Sequential Catalytic Reactions for the Synthesis of Benzofulvenes Using an Iridium Complex with Dual Function

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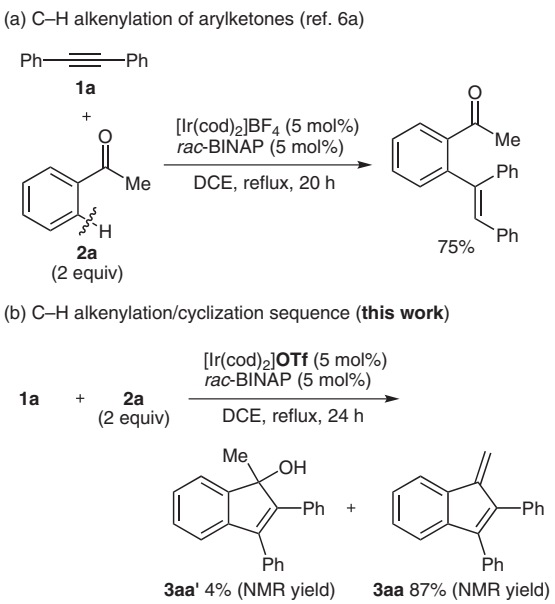
Abstract: The cationic iridium complex ([Ir(cod)$_2$]OTf + *rac*-BINAP) efficiently catalyzed a sequential process of *ortho*-C–H bond functionalization, cyclization and dehydration, leading to a concise preparation of 1-methylene indene (benzofulvene) derivatives. The iridium complex operated as a catalyst in the *ortho*-C–H bond alkenylation of aryl ketones with alkynes and as a Lewis acid catalyst in the cyclization of the alkenylated product and the subsequent dehydration.

Key words: catalysis, cyclization, C–H bond functionalization, indenes, iridium

A sequence of catalytic reactions that can be performed in one pot from simple precursors is an efficient and environmentally benign protocol for the preparation of synthetic intermediates.[1] Among various approaches toward this end, consecutive reactions promoted by a single catalyst are promising. Actually, mechanistically similar multiple transformations based on this concept are well established.[1,2] In contrast, using a single catalyst for a sequence of mechanistically distinct reactions is more intriguing and challenging.[3] For example, a palladium complex showed high catalytic activity in a consecutive Mizoroki–Heck reaction, C–H bond arylation and hydrogenation sequence.[3d] In recent work, a cationic rhodium complex was found to catalyze three sequential reactions of olefin isomerization, propargyl Claisen rearrangement and carbonyl migration.[3g] Herein, we disclose a cationic iridium-complex catalyzed sequence of *ortho*-C–H bond functionalization, cyclization and dehydration. The iridium complex showed dual functionality in the three reactions: It behaved as a catalyst for the *ortho*-C–H bond alkenylation of aryl ketones with alkynes[4–6] and acted as a Lewis acid catalyst[7] in the cyclization and dehydration. From the synthetic point of view, this protocol provides easy access to the 1-methylene indene (benzofulvene) framework.[8]

Our group has already disclosed a cationic iridium complex that exhibits high catalytic activity in the carbonyl-directed sp^2 C–H bond alkenylation of aryl ketones. We found that, in the presence of 5 mol% [Ir(cod)$_2$]BF$_4$ and *rac*-BINAP in refluxing 1,2-dichloroethane (DCE), diphenylacetylene (**1a**) added to the *ortho*-C–H bond of acetophenone (**2a**), providing the *ortho*-alkenylated adduct in good yield (Scheme 1a).[6a] Whilst modifying this catalyst, we found an unexpected cyclization occurred when the counter anion of the iridium complex was changed: when trifluoromethanesulfonate anion (OTf) was used, indenol **3aa′** and benzofulvene **3aa** were obtained in high yield in place of the *ortho*-alkenylated product (Scheme 1b). In the case of other counter anions, such as PF$_6$, SbF$_6$, and B[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_4$ (BARF), the cyclized product was not obtained and the *ortho*-alkenylated product was the only detectable product.[9]



Scheme 1

Several substituted aryl ketones were then subjected to the present protocol at a higher temperature using 10 mol% of the cationic iridium catalyst (Table 1). *Ortho*-substituents on the aryl ketones had a significant influence on the reactivity: *o*-methoxy acetophenone (**2b**) for example, afforded the benzofulvene **3ab** in excellent yield,[10] although the presence of an *o*-methyl group lowered the conversion of the substrates and the *o*-trifluoromethyl group completely prevented the reaction (entries 1–3). *Meta*-substituted acetophenones also gave the benzofulvene derivatives in moderate to high yield, and the regioselectivity varied depending on the substituents: *m*-methoxy acetophenone (**2e**) reacted at the congested *ortho*-position

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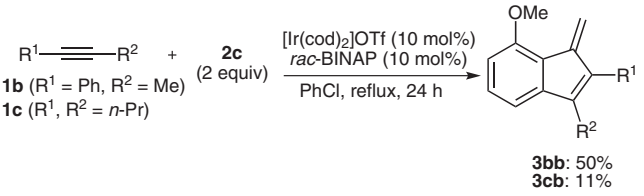
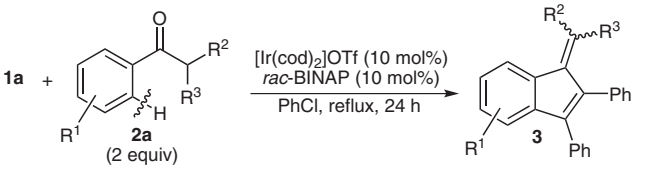


Scheme 2

between the methoxy and acetyl groups, whereas *m*-methyl acetophenone (**2f**) and *m*-trifluoromethyl acetophenone (**2g**) reacted at the less hindered *ortho*-position of the acetyl group (entries 4–6).[11] Both electron-donating and electron-withdrawing groups could be installed at the *para*-position of acetophenone and the corresponding benzofulvenes were obtained in high yield (entries 7–9). As a directing carbonyl group, ethanoyl and isopropanoyl groups were also acceptable (entries 10 and 11). As for the scope of alkynes, unsymmetrical alkyl, aryl-substituted acetylene **1b** also reacted with aryl ketone **2b** and the cyclized product **3bb** was obtained as a single regioisomer in moderate yield,[12,13] whereas 4-octyne (**1c**) afforded the product **3cb** in low yield (Scheme 2). These results illustrate that at least one aryl substituent on the alkyne terminus was required for the alkyne to be a good coupling partner.

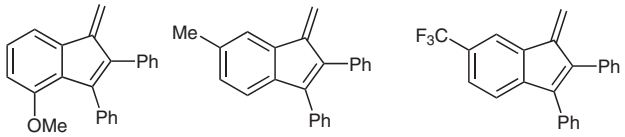
A possible mechanism for the present reaction is depicted in Scheme 3. The *ortho*-C–H bond alkenylation should proceed through iridium-catalyzed carbonyl-directed C–H bond cleavage followed by alkyne insertion.[6a] The subsequent cyclization and dehydration would be promoted by the Lewis acidity of the iridium catalyst.[14] To probe the reaction mechanism, we subjected *ortho*-alkenylated acetophenone to the present reaction conditions and found that benzofulvene **3aa** was obtained in good yield (Scheme 4). This result strongly suggests that the Lewis acid catalyzed cyclization of alkenylated product **A** is more probable than intramolecular 1,2-addition of vinyl iridium intermediate **B**, which could be generated in the C–H bond alkenylation step.[15] We also ascertained that dehydration of the isolated indenol **3aa′** efficiently proceeded only in the presence of the iridium catalyst; in the absence of the catalyst, no dehydration was observed. Furthermore, *tert*-butyl phenyl ketone (**2m**), which has no α-proton adjacent to the carbonyl group, afforded methyl- and isopropenyl-substituted indene **3am**. This could be explained by the generation of a tertiary cationic intermediate followed by a 1,2-methyl shift (Scheme 5). All these results prove the Lewis acidity of the iridium catalyst.

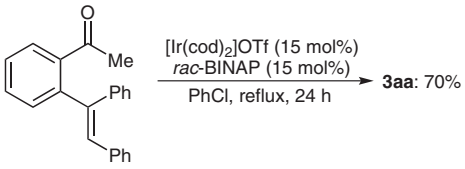
Table 1 Iridium-Catalyzed Benzofulvene Synthesis from Diphenylacetylene (**1a**) and Aryl Ketones **2**



Entry	R^1	R^2	R^3	**2**	**3**	Yield of **3** (%)
1	*o*-OMe	H	H	**2b**	**3ab**	95
2	*o*-Me	H	H	**2c**	**3ac**	48
3	*o*-CF_3	H	H	**2d**	–	n.d.[a]
4	*m*-OMe	H	H	**2e**	**3ae**	45[b]
5	*m*-Me	H	H	**2f**	**3af**	88[b]
6	*m*-CF_3	H	H	**2g**	**3ag**	59[b]
7	*p*-Me	H	H	**2h**	**3ah**	88
8	*p*-OMe	H	H	**2i**	**3ai**	82
9	*p*-CF_3	H	H	**2j**	**3aj**	80
10	H	Me	H	**2k**	**3ak**	82[c]
11	H	Me	Me	**2l**	**3al**	71

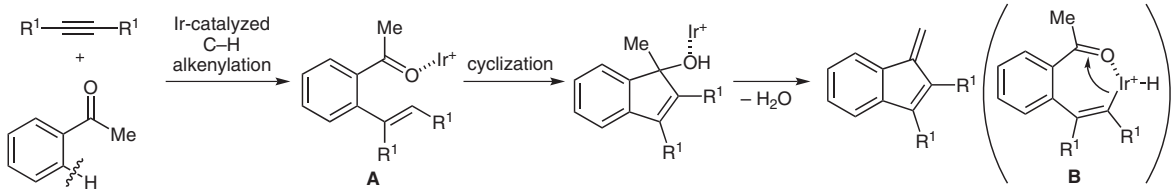
[a] No product was detected.
[b] The structures are depicted below.
[c] The product was obtained as a single stereoisomer, although the geometry was not determined.



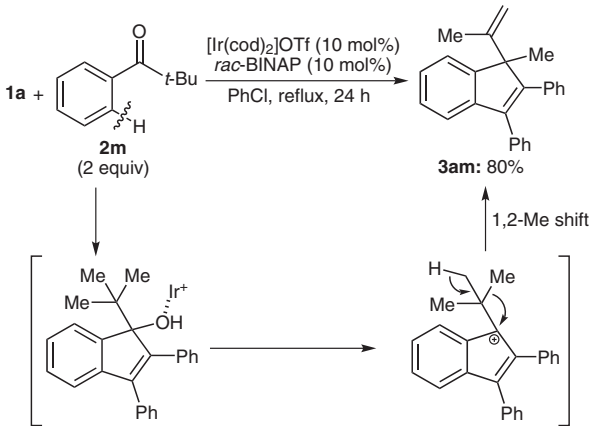


Scheme 4

In conclusion, we have discovered that the Lewis acidity of the cationic iridium-BINAP complex could be readily tuned by the counter anion without being detrimental to the catalytic activity of the C–H bond functionalization reaction. This dual catalytic activity enabled a facile proto-



Scheme 3



Scheme 5

col for the synthesis of benzofulvene derivatives via three sequential reactions of C–H bond alkenylation, cyclization and dehydration. Further studies on the application of the present catalyst are in progress.

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