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Synthesis of Indene Frameworks via Rhodium-Catalyzed Cascade Cyclization of Aromatic Ketone and Unsaturated Carbonyl Compounds

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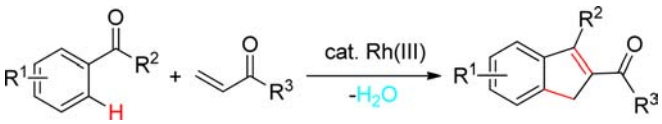
ABSTRACT



A novel rhodium(III)-catalyzed direct functionalization of the *ortho*-C−H bond of aromatic ketone derivatives and an intramolecular cyclization sequence produced indene derivatives in moderate to good yields. This cascade cyclization involves a conjugate addition of α,β-unsaturated ketone and subsequent aldol condensation. The reaction occurred efficiently in the presence of water and under an atmosphere of air.

Indene derivatives are important cyclic compounds that serve as building blocks for natural products[1] and pharmaceutical compounds possessing interesting biological activities,[2] as well as many functional materials.[3] They can also be used as valuable ligands for indenyl metal complexes, which are widely utilized in various catalytic reactions.[4] Consequently, much effort has been devoted to the construction of indene frameworks.[5,6]

Chemical transformations via transition-metal-catalyzed C−H bond activation are an important and challenging theme because the introduction of functional groups can be achieved more directly and byproducts such as metal halides are not formed.[7] Meanwhile, transition-metal-catalyzed carbocyclization is a powerful method for the construction of indene derivatives in organic synthesis. There are two typical approaches employed to form

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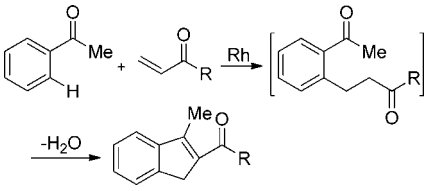
indene frameworks via C−H bond activation: intramolecular cyclization and intermolecular cyclization. The former strategy requires special starting materials to afford the cyclic products, whereas indene derivatives can be generated by intermolecular cyclization with simple and readily accessible substrates. For example, Kuninobu et al. succeeded in the catalytic synthesis of indene by the reactions of aromatic aldimines with phenyl acetylenes and aromatic ketimine with α,β-unsaturated ester.[8] Chang et al. developed the first example of Cu-catalyzed cycloaddition between alkynes and aryldiazoesters for a selective synthesis of indene derivatives.[9] Yi demonstrated a coupling reaction of arylketones with alkenes catalyzed by a tetranuclear ruthenium hydride complex to produce a mixture of indenes and a conjugated addition product.[10] Tian et al. displayed a regioselective synthesis of indene derivatives from *N*-benzylic sulfonamides and alkynes catalyzed by $FeCl_3$.[11] A new Rh(I)-catalyzed [3 + 2] annulation of *N*-unsubstituted aromatic ketimines with alkynes has been developed by Zhao to form tertiary 1*H*-inden-1-amines.[12] Cheng et al. and Glorius et al. independently reported a rhodium-catalyzed, chelation-assisted C−H activation of aryl ketones followed by the reaction with alkynes to afford substituted indene derivatives in good to excellent yields.[13] Cramer et al. illustrated the synthesis of indene with one chiral center by an enantioselective Rh(I)-catalyzed [3 + 2] annulation of aromatic ketimines and alkynes.[14] Li et al. disclosed a ruthenium(II)-catalyzed annulative coupling of *N*-sulfonyl imines of benzaldehydes with alkynes, leading to indenamines.[15] Shi et al. demonstrated a rhodium(III)/copper(II) system cocatalyzed the annulation of benzimides with internal alkynes for the synthesis of indenones.[16]

In 2011, Glorius et al. demonstrated the selective rhodium(III)-catalyzed oxidative *ortho*-olefination reaction between acetophenone and olefins and our group reported an efficient rhodium(III)-catalyzed C−H activation and subsequent conjugate addition with α,β-unsaturated ketone.[17] Inspired by these two results, we envisioned that a novel cascade reaction of conjugation addition of arene C−H activation directed by a carbonyl to α,β-unsaturated ketone and an intramolecular aldol condensation could afford indene derivatives. Herein, *we present an unprecedented rhodium(III)-catalyzed functionalization of ortho C−H bonds of acetophenone derivatives followed by an intramolecular cyclization to prepare indene derivatives* (Scheme 1).

Scheme 1. Rhodium-Catalyzed Cascade of C−H Activation to Access Indene Derivatives



We selected 3,4,5-trimethoxyacetophenone and ethyl vinyl ketone as substrates and C_6H_5Cl as the solvent at a reaction temperature of 130 °C to test the reaction. In our initial studies, several catalysts such as Cl(COD)Rh, $Rh(COD)_2BF_4$, $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$, and $(Cp^*RhCl_2)_2$ were examined. Although the yield was rather low and accompanied by the oxidative addition product, the expected cyclization product was obtained by using $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ as the catalyst (Table 1, entry 1). Since both base and acid can promote the aldol condensation, a series of bases and acids were examined for the reaction. Fortunately, Ag_2CO_3 and AgOAc can improve the yield greatly, with the latter affording a slightly higher yield of the desired product and a higher selectivity (Table 1, entries 2 and 3). The uses of Ag_2O, $Cu(OAc)_2$, and $Cu(OAc)_2H_2O$ (Table 1, entries 4−6) were less effective for the catalytic reaction, and the uses of alkali metals such as K_2CO_3, NaOAc, Na_2CO_3, and $NaHCO_3$ decreased the yield instead of improving it (Table 1, entries 7−10). The presence of CsOAc, Cs_2CO_3, or KOAc failed to give the desired product. Moreover, although the selectivity of product could reach 100% in the presence of an acid such as CF_3COOH, PivOH, and CH_3COOH, the conversion of acetophenone and yield of product were very low (Table 1, entries 11−13).

A screening of solvents revealed that, apart from C_6H_5Cl, DCE was also an effective solvent and gave **3a** in 64% yield (Table 1, entry 14). Although using an oxygen-containing solvent such as 1,4-dioxane, THF, $CH_3OC_2H_4OCH_3$, *t*-BuOH, and *tert*-amyl alcohol, can give higher conversions of 3,4,5-trimethoxyacetophenone (Table 1, entries 15−19), the selectivity of the desired compound is lower compared with DCE as solvent. Other solvents such as $C_6H_5CH_3$ and oxylene were less effective for the catalytic reaction (Table 1, entries 20 and 21), whereas no target product was detected using DMF, DMSO, and CH_3CN as solvent.

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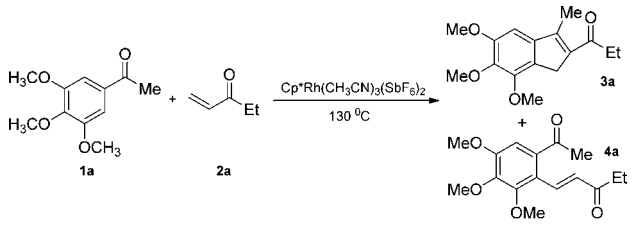
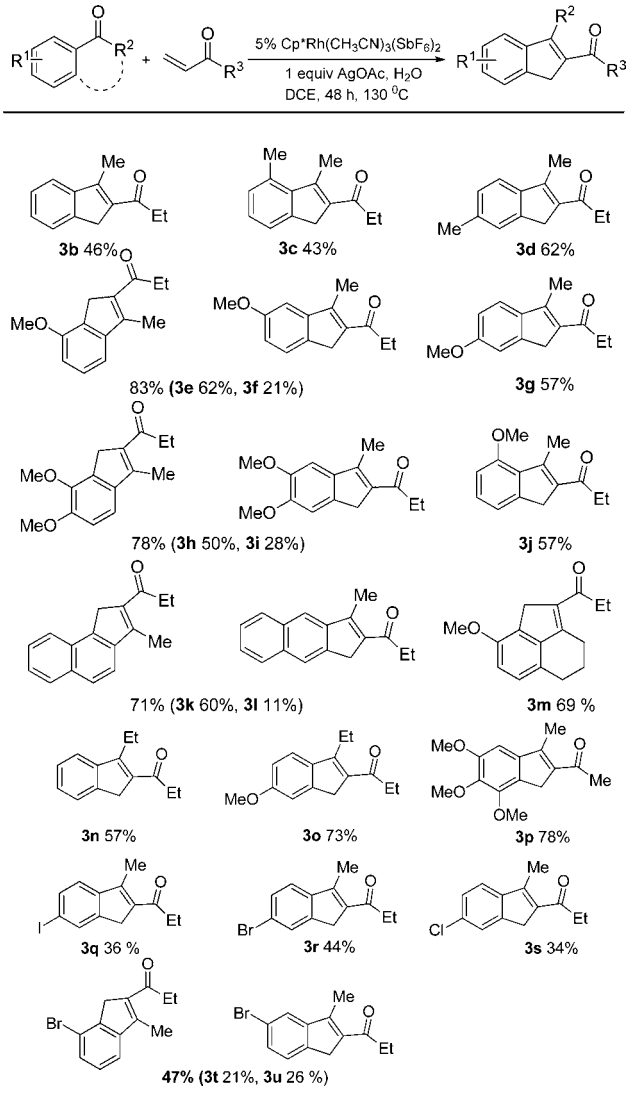
Table 1. Selected Results under the Optimized Conditions[a]



entry	additive (1 equiv)	solvent	yield (%)[b] 3a	4a
1	–	C_6H_5Cl	18	9
2	Ag_2CO_3	C_6H_5Cl	43	13
3	AgOAc	C_6H_5Cl	52	5
4	Ag_2O	C_6H_5Cl	19	11
5	$Cu(OAc)_2$	C_6H_5Cl	35	trace
6	$(CuOAc)_2H_2O$	C_6H_5Cl	33	trace
7	NaOAc	C_6H_5Cl	6	3
8	Na_2CO_3	C_6H_5Cl	8	10
9	$NaHCO_3$	C_6H_5Cl	6	7
10	K_2CO_3	C_6H_5Cl	8	8
11	CF_3COOH	C_6H_5Cl	17	ND
12	PivOH	C_6H_5Cl	21	ND
13	CH_3COOH	C_6H_5Cl	26	ND
14	AgOAc	DCE	64	8
15	AgOAc	dioxane	67	27
16	AgOAc	THF	60	17
17	AgOAc	$CH_3OC_2H_4OCH_3$	60	11
18	AgOAc	*t*-BuOH	60	29
19	AgOAc	*tert*-amyl alcohol	54	26
20	AgOAc	$C_6H_5CH_3$	39	6
21	AgOAc	oxylene	19	5
22[c]	AgOAc	DCE	75	trace
23[d]	AgOAc	DCE	89	trace

[a] Reactions were carried out with 3,4,5-trimethoxyacetophenone (0.1 mmol), ethyl vinyl ketone (0.2 mmol), $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ (2.5 mol %), additives (1 equiv), and solvent (0.5 mL) at 130 °C for 24 h, under argon in pressure tubes. [b] Determined by ^1H NMR analysis of the crude reaction mixture using mesitylene as the internal standard. [c] 3,4,5-Trimethoxyacetophenone (0.2 mmol), ethyl vinyl ketone (0.5 mmol), $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ (5 mol %), AgOAc (1 equiv), 0.5 mL of DCE, 48 h. [d] 3,4,5-Trimethoxyacetophenone (0.2 mmol), ethyl vinyl ketone (0.5 mmol), $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ (5 mol %), AgOAc (1 equiv), 0.5 mL of DCE, 30 μL of H_2O, 48 h.

Scheme 2. Substrate Scope for the C–H Functionalization–Cyclization Reaction[a]



[a] Reactions were carried out with aromatic ketone (0.2 mmol), unsaturated carbonyl compounds (0.5 mmol), AgOAc (1 equiv), $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ (5 mol %), 0.5 mL of DCE, 30 μL of H_2O, 48 h. The yield of the isolated product was reported.

Subsequently, various conditions concerning the amount of catalyst, reaction time, and additive were examined to optimize the formation of this addition–cyclization product with DCE as solvent. The yield of **3a** could be enhanced to 75% with a trace of byproduct by increasing the amount of catalyst and the reaction time (Table 1, entry 22). It is interesting to note that a small quantity of water was found to be beneficial to the reaction. With the use of 5 mol % catalyst, the reaction of 0.2 mmol of **1a** and 0.5 mmol of **2a** in 0.5 mL of DCE for 48 h together with a certain amount of water afforded the product in 89% yield (Table 1, entry 23). Notably, this transformation is easily handled under air without the protection of an inert atmosphere. Most importantly, this transformation only requires the catalyst, solvent, and water to facilitate the desired cyclization.

With the optimized conditions in hand, we sought to investigate the generality of the cyclization with respect to aromatic ketones and ethyl vinyl ketone (Scheme 2). A significant electronic effect of the substituents on the reactivity was observed. The results showed that only a 46% yield was obtained using acetophenone and ethyl vinyl as starting material (**3b**). Electron-rich acetophenones such as methyl and alkoxy, in general, gave better yields. Although acetophenones bearing weak electron-withdrawing halogen substituents led to a relatively lower efficiency, the tolerance of halides offers the opportunity for further functionalizations. The presence of a strong electron-withdrawing group in 4-nitroacetophenone failed to give the target product. 2′-Hydroxyacetophenone,

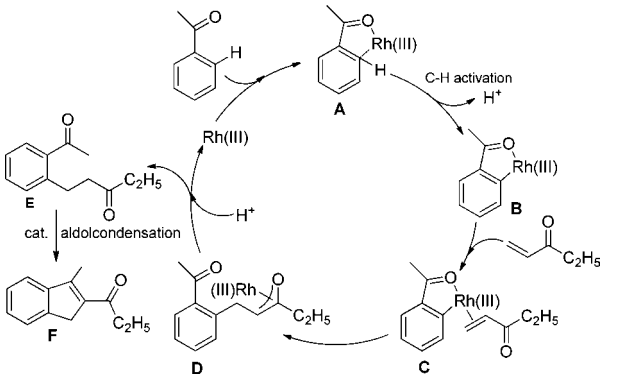
2′-iodoacetophenone, and 2′-bromoacetophenone only gave trace amounts of products. In addition to acetophenone, propiophenone and 4′-methoxypropiophenone also exhibited good reactivities and offered the corresponding products in yields of 57% and 73% respectively (**3n**, **3o**). Sterically hindered 1-tetralone still generated the desired product in 19% ^{1}H NMR yield, and 7-methoxy-1-tetralone produced the target product in 69% yield (**3m**).

On the other hand, *m*-alkoxy substituted acetophenones were easily converted into the corresponding products in higher yields and nonsymmetrical *m*-alkoxy acetophenones afforded two regioisomers (**3e**, **3f**, **3h**, **3i**). In this case, there are two possible C−H bond activation sites: at C2 and C6. To our surprise, the activation occurs at the sterically more hindered C2 rather than C6, which illustrated that the reaction was mainly under electronic control instead of steric control. For example, 3′-methoxyacetophenone afforded two regioisomers in an ∼3:1 ratio and 3′,4′-dimethoxyacetophenone produced a 50:28 mixture of products. Similarly, electron-rich 2′-acetonaphthone gave two products in a ratio of 5:1 (**3k**, **3l**) and two regioisomers were generated from 3′-bromoacetophenone (**3t**, **3u**).

Apart from ethyl vinyl ketone, the reaction of 3,4,5-trimethoxyacetophenone with low-boiling-point methyl vinyl ketone resulted in **3p** in a higher yield. However, although bearing α,*β*-unsaturated ketone, 1-acetyl-1-cyclohexene, 1-acetyl-2-methyl-1-cyclopentene, and 2-cyclohexen-1-one were not suitable substrates for the reaction.

On the basis of known metal-catalyzed, directing-group assisted C−H bond activation reactions, a proposed mechanism for the formation of the cyclization product is shown in Scheme 3. The transformation is initiated by the coordination of the oxygen atom of acetophenone to the Rh. Subsequent electrophilic insertion of Rh into the *ortho*-C−H bond generates rhodacycle intermediate **B**, releasing 1 equiv of proton at the same time. Then, the double bond of ethyl vinyl ketone coordinates to intermediate **B** to produce arylrhodium complex **C**, which is followed by the 1,4-conjugate addition of the arylrhodium species to the activated double bond to yield the rhodium-oxa-*π* species **D**. Protonolysis of **D** releases the conjugate addition product **E** and regenerates the rhodium catalyst (Rh*). With the help of AgOAc, the intramolecular aldol condensation of **E** gives the cyclization product.

Scheme 3. Tentative Mechanism for the Rhodium-Catalyzed Cascade Cyclization



In conclusion, we have successfully demonstrated the catalytic synthesis of indene derivatives via a rhodium(III)-catalyzed functionalization of an aromatic *ortho*-C−H bond directed by carbonyl. This method involves a cascade conjugate addition of α,*β*-unsaturated ketone and aldol condensation to provide a novel strategy and an atom-economical alternative to construct this important framework in a single step. The reactions only require a catalytic amount of the metal reagent, and no stoichiometric waste is formed except for water during the reaction. In addition, the reaction occurs efficiently in the presence of water and under an atmosphere of air, providing an operationally practical and cleaner method to synthesize indene derivatives. We anticipate that this methodology will find applications in the synthesis of complex molecules bearing an indene motif.

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Supporting Information Available. Available typical experimental procedure and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.