Towards Diversity-Oriented, Stereoselective Syntheses of Biaryl- or Bis(aryl)metal-Containing Medium Rings

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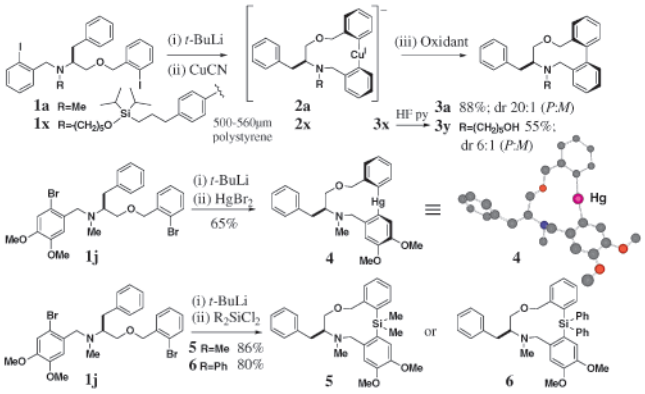
A structurally complex and diverse collection of small molecules can be used to explore cellular and organismic pathways in a process analogous to genetics.[1] Nature provides guidelines of the characteristics of small molecules suitable for effective interactions with proteins. Natural products having an axially disymmetric biaryl moiety implanted within a ring, for example members of the vancomycin and ellagitannin families,[2] attracted our attention for several reasons. One intriguing reason concerns their atropisomerism, which can influence the cellular properties of these compounds.[3]

In planning diversity-oriented syntheses of compounds such as those described above, branching reaction pathways are especially important because they increase the structural diversity of products by altering the skeletal array of connecting atoms.[4] Medium ring-forming reactions also require special attention since the formation of such rings en masse using split-pool synthesis[5] presents special challenges.[6] Described herein are readily synthesized substrates that undergo two types of medium ring-forming reactions leading to two classes of complex structures, one patterned after the biaryl natural products and the other a metal-inserted variant. The first reaction is shown to provide general, efficient and stereoselective access to medium rings by a copper-mediated, C−C biaryl bond formation,[7] and can be performed on solid phase. A subsequent thermal isomerization further expands the diversity of structures available from this branching reaction pathway by reversing the stereochemistry of the atropisomer preferentially formed under kinetically controlled conditions.

The use of organocuprates for biaryl synthesis has been recognized for about a century.[8] Whitesides and others used oxidants on aryl cuprates to give biaryls.[9] More recently, Lipshutz et al. extended this work significantly, first by using "kinetic" cuprates to form unsymmetrical biaryls intermolecularly, and

Scheme 1



second by using a chiral tether to form biaryls intramolecularly.[10] In the present study the latter approach was applied to substrates such as **1a** (Scheme 1), which were prepared by sequential reductive amination and *O*-alkylation of 1,2-amino alcohols. Treatment of **1a** with *tert*-butyllithium followed by CuCN gave, presumably, the cyclic cuprate **2a**,[10] which yielded the biaryl **3a** upon exposure to an oxidant. Initially, applying literature conditions (THF, −78 °C, $^3O_2$),[10] the reaction gave a 58% yield of biaryl with a diastereomeric ratio (dr) of 1:6 (*P*:*M*) in favor of the thermodynamically more stable atropisomer. In fact, (*M*)-**3a** was the major product only when oxygen gas was used as the oxidant; nitrobenzene oxidants reversed this selectivity. The yield and diastereoselectivity were found to depend on the reaction solvent, temperature of oxidation, and the oxidant.[11]

The highest diastereoselectivity with **1a** (20:1) was observed when 1,3-dinitrobenzene (1,3-DNB) was used as the oxidant at −40 °C, and 2-methyltetrahydrofuran (2-MeTHF) was used as the reaction solvent. This procedure effected an efficient conversion to the biaryl, with no oligomers being detected,[12] in 88% yield after chromatography. The only other products detected were species where the iodines in **1a** were substituted by hydrogens, *tert*-butyl groups or hydroxy groups, albeit totaling less than 5% yield.[13] These optimized conditions were applied to substrates displaying: (i) different aromatic rings (Table 1) and (ii) a range of 1,2-amino alcohol substitution patterns (Table 2) to give 9-, 10-, and 11-membered rings in excellent yield and purity. The configuration of the biaryls was determined by X-ray analysis in 14 cases (9- and 10-membered rings), the remainder being assigned using NMR spectroscopy.

Thiophenes, pyridines, and both electron-rich and electron-poor aromatic rings are all tolerated in the reaction. Compounds **3e**−**g**

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(11) In order of decreasing stereoselectivity (*P*:*M*): solvents: (i) 2-MeTHF; (ii) THF, Et_2O and PhMe (∼5:1); (iii) DME (1:1); oxidants: (i) 1,3-DNB (20:1); (ii) 1,4-DNB (15:1); (iii) 1,2-DNB (6:1); (iv) $PhNO_2$ (5:1).

(12) Typical concentrations of **1** were between 0.05 and 0.15 M, and was limited only by the solubility of the bis-aryllithium.

(13) Also, 3,3′-dinitroazoxybenzene and excess 1,3-DNB were observed in the crude reaction mixture.

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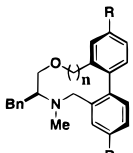
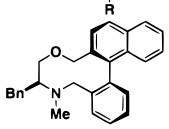
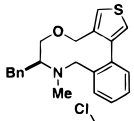
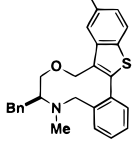
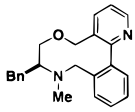
Table 1. Kinetic and Thermodynamic Ratios

Entry	Biaryl (**3**)[a]	% Yield[b]	Kinetic dr (*P*:*M*)[c]	Thermodynamic dr (*P*:*M*)[d]
a	 **R**=H **n**=1	88	20 : 1	1 : 6
b	F 1	84	13 : 1	1 : 10
c	H 2	85	1.3 : 1	1 : 4
d		92	1.5 : 1	1 : 2[e]
e		86	NA[f]	NA[f]
f		73	NA[f]	NA[f]
g		70	NA[f]	NA[f]

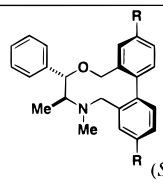
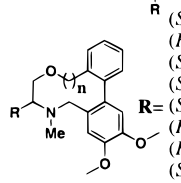
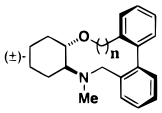
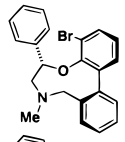
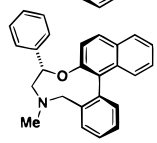
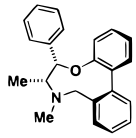
[a] Kinetic atropisomer drawn; **1b**−**w** were dibromides. [b] Combined yield. [c] $P \equiv S$ and $M \equiv R$ for a stereogenic axis. [d] Thermodynamic dr determined by heating each atropisomer (150 °C, 24−48 h); inseparable atropisomer mixtures were heated until no change in dr observed. [e] Thermodynamic dr determined by heating each atropisomer (>350 °C, 1 min). [f] No atropisomerism observed at room temperature.

showed no evidence of restricted rotation about the biaryl bond at room temperature.[14] The configuration of substrate substituents affected the stereoselectivity, but not the reaction yield. Sterically large substituents on the 1,2-amino alcohol tended to reduce both the kinetic and thermodynamic selectivity. The thermodynamic atropisomer could not be determined for nine-membered ring products (**3q**, **3r**, and **3t**−**w**); even heating with a flame failed to interconvert atropisomers.

By substituting Cu(I)CN with Hg(II)Br_2 in the cyclization reaction, it was anticipated that a stable analogue of **2** would result (Scheme 1). The solid-state conformation of the biaryl axis in **4** is *P* (cf. kinetic atropisomer **(*P*)-3j**). If the ground state conformation of **2j** is represented by **4**, then the kinetically favored atropisomer could be explained by the reductive elimination following the principle of least nuclear motion.[15] Also, this metal insertion-cyclization process proceeds effectively using either Me_2SiCl_2 or Ph_2SiCl_2, resulting in the silacycles **5** and **6**, respectively (Scheme 1). Although organometallic species such as **4**−**6** are not generally considered useful as drug candidates, due to presumed organismic toxicity in patients, they may prove to be useful as cellular probes in chemical genetic experiments.

To demonstrate the feasibility of the process on a solid-support, required for a split-pool synthesis, a cyclization precursor was prepared attached to high-capacity, large (500−560μm) polystyrene beads via a silicon linker (**1x**).[16] The reaction proceeded cleanly to give **3y** (>80% pure by HPLC and NMR) in 55% yield after release from the solid-support [dr: 6:1 (*P*:*M*)], although the reaction rate decreased. Also, the beads could be heated prior to cleavage to give **3y** [dr: 1:7 (*P*:*M*)].

Table 2. Kinetic and Thermodynamic Ratios

Entry	Biaryl (**3**)[a]	% Yield[b]	Kinetic dr (*P*:*M*)[c]	Thermodynamic dr (*P*:*M*)[d]
h	 **R**=H	94	17 : 1	1 : 1.5
i	Cl	94	6 : 1	1 : 2
j	 (*S*)-Bn 1	92	16 : 1	1 : 11
k	(*R*)-Ph 1	84	1 : 23	2 : 1
l	(*S*)-*t*-Bu 1	83	4 : 1	1 : 2
m	(*S*)-CH_2Cy 1	88	22 : 1	1 : 11
n	**R**= (*S*)-*i*-Bu **n**= 1	97	35 : 1	1 : 10
o	(*R*)-Et 1	91	1 : 25	9 : 1
p	(*R*)-Me 1	94	1 : 32	6 : 1
q	(*S*)-Bn 0	97	3 : 1	UD[g]
r	(*S*)-*i*-Bu 0	93	2 : 1	UD[g]
s	 **n**=1	77	11 : 1[h]	1 : 3[h]
t	0	96	>50 : 1[i]	UD[g]
u		81[j]	1 : >50	UD[g]
v		73	1.5 : 1	UD[g]
w		68	1 : 10	UD[g]

[a−f] See Table 1 legend. [g] Unable to determine thermodynamic dr. [h] Ratio refers to the configuration of the enantiomer drawn. [i] Atropisomeric stereochemistry not assigned. [j] Debromo-**3u** (12%) isolated.

The ability to transform simple 1,2-amino alcohol derivatives into either biaryl-containing or metal-inserted medium ring compounds, including on solid phase, illustrates the type of branching reaction pathways that are central to an evolving planning algorithm for diversity-oriented synthesis.[4a] The reaction pathway described in this communication will now be used to prepare small molecule modulators for screening in cell- and organism-based assays.[17]

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Supporting Information Available: Experimental details and X-ray structural information (PDF). An X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The conformational preference for **3e**−**g** is to have the biaryl axis distorted from planarity in the same conformation as (*M*)-**3a**.

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