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Rhodium(III)-catalyzed C–H/C–C activation sequence: vinylcyclopropanes as versatile synthons in direct C–H allylation reactions†

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Succession of C–H activation and C–C activation was achieved by using a single rhodium(III) catalyst. Vinylcyclopropanes were used as versatile coupling partners. Mechanistic studies suggest that the olefin insertion step is rate-determining and a facile β-carbon elimination is involved, which represents a novel ring opening mode of vinylcyclopropanes.

Transition-metal-catalyzed C–H activation reactions have emerged as a fertile field for the construction of C–C and C–heteroatom bonds.[1] Among the numerous transition metals, Rh^{III} stands out for its advantageous features such as high efficiency, mild reaction conditions, and broad substrate scope.[2] Due to their versatile reactivity towards transition-metal catalysis,[3] alkenes are widely used as coupling partners in C–H activation reactions.[4,5] Typically, after the C–H activation/alkene insertion steps, β-hydrogen elimination is a facile elementary step as demonstrated by the numerous examples of oxidative coupling of aryl C–H bonds with olefins in the presence of different metals (Fig. 1a). Recently, it was also disclosed that β-oxygen[6] and β-nitrogen[6d,7] elimination is feasible when Rh^{III} was the catalyst, partly driven by the release of ring strain. Because of the chemical inertness of the C–C single bond, β-carbon elimination is generally unfavored and thus far less established,[8] even though the selective C–C cleavage has attracted increasing interest in the synthetic community, as it offers a potential alternative for synthetic disconnection.[9] Vinylcyclopropanes (VCPs), bearing an olefinic moiety and a cyclopropane ring, are useful organic synthons in synthetic chemistry.[10] The catalytic ring-opening of vinylcyclopropanes can be achieved under the catalysis of Lewis acids (LA) *via* ionic reaction pathways,[11] or by a radical pathway with an organic thiyl radical catalyst.[12] Alternatively, the direct oxidative addition of cyclopropane to a low-valent nucleophilic transition metal to form a π-allyl metal complex as the key reaction intermediate is also a literature precedent (Fig. 1b).[13] We reasoned that, by taking advantage of the multifold reactivities of vinylcyclopropanes, a C–H activation/alkene insertion sequence would generate a rhodacycle **A**. Thereafter, a subsequent β-carbon elimination would be

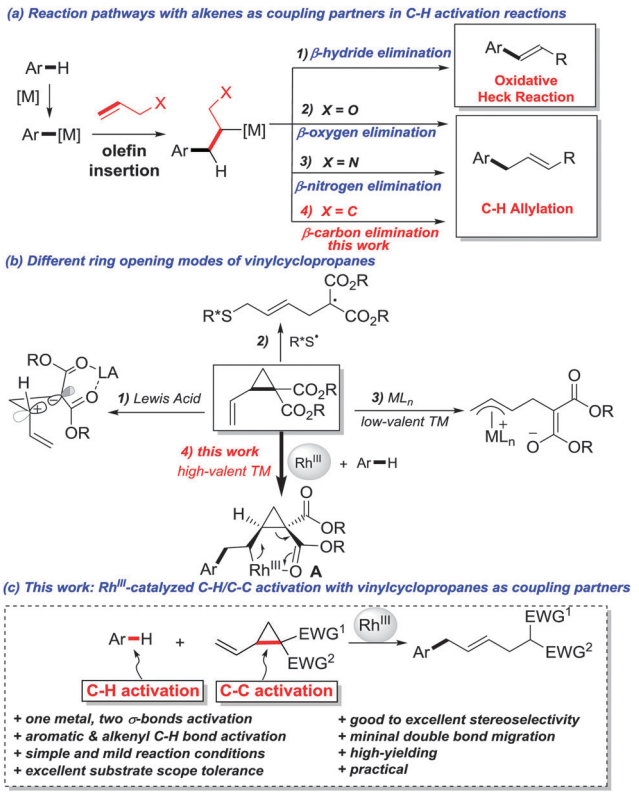

Fig. 1 (a) Alkenes as coupling partners in C–H activation reactions; (b) ring opening modes of vinylcyclopropanes; (c) this work: Rh^{III}-catalyzed C–H/C–C activation with vinylcyclopropanes as coupling partners.

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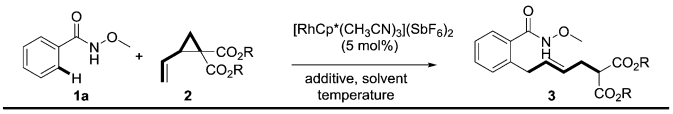
Table 1 Optimization of the reaction conditions[a]



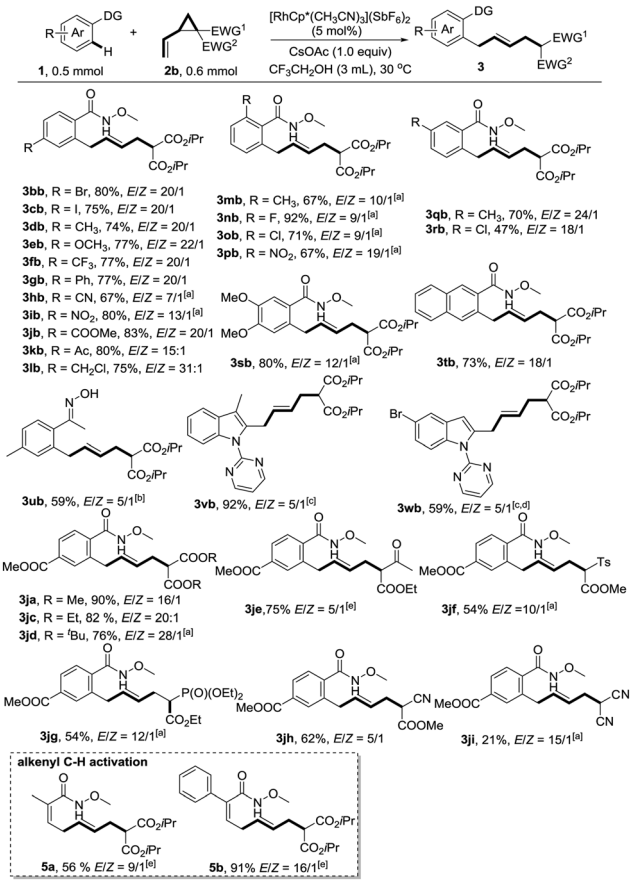
Entry	R	Solvent	Additive	T [°C]	Yield [%]	E/Z[b]
1	Me (**2a**)	MeOH	CsOAc	80	38	9 : 1
2	Me (**2a**)	MeOH	—	80	<5	—
3	Me (**2a**)	MeOH	PivOH	80	<5	—
4	Me (**2a**)	H_2O[c]	CsOAc	30	65	8 : 1
5	Me (**2a**)	CF_3CH_2OH	CsOAc	80	90	6 : 1
6	Me (**2a**)	CF_3CH_2OH	CsOAc	30	78	9 : 1
7	**iPr (2b)**	**CF_3CH_2OH**	**CsOAc**	30	**79**	21 : **1**

[a] **1a** (0.2 mmol), **2** (0.24 mmol), $[RhCp^*(CH_3CN)_3](SbF_6)_2$ (5 mol%), additive (1.0 equiv.), solvent (1 mL), 24 h, isolated yield. [b] Determined by ^1H NMR. [c] With additional tween 20 (30 mol%).

thus feasible (Fig. 1b).[14] Herein, we demonstrate that Rh^{III} is an efficient catalyst for a sequential C–H activation and C–C activation[15] (β-carbon elimination) reaction with vinylcyclopropanes as coupling partners (Fig. 1c).

N-methoxybenzamides were chosen as substrates due to their high reactivities in C–H activation reactions. The reaction of **1a** with dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** in the presence of 5 mol% $[RhCp^*(CH_3CN)_3](SbF_6)_2$ and 1 equivalent of CsOAc at 80 °C in MeOH delivered the desired product **3aa** in 38% yield with an E/Z ratio of 9 : 1 (Table 1, entry 1). It was found that CsOAc was crucial for the reaction as its omission or replacement with acid PivOH resulted in trivial reactivity (entries 2 and 3). Interestingly, water can also be used as solvent, affording 65% of the product, which demonstrates the great robustness of this novel transformation (entry 4). CF_3CH_2OH turned out to be a better solvent giving 90% yield (entry 5). Lowering the temperature from 80 °C to 30 °C gave a better stereoselectivity of 9 : 1 with a slight sacrifice in yield (78%, entry 6). A better E/Z ratio of 21 : 1 was achieved by switching the coupling partner from **2a** to more sterically hindered diisopropyl 2-vinylcyclopropane-1,1-dicarboxylate **2b** (entry 7). Notably, minimal migration of the newly formed double bond was observed under the optimized reaction conditions ($[RhCp^*(CH_3CN)_3](SbF_6)_2$ (5 mol%), CsOAc (1.0 equiv.), CF_3CH_2OH (0.2 M), 30 °C).

With the optimized reaction conditions in hand, we next explored the generality of this reaction by variation of *N*-methoxybenzamide **1** (Scheme 1). To our delight, the reaction is compatible with a variety of functionalities such as bromo (**3bb**), iodo (**3cb**), methoxy (**3eb**), trifluoromethyl (**3fb**), cyano (**3hb**), nitro (**3ib**), ester (**3jb**), acetyl (**3kb**), and even chloromethyl (**3lb**), providing ample opportunity for further derivatization of the products. *Ortho*-substituents did not hamper the reactivity (**3mb**–**3pb**). When *meta*-substituted substrates were used, good regioselectivities favouring the less hindered position were observed (**3qb**–**3sb**). *N*-Methoxy-2-naphthamide **1t** provided the allylation product at the C3 position exclusively. Oxime represents another type of applicable substrate, giving the desired product in reasonable yield (**3ub**). The selective C2-allylation of indoles also worked well under the assistance of a pyrimidyl directing group, albeit with moderate E/Z ratios (**3vb** and **3wb**).



Scheme 1 Rh^{III}-catalyzed coupling reaction of vinylcyclopropanes **2b** with various substrates. [a] 50 °C; [b] MeOH was used as solvent, rt; [c] DCE was used as solvent, rt; [d] additional 5 mol% Rh^{III} was added after 24 h; [e] 0 °C.

The substrate scope of vinylcyclopropane **2** is also remarkable. VCPs **2** could be readily prepared from the corresponding activated methylene compounds and (*E*)-1,4-dibromobut-2-ene. As mentioned before, the introduction of a more sterically hindered group gave a better E/Z ratio, but at the same time retarded the reaction (**3ja** *vs.* **3jb** *vs.* **3jd**). Thus, di-*tert*-butyl 2-vinylcyclopropane-1,1-dicarboxylate **2d** gave the highest E/Z ratio of 28 : 1. A slight increase of temperature to 50 °C was necessary to maintain the good yield (76%). A variety of other electron-withdrawing functional groups such as ketone (**3je**), sulfone (**3jf**), phosphonate (**3jg**), and cyano (**3jh**) were successfully employed in this reaction, giving the corresponding products in reasonable yields. However, the use of dicyano vinylcyclopropane provided the desired product **3ji** in low yield (21%) due to the low conversion. The reaction was also applicable to alkenyl C–H activation reactions, giving skipped dienes with valuable handles for further transformations (**5a** and **5b**). In general, good to excellent (5 : 1–31 : 1) E/Z ratios were observed. It should be mentioned that mixtures of diastereomers of **2e**–**h** were used in this transformation.

A gram-scale synthesis was performed using 2 mol% of catalyst and no decrease in efficiency was observed (eqn (1)). To document the potential utility of **3** in synthesis, the derivatization of **3** was conducted. Firstly, a Krapcho decarbalkoxylation of **3aa** in the

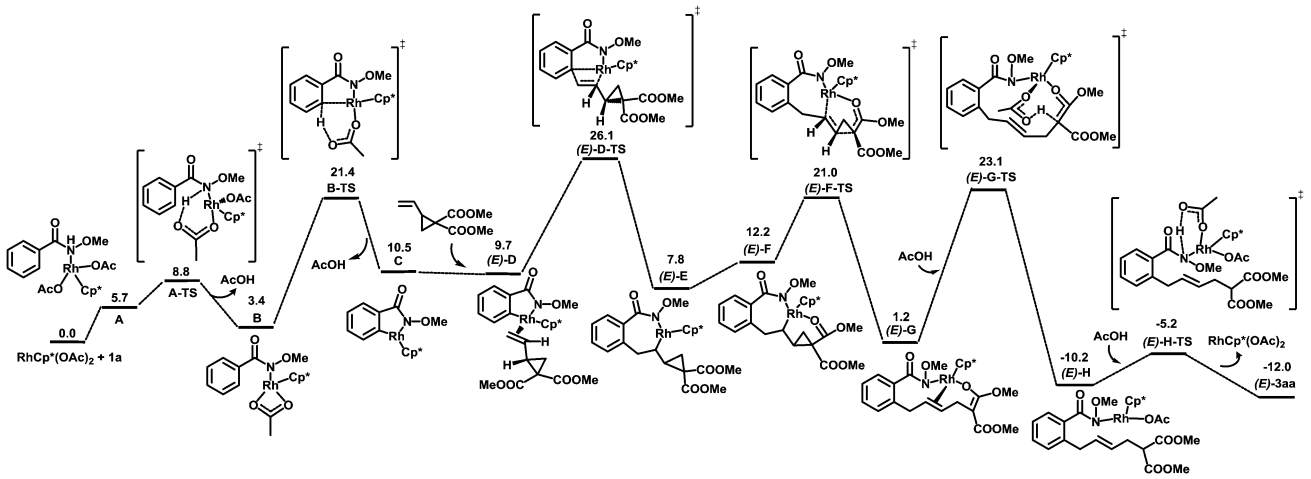


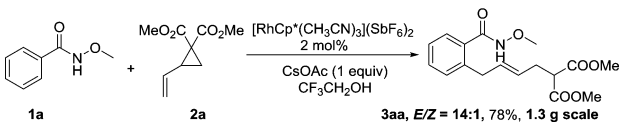
Fig. 2 Calculated energy profiles for the Rh^{III}-catalyzed sequential C–H/C–C activation reaction.

presence of NaCN in wet DMSO afforded the monoester **6** in 70% yield (eqn (2)).[16] Secondly, a palladium(II)-catalyzed aerobic oxidative cyclization and a subsequent isomerization of the double bond gave isoquinolin-1(2*H*)-one **7** in 84% yield (eqn (3)). Furthermore, epoxidation of the double bond with 3-chloroperbenzoic acid (*m*-CPBA) followed by an intramolecular epoxide ring-opening delivered 1,2-amino alcohol **8** in 48% yield (eqn (4)). Finally, the elongations of the side chain were also successful using allyl bromide and benzyl bromide as alkylation reagents, forming the corresponding products **9a** and **9b** in 64% and 91% yield, respectively (eqn (5)).

To gain insight into the mechanism, a stoichiometric amount of TEMPO was subjected to the reaction to probe the possibility of a radical initiated ring-opening of cyclopropane.[17] Comparable yield was obtained, indicating that a radical pathway is not likely.[12,18] A small kinetic isotope effect value of 1.7 was obtained from a parallel experiment,[17] suggesting that the C–H bond cleavage is not involved in the turn-over limiting step.[19]

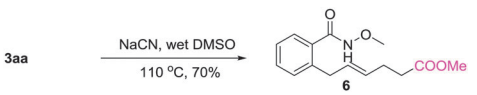
To better understand the reaction mechanism, DFT computations[17] were carried out (Fig. 2). The deprotonation of the amino group takes place first, which is followed by concerted metalation–deprotonation (CMD) to form a rhodacycle **C**.[20] The free energy of the CMD transition state is 21.4 kcal mol^{-1}. The removal of a neutral acetic acid from **C** is followed by the olefin coordination, generating **(*E*)-D** with an energy of 9.7 kcal mol^{-1}. Olefin insertion into the Rh–C bond *via* a transition state **(*E*)-D-TS** gives the intermediate **(*E*)-E**. After that, a β-carbon elimination event takes place to cleave the carbon–carbon single bond of cyclopropane in **(*E*)-F** to form the intermediate **(*E*)-G**. This step was found to be energetically favored. The protonation of **(*E*)-G** under the assistance of AcOH *via* **(*E*)-G-TS** furnishes **(*E*)-H**. A proto-demetallation leads to the final product.

Gram-scale synthesis:



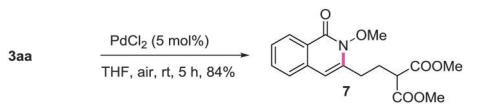
(1)

Krapcho decarbalkoxylation:



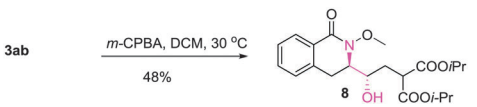
(2)

Oxidative cyclization:



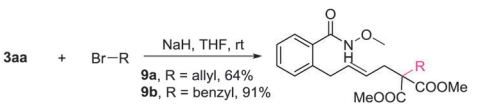
(3)

Epoxidation and subsequent cyclization:



(4)

Side chain elongation:



(5)

and regenerates the active $Cp^*Rh(OAc)_2$ catalyst. Our calculation results indicate that the rate-determining transition state corresponds to the migratory insertion of the double bond of vinylcyclopropane into the Rh–C bond with an overall activation free energy barrier of 26.1 kcal mol^{-1}. The observed good *E*/*Z* selectivity deserves some explanation. The calculations demonstrated that the relative free energies of the transition states for olefin insertion into the Rh–C bond thereby determine *E*/*Z* selectivity. The overall free energy barrier (27.6 kcal mol^{-1}) for forming the *cis* isomer is 1.5 kcal mol^{-1} higher than that for forming the *trans* isomer.[17]

In summary, we have developed a Rh^{III}-catalyzed sequential C–H/C–C activation reaction, by taking advantage of the multifold reactivity of vinylcyclopropanes. The reaction offers a simple and practical route for the synthesis of allylated arenes and skipped dienes with valuable handles. Besides, the reaction features excellent substrate scope tolerance, good stereoselectivity and is able to

produce a high yield. Valuable building blocks were synthesized from the generated products. Mechanistic studies suggest that a formal β-carbon elimination is involved in the reaction mechanism. The reaction represents a rare example of unifying C–H and C–C cleavage into a single approach to synthesize complex molecules.

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