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Intramolecular O-Arylation of Phenols with Phenylboronic Acids: Application to the Synthesis of Macrocyclic Metalloproteinase Inhibitors

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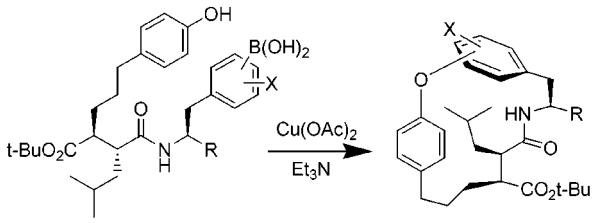
ABSTRACT



The copper acetate mediated intramolecular O-arylation of phenols with phenylboronic acid pseudopeptides is the key step in the preparation of macrocyclic biphenyl ether hydroxamic acid inhibitors of collagenase 1 and gelatinases A and B. The intramolecular macrocyclization was found to be mild and tolerant of common chemical functionality. This methodology should provide a general route to macrocyclic biphenyl ethers.

The macrocyclization of biologically active peptides (or pseudopeptides) often leads to compounds with chemical and physical properties distinct from those of their acyclic analogues. The macrocyclic structure disfavors peptide aggregation through intermolecular hydrogen bonding (β-sheet formation) and functions to sterically shield H-bonding atoms, resulting in lower desolvation energy.[1] This has led to the use of macrocylcization as a strategy for producing peptide derivatives that have acceptable pharmaceutical properties.[2] As a result of their unique structure and physicochemical properties, macrocycles are not generally recognized by peptidases, making them less prone to standard routes of in vivo degradation. In addition, they have been found to be more permeable to cell membranes, which has led to the development of orally bioavailable macrocycles. This approach has been exemplified and applied in the design of cyclic enzyme inhibitors of HIV protease,[3] renin,[4] ACE

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and NEP,[5] and, relevant to this communication, matrix metalloproteinases (MMP).[6] One of the best examples of an important orally bioavailable macrocyclic peptide is cyclosporine, which is a major drug in use for organ transplantation and immune suppression.[7]

A biologically active macrocyclic template that has been observed repeatedly in nature is the diaryl ether linker. Important examples in this class include the vancomycin family of antibiotics,[8] the chloropeptins,[9] and protease inhibitors K-13 and OF4949I-IV.[10] The medicinal significance of these molecules has resulted in intensive efforts toward their synthesis, and a number of interesting approaches to these complex natural products have been published.[11]

In drug design, the use of a diarly ether macrocyle has recently proven effective in the preparation of HIV protease inhibitors.[3] In addition our group has previously shown that succinyl peptide inhibitors of MMPs can be cyclized to produce biologically active cyclophanes as exemplified by SE205,[6a] a highly water soluble MMP inhibitor that is bioavailable in rats and dogs (Figure 1). MMPs are a class

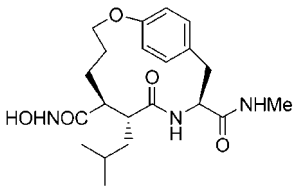

Figure 1. Structure of SE205.

of matrix degrading enzymes that have been implicated in cancer and arthritis.[12] In the further exploration of macrocyclic MMP inhibitors, we set out to examine the biphenyl ether linked macrocycle and report herein the application of the Cu(II)-assisted intramolecular O-arylation of a phenol with an aryl boronic acid as the key reaction. This mild procedure complements the intermolecular version of this reaction recently reported by Chan, Evans, and Lam.[13]

The rational design of cyclic MMP inhibitors has been facilitated through the examination of X-ray crystal structures of enzyme inhibitor complexes. The key inhibitor binding interactions with the enzyme involves a bidentate ligation of the hydroxamic acid to the active-site zinc and a series of four hydrogen bonds formed between the two amides of the inhibitor and subsite residues of the enzyme. The macrocyclic linker does not interact directly with the enzyme and is projected toward solvent.[6] This observation allows one to manipulate the physical properties of the molecule through changing the linker without having a deleterious effect on binding, provided the above key binding interactions are maintained. Computer modeling of our proposed diaryl ether macrocyclic targets suggested that the compounds could adopt an appropriate conformation suitable for binding to the enzymes in the MMP class.

A representative synthetic example is presented in Scheme 1. The desired *anti*-succinate **2** was prepared from the chiral succinyl half ester **1**.[14] Treatment of **1** with 2.1 equiv of lithium diisopropylamide (LDA), followed by monoalkylation of the dianion with 3-(4-benzyloxy)phenyliodopropane, gave a 1:1 mixture of *anti/syn* products. Equilibration of this mixture resulted in a 2:1 *anti/syn* mixture and could be subsequently improved to about 3:1 with successive deprotonation and acid quenching steps as described in the procedure of Becket et al.[14] We investigated the use of counterions other than Li in this equilibration process. It was found that deprotonation with LDA at −78 °C, warming to 0 °C and cooling to −78 °C, followed by the addition of 2 equiv of diethyl-aluminum chloride at −78 °C, subsequent warming to 0 °C and cooling to −78 °C, and rapid quenching with acidic methanol resulted in a 10:1 separable mixture of *anti*/*syn* products. The generality of this result is currently under investigation and will be fully disclosed in a future publication.

Purified *anti* product **2** was then coupled to a functionalized and appropriately protected phenethylamine derivative to obtain the succinyl peptides **3a**−**c** in good yield. Aryl boronic esters **4** were prepared using the Pd(0)-catalyzed

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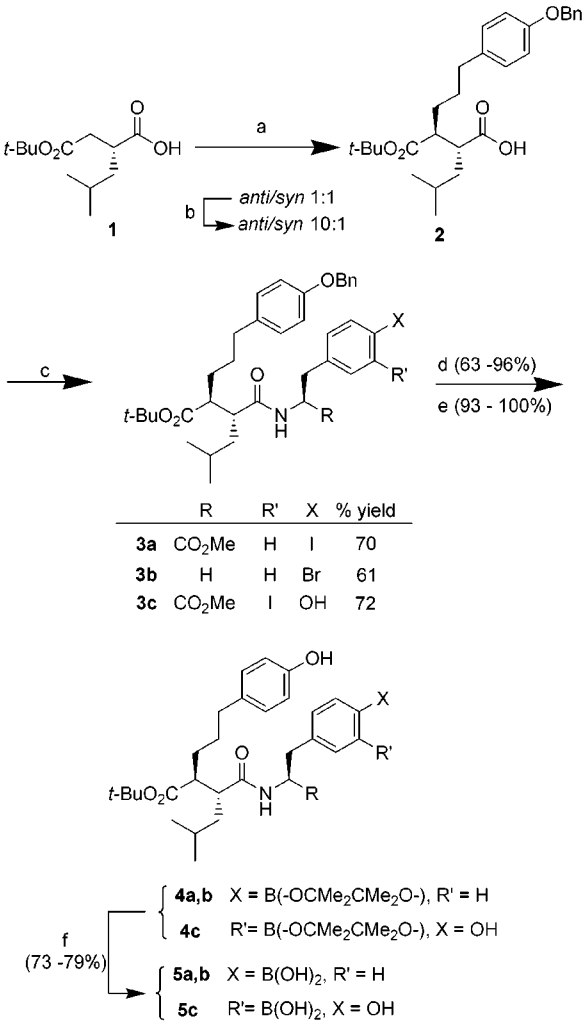
Scheme 1[a]

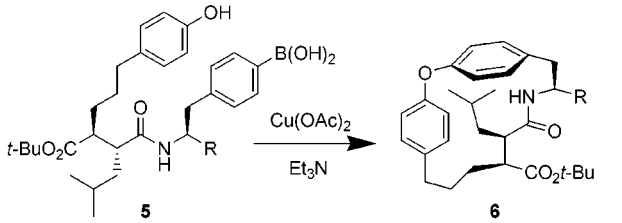


[a] Reagents and conditions: (a) 2.1 equiv LDA, 3-(4-benzyloxy)-phenyliodopropane; (b) (i) LDA; (ii) 2.2 equiv Et_2AlCl; (iii) MeOH; (c) phenylethylamine, TBTU, NMM; (d) pinacol diboron, KOAc, $PdCl_2$(pddf), DMSO; (e) H_2/Pd-C; (f) HCl (aq), $PhB(OH)_2$.

cross-coupling reaction of pinacol diboron to the aryl halide (bromide or iodide).[15] We next removed the benzyl protecting group under catalytic hydrogenation conditions. Initial attempts to effect the intramolecular coupling of the phenol to the pinacol boronate by treatment of **4** with cupric acetate and Et_3N in methylene chloride led to only a trace amount of desired cyclized product. Removal of the pinacol group through trans-boro-esterification with phenyl boronic acid and 2 N HCl provided the free boronic acid phenol **5** in high yield. The intramolecular arylation proceeded effectively with these substrates using stoichiometric copper(II), under dilute concentrations, to provide useful yields of the diaryl ether macrocycles **6**.

Tables 1 and 2 summarize the results obtained with this key reaction for a set of analogues of interest within our drug discovey program. Entries 1−3 show that the reaction

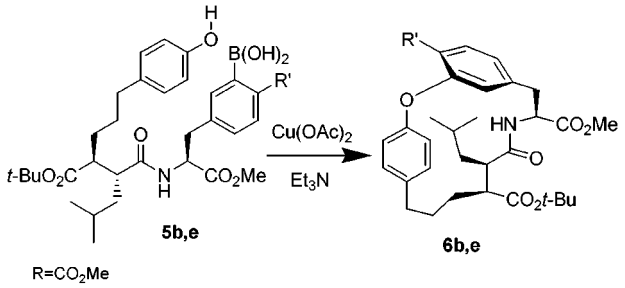
Table 1. $Cu(OAc)_2$-Assisted Macrocyclization of Phenyl Boronic Acid and Phenol



entry	R	product	yield (%)
1	CO_2Me	**6a**	54
2	CONHMe	**6d**	52
3	H	**6c**	43

is general for para-substituted phenols. The cyclization conditions are sufficiently mild to tolerate common chemical functionalities such as amides and esters. Intramolecular cross-coupling of the 4-hydroxy-3-boronic acid **5b** produced only a trace amount of product under these conditions; however, the methyl ether derivative **5e** did couple effectively to give desired product **6e** (Table 2).

Table 2. $Cu(OAc)_2$-Assisted Macrocyclization



entry	R′	product	% yield
4	OH	**6b**	<5
5	OMe	**6e**	52

Subsequent modification of the cyclized products to the corresponding hydroxamic acids provided the molecules of interest for in vitro analysis[16] against a panel of MMPs (Table 3). With the exception of compound **7a**, the targets were found to have broad activity against the gelatinases (MMP-2 and 9) and collagenase-1 (MMP-1). Compound **7c**, which lacks the P3′ amide, was suprisingly the most active compound in this class. This result suggests that the diaryl ether macrocyles may bind differently to the enzyme than the previously prepared cyclophanes.[6a]

The inhibition of matrix metalloproteinases are the subject of intensive investigation as a clinical approach to human pathological conditions involving the breakdown of tissue

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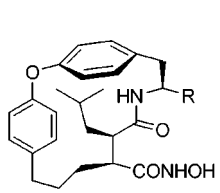
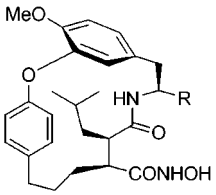
Table 3. MMP Activities of Macrocyclic Biphenyl Ethers



7a,d,c



7f

		K_i, nM		
product	R	MMP-1	MMP-2	MMP-9
7a	CO_2Me	>4949	>3333	>2128
7d	CONHMe	4338	1938	1428
7c	H	748	91	207
7f	CONHMe	2547	1418	293

extracellular matrix. The in vitro results described here indicate that the diaryl ether macrocycles represent a new active chemical scaffold against MMPs.

In summary, we have developed an intramolecular version of the Cu(II)-assisted boronic acid O-arylation reaction and applied it to the synthesis of medicinally important compounds. The reaction was found to proceed under sufficiently mild conditions to accommodate chemical functionality commonly employed in the synthesis of peptidomimetics.

Acknowledgment. The authors would like to acknowledge Dr. Richard Liu for determining the MMP K_i values and Dr. Patrick Lam for helpful discussions.

Supporting Information Available: Experimental procedures with spectroscopic data for compounds **3a**−**c**, **4a**, **4d, 4b**, **4e**, **5a**, **5d**, **5e**, **6a**, **6b**, **6d**, **6e**, **7a**, **7b**, **7d**, and **7f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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