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Diverse Strategies toward Indenol and Fulvene Derivatives: Rh-Catalyzed C−H Activation of Aryl Ketones Followed by Coupling with Internal Alkynes

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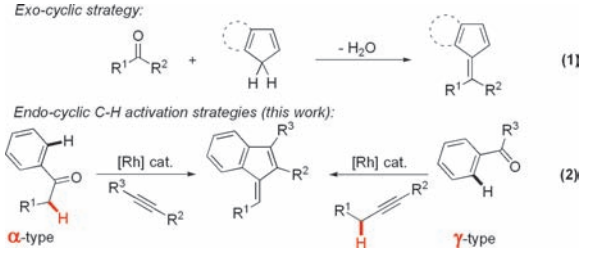
Supporting Information

ABSTRACT: The synthesis of indenols and fulvenes was achieved through Rh-catalyzed C−H bond activation of simple and diverse aryl ketone derivatives and subsequent coupling with internal alkynes. The process was found to involve either an α or γ dehydration step, depending on the substrate disposition and representing diverse pathways toward functionalized fulvenes.

Since their discovery by Thiele in 1900,[1] fulvenes and their derivatives have attracted much attention from generations of scientists due to their unique properties in the fields of materials science, organometallics and medicinal chemistry.[2] They are traditionally made by the condensation of cyclopentadienes onto ketones, a method which is typically limited by the availability of the cyclopentadienes, prepared from multistep procedures in which regioselectivity and functional group tolerance are often major difficulties (eq 1). Likewise, structurally related and biologically relevant indenols also suffer from limited access, as their preparation usually requires preactivation steps.[3]



In modern synthetic chemistry, C−C bond formation through C−H activation reactions has gained importance because it obviates the need for prior activation steps, a pivotal advantage with respect to cost and waste reduction.[4] The pioneering work on the C−H activation of phenone derivatives,[5] such as those of Murai,[5a] Brookhart,[5f] Cheng,[5j] and others,[5] and our recent work on Rh-catalyzed C−H activation of acetophenones[6] showed that phenone substrates were suited for ortho C−H functionalization reactions. Herein, we report diverse direct avenues into fulvene and indenol synthesis through C−H activation/cyclization pathways (eqs 1, 2).

Engaging pivalophenone (R^1 = *t*Bu, Scheme 1), a privileged C−H activation substrate,[5b] with 1,2-diphenylethyne[7] under optimized conditions (0.5 mol % $[RhCp^*Cl_2]_2$, 2 mol % $AgSbF_6$ and 2.1 equiv of $Cu(OAc)_2$, PhCl, 120 °C, 16 h) led to coupling product indenol **1a** in outstanding 99% isolated yield.[8−10] Although in this case $Cu(OAc)_2$ is not needed as a formal oxidant (the transformation is redox neutral), its stoichiometric presence was found essential for sufficient levels of reactivity. Interestingly, using R^1 = *i*Pr under the same conditions did not afford the α-dehydrated product that we had anticipated (corresponding fulvene derivative) but rather indenol product **1b** (66%), also when using harsher conditions (2.5 mol % Rh precatalyst, 140 °C, 1,4-dioxane). Likewise, electron-withdrawing phenones, even when bearing protons in potentially dehydrative positions, did not lead to the corresponding fulvene derivatives but interestingly to the indenol products (**1c**−**j**) in good to excellent yields. In contrast, electron-neutral and electron-rich phenones bearing protons in dehydrative positions (α or γ) generally led to the corresponding fulvene derivatives, in moderate to good yields (**2a**−**h**, **3a**−**f**, 40−80% isolated yields). In general, we found that the H^{γ} position dehydrates slightly more easily than the H^{α} position, allowing milder conditions and providing higher yields. This is evident when comparing the formation of **2a**,**b** (= **3a**,**b**) through the α- and the γ-route, respectively (Scheme 1). Having established both routes provides unique opportunities to regioselectively access fulvenes bearing diverse functional groups. For example, fulvenes **2c**−**h** are easily accessible through the α-pathway but would involve serious selectivity (and separation) issues through the γ-pathway, and vice versa for **3c**−**f**. In addition, our methodology tolerates halides (**1f**,**i**,**j**, no debromination observed), strongly electron-withdrawing groups (even phenones bearing two CF_3 groups still afforded C−H activation, **1d**,**h**), strongly electron-donating groups (up to two methoxy groups in **3c**,**d**), and heterocyclic cores such as biologically interesting indole derivatives (**2c**,**d**). Furthermore, the method is highly regioselective when using unsymmetrical alkynes (**1g**,**h**, **3c**−**f**).[11] Even in the difficult case of an unsymmetrical 1,2-diarylalkyne, the process still affords some regioselectivity (**2g**,**h**, both regioisomers display an interesting axial chirality).[12]

On the basis of previous reports by us and others,[5−8] we propose that the first step of the reaction is a cyclometalation, followed by alkyne insertion and subsequent intramolecular electrophilic attack of the carbonyl moiety (Scheme 2). Because a catalytic amount of $Cu(OAc)_2$ (typically 10 mol %) does *not* suffice to provide more than a trace amount of product, it is likely that one of the key roles of the Cu salt is to release the Rh catalyst in a transmetalation event.[13,14] Furthermore, intramolecular C−H

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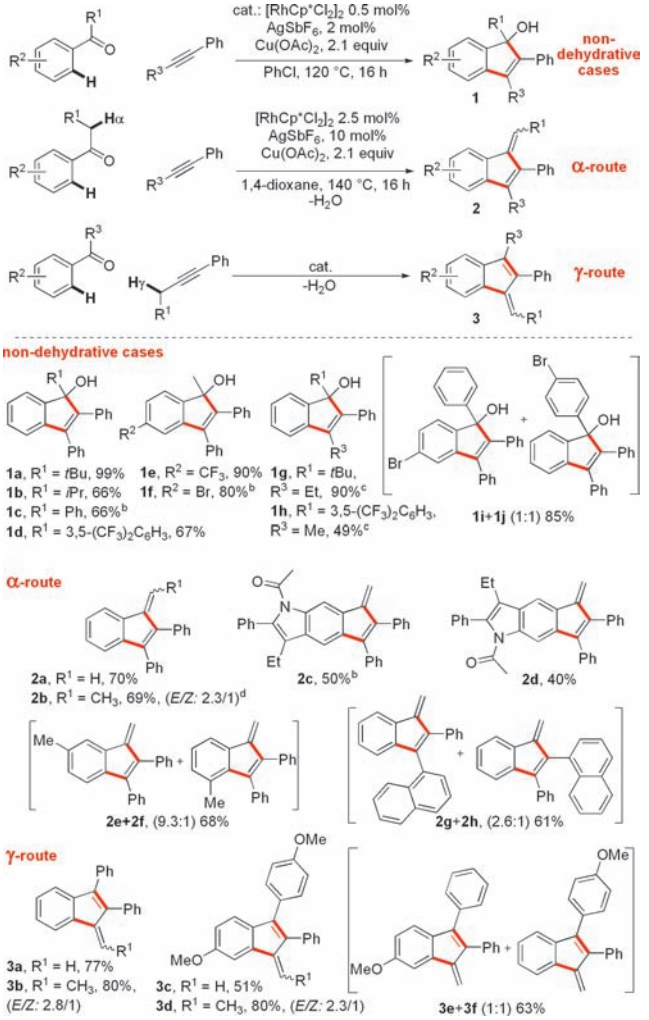
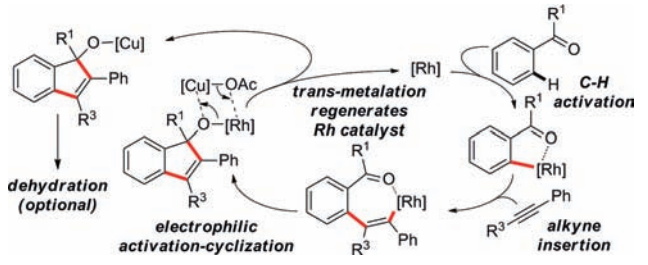
Scheme 1. Rh C−H Activation of Phenones and Coupling with Internal Alkynes, Isolated Yields[a]



[a] Reagents and conditions: (a) 1 mmol scale, 0.2 M for all entries. The phenone/alkyne ratio varies from 1:1.2 to 1.2:1, depending on purification convenience. (b) Yields of **1c,f** and **2c** were corrected for irremovable traces of solvents. (c) **1g** and **1h** are drawn as the main regioisomer, for which ratios are 9:1 and 20:1, respectively. (d) Reaction in PhCl instead of 1,4-dioxane.

Scheme 2. Proposed Reaction Mechanism



competition experiments (**1i** versus **1j**, and **3e** versus **3f**), where two C−H positions are sterically equivalent but electronically nonequivalent, do not show any regioselectivity (products were obtained exactly in a 1:1 ratio), indicating that the initial C−H activation step is not an electronically discriminating process.[15]

In conclusion, we have studied the Rh-catalyzed C−H activation of a representative set of phenone derivatives and their subsequent coupling with internal alkynes and have developed a suitable method for the comprehensive and selective preparation of diversely functionalized indenol and fulvene derivatives. We expect our method to be useful in the synthesis of 5-membered carbocyclic ring-containing targets and perhaps in the inspiration of novel and innovative transformations based on the C−H activation of other phenone-like substrates.

■ ASSOCIATED CONTENT

Supporting Information. Experimental Section and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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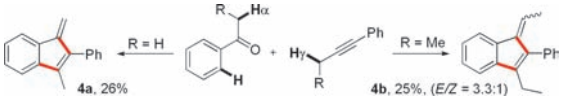
(9) See Experimental Section in the Supporting Information.

(10) Structurally reminiscent reactions using ketimines and Rh(I) catalysts were recently reported, see: (a) Sun, Z.-M.; Chen, S.-P.; Zhao, P. *Chem.—Eur. J.* **2010**, *16*, 2619. (b) Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 8181.

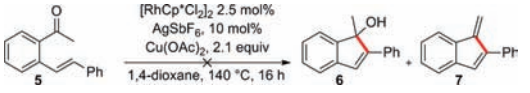
(11) Combining α- and γ-strategies did not work out well under our conditions:



(12) The chiral character of **2g** and **2h** was evidenced through chiral HPLC measurements (ODH, hexane/iPrOH (99:1), 0.8 mL/min), see ref 9.

(13) Replacement of the Cu salt with $Mn(OAc)_2$ (no reaction) or $Cu(OTf)_2$ (decomposition) did not lead to the expected products.

(14) Furthermore, submitting already olefinated acetophenone **5**[6] to our optimized conditions led to neither the corresponding indenol **6** nor to fulvene **7**, leaving mostly unreacted starting material. This indicates that **5** is not an intermediate of the reaction, thus excluding a Friedel−Crafts-type electrophilic cyclization mechanism.



(15) Nevertheless, an indication that the *electrophilic* cyclization is a critical step in the reaction can be deduced from the fact that 4-methoxyacetophenone and 4-methylacetophenone (poorly electrophilic phenones) yield only 9% and 26%, respectively (**2i,j**), whereas analogous 3-methylacetophenone yields 68% of the expected α dehydrated product (**2e,f**).