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Rh(III)-Catalyzed Coupling of Acrylic Acids and Ynenones via Olefinic C−H Activation and Michael Addition

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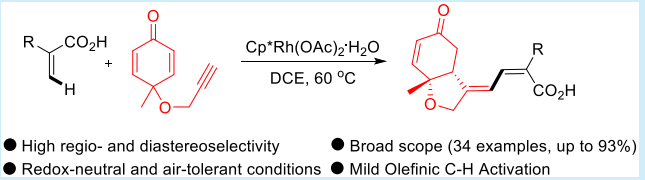
Supporting Information

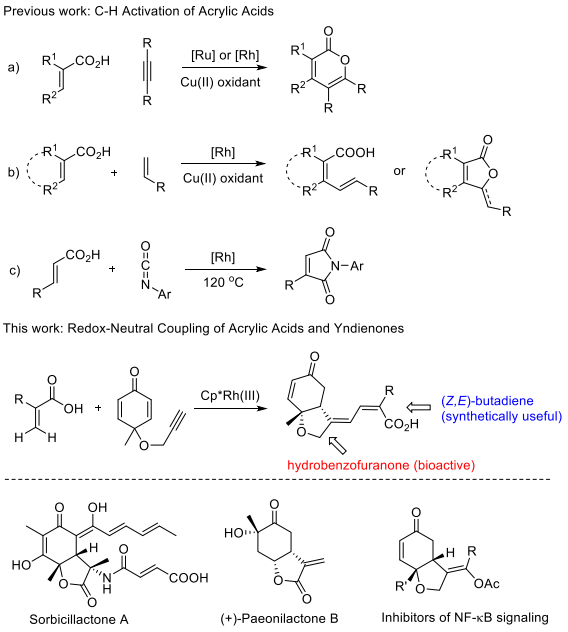
ABSTRACT: Rh(III)-catalyzed coupling between acrylic acids and yndienones has been realized for the synthesis of *cis*-hydrobenzofuranone. The reaction proceeded in excellent regio- and stereoselectivity under mild and redox-neutral conditions via a sequence of carboxylic acid-directed olefinic C−H activation, alkyne insertion, and Michael addition. Representative products were found to exhibit cytotoxicity toward the A549 cancer cell line at micromolar levels.



Carboxylate groups are useful functional groups that are relatively convenient to install and to remove, which leaves a great deal of room for manipulation in synthetic chemistry.[1] Although they are generally weakly coordinating,[2] carboxylate groups have attracted an increasing amount of attention as a powerful and functionalizable directing group in C−H activation chemistry to deliver value-added carboxylic acid derivatives or as an internal base additive to facilitate the C−H bond cleavage event.[3] Remarkable achievements have been made in aromatic C−H functionalization directed by carboxylic acids.[4] However, carboxylic-directed olefinic C−H activation was found to be more challenging because of the low stability of such a carboxylic group.[1b] Recently, the Gogoi group and the Miura group reported olefinic C−H activation/oxidative annulation of vinyl carboxylic acids with internal alkynes (Scheme 1a).[5] The Miura group realized (*E*,*E*)-diene synthesis by oxidative cross-coupling of acrylic acids and styrenes (Scheme 1b).[6] Miura, Zhu, and Zhong groups independently reported cyclization of acrylic acids with activated alkenes, affording γ-alkylidenebutenolide skeletons (Scheme 1b).[5b,7] Synthesis of cyclic *N*-aryl imides via vinyl C−H activation has also been realized by the Li group (Scheme 1c).[8] Despite these achievements, the coupling reagent is mostly limited to a simple π-bond, and COOH-directed olefinic C−H functionalization remains underexplored.

Dienes are important building blocks[9] and key structural motifs in diversified bioactive molecules.[10] In particular, the oxidative olefination of olefins allowed atom-economic access to conjugated dienes.[11−14] While Pd-catalyzed,[11,12] Rh-catalyzed,[6,13] Ru-catalyzed,[14] and Co-catalyzed[15] oxidative couplings have been explored by the groups of Gusevskaya, Loh, Glouris, and Zhong, respectively, redox-neutral couplings of olefins with alkynes seem to be more attractive but have attracted less attention. The activity of Rh(III) catalysts in C−H activation and the polarized nature of the resulting Rh(III)−C(sp^2) bond seem to favor cyclizaion reactions. We now report a C−H alkenylation/Michael addition cascade for efficient and selective synthesis of *cis*-hydrobenzofuranones tethered to a

Scheme 1. Olefinic C−H Activation Using Carboxylic Acid as a Directing Group



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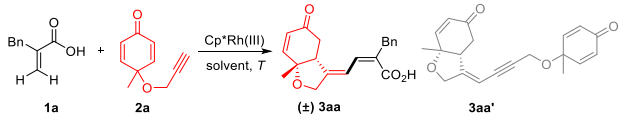
(*Z*,*E*)-butadiene mioety. Significantly, *cis*-hydrobenzofuranone motifs are known as inhibitors of NF-κB signaling,[16] and they are widely present in natural products.[17]

We initiated our studies of carboxylic acid-directed coupling of 2-benzylacrylic acid (**1a**) with yndienone **2a** in the presence of $[Cp^*RhCl_2]_2$ (4 mol %) and NaOAc (50 mol %) (Table1).

Table 1. Optimizations of the Model Reaction[a]



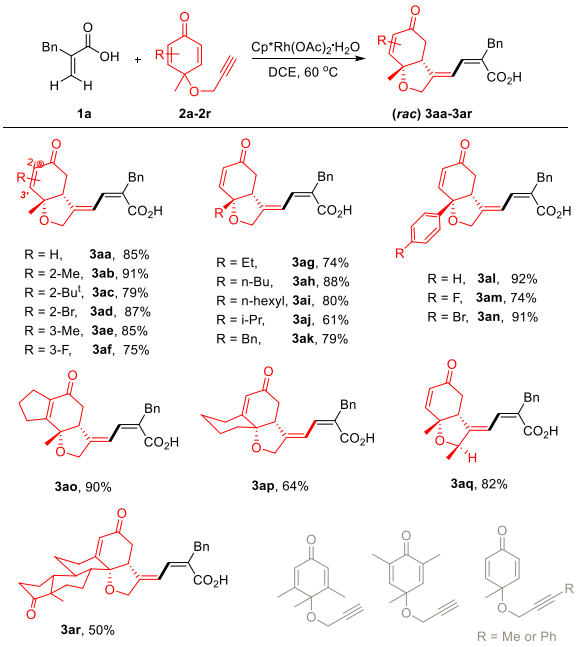
entry	additive (mmol)	solvent (mL)	yield (%)
1	NaOAc (0.1)	DCE (2)	38
2	KOAc (0.1)	DCE (2)	31
3	AgOAc (0.1)	DCE (2)	18
4	$Zn(OAc)_2$ (0.1)	DCE (2)	30
5	Na_2CO_3 (0.1)	DCE (2)	28
6	NaOAc (0.1)	PhCl (2)	26
7	NaOAc (0.1)	DCM (2)	20
8	NaOAc (0.1)	MeOH (2)	trace
9[b]	NaOAc (0.1)	DCE (2)	50
10[c]	NaOAc (0.1)	DCE (4)	58
11[c]	NaOAc (0.1)	DCE (6)	60
12[c]	NaOAc (0.1)	DCE (6)	66
13[c,d]	NaOAc (0.1)	DCE (6)	83
14[c−e]	–	DCE (6)	85

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), additive (0.1 mmol), solvent (2 mL), 80 °C, 12 h, under air. [b]With 0.3 mmol of **2a**. [c]**1a** (0.6 mmol), 60 °C. [d]**2a** was added in three portions, over 9 h. [e]$Cp^*Rh(OAc)_2{\cdot}H_2O$ (8 mol %) was used.

The desired product was isolated in 38% yield, and the (*Z*,*E*) configuration was confirmed by NOESY spectroscopy of a directly analogous product **4ab** as well as by X-ray crystallographic studies of **3eb** (CCDC 1966834). A byproduct **3aa′** was also isolated (26% yield) as a result of homocoupling of **2a** (entry 1). Via the screening of the base additive, NaOAc seems to be optimal (entries 2−5). Changing the solvent to PhCl, DCM, or MeOH gave inferior results (entry 6, 7, or 8, respectively). The yield slightly increased by using an excess of **1a** or **2a** (entry 9 or 10, respectively). Decreasing the reaction concentration also gave beneficial results (entries 11 and 12). We reasoned that a low concentration of **2a** should disfavor the homocoupling. Thus, **2a** was added in portions, and the yield was improved to 83% (entry 13). With $Cp^*Rh(OAc)_2{\cdot}H_2O$ as the catalyst, a better yield of 85% was achieved in the absence of any base (entry 14). The conditions in entry 14 were retained for further studies.

With the optimized conditions in hand, we next explored the scope of yndienones in the coupling with 2-benzylacrylic acid (Scheme 2). As shown in Scheme 2, different substituted alkyne-tethered 1,6-enynes reacted smoothly, providing the desired product with excellent stereoselectivity. The reaction tolerated functionalities such as Me, *t*Bu, and a halogen at the vinyl positions of the cyclohexa-2,5-dienone ring, providing the corresponding products in good to excellent yields (**3aa**−**3af**, 75−91% yield). Cyclohexa-2,5-dienones bearing different alkyl and aryl groups at the 4 position of the ring also showed good reactivity (**3ag**−**3an**, 61−92% yield). Fused substrates **2o** and **2p** also reacted efficiently, with the desired tricyclic compounds obtained in good or excellent yields (**3ao**, 90%; **3ap**, 64%). Importantly, only one diastereomeric product was detected for product **3aq**, and the relative configuration was as confirmed by NOESY spectroscopy (see the Supporting Information). Encouraged by the results presented above, we applied this protocol to late-stage functionalization of an estrone derivative **2r**, and product **3ar** was isolated in moderate yield, which highlighted the synthetic potential of this method. In contrast to the success mentioned above, the reaction system seems sensitive to the steric affection, and bulky substrates with two methyl groups failed to undergo the desired coupling. Coupling with several internal alkynes has been attempted but failed to give the desired products.

Scheme 2. Scope of 1,6-Enyne Substrates[a]



[a]Reaction conditions: **1a** (0.6 mmol), yndienone (0.2 mmol, in three portions, 0.067 mmol/3 h), $Cp^*Rh(OAc)_2{\cdot}H_2O$ (8 mol %), DCE (6 mL), 60 °C, 9 h, under air.

The scope of the acrylic acid was next investigated (Scheme 3). Acrylic acids with an alkyl substituent at the α position all reacted with **2b** to deliver the desired *cis*-hydrobenzofuranones in good to excellent yields (**3bb**−**3gb**, 76−93% yield). Aryl-substituted acrylic acids also gave comparably good results (**3hb**−**3nb**), where the presence of electron-donating or -withdrawing groups had a marginal influence on the reaction efficiency (**3ib**, 78%; **3mb**, 89%). The acrylic acid substrate is not limited to α-monosubstitution. The reaction of 1-cyclopentenecarboxylic acid also delivered the corresponding product (**3ob**, 59%). However, trisubstituted acyclic alkenes (*E*)-2-methylbut-2-enoic acid did not give the desired polysubstituted diene. Significantly, benzoic acid and 1-naphthoic acid were also tolerated by this catalytic protocol (**3pb** and **3qb**, 63% and 78%, respectively).[18] In contrast, no reactivity was found for simple acrylic acid and β-ethyl acrylic acid.

cis-Hydrobenzofuranones have been identified to be biologically active against the NF-κB signaling pathway.[16] Consequently, bioactivities of selected products from this protocol were evaluated toward A549 human lung cancer cells. As given in Scheme 4, several compounds showed cytotoxicity toward the A549 cancer cell line at the micromolar level, which

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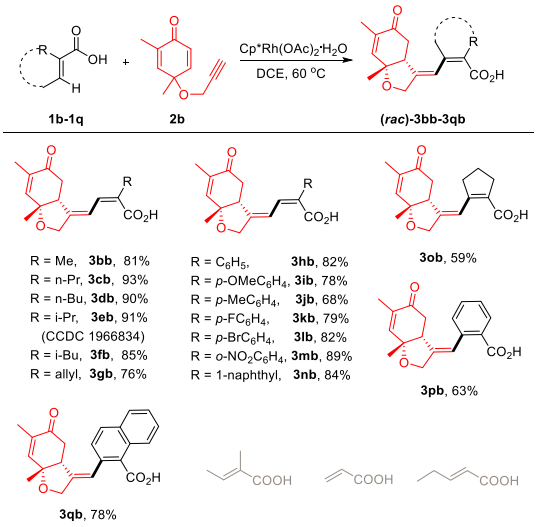
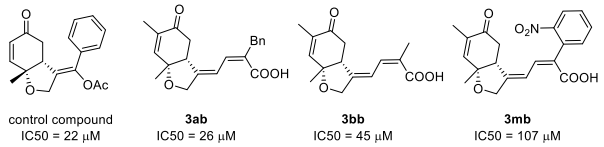
Scheme 3. Scope of Carboxylic Acids[a]



[a]Reaction conditions: **1b**−**1q** (0.6 mmol), **2b** (0.2 mmol, in three portions, 0.067 mmol/3 h), Cp*Rh(OAc)$_2$·H$_2$O (8 mol %), DCE (6 mL), 60 °C, 9 h, under air.

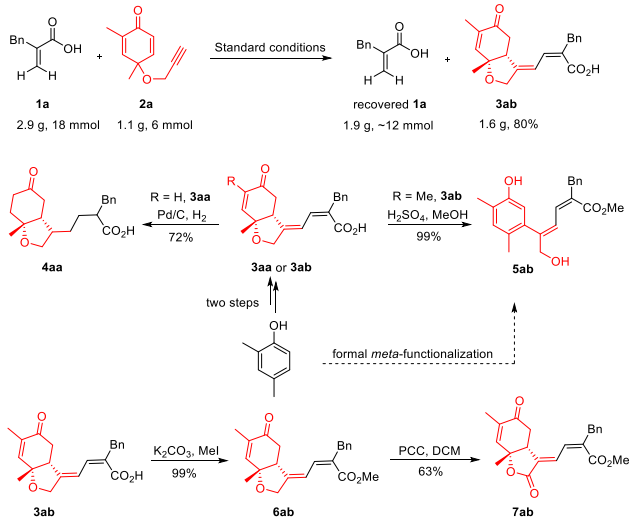
Scheme 4. Antitumor Bioactivities of Selected Compounds



may be caused by the inhibition of the induced NF-κB pathway. Our products may offer a starting point for the development of novel NF-κB inhibitors and anticancer agents.

Gram-scale synthesis of **3ab** was conducted to demonstrate the synthetic utility (Scheme 5), which proceeded smoothly in an 80% isolated yield of **3ab**, together with recovery of 2-benzylacrylic acid (1.9 g). To further showcase the synthetic applicability, derivatization reactions were carried out. Hydrogenation of **3aa** gave a diastereomeric mixture product **4aa**

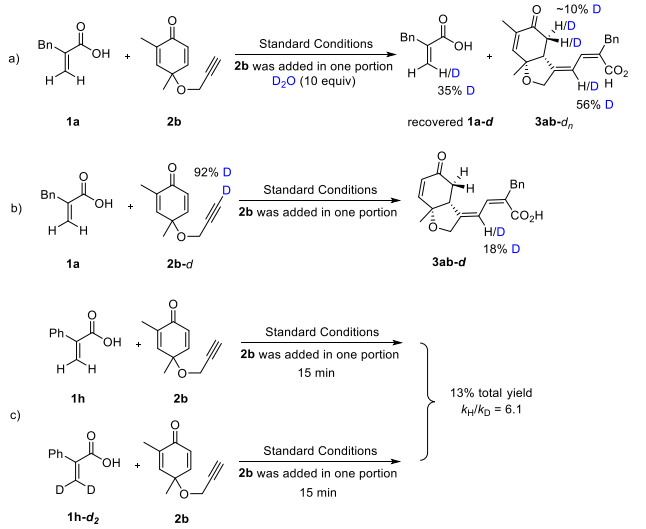
Scheme 5. Gram-Scale Synthesis and Derivatization of the Products



(3:1 dr, inseparable). Treatment of **3ab** with H_2SO_4/MeOH led to esterification together with elimination and aromatization, delivering a phenol product **5ab** in 99% yield. The formation of **5ab** eventually from 2,4-dimethylphenol represents a rare formal *meta* C−H functionalization, which would be otherwise difficult to realize. Methylation of **3ab** with MeI occurred smoothly (**6ab**, 99% yield), and subsequent PCC oxidation gave a dione **7ab** in moderate yield.

Deuterium labeling experiments were performed to gain insight into the mechanism. Under the standard conditions, H/D exchange between **1a** and D_2O was observed at the vinyl position of **1a** in the presence of **2a**, indicting the reversibility of the C−H activation (Scheme 6a). H/D exchange was also

Scheme 6. Mechanistic Studies



observed at the 4 position of the penta-2,4-dienoic acid unit. To gain more evidence, **2b**-d_1 was employed for the coupling with **1a** (Scheme 6b). ^{1}H NMR analysis of the product showed that the deuterium was mostly exchanged with hydrogen, indicative of rapid H/D exchange at the alkynyl C−H position. Intermolecular KIE experiments have been performed using **1h** and **1h**-d_2 in two parallel reactions (Scheme 6c). A KIE value of 6.1 was determined, which indicates that the cleavage of the vinyl C−H bond was involved in the turnover-limiting step.

A proposed catalytic cycle is displayed in Scheme 7. Ligand exchange between acetate and acrylate gives intermediate **A**. Oxygen-directed C−H activation[3−8] of the vinyl C−H bond affords rhodacycle **B**. Regioselective migratory insertion of the alkyne gives a Rh(III) alkenyl intermediate **C** with a (*Z*,*Z*)-configuration, which is proposed to undergo dechelation of the carboxylate group possibly with OAc coordination. Migratory insertion of the alkenyl−Rh bond into the cyclohexanedione with subsequent protonation yields the desired product together with the active catalyst.

In summary, we have realized a Rh(III)-catalyzed synthesis of *cis*-hydrobenzofuranones tethered to an exocyclic (*Z*,*E*)-butadiene unit. The reaction proceeded via COOH-directed olefinic C−H activation, alkyne insertion, and Michael addition. The reactions are atom- and step-economical, as well as highly regio- and stereoselective. The reaction products showed cytotoxicity toward the A549 cancer cell line at the micromolar level, which may offer a potential scaffold for the development of NF-κB inhibitors and anticancer agents. This

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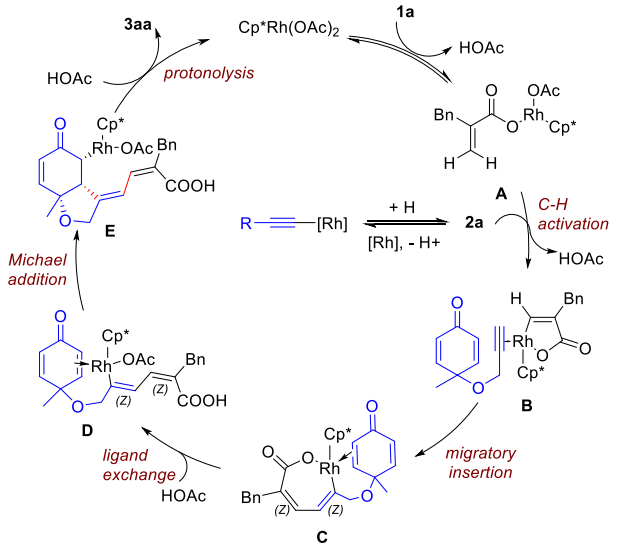
Scheme 7. Proposed Reaction Pathway



method may find useful applications in the synthesis of drug-related compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04191.

Experimental procedures, characterization of new compounds, X-ray crystallographic data of **3eb**, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1966834 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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