Rhodium Catalyzed Stereoselective Mono-alkenylation of Aryl *sp*^{2} C-H Bond *via* C-N Bond Cleavage: *N*-allylbenzimidazole as Strategic Alkenylating Agent

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ABSTRACT: A Rh-catalyzed C(sp^2)-H alkenylation has been achieved by taking *N*-allylbenzimidazole as an allylamine congener. This distinctive transformation has been observed for the first time which is attributed to the rigid benzimidazole unit. Lewis acid assisted cleavage of C(sp^3)-N bond by coordinating to the N3 of *N*-allylbenzimidazole has been established. Thus, herein we have demonstrated an unprecedented protocol of domino C-N bond cleavage followed by aryl C(sp^2)-H alkenylation. Further, detailed mechanistic studies, control experiments have been conducted to understand the mechanism. The rhodacycle-intermediates involved in the reaction have been isolated and characterized through NMR, HRMS, and single crystal X-ray.

KEYWORDS: • *Rhodium* • *C(sp^2)-H activation* • *Mono-alkenylation* • *N-allylbenzimidazole*.

INTRODUCTION

Method development for the formation of C-C bond has been the foremost topic of research in organic synthesis. Transition metal catalyzed methodologies involving organo-halides, alcohols, alkanes, olefins have played prominent role for the construction of new C-C bonds.[1-3] In this context, the transition-metal catalyzed Tsuji-Trost reaction[4a] has evolved as an efficient methodology for allylation of organo-nucleophiles by using allyl halides,[5] allyl alcohols,[6] and allyl ester derivatives[7] as electrophilic component (Figure 1a).[4-7] Here, the nucleophile attacks the metal(π-allyl) intermediate, which was formed after the cleavage of C-X (X=-halogen/-OR) bond. It has been observed that, the allyl alcohol derivatives with a better leaving group shows a positive cooperation for the allylation reactions.[7]

As compared with C-O/C-halo bond, the C-N bond is thermodynamically more stable, which is attributed to its high bond dissociation energy.[8] As the cleavage of C-N bond is very difficult and challenging, allylamines are less explored as electrophilic component. Different strategies have been employed in order to activate the robust C-N bond of allylamines.[9] The most commonly used strategies are (i) strong Lewis acid catalysis, and (ii) hydrogen bonding interaction (Figure 1b). In both of these strategies, once the allylic cation is generated, it coordinates to the metal and forms metal π-allylic cation. This in the presence of active nucleophile delivers the allylated product (Figure 1b). Tian and co-workers have exploited the Lewis acid catalysis for the coupling of allylic amines, and boronic acids.[10] In their reaction, boric acid plays a crucial role triggering the C-N bond cleavage of allylamines. Further, this concept has been extended to the synthesis of wide range of structurally diverse chiral sulfones.[10] In 2011, the Zhang research group had discovered a Pd-catalyzed α-allylation of aldehydes and ketones effectively via the C-N bond cleavage assisted by hydrogen-bonding interaction in protic solvent.[11] This methodology worked efficiently with primary, secondary as well as tertiary amines. Substrate having active methylene, and methine unit were subjected for allylation smoothly from allylamine derivatives via C-N bond cleavage.[12]

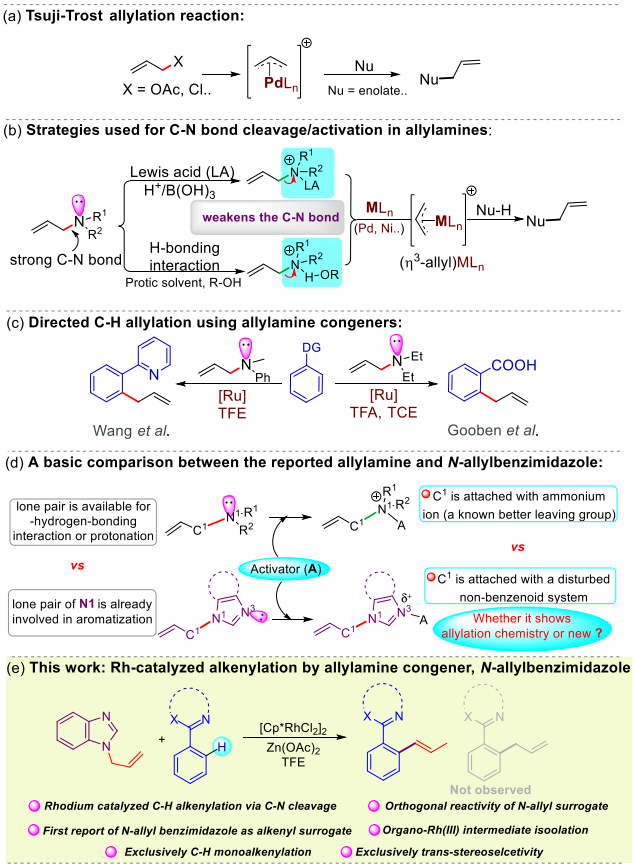


Figure 1. Transition metal catalyzed C-H allylation *vs* alkenylation.

During the last few decades, transition metal catalyzed directed C-H bond functionalization has evolved as a powerful tool for a step and atom economic transformations.[13] However, a parallel C-H activation and C-N bond cleavage for the C-C bond forming reaction is still in its infancy.[14] In 2018, the Wang research group have explored the allylation of 2-phenylpyridine via C-N bond cleavage of allyamines, where the protic solvent trifluoroethanol (TFE) was observed to trigger the C-N cleavage via hydrogen bonding interaction (Figure 1c).[14a] Recently, Gooben research group have successfully achieved the ortho-allylation of benzoic acid using *N*,*N*-dialkylallylamines as the allylating agent (Figure 1c).[14b] Here, protic solvent was found to be compatible, enhancing the reactivity.

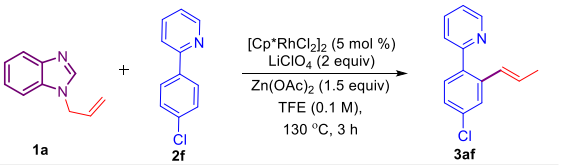
An interesting feature in the catalysis field is that, a slight change in the electronics of the substrate and the reaction condition could deliver a completely different product. Therefore, we decided to study the reactivity of *N*-allylbenzimidazole **1a** as an allylamine congener (Figure 1d). The basic difference between **1a** and the reported allylamine is that, in the case of allylamines the non-bonded electron pair on N1 is readily available for protonation/hydrogen bonding with protic solvent. Whereas, the non-bonded electron pair over N1 of **1a** is not available for hydrogen bonding or bonding with Lewis acids as it is a part of the aromatic sextet. However, the non-bonded electrons over N3 atom of **1a** could be used for this purpose in lieu of N1 atom. Upon activation (Lewis acid/H-bonding) of **1a**, the aromaticity of the non-benzenoid ring would get perturbed (Figure 1d). Now it's interesting to see, whether this disturbed non-benzenoid aromatic unit which is attached with C1, will show the same allylation chemistry or different? With these basics, we anticipated to study the chemistry of *N*-allylbenzimidazole for directed C(sp^2)-H functionalization. We carried out the reaction between 2-arylpyridine derivatives **2** and *N*-allylbenzimidazole **1a** under rhodium catalysis. To our delight, we observed selectively C(sp^2)-H alkenylation as opposed to the allylation. Salient features of this methodology are (i) orthogonal reactivity by *N*-allylbenzimidazole, (ii) selective mono-alkenylation instead of allylation, (iii) first report on C-N cleavage of *N*-allyl benzimidazole with Rh-catalysis, (iv) use of *N*-allylbenzimidazole as alkenyl surrogate, (v) detailed mechanistic study, (vi) characterization of Rh-intermediate, and (vii) exclusive trans alkenylation.

RESULTS AND DISCUSSION

Our investigation began with the reaction of *N*-allylbenzimidazole **1a** and 2-(4-chlorophenyl)pyridine **2f** (Table 1). We were delighted to find that 5 mol % of Cp*Rh catalyst, 2 equiv of $LiClO_4$ in combination with 1.5 equiv of $Zn(OAc)_2$ gave the desired mono-alkenylated product **3af** in 75% of yield (Table 1, entry 1). The use of cationic Rh-complex resulted in 31% yield of **3af** (Table 1, entry 2), whereas $Rh(OAc)_2$ dimer and Wilkinson's catalyst failed to deliver the product (Table 1, entries 3-4). When solvents other than TFE were screened for the reaction, lower yields were observed (Table 1, entries 5-7). This suggest that the protic solvent TFE playing a crucial role in the reaction. It was observed in the literature that the use of water could enhance the hydrolysis of C-N bond.[15] Therefore, to enhance the rate of C-N bond cleavage of *N*-allylbenzimidazole, 1:1 ratio of TFE:H_2O was used (Table 1, entry 8). Instead of improved yield, we observed only a trace amount of product suggesting the need of moisture-free condition for the above transformation.

Further, the rate of the reaction is highly affected by the temperature; an exponential increase in the reaction yield was observed with increasing temperature (Table 1, entries 9-11). We are surprised to observe that, $LiClO_4$ works wonderfully for this designed protocol, replacing costly silver additives such as $AgSbF_6$ and AgOAc which results in no reaction (Table 1, entries 12, and 13). In addition to that, use of $NaIO_4$ in place of $LiClO_4$ resulted in 20% yield of the product **3af** (Table 1, entries 12-13). Varying the equivalents of *N*-allylbenzimidazole resulted in lower yields (Table 1, entries 15-16). This might be due to *N*-allylbenzimidazole is going through a multi-step process, that is C-N bond cleavage and isomerization.

Table 1. Optimization of Reaction Conditions



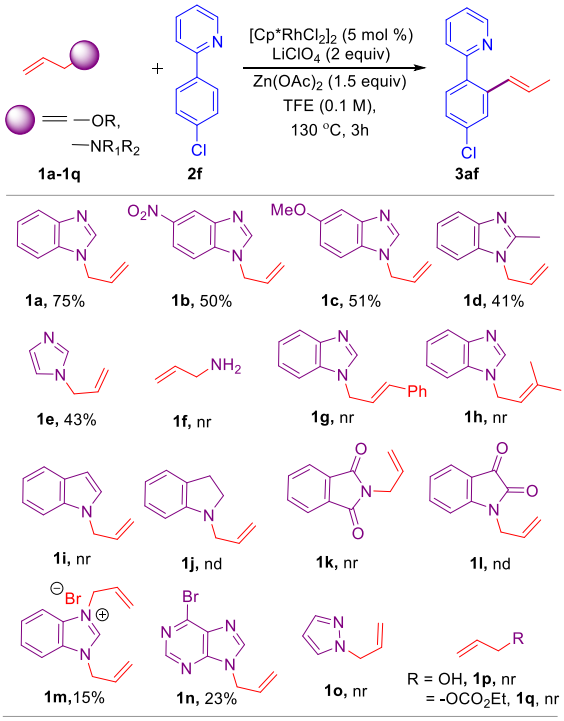
entry	deviation from the standard conditions	yield of **3af**(%)[b]
1	**none**	**75**
2	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	31
3	$Rh(OAc)_2$	nr
4	$Rh(PPh_3)_3Cl$	nr
5	MeOH	25
6	HFIP	20
7	TFT	nr
8	TFE+H_2O	trace
9	temperature 70 °C instead of 130 °C	nr
10	temperature 90 °C instead of 130 °C	trace
11	temperature 110 °C instead of 130 °C	40
12[c]	$AgSbF_6$ instead of $LiClO_4$	nr
13[c]	AgOAc instead of $LiClO_4$	nr
14	$NaIO_4$ instead of $LiClO_4$	20
15	**1a** (1 equiv) instead of 3 equiv	22
16	**1a** (2 equiv) instead of 3 equiv	46
17	$Zn(OTf)_2$ instead of $Zn(OAc)_2$	60
18	PivOH instead of $Zn(OAc)_2$	trace
19	$Cu(OTf)_2$ instead of $Zn(OAc)_2$	nr
20	2 h	35
21	4 h	73
22	6 h	20
23	with out [Rh]	nr
24	with out $LiClO_4$	trace
25[d]	with out $Zn(OAc)_2$	55

[a]Reaction conditions: **2f** (1 equiv, 0.06 mmol), **1a** (3 equiv, 0.18 mmol), $[Cp^*RhCl_2]_2$ (5 mol %, 0.003 mmol), $LiClO_4$ (2 equiv, 0.12 mmol), $Zn(OAc)_2$ (1.5 equiv, 0.09 mmol), TFE (0.1 M, 0.6 mL), 130 °C, N_2, [b]Isolated yield. [c](20 mol%, 0.2 equiv) of silver additives were used, [d]Isolated yield after 12 h.

Further evaluation of lewis acid/acid additive such as $Zn(OTf)_2$, PivOH, and $Cu(OTf)_2$ didn't result in an improved yield of **3af** (Table 1, entries 17-19). To know the effect of time, three parallel reactions were performed, and it was observed that after 4 hours the product starts to decompose under the reaction conditions (Table 1, entries 20-22). Finally, the control experiments confirmed the necessity of catalyst $[Cp^*RhCl_2]_2$, additive $LiClO_4$, and $Zn(OAc)_2$ (Table 1, entries 23-25). From the experiments it is clear that the reaction is triggered by the addition

of Lewis acid. Thus, it is confirmed that the role of $LiClO_4$ is crucial for this reaction and $Zn(OAc)_2$ acts as a promoter.

Scheme 1: Screening of allylamines, allylalcohol and esters.



[a]Reaction conditions: **2f** (1 equiv, 0.1 mmol), **1** (3 equiv, 0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol %, 0.05 mmol), $LiClO_4$ (2 equiv, 0.2 mmol), $Zn(OAc)_2$ (1.5 equiv, 0.15 mmol), TFE (0.1 M, 1.0 mL), 130 °C, N_2, [b]Isolated yield.

With the optimized condition in hand, we proceeded to study the electronic influence of the *N*-allyl coupling partner, for C-H alkenylation of 2-arylpyridines. When, **1a** containing electron donating group (-OMe) **1b**, and electron withdrawing group (-NO_2) **1c** were screened, similar reactivity was observed yielding 50% of **3af**. It indicates that, -OMe/-NO_2 substituent in the benzenoid system has no remarkable impact for this transformation. When 2-methyl-*N*-allylbenzimidazole **1d** was taken as an alkenylating source, we got 41% yield of **3af**. Further, to check the influence of benzenoid ring, *N*-allylimidazole **1e** and allylamine **1f**, were taken instead of **1a**, but inferior result was observed in both cases. This implies that the presence of benzene ring is necessary for this transformation. Disubstituted alkenes (**1g** and **1h**) could not deliver the respective alkenylated products. It indicates that, alkene insertion in to the C-Rh bond is sterically controlled and occurs prior to the C-N bond cleavage. To check the role of N3 nitrogen atom of **1a**, *N*-allylindole **1i** was employed as the coupling partner. In this case, we did not observe any product **3af**, which implies that the reaction is facilitated by the chelation of Lewis acid at N3 atom of **1a**. Further, *N*-Allyl indoline **1j** was also tested and found to be ineffective for this transformation. When more electron deficient N-allyl phthalimide **1k**, and *N*-allyl isatin **1l** were chosen as alkenylating agents they failed to deliver the product **3af**. The use of 1,3-diallylbenzimidazole **1m** and *N*-allyl-4-bromopurine **1n** gave the mixture of alkenylated as well as allylated products in poor yields. In contrast to imidazole **1e**, N-allyl pyrazole **1o** did not give the product **3af**. Moreover, aryl pyridine **2a** was subjected to the standard reaction condition with the more frequently used allylating reagents such as allyl alcohol **1p**, and allyl ethyl carbonate **1q**, but none of them could produce C-H allylation or C-H alkenylation product. All these studies discussed above confirms the efficiency and selectivity of *N*-allylbenzimidazole 1a for this transformation.

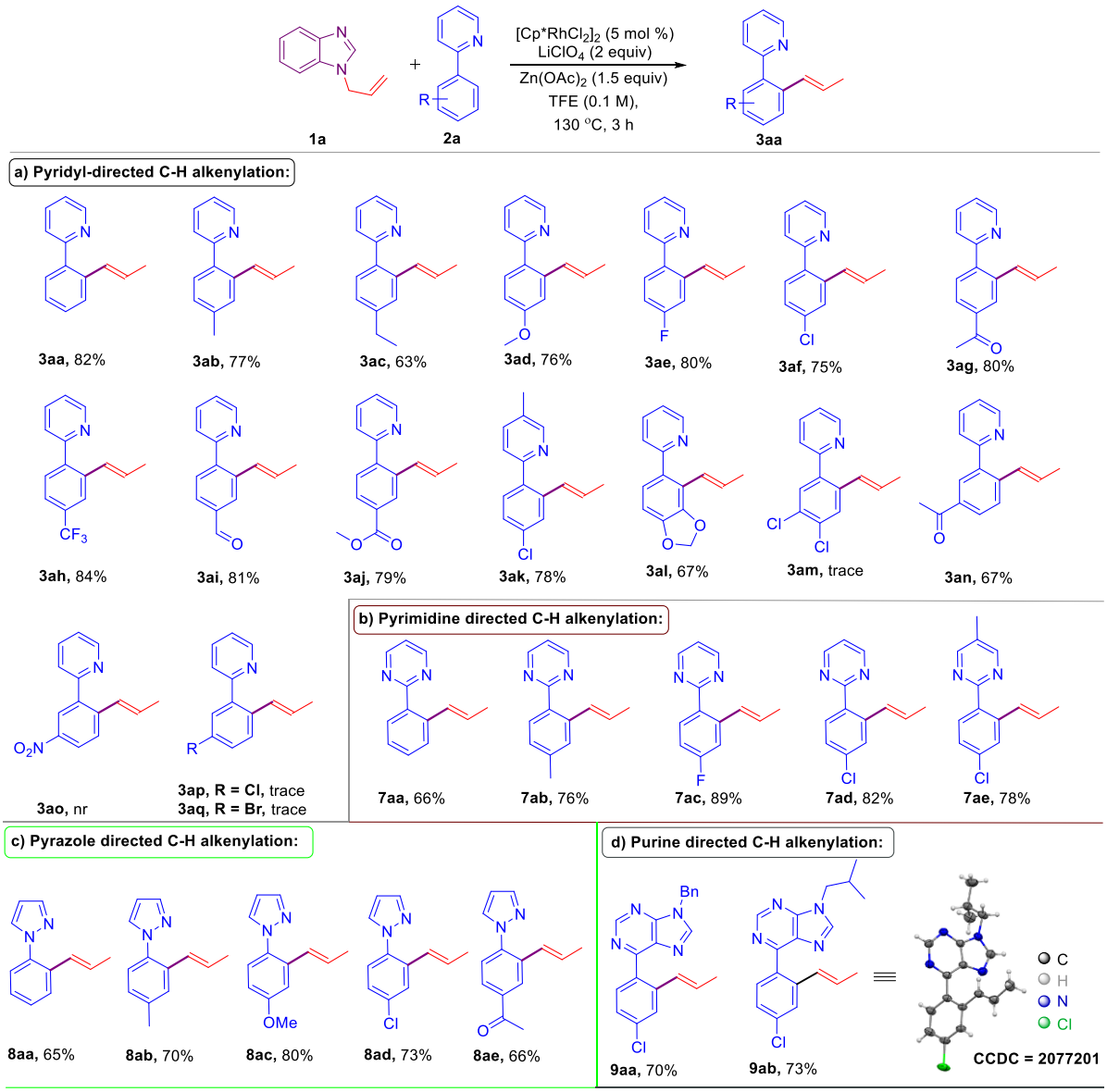
To test the generality of this methodology by using *N*-allylbenzimidazole **1a** as alkenylating surrogate, various substituted 2-arylpyridines were tested. The scope of 2-arylpyridines were outlined in Scheme 2a. The aryl unit containing both electron donating groups EDGs (-CH_3, -C_2H_5, -OMe, -F/Cl) and electron withdrawing groups EWGs (-CHO, -$COCH_3$, -CF_3, -CO_2Me) were well tolerated under this condition delivering moderate to very good yields of the respective C-H alkenylated products. It has been observed that, the substrates with EDGs were giving lesser yields (Scheme 2, **3ab**-**3af**, **3ak**, and **3al**) as compared to the substrates with EWGs (Scheme 2, **3ag**-**3aj**). Interestingly, sensitive functional groups such as -formyl **3ai** and -ester **3aj** were retained in the final product. The unsymmetrical substrate bearing dioxolane ring selectively gave **3al** in 67% yield, by activating ortho-hydrogen from more sterically hindered site. The origin of this selectivity might be due to the additional stability gained from the chelation of oxygen atom in the cyclometallated intermediate.[16] Further, the scope of the reaction has been extended to the heterocycles such as 2-arylpyrimidines, and 2-arylpyrazoles (Scheme 2, b and c). These heterocycles were found very cooperative to deliver their corresponding mono-alkenylated products without any variation in the standard reaction conditions. The substrates bearing EDGs or EWGs worked smoothly, giving products in good yields (Scheme 2, **7aa**-**7ae**, and **8aa**-**8ae**).

Purine unit has a special role being as a nucleobase, and a core unit in nucleic acid. Transition metal-catalyzed purine directed C-H alkenylations have been reported using phenylacetylene or vinylcarboxylic acids by Yu[17a] and Xu group[17b] respectively. We envisioned that, our protocol could install selective alkelyl unit in this system. Gratifyingly, this reaction condition was found viable for purine directed alkenylated products **9aa**, and **9ab** in good yields (Scheme 2d). The *trans*-stereochemistry was confirmed unambiguously from the single crystal X-ray analysis of product **9ab** (CCDC 2077201).

In order to get better understanding about the influence of electronics on the substrate, intermolecular competition experiments were conducted between different arylpyridines (Scheme 3). The results indicate that, electronically poor substrates were reacting relatively faster than electronically rich substrates with the reactivity trends **2g**>**2a**>**2d** (Scheme 3a and 3b). In order to check the feasibility of di-alkenylation under the standard reaction condition, **3aa** was employed as a substrate. However, we did not observe any di-alkenylation product, rather 94% of **3aa** was recovered (Scheme 3c). It shows the highly selective induction of mono-alkenyl group into the substrate. To gain further insight into the mechanism, we conducted several mechanistic experiments (Scheme **3d**-**3k**). When **2f** was allowed to react with deuterium source D_2O or CD_3OD in absence of **1a**, 13% and 11% of deuterium exchange were observed with D_2O and CD_3OD respectively (Scheme 3d). Additionally, the reaction of **2f** and D_2O in presence of **1a** shows 30% H/D-scrambling at the ortho-position of **3af** (Scheme 3e). Both of the experiments

together indicate that, the C-H bond metalation step might be reversible.[18] The reaction of **2f** with stoichiometric amount of $[Cp^*RhCl_2]_2$ under the standard reaction condition in absence of **1a** yielded rhodacycle **Int-1** in 70% yield, which was characterized by NMR spectroscopy, and HRMS (Scheme 3f). Similarly, rhodacycle **Int-2** was synthesized from the substrate **2l**, which was confirmed by NMR spectroscopy, HRMS, and X-ray crystallography (Scheme 3g) (See supporting information).

Scheme 2: Scopes of Rh-catalyzed alkenylation reactions[a,b]

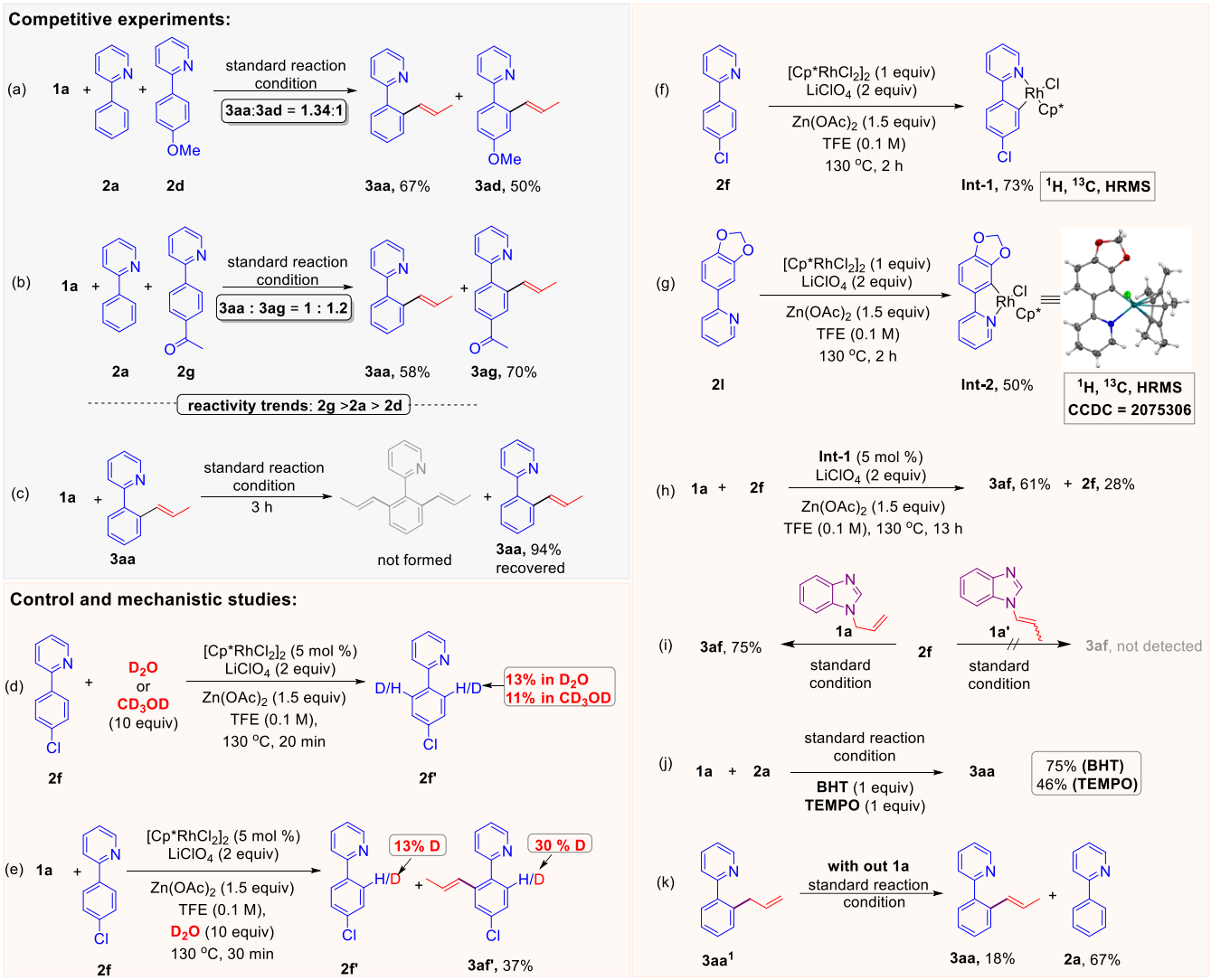


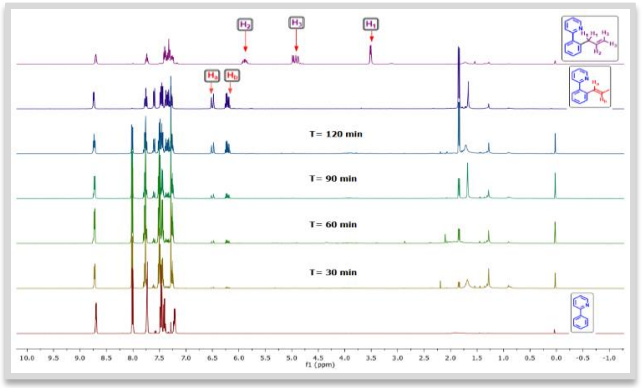
[a]Reaction conditions: **1a** (3 equiv, 0.3 mmol), **2/4/5/6** (1 equiv, 0.1 mmol), $[Cp^*RhCl_2]_2$ (5 mol %, 0.05 mmol), $LiClO_4$ (2 equiv, 0.2 mmol), $Zn(OAc)_2$ (1.5 equiv, 0.15 mmol), TFE (0.1 M, 1.0 mL), 130 °C, N_2, [b]Isolated yield.

The active involvement of **Int-1** in the catalytic cycle was confirmed when 5 mol% of **Int-1** was used as catalyst for the reaction of **2f** with **1a**, afforded 61% yield of **3af** (Scheme 3h). There are several reports on transition metal-catalyzed in situ isomerization of terminal alkene to internal alkene.[19] Thus, we envisaged whether internal alkene **1a'** is an active coupling partner in the course of this reaction or not. To rule out this possibility, a reaction has been performed employing **1a'**, resulted in no reaction (Scheme 3i). This confirms that, the terminal alkene **1a** is participating in the reaction not the internal alkene **1a'**. The formation of **3aa** was observed even in the presence of stoichiometric amount of radical scavenger BHT and TEMPO in 75% and 46% respectively; which rule out the involvement of radical mechanism (Scheme 3j). Furthermore, to check whether the reaction is proceeding through 2'-allylphenylpyridine **3aa**[1] as an initial product, it was subjected to the standard condition, which resulted in 67% of **2a** and 18% of **3aa** (Scheme 3k). These results are well supported by the literature

reports.[20] As, 2-phenyl pyridine **2a** is the major product not **3aa** under the rhodium catalyzed condition, it shows that, 2'-allylphenylpyridine **3aa**[1] is not a key intermediate in the reaction. This has been further verified by performing a series of parallel experiments and the reaction progress has been checked in NMR at different time (Figure 2, for details see Supporting information). Throughout the series of experiments, the peaks correspond to the allyl group.

Scheme 3. Control experiment and mechanistic studies.

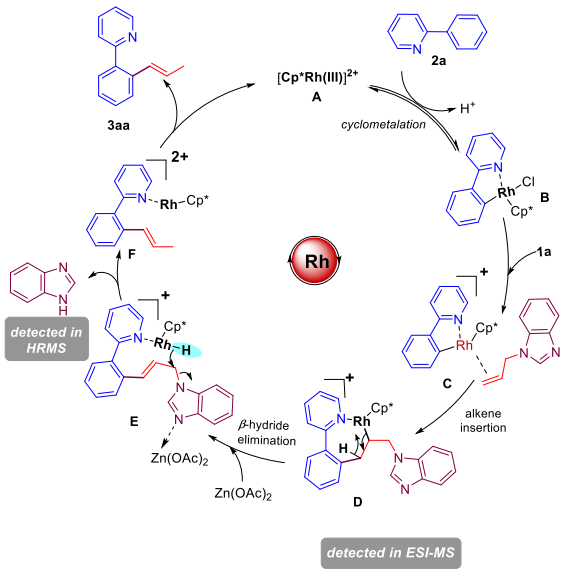




Based on the experimental observations and literature precedents, a catalytic cycle has been proposed (Scheme 4). The Rh(III) catalyst **A** initially undergoes cyclometallation with the pyridyl-N atom of the **2a** reversibly, forming intermediate **B**. (characterized by NMR, HRMS, and XRD). π-complexation of the complex **B** with **1a**, followed by alkene insertion into the C-Rh bond gave intermediate **D** (detected in LRMS, see supporting information). β-hydride elimination of **D** leads to the alkenylated intermediate **E**. 1,8-hydride migration[20] displaces the benzimidazole unit (detected in HRMS from the crude reaction mixture) leads to the formation of corresponding stereoselective alkenylated product **3aa**.

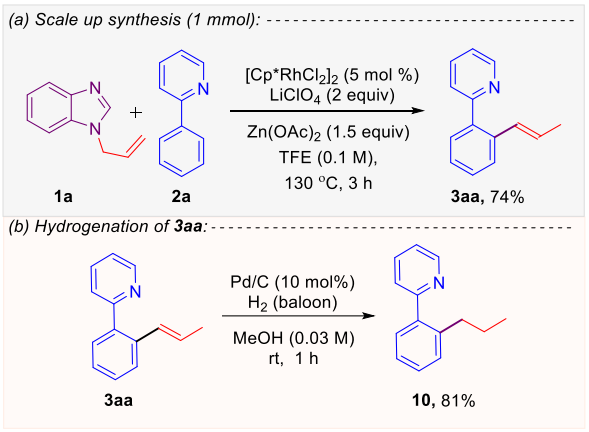
Figure 2. NMR studies for reaction progress and intermediate.

Scheme 4. Proposed mechanism.



The synthetic utility of the reaction has been demonstrated by performing a 1 mmol scale reaction, which afforded 74% of **3aa** (Scheme 5a). Further, to show the applicability of the alkenylated product, hydrogenation of **3aa** was performed. The hydrogenated product 2-(2-propylphenyl)pyridine **10** was obtained in 81% of yield as colorless oil (Scheme 5b).

Scheme 5. Synthetic utility of this methodology.



CONCLUSIONS

In conclusion, for the first time a rhodium(III)-catalyzed stereoselective C(sp^2)-H trans alkenylation has been depicted by using *N*-allylbenzimidazole as alkenyl-surrogate. This methodology found applicable with a wide range of functional groups, and directing groups. More importantly, the nucleobase purine could be stereoselectivity monoalkenylated under the developed protocol. Mechanistic studies, organo-rhodium intermediate isolation, and single crystal structure confirms the reaction pathway. The formation of stereoselective *trans*-alkene among other possibilities like allylation/cis-alkenylation is a big success of this methodology.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/
Mechanistic studies and control experiments; NMR data (^{1}H, ^{13}C, and ^{19}F NMR) of the compounds; X-ray crystallography data (PDF) Crystal data for compound **9ab** and **Int-2**; NMR FID data of compounds **3aa**–**3an**, **7aa**-**3ae**, **8aa**–**8ae**, and **9aa**–**9ae** (ZIP).

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Notes

The authors declare no competing financial interest.

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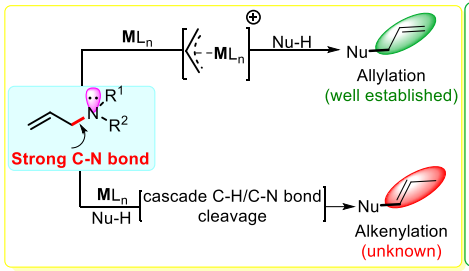

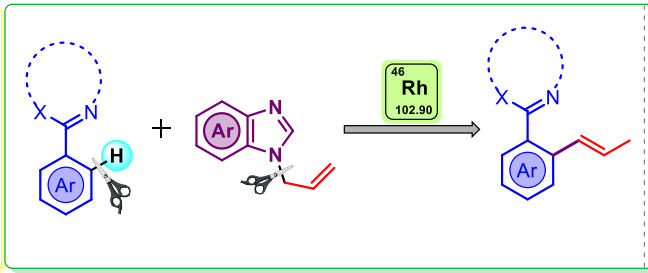

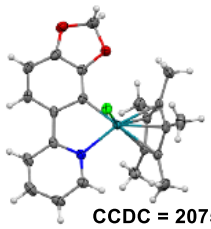

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^{1}H, ^{13}C, HRMS

- *Rhodium catalyzed C-H alkenylation/C-N cleavage*
- *Orthogonal reactivity of N-allylamine surrogate*
- *First report of N–allylbenzimidazole as alkenyl surrogate*
- *Detail mechanistic study, rhodacycle intermediate*
- *Trans-stereoselcetivity*
- *Exclusively C-H monoalkenylation*