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$[Cp^*IrCl_2]_2$ Catalyzed Formation of 2,2′-Biindoles from 2-Ethynylanilines

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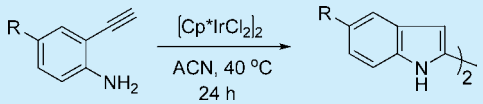
Supporting Information

ABSTRACT: $[Cp^*IrCl_2]_2$ catalyzes the cyclization of 2-ethynylanilines to 2,2′-biindoles via intramolecular hydroamination. A reaction pathway has been proposed on the basis of deuterium labeling experiments and computational studies.

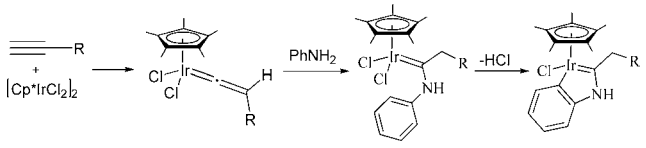


Nitrogen heterocyclic compounds occupy a very important role in synthetic organic chemistry because of the useful properties of many members of this class of compounds.[1] Over 50 naturally occurring alkaloids containing the 2,2′-biindole subunit have been isolated and characterized.[2] This subunit is stable and can be found in a vast number of biologically active natural products such as the tjipanazoles, staurosporine, *ent*-staurosporine, holyrine, arcyriaflavin, rebeccamycin, and staurosporinone[3] and has also been utilized in synthetic biologically active molecules such as (−)-K252a[4] and in anion sensor organic materials.[5] The 2,2′-biindole structure can be prepared by the condensation of *N*-aryl oxamide derivatives (Madelung cyclization),[3a,6] intramolecular cyclization of the corresponding 1,3-diynes,[7] or coupling of the corresponding indole derivatives.[8] In most cases, however, low-yield multistep syntheses[8] or harsh reaction conditions are required,[3a,6] although a two-step conversion of 2-ethynylanilines to 2,2′-biindoles can proceed in very good overall yields.[7] The development of an efficient new synthetic route to 2,2′-biindole derivatives would therefore be of interest to synthetic organic chemists.

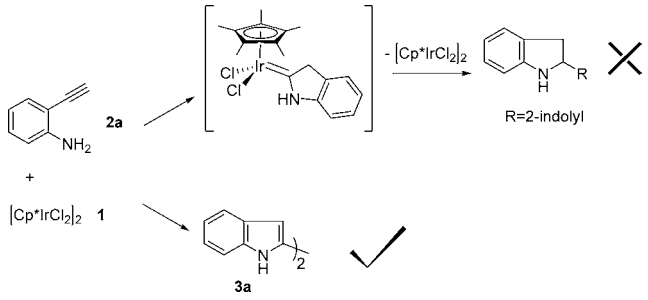
We have recently reported that the reaction of $[Cp^*IrCl_2]_2$, **1**, with an aniline and a terminal alkyne led to the formation of an orthometalated iridium amino-carbene.[9] The proposed reaction pathway involved the formation of a vinylidene intermediate, followed by nucleophilic attack of aniline at the α-carbon and a proton transfer to an aminocarbene, and orthometalation (Scheme 1).[9]

It occurred to us that an intramolecular hydroamination using a 2-ethynylaniline, **2a**, would lead to an iridium amino-carbene which cannot undergo orthometalation due to ring strain. This amino-carbene may instead undergo dimerization and isomerization to afford 2-indolylindoline. What we have found, however, was that the reaction proceeded cleanly to afford fluorescent 2,2′-biindole, **3a** (Scheme 2).

Scheme 1. Formation of Iridium Amino-carbenes



Scheme 2. Reaction of 1 and 2a; Proposed Formation of 2-Indolylindoline and the Observed Formation of 2,2′-Biindole



The biindole has been completely characterized, including by a single-crystal X-ray structural analysis. Cyclization of an alkynylaniline such as **2a** to an indole is known to be catalyzed by a number of transition metal complexes, including those of rhodium,[10] ruthenium,[11] gold,[7d] and molybdenum,[12] and several iridium complexes have also been reported to catalyze the cyclization of internal 2-alkynylanilines to the corresponding indole derivatives.[13] There is also a recent report on a one-pot, two-step synthesis of 3,3′-biindoles through the cyclization of internal alkynylanilines using a gold catalyst.[14] Besides a long reaction time and high temperature (4 d and 70 °C), this reaction also tended to yield a mixture of the indole and the 3,3′-biindole which was substrate-dependent.

To the best of our knowledge, there has been no report on a single-step synthesis of 2,2′-biindoles from simple and readily available alkynylanilines.

An optimization study showed that a good yield could be obtained at elevated temperature (Table 1, entries 1, 3, and 4) or at ambient temperature albeit with a longer reaction time

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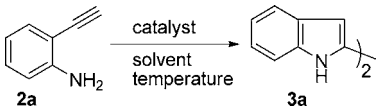
Table 1. Optimization Study for 1-Catalyzed Cyclization of 2a to 3a[a]



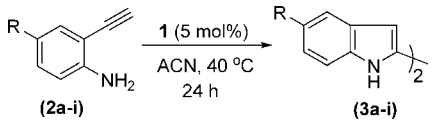
entry	catalyst (mol %)	solvent	T (°C)	yield (%)[c]
1	**1** (5)	DCE	40	58
2	**1** (5)	DCE	50	68
3	**1** (5)	DCE	80	82
4	**1** (2.5)	DCE	80	81
5	**1** (1)	DCE	80	71
6[b]	**1** (2.5)	DCE	40	78
7	$[Cp^*RhCl_2]_2$ (2.5)	DCE	80	–
8	$[Ir(cod)Cl]_2$ (2.5)	DCE	80	–
9	**1** (2.5)	toluene	80	75
10	**1** (2.5)	THF	60	77
11	**1** (2.5)	MeOH	60	–
12	**1** (2.5)	ACN	80	87
13[b]	**1** (2.5)	ACN	40	89
14	**1** (2.5)	DMF	80	60
15	**1** (2.5)	CH_2Br_2	80	70

[a]The cyclization of **2a** (0.05 mmol) was carried out in the presence of **1** in a solvent (3 mL) at various temperatures for 12 h. [b]Reaction was carried out for 24 h. [c]Isolated yields.

(Table 1, entries 6 and 13). A lower catalyst loading could be tolerated somewhat (Table 1, entries 3–5), as well as a range of solvents, from toluene to acetonitrile (Table 1, entries 9–15); the last is optimal, but the use of methanol afforded the hydration product, 2-aminoacetophenone. Two other catalytic systems, *viz.*, $[Cp^*RhCl_2]_2$ and $[Ir(cod)Cl]_2$, were also tested, but they failed to furnish **3a** under similar conditions (entries 7 and 8).

This reaction represents a very attractive route to biindoles, as straightforward synthetic routes to 2-ethynylanilines are available.[10a] For example, Sonogashira cross-coupling of 2-iodo-4-methylaniline with trimethylsilylacetylene followed by proto-desilylation provided the desired substrate **2b** in an overall yield of 81%. The substrate scope study (Table 2) showed that

Table 2. Cyclization of 2 to 3 Catalyzed by 1[a]



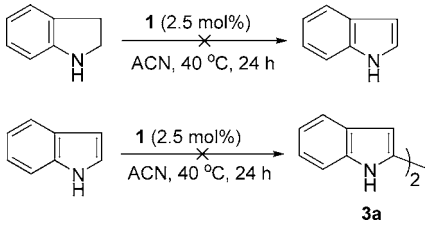
entry	R	yield (%)[b]
1	H	**3a**, 89
2	CH_3	**3b**, 81
3	^{t}Bu	**3c**, 79
4	Br	**3d**, 86
5	Cl	**3e**, 84
6	NO_2	**3f**, 89
7	CN	**3g**, 73
8	CO_2CH_3	**3h**, 79
9	$CO_2C_2H_5$	**3i**, 87
10[c]	CH_3	**3j**, 78

[a]The cyclization of **2a** (0.05 mmol) was carried out in the presence of **1** (0.0125 mmol) in acetonitrile (3 mL) at 40 °C for 24 h. [b]Isolated yields. [c]R = 5-CH_3.

functional group tolerance was excellent, and a wide range of functional groups (alkyls, halides, CN, NO_2, and esters) was tolerated, although the reaction failed with secondary alkynylanilines (*N*-methyl and *N*-benzyl-2-ethynylanilines). Substitution at the 5- instead of the 4-position was also tolerated (entry 10), and a reaction with a larger scale of **2b** (250 mg) gave a 78% yield, demonstrating that the reaction was amenable to scaling-up.

A number of possible reaction pathways to **3** were considered. Pathways involving the intermediate formation of 2-indolylindoline (Scheme 2), followed by **1**-catalyzed dehydrogenation of the indoline moiety, could be ruled out, as **1** failed to react with indoline to afford indole under similar conditions (Scheme 3 top); the computed ΔG° for the carbene

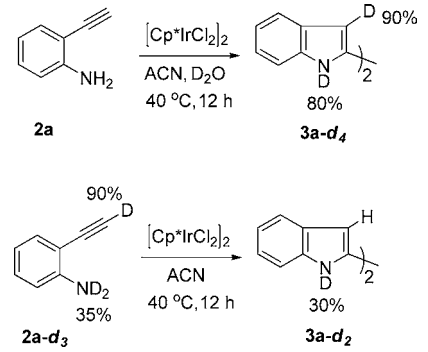
Scheme 3. Attempted Reactions of 1 with Indoline and Indole



dimerization needed was also high (+64 kJ mol^{-1}). Pathways involving the intermediate formation of indole, via intramolecular cyclization, presumably followed by oxidative coupling catalyzed by **1**, were also ruled out, as the reaction of **1** with indole did not give **3a** (Scheme 3 bottom).

Isotopic labeling experiments employing 2-ethynylaniline and D_2O afforded deuteration of the 3 and 3′ positions in **3a**; with d_3-ethynylaniline alone, deuteration at these positions was not observed (Scheme 4). These results clearly pointed to water as

Scheme 4. Isotope Labelling Studies



the source for the 3 and 3′ protons in **3a** and are consistent with the formation of a vinylidene intermediate via an intermolecular 1,2-H shift in the reaction pathway.[9,14]

Our proposed reaction pathway is given in Figure 1; the energetics for the various steps (for 2-ethynylaniline) have also been computed with density functional theory, and the computed free energies (ΔG°, in kJ mol^{-1}) are also shown. The reaction free energies indicate that the proposed steps are not unreasonable.

As has been proposed earlier, cleavage of dimeric **1** is most probably through coordination of the amine group of the aminoalkyne but this is probably in equilibrium with

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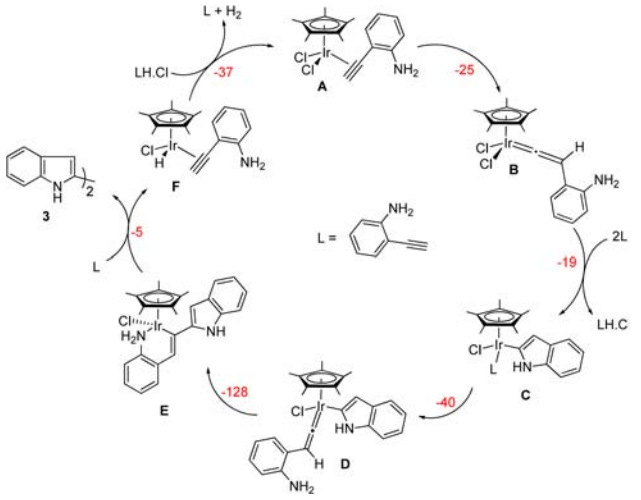
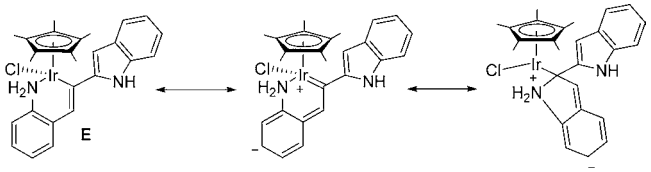


Figure 1. Proposed catalytic cycle for the formation of **3**. Numbers in red are the computed free energies in kJ mol^{-1}.

intermediate **A**, in which the C≡C bond is coordinated.[9,15] A rapid rearrangement to the vinylidene **B** follows,[9] and nucleophilic attack of the amine group at the α-carbon, followed by HCl elimination as the ammonium salt and coordination of another molecule of aminoalkyne, gives intermediate **C**. Up to this point, the pathway is similar to that which we have proposed earlier for the rhodium metallacyclic complexes.[15] From **C**, a second vinylidene rearrangement to **D**, followed by a 1,2-migratory insertion of the indolyl unit into the vinylidene, affords intermediate **E**. A Meisenheimer-type rearrangement (Scheme 5) of this affords the biindole and the hydride species **F**. In the final step, protonolysis of **F** (presumably by the ammonium salt) regenerates **A**.[16]

Scheme 5. Meisenheimer-Type Rearrangement for the Formation of 3

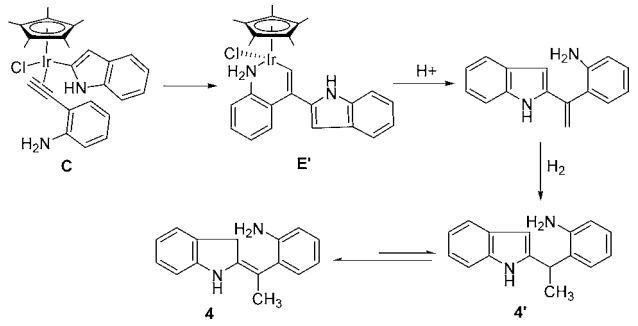


Attempts to detect the elimination of H_2 (by mass spectral analysis of the headspace, including analysis for the presence of HD or D_2 from a reaction in the presence of D_2O) failed. The presence of styrene, a possible byproduct if there is H transfer to an alkyne, was also not detected.

Nevertheless, support for this pathway is the observation of a side product **4** (3% yield) from the reaction. This side product could have been formed via a 1,2-alkyne insertion in **C** to form the intermediate **E′**, with subsequent protonolysis, hydrogenation, and rearrangement (Scheme 6). Although the precise pathway to **4** is unclear, its formation suggests that the proposed intermediate **E** is reasonable.

In conclusion, we have described a novel, clean, and efficient iridium-catalyzed process for the synthesis of 2,2′-biindole from 2-ethynylanilines. A reaction pathway has been proposed, on the basis of experimental and computational studies, which involves the formation of a vinylidene intermediate, intramolecular hydroamination, and a subsequent insertion reaction.

Scheme 6. Formation of Side Product 4



■ ASSOCIATED CONTENT

Supporting Information

Experimental and computational details. 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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