ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, 50, 6274

Received 13th March 2014,
Accepted 16th April 2014

DOI: 10.1039/c4cc01874e

www.rsc.org/chemcomm

Catalytic [3 + 2] annulation of ketimines with alkynes *via* C–H activation by a cationic iridium(cod) complex†

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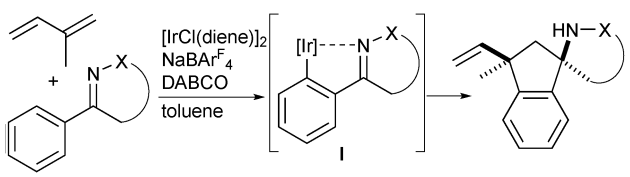
[3 + 2] Annulation of ketimines with internal and terminal alkynes proceeded *via* C–H activation to give aminoindene derivatives in high yields, which is catalyzed by a cationic iridium complex coordinated with 1,5-cyclooctadiene (cod).

Transition metal-catalyzed *ortho*-C–H functionalization of aromatic compounds has been achieved by use of appropriate directing groups such as carbonyl groups and imines.[1] The annulation reaction *via* the C–H bond activation involving a transformation of the directing group offers a straightforward route to the synthesis of complicated cyclic compounds,[2] and in particular, a redox-neutral annulation[3] enables an atom-efficient reaction.[4] For example, the catalytic annulation reactions of aromatic ketones or imines with C–C unsaturated bonds leading to indene derivatives have been developed by use of Re,[5] Ru,[6] Rh,[7] and Ir[8] catalysts. There have also been several reports on the oxidative coupling reactions of aromatic imines or ketones to give indene or indane derivatives.[9]

Recently, we reported the Ir-catalyzed annulation of ketimines with 1,3-dienes giving 1-aminoindanes (eqn (1)).[10,11] The reaction proceeds *via ortho*-C–H activation forming an aryliridium(I) species **I** as a key intermediate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base for a successive oxidative cyclization with 1,3-dienes. Here we report that cyclic *N*-acyl ketimines react with alkynes to give annulation products in the presence of the Ir catalyst without the use of any bases.



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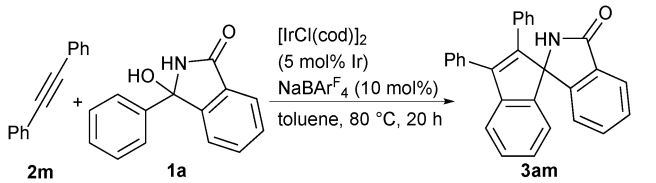
† Electronic supplementary information (ESI) available: Experimental procedures, and compound characterization data. See DOI: 10.1039/c4cc01874e

Table 1 Ir-catalyzed annulation of 3-phenyl-3-hydroxyisoindolin-1-one (**1a**) with diphenylacetylene (**2m**)[a]

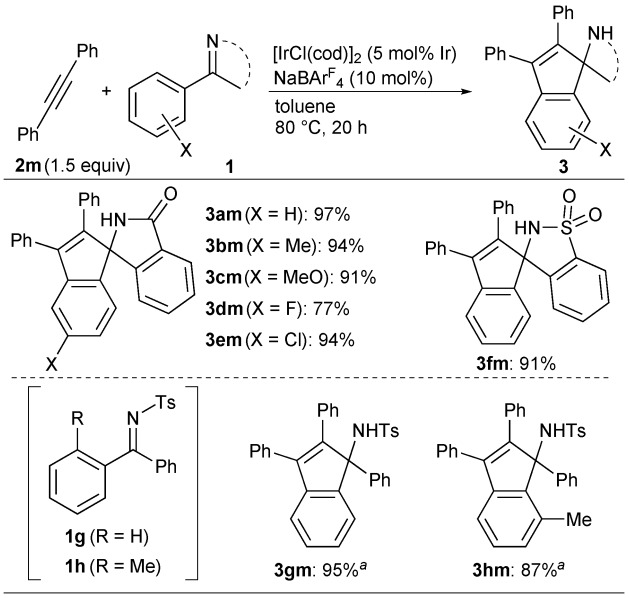


2m 1a 3am

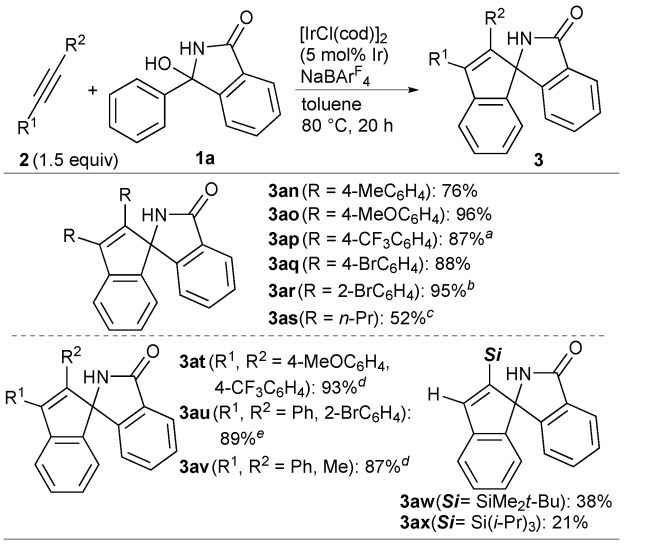
Entry	Change from the optimized condition	Yield[b] (%)
1	With DABCO (5 mol%)	21
2	With DABCO (10 mol%)	0
3	None	97[c]
4	Without $NaBAr^F_4$	0
5	$AgPF_6$ instead of $NaBAr^F_4$	31
6	$[IrCl(coe)_2]_2$ instead of $[IrCl(cod)]_2$	0
7	$[IrCl(coe)_2]_2$/(*R*)-binap instead of $[IrCl(cod)]_2$	9
8	$[RhCl(cod)]_2$ instead of $[IrCl(cod)]_2$	0

[a] Reaction conditions: **1a** (0.20 mmol), **2m** (0.30 mmol), Ir catalyst (5 mol% of Ir), $NaBAr^F_4$ (10 mol%) in toluene (0.8 mL) at 80 °C for 20 h. [b] Determined by ^1H NMR analysis. [c] Isolated yield.

Treatment of 3-hydroxy-3-phenylisoindolin-1-one (**1a**), which *in situ* generates the corresponding ketimine by dehydration,[10b] with diphenylacetylene (**2m**) in toluene in the presence of $[IrCl(cod)]_2$ (5 mol% of Ir, cod = 1,5-cyclooctadiene), $NaBAr^F_4$ (Ar^F = 3,5-$(CF_3)_2C_6H_3$), and DABCO at 80 °C for 20 h gave 1-aminoindene **3am** in 21% yield (Table 1, entry 1). The reaction conditions are the optimized ones in the annulation of **1a** with 1,3-dienes, where it is proposed that the formation of the aryliridium(I) species from an initially formed cationic Ir(III)-hydride species occurred by deprotonation promoted by DABCO.[8] The use of an increased amount of DABCO (10 mol%) completely inhibited the formation of **3am** (entry 2). On the other hand, the catalytic activity was greatly improved by removing DABCO from the previous reaction system to give **3am** in 97% yield (entry 3). The formation of the annulation product **3am** was not observed at all in the reaction without $NaBAr^F_4$ (entry 4). These results indicate that a cationic Ir(I) complex efficiently catalyzes the present reaction and the Ir(III)-hydride species would be involved as a key intermediate for a successive alkyne insertion (*vide infra*). The counter anion of the



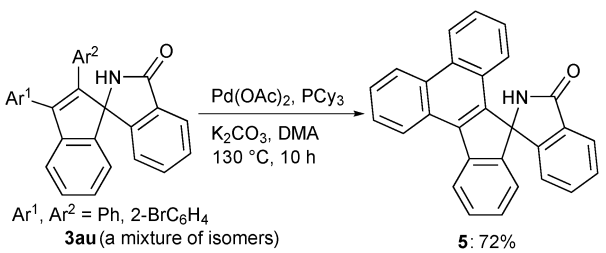
Scheme 1 Annulation of ketimines with diphenylacetylene. Reaction conditions: **1** (0.20 mmol), **2m** (0.30 mmol), $[IrCl(cod)]_2$ (5 mol% of Ir), and $NaBAr^F_4$ (10 mol%) in toluene (0.8 mL) at 80 °C for 20 h. Isolated yields are shown. [a] For 48 h.



Scheme 2 Annulation of 3-hydroxy-3-phenylisoindolin-1-one with alkynes. Reaction conditions: **1a** (0.20 mmol), **2** (0.30 mmol), $[IrCl(cod)]_2$ (5 mol% of Ir), $NaBAr^F_4$ (10 mol%), and toluene (0.8 mL) at 80 °C for 20 h. Isolated yields are shown. [a] Performed with **1a** (0.24 mmol) and **2q** (0.20 mmol). [b] Ratio of atropisomers: 44 : 36 : 13 : 7. [c] Performed with $[IrCl(cod)]_2$ (10 mol% of Ir) and $NaBAr^F_4$ (20 mol%). [d] 1 : 1 mixture of regioisomers. [e] Ratio of isomers: 54 : 23 : 23.

cationic iridium plays a certain role in the catalytic activity: the use of $AgPF_6$ gave a lower yield (31%) of **3am** (entry 5) than that obtained using $NaBAr^F_4$ (entry 3). The use of $[IrCl(coe)_2]_2$ (coe = cyclooctene) as a catalyst gave no annulation product (entry 6), indicating that cod (entry 3) works as a chelating ligand. On the other hand, the catalytic activity coordinated with a bisphosphine ligand, binap, was low, resulting in a low yield (9%) of **3am** (entry 7). $[RhCl(cod)]_2$ did not promote the present reaction (entry 8).

The results obtained for the Ir-catalyzed annulation of several hemiaminals or ketimines **1** with diphenylacetylene (**2m**) are summarized in Scheme 1. The reactions of hemiaminals having *para*-substituted phenyl groups **1b–1e** gave high yields of annulation products **3bm–3em**. Not only the cyclic *N*-acyl ketimines, but also a cyclic *N*-sulfonyl ketimine **1f** and acyclic *N*-tosyl ketimines **1g** and **1h** are good substrates to give the corresponding aminoindenes **3fm–3hm** in high yields. It should be noted that the selective C–H bond activation of the 2-methylphenyl group of **1h** occurred to give **3hm** as a single isomer. This is probably because the *E*-geometry of **1h**, which is stabilized by the steric hindrance of the 2-methylphenyl group, allows the coordination of the imine nitrogen to the Ir center directing toward the 2-methylphenyl group.

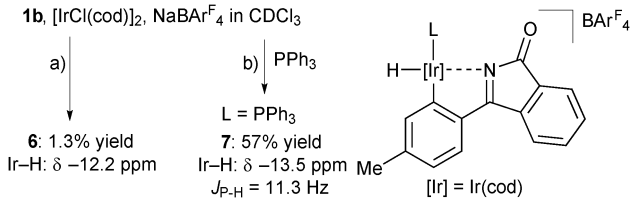


(2)

Scheme 2 summarizes the results obtained for the reaction of 3-hydroxy-3-phenylisoindolin-1-one (**1a**) with several alkynes **2**. Symmetrically substituted diaryl alkynes **2n–2r** reacted with **1a** to give the corresponding annulation products **3an–3ar** in 76–96% yields. 1-Octyne (**2s**) also reacted with **1a** to give the annulation product **3as** although the yield was modest (52%). The reactions of unsymmetrically substituted diaryl alkynes **2t** and **2u** proceeded to give **3at** and **3au** in 93 and 89% yields, respectively. Unfortunately, however, no regioselectivity was observed for **3at** and **3au**. The reaction of 1-phenyl-1-propyne (**2v**) gave a mixture of regioisomers **3av** in 87% yield. These results indicate that the regioselectivity of the alkyne insertion is less affected by electronic and steric differences of the substituents of alkynes. Terminal alkynes **2w** and **2x** were also applicable to give **3aw** and **3ax** as the single regioisomers in 38 and 21% yields, respectively.[12]

The regio- and atropisomeric mixture of **3au** was transformed into a fused aromatic compound **5** by Pd-catalyzed intramolecular C–H arylation (eqn (2)).[13]

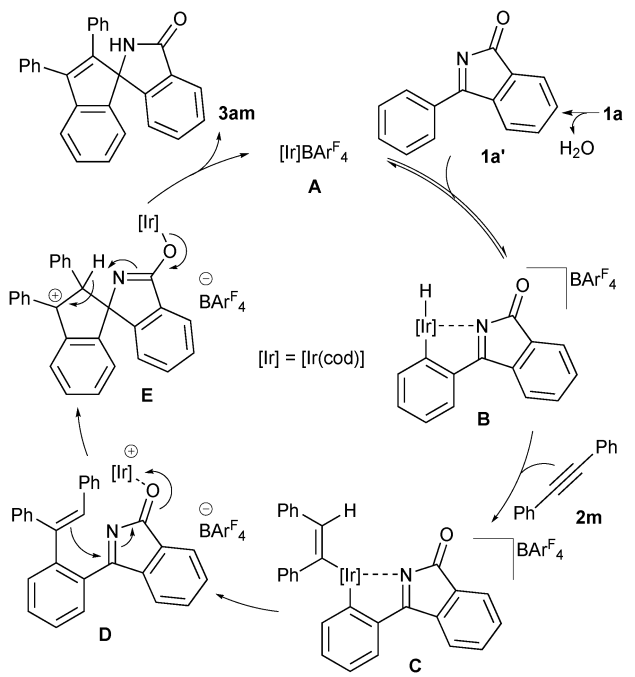
To gain some insight into the mechanism of the C–H activation, we conducted a substoichiometric reaction of **1b** (2 equiv. to Ir) with $[IrCl(cod)]_2$ in $CDCl_3$ in the presence of $NaBAr^F_4$ (Scheme 3a). The reaction at room temperature for 3 h brought about the formation of a small amount (1.3%) of a new hydridoiridium complex **6**, which showed a singlet peak at −12.2 ppm by ^1H NMR analysis. The hydridoiridium complex stabilized by the coordination of PPh_3 was also formed in modest yield (Scheme 3b). The reaction of **1b** (1 equiv. to Ir) with $[IrCl(cod)]_2$ in the presence of $NaBAr^F_4$ and PPh_3 (1 equiv. to Ir) in $CDCl_3$ at room temperature for 20 h gave complex **7**, whose yield was estimated to be 57% by ^1H NMR analysis. The ^1H NMR spectrum of the isolated complex **7** passing through a short alumina column showed a doublet peak at



Scheme 3 Stoichiometric reactions. (a) **1b** (2 equiv. to Ir), $[IrCl(cod)]_2$, and $NaBAr^F_4$ in $CDCl_3$ at room temperature for 3 h. (b) **1b** (1 equiv. to Ir), $[IrCl(cod)]_2$, $NaBAr^F_4$, and PPh_3 (1 equiv. to Ir) in $CDCl_3$ at room temperature for 20 h.

−13.5 ppm (J_{P-H} = 11.3 Hz), which was assigned to a hydridoiridium complex coordinated with PPh_3 *cis* to the hydride.[14] These results indicate that the *ortho*-C–H activation forms the aryl-hydridoiridium(III) species as a key intermediate in the present reaction.

Shibata and co-workers reported sequential catalytic reactions of aromatic ketones with alkynes using an iridium–binap complex, where the iridium complex operates as a catalyst in the *ortho*-C–H bond alkenylation of aromatic ketones and as a Lewis acid catalyst in the cyclization of the alkenylated products leading to benzofulvenes.[8] In a similar manner, the present annulation reaction may involve the sequential steps, *ortho*-C–H alkenylation and cyclization.[15] The catalytic cycle is postulated as illustrated in Scheme 4. *ortho*-C–H activation of ketimine **1a′**, which involves oxidative addition of the C–H bond to Ir, forms arylhydridoiridium(III) intermediate **B**. The alkyne insertion to the Ir–H bond forms alkenyliridium(III) **C** and the successive reductive elimination gives *ortho*-alkenylated product **D**, which may be activated by coordination to the cationic iridium center. An intramolecular cyclization *via* intermediate **E** gives aminoindene **3am** and regenerates the cationic iridium **A**. Alternatively, alkenylated product **D** undergoes cyclization without activation by the cationic iridium species due to the high reactivity of the imine moiety.



Scheme 4 Proposed catalytic cycle.

In summary, we have developed an annulation reaction of ketimines with alkynes *via* C–H activation catalyzed by a cationic iridium complex coordinated with 1,5-cyclooctadiene. A variety of alkynes including a terminal alkyne were successfully employed to give 1-aminoindene derivatives. The NMR experiments indicated that the Ir(III)-hydride species as an intermediate is formed *via* a directed C–H activation under chelation assistance of *N*-acyl and *N*-sulfonyl imines.

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas ''Molecular Activation Directed toward Straightforward Synthesis'', from the MEXT, Japan.

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