Tetrahedron Letters 55 (2014) 5495–5498

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

[Cp*IrCl$_2$]$_2$-catalysed cyclization of 2-alkynylanilines into indoles

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ARTICLE INFO

Article history:
Received 2 June 2014
Revised 18 July 2014
Accepted 13 August 2014
Available online 19 August 2014

Keywords:
Catalytic hydroamination
Indole
2-Alkynylaniline
Iridium

ABSTRACT

[Cp*IrCl$_2$]$_2$ catalyses the cyclization of 2-alkynylanilines into indoles. A wide variety of substrates is tolerated. A reaction pathway involving intramolecular hydroamination is proposed.

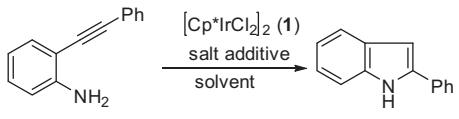
On binding to transition metals, alkynes are activated towards nucleophilic attack. This has been demonstrated with a variety of nucleophiles, including amines,[1] imines,[2] water,[3] alcohols,[4] phenols,[5] halides,[6] carboxylic acids,[7] nitro groups,[8] carbonyl groups[9] and enol ethers.[10] Catalytic transformations of alkynes based on such activation have 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*IrCl$_2$]$_2$ (**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 also 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 cyclization to form indoles.

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

An optimization study (Table 1) showed that the reaction was more effective in higher polarity solvents such as methanol or acetonitrile (entries 2–6). The catalyst loading could be 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 ($NaPF_6$, $NaBF_4$, NH_4BF_4 or NH_4PF_6) were effective (entries 9–12), $NaBF_4$ showed the best catalytic activity; $NaBF_4$ itself was not catalytically active (entry 13).

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,[18b,c,17d,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



2a 3a

Scheme 1.

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http://dx.doi.org/10.1016/j.tetlet.2014.08.053
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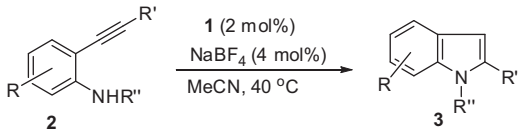
Table 1
Optimization of the intramolecular cyclization of **2a** to give **3a** catalysed by $[Cp^*IrCl_2]_2$ (**1**)

Entry	Catalyst (mol %)	Additive (mol %)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	**1** (5)	—	Acetonitrile-d_3	60	12	76
2	**1** (5)	$NaBF_4$ (10)	Acetonitrile-d_3	60	4	95
3	**1** (5)	$NaBF_4$ (10)	Toluene-d_8	60	18	89
4	**1** (5)	$NaBF_4$ (10)	Chloroform-d_3	60	30	30
5	**1** (5)	$NaBF_4$ (10)	THF-d_8	60	24	76
6	**1** (5)	$NaBF_4$ (10)	Methanol-d_4	60	4	95
7	**1** (2)	$NaBF_4$ (4)	Acetonitrile-d_3	60	8	93
8	**1** (1)	$NaBF_4$ (2)	Acetonitrile-d_3	60	8	59
9	**1** (2)	$NaBF_4$ (4)	Acetonitrile-d_3	40	8	96
10	**1** (2)	NH_4PF_6 (4)	Acetonitrile-d_3	40	8	78
11	**1** (2)	NH_4BF_4 (4)	Acetonitrile-d_3	40	8	83
12	**1** (2)	$NaPF_6$ (4)	Acetonitrile-d_3	40	8	67
13	—	$NaBF_4$ (4)	Acetonitrile-d_3	40	8	—

[a] Yield determined by NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

Table 2
A substrate scope study for the intramolecular cyclization catalysed by **1**



Entry	R[a]	R′	R″	Yield[b] (%)
1	H	C_6H_5	H	**3a**, 90
2	4-CH_3	C_6H_5	H	**3b**, 92
3	4-$C(CH_3)_3$	C_6H_5	H	**3c**, 93
4	4-Cl	C_6H_5	H	**3d**, 91
5	4-NO_2	C_6H_5	H	**3e**, 89
6	4-CO_2Et	C_6H_5	H	**3f**, 92
7	4-CO_2Et, 6-C_2Ph	C_6H_5	H	**3g**, 85
8	H	4-*n*-BuC_6H_5	H	**3h**, 87
9	H	4-ClC_6H_5	H	**3i**, 81
10	H	*n*-Bu	H	**3j**, 91
11[c]	H	$Si(CH_3)_3$	H	**3k**, 86
12[c]	4-NO_2	$Si(CH_3)_3$	H	**3l**, 76
13[c]	4-CO_2Me	$Si(CH_3)_3$	H	**3m**, 78
14	H	C_6H_5	CH_3	**3n**, 83
15	H	C_6H_5	CH_2Ph	**3o**, 85
16	H	C_6H_5	SO_2Me	**3p**, 82

[a] Designations refer to the ethynylanilines.
[b] Isolated yield.
[c] No salt additive, with DCE as the solvent.

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.[18c,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).

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).

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 (Fig. 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**. 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.

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.

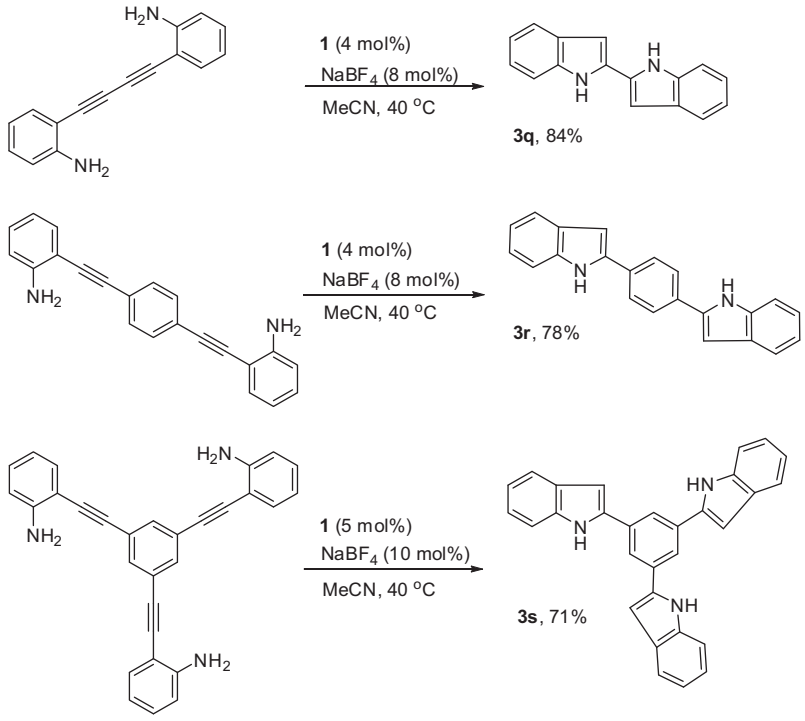
Acknowledgments

This work was supported by Nanyang Technological University and the Ministry of Education (Research Grant No. M4011017). One of us (E.K.) thanks the Nanyang Technological University for a Research Scholarship.

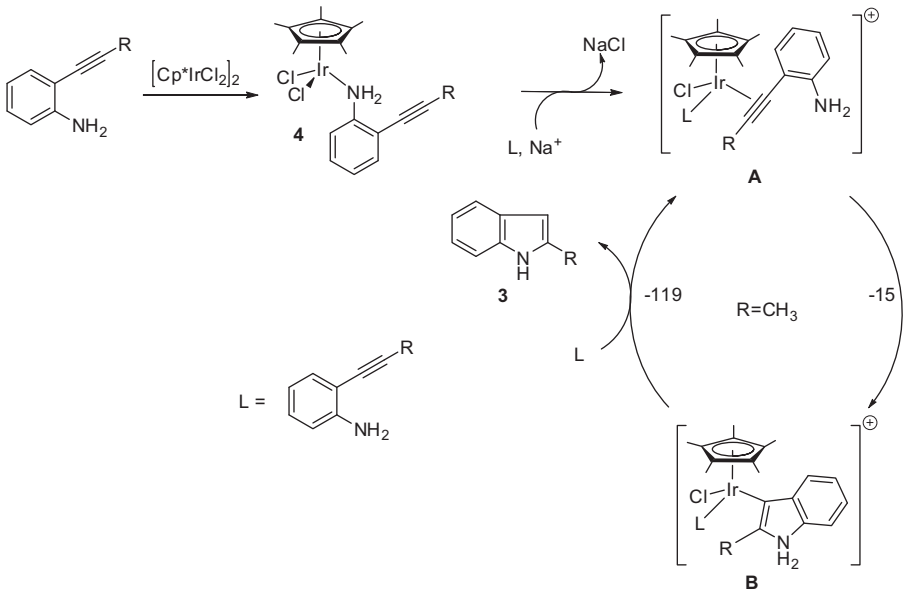
Supplementary data

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/1.1016/j.tetlet.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.053.



Scheme 2.



Scheme 3.

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