Homogeneous Catalysis

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Palladium(II)-Catalyzed Cyclizative Cross-Coupling of *ortho*-Alkynylanilines with *ortho*-Alkynylbenzamides under Aerobic Conditions**

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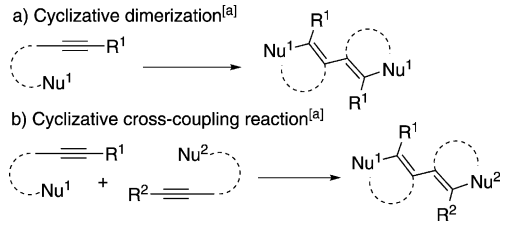
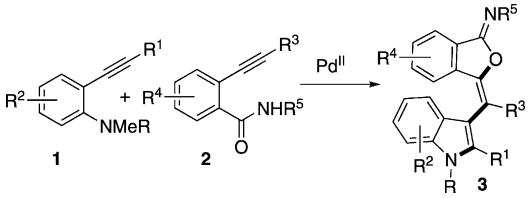
Dedicated to Professor Yulin Li on the occasion of his 80th birthday

In light of the importance of heterocycles in medicinal chemistry and from the viewpoint of synthetic efficiency, cyclizative dimerization is of particular interest as it allows the preparation of cyclic dimers from linear starting materials and indeed a few successful examples have recently been reported wherein heteronucleometallation[1] is used as a key initiation step (Scheme 1 a).[2,3] Concurrently, palladium(0)-catalyzed co-cyclization of two internal alkynes, one bearing an electrophile and the other a nucleophile, by a sequence of carbopalladation and reductive elimination has been developed by the group of Wu.[4] An even more challenging but synthetically powerful transformation would be cyclizative cross-coupling reaction of two different nucleophile-bearing internal alkynes for the one-step construction of heterodimers (Scheme 1 b). To the best of our knowledge, there are only few examples developed by Ma and Yu wherein allenes are used as cyclization partners.[3a–c] We report herein that the cyclizative cross-coupling reaction between *o*-alkynylanilines (**1**) and *o*-alkynylbenzamides (**2**) takes place efficiently to afford the bis(heterocycle)s **3** (Scheme 2). In this reaction, three chemical bonds are created, thus leading to the formation of two heterocycles, an indole and an iminoisobenzofuranone, which are tethered by a geometrically defined tetrasubstituted double bond.



Scheme 1. Strategies of cyclizative cross-coupling reaction. [a] For the sake of clarity, only the product resulting from the *endo-n*-dig cyclization mode is shown.



Scheme 2. Cyclizative cross-coupling reaction of *o*-alkynylanilines (**1**) and *o*-alkynylbenzamides (**2**).

Although conceptually appealing, the practical execution of the cyclizative cross-coupling between **1** and **2** is challenging. Indeed, both **1** and **2** have a high propensity to undergo the cyclization leading to cyclic monomers[5] and recently, their cyclizative dimerizations[2h,6] have also been reported. In addition, while the *o*-alkynylanilines **1** are known to undergo only the 5-*endo*-dig cyclization,[7] the *o*-alkynylbenzamides **2** can cyclize by both the 5-*exo*-dig and the 6-*endo*-dig modes using either an oxygen or nitrogen center as an internal nucleophile.[8–10] Therefore, to realize the projected reaction, one might address not only the regio- (*endo* versus *exo* cyclization) and chemoselectivity (O versus N cyclization), but also the homo- versus heterocoupling processes.

We began our studies by investigating the cyclizative cross-coupling reaction between *N,N*-dimethyl-2-(*p*-tolylethynyl)aniline (**1a**) and *N*-benzyl-2-(phenylethynyl)benzamide (**2a**). Some representative results are shown in Table 1 (for details see Tables S1–S8 in the Supporting Information). Key observations, pertinent to optimization of the reaction conditions, which ultimately led to high yield of **3aa** are summarized as follows: a) $Pd(OAc)_2$ was essential (entry 5), while the presence of $Cu(OAc)_2$ increased significantly the efficiency of the desired transformation (entry 1 versus entries 2–4); b) the presence of iodide increased the selectivity of heterodimerization (**3aa**) versus homodimerization (**4a**; entries 3 versus 4) with nBu$_4$NI being the best; c) HOAc was needed to ensure the Pd^{II} turnover; d) the reaction temperature of 80 °C with DMSO as the solvent was deemed to be optimal. Lower temperature increased the yield of the homodimers; e) although the reaction proceeded with 0.01 equivalents of $Pd(OAc)_2$ (entries 6–9), a higher yield of **3aa** was obtained when the loading of $Pd(OAc)_2$ was increased (entry 10–13). Finally, the optimum reaction con-

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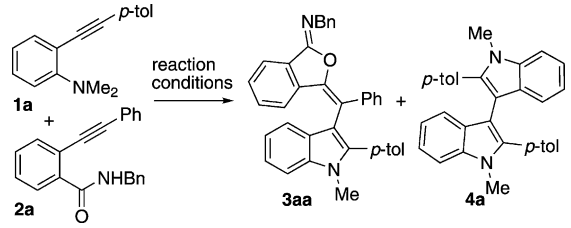
Table 1: Optimization of reaction conditions.[a]



Entry	Pd^{II} [equiv]	Cu^{II} [equiv]	nBu_4NI [equiv]	t [h]	**3aa/4a**	**3aa** Yield [%][b]
1[c,d]	0.10	–	1.0	2	1.3:1	32
2[c,d]	0.10	0.5	1.0	12	2.9:1	59
3[d]	0.02	0.2	1.0	11	2.9:1	59
4[d]	0.02	0.2	–	11	1.9:1	50
5	–	0.2	1.0	3	–	trace
6	0.01	0.4	1.0	11	4:1	66
7	0.01	0.8	1.0	11	4:1	66
8	0.01	1.2	1.0	11	4:1	66
9	0.01	0.8	2.0	11	5:1	68
10	0.05	0.8	2.0	2	6:1	73
11	0.05	1.6	4.0	2	6:1	68
12	0.10	0.8	2.0	1.5	9:1	81
13[e]	0.10	0.8	2.0	1.5	16:1	89

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (1.5 equiv), $Pd(OAc)_2$ (0.01–0.10 equiv), $Cu(OAc)_2$ (0.2–1.6 equiv), nBu_4NI (1.0–4.0 equiv), HOAc (1.0 equiv) in DMSO (1.0 mL), air atmosphere, 80 °C. [b] Yield of isolated product. [c] 50 °C. [d] **2a** (1.0 equiv). [e] **2a** (2.0 equiv).

ditions were determined to be: **1a** (0.05 mmol, 1.0 equiv), **2a** (2.0 equiv), $Pd(OAc)_2$ (0.1 equiv), $Cu(OAc)_2$ (0.8 equiv), nBu_4NI (2.0 equiv), HOAc (1.0 equiv), DMSO (1.0 mL), 80 °C, air. Under these reaction conditions, the cyclizative cross-coupling product **3aa** was isolated in 89 % yield with an excellent product selectivity (**3aa**/**4a** = 16:1; entry 13).

With the optimum reaction conditions in hand, the scope of the reaction was examined. The substrates used are listed in Figure 1 and the structures of the products are shown in Table 2. With respect to the scope of the *o*-alkynylanilines **1**, both the aromatic and aliphatic substituents (R^1 = Ar or alkyl), including the functionalized **1d**, were well tolerated and the reaction of **1b–h** with **2a** furnished the cross-coupling products **3ba–ha** in good to excellent yields with high product selectivity (**3**/**4**). No intramolecular bis(amination) product was detected with **1d**, which contains an amide unit.[11] It is worth noting that in the case of aliphatic *o*-alkynylanilines (**1c** and **1d**), only a slightly excess (1.2 equiv) of *o*-alkynylbenzamides (**2a–c** and **2n**) was needed to deliver the desired products (**3ca–cc**, **3da**, **3cn**) in good yields. Presumably, the alkyl substituent disfavored the competitive homodimerization process. The reaction conditions were applicable not only to *N*,*N*-dimethyl substrates, but also to N-methyl-N-alkyl derivatives. In the latter case, the N-methyl group was removed selectively.[12] For example, reaction of **1i** with **2f** gave the N-pentyl bis(heterocycle) **3if** in 68 % yield. A series of *o*-(arylethynyl)benzamides (**2a–n**) bearing various substituents with different electronic properties were tested. The nature of the alkyl residue of the N-alkyl amides (R^5 = Bn, *n*-Pr, *n*Bu, *i*Bu) did not impact the reaction outcome, thus affording the products (**3ga**, **3gk**, **3fl**, and **3fm**) in good yields and selectivities. A variety of substituents such as methyl, methoxy, chlorine, and fluorine at different positions of the two aromatic rings were tolerated. However, the reaction involving 6-methyl-2-phenylethynylbenzamide (**2i**) as the coupling partner delivered the desired product (**3ai**) in reduced yields with concurrent increase of the homocoupling product **4a**. Interestingly, the reaction efficiency was restored with 6-methoxy-2-phenylethynylbenzamide (**2j**), thus affording **3aj** in excellent yield and selectivity.

The structure of **3ae** was determined by X-ray structural analysis.[13] The stereochemistry of the C=N and C=C bonds was assigned to be *Z* and *E*, respectively. Two enantiomers with axial chirality were seen in the crystal structure because of the restricted rotation of the C–C σ bond. Indeed, the reaction of a chiral benzamide **2n** with **1c** delivered a mixture of two diastereomers (**3cn**) in 62 % yield (d.r. = 1:1).

Mechanistically, the present cyclizative cross-coupling reaction could be initiated by either aminopalladation of **1** or oxypalladation of **2** to form the intermediates **A** or **A′**, respectively (Scheme 3). To gain insight into the mechanism, a series of control experiments were performed. Firstly, addition of $Pd(OAc)_2$ (0.8 equiv) to the mixture of **1a** (1.0 equiv) and **2a** (1.0 equiv) in $[D_6]$DMSO at room temperature gave, after 5 minutes, the intermediate **A** as the only product in about 56 % yield [Eq. (1), Scheme 3].[6,11,14] In a set of two parallel experiments, we found that reaction of $Pd(OAc)_2$ with **1a** at room temperature afforded **A** cleanly, while reaction of $Pd(OAc)_2$ with **2a** directly afforded the cyclic dimer.[15] These results clearly showed that $Pd(OAc)_2$ can catalyze the cyclization of both **1** and **2**. Nevertheless, it is capable of selectively activating the **1** in the presence of **2**. Secondly, mixing the freshly prepared solution of **A** in $[D_6]$DMSO with **1a** (1.0 equiv) and **2a** (1.0 equiv) under argon at RT for 12 hours delivered **3aa** and **4a** in a ratio of 7:1 at 30 % conversion [Eq. (2), Scheme 3]. Therefore, **A** reacted with **2a** much faster than with **1a**. Overall, the results of these control experiments indicated that $Pd(OAc)_2$ mediated preferentially the cyclization of **1**, while the resulting vinylpalladium selectively catalyzed the ring closure of **2**.

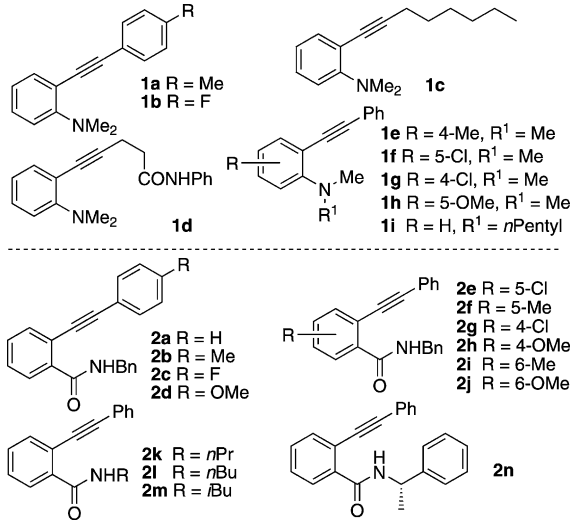
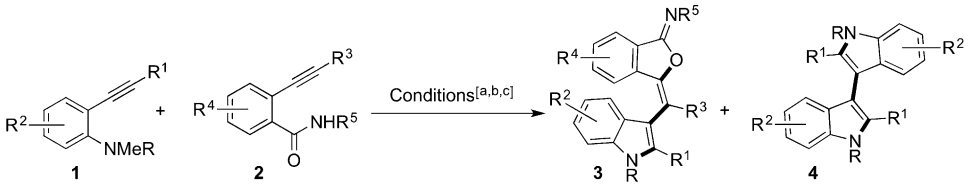
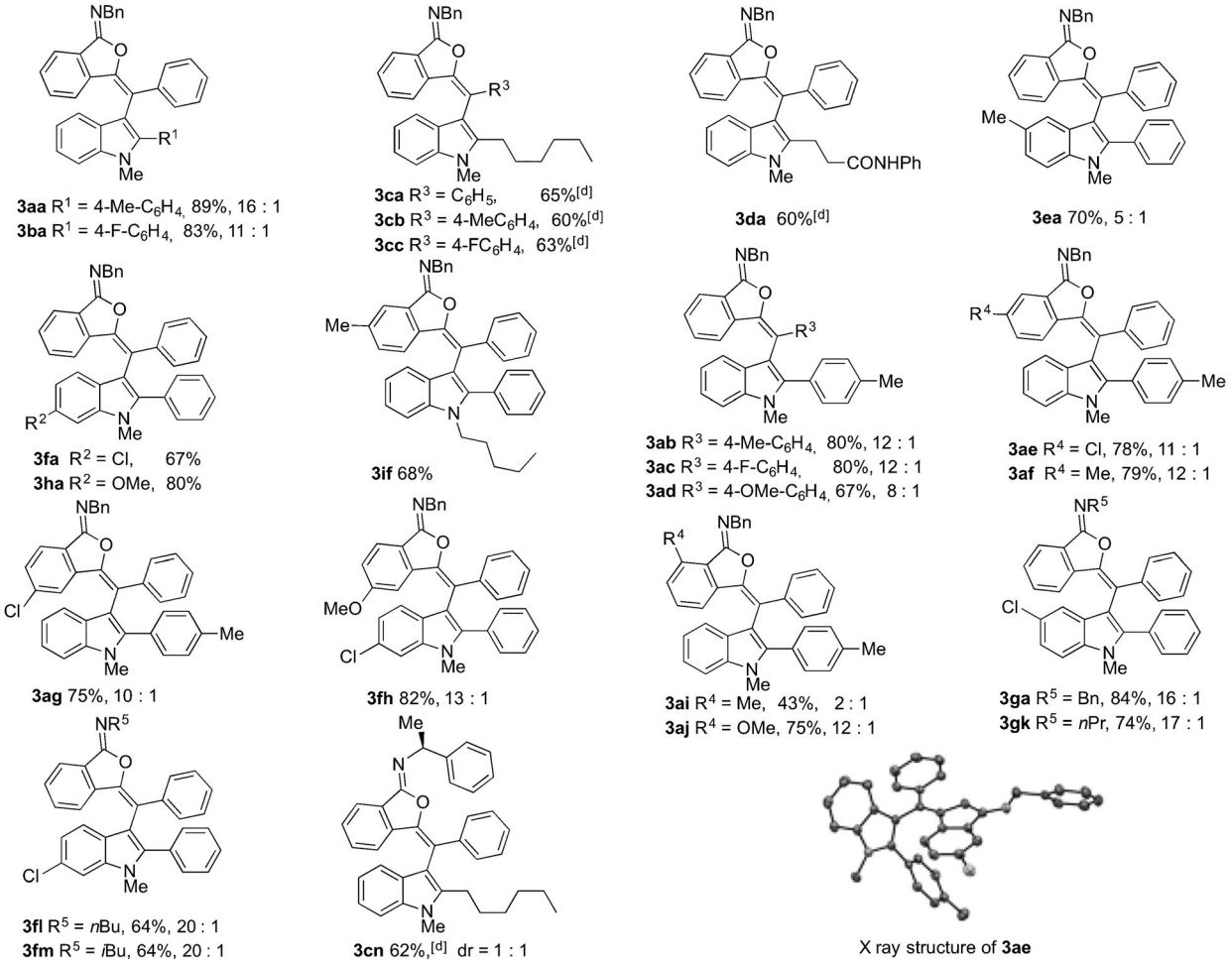


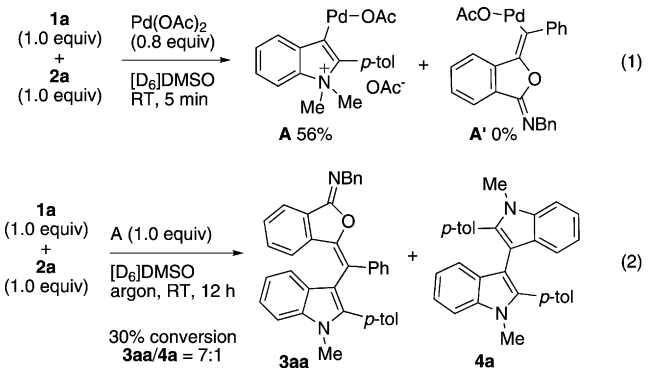
Figure 1. Substrates for the cyclizative cross-coupling reaction.

Table 2: Scope of cyclizative cross-coupling between *o*-alkynylanilines (**1**) and *o*-alkynylbenzamides (**2**).





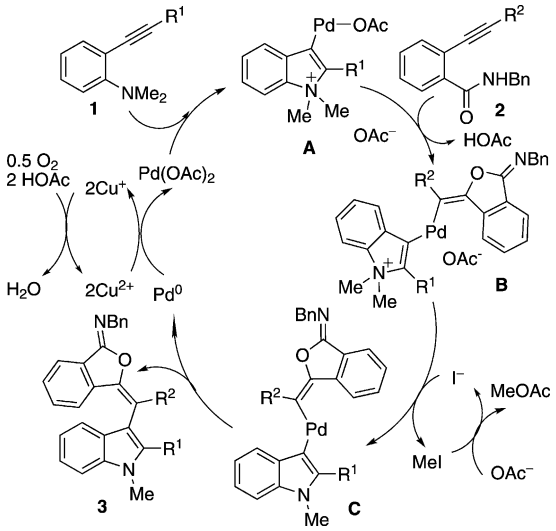
[a] Reaction conditions: **1** (0.05 mmol), **2** (0.10 mmol), $Pd(OAc)_2$ (0.10 equiv), $Cu(OAc)_2$ (0.8 equiv), nBu_4NI (2.0 equiv), HOAc (1.0 equiv), and DMSO (1.0 mL) was heated in a 5 mL reaction tube at 80 °C under an air atmosphere for 1.5 h. [b] Yield of isolated product. [c] Ratio of **3** to **4**, calculated according to the ^1H NMR spectra of the crude reaction mixture. [d] Used 1.2 equiv of **2**, and no 3,3′-bisindole **4** was detected.



Scheme 3. Control experiments.

Although reasons behind these selectivities are at present unclear, the different reactivity of $Pd(OAc)_2$ and **A** towards two arylalkynes ensured the occurrence of the desired reaction at the expense of the homodimerization processes.

A tentative reaction pathway is depicted in Scheme 4. Selective coordination of $Pd(OAc)_2$ to the triple bond of **1** and subsequent *anti* aminopalladation (5-*endo*-dig) affords **A**, which would then act as Lewis acid to selectively activate the **2**.[16] The subsequent chemo- and regioselective *anti*-5-*exo*-dig oxypalladation provides the intermediate **B** which, upon N-demethylation by nucleophilic attack of I^- or OAc^-, provided **C**. Reductive elimination from **C** furnishes **3** and



Scheme 4. A plausible reaction pathway. Ligands on Pd were omitted for clarity.

Pd^0. The oxidation of Pd^0 to Pd^{II} by $Cu(OAc)_2$ completes the catalytic cycle.

In conclusion, an efficient palladium(II)-catalyzed cyclizative cross-coupling of two internal alkynes has been developed. In this operationally simple reaction, three chemical bonds are formed, thus leading to the formation of two different heterocycles which are tethered by a tetrasubstituted double bond. Further work is in progress to exploit the power of this reaction for the synthesis of other bis(heterocyclic) compounds.

Experimental Section

General procedure: A 5 mL-vial was charged with **1a** (0.05 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (0.1 equiv), $Cu(OAc)_2$ (0.8 equiv), nBu$_4$NI (2.0 equiv), HOAc (1.0 equiv), and DMSO (1.0 mL). After being heated under air (1 atm) at 80 °C for 1.5 h, the reaction was quenched with water and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was dissolved in $CDCl_3$ (0.6 mL) for ^{1}H NMR analysis to calculate the ratio of **3aa** to **4a**. Then the sample was purified by silica gel chromatography (petroleum ether/ethyl acetate 20:1) to give the cross-coupling product **3aa** (23.6 mg, 89% yield, foam). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.79 (m, 1H), 7.61–7.54 (m, 2H), 7.49 (d, J = 8.2 Hz, 1H), 7.47–7.43 (m, 2H), 7.40–7.22 (m, 9H), 7.22–7.16 (m, 1H), 7.16–7.10 (m, 1H), 7.10–7.03 (m, 3H), 7.00 (d, J = 7.9 Hz, 2H), 6.39 (d, J = 8.0 Hz, 1H), 4.86 (s, 2H), 3.79 (s, 3H), 2.27 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.3, 147.4, 140.6, 140.1, 139.2, 138.0, 137.8, 137.2, 131.6, 130.2, 129.8, 129.6, 129.0, 128.9, 128.5, 128.3, 128.1, 128.0, 127.9, 127.0, 126.8, 123.4, 122.8, 122.4, 120.5, 120.1, 112.2, 110.5, 109.8, 52.1, 31.6, 21.4 ppm; ATR-IR (neat): $\tilde{\nu}$ =3052 (w), 3051 (w), 3028 (w), 2920 (w), 1695 (m), 1465 (m), 1061 (m), 1033 (m), 1021 (s), 987 (m), 764 (m), 740 (s), 739 (s), 696 (s); HRMS (ESI) calcd for $C_{38}H_{31}N_2O^+$ $[M+H]^+$ 531.2431; found 531.2432.

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[12] C_3-unsubstituted indoles were the major products if primary and secondary anilines were used as reaction partners.

[13] CCDC 958685 (**3ae**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[15] A minor compound that matches the structure of **A′** was detected in the NMR spectrum of the crude reaction mixture of this control experiment. However, we did not have convincing evidence to support this structural assignment.

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