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Access to Quaternary Stereogenic Centers via Rhodium(III)-Catalyzed Annulations between 2-Phenylindoles and Ketenes

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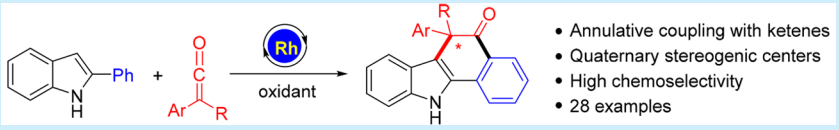
Supporting Information

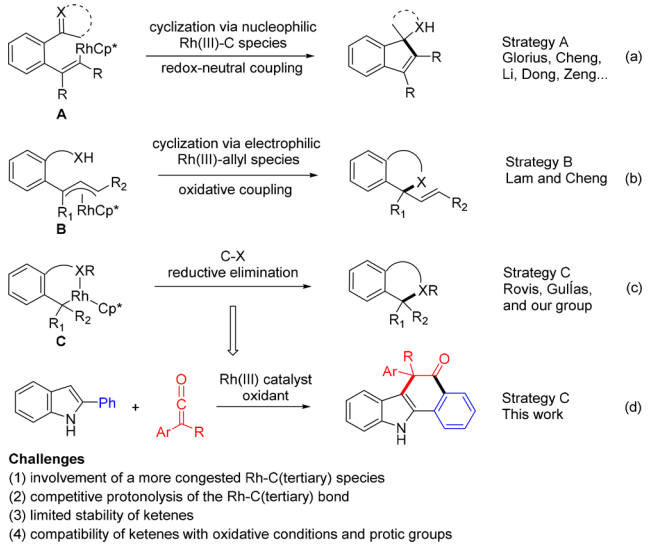


ABSTRACT: Rh(III)-catalyzed C−H activation of arenes and mild oxidative [4 + 2] annulative coupling with ketenes have been realized. The uniquely high reactivity of the C(3) of 2-phenylindoles was successfully utilized to facilitate the reductive elimination process, leading to efficient synthesis of cyclic products with a quaternary carbon stereocenter.

Over the past few decades, transition-metal-catalyzed C−H activation of arenes has emerged as one of the most important and powerful strategies in the synthesis of complex organic molecules.[1] Among the transition metals, half-sandwich Cp*Rh(III) catalysts have stood out with high activity, selectivity, mild conditions, and functional group compatibility in C−H activation systems.[2] In particular, activation of C−H bonds of arenes and coupling with various π-bonds/electrophilic molecules such as alkynes,[3] carbene precursors,[4] alkenes,[5] strained/reactive rings,[6] isocyanates,[7] allenes,[8] and imines[9] were extensively explored for construction of diverse cyclic functional molecules. Although ketenes are highly electrophilic with two π-bonds and have been well-studied in organic synthesis,[10] they have been rarely employed as a coupling partner in C−H activation systems.[11]

Carbo/heterocyclic scaffolds with a carbon stereogenic center are of vital significance in natural products, drugs, and bioactive compounds.[12] Whereas the high activity of Rh(III) catalysts in C−H activation has allowed synthesis of various stereogenic tertiary carbon-containing heterocycles,[4a,13] reports on construction of quaternary stereocenters are much less common. Among these reports, Glorius, Cheng, Li, Dong, and other groups have independently taken advantage of the nucleophilicity of a Rh(III)−C species to deliver a quaternary carbon stereocenter (Scheme 1a).[14] During the preparation of this paper, the Zeng group achieved synthesis of 2-oxindoles via cobalt(III)-catalyzed annulation of *N*-nitrosoanilines with α-diazo-β-ketoesters through a combined C−H activation/Wolff rearrangement.[15] In this process, the quaternary stereocenter was generated via insertion of ketene into the nucleophilic Co(III)−C species. Lam and others demonstrated that the electrophilic Rh(III) π-allyl species in the context of C−H activation can be nucleophilically attacked by a protic directing group, providing another avenue to access quaternary carbon stereocenters under oxidative conditions (Scheme 1b).[16] In addition, Rovis, Gulías, and our group have reported the synthesis of quaternary carbon stereocenter containing (QCSC) cycles via C−N or C−C reductive elimination, in which a Rh(III) tertiary alkyl species was involved (Scheme 1c).[17] However, examples in this category are rather rare because Rh(III)−C(tertiary) species are less prone to reductive elimination for steric reasons. Instead, protonolysis may preferentially take place.[11b] So far, the coupling partner of the reported systems was limited to reactive diazo compounds and alkynes. Given the wide existence of anionic (directing) groups that can participate in reductive elimination and the challenges in construction of quaternary carbon stereocenters,[12b,e,18] it is necessary to develop new QCSC

Scheme 1. Construction of Stereogenic Quaternary Centers via C−H Activation



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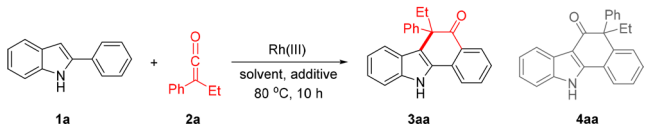
systems by following the third strategy to broaden the utility of C−H activation.

With these criterions in mind, we pondered the feasibility of using ketenes as a coupling reagent to afford QCSC cycles. To achieve this goal, several challenges nevertheless need to be overcome: (1) So far, only disubstituted ketenes are applicable in C−H activation systems because competitive ketene dimerization leads to inactivity. The insertion of ketene into a Rh−C(aryl) bond generates a rhodium(III) tertiary enolate. However, reductive elimination involving a sterically hindered tertiary carbon generally requires a higher activation barrier. (2) In contrast to the prominent driving force by the relief of ring strain or aromatization in the synthesis of aromatics and functionalized products,[19] the synthesis of QCSC molecules relies heavily on a proper arene substrate to facilate the Rh(III)−C(tertiary) species toward reductive elimination other than protonolysis. (3) Given the electrophilic nature of ketenes as well as the tendency to decompose or dimerize, it remains questionable whether the oxidants, bases, and protic groups can be compatible with the catalytic conditions.[20,21] We now report Rh(III)-catalyzed oxidative synthesis of diverse QCSC heterocycles using ketene as a C_2 synthon (Scheme 1d).

Given the high reactivity of indoles in two-fold C−H oxidative cross-coupling reactions,[22] we reasoned that the multiple nucleophilic sites in NH indoles render them bifunctional arenes for QCSC synthesis under oxidative conditions. We thus focused on 2-phenylindoles (**1a**), where the nucleophilic C(3)-position or the NH group might provide an anionic site for reductive elimination.[22,23] However, the NH group might undergo side nucleophilic addition to a ketene. We began our studies with the screening of reaction conditions in the coupling of the 2-phenylindole with ethylphenylketene using $[Cp^*RhCl_2]_2$/$AgSbF_6$ and AgOAc as the system in the presence of different bases at 80 °C (Table 1). Instead of affording annulation product **3aa**, **4aa** was initially isolated as the only product in DCE (entries 1−6). When the reaction was carried out in benzotrifluoride, two regioisomeric products **3aa** and **4aa** were obtained in 8 and 10% yields, respectively (entry 7). Introducing PivOH additive in the DCE has no obvious improvement in the yields or the ratio of **3aa** and **4aa** (entry 7 vs 8), and the desired product **3aa** was exclusively obtained in 43% yield using Ag_2CO_3 as an oxidant and NaOAc as the base (entries 7 and 8 vs 9). Switching the base to KOAc and CsOAc led to no reaction (entries 10 and 11). The yield was improved to 53% when the solvent was switched to cyclohexane (entries 12−16). Changing the additive to AgOAc gave the product in 57% yield (entry 17). Further improvement was realized when AgOAc (40 mol %) replaced $AgSbF_6$ (entries 18−23), and the concentration also slightly affected the reaction efficiency. After extensive studies (see the Supporting Information for more details), the following conditions were established: $[RhCp^*Cl_2]_2$ (4 mol %), AgOAc (40 mol %), Ag_2CO_3 (2.0 equiv), NaOAc (2.0 equiv) at 80 °C in cyclohexane (entry 22). The structure of **3aa** was confirmed by X-ray crystallography (Figure 1, CCDC 1569402), with C(3) involved in annulation.

The scope of this oxidative coupling was next investigated (Scheme 2). Introduction of various substituents to the 4-, 5-, and 6-positions of 2-phenylindole was fully tolerated, and the corresponding products were isolated in 38−70% yields (**3aa**−**3la**). The scope with respect to the substituent in the benzene ring was also quite broad, and various *para*-substituents (CH_3, ^{t}Bu, CF_3, OMe, and halides) were all tolerated, affording the products in 46−63% yields (**3ma**−**3ra**), although an electron-donating group tends to attenuate the efficiency (**3pa**). Introduction of *ortho*-Me into the benzene ring resulted in a slightly lower yield (**3sa**). Various *meta*-substituted substrates also coupled efficiently (**3ta**−**3wa**). Switching the 2-phenylindole to 2-(naphthalen-2-yl)-1*H*-indole furnished the desired product **3xa** in 50% yield. Unfortunately, 7-chloro-2-phenylindole, 1-methyl-2-phenylindole, and 3-methyl-2-phenylindole all failed to undergo any coupling under the current catalytic system, suggesting the significance of the NH coordination and

Table 1. Optimization Studies[a]



entry	oxidant (equiv)	base	solvent	yield (%)[a] 3aa/4aa
1	Ag_2CO_3 (2.0)	CS_2CO_3	DCE	NR
2	AgOAc (2.2)	K_2CO_3	DCE	ND/28
3	**AgOAc (2.2)**	**LiOAc**	**DCE**	**ND/45**
4	AgOAc (2.2)	KOAc	DCE	5/ND
5	AgOAc (2.2)	Li_2CO_3	DCE	ND/41
6	AgOAc (2.2)	Na_2CO_3	DCE	ND/36
7	AgOAc (2.2)	Na_2CO_3	CF_3Ph	8/10
8[b]	AgOAc (2.2)	Na_2CO_3	DCE	15/5
9	Ag_2CO_3 (2.2)	NaOAc	DCE	43/ND
10	Ag_2CO_3 (2.0)	KOAc	DCE	NR
11	Ag_2CO_3 (2.0)	CsOAc	DCE	NR
12	Ag_2CO_3 (2.0)	NaOAc	DCE	45/ND
13	Ag_2CO_3 (2.0)	NaOAc	CF_3Ph	50/ND
14	Ag_2CO_3 (2.0)	NaOAc	PhCl	50/ND
15	Ag_2CO_3 (2.0)	NaOAc	cyclohexane	53/ND
16	Ag_2CO_3 (2.0)	NaOAc	*n*-hexane	NR
17[c]	Ag_2CO_3 (2.0)	NaOAc	cyclohexane	57/ND
19[c,d]	Ag_2CO_3 (2.0)	NaOAc	cyclohexane	66/ND
20[e]	Ag_2CO_3 (2.0)	NaOAc (3.0)	cyclohexane	61/ND
21[e]	Ag_2CO_3 (2.0)	NaOAc	cyclohexane	67/ND
22[e,f]	**Ag_2CO_3 (2.0)**	**NaOAc**	**cyclohexane**	**70/ND**
23[e]	Ag_2CO_3 (2.0)	NaOAc (1.5)	cyclohexane	22/ND

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), base (2.0 equiv), solvent (2.0 mL) under N_2 at 80 °C for 10 h, isolated yield after column chromatography. [b]PivOH (1.0 equiv), 60 °C. [c]AgOAc was used instead of $AgSbF_6$. [d]AgOAc (0.2 mmol), 15 h. [e]AgOAc (40 mol %) instead of $AgSbF_6$, 15 h. [f]Solvent (3.0 mL).

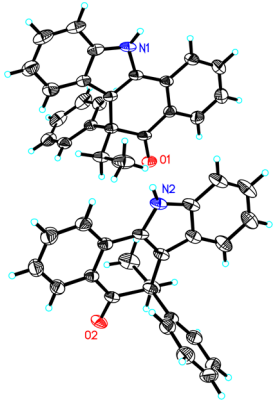


Figure 1. Molecular structure (ORTEP) of **3aa**.

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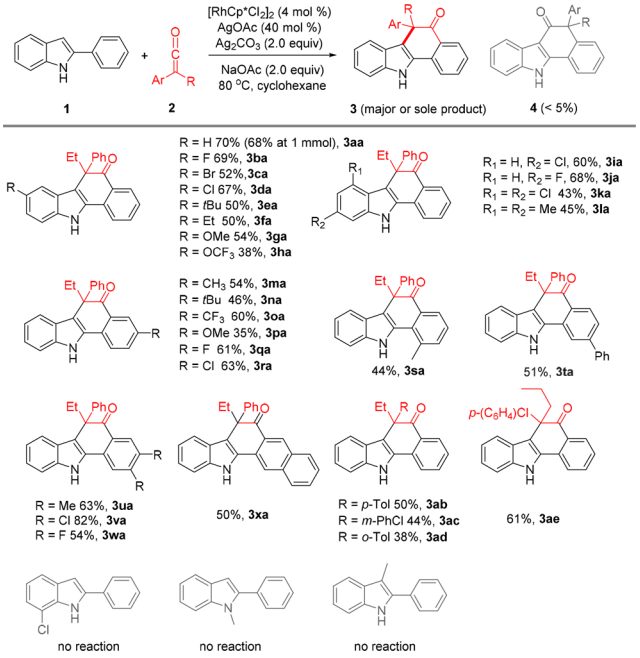
Scheme 2. Scope of Annulation between 2-Phenylindoles and Ketenes[a,b]



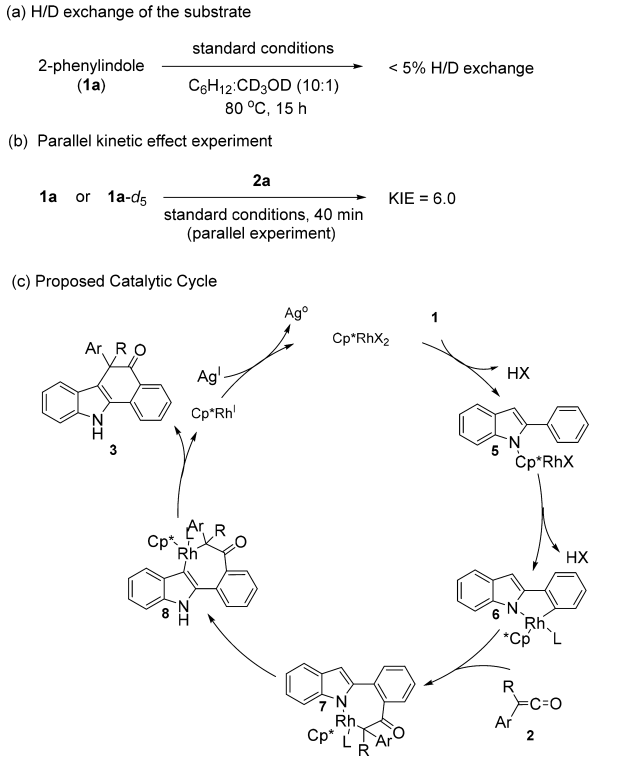
[a]Reaction conditions: 2-arylindole (0.2 mmol), disubstituted ketene (0.4 mmol), $[RhCp^*Cl_2]_2$ (4 mol %), AgOAc (0.08 mmol), Ag_2CO_3 (0.4 mmol), NaOAc (0.4 mmol), and cyclohexane (3.0 mL) under N_2 for 15 h. [b]Isolated yield.

the C(3) site for annulation. The scope of the ketene was next briefly examined. Ethyl aryl ketenes bearing a methyl or chloro group at different positions of the benzene ring all proved to be viable, albeit with lower yields (**3ab**−**3ad**). In addition, propyl-substituted arylketene also coupled smoothly in good yield (**3ae**).

To gain insight into the mechanism of this coupling reaction, H/D exchange of 2-phenylindole (**1a**) was performed under the standard conditions in the presence of CD_3OD. Essentially no exchange (<5%) at the *ortho*-position or at the 3-position was observed (Scheme 3a). Furthermore, kinetic isotope effect was measured from two side-by-side experiments using **1a** and **1a**-d_5 with **2a** being a coupling partner. A value of k_H/k_D = 6.0 was obtained on the basis of ^1H NMR analysis, and this large value indicated that C−H bond cleavage is likely involved in the turnover-limiting step (Scheme 3b). Based on these results and previous reports,[9c,d,22,23] a plausible mechanism is proposed (Scheme 3c). Initial coordination of the nitrogen atom of **1a** to Cp*Rh(III)X_2 species **5** followed by C−H bond activation gives a five-membered rhodacycle **6**. Migratory insertion of the Rh−C bond into the ketene affords a seven-membered rhodacycle **7**. This intermediate is proposed to undergo nitrogen decoordination and rollover C_3 metalization to afford intermediate **8**. Subsequent C−C reductive elimination of intermediate **8** furnishes the coupled product **3** together with a Rh(I) species, which is oxidized by the Ag(I) salt to regenerate the Rh(III) catalyst and close the catalytic cycle.

In summary, we have developed a novel Rh(III)-catalyzed annulative coupling between arenes and ketenes, leading to exclusive formation of QCSC indoles instead of N−H annulation or C−H acylation products. Future studies toward applications of these concise protocols to access other bioactive scaffolds are currently underway in our laboratory.

Scheme 3. Mechanistic Studies and Proposed Catalytic Cycle



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00497.

Detailed experimental procedures, characterization of new compounds, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1569402 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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