Rh(I) and Ir(I) catalysed intermolecular hydroamination with substituted hydrazines†

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The catalysed intermolecular hydroamination of a series of terminal alkynes with substituted hydrazines was achieved using Rh(I) and Ir(I) complexes.

The intermolecular hydroamination of alkynes or alkenes with amines is an atom efficient route to new, synthetically useful and biologically significant organonitrogen compounds.[1,2] The hydroamination of unsaturated carbon-carbon bonds using hydrazines can lead to potentially useful products, such as hydrazones. Hydrazine is an important substrate for metal-mediated reactions as hydrazine and hydrazido species are postulated intermediates in the reduction of N_2, both by biological systems and by organometallic complexes.[3–5] There are, however, only a limited number of reports of catalysed hydroamination using hydrazines in place of amine substrates. The titanium catalysed hydroamination of alkynes with 1,1-disubstituted hydrazines to yield hydrazone or indole products has been the main focus of previous work.[6–11] The efficient catalysed hydroamination of phenylethyne with phenylhydrazine to yield acetophenone phenylhydrazone (**1**) using a gold-based catalytic system is the only previously reported example of the use of a late transition metal complex as catalyst for this transformation.[12]

Reported here is the investigation into the use of known Rh(I) and Ir(I) intramolecular hydroamination catalysts[13–18] as catalysts for the intermolecular hydroamination of alkynes with hydrazines. Selected complexes of general formula $[M(L^{\frown}L)(C_2)]X$, where $L^{\frown}L$ is either a bidentate *N,N*[13–16,18] or a *P,N*[17,18] donor ligand (Fig. 1), C_2 is either two carbon monoxide (CO) co-ligands or one 1,5-cyclooctadiene (COD) ligand and X is BPh_4^- or $BArF^-$ (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) (**2–6**), were tested as catalysts for the intermolecular hydroamination of phenylethyne with phenylhydrazine to yield actophenone phenylhydrazone (**1**) (Table 1).

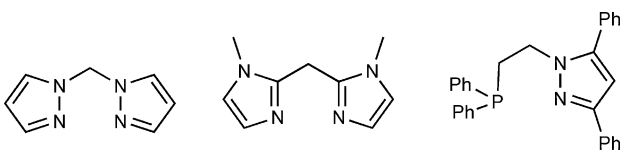

Fig. 1 Bidentate ligands contained in the hydroamination catalysts.

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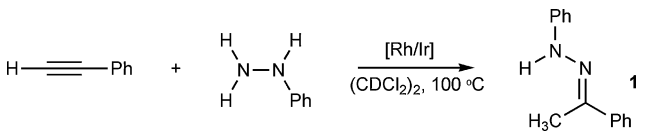
Table 1 Rh(I) and Ir(I) (5 mol%) catalysed addition of phenylhydrazine to phenylethyne to yield **1**[a] A typical catalysis reaction was performed as follows: $[Ir(bpm)(CO)_2]BArF$ (**2**) (14.7 mg, 0.012 mmol) was weighed into an NMR tube and dissolved in $(CDCl_2)_2$ (~0.6 mL) in a $Ar_{(g)}$ glove box. Cyclooctane (40.6 mg, 0.382 mmol) (internal standard), phenylethyne (23.7 mg, 0.232 mmol) and phenylhydrazine (25.5 mg, 0.236 mmol) were successively injected directly into the NMR tube. The NMR tube was placed in an oil bath heated to 100 °C. The reaction was monitored by ^1H NMR spectroscopy at pre-selected intervals.



	% Conversion[a]			
Catalyst	1 h	5 h	22 h[a]	45 h[b]
$[Ir(bpm)(CO)_2]BArF$ (**2**)	51	66	70	70
$[Ir(bpm)(CO)_2]BPh_4$ (**3**)[c]	7	20	36	43
$[Ir(CO)_2Cl]_n$	6	17	34	44
$[Rh(CO)_2Cl]_2$	5	12	28	40
$[Rh(bpm)(CO)_2]BArF$ (**4**)	17	26	30	30
$[Ir(Ph_2PyP)(COD)]BArF$ (**5**)	8	12	21	25
$[Rh(bim)(CO)_2]BPh_4$ (**6**)	0	1	4	8

[a] Only the *E*-isomer was observed. [b] Monitored between 21–24 h. [c] Monitored between 44–47 h.

$[Ir(bpm)(CO)_2]BArF$ (**2**) was the best catalyst by far with 70% conversion of substrate to **1** after 22 hours. The initial conversion rate was much faster with 51% conversion after only 1 hour. Complex **2** was the only catalyst to promote conversion of substrates to **1** greater than 50%, even after 45 hours.

The $BArF^-$ complex **2** achieved almost twice the rate of conversion of substrates to hydrazone **1** compared to the BPh_4^- analogue **3** (71% compared to 36% at 22 hours). The $BArF^-$ complex **4** (Table 1) also promoted a dramatic increase in rate of conversion of substrate when compared to the BPh_4^- complex **6**. Rh complexes **4** and **6** both contain similar cationic fragments—with CO co-ligands and a *N,N*-donor ligand. The higher catalytic efficiency of complexes containing the $BArF^-$ counter-ion and a *N,N*-donor ligand (such as **2** and **4**) compared to analogous complexes containing BPh_4^- has been demonstrated previously for the intramolecular hydroamination of alkynylamines.[18]

$[Rh(CO)_2Cl]_2$ and $[Ir(CO)_2Cl]_n$ with no additional ligand were also investigated as catalysts for the addition of hydrazines to alkynes. The maximum conversion promoted by these catalysts was 40–44%. The conversion promoted by $[Ir(CO)_2Cl]_n$ exhibited a similar reaction profile to that of Ir(I) complex **3**, as can be seen from the similar quantity of conversions of substrates at 1, 5, 22 and 45 hours. $[Rh(CO)_2Cl]_2$ promoted much higher rates

of conversion than the Rh(I) complex **6**, and was similar to $[Ir(CO)_2Cl]_n$ and **3** in efficiency.

Although complexes incorporating the $BArF^-$ counter-ion promoted higher catalytic efficiency compared to the analogous complexes containing BPh_4^-, $[Ir(bpm)(CO)_2]BPh_4$ (**3**) and $[Ir(CO)_2Cl]_n$ were better catalysts than $BArF^-$ complexes **4** and **5**. These results indicate that the $[Ir(CO)_2]^+$ fragment is also an integral part of the active catalyst for the hydroamination of phenylethyne with phenylhydrazine.

The reaction conditions for the intermolecular hydroamination of phenylethyne with phenylhydrazine using $[Ir(bpm)(CO)_2]BArF$ (**2**) were optimised by performing the reaction in different solvents at either 60 or 100 °C (Table 2). The ether solvents promoted the lowest catalyst efficiency, with reactions performed in THF-d_8 and 1,4-dioxane-d_8 only reaching 12% and 44% conversion of substrates, respectively, even after 42 hours. The remaining four solvents tested all led to similar conversions after 43 hours (66–79%), whether the reactions were performed at 60 °C or 100 °C, indicating that the higher temperature is not necessary for this reaction. Significant increases of conversion between 22 and 43 hours was not observed under any of the reaction conditions tested. In the ^1H NMR spectra, the ^1H resonances of phenylethyne had almost disappeared after 22 hours, indicating that the starting material either decomposes or that a side-reaction is occurring (such as oligomerisation).

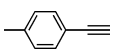
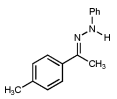
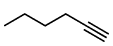
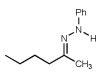
Table 2 Comparison of solvents for the catalysed addition of phenylhydrazine to phenylethyne using $[Ir(bpm)(CO)_2]BArF$ (**2**)

		% Conversion			
Solvent	Temp./°C	1 h	5 h	22 h[a]	45 h[b]
Toluene-d_8	100	39	63	74	79
Benzene-d_6	60	12	32	61	66
$(CDCl_2)_2$	100	51	66	70	70
$CDCl_3$	60	17	45	73	76
$CDCl_3$[c]	60	14	35	65	81
1,4-Dioxane-d_8	100	17	32	42	44
THF-d_8	60	2	5	10	12

[a] Monitored between 21–24 h. [b] Monitored between 44–47 h. [c] Reaction not performed under anhydrous or O_2 free conditions.

A control experiment for the intermolecular hydroamination of phenylethyne with phenylhydrazine was performed in $CDCl_3$ at

Table 3 Intermolecular hydroamination of terminal alkynes with substituted hydrazines and aniline to yield hydrazone and imine products[a] using **2**

					% Conversion[b]		
Alkyne	Amine	Product	Solvent	Temp./°C	1 h	5 h	22 h[c]
Ph—≡—H			Tol-d_8	100	39	63	74
			$CDCl_3$ Tol-d_8	60 100	17 41	45 66	73 69
n-Hex—≡			$CDCl_3$ $(CDCl_2)_2$	60 100	25 14	48 31	73 48
			$CDCl_3$ $CDCl_3$	60 60	3 2	8 8	18 14
Ph—≡—H			Tol-d_8	100	7	25	35
			$CDCl_3$ $CDCl_3$	60 60	2 1	8 6	28 15
			$CDCl_3$	60	6	18	13
	$PhNH_2$		$CDCl_3$	60	24	47	57

[a] ^1H NMR spectra were compared to that of authentic samples of the hydrazone and imine products.† [b] Only the *E*-isomer was observed. [c] Monitored between 21–24 h.

60 °C with no catalyst, and under these conditions no formation of acetophenone phenylhydrazone (**1**) was observed after 45 hours.

The ability of [Ir(bpm)(CO)$_2$]BArF (**2**) to catalyse the hydroamination of phenylethyne with phenylhydrazine was also tested under conditions that were not inert. The sample was prepared in air using $CDCl_3$ which had not been pre-dried or degassed and the conversion obtained was comparable to that performed under an inert atmosphere, although slightly slower in the beginning of the reaction (Table 2). This result demonstrates the robust nature of the $BArF^-$ complex **2**, and its potential application in industry compared to many more air-sensitive catalysts.

With optimum reaction conditions for the intermolecular hydroamination of phenylethyne with phenylhydrazine using **2** established as $CDCl_3$ as solvent at 60 °C and toleune-d_8 as solvent at 100 °C the reaction scope was extended to include other terminal alkynes (4-ethynyltoluene, 1-hexyne and 1-octyne) and substituted hydrazines (*N*-aminopiperidine, 1,1-dimethylhydrazine and methylhydrazine) (Table 3).

The overall efficiency of conversion of the two aromatic alkynes was higher than the efficiency of conversion of the two aliphatic alkynes, with conversions of approximately 70% for phenylethyne and 4-ethynyltoluene after 21 hours, but only 48% for 1-octyne at the same temperature. The *para*-substituent on the phenyl ring of 4-ethynyltoluene had minimal affect on the efficiency of the catalysed hydroamination reaction when compared to the efficiency of conversion of the unsubstituted phenylethyne.

The efficiency of the catalysed conversions of 1-octyne and 1-hexyne to 2-octanone phenylhydrazone (**7**) and 2-hexanone phenylhydrazone, respectively, were almost identical, when performed under the same reaction conditions ($CDCl_3$ at 60 °C). The catalysed conversion of 1-octyne to the hydrazone **7** over 22 hours was increased by a factor of 2 when the temperature of the reaction was raised from 60 °C to 100 °C. This is opposite to the trend observed for the aromatic alkynes, which showed comparable, if not lower, conversions when temperatures were raised.

The low efficiency of conversion of 1-hexyne and 1-octyne to the expected hydrazones was most likely due to the decomposition of the starting materials or conversion of the starting material into other products. Possible side-products being formed during the catalysed reaction could be those due to anti-Markovnikov addition of the hydrazine to the terminal alkyne. Previous work performed by Odom and co-workers[10] on the metal catalysed hydroamination of terminal alkynes with 1,1-dimethylhydrazine indicated that the regioselectivity of the reaction was influenced by the electronic structure of the alkyne substrate. However, in the reactions described here there was no evidence of the formation of either of the *E*- or *Z*-isomers of the product of anti-Markovnikov addition.

The hydroamination of phenylethyne with phenylhydrazine was much more successful than the hydroamination reactions using other substituted hydrazines, with a conversion of alkyne to acetophenone phenylhydrazone (**1**) more than twice that of the other substituted hydrazines (79% compared to *N*-aminopiperidine which gave the next highest conversion of 35%). Methylhydrazine gave a very poor level of hydroamination with only 12% conversion after 42 hours. Monitoring the reaction by ^{1}H NMR spectroscopy showed that over 80% of the methylhydrazine had been consumed after 5 hours leading to the formation of by-products, which would account for the low conversion to the desired acetophenone methylhydrazone. The efficiency of the catalysed addition of the two di-substituted hydrazines, 1,1-dimethylhydrazine and *N*-aminopiperidine, to phenylethyne was similar in $CDCl_3$ at 60 °C, with conversions of around 25% after 42 hours for each. Increasing the temperature to 100 °C only improved the conversion of *N*-aminopiperidine to *N*-(1-phenylethylidene)-1-piperidinamine from 28% to 35% after 21 hours, with no significant change after that time.

The catalysed intermolecular hydroamination of phenylethyne was also performed using aniline in place of a hydrazine substrate. The efficiency of conversion of phenylethyne with aniline to *N*-(1-phenylethylidene)-benzenamine in $CDCl_3$ at 60 °C was far less than the efficiency of the hydroamination reaction using phenylhydrazine. This indicates that substituted hydrazines undergo catalysed intermolecular hydroamination of terminal alkynes much more readily than primary amines when the catalytic system described in this work is used.

Microwave heating, as opposed to conventional thermal heating, has been shown to dramatically improve the efficiency of both standard synthetic, as well as catalysed, reactions.[19,20] The efficiency of catalysed hydroamination of phenylethyne with phenylhydrazine using [Ir(bpm)(CO)$_2$]BArF (**2**) (5 mol%) was tested using microwave irradiation as the heating mechanism in order to improve the yield of the hydrazone product, however the rate of conversion to acetophenone phenylhydrazone (**1**) was not improved by employing microwave irradiation, even when the maximum power (300 W) was maintained over the whole heating time. Comparable conversions of substrates to **1** were obtained when the catalysed reaction was performed in both $CDCl_3$ at 60 °C and toluene-d_8 at 100 °C for the two heating methods.

The best previously reported catalysed addition of phenylhydrazine to phenylethyne to yield **1** is with a system incorporating (Ph_3P)Au(CH_3) (0.2 mol%) and NH_4PF_6 (1 mol%) which promoted a conversion of 99% after 4 hours.[12] The efficiency of this catalyst for other substrates was not demonstrated, however. Other previously reported intermolecular hydroamination reactions with 1,1-disubstituted hydrazines were catalysed by titanium complexes and achieved conversions of alkynes to hydrazone products of up to 88% in 2 hours.[10] These reactions, however, produced a mixture of Markovnikov and anti-Markovnikov products, depending on the substituent on the alkyne group.

In conclusion, we have demonstrated the efficient and selective intermolecular hydroamination of alkynes with hydrazines using Rh(I) and Ir(I) metal complexes. [Ir(bpm)(CO)$_2$]BArF (**2**) was found to be the best catalyst for the conversion of phenylethyne and phenylhydrazine to a single product, acetophenone phenylhydrazone (**1**), promoting a conversion of 70% after 22 hours. The complexes reported here containing the $BArF^-$ counterion increased the rate of conversion for the hydroamination reaction by at least a factor of 2, when compared to tetraphenylborate complexes of similar structures. Overall, the catalysed hydroamination reactions performed with both substrates containing an aromatic group were the most efficient at yielding the hydrazone products. In most of the catalysed hydroamination reactions performed the substrates were consumed before full conversion of substrates to products could be achieved, indicating side-reactions were taking place.

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