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A Novel Synthesis of Biaryl-Containing Macrocycles by a Domino Miyaura Arylboronate Formation: Intramolecular Suzuki Reaction

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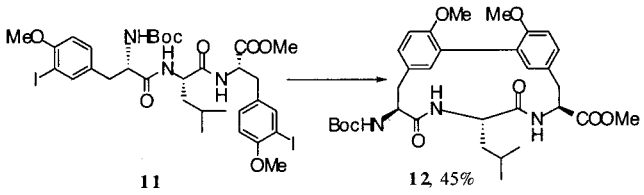
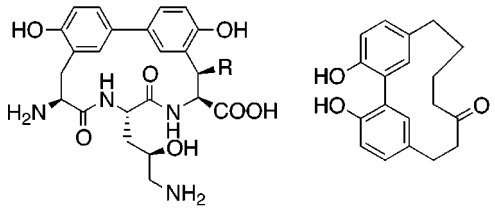
ABSTRACT



Pd(dppf) $_2$Cl $_2$, KOAc, DMSO (0.02 M), 80-85°C, bispinacol diborane

A novel macrocyclization procedure is developed on the basis of a domino process. Thus, treatment of linear diiodide 11 under defined conditions gave the 15-membered *m*,*m*-cyclophane 12 via aryl−aryl bond formation. Two distinct cross-coupling manifolds, Miyaura's arylboronic ester synthesis and intramolecular Suzuki reaction, proceed in an ordered fashion. Concentration is an important factor for the success of this process.

Macrocyclic compounds, by virtue of their outstanding pharmaceutical activity, have played a key role in drug development enterprise.[1] A unique family of macrocycles are those containing an *endo* aryl−aryl bond such as biphenomycin (**1**),[2,3] acerogenin K (**2**)[4] (Figure 1), and



1a biphenomycin A, R = OH
1b biphenomycin B, R = H

2 acerogenin K

Figure 1.

structurally complex vancomycin-type glycopeptide antibiotics.[5] Due to ring strain, rotation of the aryl−aryl bond may be hindered in certain macrocycles even in the absence of the *ortho* substituents. Consequently, the synthesis of such molecules becomes even more challenging as one has to not only find the right way to perform the cyclization but also to control the atropisomerism.[6]

In planning a synthesis of biaryl bridged macrocycles, ring closure via formation of an aryl−aryl bond is particularly

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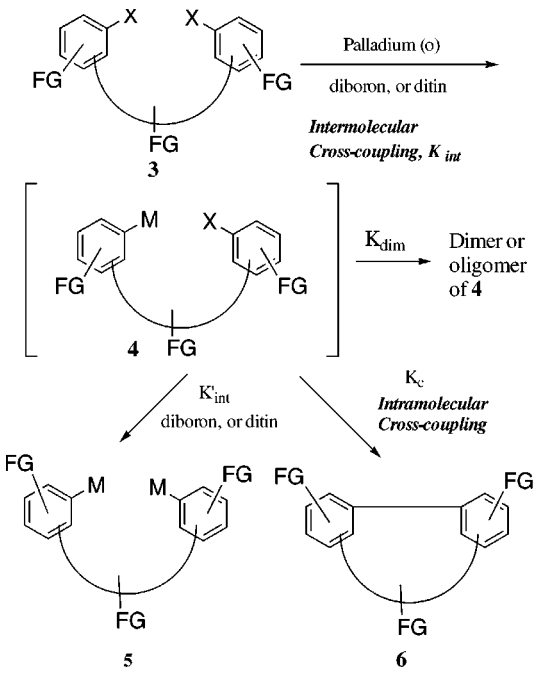
attractive by virtue of its inherent convergence. Not surprisingly, synthetic activities in such a field are numerous and, at the same time, rewarding. Thus, nickel(0)-promoted intramolecular Ullmann-type reductive coupling of aryl halide,[7] biogenetically relevant intramolecular oxidative coupling of electron rich arenes,[8] and redox-neutral photochemical cyclization[9] have been developed and applied in the natural product syntheses to form aryl−aryl bonds. Diastereoselective ring formation with control of axial chirality has recently been developed.[10]

Realizing that the above-mentioned cyclizations were generally low yielding with few important exceptions, we were interested in the development of a new cyclization protocol in connection with our ongoing project on the total synthesis of macrocyclic natural products.[11] The underlying principle that we sought to pursue was shown in Scheme 1.

Scheme 1



FG = Functional group, M = Metal

Starting from a linear diaryl halide, transition metal catalyzed halogen−metal exchange followed by in situ intramolecular cross-coupling would give the desired macrocycle. The constraints of such a strategy are as follows: (a) conditions might be worked out for realizing the two distinct cross-coupling reactions, one inter- and one intramolecular, in a one-pot fashion; (b) the observed rate of macrocyclization (**4** to **6**) must be faster than a second intermolecular event leading to **5** and the dimerization or oligomerization of **4** leading to linear biaryl compounds; (c) concentration dilemma—the desired macrocycle **6** will only be produced by initial *bi*molecular and subsequent *uni*molecular events. Clearly, the concentration of **3** will have an important impact on the overall process and has to be carefully balanced such that it will promote the formation of **4** with reasonable kinetics and at the same time discourage any intermolecular process of intermediate **4**. The powerful palladium-catalyzed Stille coupling[12] and Suzuki reaction[13] among other variants[14] seems particularly suitable to our purpose. Even more relevant is that aryltrialkyltin and arylboronic ester, one of the two reaction partners in the Stille and Suzuki reaction, respectively, can be prepared by palladium-catalyzed reaction of hexaalkylditin[15] and alkoxydiboron[16] with aryl halide.

We report herein development of a domino sequence involving Miyura arylboronic ester formation−intramolecular Suzuki reaction[17,18] and a synthesis of biphenomycin model **12**. Compound **12** was selected as a target since its precursor **11** is easily accessible and it contains two *ortho*-substituents, thus representing a more stringent test than the synthesis of biphenomycin itself.[19]

The synthesis of cyclization precursor was summarized in Scheme 2. Coupling of L-Tyr(OMe) methyl ester (**7**)[20] with L-*N*-Boc Leu (**8**) (EDC, HOBt) gave the dipeptide **9**. Removal of *N*-Boc of **9** followed by its reaction with L-*N*-Boc-Tyr(OMe) (**10**) gave then linear tripeptide **11** in excellent overall yield.

Cyclization of **11** was performed using $Pd(dppf)_2Cl_2$ as a catalyst in the presence of the pinacol ester of diboronic acid **13**. Some representative experimental results are listed in Table 1. The best conditions found consist of heating a

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(17) Reagent combination: $Pd(0)-Me_3SnSnMe_3$ has been used to promote the formation of six-membered rings, see: Kelly, T. R.; Li, Q.; Bhushan, V. *Tetrahedron Lett*. **1990**, *31*, 161−164. For earlier examples of ditin-mediated intermolecular cross-coupling, see: Yokoyama, Y.; Ito, S.; Takahashi, Y.; Murakami, Y. *Tetrahedron Lett*. **1985**, *26*, 6457−6460.

(18) Intramolecular Suzuki coupling, see: Elder, A. M.; Rich, D. H. *Org. Lett*. **1999**, *1*, 1443−1446.

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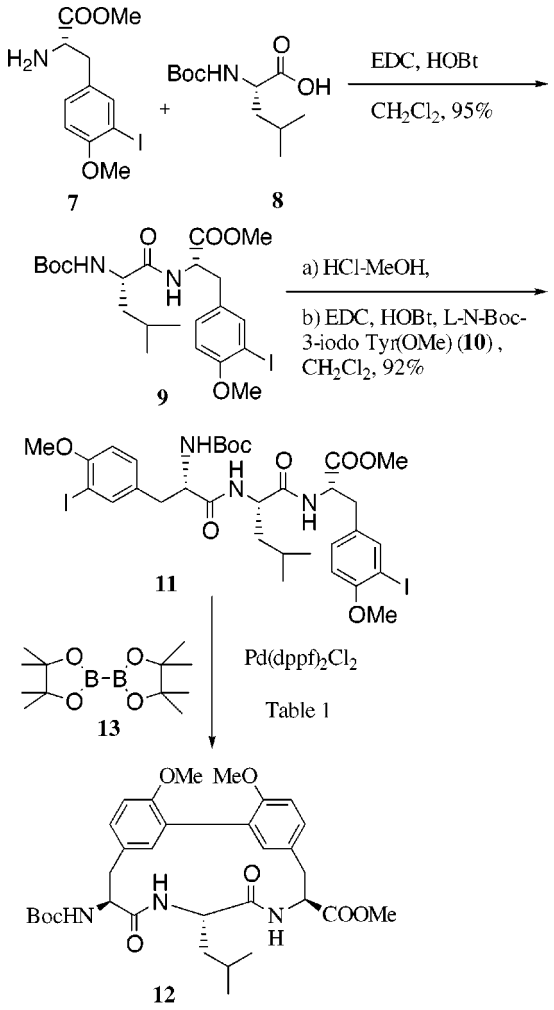
Scheme 2



degassed DMSO solution of diiodide **11** (0.02 M) in the presence of palladium catalyst, diboron **13**, and KOAc as a base at 80−85 °C. Under these conditions, macrocycle **12** was obtained in a 45% isolated yield (entry 4). Switching the solvent to DME (entry 6), lowering the temperature (entries 1 and 2), or further diluting/concentrating the reaction mixture (entries 3, 5) all led to the failure of the cyclization.[21] In their pioneer studies, Miyaura and co-workers[16a] observed that potassium carbonate was not a suitable base for the preparation of arylboronate since it promoted the in situ Suzuki coupling leading to the homodimer of aryl halide—a highly desired process for our projected domino sequence. It is thus interesting to observe that potassium as well as sodium carbonate was completely ineffective (entries 7 and 8).[22] Furthermore, potassium carbonate seems to be harmful to the overall process since a base combination K_2CO_3−KOAc failed to promote the cyclization (entry 9). The unique role of KOAc may be explained by the formation of an acetoxypalladium(II) intermediate which is known to undergo facile transmetalation with organoboron compound.[16a] In an attempt to isolate the arylboronate intermediate **4** [M = $B(OR)_2$], aliquots of the reaction mixture were examined at different time intervals. However, in none of the experiments (concentration: 0.05 and 0.005 M in DMSO) was the intermediate **4** detected.

Table 1. $Pd(dppf)_2Cl_2$ (0.05 equiv) Catalyzed Cyclization of **11** in the Presence of Diboron Ester **13** (1.1 equiv)

entry	base	solvent	concn, M	temp, °C	**12** (%)[a]
1	KOAc	DMSO	0.005	40−45	trace[b]
2	KOAc	DMSO	0.02	40−45	trace[b]
3	KOAc	DMSO	0.005	80−85	10%[c]
4	KOAc	DMSO	0.02	80−85	45%[c]
5	KOAc	DME	0.2	80−85	0%[b]
6	KOAc	DME	0.02	80−85	0%[b]
7	Na_2CO_3	DME	0.02	80−85	0%[b]
8	K_2CO_3	DMSO	0.02	80−85	trace[b]
9	KOAc−K_2CO_3	DMSO	0.02	80−85	trace[b]

[a] Mono- and bisdeiodination products are the major isolable side products. However, the overall mass balance was generally poor. [b] Detected by MS. [c] Isolated yield.

A control experiment demonstrated that the presence of diboron ester **13** was obligatory for the success of this cyclization, since $Pd(dppf)_2Cl_2$ or $Pd(PPh_3)_4$ alone did not promote the intramolecular coupling of compound **11**.[23]

The structure of **12** was determined by NMR spectroscopy and ESI-MS which clearly indicate that it is a cyclic monomer and not the cyclodimer. Interestingly, the room temperature ^{1}H NMR spectrum of compound **12** contains two sets of peaks with a ratio of 3/1 in both chloroform-d_3 and DMSO-d_6 solution. Two peaks coalesced when the spectrum was recorded at 343 K in the latter solvent. The presence of atropisomerism of compound **12** can explain this phenomenon and the observed atroposelectivity (3/1) indicated that the asymmetry could in principle be transmitted from chiral center of the tether into the chiral axis by the present methodology.

To evaluate the relative efficiency of this process, nickel(0)-promoted cyclization of **11** was studied.[7] Under a different set of conditions varying the source and the stoichiometry of Ni(0),[24] the solvent (DME and *N*,*N*-dimethylacetamide), and the temperature, only a trace of the cyclic compound at best was detected by mass spectrometry.[25] On the other hand, Edwards et al. have previously reported that attempted intramolecular oxidative coupling of

(21) We were unable to isolate dimer or oligomers of **11** under all these conditions. Longer reaction time (24 h) under our optimized conditions failed to improve the yield of cyclic compound.

(22) Dimerization under conditions [$PdCl_2(dppf)_2$/Na_2CO_3/EtOH], see: Marcuccio, M.; Rodopoulos, H. Weihold, H. *Abstracts of the 10th International Conference on Boron Chemistry*, Duram, July; 1999, PB-36.

(23) For recent work on the palladium-catalyzed Ullmann-type reductive coupling of aryl halides, see: (a) Hassan, J.; Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793-13804. (b) Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 1205−1208. (c) Venkatraman, S.; Li, C. J. *Tetrahedron Lett.* **2000**, *41*, 4831−4834 and references therein.

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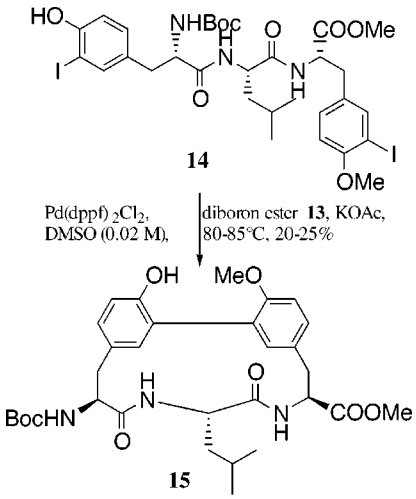
suitably functionalized tripeptide failed to give the cyclic compound.[19d]

We next examined the cyclization of diiodide **14** (Scheme 3) containing a free phenol function since the presence of

Scheme 3



suitable anchoring groups are known to accelerate both palladium-catalyzed transmetalation and cross-coupling reactions.[26] However, the presence of free phenol appeared to have a slightly negative effect on the cyclization as the yield of cyclic compound **15** decreased.[27] It is interesting to note that only one set of peaks was observed in the ^{1}H NMR spectrum of compound **15** recorded at room temperature. Whether this is the result of a free rotation around the aryl axis due to the decreased steric hindrance (OMe to OH) or of a highly atropselective cyclization remains to be clarified.

In summary, we have developed a novel *palladium catalyzed−diboron ester mediated* cyclization reaction of a linear diaryl halide. Two distinct cross-coupling reactions, each involving an oxidative addition−transmetalation−reductive elimination manifold, were channeled into an efficient domino process under defined conditions. The chemistry described in Scheme 2 represents the most convergent approach to the biphenomycin skeleton. Further optimization and application of this cyclization technology in natural product syntheses are in progress.

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(26) Crisp, G. T.; Gebauer, M. G. *Tetrahedron Lett.* **1995**, *36*, 3389−3392.

(27) **General procedure:** To a flask containing melted KOAc (10 equiv), $Pd(dppf)_2Cl_2$ (0.05 equiv), diboron **13** (1.1 equiv), and diiodide was added degassed DMSO (final concentration: 0.02 M). After being heated under argon at 80 °C for 12 h, the reaction mixture was worked up as usual. Compound **12**: $[\alpha]_D = +11$ (*c* 0.30, $CHCl_3$); IR ($CHCl_3$) ν 2956, 1740, 1705, 1651, 1557, 1505 cm^{-1}; ^{1}H NMR (DMSO-d_6, 343 K, 400 MHz) δ 0.78 (m, 1H), 0.88 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 1.45 (s, 9H), 1.40−1.50 (m, 1H), 1.63 (m, 1H), 2.70−3.20 (m, 4H), 3.69 (s, 3H), 3.70 (s, 6H), 4.35−4.45 (m, 2H), 4.65 (m, 1H), 6.67 (s, 1H), 6.80−7.04 (m, 4H), 7.13 (dd, J = 2.0, 8.2 Hz, 1H); 8.20 (d, J = 7.5 Hz, 1H, NH), 8.69 (d, J = 8.0 Hz, 2H, NH); ESI-MS *m*/*z* 620 $(M + 23)^+$. Compound **15**: $[\alpha]_D = +14$ (*c* 0.24, $CHCl_3$); IR ($CHCl_3$) ν 3291, 2927, 1745, 1708, 1649, 1560, 1499 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (m, 1H), 0.89 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 6.0 Hz, 3H), 1.46 (s, 9H), 1.50−1.60 (m, 2H), 2.70 (dd, J = 8.6, 13.0 Hz, 1H), 2.82 (dd, J = 1.8, 13.5 Hz, 1H), 3.08 (br d, J = 13.0 Hz, 1H), 3.28 (dd, J = 7.7, 13.5 Hz, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 4.40 (m, 1H), 4.65−4.78 (m, 2H), 5.45 (d, J = 8.1 Hz, 1H, NH), 6.47 (s, 1H, OH), 6.63 (d, J = 8.8 Hz, 1H, NH), 6.80−6.90 (m, 3H), 6.97 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 171.6, 170.9, 155.3, 154.0, 152.8, 133.2, 132.2, 131.2, 130.8, 129.6, 128.4, 127.5, 126.4, 117.2, 111.4, 79.5, 56.4, 54.9, 53.6, 52.6, 52.0, 42.3, 37.2, 36.8, 28.4, 24.5, 22.7, 22.3; ESI-MS *m*/*z* 606 $(M + Na)^+$.