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Cu(I)-Catalyzed Macrocyclic Sonogashira-Type Cross-Coupling

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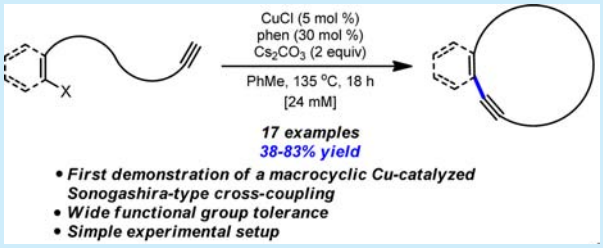
Supporting Information

ABSTRACT: A macrocyclic Cu-catalyzed Sonogashira-type cross-coupling reaction has been developed that employs an operationally simple CuCl/phen/Cs_2CO_3 catalyst system. Macrocyclizations can be performed at relatively high concentrations without the need for slow addition techniques and form macrocycles with various ring sizes and functional groups. The optimized protocol was employed in the synthesis of (*S*)-zearalane, demonstrating applicability toward the synthesis of a macrocycle with known biological activity.



As applications of macrocycles continue to emerge in diverse fields,[1] the development of strategies for the synthesis of macrocycles has attracted increased interest. While the design of conformational control techniques and solutions for the control of dilution effects have emerged, the discovery of catalysts and/or catalytic transformations remains a challenging aspect in macrocyclization chemistry. The development of catalysis is particularly critical for macrocyclization via the formation of carbon−carbon bonds. In a recent account of the synthesis of the drug candidate vaniprevir,[2] various Pd-catalyzed cross-coupling strategies were investigated for macrocyclization via carbon−carbon bond formation; an intramolecular Sonogashira cross-coupling[3] was plagued by various difficulties that made it unappealing in the context of drug discovery efforts (Figure 1).[4] The Sonogashira cross-coupling

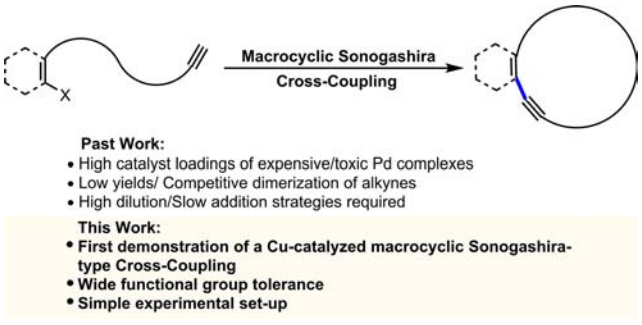


Figure 1. Macrocyclic Sonogashira cross-coupling processes.

traditionally employs a Pd-based catalyst and a Cu-based additive (catalytic or stoichiometric), and high catalyst loadings are often used to improve macrocyclizations. Consequently, the high cost and toxicity of Pd combined with the high dilution often necessary can render macrocyclic Sonogashira reactions problematic. In addition, the coupling of terminal alkynes and aryl/alkenyl electrophiles can be complicated by competing alkyne dimerization resulting in low yields in many macrocyclization reactions. One avenue for an improved macrocyclic process would involve developing a Cu-catalyzed variant that would include lower costs, lower toxicity, and greater availability relative to Pd-based strategies.[5] Current Cu-catalyzed reactions[6] inspired by the original Castro−Stephens cross-coupling[7] (CuI/PPh_3, Cu(neo)(PPh_3), and [Cu(DMEDA)$_2$]Cl_2) focus on couplings of aryl alkynes, with little emphasis placed on aliphatic alkynes and no reports of intramolecular variants. Herein we report the development of an efficient macrocyclic Cu(I)-catalyzed macrocyclic Sonogashira-type cross-coupling process, with high functional group tolerance and demonstrate its applicability to the synthesis of biologically active natural products.

To investigate the development of a macrocyclic Sonogashira cross-coupling, the cyclization of the iodoarene **1** to afford the 15-membered macrolactone **2** was selected as a model macrocyclization. The acyclic precursor **1** possesses a long, flexible alkyl chain with little conformational bias toward cyclization. As such, it is not surprising that Bracher et al. reported that the cyclization of alkyne **1** to form benzolactone **2** was challenging, requiring high catalyst loadings ($Pd(PPh_3)_2Cl_2$ (35 mol %), CuI (1.5 equiv)) and providing low yields (15%).[3f] Attempts at improving the process through modification of the ligand or the Pd source did not improve the yield of benzolactone **2**.[8] Consequently, the use of Cu-based catalysis for the intramolecular Sonogashira-type cross-coupling of alkyl alkynes and aryl iodides was investigated for the first time.

Optimization of the macrocyclic Cu-catalyzed Sonogashira cross-coupling involved the macrocyclization of alkyne **1** using CuCl as a Cu source with various other amine-based ligands (Table 1). Furthermore, Cs_2CO_3 was selected as base and toluene at 135 °C (oil bath temperature) as solvent. When CuCl was investigated for the macrocyclization of iodide **1** using 2,2′-bipyridine **3a** or the more electron-donating ligand

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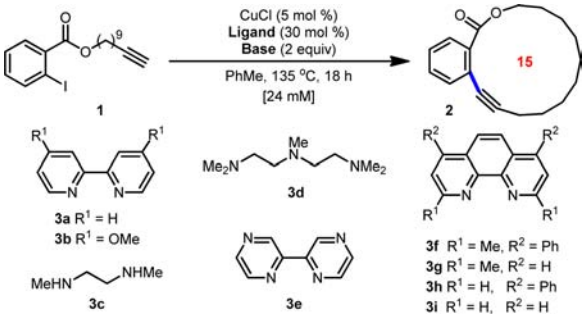
Table 1. Optimization of a Cu(I)-Catalyzed Macrocyclic Sonogashira-Type Cross-Coupling



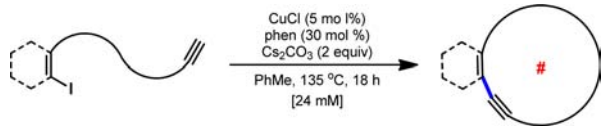
entry	ligand	base	yield **2** (%)[a]	recovered **1** (%)[a]
1	**3a**	Cs_2CO_3	25	38
2	**3b**	Cs_2CO_3	25	<5
3	**3c**[b]	Cs_2CO_3	30	19
4	**3c**[c]	Cs_2CO_3	58	<5
5	**3d**	Cs_2CO_3	30	19
6	**3f**	Cs_2CO_3	32	48
7	**3g**	Cs_2CO_3	58	19
8	**3e**	Cs_2CO_3	73	<5
9	**3h**	Cs_2CO_3	78	<5
10	**3i**	Cs_2CO_3	78	<5
11	**3i**	Cs_2CO_3	81[d]	<5
12	**3i**	K_2CO_3	70	32
13	**3i**	K_3PO_4	63	46

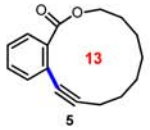
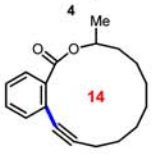
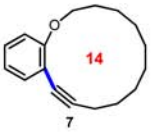
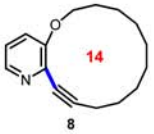
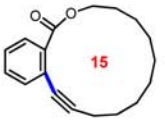
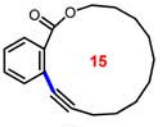
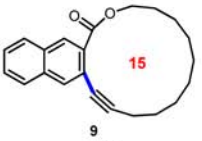
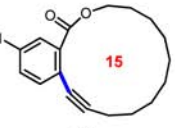
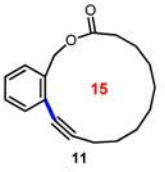
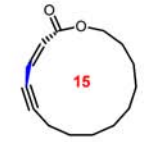
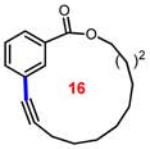
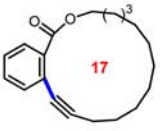
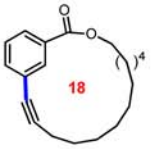
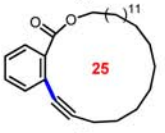
[a]Yields following chromatography. Reactions run on 0.12 mmol scale. Temperature refers to the temperature of the oil bath. [b]In place of CuCl, the preformed catalyst $[Cu(DMEDA)_2]Cl_2$ (5 mol %) was used without any other added ligand. [c]In place of CuCl, the preformed catalyst $[Cu(DMEDA)_2]Cl_2$ (5 mol %) was used. [d]Using 20 mol % of **3i**.

3b, a 25% yield of the desired macrocycle **2** was obtained, along with significant amounts of starting material **1** (38%). Using the preformed catalyst $[Cu(DMEDA)_2]Cl_2$ (5 mol %) developed by Bolm et al. afforded a low yield of **2** as well (30%); however, employing $[Cu(DMEDA)_2]Cl_2$ with 30 mol % added **3c** provided an increased yield of 58%. Similarly higher yields of the macrocycle resulted when employing the neocuproine **3g** or bipyrazine ligand **3e** (58% and 73% of **2** respectively); however, the most efficient ligands surveyed were bathophenanthroline **3h** and 1,10-phenanthroline (phen) **3i**, which afforded the macrocycle **2** in an identical 78% yield. The ligand loading of phen (**3i**) was subsequently investigated, and catalyst loadings of 20 → 30 mol % afforded the best yields.[8] Conducting the macrocyclization in the absence of phen resulted in only 19% of the desired macrocycle **2**. When the reaction was repeated in the absence of CuCl or Cs_2CO_3, no reaction was observed.[9] Exchanging the Cs_2CO_3 base for other bases (K_2CO_3, K_3PO_4) did not afford improvements in the yield of macrocycle **2**. Decreasing the concentration led to very slow reactions and low yields of desired macrocycle **2**.[8] As CuCl/phen/Cs_2CO_3 was identified as a promising catalyst system, the synthesis of various macrocycles with varying ring sizes and functionality was explored (Table 2).

A 10-membered macrolactone **4** could be prepared in modest yield (46%) demonstrating the viability of the method for forming strained macrocycles. An analogous 13-membered macrocycle **5** could be formed in higher yield (83%, entry 2). A variety of 14-membered macrocycles were also prepared

Table 2. Scope of the Cu(I)-Catalyzed Macrocyclic Sonogashira-Type Cross-Coupling



entry	macrocycle	yield (%)[a]	entry	macrocycle	yield (%)[a]
1	 **4**	46	2	 **5**	83
3	 **6**	78	4	 **7**	71[c]
5	 **8**	58	6	 **2**	81[b]
7	 **2**	54[c,d]	8	 **9**	71
9	 **10**	77	10	 **11**	59[b]
11	 **12**	38[b]	12	 **13**	72
13	 **14**	66[c]	14	 **15**	62
15	 **16**	65[b]	16	 **17**	61[b]

[a]Yields following chromatography. Reactions typically performed on 0.12 mmol scale. Ring size of the macrocycles are indicated in red. [b]Using 20 mol % of phen. [c]Reaction time was 48 h. [d]Starting material was the corresponding aryl bromide.

(entries 3 → 5): the benzolactone **6** was cyclized in 78% yield. Replacing the ester functionality of **6** with an ether afforded the macrocycle **7** in 71% yield. A pyridine-containing analogue **8** was also prepared in good yield (58%). The 15-membered macrocycle **2** was prepared in 81% yield, and the macrocyclization could easily be scaled up to gram scale (~2.5 mmol, 75%, 48 h). The macrocycle **2** could also be prepared from the corresponding aryl bromide. Although the yield was

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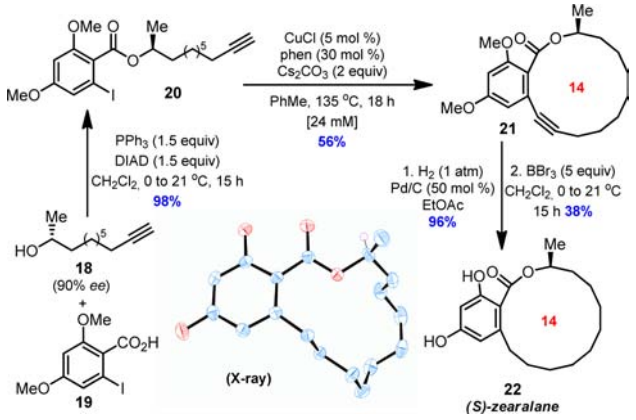
slightly lower (54%), the Cu-catalyzed macrocyclic Sonogashira-type coupling represents a rare example of such a transformation from a corresponding aryl bromide.[10] The aryl iodide moiety could be extended to naphthalene-derived motifs, and the corresponding macrocycle **9** was isolated in good yield (71%). The macrocycle **10** was formed from a corresponding aryl diiodide. Interestingly, macrocyclization was observed with complete selectivity to afford the 15-membered **10** in 77% yield. The macrocyclization was also tolerant to varying the position of the ester unit, as in the 15-membered macrocycle **11** (59% yield). Macrocyclization to form the enyne containing 15-membered macrolactone **12** was hampered by the stability of the corresponding starting material. While the macrocycle **12** could be isolated in 38% yield (entry 11), the β-iodo alkenyl ester was sensitive to the basic conditions employed. Macrocyclization to form *meta*-substituted benzolactones occurred in good yields; the 16- and 18-membered macrocycles **13** and **15** were obtained in 72% and 62% yields respectively (entries 12 and 14). Finally, the synthesis of larger rings was explored (entries 13, 15, and 16). The 17-membered macrocycle **14** was prepared in 66% yield, while the analogous 23- and 25-membered benzolactones **16** and **17** were obtained in 65% and 61% yield, respectively.

To further demonstrate the utility of the Cu-catalyzed macrocyclic Sonogashira-type strategy, the polyketide-derived product (*S*)-zearalane was prepared, which has been reported to have interesting anabolic, estrogenic, anthelminthic, and immunomodulating properties (Scheme 1).[11] The enantioen-

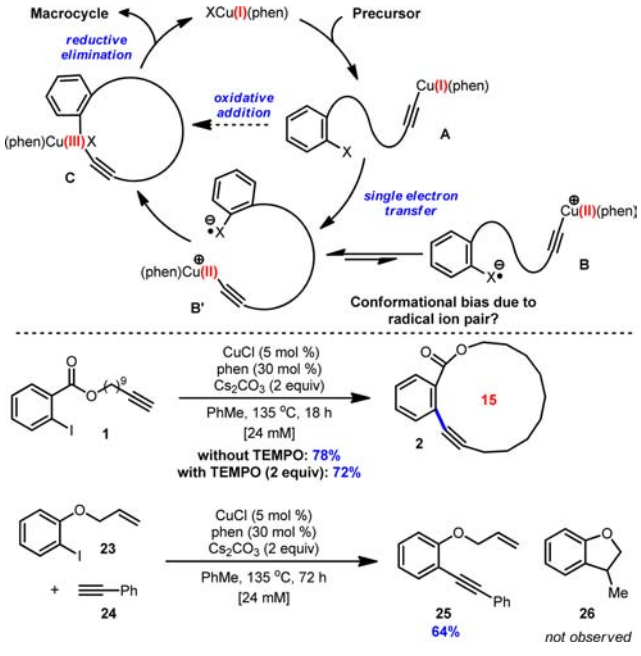
Scheme 1. Total Synthesis of (*S*)-Zearalane Using a Cu-Catalyzed Macrocyclic Sonogashira-Type Coupling



riched secondary alcohol **18**, prepared via known procedures,[12a] underwent Mitsunobu-type coupling with known acid **19**[12b] to provide the ester **20** (98% yield). Attempts at conducting the macrocyclization of ester **20** using known Pd-based cross-coupling conditions ($Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), THF, 18 h) were unsuccessful. When using slow addition and high dilution ([24 or 2.4 mM]), Sonogashira cross-coupling of alkyne **20** did not afford any of the desired product **21**, despite 100% consumption of the starting material **20**. In contrast, treating ester **20** with the catalytic system afforded the 14-membered macrolactone **21** in 56% yield. Hydrogenation of the aryl alkyne (96% yield) and subsequent BBr_3-mediated cleavage of the methyl ethers afforded (*S*)-zearalane **22** in 36% yield over two steps. X-ray quality crystals of (*S*)-zearalane were obtained from slow diffusion of a CH_2Cl_2 solution into hexanes, and subsequent analysis[13] confirmed the macrocyclic structure of **22** (Scheme 1).

The mechanisms of existing Cu-catalyzed Sonogashira-type cross-couplings have not all been studied in detail, and many imply similar mechanistic proposals that have been described for related Cu-catalyzed C−O, C−N, and C−X bond formations.[14] Recently, Bolm et al. have put forth some mechanistic evidence for intermolecular Cu-catalyzed couplings.[15] A likely first step would involve in situ formation of copper acetylide **A** (Scheme 2). Bolm reported experimental

Scheme 2. (Top) Possible Mechanism for the Cu-Catalyzed Macrocyclic Sonogashira-Type Cross-Coupling; (Bottom) Preliminary Mechanistic Investigations



evidence for the importance of excess ligand to promote the formation of species such as copper acetylide **A** versus other polymeric Cu acetylide complexes.[15] Bolm also reported computational studies suggesting against the formation of a high energy Cu(III)-intermediate **C** via direct oxidative addition. Alternatively, single electron transfer (SET) could generate the radical anion **B** or **B′**. The formation of a radical ion pair may help to induce a conformational preference which is conducive to the formation of Cu(III)-intermediate **C**. Preliminary investigations reveal a strong solvent dependence for the macrocyclization. When the cyclization (**1** → **2**, CuCl (5 mol %), phen (30 mol %), Cs_2CO_3 (2 equiv), 135 °C) was carried out in nonpolar solvents the yields were typically higher (PhMe: 78%; PhCl: 74%; xylenes: 72%) than in polar solvents (DMF: <5%; dioxane: 57%) which favor disassociation in the proposed radical ion pair. As radical ion pairs are not commonly invoked in mechanisms of the Pd-catalyzed Sonogashira, it is possible that these mechanistic differences are partially responsible for the efficiency of the Cu-catalyzed strategy. Similar SET pathways for Cu-intermediates have been proposed for photocatalytic Sonogashira cross-couplings.[16] Formation of a carbon centered radical from **B** was investigated: macrocyclization of alkyne **1** in the presence of TEMPO as a radical trap still proceeded in high yield (72% vs 78% in the absence of TEMPO) (Scheme 2). In addition,

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submitting the allylated iodophenol **23** to the optimized conditions for cross-coupling did not afford any of the cyclized **26**.[17] This is in contrast to recently reported Cu-catalyzed photoinduced C−N bond formation in which C−I bond cleavage was observed.[18] The final step would involve reductive elimination from **C** and regeneration of the active catalyst.[19]

In summary, a Cu-catalyzed macrocyclic Sonogashira-type cross-coupling reaction has been developed that outperforms other Pd-catalyzed protocols. Utilization of an operationally simple CuCl/phen/Cs_2CO_3 catalyst system promotes macrocyclization at relatively high concentrations without the need for slow addition techniques and does not afford homodimerization side products. The macrocyclizations are efficient even when employing alkyl alkyne coupling partners which have rarely been reported.[6] Macrocycles with various ring sizes (10- to 25-membered rings), functional groups, and arene substituents (poly- and heteroaromatic) are accessible using the optimized conditions. The protocol described herein demonstrates that copper can replace the conventional, expensive, and toxic Pd-catalyzed macrocyclic Sonogashira cross-coupling reactions. The synthesis of biologically active (*S*)-zearalane has been demonstrated and suggests that further application in the synthesis of other natural products and compounds of medicinal interest is possible.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) For a full description of the attempts to catalyze **1**→**2** using Pd-catalysis, as well as more details concerning optimization of catalyst loadings and concentrations, see the Supporting Information.

(9) The Pd-content of the starting materials was not measured. Note that it has been shown that various chemicals can have trace amounts of Pd that can promote Sonogashira couplings; see: Gonda, Z.; Tolnai, G. L.; Novák, Z. *Chem.—Eur. J.* **2010**, *16*, 11822.

(10) Cu-catalyzed Sonogashira of aryl bromides are rare, see: (a) Thakur, K. G.; Jaseer, E. A.; Naidu, A. B.; Sekar, G. *Tetrahedron Lett.* **2009**, *50*, 2865 (three examples, yields 35%−51%). (b) Mao, J.; Guo, J.; Ji, S.-j.; Mao, J. *J. Mol. Catal. A: Chem.* **2008**, *284*, 85 (two examples, yields 23%). (c) Yang, D.; Li, B.; Yang, H.; Fu, H.; Hu, L. *Synlett* **2011**, *5*, 702 (four examples, yields 48%−72%).

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