinium ion **1** than compound **16**. The use of receptor **1** as a stereoselective catalyst in chirogenic[11] reactions of diketone **16** is the topic of present work.



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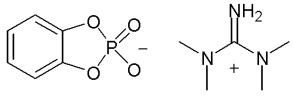

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References and Notes

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(9) For a detailed explanation see (5).
(10) Selected physical data of amidinium picrate **1a**: M.p. 202 – 204°C (ethanol / water). $[\alpha]_D^{20}$ = + 147.6° (*c* = 0.27, methanol). ^{1}H NMR (270 MHz, d_6-DMSO): δ = 1.17 (d, 3 H, *J* = 6.7 Hz, Me), 3.58 - 3.76 (m, 1 H, CHN), 4.13 (dd, 1 H, *J* = 12.4, 3.7 Hz, H_{eq}), 4.47 (dd, 1 H, *J* = 12.3, 10.7 Hz, H_{ax}), 6.43 (d, 2 H, *J* = 8.1 Hz, H-C(3''), H-C(5'')), 6.95 (t, 1 H, *J* = 8.1 Hz, H-C(4'')), 7.47 (dd, 1 H, *J* = 8.5, 1.6 Hz, H-C(7')), 7.53 (dd, 1 H, *J* = 7.1, 1.2 Hz, H-C(7)), 7.62 (dd, 1 H, *J* = 7.0, 1.2 Hz, H-C(2)), 7.68 (s, 1 H, H-C(1')), 7.73 (t, 1 H, *J* = 7.6 Hz, H-C(3)), 7.74 (t, 1 H, *J* = 7.7 Hz, H-C(6)), 7.80 (s, 1 H, H-C(5')), 7.82 (s, 1 H, H-C(4')), 7.83 (d, 1 H, *J* = 8.5 Hz, H-C(8')), 8.11 (s, 1 H, NH_{ax}), 8.18 (dd, 1 H, *J* = 8.4, 1.1 Hz, H-C(5)), 8.33 (dd, 1 H, *J* = 8.3, 1.1 Hz, H-C(4)), 8.59 (s, 2 H, picrate), 8.96 (s, 1 H, NH_{eq}), 9.16 (s, 2 H, OH), 9.18 (d, 1 H, *J* about 10 Hz, NH_{ax}). Anal. calc for $C_{36}H_{27}N_5O_{10}$ · 2 EtOH (781.77): C 61.45, H 5.03, N 8.96; found: C 61.66, H 4.82, N 9.02.
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