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# Tandem Catalysis: Rh(III)-Catalyzed C−H Allylation/Pd(II)-Catalyzed *N*-Allylation Toward the Synthesis of Vinyl-Substituted *N*-Heterocycles

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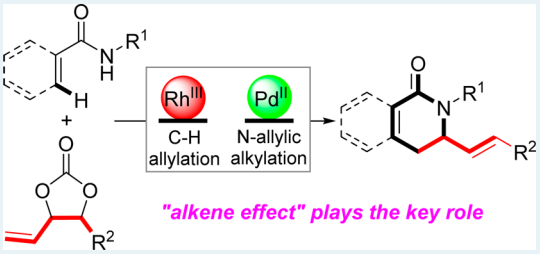
Supporting Information

**ABSTRACT:** Tandem catalysis by Rh(III)/Pd(II) was realized, enabling rapid access to two important *N*-heterocycles that bear a synthetically valuable vinyl substituent. The reaction occurred under mild reaction conditions and was easy to handle. Good substrate scope and high regio- and stereoselectivities were observed. The vinyl group was demonstrated to be a reliable handle for functional group interconversions. The alkene effect was found to be the key factor for the success of this process.




**KEYWORDS:** *tandem catalysis, C−H bond activation, N-heterocycles, palladium(II), rhodium(III)*

There is growing interest in sustainable chemistry, which aims to provide rapid access to fine chemicals while minimizing the production of waste.[1] Toward this goal, domino reactions promoted by a single catalyst have presented great success, although the development of such processes might be hindered by the need for specially designed starting materials and by the intrinsic limiting reactivity of the single catalyst applied.[2] Tandem catalysis, in which two or more sequential bond-forming events are promoted independently by two or more catalysts in a single flask, have gained increasing attention.[3,4] The advantages of tandem catalysis are apparent in terms of time, materials, effort and waste. Importantly, by fully utilizing the diverse reactivities of different catalysts, tandem catalysis could offer unprecedented opportunities for the synthesis of a complex molecule starting from simple chemical feedstock. The key to success is to find the optimal reaction conditions that are compatible for discrete catalytic processes while minimizing the negative interactions between the applied catalysts. Due to the unique and abundant modes for activating chemically inactive bonds, transition metal catalysts have been extremely successful in organic synthesis.[5] The combination of two or more transition metals, especially the late transition metals in a multicatalytic process, is therefore of great interest, and has seen a significant growth,[6] especially recently.[7] In this regard, the applications of rhodium[8] and palladium[9] in a tandem catalytic manner have met with relatively fruitful success thanks to the intensively studies from the groups of Lautens[7m−q] and others.[6b,d] Still, the development of a tandem catalysis utilizing the different reactivities of rhodium and palladium is attractive in exploring new transformations. Herein, we report a realization of novel tandem catalysis enabled by Rh(III)/Pd(II) for the synthesis of vinyl substituted *N*-heterocycles. The Rh(III) is responsible for a C−H allylation reaction,[10,11] and Pd(II) catalyzes a subsequent intramolecular *N*-allylic alkylation event.[12]

3,4-Dihydroisoquinolin-1(2*H*)-one and 5,6-dihydropyridin-2(1*H*)-one are frequently encountered scaffolds in biologically active compounds (Figure 1a).[13] Although important, a concise synthetic method for these *N*-heterocycles bearing an easily transformable substituent is still lacking.[14] We hypothesized that, by using a tandem catalytic process, vinyl-substituted 5,6-

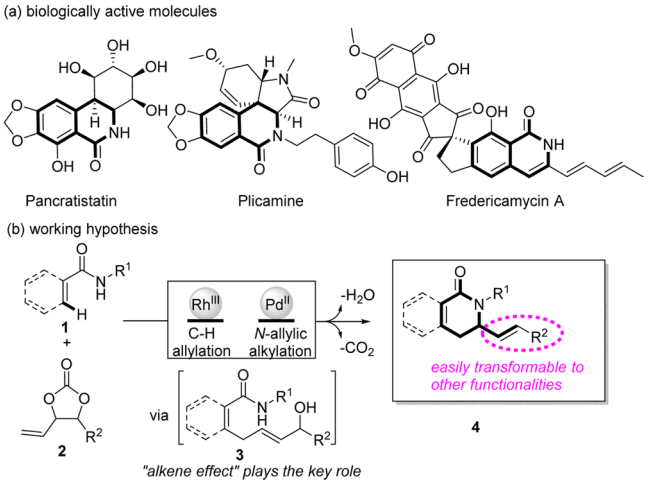



**Figure 1.** (a) Biologically active molecules containing a 3,4-dihydroisoquinolin-1(2*H*)-one scaffold. (b) Working hypothesis toward the synthesis of vinyl-substituted 3,4-dihydroisoquinolin-1(2*H*)-ones.

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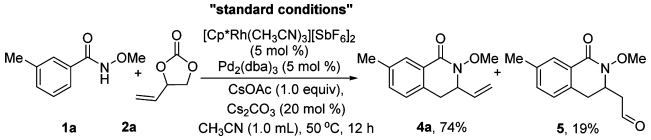
dihydropyridin-2(1*H*)-one and 3,4-dihydroisoquinolin-1(2*H*)-one could be synthesized in one pot from readily available materials. If successful, the incorporated vinyl group would then serve as a versatile transformable functional group for further decoration. Our working hypothesis is shown in Figure 1b. Inspired by the recent work of Glorius[15] and Li,[16] we assumed that, upon a rhodium(III)-catalyzed C−H coupling of benzamide **1** with 4-vinyl-1,3-dioxolan-2-one **2**, the direct allylation product **3** bearing a hydroxyl group at the allylic position would be generated. Subsequently, a palladium(II)-catalyzed intramolecular *N*-allylic alkylation would enable a cyclization to afford the desired product.[12] The challenges in the proposed processes are as follows: (1) the compatibility of rhodium(III) and palladium(II) in the same medium without the undesired interruption of each individual catalytic cycle; (2) the realization of the optimal reaction conditions that are effective for both processes; and (3) the minimization of double bond migration both in intermediate **3** and in the final product **4** in the presence of two transition metals.

We initiated our study by examining the reaction of *N*-methoxy-3-methylbenzamide **1a** with vinyl-1,3-dioxolan-2-one **2a** under the tandem catalytic system by subjecting the reaction to rhodium and palladium from the beginning. After extensive investigation, we determined that the reaction proceeded smoothly to afford **4a** in 74% yield under the optimized reaction conditions ($[RhCp^*(CH_3CN)_3](SbF_6)_2$ (5 mol %), $Pd_2(dba)_3$ (5 mol %), CsOAc (1.0 equiv), $Cs_2CO_3$ (0.2 equiv) in $CH_3CN$ (1.0 mL) at 50 °C for 12 h) (Table 1, entry 1). The reaction is very easy to handle because no special exclusion of air and moisture is required. Interestingly, aldehyde **5** is the major byproduct of this reaction (vide infra for discussion). Notably, only one regio-isomer favoring C−H activation at the less-hindered position was observed. Furthermore, no double bond migration into the ring system was detected. Although $Pd(PPh_3)_2Cl_2$ exhibited negligible reactivity (entry 2), other palladium sources such as $Pd(OAc)_2$ and $PdCl_2(CH_3CN)_2$ were also effective (entries 3 and 4). The substitution of $CH_3CN$ with $CF_3CH_2OH$ or DCE led to significantly lower yields (entries 5 and 6). The choice of base is important for this transformation. For instance, the omission of bases completely removed the reactivity (entry 7). Additionally, the use of CsOAc or $Cs_2CO_3$ alone afforded reduced yields (entries 8 and 9). Control experiments showed that both palladium and rhodium are required for the reactivity. For example, when omitting palladium catalyst, only a trace amount of **4a** was detected (entry 10, vide infra for details); without rhodium, no conversion of **1a** was observed at all (entry 11).

With the optimized reaction conditions in hand, we then examined the substrate scope of this tandem catalytic process (Scheme 1). A variety of valuable functionalities such as ester (**4c** and **4m**), trifluoromethyl (**4d** and **4n**), cyano (**4e**), acetyl (**4f**), nitro (**4g** and **4i**), and amino (**4j**) were well tolerated, providing the corresponding products in moderate-to-good yields. In addition, the halogen atoms were untouched under this bimetals catalytic system (**4k**, **4l**, **4p**−**4r**). In general, *para*-substituted substrates provided lower yields due to the diallylation reaction in the C−H activation step. Fortunately, this undesired diallylation could be suppressed when *meta*-substituted substrates were employed. In these cases, the cyclization occurred at the sterically less-hindered position (**4h**-**4o**, > 20:1 regioselectivity). Interestingly, when *meta*-chloro-substituted substrates were used, the regioselectivities were moderate (**4p**−**4r**). *N*-Methoxy-2-naphthamide cyclized at the *β*-position to afford the tricyclic product in 38% yield. Moreover, electron-rich heterocyclic amide derivatives also worked well (**4t** and **4u**). Gratifyingly, the tandem catalytic process is not limited to aromatic amides. Alkenyl amides also

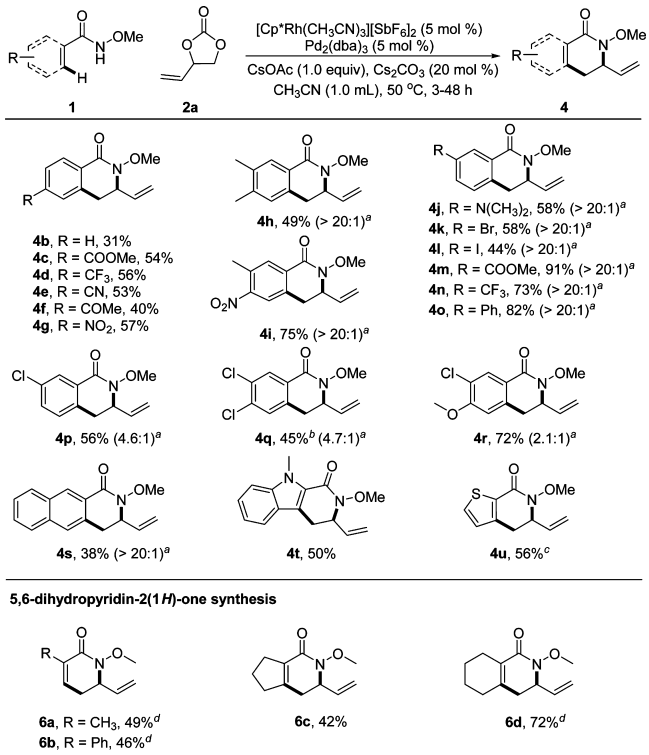
**Table 1. Optimization of the Reaction Conditions**




| entry | variation of the standard conditions | yield of **4a**[b] |
|---|---|---|
| 1[a] | none | 74% |
| 2 | $Pd(PPh_3)_2Cl_2$ instead of $Pd_2(dba)_3$ | trace |
| 3 | $Pd(OAc)_2$ instead of $Pd_2(dba)_3$ | 66% |
| 4 | $PdCl_2(CH_3CN)_2$ instead of $Pd_2(dba)_3$ | 61% |
| 5 | $CF_3CH_2OH$ instead of $CH_3CN$ | 17% |
| 6 | DCE instead of $CH_3CN$ | 32% |
| 7 | no bases | 0 |
| 8 | CsOAc (1.0 equiv) alone as base | 56% |
| 9 | $Cs_2CO_3$ (1.0 equiv) alone as base | 43% |
| 10 | no $Pd_2(dba)_3$ | trace |
| 11 | no $[RhCp(CH_3CN)_3](SbF_6)_2$ | 0 |

[a]**1a** (0.2 mmol), **2a** (0.3 mmol), $[RhCp^*(CH_3CN)_3](SbF_6)_2$ (5 mol %), $Pd_2(dba)_3$ (5 mol %), CsOAc (1.0 equiv), $Cs_2CO_3$ (0.2 equiv), $CH_3CN$ (1.0 mL), 50 °C, 12 h, isolated yield. [b]Determined by $^1H$ NMR.

**Scheme 1. Tandem Catalysis by $Rh^{III}/Pd^{II}$ with 2a as Coupling Partner**




[a]Regioselectivity. [b]80 °C was used. [c]$PdCl_2(CH_3CN)_2$ (10 mol %) was used instead of $Pd_2(dba)_3$ (5 mol %). [d]DCM (1.0 mL) was used as the solvent.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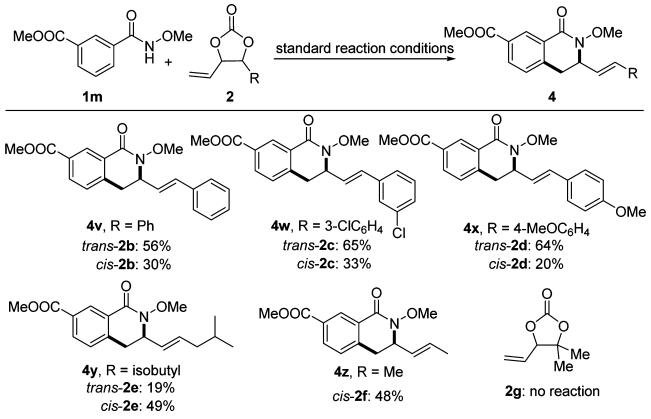
afforded the vinyl-substituted 5,6-dihydropyridin-2(1*H*)-one products in moderate-to-good yields (**6a**−**6d**), thereby greatly extending the scope of this novel transformation.

To further demonstrate the versatility of this tandem catalytic process, substituted vinyl-1,3-dioxolan-2-ones **2** were synthesized and tested (Scheme 2). Interestingly, while *cis*-**2b** (R = Ph) resulted in a poor yield, its diastereoisomer, *trans*-**2b**, provided the desired product **4v** in a moderate yield of 56% as a single *E* isomer. Not surprisingly, **2c** and **2d** with a chloro and methoxyl substituent, respectively, were well tolerated and exhibited similar trends (**4w** and **4x**). However, when alkyl-substituted **2** were used, the *cis* isomer provided a better yield. Dimethyl-substituted vinyl-1,3-dioxolan-2-one **2g** was ineffective, probably for steric reasons.

**Scheme 2. Substrate Scope on the Use of Substituted Vinyl-1,3-dioxolan-2-one 2**




To our delight, the reaction was applicable for gram-scale synthesis, affording **4o** in 71% yield (eq 1). To demonstrate the synthetic utility of vinyl-substituted 3,4-dihydroisoquinolin-1(2*H*)-one **4**, a series of experiments were conducted. The cleavage of the N−O bond in the presence of NaH in DMF was followed by the in situ oxidation, affording isoquinolin-1(2*H*)-one **7** in 89% yield (eq 2).[17] The hydrogenation of the vinyl group occurred without difficulty to give the ethyl-substituted dihydroisoquinolin-1(2*H*)-one **8** in 91% yield (eq 3). Importantly, the vinyl group is a reliable handle for olefin metathesis, offering a complementary route to the synthesis of more substituted **4** described in Scheme 2. For instance, treatment of **4a** with hex-1-ene under catalysis by the second-generation Grubbs catalyst afforded **4aa** in 85% yield as an *E* stereoisomer (eq 4).[18] Upon a Sharpless dihydroxylation followed by an oxidative cleavage of the generated 1,2-diols, formyl-substituted isoquinolin-1(2*H*)-one **9** could be obtained in almost quantitative yield, and the methoxyl group was removed at the same time (eq 5).[19]

To determine whether this tandem catalytic system could provide superior efficiency compared to its stepwise counterpart and to shed light on the mechanism, several experiments were performed. First, **1a** was subjected to a C−H activation reaction using only rhodium(III) as the catalyst. No reaction occurred without the use of bases. Surprisingly, when bases were present, although complete consumption of **1a** was observed, the allylation product **3a** was isolated in only 20% yield after 12 h (eq 6). We also examined the efficiency of the stepwise intramolecular *N*-allylic alkylation reaction (Table 2). Interestingly, with palladium as the sole catalyst, the reaction of

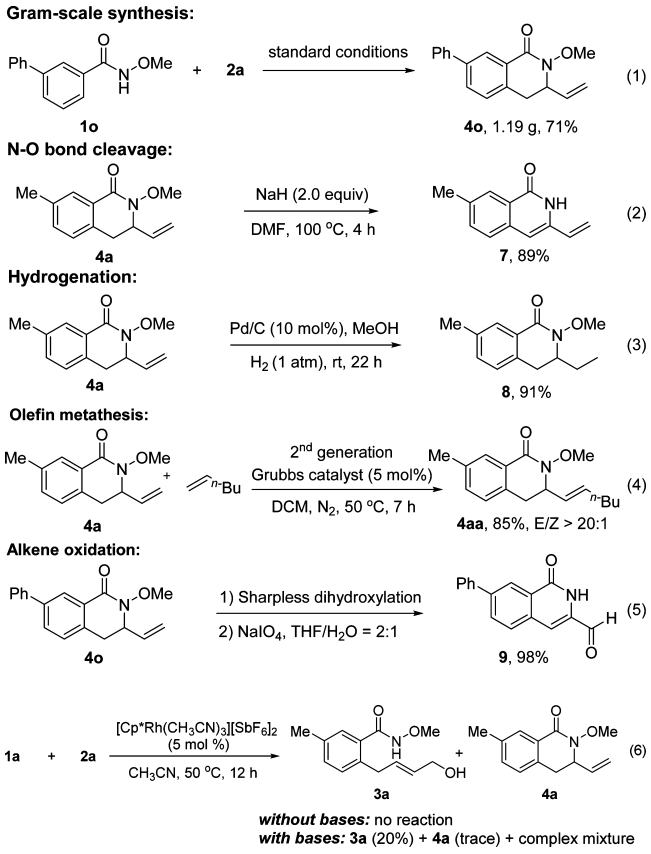
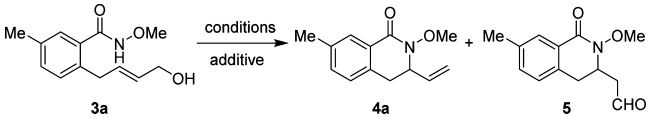



**Table 2. Stepwise N-Allylic Alkylation**




| entry | reaction conditions | additive | **4a** [%] | **5** [%] |
|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ (5 mol %), CsOAc (1.0 equiv), $Cs_2CO_3$ (0.2 equiv), $CH_3CN$, 50 °C, 12 h | none | 9 | 48 |
| 2 | | **2a** (50 mol %) | 88 | 8 |
| 3 | | hex-1-ene (50 mol %) | 42 | 34 |
| 4 | standard conditions | none | 17 | 21 |
| 5 | | **2a** (50 mol %) | 40 | 14 |
| 6 | | hex-1-ene (50 mol %) | 36 | 26 |

**3a** afforded the desired cyclization product **4a** in only 9% yield (entry 1). The yield was slightly improved to 17% under the standard reaction conditions in which both rhodium and palladium were present (entry 4). In both cases, aldehyde **5**, presumably derived from the Wack-type oxidation of alkene, was found to be the predominant product. These results clearly demonstrated the enhanced efficiency of the tandem catalytic reaction. We were intrigued by these results and questioned whether the excess amount of the alkene **2a** plays some role for the success of the second step (1.5 equiv of **2a** was used for the title reaction). Indeed, when 50 mol % of **2a** was added to the reaction mixture, the yield of **4a** was increased to 88% with only 8% of **5** detected (entry 2). The same effect was observed when standard condition were used, although not as significant (entries 5 and 6). Moreover, hex-1-ene also affect the product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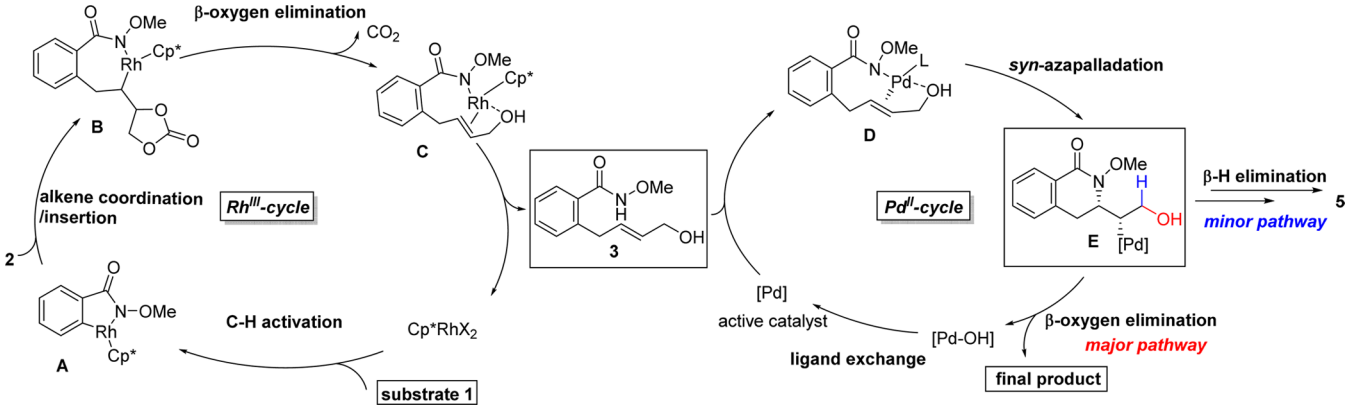
**Scheme 3. Mechanistic Rationale**




distribution with the same trend, indicating that it is the double bonds of alkenes played the key role.

A tentative mechanism for rationalizing the reaction outcomes is outlined in Scheme 3. This novel transformation consists of two catalytic cycles. In the rhodium(III) cycle, the C−H activation is followed by alkene coordination and insertion to afford a rhodacycle **B**. Thereafter, $\beta$-oxygen elimination occurs to form a double bond with an allylic alcohol coordinated to rhodium. A KIE value of 1.0 was observed (see Supporting Information for details), which suggests the C−H activation is not involved in the turnover-limiting step of the rhodium(III) cycle. The resulting allyl alcohol **3** is then released and enters the palladium(II) cycle. It is reasonable to propose that a palladium $\pi$-complex **D** similar to intermediate **C** could initially be formed. *syn*-Azapalladation would produce a $\sigma$-palladium complex **E**, which sets the stage for the subsequent $\beta$ elimination.[12a,20] In the one-pot reaction, in the presence of excess amount of **2**, $\beta$-oxygen elimination dominates to give the major product **4** substituted with a vinyl functionality. $\beta$-H elimination represents the minor reaction pathway, which affords the undesired aldehyde product **5**.[21] The role of the additional alkene in affecting the product distribution is not clear at this stage. One possibility is that the alkene serves as a ligand of palladium.[22] By tuning the electronic property of the metal center, the preference of $\beta$-oxygen elimination is realized.[23]

In summary, we have identified a tandem catalytic system that provides rapid access to of vinyl-substituted 5,6-dihydropyridin-2(1*H*)-ones and 3,4-dihydroisoquinolin-1(2*H*)-ones. The reaction proceeds under mild reaction conditions with the generation of water and $CO_2$ as the only byproducts. A variety of aromatic amides and alkenyl amides bearing diverse substituents are compatible with the reaction conditions, delivering the cyclization product with high regio- and stereoselectivities. The vinyl group has been demonstrated to be a reliable handle for functional group interconversions. The alkene effect is found to be the key factor for the success of the reaction.

## ■ ASSOCIATED CONTENT

### Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs501601c.

Experimental details of the synthesis and characterization of starting materials and final compounds; copies of $^1$H NMR and $^{13}$C NMR spectra of all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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