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Rapid synthesis of bicyclic lactones *via* palladium-catalyzed aminocarbonylative lactonizations†

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A novel and efficient palladium-catalyzed aminocarbonylative lactonization of amino propargylic alcohols has been developed to provide rapid access to various bicyclic lactones especially dihydropyrrole-fused furanones, which are novel structures and have not been explored in biological and medicinal settings. This method can also be used to access β-lactone products such as 16. Preliminary biological evaluations revealed that compounds 13h and 13s demonstrated promising activity against *Clostridium difficile* and compounds 13h, 13k, 13s, and 16b showed activity against several important fungal pathogens.

Our recent efforts[1–3] in developing tandem palladium-catalyzed carbonylation reactions[4–8] for complex natural product synthesis have resulted in a novel method to synthesize oxaspirolactones from hydroxyl cyclopropanol starting materials (Fig. 1A).[2] We envisioned that this new synthetic capability could be potentially used to synthesize oxaspirolactone **5**, an important precursor for the total syntheses of stemofoline alkaloids (*cf.* **4**).[9–14] We proposed a tandem process to prepare **5** from **7** *via* a tandem Mannich reaction and ketalization. Compound **7** could be derived from hydroxyl cyclopropanol **8** *via* the palladium-catalyzed carbonylative oxaspirolactonization we have developed. Compound **8** could be synthesized from dihydropyrrole-fused furanone **10**. In order to quickly access **10**, we envisioned another palladium-catalyzed amino-carbonylative lactonization of amino propargylic alcohol **11**. Surprisingly, there was no documented synthesis of dihydropyrrole-fused furanone (*cf.* **10**), which turned out to be a novel scaffold. Their potential biological activities and use in medicinal chemistry remain unknown. Therefore, we decided to develop and generalize the proposed palladium-catalyzed aminocarbonylative lactonizations to provide expedient avenues toward dihydropyrrole-fused furanones.

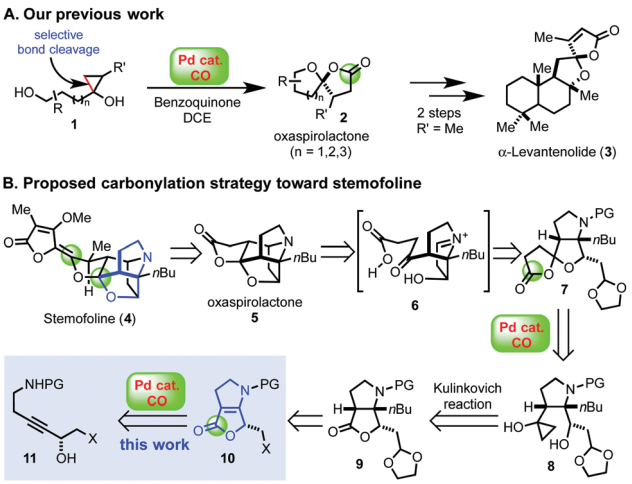

Fig. 1 Background and research design.

Significant advances have been made in the area of metal-catalyzed carbonylation of alkynes.[15] In 1979, Murray and Norton reported an elegant palladium-catalyzed carbonylation of homo-propargylic alcohols to synthesize α-methylene γ-lactones.[16,17] Since then, many palladium-catalyzed cyclocarbonylations of alkynes have been reported. Notably, Alper and co-workers reported carbonylative syntheses of 2(5*H*)-furanones from propargylic alcohols;[18–20] Yang,[21–25] Akita,[26] Gabriele[27–29] and others[30–34] have reported oxy or amino-palladation-alkoxycarbonylation of alkynes to synthesize various heterocycles. Despite these progresses, the intramolecular aminopalladation-carbonylative lactonization of amino propargylic alcohols of type **11** to synthesize dihydropyrrole-fused furanones (*cf.* **10**) has not been reported. Herein, we describe elements of our recent efforts in developing such transformations to rapidly construct dihydropyrrole-fused furanones, which would not only facilitate total syntheses of complex natural products such as

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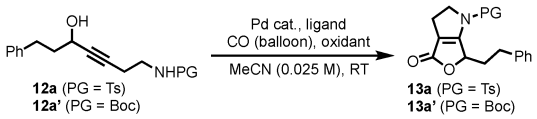
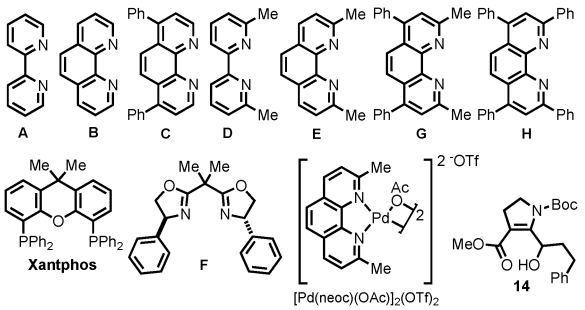
Table 1 Reaction condition optimizations



12a (PG = Ts)
12a' (PG = Boc)

13a (PG = Ts)
13a' (PG = Boc)

Entry	Reaction conditions (equiv.)	Yield[a] (%)
1	$PdCl_2$ (0.1), **A** (0.1), BQ (1.5), PG = Ts	0
2	$Pd(tfa)_2$ (0.1), **A** (0.1), BQ (1.5), PG = Ts	63
3	$Pd(tfa)_2$ (0.1), **B** (0.1), BQ (1.5), PG = Ts	58
4	$Pd(tfa)_2$ (0.1), **C** (0.1), BQ (1.5), PG = Ts	63
5	$Pd(tfa)_2$ (0.1), **D** (0.1), BQ (1.5), PG = Ts	58
6	$Pd(tfa)_2$ (0.1), **E** (0.1), BQ (1.5), PG = Ts	53
7	$Pd(tfa)_2$ (0.1), **Xantphos** (0.1), BQ (1.5), PG = Ts	Trace
8	$Pd(tfa)_2$ (0.1), **F** (0.1), BQ (1.5), PG = Ts	33
9	$PdCl_2(MeCN)_2$ (0.1), **E** (0.1), BQ (1.5), PG = Ts	0
10	$Pd(tfa)_2$ (0.1), **C** (0.2), BQ (1.5), PG = Ts	41
11	$Pd(tfa)_2$ (0.1), **C** (0.1), BQ (3.0), PG = Ts	51
12	$Pd(tfa)_2$ (0.1), **C** (0.1), BQ (1.0), PG = Ts	61
13	$Pd(tfa)_2$ (0.1), **C** (0.1), BQ (1.0), PG = Ts, Cs_2CO_3 (1.0)	0
14	$Pd(tfa)_2$ (0.1), **C** (0.1), BQ (1.5), PG = Ts, CO (7 atm)	31
15	$PdCl_2(MeCN)_2$ (0.1)/AgOTf (0.2), **C** (0.1), BQ (1.5), PG = Ts	72
16	$PdCl_2(MeCN)_2$ (0.1)/AgOTf (0.2), **G** (0.1), BQ (1.5), PG = Ts	81
17	$PdCl_2(MeCN)_2$ (0.1)/AgOTf (0.2), **H** (0.1), BQ (1.5), PG = Ts	42
18	$[Pd(neoc)(OAc)]_2(OTf)_2$ (0.1), BQ (1.5), PG = Ts	69
19	$PdCl_2(MeCN)_2$ (0.1)/AgOTf (0.2), **G** (0.1), $CuCl_2$ (1.5), PG = Ts	0
20	**$PdCl_2(MeCN)_2$ (0.1)/AgOTf (0.2), G (0.1), DDQ (1.5), PG = Ts**	**90**
21	$PdCl_2(MeCN)_2$ (0.1)/AgOTf (0.2), **G** (0.1), DDQ (1.5), PG = Boc	0
22	$Pd(tfa)_2$ (0.1), BQ (1.5), PG = Boc, MeOH	24[b]

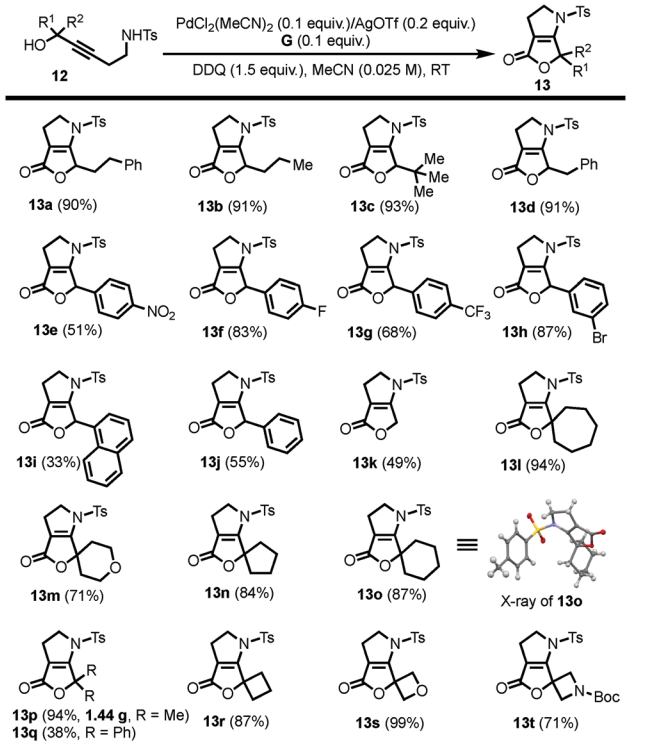


[a] Isolated yield. [b] Yield of **14** with MeOH as the solvent.

the stemofoline alkaloids, but also provide novel molecules for therapeutic development.

Our investigation started with model substrate **12a** (Table 1), which was readily prepared *via* 1,2-addition of acetylide to hydrocinnamaldehyde (see the ESI†). When the commonly used carbonylation catalyst $PdCl_2$ was used in combination with 2,2-bipyridine ligand **A**, no desired product **13a** was obtained. We hypothesized that a more cationic and electron-deficient palladium catalyst should function better to activate the triple bond for the aminopalladation step than the neutral $PdCl_2$ catalyst. Thus, $Pd(tfa)_2$ was explored next. To our delight, the desired product **13a** was produced in 63% yield with *p*-benzoquinone (BQ, 1.5 equiv.) as an oxidant and MeCN as a solvent. We then investigated the effect of different ligands and several bipyridine and 1,10-phenanthroline-based ligands (entries 3–6) were evaluated. These ligands are either the same as ligand **A** or slightly less effective, but are much more effective than BOX-ligand **F** (entry 8). Bidentate phosphine ligand Xantphos (entry 7) turned off the reaction almost completely and only a trace amount of **13a** was obtained. We further found that a 1 : 2 ratio of the palladium catalyst and the ligand is not as good as 1 : 1. Increasing the amount of BQ from 1.5 equiv. to 3.0 equiv. (entry 11) made the reaction messier with 51% yield of the desired product, and decreasing the amount to 1.0 equiv. slightly reduced the reaction yield (61%, entry 12). Adding a base such as Cs_2CO_3 was detrimental (entry 13) and increasing the carbon monoxide pressure to 7 atm showed an inhibitory effect (entry 14). To further improve the reaction yield, we explored the more electron deficient $Pd(OTf)_2$ (0.1 equiv.) complex generated from a combination of $PdCl_2(MeCN)_2$ and AgOTf (1 : 2 ratio). The yield did increase to 72% (entry 15). Ligand **G** (entry 16, 81% yield) was found to be superior to ligand **C** (entry 4) and ligand **H** (entry 16). $[Pd(neoc)(OAc)]_2(OTf)_2$, a cationic dimeric palladium complex developed by the Waymouth lab[35] also worked for this transformation but with reduced reaction yield. While $CuCl_2$ as an oxidant was deleterious, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) increased the yield to 90% (entry 20). Interesting, when the nitrogen-protecting group was changed to Boc (**12a'**), even the optimized reaction conditions did not give any desired product **13a'** (entry 21). When MeOH

Table 2 Substrate scope



was used as the solvent with $Pd(tfa)_2$ as the catalyst and BQ as the oxidant, product **14** was produced in 24% yield (entry 22), which indicates that with the Boc-protected substrate, the aminopalladation and alkoxycarbonylation steps could take place, but not the lactonization step. These results suggest that the formation of the furanone ring is the problematic step presumably due to pseudo-$A_{(1,3)}$ interaction between the Boc group and the alkyl side chain.

With optimized reaction conditions established, the substrate scope of this new aminocarbonylative lactonization method was assessed (Table 2). A variety of hydropyrrole-fused furanones can be prepared. In general, for secondary propargylic alcohols with an alkyl substituent, the reaction yield is excellent (*cf.* **13a–d**). The yield for secondary propargylic alcohols with an aryl substituent dropped slightly (*cf.* **13f–h**) or significantly (*cf.* **13e**, **13i–j**) presumably due to the ease of oxidizing the secondary alcohol to a ketone and other undesired reaction pathways. A primary propargylic alcohol substrate gave modest yield of the desired hydropyrrole-fused furanone product (*cf.* **13k**). Notably, sterically hindered tertiary alcohols (**13i–t**) are excellent substrates and high yields were obtained except for the case of **13q**. Tricyclic products **13l–o** and **13r–t** containing a spirocyclic ring system were produced in excellent yields. The structure of **13o** was unambiguously confirmed by X-ray analysis.[36] Due to the mild reaction conditions, functional groups such as sulfonamide, Boc-carbamate, bromide, and nitro group are well tolerated. The reaction can also be conducted on a gram-scale (**13p**).

We then prepared substrate **15** and wondered the possibility of forming a 5,6-fused furanone product (*cf.* **17**, Fig. 2). With one

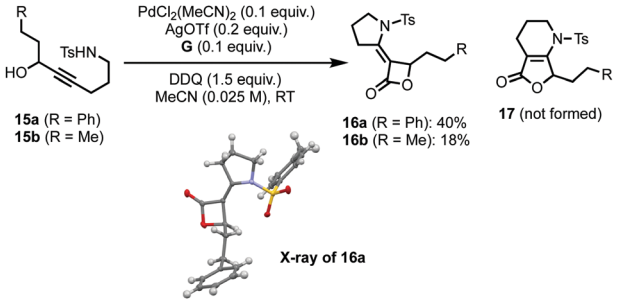


Fig. 2 Formation of β-lactone product.

carbon added between the nitrogen nucleophile and the triple bond, in addition to the expected 6-*endo-dig* amino-palladation, a 5-*exo-dig* amino-palladation becomes a potential competing pathway. If the latter occurs, we would be expecting a strained β-lactone product (*cf.* **16**). Interestingly, under the optimal reaction conditions for the formation of 5,5-fused furanones, no fused product **17** was identified in the reaction mixture, instead β-lactone product **16** was produced in 40% (R = Ph) or 18% (R = Me) yield.[37] The structure and double bond geometry of **16a** were unambiguously validated by X-ray analysis (Fig. 2).[36]

Mechanistically, as shown in Fig. 3, after ligand exchange, a hydroxyl group-directed activation of the alkyne with the Pd(II) catalyst would trigger a 5-*endo-dig anti*-aminopalladation to form the dihydropyrrole ring and produce vinyl-palladium species **19** from **18**. Carbon monoxide migratory insertion followed by lactonization would lead to product **13** and a Pd(0) catalyst. The latter would be oxidized to a Pd(II) catalyst by DDQ to continue the next catalytic cycle. For the formation of **16**, a 5-*exo-dig anti*-aminopalladation overrides a 6-*endo-dig* amino-palladation. The *trans* double bond geometry of **16** supported the *anti*-aminopalladation process over a *syn*-aminopalladation process.

Due to the structural novelty of the aminocarbonylative lactonization products, we evaluated them against several important bacterial, yeast and mold pathogens (see the ESI†). Our preliminary results showed that compounds **13h** and **13s** exhibited promising activity against toxigenic strains of *Clostridium difficile* with 128 μM and 64 μM minimum inhibitory concentration (MIC) values. Interestingly, these two compounds did not show side effects on the beneficial intestinal microflora and were nontoxic to Caco-2 cell lines up to 256 μM. Compounds **13h**, **13k**, **13s**, and **16b**

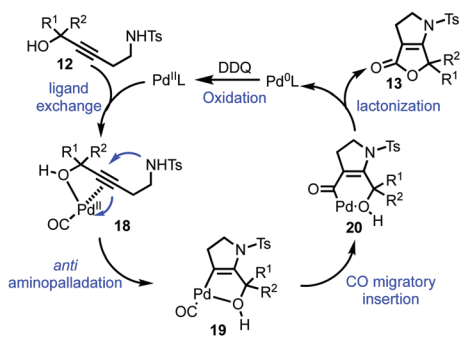


Fig. 3 Proposed catalytic cycle.

showed activity against several important fungal pathogens including strains of *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Cryptococcus gattii*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Aspergillus niger*, and *Aspergillus brasiliensis* with 64–128 μM MIC values.

In summary, we have developed an efficient palladium-catalyzed aminocarbonylative lactonization to synthesize various novel dihydropyrrole-fused furanones. This method can also be used to access β-lactone product such as **16**, another novel scaffold with potential biological functions. Our preliminary biological evaluations have identified several compounds including **13h**, **13k**, **13s**, and **16b** with promising antibacterial and antifungal activity. We are currently using this new synthetic capability to facilitate total syntheses of complex natural products as well as preparing analogues of the antibacterial and antifungal lead compounds to improve potency and physicochemical properties for new therapeutic development.

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