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Rh(III)-Catalyzed allylic C–H amidation of unactivated alkenes with *in situ* generated iminoiodinanes†

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Rh(III)-catalyzed allylic C–H amidation of substituted alkenes with *in situ* generated iminoiodinanes is demonstrated. The presented protocol is compatible with differently functionalized unactivated terminal alkenes and internal alkenes. In terminal alkenes, branch selectivity was observed exclusively. Based on the detailed mechanistic investigation, a possible reaction mechanism involving the *in situ* generated π-allyl as well as metal–nitrene intermediates has been proposed.

The construction of C–N bonds in a step economical manner *via* transition metal-catalyzed C–H amination reactions has attracted much attention in organic synthesis due to the ubiquity of nitrogen moieties in various natural and pharmaceutical products.[1] Among the widely utilized aminating reagents, iminoiodinane is a viable nitrene precursor and an efficient amidation source to carry out C–H insertion or aziridination reactions in inter- as well as intra-molecular manner.[2] Che and Blakey have performed preliminary work involving *in situ* generation of iminoiodinanes for amidation of saturated C–H bonds.[2b,c] This iminoiodinane precursor has been derived by *in situ* oxidation of sulfonamide with the environmentally benign and easily available hypervalent iodine oxidants. This also overcomes the pitfalls of the synthesis and characterization of iminoiodinanes.[2] However, in the case of alkenes, chemoselective or site-selective amination exhibits a competition between allylic C–H bonds and olefinic π-bonds with nitrenoids by modulating/tuning the catalyst system.[3,4] In the literature, reports related to hypervalent iodine promoted iminoiodinane mainly include intramolecular cycloamidation reactions of saturated (sp^3) C–H bonds catalyzed by dirhodium, Mn-salen, ruthenium–porphyrin or disilver complexes and amidation of sp^2 C–H bonds of ketoximes catalyzed by a $[Cp^*RhCl_2]_2$.[5]

Allylic functionalization of alkenes proceeding *via* π-allyl intermediates has been established as a predominant transformation for the synthesis of many important therapeutic and biologically active compounds.[6] White's pioneering report on Pd(II)-catalyzed direct allylic functionalization of simple alkenes *via* the π-allyl complex was a breakthrough in the allylic functionalization reaction as it avoids the requirement of leaving groups at the allylic position.[7] Very recently, high valent transition metal complex catalyzed direct allylic functionalization of various internal as well as terminal alkenes has been extensively explored by carrying out functionalization with different hard N, C and O nucleophiles.[8] In 2017, Blakey reported the reductive elimination assisted allylic amination of β-substituted styrenes using Cp*Rh(III) as the catalyst.[8d,e] Subsequently, our group has reported a Cp*Ir-catalyzed allylic amination of substituted internal alkenes.[8f] This assorted allylic functionalization of internal alkenes mainly requires a stoichiometric amount of metal oxidants. Furthermore, Glorius, Blakey and Rovis have independently reported the allylic amidation of various terminal alkenes using dioxazolones and tosyl azides as an amidation source involving metal nitrene intermediate.[8g–i] However, the use of sulfonamide as a nitrene precursor in the direct allylic C–H activation of unactivated alkenes is still unexplored. With our continued interest in direct allylic C–H activation,[8f] we sought to develop a methodology to functionalize unactivated olefins with sulfonamide by avoiding the use of expensive metal oxidants.

Hence, with the idea of amide functionalization of unactivated olefins by avoiding the usage of metal oxidants, we began our investigation by using allyl benzene and *p*-nitrobenzene sulfonamide as model substrates for optimization studies (for detailed optimization studies, see the ESI†). Treatment of allylbenzene **1a** (2.0 equiv.) with *p*-nitrobenzene sulfonamide (**2a**) in the presence of $[Cp^*RhCl_2]_2$ (2 mol%), $AgSbF_6$ (8 mol%), $PhI(OAc)_2$ (2.0 equiv.) and $Na_2HPO_4{\cdot}2H_2O$ (1.0 equiv.) in CF_3CH_2OH for 24 h at 65 °C gave allylic C–H amidation product **3aa** in 96% yield with upto 99% branched selectivity (Scheme 1). The excess of allyl benzene is used in the reaction

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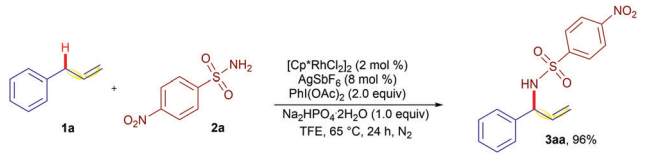


Scheme 1 Branched selective allylic C–H amidation.

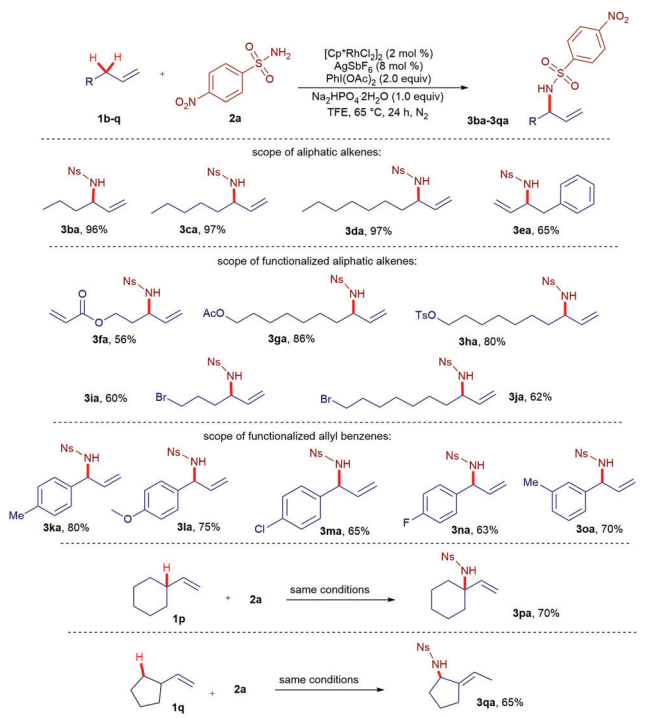
due to the isomerization of allyl benzene into 1-phenyl-1-propene. The structure of product **3aa** was confirmed by single crystal XRD (CCDC 2062182). The reaction was examined with various solvents. The result shows that the alcoholic solvent, HFIP, was also found to be effective, providing product **3aa** in 86% yield. It can be concluded that the *in situ* formed iminoiodinane might be stabilized in alcoholic solvents such as TFE and HFIP.[9]

With the optimal reaction conditions in hand, we set out to explore the substrate scope for this C(sp^3)–H amidation for various terminal and internal alkenes. As shown in Scheme 2, a variety of unfunctionalized as well as functionalized terminal olefins were aminated in good to excellent yields with upto 99% branched selectivity observed in ^{1}H NMR of crude reaction mixture. The reaction offers compatibility with various alkenes containing a broad range of functional groups, giving rise to different branched amidation products. Various linear unfunctionalized alkenes such as 1-hexene (**1b**), 1-octene (**1c**), 1-decene (**1d**) and 4-phenyl-1-butene (**1e**) were explored, and branched products **3ba–3ea** were obtained in excellent 96%, 97%, 97% and 65% yields, respectively.

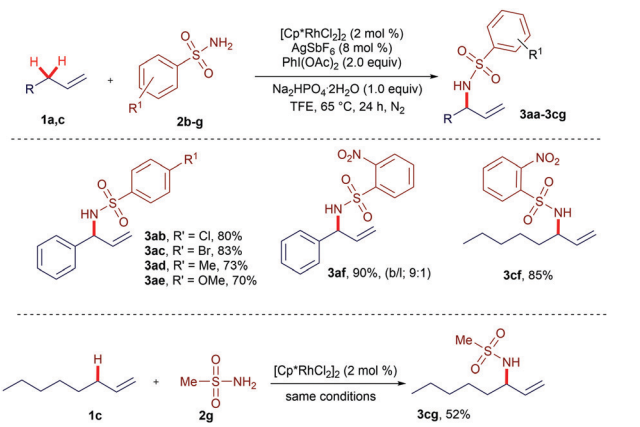
To further investigate the effect of different functional groups on the reaction course, the reaction was explored with various functionalized alkenes. Alkenes containing various alcohol protection groups such as acrylate **1f**, acetate **1g**, and tosylate **1h** on reaction with **2a** resulted in products **3fa–3ha** in 56–86% yields. 6-Bromo-1-hexene (**1i**) and 10-bromo-1-decene (**1j**) also show compatibility with this methodology and resulted in **3ia** and **3ja** in 60% and 62% yields, respectively. Various substituted allyl benzenes **1k–o** were also examined. Substituted allyl benzene containing methyl **1k**, methoxy **1l**, chloro **1m**, and fluoro **1n** at the *para* position resulted in **3ka–3na** in 80%, 75%, 65%, and 63%, respectively. 3-Methyl allyl benzene (**1o**) also resulted in the expected product **3oa** in 70% yield. Furthermore, this reaction also shows compatibility with vinyl cyclohexane (**1p**) and it has been observed that the functionalization exclusively occurs at tertiary carbon yielding product **3pa** in good yield of 70%. But, in the case of a smaller ring system, vinyl cyclopentane (**1q**), functionalization occurs at the ring carbon by shifting of double bonds, providing allylic amidation product **3qa** in 65% yield. The formation of unexpected product **3qa** can be attributed to olefin isomerization which leads to the internal alkenes followed by the formation of the π-allyl intermediates and subsequent amination.

The reaction was further examined with various substituted benzene sulfonamides (**2b–g**) (Scheme 3). *para*-Substituted sulfonamides having electron-donating as well as electron-withdrawing groups such as Cl (**2b**), Br (**2c**), Me (**2d**) and OMe (**2e**) were well tolerated, resulting in products **3ab–ae** in good yields of 80%, 83%, 73% and 70%, respectively. In the case of the reaction of *ortho*-nitro benzenesulfonamide (**2f**) with allyl benzene (**1a**) the formation of linear and branched product (**3af′** and **3af**) in 90% yield in 9 : 1 ratio was observed. Alkyl sulfonamide **1c** on reaction with *ortho*-nitro benzenesulfonamide (**2f**) resulted in product **3cf** in 85% yield. Interestingly, alkyl sulfonamide (**2g**) also shows reactivity toward the reaction, giving product **3cg** in 52% yield.

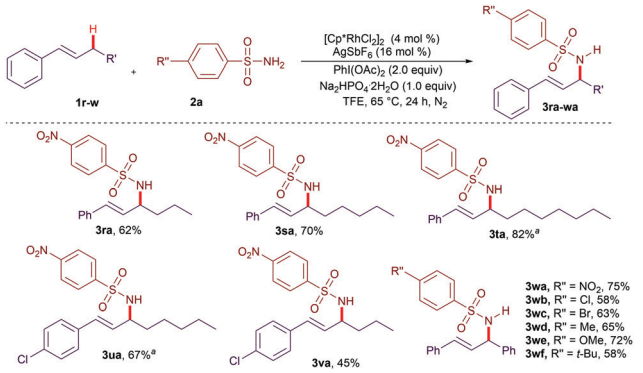
We next evaluated the substrate applicability of internal alkenes with this methodology. The reaction was examined with various unsymmetrical aryl–alkyl alkenes **1r–w** (Scheme 4). It was observed that the reaction was regioselective giving allylic amidation products by the nucleophilic attack at the allylic



Scheme 2 Scope of various terminal alkenes.



Scheme 3 Scope of substituted sulfonamides **2b–f**, **2g**.

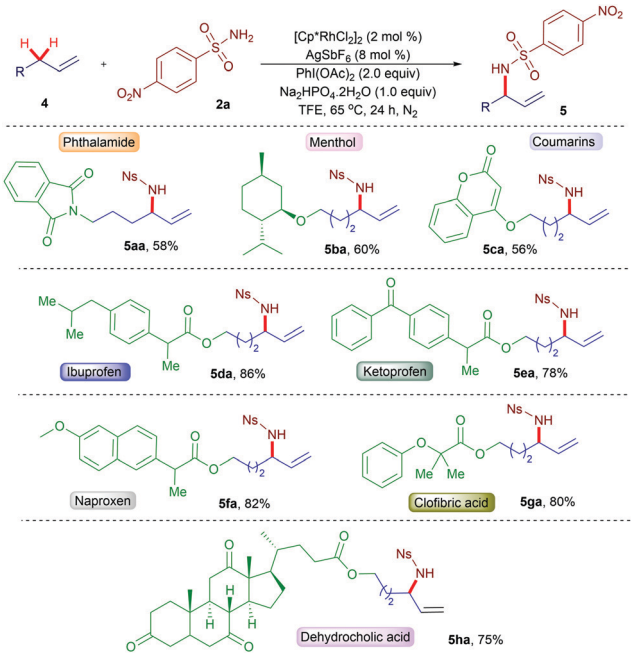


Scheme 4 Scope of unfunctionalized internal alkenes. [a]A trace amount (approx. 15 : 1) of other regioisomer was observed in ^{1}H NMR.

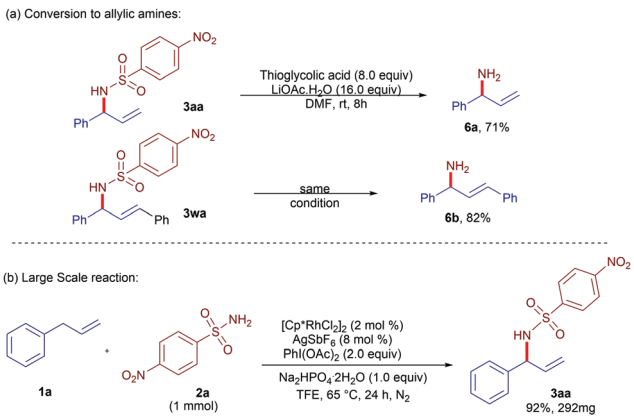
sp^3-carbon atom in most of the cases. The reaction of alkene **1r** with **2a** provided a single product **3ra** in yield of 62%. However, on increasing the length of the carbon chain from hexyl to octyl, expected products **3sa** and **3ta** were observed in good yields of 70% and 82%, respectively. Similarly, the reaction of *p*-Cl substituent on the aryl ring of alkenes with different alkyl chain lengths **1u** and **1v** with **2a** gave products **3ua** and **3va** in 67% and 45% yields, respectively. In the reaction of **1t** and **1u** with **2a**, a trace amount of other regioisomers **3ta′** and **3ua′** was also observed, respectively. The reaction of symmetrical internal alkene **1w** with substituted sulphonamides **2a–f** provided the expected products **3wa–wf** in 58–75% yields, respectively. The reaction of *trans*-4-octene under similar reaction conditions did not result in the expected product.

Furthermore, this methodology was used for the diversification of different naturally occurring and biologically pertinent molecules resulting into amidation product in good to excellent yields with upto 99% branched selectivity (Scheme 5). Phthalamide functionalized alkene **4a** on reaction with **2a** yielded product **5aa** in 58% yield. The reaction of cyclic monoterpene chiral (−) menthol functionalized alkene **4b** with **2a** provided amination product **5ba** in 60% yield as a mixture of diastereomers in the ratio of 1 : 0.3. Alkene functionalized with a plant-derived natural product **4c**, coumarin also reacts with **2a** resulting in amination product **5ca** with 56% yield. The essential nonsteroidal anti-inflammatory drugs (NSAIDs) used in treating inflammation are profens or 2-aryl-propionic acids such as ibuprofen, naproxen, ketoprofen, *etc.* Functionalization of these profens **4d–f** with **2a** was carried out. In this reaction, the expected products **5da–fa** were obtained in good yields of 86%, 78% and 82%, respectively. Plant growth promoter, clofibric acid functionalized alkene **4g** also reacts with sulfonamide **2a** giving expected product **5ga** in 80% yield. Furthermore, the derivative of therapeutically relevant synthetic bile acid, dehydrocholic acid, **4h** is functionalized with **2a, which** resulted in amidation product **5ha** in 75% yield.

The synthesized nosyl functionalized terminal and internal alkenes were converted into allylic amines using a thiol reagent under basic conditions (Scheme 6a). Hence, treatment of allylic sulfonamide products **3aa** and **3wa** with thioglycolic acid (8 equiv.) and lithium hydroxide (16 equiv.) in DMF yielded



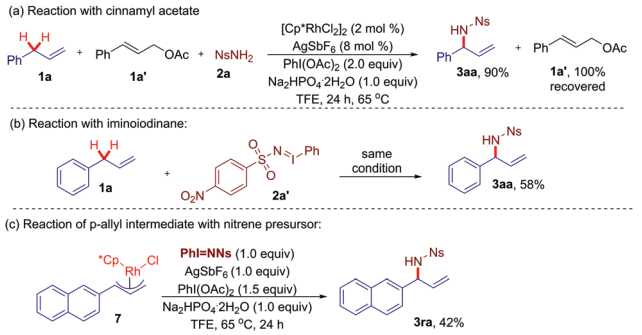
Scheme 5 Diversification of various natural and therapeutic compounds.



Scheme 6 Synthetic transformation.

allylic amines **6a–b** in good yields.[10] Furthermore, to test the applicability of the methodology, a large scale (1 mmol scale) reaction of **1a** with **2a** was carried out. In this reaction, desired product **3aa** was obtained in excellent yield of 92% (Scheme 6b).

To get a better understanding of the reaction mechanism, control experiments were carried out (Scheme 7). The reaction of allyl benzene (**1a**) with **2a** and cinnamyl acetate (**1a′**) under the optimized reaction conditions resulted in the desired amination product **3aa** along with the recovery of cinnamyl acetate (**1a′**) (Scheme 7a). It clearly indicates that the formation of cinnamyl acetate as an intermediate is not involved in the reaction. Furthermore, the reaction of **1a** with iminoiodinane **2a′** as a nitrene precursor provided the desired amination product **3aa** in 58% yield which indicates the *in situ* formation

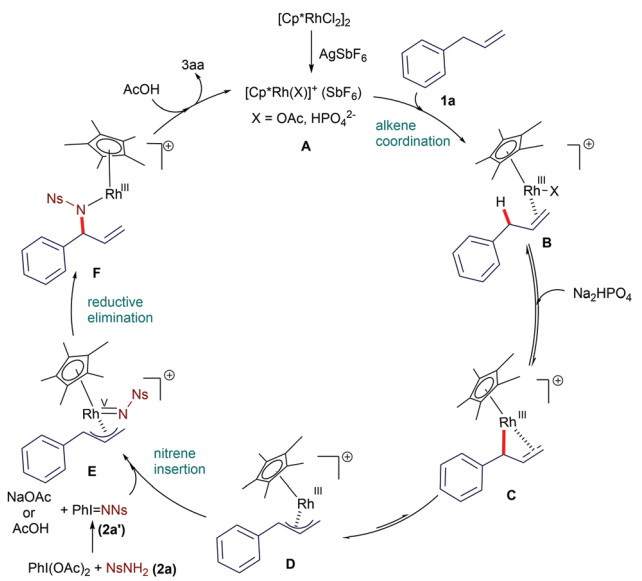


Scheme 7 Mechanistic investigation.

of iminoiodinane in the reaction medium (Scheme 7b). Furthermore, the reaction of π-allyl rhodium complex **7** with iminoiodinane **2a′** resulted in the formation of the amination product **3ra** in 42% yield (Scheme 7c) indicating the involvement of the π-allyl intermediate in the reaction.

A plausible mechanism is proposed to account for the present allylic amidation reaction, which is shown in Scheme 8. The reaction of $[Cp^*RhCl_2]_2$ with $AgSbF_6$ provides the active cationic complex $[Cp^*Rh(X)][SbF_6]$ A. The coordination of the double bond of alkene **1a** with a rhodium complex **A** gives complex **B**. The allylic C–H bonds of alkenes of complex **B** deprotonate affording σ-allyl rhodium complex **C**. Intermediate **C** undergoes allylic isomerization giving π-allyl rhodium complex **D**. Furthermore, *in situ* generated iminoiodinane **2a′** undergoes nitrene insertion, which leads to the formation of Rh(v)–nitrene complex **E**. Metal nitrene complex **E** undergoes reductive elimination which generates complex **F**. The protonation of the complex **F** forms amination product **3aa** along with the regeneration of the catalyst for the next cycle.

In conclusion, we have successfully demonstrated allylic C–H amidation of various alkenes using an Rh(III) catalyst utilizing *in situ* generated iminoiodinane as an amidation source, using an environmentally benign hypervalent iodine oxidant. The presented protocol is compatible with differently functionalized unactivated internal alkenes as well as terminal alkenes. A possible reaction mechanism involving π-allyl and metal–nitrene intermediates has been proposed and supported by mechanistic studies.



Scheme 8 Proposed mechanism.

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Conflicts of interest

There are no conflicts to declare.

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