One-Pot Tandem Hydroamination/Hydrosilation Catalyzed by Cationic Iridium(I) Complexes

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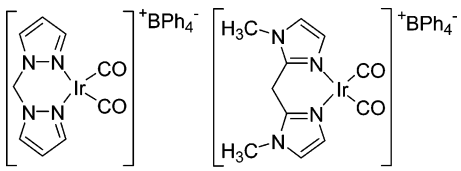
*Summary: The cationic Ir(I) complex [{Ir(bis(pyrazol-1-yl)methane)(CO)$_2$}BPh$_4$] (**1**) catalyzes the hydroamination of 4-pentyn-1-amine to form 2-methylpyrroline and subsequent hydrosilation to form 1-(triethylsilyl)-2-methylpyrrolidine in a one-pot, tandem procedure in a short time frame and with essentially quantitative yields. The tandem transformation can also be achieved using the related Ir(I) complex [{Ir(bis(1-methylimidazol-2-yl)-methane)(CO)$_2$}BPh$_4$] (**2**) as catalyst.*

The demand for cleaner and more efficient organic syntheses has led to increasing interest in catalysts which are able to catalyze multiple, mechanistically distinct reactions. This "one-pot" methodology is attractive, as it saves on the quantity of solvent and catalyst utilized and is time and energy efficient in reducing the number of steps with individual workup procedures. Tandem hydrogenation−hydroformylation catalyzed by a rhodium phosphine complex leads to cyclic α-amino acids,[1] and in the synthesis of polymers a Ru complex has been used to efficiently catalyze simultaneous ROMP (ring-opening metathesis polymerization) and ATRP (atom-transfer radical polymerization).[2] Many pharmaceuticals are built around central heterocyclic scaffolds and commonly contain N-heterocycles. The synthesis of complex heterocycles has been demonstrated using a single catalyst for a series of domino or tandem reactions with a carefully designed organic precursor.[3]

Catalyzed hydroamination, where an N−H bond is added across a carbon−carbon triple bond, provides an atom-efficient route for the synthesis of N-heterocycles containing imines,[4] and the further catalyzed reduction of these imines can be achieved by hydrogenation,[5] by hydrogen transfer,[6] or by hydrosilation,[7] where the Si−H bond is added across the carbon−nitrogen double bond. The saturated N-heterocycles that are formed are important core structures in many natural products; therefore, efficient syntheses of these is an important goal.[8] A one-pot reaction to form cyclic amines has been reported by Bytschkov and Doye,[9] with the hydroamination step catalyzed by Cp_2TiMe_2 at 110 °C in toluene and the reduction effected by reaction with a stoichiometric quantity of zinc-modified $NaBH_3CN$. In this paper, we describe the efficient, one-pot synthesis of 1-(triethylsilyl)-2-methylpyrrolidine via catalyzed hydroamination followed by catalyzed hydrosilation under mild conditions. The catalysts used in these investigations are the cationic Ir(I) dicarbonyl complexes [{Ir(bpm)(CO)$_2$}BPh$_4$] (**1**; bpm = bis(pyrazol-1-yl)-methane) and [{Ir(bim)(CO)$_2$}BPh$_4$] (**2**; bim = bis(1-methylimidazol-2-yl)methane).



1 **2**

In previous work, the Ir(I) complexes with bidentate N-donor ligands (**1** and **2**) were shown to be efficient catalysts for the intramolecular hydroamination of aminoalkynes, under mild conditions.[10] In particular, complex **1** efficiently catalyzes the hydroamination of 4-pentyn-1-amine (**5**) (using 1.5 mol % of **1**) in THF at 60 °C, to give quantitative conversion[11] to 2-methyl-1-pyrroline in 135 min. Complex **1** also catalyzes the alcoholysis of silanes under mild conditions.[12]

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(11) Quantitative conversion means >99% conversion. This is the time where no remaining substrate peaks are evident in the ^{1}H NMR spectrum of the reaction mixture. Only one product is evident in the ^{1}H NMR spectrum.
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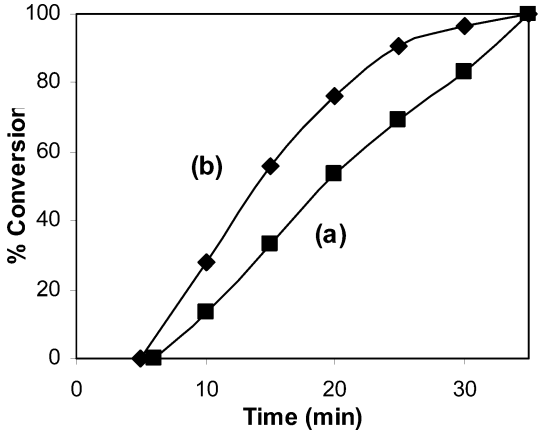
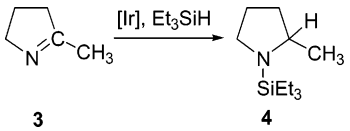


Figure 1. Formation of 1-(triethylsilyl)-2-methylpyrrolidine (**4**) from 2-methyl-1-pyrroline (**3**): (a) catalyzed by **1** (2 mol %, 60 °C in THF-d_8); (b) catalyzed by **2** (2 mol %, 60 °C in THF-d_8).

Scheme 1



The Ir(I) complexes **1** and **2** were further tested for their catalytic activity in the reduction of imines via hydrosilation. The hydrosilation of 2-methyl-1-pyrroline (**3**) with triethylsilane to give 1-(triethylsilyl)-2-methylpyrrolidine (**4**) (Scheme 1) was conducted at 60 °C in THF-d_8, using 2 mol % of the catalyst, while the reaction was monitored by ^{1}H NMR spectroscopy.[13] Both complexes **1** and **2** efficiently catalyze this reaction, giving >99% conversion to the *N*-silylamine **4**[14] in 35 min (Figure 1). In one experiment, 2-methylpyrrolidine was formed as a minor product;[15] this probably arises by hydrolysis of the *N*-silylamine by traces of adventitious water in the reaction mixture. This was confirmed by conducting the hydrosilation experiment in the presence of 1 mol equiv of water (relative to pyrroline substrate), which led to the exclusive formation of 2-methylpyrrolidine.

To synthesize 1-(triethylsilyl)-2-methylpyrrolidine directly from 4-pentyn-1-amine (**5**), the hydroamination and hydrosilation steps were undertaken initially as a one-pot, two-step procedure, in which the hydroamination reaction was allowed to proceed to completion and then triethylsilane was injected into the same reaction vessel. This was undertaken using 2 mol % of complex **1**, in THF-d_8 at 60 °C, and the reaction was monitored by ^{1}H NMR spectroscopy (Scheme 2). Using this one-pot, two-step methodology, 1-(triethylsilyl)-2-methylpyrrolidine (**4**) was produced in quantitative yield after a total reaction time of 5 h. As can be seen from the reaction profile in Figure 2, the hydroamination step was complete within 3 h, at which time the triethylsilane was injected. The hydrosilation reaction was then complete with quantitative conversion within a further 2 h.[11] Initial calculations show that the hydroamination step is first order with respect to substrate, while the hydrosilation step is zero order with respect to substrate. A more detailed kinetics analysis is currently underway.

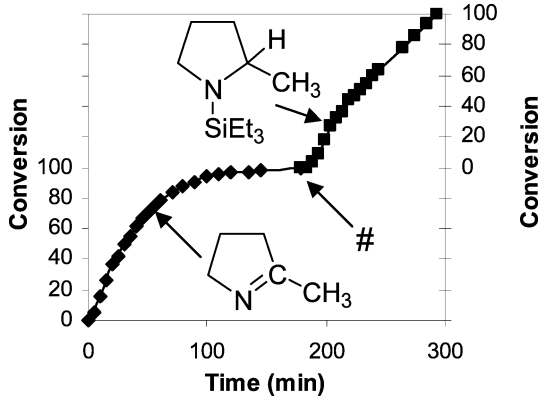
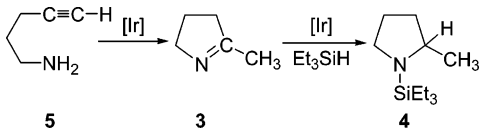
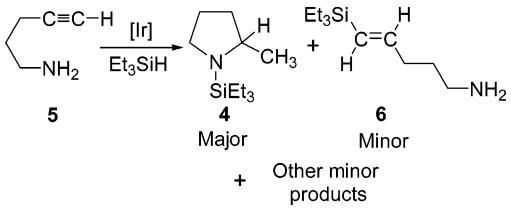


Figure 2. Formation of 1-(triethylsilyl)-2-methylpyrrolidine (**4**) from 4-pentyn-1-amine (**5**), catalyzed by **1** (2 mol %, 60 °C in THF-d_8) in a one-pot, two-step reaction (Scheme 2). The addition of Et_3SiH is indicated by #.

Scheme 2



Scheme 3



The two-step reaction also proceeds well if triethylsilane is present from the beginning of the reaction. 4-Pentyn-1-amine (**5**) and triethylsilane were allowed to react in the presence of 2 mol % of complex **1** in THF-d_8 at 60 °C, and the reaction was monitored by ^{1}H NMR spectroscopy. After 6.5 h, the reaction was complete, with the formation of the major product 1-(triethylsilyl)-2-methylpyrrolidine (**4**), the minor product *trans*-5-(triethylsilyl)-4-pentenylamine (**6**),[16] and trace amounts of additional products (Scheme 3). During the course of the reaction, the formation of 2-methyl-1-pyrroline (**3**) as an intermediate was observed (by ^{1}H NMR spectroscopy). *cis*-5-(Triethylsilyl)-4-pentenylamine was also observed as a minor byproduct; however, this was isomerized to the trans product **6** under the reaction

(13) **General procedure for monitoring catalytic reactions**: all catalytic reactions were performed on a small scale, under N_2 in NMR tubes fitted with a concentric Teflon valve. Reactions were carried out in freshly distilled THF-d_8, with approximately 0.5 mmol of substrate and 2 mol % of the catalyst. The reaction mixtures were heated at elevated temperatures (usually 60 °C) either in the NMR spectrometer or in an oil bath. The reactions were monitored by ^{1}H NMR, and the conversion rates were determined by integration of the product resonances relative to the substrate peaks. All yields refer to the NMR yield.

(14) Assignment of the product was based on ^{1}H COSY NMR spectra and GC/MS analysis. Spectroscopic data for **4**: ^{1}H NMR (THF-d_8, 600 MHz) δ 3.54 (m, ^3J = 6.2 Hz, 1H, *H*2), 3.11−3.03 (m, 2H, *H*5α, *H*5*β*), 1.90−1.77 (m, 2H, *H*3*β*, *H*4α), 1.71−1.64 (m, 1H, *H*4*β*), 1.46−1.40 (m, 1H, *H*3α), 1.01 (d, ^3J = 6.2 Hz, 3H, CH_3), 0.97 (t, ^3J = 7.7 Hz, 9H, Si(CH$_2$CH_3)$_3$), 0.63 (q, ^3J = 7.7 Hz, 6H, Si(CH_2CH$_3$)$_3$) ppm.

(15) Assignment was based on comparison with an authentic sample.

(16) Assignment of the product was based on ^{1}H NMR and GC/MS analysis.

conditions. Complex **1** has previously been shown to be a relatively inefficient catalyst for the addition of hydrosilanes to alkynes to form hydrosilated alkene products.[17]

The one-pot, two-step hydroamination/hydrosilation was also catalyzed by complex **2**. The reaction was again conducted in THF-d_8 at 60 °C, using 2 mol % of complex **2**, and the reaction was monitored by ^{1}H NMR spectroscopy. The time for the completion of the catalyzed hydroamination step was longer than that found using complex **1** (21 h for complex **2** compared with 3 h for complex **1**), but the hydrosilation step reached quantitative conversion[11] in a comparable time of 1 h and 48 min. The mechanistic steps by which complexes **1** and **2** catalyze either the hydroamination or hydrosilation reactions have yet to be studied in detail; however, the observed rate differences could be due to changes to the metal reactivity arising from the different electronic contributions from the pyrazolyl and imidazolyl donors or or from differences in the lability of the two ligands.[18]

In summary, we have shown that the cationic Ir(I) complexes **1** and **2** efficiently catalyze two mechanistically distinct reactions, namely hydroamination and hydrosilation, in a tandem, one-pot procedure. Further work is being undertaken to elucidate the mechanism of these reactions and to examine the scope of the catalysts for other tandem reactions.

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(18) Ligand exchange studies have shown that the bis(pyrazol-1-yl)methane ligand is significantly more labile than the bis(1-methylimidazol-2-yl)methane ligand (Burling, S. Ph.D. Thesis, University of Sydney, 2001).