Cyclization-Carbonylation-Cyclization Coupling Reaction of Propargyl Ureas with Palladium(II)-Bisoxazoline Catalyst

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Abstract: The cyclization-carbonylation-cyclization coupling reaction (CCC-coupling reaction) of propargyl ureas catalyzed by Pd II(box) complexes afforded symmetrical ketones bearing two 2-amino-2-oxazoline groups in good to moderate yields.

Keywords: CCC-coupling; bisoxazoline; palladium; carbonylation; propargyl urea

1. Introduction

Oxazolines appear in numerous medicinally active compounds and natural products [1–3]. Among them, 2-amino-2-oxazolines show various interesting pharmacological properties such as anti-hypertensive [4], antidepressant [5], appetite suppressant [6], nitric oxide synthase inhibitor [7] and central nervous system activity [8]. Diarylketones are also frequently found in natural products and pharmaceuticals [9,10]. In addition, they are good precursors for non-steroidal antiestrogen drugs (e.g., tamoxifen) and diarylmethyl compounds [11]. Cascade reactions are important tools for constructing a variety of heterocycles in one step starting from simple compounds [12,13]. Recently, we reported the cyclization-carbonylation-cyclization (CCC)-coupling reaction of propargylic acetates, amides, γ-propynyl-1,3-diketones, N-propargylanilines and o-alkynylphenols catalyzed by palladium(II)-bisoxazoline (box) complexes (Scheme 1). Symmetrical ketones bearing two cyclic...
orthoesters [14], oxazolines [14], oxabicyclic groups [15], quinolines [16] and benzofurans [16] were obtained in a one-step reaction.

**Scheme 1.** Previous works and this work: CCC-coupling reaction of propargyl acetates, amides and ureas.

In these transformations, the triple bond of the substrate coordinates to palladium(II) and undergoes nucleophilic attack by the intramolecular nucleophile X, followed by CO insertion to produce the acyl palladium intermediate A (Scheme 2). Coordination of the triple bond of a second molecule induces the second cyclization. Reductive elimination then leads to formation of a ketone bearing two heterocyclic groups. We believe that the box ligand enhances the \( \pi \)-electrophilicity of palladium(II) [14–19], and thus promotes coordination of the second triple bond to the acyl palladium intermediate A, leading to dimerization. Previously, Bacchi *et al.* reported that the PdI\(_2\)-KI catalyzed cyclization-alkoxycarbonylation of propargyl urea 1a afforded 2-amino-2-oxazoline derivative 2a in 70% yield along with imidazoline derivative 3a in 23% yield (Scheme 3) [20,21]. To extend our concept of the CCC-coupling reaction, we investigated the Pd\(^{II}\)(box) catalyzed carbonylation reaction of propargyl ureas 1 (Scheme 1).

**Scheme 2.** Our concept of a cyclization-carbonylation-cyclization coupling reaction (CCC coupling reaction) of propargylic compounds.
Scheme 3. Bacchi et al.: PdI₂-KI catalyzed cyclization-alkoxycarbonylation of 1 [20,21].

2. Results and Discussion

2.1. Optimization Studies

Initially, we selected 1a as a standard substrate to search for potential catalysts (Table 1). The reaction of 1a with (CH₃CN)₂PdCl₂ (5 mol %) in the presence of p-benzoquinone (1.5 equiv.) in methanol under a carbon monoxide atmosphere (balloon) generated the dimeric ketone 4a in 46% yield, along with monomeric ester 2a (36% yield) (Table 1, entry 1). These products were easily separated by chromatography on silica gel.

Table 1. Optimization of reaction condition.

| Entry | Catalyst (5 mol %) | Conditions     | Yield of 4a (%) | Yield of 2a (%) |
|-------|--------------------|----------------|-----------------|-----------------|
| 1     | (CH₃CN)₂PdCl₂      | rt, 24 h       | 4a: 46          | 2a: 36          |
| 2     | Pd(tfa)₂           | −20 °C, 24 h   | 4a: 24          | 2a: 20          |
| 3     | [Pd(bipy)Cl₂]      | rt, 24 h       | 4a: 29          | 2a: 13          |
| 4     | (P₂H₃)₂PdCl₂       | rt, 19 h       | 4a: 16          | 2a: 61          |
| 5     | Pd(PPh₃)₄         | rt, 24 h       | 4a: 83          | 2a: 17          |
| 6     | [Pd(L)(tfa)₂]      | rt, 24 h       | 4a: 61          | 2a: 21          |
| 7     | [Pd(L)(tfa)₂]      | 50 °C, 3 h     | 4a: 30          | 2a: 29          |
| 8     | [Pd(L)(tfa)₂]      | −20 °C, 24 h   |                |                 |
| 9 a   | [Pd(L)(tfa)₂]      | rt, 24 h       | N.R.            |                 |
| 10 a  | [Pd(L)(tfa)₂]      | rt, 24 h       | N.R.            |                 |

a CH₂Cl₂ was used as solvent; b DMF was used as solvent.

Pd(tfa)₂ and 2,2'-bipyridine complex also gave a mixture of products 4a and 2a in low yields (Table 1, entries 2–3). The use of phosphine complexes, (P₂H₃)₂PdCl₂ and Pd(PPh₃)₄, afforded monomeric ester 2a as a major product (Table 1, entries 4–5). Next, an attempt was made to use the box complex [Pd(L)(tfa)₂] according to our previous results [14–19]. As expected, the reaction occurred smoothly, and the yield of 4a improved to 83% (Table 1, entry 6). Higher temperatures reduced both the reaction time and the dimer 4a:monomer 2a ratio (Table 1, entry 7). Lower temperatures reduced the yields of both products (Table 1, entry 8). Furthermore, CH₂Cl₂ and DMF were not suitable as solvents (Table 1,
entries 9–10). The structure of the dimeric ketone 4a was confirmed by comparing the corresponding $^1$H- and $^{13}$C-NMR data with those of similar oxazolines [22].

2.2. Substrate Scope and Limitations

Having optimized the reaction conditions, we examined the reaction of various propargyl ureas 1b–j with the box complex [Pd(L)(tfa)$_2$] (Table 2).

Table 2. CCC-coupling reaction of propargyl ureas 1.

| Entry | R$^1$ | R$^2$     | Conditions     | Yield of 4 (%) | Yield of 2 (%) |
|-------|-------|-----------|----------------|----------------|----------------|
| 1     | Me    | nPr       | rt, 24 h       | 4a: 83         | 2a: 17         |
| 2     | Me    | Bn        | rt, 18 h       | 4b: 73         | 2b: 10         |
| 3     | Me    | nBu       | rt, 20 h       | 4c: 61         | 2c: 25         |
| 4     | Me    | Phenethyl | 7 $^\circ$C, 48 h | 4d: 58         | 2d: 20         |
| 5     | Me    | Cyclohexyl | rt, 24 h       | 4e: 66         | 2e: 30         |
| 6     | -(CH$_2$)$_5$- | Phenethyl | rt, 24 h       | 4f: 89         | 2f: 11         |
| 7     | -(CH$_2$)$_5$- | Cyclohexyl | rt, 24 h       | 4g: 74         | 2g: 20         |
| 8     | -(CH$_2$)$_5$- | Ph        | rt, 40 h       | 4h: 24         | 2h: 23         |
| 9     | -(CH$_2$)$_5$- | H         | rt, 48 h       | N.R.           |                |
| 10    | H     | Phenethyl | rt, 24 h       | N.R.           |                |

* 1i was recovered (41%).

The reactions proceeded well for substrates 1a–g bearing two methyl groups in the propargylic position (R$^1$ = Me) (Table 2, entries 1–5). The bulky cyclohexyl group in the propargylic position (R$^1$ = -(CH$_2$)$_5$-) did not affect the yields of 4f and 4g (Table 2, entries 6 and 7). The alkyl substituent of the terminal nitrogen (R$^2$) was found to be important for promoting the cyclization; lower yields were obtained for 1h (R$^2$ = Ph) (Table 2, entry 8). The reaction of unsubstituted 1i (R$^2$ = H) did not proceed (Table 2, entry 9). In addition, the gem-dialkyl effect [23] plays a fundamental role for the success of the reaction; the reaction of substrate 1j having no substituent on the propargylic position did not proceed (Table 2, entry 10).

2.3. Preparation of [Pd(L)(tfa)$_2$]

Ligand L was prepared according to the previously reported procedure (Scheme 4) [24,25]. Condensation of 2,2-dimethyl-malononitrile with (±)-phenylglycinol using Zn(OTf)$_2$ in toluene afforded a mixture of L (racemic) and L’ (meso) [18,26]. Chromatographic separation of the mixture gave the compounds in 34% and 38% yields, respectively. The key [Pd(L)(tfa)$_2$] [28] catalyst was easily obtained as a stable solid by simple filtration from a methanolic mixture of L and Pd(tfa)$_2$. 
3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. $^1$H-, $^{13}$C-NMR and HMBC spectra were recorded on JEOL AL 400 and JEOL Lambda 500 spectrometer spectrometers in CDCl$_3$ with Me$_4$Si as an internal reference. $^{13}$C-NMR spectra were recorded at 100 MHz. In the case of CD$_2$Cl$_2$, solvent peaks were used as a reference (5.32 ppm for $^1$H, and 53.8 ppm for $^{13}$C). High-resolution mass spectra (HR-MS) were obtained with JEOL GC Mate II, JMS-SX102 and JEOL JMS 600H spectrometer. IR spectra were recorded with JASCO FT/IR-300 spectrometer. All reagents were purchased from commercial sources and used without purification. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

3.2. Preparation of Substrates 1a–j

The substrates 1a–j were prepared according to the literature [27]. The substrates 1, except for 1a [20] and 1b [20] are new compounds [22].

3.3. General Procedure for the CCC-Coupling Reaction of 1

A 50-mL two-neck round-bottom flask containing a magnetic stirring bar, substrate 1 (0.5 mmol), p-benzoquinone (1.5 mmol) and MeOH (7 mL) was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pump-filling via the three-way stopcock. A MeOH (1 mL) suspension of [Pd(L)(tfa)$_2$] (0.025 mmol) was added to the stirred solution at an appropriate temperature using a syringe. The remaining [Pd(L)(tfa)$_2$] was washed in MeOH (1 mL) twice. After stirring at the appropriate temperature for a period of time, the mixture was diluted with CH$_2$Cl$_2$ (50 mL) and washed with 3% NaOH (40 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (50 mL) twice and the combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by
chromatography on silica gel. The fraction eluted with hexane-AcOEt (30/1–1/1) afforded the monomeric ester 2 and the dimeric ketone 4. 4 was then precipitated from the reaction mixture and the resulting precipitate was collected by filtration and washed with cold MeOH (1 mL × 2). The filtrate was reprocessed via the above procedure to provide additional products after chromatography.

3.3.1. Dimeric Ketone 4a

Hexane/AcOEt = 1/1. Colorless needles; mp 186–191 °C; $^1$H-NMR (CDCl$_3$) δ 0.95 (6 H, t, $J = 7.2$ Hz), 1.55–1.65 (4 H, m), 1.63 (12 H, s), 3.20 (4 H, t, $J = 7.2$ Hz), 4.11 (2 H, br-s), 5.91 (2 H, s); $^{13}$C-NMR (CDCl$_3$) δ 11.2 (2C), 22.9 (2C), 25.4 (4C), 44.6 (2C), 71.0 (2C), 103.2 (2C), 154.4 (2C), 177.2 (2C), 186.4; IR (KBr): 3203, 3114, 2963, 2877, 1724, 1629, 1370, 1183, 969, 930 cm$^{-1}$; HRMS-EI: m/z [M$^+$] calcd for C$_{19}$H$_{30}$N$_4$O$_3$: 362.2318; found: 362.2315.

3.3.2. (2E)-Methyl 2-[4,4-dimethyl-2-(propylamino)-5(4H)-oxazolylidene]acetate (2a)

Hexane/AcOEt = 4/1. Spectral data were identical to those described in the literature [20].

3.3.3. Dimeric Ketone 4b

Hexane/AcOEt = 1/1. Colorless needles; mp 155–158 °C; $^1$H-NMR (CDCl$_3$) δ 1.65 (12 H, s), 4.40 (2 H, s), 5.92 (2 H, s), 7.26–7.36 (10 H, m); $^{13}$C-NMR (CDCl$_3$) δ 25.4 (4C), 46.8 (2C), 70.9 (2C), 103.5 (2C), 127.6 (4C), 127.7 (2C), 128.7 (4C), 137.8 (2C), 154.6 (2C), 176.9 (2C), 186.2; IR (KBr): 2930, 1730, 1630, 1182, 966, 933 cm$^{-1}$; HRMS-EI: m/z [M$^+$] calcd for C$_{27}$H$_{30}$N$_4$O$_3$: 458.2318; found: 458.2320.

3.3.4. (2E)-Methyl 2-[4,4-dimethyl-2-(phenylmethylamino)-5(4H)-oxazolylidene]acetate (2b)

Hexane/AcOEt = 4/1. Spectral data were identical to those described in the literature [20].

3.3.5. Dimeric Ketone 4c

Hexane/AcOEt = 1/1. Colorless needles; mp 189–191 °C; $^1$H-NMR (CDCl$_3$) δ 0.94 (6 H, t, $J = 7.2$ Hz), 1.33–1.59 (8 H, m), 3.23 (4 H, t, $J = 7.2$ Hz), 4.07 (2 H, br-s), 5.91 (2 H, s); $^{13}$C-NMR (CDCl$_3$) δ 13.8 (2C), 19.9 (2C), 25.4 (4C), 31.7(2C), 42.6 (2C), 71.0 (2C), 103.2 (2C), 154.4 (2C), 177.1 (2C), 186.4; IR (KBr): 3206, 2965, 1725, 1627, 1184, 929 cm$^{-1}$; HRMS-EI: m/z [M$^+$] calcd for C$_{21}$H$_{34}$N$_4$O$_3$: 390.2631; found: 390.2632.

3.3.6. (2E)-Methyl 2-[4,4-dimethyl-2-(butylamino)-5(4H)-oxazolylidene]acetate (2c)

Hexane/AcOEt = 4/1. Colorless needles; mp 96–99 °C; $^1$H-NMR (CDCl$_3$) δ 0.94 (3 H, t, $J = 7.2$ Hz), 1.35–1.43 (2 H, m), 1.52–1.62 (8 H, m), 3.23 (2 H, t, $J = 7.2$ Hz), 4.07 (3 H, s), 4.13 (1 H, br-s), 5.54 (1 H, s); $^{13}$C-NMR (CDCl$_3$) δ 13.7, 19.9, 25.9 (2C), 31.7, 42.6, 51.1, 70.7, 92.6, 154.3, 166.6, 178.5; IR (KBr): 3179, 2967, 1723, 1708, 1689, 1656, 1172, 1095 cm$^{-1}$; HRMS-EI: m/z [M$^+$] calcd for C$_{12}$H$_{20}$N$_2$O$_3$: 240.1474; found: 240.1473.
3.3.7. Dimeric Ketone 4d

Hexane/AcOEt = 1/1. Colorless needles; mp 180–182 °C; 1H-NMR (CDCl3) δ 1.63 (12 H, s), 2.89 (4 H, t, J = 6.8 Hz), 3.51 (4 H, t, J = 6.8 Hz), 4.01 (2 H, br-s), 5.87 (2 H, s), 7.19–7.33 (10 H, m); 13C-NMR (CDCl3) δ 25.4 (4C), 35.4 (2C), 43.7 (2C), 71.0 (2C), 103.3 (2C), 126.7 (2C), 128.7 (4C), 128.8 (4C), 138.4 (2C), 154.2 (2C), 177.0 (2C), 186.4; IR (KBr): 3211, 3108, 2942, 1736, 1626, 1180, 966, 931 cm⁻¹; HRMS-EI: m/z [M⁺] calcd for C29H34N4O3: 486.2631; found: 486.2631.

3.3.8. (2E)-Methyl 2-[4,4-dimethyl-2-(phenylethylamino)-5(4H)-oxazolylidene]acetate (2d)

Hexane/AcOEt = 3/1. Brown oil; 1H-NMR (CDCl3) δ 1.62 (6 H, s), 2.89 (2 H, t, J = 6.8 Hz), 3.51 (2 H, t, J = 6.8 Hz), 3.68 (3 H, s), 4.35 (1 H, br-s), 5.52 (1 H, s), 7.19–7.31 (5 H, m); 13C-NMR (CDCl3) δ 25.9 (2C), 35.5, 43.6, 51.1, 70.7, 92.9, 126.7, 128.7 (2C), 128.8 (2C), 138.3, 154.3, 166.5, 178.2; IR (KBr): 3360, 3193, 2972, 1724, 1657, 1106, 1048 cm⁻¹; HRMS-EI: m/z [M⁺] calcd for C16H20N2O3: 288.1474; found: 288.1471.

3.3.9. Dimeric Ketone 4e

Hexane/AcOEt = 4/1. Colorless needles; mp 243–246 °C; 1H-NMR (CDCl3) δ 1.19–1.95 (22 H, m), 1.85 (12 H, s), 3.55 (2 H, m), 6.25 (2 H, s); 13C-NMR (CDCl3) δ 24.5 (4C), 24.7 (4C), 24.7 (2C), 32.7 (4C), 53.2 (2C), 64.9 (2C), 107.0 (2C), 156.4 (2C), 170.5 (2C), 184.1; IR (KBr): 3205, 2933, 2857, 1729, 1625, 1367, 1182, 990, 928 cm⁻¹; HRMS-EI: m/z [M⁺] calcd for C25H38N4O3: 442.2944; found: 442.2943.

3.3.10. (2E)-Methyl 2-[4,4-dimethyl-2-(cyclohexylethylamino)-5(4H)-oxazolylidene]acetate (2e)

Hexane/AcOEt = 5/1. Colorless needles; mp 125–127 °C; 1H-NMR (CDCl3) δ 1.15–2.06 (10 H, m), 1.62 (6 H, s), 3.46 (1 H, m), 3.69 (3 H, s), 4.04 (1 H, br-s), 5.53 (1 H, s); 13C-NMR (CDCl3) δ 24.6, 25.5 (2C), 25.9 (2C), 33.3 (2C), 51.0, 51.3, 70.8, 92.4, 153.3, 166.6, 178.5; IR (KBr): 3206, 2934, 2856, 1717, 1658, 1538, 1102 cm⁻¹; HRMS-EI: m/z [M⁺] calcd for C14H22N2O3: 266.1631; found: 266.1633.

3.3.11. Dimeric Ketone 4f

Hexane/AcOEt = 10/1. Colorless needles; mp 186–190 °C; 1H-NMR (CDCl3) δ 1.32–1.80 (16 H, m), 2.65–2.72 (4 H, m), 2.89 (4 H, t, J = 6.8 Hz), 3.51 (4 H, t, J = 6.8 Hz), 4.06 (2 H, br-s), 5.88 (2 H, s), 7.19–7.31 (10 H, m); 13C-NMR (CDCl3) δ 22.3 (4C), 25.2 (2C), 32.9 (4C), 35.7 (2C), 43.9 (2C), 74.4 (2C), 103.6 (2C), 126.6 (2C), 128.7 (4C), 128.9 (4C), 138.6 (2C), 153.6 (2C), 177.3 (2C), 186.3; IR (KBr): 3418, 2930, 2860, 1720, 1625, 1014, 976, 931 cm⁻¹; HRMS-EI: m/z [M⁺] calcd for C35H42N4O3: 566.3257; found: 566.3260.

3.3.12. Monomeric Ester 2f

Hexane/AcOEt = 15/1. Colorless needles; mp 104–106 °C; 1H-NMR (CDCl3) δ 1.37–1.82 (8 H, m), 2.55–2.62 (2 H, m), 2.89 (2 H, t, J = 6.8 Hz), 3.51 (2 H, t, J = 6.8 Hz), 3.68 (3 H, s), 4.09 (1 H, br-s), 5.52 (1 H, s); 13C-NMR (CDCl3) δ 22.2 (2C), 25.1, 33.6 (2C), 35.6, 43.9, 51.1, 74.2, 92.6, 126.6,
128.7, 128.8, 138.6, 153.5, 166.7, 179.2; IR (KBr): 3111, 2969, 1732, 1655, 1127, 1065 cm$^{-1}$; HRMS-EI:$m/z$ [M$^+$] calcd for C$_{19}$H$_{24}$N$_2$O$_3$: 328.1787; found: 328.1786.

3.3.13. Dimeric Ketone 4g

Hexane/AcOEt = 15/1. Colorless needles; mp 189–191 °C; $^1$H-NMR (CDCl$_3$) $\delta$ 1.11–1.79 (32 H, m), 2.60–2.72 (4 H, m), 3.40–3.47 (2 H, m), 3.94 (2 H, br-s), 5.91 (2 H, s); $^{13}$C-NMR (CDCl$_3$) $\delta$ 22.3 (4C), 24.6 (4C), 25.1 (2C), 25.5 (2C), 32.8 (4C), 33.2 (4C), 51.3 (2C), 74.2 (2C), 103.4 (2C), 153.0 (2C), 177.3 (2C), 186.3; IR (KBr): 3430, 2928, 2855, 1710, 1624, 1498, 996, 927 cm$^{-1}$; HRMS-EI:$m/z$ [M$^+$] calcd for C$_{31}$H$_{46}$N$_4$O$_3$: 522.3570; found: 522.3568.

3.3.14. Monomeric Estere 2g

Hexane/AcOEt = 20/1. Colorless needles; mp 133–135 °C; $^1$H-NMR (CDCl$_3$) $\delta$ 1.12–2.05 (18 H, m), 2.55–2.62 (2 H, m), 3.42–3.50 (1 H, m), 3.69 (3 H, s), 3.96 (1 H, br-s), 5.54 (1 H, s); $^{13}$C-NMR (CDCl$_3$) $\delta$ 22.2 (2C), 24.6 (2C), 25.2, 25.6, 33.2 (2C), 33.4 (2C), 51.1, 51.4, 74.2, 92.4, 152.8, 166.8, 179.3; IR (KBr): 3358, 2932, 2857, 1707, 1644, 1518, 1125, 1066 cm$^{-1}$; HRMS-EI:$m/z$ [M$^+$] calcd for C$_{17}$H$_{26}$N$_2$O$_3$: 306.1944; found: 306.1945.

3.3.15. Dimeric Ketone 4h

Hexane/AcOEt = 10/1. Colorless needles; mp 300 °C; $^1$H-NMR (CDCl$_3$) $\delta$ 1.46–1.91 (16 H, m), 2.67–2.73 (4 H, m), 6.30 (2 H, s), 7.16–7.56 (10 H, m); $^{13}$C-NMR (CDCl$_3$) $\delta$ 21.4 (4C), 23.9 (2C), 31.9 (4C), 69.4 (2C), 108.4 (2C), 122.5 (4C), 127.8 (2C), 129.8 (4C), 133.2 (2C), 155.9 (2C), 169.3 (2C), 183.7; IR (KBr): 3411, 2929, 2859, 1715, 1628, 1603, 1535, 996 cm$^{-1}$; HRMS-EI:$m/z$ [M$^+$] calcd for C$_{31}$H$_{34}$N$_4$O$_3$: 510.2631; found: 510.2629.

3.3.16. Dimeric Ketone 2h

Hexane/AcOEt = 30/1. Colorless needles; mp 121–124 °C; $^1$H-NMR (CD$_2$Cl$_2$) $\delta$ 1.40–1.89 (8 H, m), 2.61–2.68 (2 H, m), 3.68 (3 H, s), 5.62 (1 H, s), 7.03 (1 H, t, $J$ = 7.6 Hz), 7.32 (2 H, dd, $J$ = 7.6, 8.0 Hz), 7.55 (2 H, d, $J$ = 8.0 Hz); $^{13}$C-NMR (CD$_2$Cl$_2$) $\delta$ 22.7 (2C), 25.6, 33.6 (2C), 51.4, 75.4, 93.4, 118.2 (2C), 122.9, 129.3 (2C), 139.1, 149.5, 166.7, 177.4; IR (KBr): 3298, 2929, 1688, 1605, 1552, 1315, 1151, 1064 cm$^{-1}$; HRMS-EI:$m/z$ [M$^+$] calcd for C$_{17}$H$_{20}$N$_2$O$_3$: 300.1474; found: 300.1472.

3.4. Preparation of Ligands and Racemic-[Pd(L)(tfa)$_2$]

3.4.1. Preparation of L and L$'$

To a mixture of dimethylmalononitrile (681 mg, 7.23 mmol) and (±)-phenylglycinol (2.00 g, 14.5 mmol) in anhydrous toluene (160 mL) under Ar was added zinc triflate (2.63 g, 7.23 mmol), and the mixture was refluxed for 3 days. The mixture was allowed to cool, and was then diluted with a saturated NaHCO$_3$ aqueous solution (200 mL) and CHCl$_3$ (300 mL). After vigorously stirring for 1 h, the layers were separated. The aqueous layer was extracted with CHCl$_3$ (50 mL) twice. The combined organic layers were dried with MgSO$_4$ and concentrated in vacuo. The crude products were purified by
column chromatography on silica-gel (70 g). The fraction eluted with hexane/ethyl acetate (7/1) (containing 0.5% Et3N) afforded \( \mathbf{L'} \) (914 mg, 38%) [10] and \( \mathbf{L} \) (818 mg, 34%) as pale yellow oils.

3.4.2. Preparation of \([\text{Pd(}L\text{)(tfa)}_2\text{]}\)

To a stirring solution of \( \mathbf{L} \) (307 mg, 0.92 mmol) in MeOH (4 mL) was added \( \text{Pd(tfa)}_2 \) (305 mg, 0.92 mmol) in MeOH (3 mL). The \([\text{Pd(}L\text{)(tfa)}_2\text{]}\) was then precipitated from the reaction mixture, and the resulting precipitate was collected by filtration and washed with cold MeOH (1 mL) to give racemic-[\text{Pd(}L\text{)(tfa)}_2\text{]} [28] as a white powder (483 mg, 79%).

4. Conclusions

In conclusion, we have presented a cyclization-carbonylation-cyclization coupling reaction (CCC-coupling reaction) of propargyl ureas \( \mathbf{1} \) catalyzed by \( \text{Pd}^{II}(\text{box}) \) complexes. Symmetrical ketones possessing two 2-amino-2-oxazoline groups were obtained in moderate to good yields. We believe that the box ligand enhances the \( \pi \)-electrophilicity of palladium(II), and thus promotes coordination of the triple bond (second molecule) to the acyl palladium intermediate \( \mathbf{A} \), leading to the dimerization reaction. We are currently investigating additional cascade reactions based on the cyclization-carbonylation-cyclization strategy for the synthesis of other types of ketones containing two heterocyclic groups.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/17/8/9220/s1.

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References

1. Chaudhry, P.; Schoenen, F.; Neuenswander, B.; Lushington, G.H.; Aubé, J. One-Step Synthesis of Oxazoline and Dihydrooxazine Libraries. *J. Comb. Chem.* 2007, 9, 473–476.
2. Onishi, H.R.; Pelak, B.A.; Lynn, S.; Silver, L.L.; Kahan, F.M.; Chen, M.-H.; Patchett, A.A.; Galloway, S.M.; Hyland, S.A.; Anderson, M.S.; et al. Antibacterial Agents That Inhibit Lipid A Biosynthesis. *Science* 1996, 274, 980–982.
3. Prinsep, M.R.; Moore, R.E.; Levine, I.A.; Patterson, G.M.L. Westiellamide, A Bistratamide-related Cyclic Peptide From The Blue-Green Alga *Westiellopsis Prolifica*. *J. Nat. Prod.* 1992, 55, 140–142.
4. Bruban, V.; Feldman, J.; Greney, H.; Dontenwill, M.; Schann, S.; Jarry, C.; Payard, M.; Boutin, J.; Scalbert, E.; Pfeiffer, B.; et al. Respective contributions of \( \alpha \)-adrenergic and non-adrenergic mechanisms in the hypotensive effect of imidazoline-like drugs. *Br. J. Pharmacol.* 2001, 133, 261–266.
5. Bosc, J.J.; Forfar, I.; Jarry, C.; Laguerre, M.; Carpy, A. 2-Amino-2-oxazolines, VII: Influence of Structural Parameters on The Antidepressant Activity of 5-(1-Aryl-4-piperazino)methyl-2-amino-2-oxazolines. *Arch. Pharm.* **1994**, *327*, 187–192.

6. Kay, J.M.; Smith, P.; Heath, D. Aminorex and the Pulmonary Circulation. *Thorax* **1971**, *26*, 262–270.

7. Ueda, S.; Terauchi, H.; Yano, A.; Ido, M.; Matsumoto, M.; Kawasaki, M. 4,5-Disubstituted-1,3-oxazolidin-2-imine Derivatives: A New Class of Orally Bioavailable Nitric Oxide Synthase Inhibitor. *Bioorg. Med. Chem.* **2004**, *14*, 313–316.

8. Gally, G.; Norcross, R.; Polara, Preparation of aminooxazoline derivatives for use as TAAR1 ligands. *U.S. Pat. Appl. Publ.* **2011**, US 20110112080 A1 20110512.

9. Neumann, H.; Brennführer, A.; Beller, M. A General Synthesis of Diarylketones by Means of a Three-Component Cross-Coupling of Aryl and Heteroaryl Bromides, Carbon Monoxide, and Boronic acids. *Chem. Eur. J.* **2008**, *14*, 3645–3652, and references cited therein.

10. Lo Fiego, M.J.; Silbestri, G.F.; Chopa, A.B.; Lockhart, M.T. Selective Synthetic Routes to Sterically Hindered Unsymmetrical Diaryl Ketones via Arylstannanes. *J. Org. Chem.* **2011**, *76*, 1707–1714, and references cited therein.

11. Chao, E.Y.H.; Collins, J.L.; Gaillard, S.; Miller, A. B.; Wang, L.; Orbán-Miller, L.A.; Nolte, R.T.; McDonnell, D.P.; Willson, T.M.; Zuercher, W.J. Structure-guided Synthesis of Tamoxifen Analogs with Improved Selectivity for The Orphan ERRγ. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 821–824.

12. Vlaar, T.; Ruijter, E.; Orru, R.V.A. Recent Advances in Palladium-Catalyzed Cascade Cyclizations. *Adv. Synth. Catal.* **2011**, *353*, 809–841.

13. Brennführer, A.; Neumann, H.; Beller, M. Palladium-catalyzed Carboxylation Reactions of Alkenes and Alkynes. *ChemCatChem* **2009**, *1*, 28–41.

14. Yasuhara, S.; Sasa, M.; Kusakabe, T.; Takayama, H.; Kimura, M.; Mochida, T.; Kato, K. Cyclization–Carboxylation–Cyclization Coupling Reactions of Propargyl Acetates and Amides with Palladium(II)–Bisoxazoline Catalysts. *Angew. Chem. Int. Ed.* **2011**, *50*, 3912–3915.

15. Kusakabe, T.; Kawai, Y.; Shen, R.; Mochida, T.; Kato, K. Cyclization–carbonylation–cyclization coupling reactions of γ-propynyl-1,3-diketones with palladium(II)–bisoxazoline catalysts. *Org. Biomol. Chem.* **2012**, *10*, 3192–3194.

16. Kusakabe, T.; Sekiyama, E.; Motodate, S.; Kato, S.; Mochida, T.; Kato, K. Cyclization–Carboxylation–Cyclization Coupling Reactions of N-Propargylanilines and o-Alkynylphenols with Palladium(II)–Bisoxazoline Catalysts. *Synthesis* **2012**, *44*, 1825–1832.

17. Kato, K.; Teraguchi, R.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T.A.; Vologdin, N.V.; Gusev, O.V. Ligand-controlled intramolecular carboxylative cyclization of 1,1-diethynyl acetates: New entry to the functionalized 4-cyclopentene-1,3-diones. *Synlett* **2007**, 638–642.

18. Kato, K.; Teraguchi, R.; Motodate, S.; Uchida, A.; Mochida, T.; Peganova, T.A.; Vologdin, N.V.; Akita, H. *meso*-Phbox-Pd(II) Catalyzed Tandem Carboxylative Cyclization of 1-Ethynyl-1-propargyl Acetate. *Chem. Commun.* **2008**, *3687–3689.

19. Kato, K.; Motodate, S.; Mochida, T.; Kobayashi, T.; Akita, H. Intermolecular Methoxy-carbonylation of Terminal Alkynes Catalyzed by Palladium(II) Bis(oxazoline) Complexes. *Angew. Chem. Int. Ed.* **2009**, *48*, 3326–3328.
20. Bacchi, A.; Chiusoli, G.P.; Costa, M.; Sani, C.; Gabriele, B.; Salerno, G. Nitrogen Heterocycles from palladium-catalysed oxidative cyclization-alkoxycarbonylation of acetylenic ureas. *J. Organomet. Chem.* 1998, 562, 35–43.

21. Costa, M.; Della Cà, N.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. Synthesis of 4H-3,1-Benzoxazines, Quinazolin-2-ones, and Quinoline-4-ones by Palladium-Catalyzed Oxidative Carbonylation of 2-Ethynylaniline Derivatives. *J. Org. Chem.* 2004, 69, 2469–2477.

22. See the electronic supporting information.

23. Sammes, P.G.; Weller, D.J. Steric Promotion of Ring Formation. *Synthesis* 1995, 1205–1222.

24. Cornejo, A.; Fraile, J.M.; García, J.I.; Gil, M.J.; Martínez-Merino, V.; Mayoral, J.A.; Pires, E.; Villalba, I. An Efficient and General One-Pot Method for the Synthesis of Chiral Bis(oxazoline) and Pyridine Bis(oxazoline) Ligands. *Synlett* 2005, 2321–2324.

25. García, J.I.; Mayoral, J.A.; Pires, E.; Villalba, I. Synthesis of non-symmetric bisoxazoline compounds. An easy way to reach tailored chiral ligands. *Tetrahedron: Asymmetry* 2006, 17, 2270–2275.

26. Foltz, C.; Stecker, B.; Marconi, G.; Bellemín-Laponnaz, S.; Wadepohl, H.; Gade, L.H. Stereochemical Consequences of Threefold Symmetry in Asymmetric Catalysis: Distorting C3 Chiral 1,1,1-Tris(oxazolinyl)ethanes (“Trisox”) in CuII Lewis Acid Catalysts. *Chem. Eur. J.* 2007, 13, 9912–9923.

27. Michael, F.E.; Sibbald, P.A.; Cochran, B.M. Palladium-catalyzed intramolecular chloroamination of alkenes. *Org. Lett.* 2008, 10, 793–796.

28. Kato, K.; Matsuba, C.; Kusakabe, T.; Takayama, H.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T.A.; Vologdin, N.V.; Gusev, O.V. 2,2′-Isopropylidenebis[(4S,5R)-4,5-di(2-naphthyl)-2-oxazoline] ligand for asymmetric cyclization-carbonylation of meso-2-alkyl-2-propargylocyclohexane-1,3-diols. *Tetrahedron* 2006, 62, 9988–9999.

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