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2014

Kumaran, E., Fan, W. Y., & Leong, W. K. (2014). [Cp*IrCl₂]₂ catalyzed formation of 2,2'-biindoles from 2-ethynylanilines. *Organic letters*, 16(5), 1342-1345.

<https://hdl.handle.net/10356/103801>

<https://doi.org/10.1021/ol5000692>

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[Cp*IrCl₂]₂ Catalysed Formation of 2,2'-Biindoles from 2-Ethynylanilines

Elumalai Kumaran,[†] Wai Yip Fan,[‡] and Weng Kee Leong^{†*}

[†]Division of Chemistry and Biological Chemistry, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

[‡]Department of Chemistry, National University of Singapore, Science Drive3, Singapore 117543

Supporting Information Placeholder

ABSTRACT: [Cp*IrCl₂]₂ catalyses the cyclization of 2-ethynylanilines to 2,2'-biindoles via intramolecular hydroamination. A reaction pathway has been proposed on the basis of deuterium labelling 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 tjianazoles, staurosporine, ent-staurosporine, holtryne, arcyliaflavin, rebeccamycin and staurosporinone,³ and has also been utilized in synthetic biologically active molecules like (-)-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*IrCl₂]₂, **1** with an aniline and a terminal alkyne led to the formation of an ortho-metallated 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 orthometallation (Scheme 1).⁹

Scheme 1. Formation of iridium amino-carbenes.

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

Scheme 2. The reaction of **1** and **2a**; proposed formation of 2-indolyindoline and the observed formation of 2,2'-biindole.

The biindole has been completely characterized, including by a single-crystal X-ray structural analysis. Cyclisation of an alkynylaniline such as **2a** to an indole is known to be catalysed 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 catalyse the cyclisation 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 (4d 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 optimisation 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 (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*RhCl₂]₂ and [Ir(cod)Cl]₂, were also tested but they failed to furnish **3a** under similar conditions (entries 7 & 8).

Table 1. Optimization study for **1**-catalysed cyclization of **2a** to **3a**.

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 ₂ Br ₂	80	70

^aThe cyclization of **2a** (0.05 mmol) was carried out in the presence of **1** in a solvent (3 mL) at various temperature for 12 h. ^bReaction was carried out for 24 h. ^[c] Isolated yields.

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 protodesilylation provided the desired substrate **2b** in an overall yield of 81%. The substrate scope study (Table 2) showed that functional group tolerance was excellent, and a wide range of functional groups (alkyls, halides, CN, NO₂ 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-indolyindoline (Scheme 2) followed by **1**-catalysed 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 dimerization needed was also high (+64 kJ mol⁻¹). Pathways involving the intermediate formation of indole, via intramolecular cyclization, presumably followed by oxidative coupling catalysed by **1**, were also ruled out as the reaction of **1** with indole did not give **3a** (Scheme 3 bottom).

Table 2. Cyclization of **2** to **3** catalysed by **1**.

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 ₂ CH ₃	3h , 79
9	CO ₂ C ₂ H ₅	3i , 87
10 ^c	CH ₃	3j , 78

^aThe 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. ^bIsolated yields. ^cR = 5-CH₃.

Scheme 3. Attempted reactions of **1** with indoline and indole.

Isotopic labelling experiments employing 2-ethynylaniline and D₂O afforded deuteration of the 3 and 3' positions in **3a**; with d₃-ethynylaniline alone, deuteration at these positions was not observed (Scheme 4). These results clearly pointed to water as 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}

Scheme 4. Isotope labelling studies.

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.

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

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 intermediate **A**, in which the $\text{C}\equiv\text{C}$ 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 by-product 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-catalysed 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>

AUTHOR INFORMATION

Corresponding Author

* E-mail: chmlwk@ntu.edu.sg

ACKNOWLEDGMENT

This work was supported by Nanyang Technological University and the Ministry of Education (Research Grant No. M4011017). Assistance on the crystallographic studies by Dr Rakesh Ganguly is acknowledged, and one of us (E. K.) thanks the university for a Research Scholarship.

REFERENCES

- (1) (a) Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*; Stanley Thornes: Cheltenham, **1998**. (b) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Elsevier Science; Oxford, **2000**.

- (2) (a) Bergman, J. *Stud. Nat. Prod. Chem., Part A* **1988**, *1*, 3. (b) Gribble, G. W.; Berthel, S. J. *Stud. Nat. Prod. Chem.* **1993**, *12*, 365. (c) Steglich, W. *Fortschr. Chem. Org. Naturst.* **1987**, *51*, 216. (d) Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot.* **1995**, *48*, 535.
- (3) (a) Wood, J. L.; Stoltz, B. M.; Dietrich, H. J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641. (b) Link, J. T.; Raghavan, S.; Danishefsky, S. J. *Am. Chem. Soc.* **1995**, *117*, 552. (c) Somei, M.; Kodama, A. *Heterocycles* **1992**, *34*, 1285. (d) Somei, M.; Hayashi, H.; Ohmoto, S.; *Heterocycles* **1997**, *44*, 169. (e) Hayashi, H.; Ohmoto, S.; Somei, M. *Heterocycles* **1997**, *45*, 1647. (f) Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177. (g) Wada, Y.; Nagasaki, H.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2007**, *72*, 2008. (h) Shintani, A.; Toume, K.; Rifai, Y.; Arai, M. A.; Ishibashi, M. *J. Nat. Prod.* **2010**, *73*, 1711.
- (4) Wood, J. L.; Stoltz, B. M.; Dietrich, H. J. *J. Am. Chem. Soc.* **1995**, *117*, 10413.
- (5) (a) Lin, C. I.; Selvi, S.; Fang, J. M.; Chou, P. T.; Lai, C. H.; Cheng, Y. M. *J. Org. Chem.* **2007**, *72*, 3537. (b) Curiel, D.; Cowley, A.; Beer, P. D. *Chem. Com.* **2005**, 236. (c) Kim, N. K.; Chang, K. J.; Moon, D.; Lah, M. S.; Jeong, K. S. *Chem. Com.* **2007**, 3401.
- (6) (a) Pelly, S. C.; Parkinson, C. J.; Van Otterlo, W. A. L.; Koning, C. B. *J. Org. Chem.* **2005**, *70*, 10474.
- (7) (a) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571. (b) Abbiati, G.; Arcadi, A.; Beccalli, E.; Bianchi, G.; Marinelli, F.; Rossi, E. *Tetrahedron* **2006**, *62*, 3033. (c) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841. (d) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610. (e) Lee, J. Y.; Lee, M. H.; Jeong, K. S. *Supramolecular Chemistry*, **2007**, *19*, 257. (f) Kim, U.; Suk, J. M.; Naidu, V. R.; Jeong, K. S. *Chem. Eur. J.* **2008**, *14*, 11406.
- (8) (a) Rubia, A. G.; Urones, B.; Arrayàs, R. G.; Carretero, J. C. *Chem. Eur. J.* **2010**, *16*, 9676. (b) Bergman, J.; Eklund, N. *Tetrahedron* **1980**, *36*, 1439. (c) Merlic, C. A.; You, Y.; McInnes, D. M.; Zechman, A. L.; Miller, M. M.; Deng, Q. *Tetrahedron* **2001**, *57*, 5199. (d) Hudkins, R. L.; Diebold, J. L.; Marsh, F. D. *J. Org. Chem.* **1995**, *60*, 6218.
- (9) Kumaran, E.; Sridevi, V. S.; Leong, W. K. *Organometallics* **2010**, *29*, 6417.
- (10) (a) Trost, B. M.; McClory, A. *Angew. Chem. Int. ed.* **2007**, *46*, 2074. (b) Burling, S.; Field, L. D.; Messerle, B. A. *Organometallics* **2000**, *19*, 87.
- (11) (a) Fernández, A. V.; Varela, J. A.; Saá, C. *Adv. Synth. Catal.* **2011**, *353*, 1933. (b) Kondo, T.; Okada, T.; Suzuki, T.; Mitsudo, T. *J. Organomet. Chem.* **2001**, *622*, 149. (c) Nair, R. N.; Lee, P. J.; Rheingold, A. R.; Grotjahn, D. B. *Chem. Eur. J.* **2010**, *16*, 7992.
- (12) McDonald, F. E.; Chatterjee, A. K. *Tetrahedron. Lett.* **1997**, *38*, 7687.
- (13) (a) Kennedy, D. F.; Messerle, B. A.; Rumble, S. L. *New J. Chem.* **2009**, *33*, 818. (b) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437. (c) Lai, R. Y.; Surekha, K.; Hayashi, A.; Ozawa, F.; Liu, Y. H.; Peng, S. M.; Liu, S. T. *Organometallics* **2007**, *26*, 1062.
- (14) Perea-Buceta, J. E.; Wirtanen, T.; Laukkanen, O. V.; Mäkelä, M. K.; Nieger, M.; Melchionna, M.; Huittinen, N.; Lopez-Sanchez, J. A.; Helaja, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 11835.
- (15) Sridevi, V. S.; Fan, W. Y.; Leong, W. K. *Organometallics* **2007**, *26*, 1173-1177.
- (16) O'Connor, J. M.; Pu, L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, *112*, 6232-6247.

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