[Cp*IrCl₂]₂-catalysed cyclisation of 2-alkynylanilines into indoles

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Abstract: [Cp*IrCl₂]₂ catalyses the cyclisation of 2-alkynylanilines into indoles. A wide variety of substrates is tolerated. A reaction pathway involving intramolecular hydroamination is proposed.

Keywords: Catalytic hydroamination; indole; 2-alkynylaniline; iridium

On binding to transition metals, alkynes are activated toward nucleophilic attack. This has been demonstrated with a variety of nucleophiles, including amines,¹ imines,² water,³ alcohols,⁴ phenols,⁵ halides,⁶ carboxylic acids,⁷ nitro groups,⁸ carbonyl groups⁹ and enol ethers.¹⁰ Catalytic transformation of alkynes based on such activation has been studied with a number of different metals, and intramolecular versions are very useful in providing heterocyclic compounds. In particular, inter- and intramolecular alkyne hydroamination reactions have been extensively explored because the resulting N-heterocycles have broad synthetic interest and applications.¹¹

We have previously reported that [Cp*IrCl₂]₂ (**1**) can activate the C≡C bond for transformations that include hydrosilylation,¹² dimerization,¹³ and C≡C bond cleavage.¹⁴ This catalyst was also found to lead to the formation of a variety of iridium amino-carbene derivatives in the presence of an alkyne and an arylamine.¹⁵ Quite surprisingly, it catalysed the formation of 2,2'-biindoles from 2-ethynylanilines under similar reaction conditions.¹⁶ These reactions all involved terminal alkynes or alkynyl moieties, and they were proposed to proceed via initial coordination of the alkyne moiety followed by rearrangement into a vinylidene. As expected, internal 2-alkynylanilines cannot undergo rearrangement into a

vinylidene and hence cannot form 2,2'-biindoles. We have found, instead, that these undergo cyclisation to form indoles.

Complex **1** catalysed the cyclisation of 2-(2-phenylethynyl)aniline (**2a**) to afford 2-phenylindole (**3a**) in 76% yield (Scheme 1).

Scheme 1

An optimization study (Table 1) showed that the reaction was more effective in more polar solvents such as methanol or acetonitrile (entries 2-6). The catalyst loading could be effectively lowered from 5 to 2 mol% without detriment, but further lowering to 1 mol% led to a significantly lower yield (entries 2, 7 and 8). Although a number of salt additives (NaPF₆, NaBF₄, NH₄BF₄ or NH₄PF₆) were effective (entries 9-12), NaBF₄ showed the best catalytic activity; NaBF₄ itself was not catalytically active (entry 13).

Table 1. Optimization study for the intramolecular cyclization of **2a** to give **3a** catalysed by [Cp*IrCl₂]₂ (**1**).

Entry	Catalyst (mol%)	Additive (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%) ^a
1	1 (5)	-	Acetonitrile- <i>d</i> ₃	60	12	76
2	1 (5)	NaBF ₄ (10)	Acetonitrile- <i>d</i> ₃	60	4	95
3	1 (5)	NaBF ₄ (10)	Toluene- <i>d</i> ₈	60	18	89
4	1 (5)	NaBF ₄ (10)	Chloroform- <i>d</i> ₃	60	30	30
5	1 (5)	NaBF ₄ (10)	THF- <i>d</i> ₈	60	24	76
6	1 (5)	NaBF ₄ (10)	Methanol- <i>d</i> ₄	60	4	95
7	1 (2)	NaBF ₄ (4)	Acetonitrile- <i>d</i> ₃	60	8	93
8	1 (1)	NaBF ₄ (2)	Acetonitrile- <i>d</i> ₃	60	8	59
9	1 (2)	NaBF ₄ (4)	Acetonitrile- <i>d</i> ₃	40	8	96
10	1 (2)	NH ₄ PF ₆ (4)	Acetonitrile- <i>d</i> ₃	40	8	78
11	1 (2)	NH ₄ BF ₄ (4)	Acetonitrile- <i>d</i> ₃	40	8	83
12	1 (2)	NaPF ₆ (4)	Acetonitrile- <i>d</i> ₃	40	8	67
13	-	NaBF ₄ (4)	Acetonitrile- <i>d</i> ₃	40	8	-

^aYield determined by NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

Similar cyclization reactions have been studied with a number of transition metals including Au,¹⁷ Pd,¹⁸ Rh,¹⁹ and others,²⁰ although some of them have disadvantages such as higher catalyst loading,^{20a} high temperature,^{17d,8b-c,19-20} or the need for protection of the amino group.^{20a} Several iridium complexes have also been examined,^{1a,19a,21} but the functional group tolerance was tested with only two catalytic systems,^{1a,21b} both of which showed very limited functional group compatibility. For example, Liu et. al. reported the iridium-catalysed intramolecular cyclization of aminoalkynes,^{1a} but their catalyst failed with alkynylanilines containing electron-withdrawing substituents on the aniline moiety. Similarly, the catalyst reported by Fukuzawa was not effective for alkynylanilines with an electron-withdrawing substituent on the alkyne moiety.^{21b} Unlike these iridium-based catalytic systems,^{1a,21b} however, complex **1** showed good catalytic performance with a wide range of substrates; electron-donating and electron-withdrawing substituents on either the aniline or the alkyne moiety were tolerated, as were secondary (entries 14 and 15) and sterically crowded (entry 7) 2-alkynylanilines and N-protected (entry 16) alkynylanilines (Table 2). Formation of 2-trimethylsilylindole using the optimized conditions failed; this problem has been reported with some of the other catalytic systems.^{18e,20a,b} In our case, however, the reaction could be made to work with a slight modification of the conditions (no salt additive and with DCE as the solvent).

Table 2. Substrate scope study for the intramolecular cyclization catalysed by **1**.

5	4-NO ₂	C ₆ H ₅	H	3e , 89
6	4-CO ₂ Et	C ₆ H ₅	H	3f , 92
7	4-CO ₂ Et, 6-C ₂ Ph	C ₆ H ₅	H	3g , 85
8	H	4-n-BuC ₆ H ₅	H	3h , 87
9	H	4-ClC ₆ H ₅	H	3i , 81
10	H	ⁿ Bu	H	3j , 91
11 ^b	H	Si(CH ₃) ₃	H	3k , 86
12 ^b	4-NO ₂	Si(CH ₃) ₃	H	3l , 76
13 ^b	4-CO ₂ Me	Si(CH ₃) ₃	H	3m , 78
14	H	C ₆ H ₅	CH ₃	3n , 83
15	H	C ₆ H ₅	CH ₂ Ph	3o , 85
16	H	C ₆ H ₅	SO ₂ Me	3p , 82

^aIsolated yield. ^bNo salt additive, with DCE as the solvent.

As a demonstration of the utility of this reaction for the construction of more complex N-heterocycles, we also synthesized 2,2'-biindole (**3q**), 1,4-diindolylbenzene (**3r**) and 1,3,5-triindolylbenzene (**3s**) in good yields using this methodology (Scheme 2).

Scheme 2

The reaction presumably involves initial binding of the alkyne moiety, in a similar manner to that proposed earlier for the formation of biindoles from 2-ethynylanilines,¹⁶ but with the loss of a chloride to form a cationic intermediate **A** (Scheme 3). Formation of a cationic species is favoured by a polar environment – in the presence of a salt or in a polar solvent. Such a cationic species has been proposed earlier for a related rhodium catalytic system,^{1b} and similarly, the alkyne is asymmetrically bound (Figure S1). The third ligand L is presumably a solvent molecule or, more likely, a second N-bound alkynylaniline. Intramolecular nucleophilic attack by the aniline moiety onto the coordinated alkyne would form **B**; the regiochemistry of this is controlled by the bulkiness of the R group on the alkyne as well as the favourable formation of the five-membered heterocyclic ring. Loss of a proton from the aniline moiety and protonolysis at the alkenyl-iridium bond would give the indole, and recoordination of the alkynylaniline would regenerate **A**. We have examined this pathway computationally at the B3LYP/LanL2DZ level using density functional theory (DFT); the free energy changes (in kJ mol⁻¹) from **A** are also shown in Scheme 3, and are reasonable.

Scheme 3

In conclusion, we have found that complex **1**, in the presence of a salt additive, acts as an effective catalyst for the intramolecular hydroamination of internal alkynylanilines **2** to afford indoles **3**. A wide variety of substrates was tolerated. The reaction pathway proposed involved initial coordination of the alkynylaniline via the alkyne moiety to a cationic intermediate, which subsequently underwent intramolecular attack by the aniline to form the indole.

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Supplementary data: Experimental procedures and characterization data for all substrates, computationally optimized structures of intermediates **A** and **B**, and 1H NMR and ^{13}C NMR spectra for new compounds. This material is available free of charge via the internet at

<http://dx.doi.org/10.1016/j.tetlet>.

References

- (1) (a) Lai, R.-Y.; Surekha, K.; Hayashi, A.; Ozawa, F.; Liu, Y.-H.; Peng, S.-M.; Liu, S.-T. *Organometallics* **2007**, *26*, 1062-1068. (b) Kumaran, E.; Leong, W. K. *Organometallics* **2012**, *31*, 1068-1072.
- (2) (a) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035-4039. (b) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86-91.
- (3) (a) Lukas, H.; Aurélie, L. *Synthesis* **2007**, 1121-1150. (b) Ogo, S.; Uehara, K.; Abura, T.; Watanabe, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **2004**, *126*, 16520.
- (4) (a) Messerle, B. A.; Vuong, K. Q. *Organometallics* **2007**, *26*, 3031-3040. (b) Fjermestad, T.; Ho, J. H. H.; Macgregor, S. A.; Messerle, B. A.; Tuna, D. *Organometallics* **2011**, *30*, 618-626.
- (5) (a) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297-301. (b) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387-1391.
- (6) Wang, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 5213-5216.
- (7) (a) Hua, R.; Tian, X. *J. Org. Chem.* **2004**, *69*, 5782-5786. (b) Haruki, S.; Atsushi, K. *Synthesis* **1999**, 1145-1151.
- (8) Asao, N.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 5675-5677.
- (9) (a) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458-7461. (b) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650-12655. (c) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814-5819.
- (10) (a) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978-15982. (b) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928-1933.

- (11) (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368-3372. (b) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675-703. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079-3159.
- (12) Sridevi, V. S.; Fan, W. Y.; Leong, W. K. *Organometallics* **2007**, *26*, 1157-1160.
- (13) (a) Wong, K. N.; Mak, K. H. G.; Fan, W. Y.; Sridevi, V. S.; Leong, W. K. *J. Organomet. Chem.* **2013**, *741-742*, 40-46. (b) Mak, K. H. G.; Fan, W. P.; Sridevi, V. S.; Leong, W. K. *J. Organomet. Chem.* **2013**, *739*, 52-56.
- (14) Sridevi, V. S.; Fan, W. Y.; Leong, W. K. *Organometallics* **2007**, *26*, 1173-1177.
- (15) (a) Kumaran, E.; Sridevi, V. S.; Leong, W. K. *Organometallics* **2010**, *29*, 6417-6421. (b) Kumaran, E.; Sonia, K. T.; Ganguly, R.; Li, Y.; Leong, W. K. *Organometallics* **2013**, *32*, 4149-4152.
- (16) Kumaran, E.; Fan, W. Y.; Leong, W. K. *Org. Lett.* **2014**, *16*, 1342-1345.
- (17) (a) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239-3265. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266-3325. (c) Corma, A.; Pérez, L.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657-1712. (d) Majumdar, K. C.; Samanta, S.; Chattopadhyay, B. *Tetrahedron Lett.* **2008**, *49*, 7213-7216. (e) Zhang, Y.; Donahue, J. P.; Li, C. J. *Org. Lett.* **2007**, *9*, 627-630. (f) Buceta, J. E. P.; Wirtanen, T.; Laukkanen, O.-V.; Mäkelä, M. K.; Nieger, M.; Melchionna, M.; Huittinen, N.; Sanchez, J. A. L.; Helaja, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 11835-11839.
- (18) (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873-2920. (b) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581-2584. (c) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799-1802. (d) Janreddy, D.; Kavala, V.; Kuo, C. W.; Kuo, T. S.; He, C. H.; Yao, C. F. *Tetrahedron* **2013**, *69*, 3323-3330.
- (19) (a) Kennedy, D. F.; Messerle, B. A.; Rumble, S. L. *New J. Chem.*, **2009**, *33*, 818-824. (b) Burling, S.; Field, L. D.; Messerle, B. A. *Organometallics* **2000**, *19*, 87-90. (c)

- Clentsmith, G. K. B.; Field, L. D.; Messerle, B. A.; Shasha, A.; Turner, P. *Tetrahedron. Lett.* **2009**, *50*, 1469-1471. (d) Isono, N.; Lautens, M. *Org. Lett.* **2009**, *11*, 1329-1331.
- (20) (a) Yin, Y.; Ma, W.; Chai, Z.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 5731-5736. (b) Li, X.; Wang, J. Y.; Yu, W.; Wu, L. M. *Tetrahedron*, **2009**, *66*, 1140-1146. (c) Sakai, N.; Annaka, K.; Konakahara, T. *Tetrahedron Lett.* **2006**, *47*, 631-634. (d) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160-4165. (e) Kurisaki, T.; Naniwa, T.; Yamamoto, H.; Imagawa, H.; Nishizawa, M. *Tetrahedron. Lett.* **2007**, *48*, 1871-1874. (f) Terrason, V.; Michaux, J.; Gaucher, A.; Wehbe, J.; Marque, S.; Prim, D.; Campagne, J. M. *Eur. J. Org. Chem.* **2007**, 5332-5335. (g) Nakamura, I.; Sato, Y.; Konta, S.; Terada, M. *Tetrahedron. Lett.* **2009**, *50*, 2075-2077. (h) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126-1136. (i) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Pérez, M.; Martin, M. A. G.; González. *J. Org. Chem.* **1996**, *61*, 5804-5812.
- (21) (a) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437-5440. (b) Ogata, K.; Nagaya, T.; Fukuzawa, S. I. *J. Organomet. Chem.* **2010**, *695*, 1675-1681. (c) Gray, K.; Page, M. J.; Wagler, J.; Messerle, B. A. *Organometallics* **2012**, *31*, 6270-6277.