

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

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Supporting Information

ABSTRACT: A macrocyclic Cu-catalyzed Sonogashira-type crosscoupling reaction has been developed that employs an operationally simple CuCl/phen/Cs₂CO₃ 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 Pdcatalyzed cross-coupling strategies were investigated for macrocyclization via carbon–carbon bond formation; an intramolecular Sonogashira cross-coupling³ was plagued by various difficulties that made it unappealing in the context of drug discovery efforts (Figure 1).⁴ The Sonogashira cross-coupling





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 macro-



cyclization 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 reactions⁶ inspired by the original Castro–Stephens cross-coupling⁷ (CuI/PPh₃, Cu(neo)(PPh₃), and [Cu-(DMEDA)₂]Cl₂) 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



"Yields following chromatography. Reactions run on 0.12 mmol scale. Temperature refers to the temperature of the oil bath. ^bIn place of CuCl, the preformed catalyst $[Cu(DMEDA)_2]Cl_2$ (5 mol %) was used without any other added ligand. ^cIn place of CuCl, the preformed catalyst $[Cu(DMEDA)_2]Cl_2$ (5 mol %) was used. ^dUsing 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]Cl₂ (5 mol %) developed by Bolm et al. afforded a low yield of 2 as well (30%); however, employing [Cu(DMEDA)₂]Cl₂ 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 \rightarrow 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 Cs₂CO₃, 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/Cs2CO3 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

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Table 2. Scope of the Cu(I)-Catalyzed Macrocyclic

Sonogashira-Type Cross-Coupling

^{*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 $3 \rightarrow 5$): 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 envne containing 15membered 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 25membered 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(PPh₃)₂Cl₂ (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 BBr₃-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 CH₂Cl₂ solution into hexanes,

and subsequent analysis¹³ 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





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 \mathbf{B} or \mathbf{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 $(1 \rightarrow 2, \text{CuCl})$ mol %), phen (30 mol %), Cs₂CO₃ (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,

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/Cs₂CO₃ 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 (10to 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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