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Intramolecular cyclization of *ortho*-alkynylanilines by Rh(I)-catalyzed hydroamination to yield benzo(dipyrroles)

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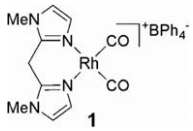
ABSTRACT

The methylene-bridged Rh(I) dicarbonyl complex, [Rh(bim)$(CO)_2{}^+BPh_4{}^-$] (**1**) (bim = bis(*N*-methylimidazol-2-yl)methane), is an effective catalyst for the intramolecular hydroamination of selected *ortho*-alkynylanilines to give a range of benzo(dipyrroles).

The hydroamination of alkynes (Scheme 1a) is an atom-economical approach to commercially desirable imine and enamine products, and is generally regarded as a more facile transformation than the hydroamination of olefins (Scheme 1b).[1–5]

The hydroamination of alkynes results in reactive enamine or imine products, both of which are capable of undergoing further reduction.[2] Importantly, given the ubiquity of the indole system in many biologically significant compounds, ring-closure reactions of alkyne-substituted anilines may be exploited in the syntheses of aromatic systems containing five- and six-membered nitrogen heterocycles. Previous work established the competence of cationic Rh(I) and Ir(I) complexes with methylene-bridged bidentate imidazole ligands as catalysts for the intramolecular hydroamination of both aliphatic and aromatic alkynes.[6] The potential of these systems to mediate the formation of more highly condensed nitrogen heterocycles from a range of selected substrates is assessed here. Of specific interest are the formation of benzo(dipyrrole) systems formed by double cyclizations of the appropriate *ortho*-alkynylaniline starting materials (Scheme 2), and comparison with the formation of isoquinolines.

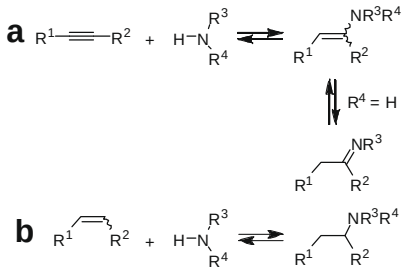
The methylene-bridged Rh(I) dicarbonyl complex, [Rh(bim)$(CO)_2{}^+BPh_4{}^-$] (**1**) (bim = bis(*N*-methylimidazol-2-yl)methane), is particularly effective as a catalyst for hydroamination;[6–9] **1** is able to cyclize both aromatic and aliphatic alkynylamines and is also effective in similar reactions with organic amides.



1

Hydroaminations using **1** as a catalyst were characterized by low catalyst loadings and relatively high turnover numbers. While the details of the mechanism were not actively pursued, the success of **1** as a catalyst may be attributed to (i) the potential for vacant coordination sites at the metal centre resulting from loss of a carbonyl, (ii) the poorly coordinating $BPh_4{}^-$ counter ion[9] and (iii) the formal positive charge at the metal centre constituting an acidic site to which either the amine or alkyne would readily coordinate.[10,11] Univalent **1** may also potentially undergo oxidative addition by NH bonds, a catalytic step suggested by early studies,[12] but the redox behaviour of this system under the reaction conditions remains unknown and it seems likely for at least Rh(I) and Pd(II) catalysts that a redox cycle does not operate during the hydroamination reaction.[13] Presumably, loss of a carbonyl from **1** opens a coordination site at the metal centre to allow ligation of the π-system of the acetylene followed by intramolecular nucleophilic attack by the amine group at the electron-deficient acetylene to form a metal-bound enamine. Plausible mechanisms for Rh(I), by oxidative or non-oxidative means, have been advanced in the literature.[14]

With substrates (Table 1), namely **2**, **4**, **6**, **8**, **10**, **12** and **13**, intramolecular cyclization catalyzed by **1** gave a range of nitrogen-con-



Scheme 1.

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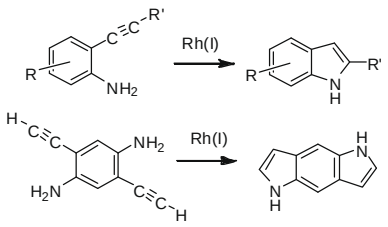


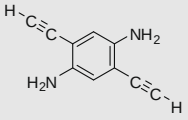
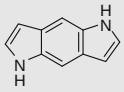
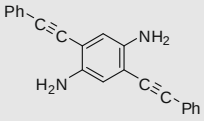
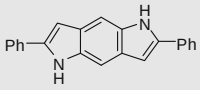
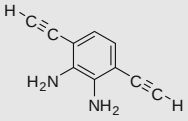
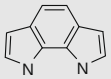
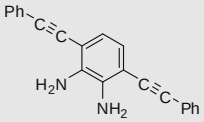
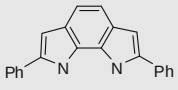
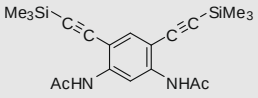
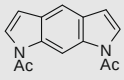
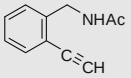
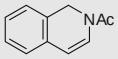
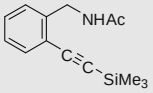
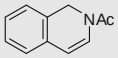
Scheme 2.

taining heterocycles, **3**, **5**, **7**, **9**, **11** (from either **10** or **12**) and **14**, respectively. By ^{1}H NMR spectroscopy, the formation of products was quantitative in each reaction, and the final isolated yields were reasonable given their challenging isolation by column chromatography. Details of the catalyses, including loadings, yields and duration, appear in Table 1. Other experimental details, including precursor synthesis and catalytic protocols, appear as **Supplementary** data. As the aromatic *N-heterocycles* so produced are liable to coordinate to the transition metal centre, catalyst loadings are relatively high to enable the alkynylaniline reactants to compete as effective ligands with the indole products.

The cyclization of 1,4-diamino-2,5-bis(ethynyl)benzene (**2**) to give 1,5-dihydropyrrolo[2,3-*f*]indole (**3**) was monitored by ^{1}H NMR spectroscopy (Fig. 1) and the conversion was effectively complete within 7.2 h in THF-d_8 at 60 °C. It is noteworthy that the acetylenic protons of the starting material (δ = 4.78 ppm) disappear as the equivalent indole nitrogen protons of **3** appear at low field (δ = 9.75 ppm). The two cyclizations occur sequentially and can be clearly monitored in the NMR spectrum. The presence of two sets of indole NH resonances in the intermediate spectrum (Fig. 1b) results from a mixture of singly and doubly cyclized products. The alternative literature syntheses of **3** involve electrophilic substitution of a 5-aminoindole[15] or a double condensation of *N*,*N*-dimethylformamide dimethyl acetal with dinitroxylene.[16]

The cyclization of **4** to give benzo(dipyrrole) **5** was particularly striking (entry 2); quantitative conversion of the starting material, as judged by ^{1}H NMR spectroscopy, was achieved within 36 minutes. Cyclization of both acetylene arms of **4** and the connectivity of **5** (and by extension the connectivities of the other benzo(dipyr-

Table 1
Hydroamination of selected alkynylanilines and amides catalyzed by **1**

Entry	Substrate	Product	Catalyst loading (mol %)	Time (h) at >99% conversion[a]	Isolated yield (%)
1	 **2**	 **3**	30	7.2	20
2	 **4**	 **5**	26	0.6	24
3	 **6**	 **7**	16	34	31
4	 **8**	 **9**	20	44	41
5	 **13**	 **14**	30	120	[b]
6	 **10**	 **11**	10	48	62
7	 **12**	 **11**	10	120	[b]

[a] Conversion determined by ^{1}H NMR spectroscopy, >99% means that substrate could no longer be detected in the mixture by spectroscopic means.
[b] Product identified by ^{1}H NMR spectroscopy only.

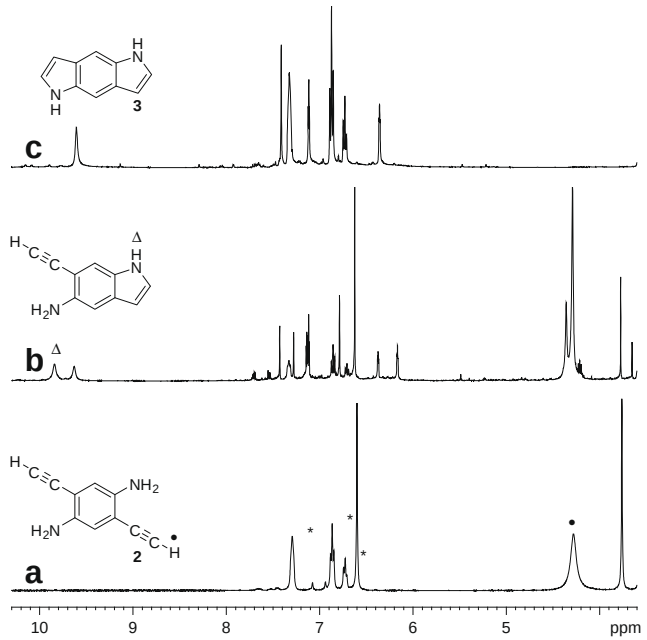


Figure 1. ^{1}H NMR spectra (400 MHz, THF-d_8, 60 °C) of the cyclization of 1,4-diamino-2,5-bis(ethynyl)benzene (**2**) to 1,5-dihydropyrrolo[2,3-*f*]indole (**3**): (a) starting material and catalyst **1** (*); (b) a mixture of **2**, **3** and singly-cyclized intermediate; (c) complete reaction to **3**.

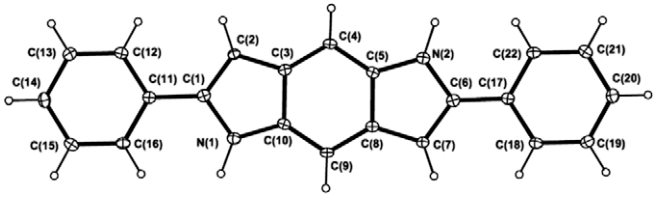


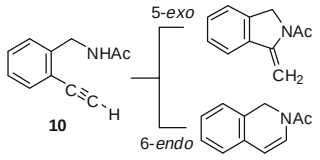
Figure 2. ORTEP representation and numbering scheme for 1,5-dihydro-2,6-diphenylpyrrolo[2,3-*f*]indole (**5**).

roles) in the series) were unequivocally confirmed by a single crystal X-ray diffraction experiment (Fig. 2).[17] Selected bond lengths and bond angles appear in Table 2.

The direct synthesis of **5** by the hydroamination route can be compared with the classical Madelung indole synthesis of Geise utilizing 2,5-dimethyl-1,4-phenylenediamine, benzoyl chloride and KOBu^t, which requires conditions of elevated temperature (>300 °C).[18] At present, no rationalization can be advanced for the rapid conversion of **4** to give **5** as reported here, given the comparatively slow rate of conversion of **8** to the isomeric compound **9** (Table 1, entry 4), and the fact that the catalyzed ring closure of 2-(2-phenylethynyl)aniline to give 2-phenylindole also occurs at a significantly reduced rate.[7]

Table 2
Selected bond lengths (Å) and bond angles (°) of 1,5-dihydro-2,6-diphenylpyrrolo[2,3-*f*]indole (**5**)

Entry	Atoms	Bond length (Å)	Atoms	Bond angle (°)
1	N(1)–C(1)	1.389(3)	C(1)–N(1) C(10)	109.41(14)
2	N(2)–C(6)	1.381(3)	C(6)–N(2)–C(5)	109.58(17)
3	N(1)–C(10)	1.391(3)	C(2)–C(1) N(1)	108.23(17)
4	N(2)–C(5)	1.398(3)	C(7)–C(6) N(2)	108.25(17)
5	C(1)–C(2)	1.369(3)	C(1)–C(2)–C(3)	109.14(17)
6	C(6)–C(7)	1.372(3)	C(6)–C(7)–C(8)	109.04(17)
7	C(1)–C(11)	1.460(3)	N(1)–C(1)–C(11)	123.60(18)
8	C(6)–C(17)	1.463(3)	N(2)–C(6)–C(17)	123.43(18)



Scheme 3.

Intramolecular cyclization of **10** and **12** could give rise to two isomeric products, depending on whether 5-*exo* or 6-*endo* ring closure occurs (Scheme 3).

In fact, only the *endo*-cyclization product was observed, that is, *N*-(acetyl)-1,2-dihydroisoquinoline (**11**) (entries 6 and 7), in which the ring cyclizes in an *anti*-Markovnikov fashion.[3] The ^{1}H NMR spectrum of **11** indicated a mixture of two isomers due to restricted rotation about the amide bond in a ratio of 4:1, which has been observed previously.[19] Cyclization of the trimethylsilyl-substituted **12** likewise resulted in formation of **11**, although at a dramatically slower rate. Upon standing in chloroform-*d* at room temperature for several days, **11** underwent aromatization to give isoquinoline. Isoquinoline could be formed from **11** directly by addition of DDQ (2,3-dichloro-5,6-dicyanobenzoquinone).

The Rh(I) system presented in this Letter has been established as a very effective catalyst for the synthesis of a series of benzo(dipyrroles) and also an isoquinoline by means of hydroamination. The atom-economy of the catalysis is notable, and represents a clear advance on classical methods of indole synthesis. Attempts to examine the mechanistic path of the catalysis and to adapt this system to give intermolecular hydroamination are underway.

Supplementary data

Experimental details including precursor synthesis and catalytic protocols appear as supplementary material and can be found in the pdf associated with this article.

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17. Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 694651. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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