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Synthesis and Structure of 1,4-Dipiperazino Benzenes: Chiral Terphenyl-type Peptide Helix Mimetics

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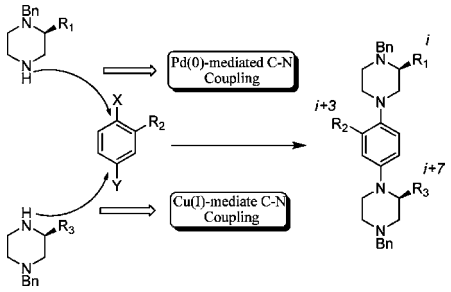
ABSTRACT



The terphenyl structure has been proven to be an ideal scaffold mimicking side-chain functionalities of peptidic α-helices. The synthesis of 1,4-dipiperazino benzenes, using stepwise transition metal-catalyzed N-arylation of chiral piperazines to a central benzene core is reported. The structure determination by X-ray crystallography reveals a geometrical arrangement of the hydrophobic side chains resembling the orientation of key *i*, *i* + 3, and *i* + 7 positions in a peptidic α-helix or in terphenyl helix mimetics.

The α-helix is one of the most common structural motifs in protein secondary structures[1] and is of particular importance for protein−protein, protein−DNA, and protein−RNA interactions.[2] However, studying or intercepting such interactions using peptides is difficult because they are flexible and proteolytically unstable. Therefore, structural mimetics[3] have been developed that display side-chain functionalities with similar distance and angular relationships to those found in α-helices. Important functional groups are typically found along one 'face' of a peptide helix involving side chains from the *i*, *i* + 3 or *i* + 4, *i* + 7, and *i* + 11 amino acids.[4] Reported helix mimetics are based on a variety of molecular structures: Kahne[5] reported a pentasaccharide scaffold as an α-helix mimic presenting multiple charged groups that selectively bind the minor grove of DNA and not RNA. β-Peptides have been used by Gellman[6] and Schepartz[7] to mimic an α-helix. Recently, Hamilton and co-workers[8] have

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developed mimetics of the hydrophobic face of an α-helix using the terphenyl scaffold. The tris-*ortho*-substituted terphenyl can mimic the *i*, *i* + 4, and *i* + 7 residues of the α-helix by adopting a staggered conformation that closely reproduces the angular orientation of the peripheral functionalities on the helical surface. Synthetic foldamers mimicking extended α-helices are accessible using benzoylurea oligomers.[9] Rebek recently reported the synthesis of small libraries of low-molecular-weight α-helix mimetics having a pyridazine ring in the central position.[10] Such terphenyl-type compounds effectively mimic the geometrical arrangement of amino acid side chains along one face of a peptide helix. However, most of the compounds lack chirality.

We describe here the synthesis of chiral piperazines bearing hydrophobic side chains and their transition metal-catalyzed assembly into helix mimetics of the terphenyl type. The new compounds keep the relative orientation of the key side chain functionalities as in terphenyl-type helix mimetics. Figure 1 shows the structure of the most stable conformer[11]

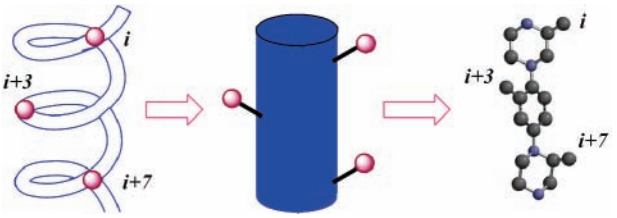
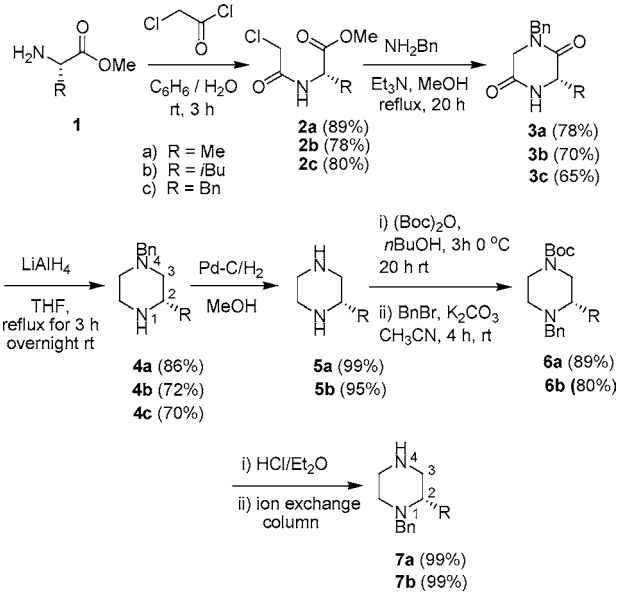


Figure 1. Orientation of residues in an idealized α-helix and in substituted 1,4-dipiperazino benzene

of a methyl-substituted 1,4-dipiperazino benzene and its relation to the α-helix structure. In addition, they are water soluble and chiral, which will facilitate the study of stereochemical effects in helix binding.[12]

We follow a previously reported general route[13] to synthesize enantiomerically pure monosubstituted piperazines (Scheme 1) starting from chiral amino acids. The amino

Scheme 1. Synthesis of Protected Chiral Piperazines **4a**−**c** and **7a**−**b**



esters **1** were treated with $ClCH_2COCl$ and $NaHCO_3$ in a mixture of water and benzene, which gave the products **2a**−**c** in high purity and good yields. The crude products were subsequently reacted with benzylamine in methanol yielding diketopiperazines **3a**−**c** in good yield through a 1,5-cyclocondensation reaction.[14] The diketopiperazines were reduced by $LiAlH_4$ to give monosubstituted piperazines **4a**−**c** bearing a Bn protecting group on nitrogen atom 4. A series of deprotection and reprotection steps leads to piperazines **7a**−**b** which are Bn protected at nitrogen atom 1.

The synthesis of 1, 4-dipiperazino benzene starts from 2-bromo-5-iodotoluene (**8**) and (*S*)-1-benzyl-3-alkylpiperazine (**4a**−**c**). The preferred substitution of the iodo-substituent is expected in transition metal-catalyzed N-arylation reactions. Several ligands have been introduced to promote copper-catalyzed N-arylation of aliphatic secondary amines, most notably *N*,*N*-diethylsalicylamide,[15] amino acids,[16] and

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(12) Protein helices derived from natural amino acids are chiral. Many examples from medicinal chemistry show that the interaction of proteins with chiral molecules significantly depends on their chirality: *Chirality in Drug Research*; Francotte, E., Lindner, W., Eds.; Wiley: New York, 2007; Vol. 33. *Methods and Principles in Medicinal Chemistry*; Mannhold, R., Kubinyi, H., Folkers, G., Eds.; Wiley-VCH: Weinheim, 2006. 1,4-Dipiperazino benzene helix mimetics with different chirality are therefore expected to interact differently with helix-binding proteins.

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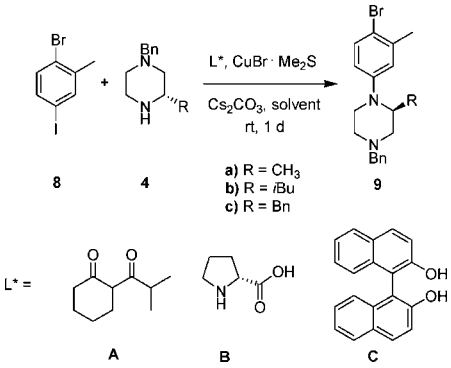
amino alcohols.[17] Wan and co-workers reported copper powder/*rac*-BINOL or (copper + CuI)/*rac*-BINOL as catalytic system, but the N-arylation requires elevated temperatures of 90−125 °C.[18] Recently, Buchwald and co-workers developed a highly selective room-temperature copper-catalyzed N-aryl coupling reaction using CuI and a cyclic β-diketone as the catalytic system and Cs_2CO_3 as base.[19] Jiang and co-workers reported room-temperature copper-catalyzed C_{aryl}−N coupling using CuBr/ *rac*-BINOL as the catalytic system.[20] The number of reported examples of room-temperature coupling reactions of aryl-iodides and ortho-substituted cyclic secondary amines is still small.[21] We used the inexpensive and readily available catalytic system consisting of CuBr, racemic BINOL (1,1′-binapthyl-2,2′-diol) and Cs_2CO_3 as base to achieve the formation of C_{aryl}−N (ortho-substituted piperazine) bonds at room temperature. The reaction conditions were optimized (Table 1) with (*S*)-1-benzyl-3-methylpiperazine (**4a**) and 2-bromo-5-iodotoluene (**8**). 2-Isobutyrylcyclohexanone, L-proline, and racemic BINOL as ligands were reacted in DMF or DMSO with 20 mol % CuBr and Cs_2CO_3 as the base. Racemic BINOL (30 mol %) gave the highest yields and 90% of the racemic BINOL was recovered. The yields of the N-arylation depend on the piperazine substituent and decreases with increasing steric bulk of the alkyl side chain.

Table 1. Optimization of Reaction Conditions for the Copper-Catalyzed C_{aryl}−N Bond Formation of 2-Bromo-5-iodotoluene (**8**) and (*S*)-1-Benzyl-3-alkylpiperazine (**4a**−**c**) to Give Compound **9**



ligand	base	solvent	R	yield (%)
A	K_3PO_4	DMF	CH_3	10
A	K_3PO_4	DMSO	CH_3	7
A	Cs_2CO_3	DMF	CH_3	16
B	Cs_2CO_3	DMSO	CH_3	0
C (20%)	K_3PO_4	DMF	CH_3	30
C (20%)	Cs_2CO_3	DMF	CH_3	40
C (30%)	Cs_2CO_3	DMF	CH_3	60
C (30%)	Cs_2CO_3	DMF	*i*Bu	48
C (30%)	Cs_2CO_3	DMF	Bn	54

The X-ray diffraction analysis of compound **9b** (Figure 2) reveals a flattened chair conformation of the piperazine ring in the solid state. The *i*-Bu substituent occupies an axial position.

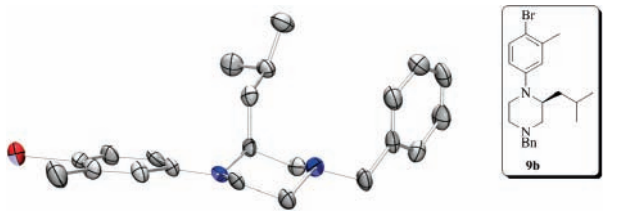
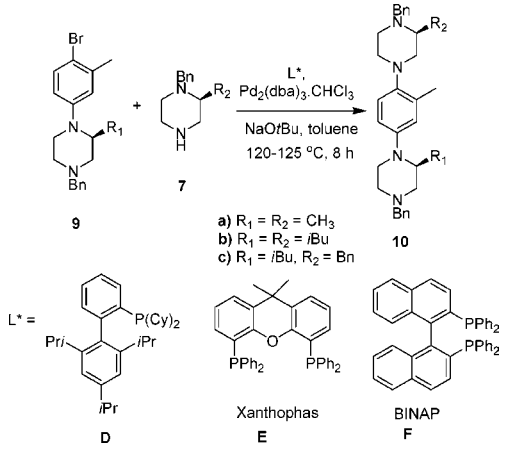


Figure 2. Structure of compound **9b** in the solid state determined by X-ray diffraction analysis. For clarity all H atoms are omitted.

The second C_{aryl}−N bond formation was accomplished by a palladium-catalyzed reaction (Table 2). Palladium-catalyzed amination of aryl halides has been shown to be a general method for the formation of aromatic carbon−nitrogen bonds.[22] More recently, Buchwald and co-workers[23] reported substituted and unsubstituted biaryl monophosphine ligands (**D**), which are very effective in C_{aryl}−N bond forming

Table 2. Optimization of the Reaction Conditions for the Palladium-Catalyzed C_{aryl}−N Bond Formation of Compounds **9a**−**c** and (*S*)-1-Benzyl-2-alkylpiperazine (**7a,b**) Giving Compounds **10**



ligand	R_1	R_2	yield (%)
D	CH_3	CH_3	0
E	CH_3	CH_3	5
F	CH_3	CH_3	75
F	*i*Bu	*i*Bu	70
F	*i*Bu	Bn	72

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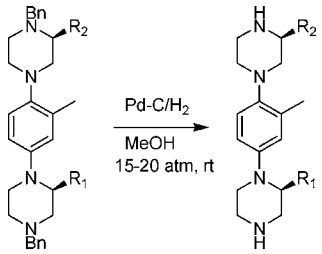
processes. We have tested the three ligands **D**, **E**, and **F** for the formation of the second C_{aryl}−N bond in compounds **9**. In all cases, $Pd_2(dba)_3$·$CHCl_3$/L* (**D/E/F**) was used as the catalyst, NaO*t*Bu as the base, and toluene as solvent. Racemic BINAP (**F**) gave the highest reaction yield (up to 75%) at 125−128 °C for this reaction in our hand (Table 2).

The dibenzyl protected compounds **10a**−**c** were deprotected by Pd−C/H_2 conditions (Scheme 2) to afford compounds **11a**−**c** which show good water solubility.

Scheme 2. 1,4-Dipiperazino Benzene



a) $R_1 = R_2 = CH_3$
b) $R_1 = R_2 = t$Bu
c) $R_1 = t$Bu, R_2 = Bn

The distances between the substituents in the key position [*i* to *i* + 3 = 5.55 Å, *i* + 3 to *i* + 7 = 6.22 Å, *i* to *i* + 7= 8.89 Å] were calculated from the X-ray diffraction structure (Figure 3b). The values are similar to those found in an idealized alanine α-helix [*i* to *i* + 3 = 5.6 Å, *i* + 3 to *i* + 7 = 6.3 Å, *i* to *i* + 7= 10.6 Å]. A comparison of the structure of compound **11a** with the reported structure of Hamilton's methyl-substitued terphenyl compound[9a] shows a striking similarity of the arrangement of the methyl substituents in space.

A circular dichroism (CD) spectrum of compound **11b** was measured at 21 °C between 200 and 300 nm in water (see Supporting Information for experimental details and CD spectrum). The CD spectrum shows a signal in the range of 245−255 nm arising from the aromatic chromophore in its chiral environment. The intensity of the CD signal depends on the concentration of **11b**: With increasing concentration, the signal intensity decreases, which indicates an increasing aggregation induced by the hydrophobic substituents. Changes in the proton NMR coupling pattern (see Supporting Information for data) in aqueous solutions at concentrations higher than 10 μmol/L support this interpretation.

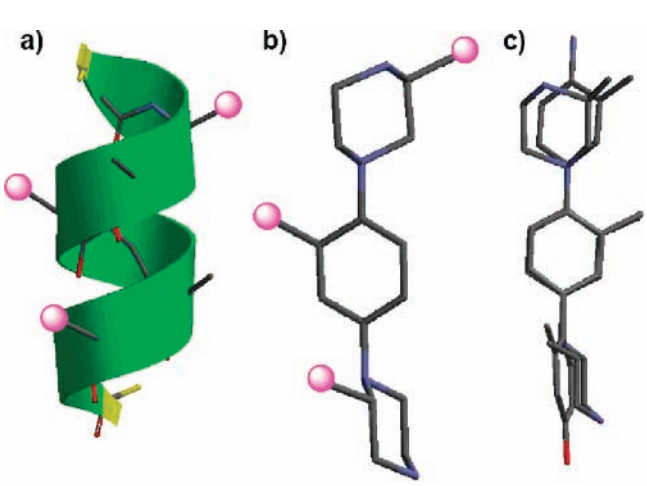


Figure 3. (a) Idealized alanine α-helix structure, (b) structure of compound **11a** in the solid state as determined by X-ray analysis, and (c) superposition of the structure of Hamiltons methyl-substituted terphenyl with the structure of compound **11a**; both X-ray analyses.

To conclude, 1,4-dipiperazino benzenes have been prepared as a new class of inherently chiral α-helix structural mimetics. Protected piperazines as the key synthetic intermediates were synthesized from chiral amino acids. Subsequent copper- and palladium-catalyzed C_{arly}−N coupling reactions lead to the target products in good yields. Racemic BINAP proved to be the best ligand for both reactions. The compounds aggregate in aqueous solution at concentrations exceeding 10 μmol/L, as indicated by CD and NMR. The X-ray structure analysis of 1,4-dipiperazino benzene **11a** reveals a geometrical arrangement of the key substituents, which is similar to an idealized α-helical structure and matches the structure of terphenyl α-helix mimetics. Being structurally similar, but chiral, 1,4-dipiperazino benzenes will allow the investigation of stereochemical aspects of protein−helix mimetic recognition. Work in this direction is in progress.

Acknowledgment. We thank the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft (GRK 760), and the University of Regensburg for support of this work.

Supporting Information Available: Synthetic procedures and characterization data of all new compounds; CD and NMR spectra of compound **11b** in aqueous solution at different concentrations; X-ray analyses data for compounds **9a**, **9b**, and **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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