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Rh(III)-Catalyzed Chemodivergent Coupling of *N*-Phenoxyacetamides and Alkylidenecyclopropanes via C−H Activation

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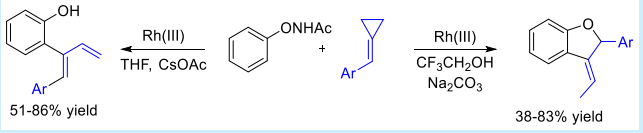
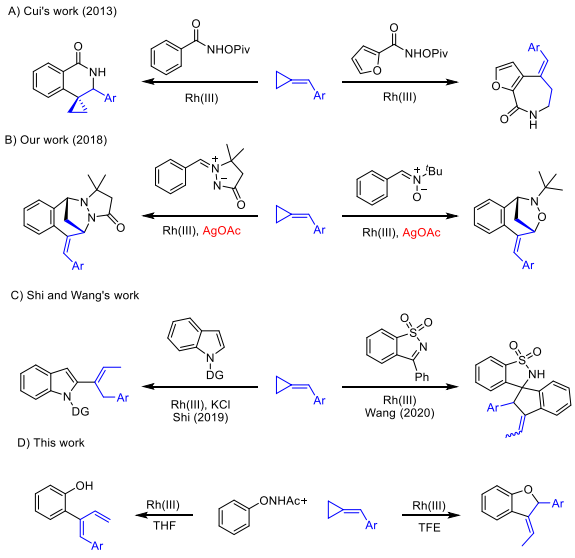
ABSTRACT: Rh(III)-catalyzed C−H activation of *N*-phenoxyacetamides and chemodivergent coupling to alkylidenecyclopropanes (ACPs) have been accomplished. With the assistance of the ring strain of ACPs, the coupling can be transannulative or nonannulative, delivering 3-ethylidenedihydrobenzofurans or dienes, respectively, under different reaction conditions, and the selectivity is mainly solvent-controlled. All of the reactions proceeded under mild conditions with a good substrate scope and excellent chemo- and diastereoselectivity.



Metal-catalyzed C−H bond activation has been extensively explored as a step-economy strategy for the facile synthesis of complex organic structures.[1] In particular, rhodium(III) catalysts have gained significant attention owing to their high reactivity, selectivity, and compatibility.[2] In general, the directing group (DG) and stoichiometric amounts of external oxidants constitute the most effective and practical strategy for chemoselective transformations under oxidative conditions. To address the restriction of the employment of stoichiometric amounts of external oxidants, an oxidizing DG has been developed. In addition to their role of offering a chelating effect, they act as internal oxidants to enable novel transformations for the construction of highly valuable structural platforms under mild and simple reaction conditions.[3] Thus oxidizing DGs bearing N−O, N−N, N−S, and O−O bonds have been widely employed. So far, the O−NH (electron-withdrawing (EWG)) group has been one of the most important oxidizing DGs in C−H activation. However, the coupling partner that reacts with such arenes has been mostly limited to alkynes, allenes, alkenes, and diazo compounds, and the coupling pattern is often annulative.[1−3]

On the contrary, alkylidenecyclopropanes (ACPs) are readily available olefins with a highly strained ring. They act as useful building blocks in organic synthesis via ring scission, affording many important scaffolds.[4] Being a special polysubstituted olefin, ACPs have also attracted great interest in metal-catalyzed C−H bond activation.[5] In 2013, Cui reported the Rh(III)-catalyzed C−H activation and annulative coupling of arenes with ACPs for the synthesis of azacycles, where the ring opening of ACPs only occurred for furan-derived carboxamides (Scheme 1A).[6] In 2018, our group developed the Rh(III)-catalyzed C−H bond activation of arylnitrones and azomethine imines, and their oxidative coupling with ACPs afforded the corresponding bridged azacycles. In these couplings, the ACPs underwent ring scission to give a 1,3-diene intermediate, followed by intramolecular [3 + 2] dipolar addition. Silver acetate was used as an external oxidant for the catalyst turnover (Scheme 1B).[7] Recently, the Shi group

Scheme 1. Ring Scission of Alkylidenecyclopropanes (ACPs) in Rh(III)-Catalyzed C−H Activation



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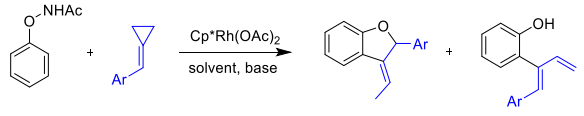
reported the insertion of Rh−H in the 1,3-diene species generated from the ring opening of ACPs via the C−H activation process.[8] Wang's group reported the Rh(III)-catalyzed annulation of *N*-sulfonyl ketimines and coupling to ACPs via C−H activation and the formation of allyl species (Scheme 1C),[9] where the nucleophilic Rh−allyl inserts into the activated imines to give spirocycles. However, the reaction seems to suffer from the employment of highly reactive imines and the limited stereoselectivity of the C=C bond in the product. We reasoned that a two-fold substrate activation strategy by integration of the oxidizing DG-assisted C−H activation and the scission of ACPs may lead to diverse selectivity as a result of the interaction of Rh(III) allyl species and the proximal O−N bond. Herein we report solvent-controlled divergent access to 3-ethylidenedihydrobenzofurans and 1,3-dienes via the Rh(III)-catalyzed C−H of *N*-phenoxyacetamides and coupling to ACPs (Scheme 1D).

We began our investigation by evaluating the reaction parameters of the coupling of *N*-phenoxyacetamide (**1a**) and 1-(4-*tert*-butylphenyl)methylenecyclopropane (**2a**, Table 1).

Table 1. Optimization Studies[a]



1a 2a 3aa 4aa

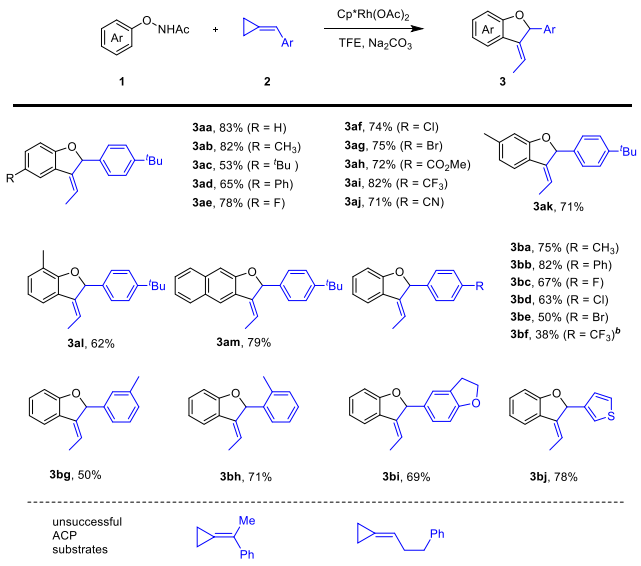
entry	solvent	additive	yield **3aa** (%)	yield **4aa** (%)
1	CF_3CH_2OH		42	nd
2	CF_3CH_2OH	K_2CO_3	78	nd
3	toluene	K_2CO_3	nd	36
4	$PhCF_3$	K_2CO_3	nd	27
5	THF	K_2CO_3	nd	45
6	CF_3CH_2OH	KOAc	64	nd
7	CF_3CH_2OH	Na_2CO_3	83	nd
8	CF_3CH_2OH	Cs_2CO_3	80	nd
9	CF_3CH_2OH	CsOAc	68	nd
10	CF_3CH_2OH	NaOAc	73	nd
11[b]	CF_3CH_2OH	K_2CO_3	73	nd
12[c]	EtOH	K_2CO_3	nd	9
13[c]	^{t}AmOH	K_2CO_3	nd	72
14[c]	^{t}AmOH	CsOAc	nd	81
15[c]	DCE	CsOAc	nd	nd
16[c]	THF	CsOAc	nd	82

[a]Reaction conditions: **1a** (0.2 mmol), ACP **2a** (0.4 mmol), Cp*Rh(OAc)$_2$ (5 mol %), additive (2 equiv), CF_3CH_2OH (2.0 mL), 35 °C, 24 h, isolated yield. [b]40 °C. [c]48 h.

By using Cp*Rh(OAc)$_2$ as a catalyst, 3-ethylidenedihydrobenzofuran **3aa** was isolated in 42% yield in trifluoroethanol (TFE) at 35 °C as a result of [3 + 2] transannulation (entry 1). The geometry of the C=C bond in **3aa** was determined by nuclear Overhauser effect (NOE) analysis. A 78% yield was obtained when K_2CO_3 was used as a base (entry 2). Investigation of solvent effect showed that TFE seemed to be critical for **3aa** formation, whereas a diene product **4aa** was produced when a less polar solvent such as toluene, tetrahydrofuran (THF), or $PhCF_3$ was used (entries 2−5; for details, see the Supporting Information). The yield of **3aa** was increased to 83% when Na_2CO_3 was used as a base (entries 6−10). A higher temperature failed to improve the yield of **3aa** (entry 11). After systematic screening of several parameters such as the base, the solvent, and the reaction time, the yield of diene product **4aa** could be increased to 82% (entries 12−16 and the Supporting Information). Thus the optimal conditions for the synthesis of **3aa** (entry 7) and **4aa** (entry 16) have been established with excellent chemoselectivity, and no Z/E isomeric product of the C=C bond was detected. Control experiments indicated that the rhodium(III) catalyst was essential. It should be noted that the product **3aa** underwent aromatization to benzofurans during purification, but the aromatized product could be minimized when the purification was sufficiently rapid.

We next examined the scope and generality of the [3 + 2] annulation reaction system (Scheme 2). *N*-Phenoxyamides

Scheme 2. Scope of [3 + 2] Annulation Reaction[a]



[a]Reaction conditions: **1** (0.2 mmol), ACP **2** (0.4 mmol), Cp*Rh(OAc)$_2$ (5 mol %), Na_2CO_3 (2.0 equiv), CF_3CH_2OH (2.0 mL), 35 °C, 24 h, isolated yield. [b]HFIP was used as solvent, 60 °C.

with a variety of electron-donating and halogen- and electron-withdrawing groups at the para position of benzene ring were fully tolerated (**3aa**−**3aj**, 53−83% yield). The reaction also proceeded smoothly with *meta*-methyl-substituted phenoxyamide (**3ak**, 71% yield). The introduction of an *ortho*-Me group afforded the cyclic product **3al** in 62% yield. Moving the arene to a 2-naphthyl-substituted group also gave the corresponding product **3am** in 79% yield. The ACP substrates with an alkyl, phenyl, halogen, or CF_3 group at different positions reacted smoothly, affording the 3-ethylidenedihydrobenzofurans in 38−82% yield (**3ba**−**3bh**). In all cases, excellent chemoselectivity was obtained. In contrast, a 1,1-disubstituted ACP and a 1-alkyl-substituted ACP both failed to give the desired products under the present conditions.

The generality of the dienes synthesis was next explored (Scheme 3). The introduction of methyl, *tert*-butyl phenyl, halogen, ester, and CF_3 groups at the para position of the benzene ring afforded the desired diene products in moderate to high yields (**4aa**−**4ai**, 62−82% yield). The coupling also proceeded well when a *meta*-methyl, *ortho*-methyl, or an *ortho*-chloro group was present in the benzene ring (**4aj**−**4al**, 49−72% yield). The corresponding 2-naphthyl-substituted product was obtained in 53% yield (**4am**). A series of 1-aryl-

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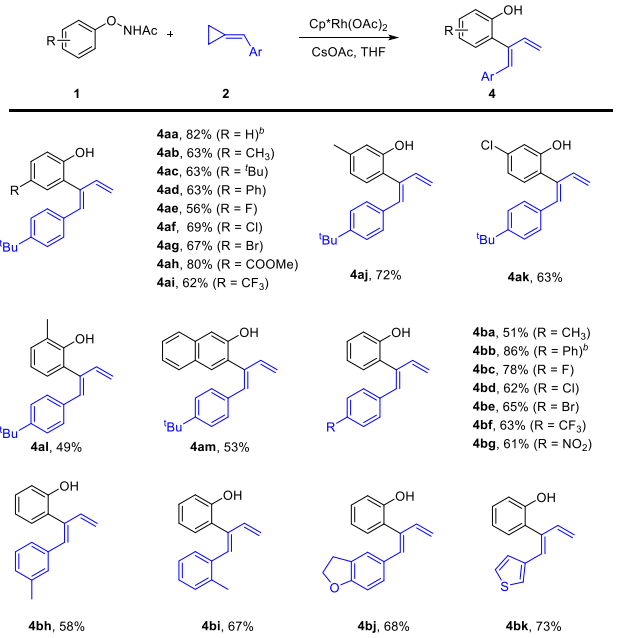
Scheme 3. Scope of the Diene Products[a]

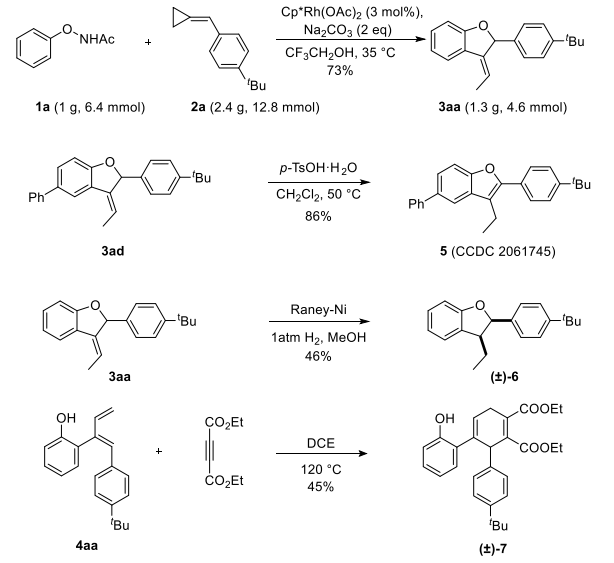


[a]Reaction conditions: **1** (0.2 mmol), ACP **2** (0.4 mmol), Cp*Rh-$(OAc)_2$ (5 mol %), CsOAc (2 equiv), THF (2.0 mL), 60 °C, 48 h, isolated yield. [b]35 °C.

methylenecyclopropanes were also tolerated, with the isolation of the diene products **4ba**−**4bk** in 51−86% yields.

The synthetic utility has been briefly demonstrated (Scheme 4). The coupling system was scaled up to the gram scale with 3

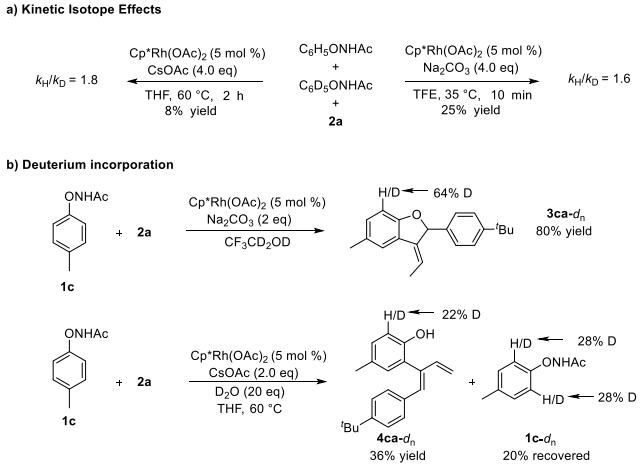
Scheme 4. Gram-Scale Synthesis and Derivatization Reactions



mol % catalyst loading, giving the cyclic product **3aa** in 73% yield. The treatment of **3ad** with *p*-toluenesulfonic acid afforded benzofuran **5** in 86% yield.[10] The structure of **5** has been confirmed by X-ray crystallography (CCDC 2061745). The reduction of **3aa** in the presence of Raney-Ni by H_2 (1 atm) gave the corresponding cis-substituted dihydrofuran product **6** in 46% yield as the sole diastereomer. The Diels−Alder reaction of 1,3-diene **4aa** and diethyl acetylenedicarboxylate proceeded smoothly to give the cyclohexadiene adduct **7** in 45% yield, which is a useful synthetic building block.

We next performed a series of experiments to probe the reaction mechanism (Scheme 5). The kinetic isotope effect

Scheme 5. Mechanistic Studies



(KIE) was measured to be 1.6 under the annulative conditions and 1.8 under the nonannulative conditions, which indicates that C−H cleavage is probably not the turnover-limiting step in either system (Scheme 5a).[11] Moreover, when CF_3CD_2OD was used as the solvent in the reaction of **1c** and **2a**, the ortho position of the cyclic product **3ca-d_n** was heavily deuterated. In addition, D_2O was added to the reaction of **1c** with **2a** under diene-forming conditions. The starting material **1c-d_n** was recovered with 28% deuteration at the ortho positions of the *N*-phenoxyacetamide, and the diene product **3ca** was 22% deuterated at the ortho position (Scheme 5b). These results suggest the reversibility of the C−H activation under both catalytic conditions

A proposed reaction pathway is given in Scheme 6. Rhodacyclic intermediate **B** is formed through the C−H activation of **1a**; then, the Rh−aryl bond migratorily inserts into the double bond of **2a** to provide the alkyl intermediate **C**, which is proposed to undergo *β*-C elimination and ring scission to produce a Rh(III) homoallyl species **D**. The subsequent *β*-H elimination provides a diene intermediate **E** together with a rhodium(III) hydride intermediate.[2,12] In the case of the TFE solvent, the Rh(III)−H bond inserts into the diene species **E** to give an allyl intermediate **G**.[9,13] The subsequent C−O reductive elimination or nucleophilic substitution of intermediate **G** is proposed to generate a Rh(I) species together with **H**. The N−O bond of **H** then oxidatively adds to the Rh(I) species, and subsequent protonation furnishes the final annulated product **3aa** with regeneration of the active catalyst. The stereochemistry of the **3aa** is dependent on the structure of the allyl species. Alternatively, the Rh−H species, which is a direct precursor to a Rh(I) species, could be oxidized by the O−NHAc bond of **E** to give the intermediate **F** without Rh(III)−H insertion to the diene. Finally, protonolysis of the intermediate **F** gives the product **4aa**. The fate of the Rh(III) hydride species is strongly solvent-dependent. In the case of the TFE/HFIP (hexafluoroisopropanol) solvent, it is likely that the acidity of the solvent contributes to stabilization of Rh−H by inhibiting its reversible

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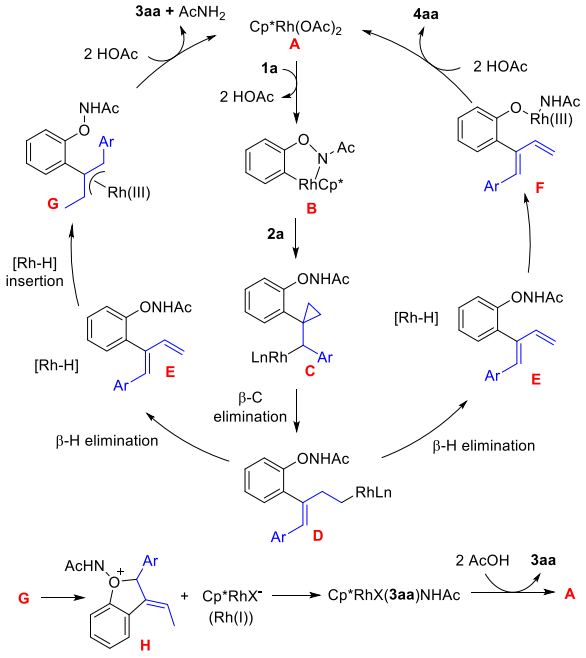
Scheme 6. Proposed Mechanism



deprotonation. In addition, Rh−H may also be stabilized by hydrogen bonding with such a solvent.

In summary, we have developed an operationally simple method to divergently access 3-ethylidenedihydrobenzofurans and dienes through the Rh(III)-catalyzed C−H/C−C cleavage of *N*-phenoxyacetamides and ACPs. The reactions featured mild reaction conditions, a broad substrate scope, and excellent chemoselectivity. We also demonstrated the synthetic utility of the products with some derivatization reactions. Further studies of the enantioselective synthesis of the chiral 3-ethylidenedihydrobenzofurans are currently under way in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00565.

Experimental procedures and spectra data for new compounds (PDF)

Accession Codes

CCDC 2061745 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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