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Ru(II)-catalyzed allenylation and sequential annulation of *N*-tosylbenzamides with propargyl alcohols†

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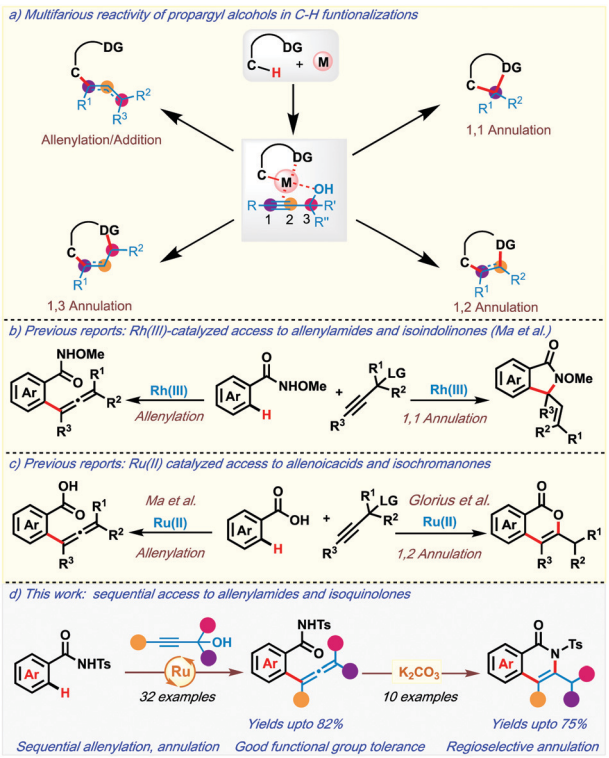
We hereby report Ru(II)-catalyzed C(sp^2)–H allenylation of *N*-tosylbenzamides to access multi-substituted allenylamides. Furthermore, the allenylamides were converted to the corresponding isoquinolone derivatives *via* base mediated annulation. The current protocol features low catalyst loading, mild reaction conditions, high functional group compatibility and desired scalability. The unique functionality of the afforded allenes allowed further transformations to expand the practicality of the protocol.

The past decade has witnessed a revolution in the field of transition-metal catalysed C–H activation, offering new disconnections in retrosynthetic analysis for accessing active pharmaceutical ingredients, natural products and functional materials.[1] The selective conversion of unreactive C–H bonds to C–C and C–X bonds has become an efficient alternative to traditional cross coupling reactions. In general, a vast majority of these C–H functionalizations rely on the use of rare and expensive Pd(II),[2] Rh(III)[3] and Ir(III)[4] complexes which often hamper their practicality. Subsequently, the desire to explore the catalytic potential of readily available inexpensive transition metals has led to the emergence of ruthenium complexes as viable catalysts for C–H functionalizations.[5] In particular, the emanation of $[RuCl_2(p\text{-cymene})]_2$ as an inexpensive alternative to Ir(III) and Rh(III) complexes has contributed enormously towards the development of economical and resourceful catalytic systems. The ability of this catalyst to chelate with weakly coordinating directing groups has translated to novel reaction outcomes.[6] Additionally, facile formation of a cyclometalated ruthenacycle *via* C–H activation along with its superior air and moisture stability has translated to the near versatility of this catalyst.

On the other hand, propargyl alcohols owing to their feedstock availability have received significant attention as coupling partners in C–H functionalization reactions.[7] The presence of three carbon centers, which react differently depending upon the nature of the metal and the directing group, give rise to their multifarious reactivity leading to 1,1-annulations, 1,2-annulations, 1,3-annulations or allenylations (Scheme 1a). Intriguingly, C–H allenylation with propargyl alcohols has emerged as a valuable tool to access functionalized allenes, which have huge synthetic potential.[8,9] At the same time, the superior reactivity of allenes adds a challenge in the presence of



Scheme 1 Overview of the work.

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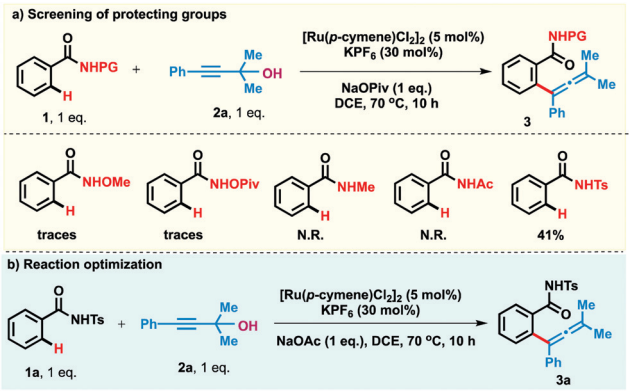
† Electronic supplementary information (ESI) available: Synthetic procedures and full characterization details of all the products (**3a–3ag**, **4a–4j**, **5–7**), spectroscopic data, NMR spectra, kinetic studies *etc.* CCDC 2072388. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc01768c

nucleophilic directing groups to culminate the reaction at the allenylation stage, avoiding the subsequent nucleophilic addition.[10] In this regard, Ma, in a landmark report, documented a Rh(III)-catalyzed C–H allenylation of amides using propargyl alcohols employing mild reaction conditions (Scheme 1b-left)[9a] averting the subsequent 1,1 annulation (Scheme 1b-right).[10a]

A vast majority of C–H activation reactions with propargyl alcohols rely on the use of expensive Rh catalysts,[7a] while in comparison only a handful of reports exist based on Ru complexes.[11] Glorius in an elegant work documented the synthesis of iso-chromanones *via* cascade C–H activation, allenylation and annulation of benzoic acids under Ru(II) catalysis (Scheme 1c-right).[12] Independently, Ma reported Ru(II)-catalyzed *ortho*-C–H activation, and allenylation of benzoic acids with propargylic alcohols to furnish allenoic acids, using mild conditions to avert the subsequent annulation as reported by Glorius (Scheme 1c-left).[13] Only a single report exists on C–H allenylation of benzamides under Ru catalysis by Ackermann *et al.* employing silyl allenes as coupling partners.[6e] Considering our interest in Ru(II)-catalyzed C–H activations,[14] we envisioned developing a Ru(II)-catalyzed C–H allenylation of benzamide derivatives using propargyl alcohols. Additionally, the obtained allenylamides could be subjected to subsequent annulation to access valuable nitrogen containing heterocycles. Consequently, we hereby report a $[RuCl_2(p\text{-cymene})]_2$ catalyzed *ortho*-C–H allenylation and sequential K_2CO_3 mediated 1, 2-annulation of *N*-tosylbenzamides with propargyl alcohols to access diversely substituted allenylamides and isoquinolones (Scheme 1d).

The nature of the protecting group on the amide group is quite detrimental for coordination with the metal and the subsequent cyclometalation. Hence, we initiated our studies by exploring a suitable protecting group for deliberating a Ru(II)-catalyzed C–H allenylation (Table 1a). No product formation was observed when *N*-methoxybenzamide was reacted with propargyl alcohol **2a** using $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in DCE. Further studies with different protecting groups like –OPiv, –Ac and –Me also failed to deliver the envisioned allenylation. At this juncture, we postulated that a protecting group that could make the amide more acidic would facilitate the process of carboruthenation. Furthermore, the low nucleophilicity of the amide nitrogen would impede the subsequent undesired nucleophilic addition onto the allene. Consequently, we screened the reactivity of *N*-tosylbenzamide and were delighted to observe the formation of allenylamide **3a** in 41% yield. Motivated by these initial results, we then proceeded to optimize the reaction. After the rigorous screening of various reaction parameters, we arrived at the following optimized conditions (Table 1b): **1a** (1 equiv.) with **2a** (1 equiv.) in the presence of 5 mol% $[RuCl_2(p\text{-cymene})]_2$, 30 mol% KPF_6 and 1 equiv. NaOAc in DCE at 70 °C for 10 h delivered 82% of the allene **3a** (entry 2). Other bases like Na_2CO_3, $NaHCO_3$, KOAc and CsOAc were found to be inferior (entry 3). The reaction does not proceed in the absence of either the catalyst or the additive KPF_6 indicating their key role in the formation of the

Table 1 Screening the directing groups and reaction optimization



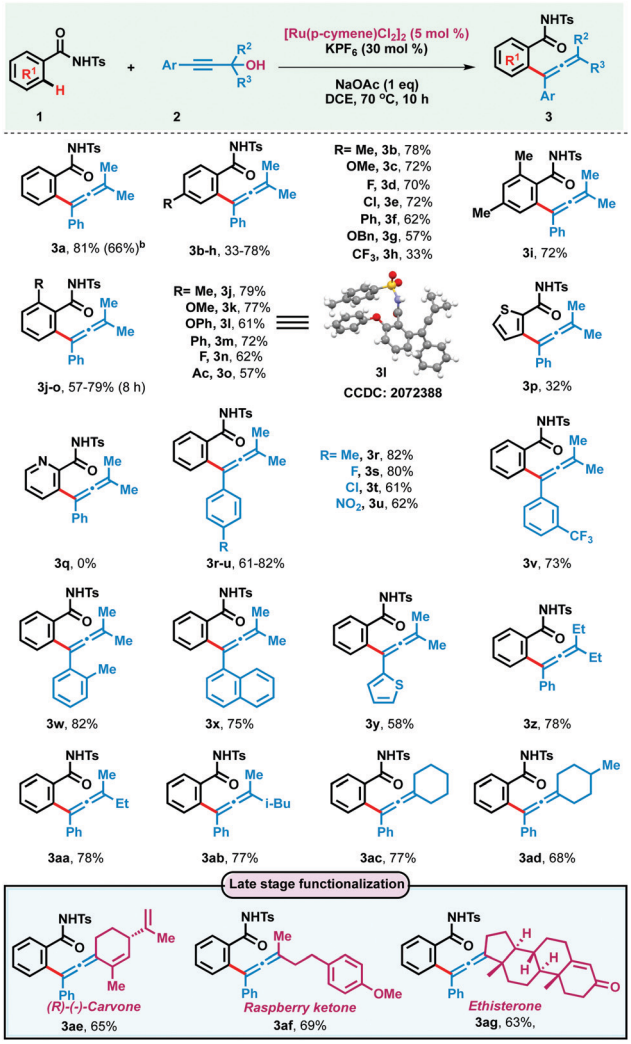
Entry	Variation from standard conditions	Yields[a] (%)
1	NaOPiv as base	45 (41)
2	None	82 (81)
3	Na_2CO_3, $NaHCO_3$, KOAc or CsOAc as base	<67
4	Without Ru(II) catalyst	Traces
5	Without KPF_6	Traces
6	Toulene, MeCN, DCM or 1,4-dioxane as solvent	<62
7	Reaction at 60 °C	63
8	Reaction at 90 °C	70
9	30 mol% of NaOAc	39

[a] NMR yields calculated using 1,3,5-trimethoxybenzene as internal standard. Isolated yields in parentheses.

product (entries 4 and 5). Other solvents like toluene, MeCN, DCM or 1,4-dioxane instead of DCE were found to be deleterious (entry 6). Decreasing or increasing the temperature of the reaction leads to diminished yields of the allenylated product **3a** (entries 7 and 8). The use of a sub-stoichiometric quantity of the base also leads to diminished yields (entry 9).

With the optimized conditions in hand, we proceeded to probe the substrate scope of the allenylation protocol. The reactivity with an array of substituted *N*-tosylbenzamides **1** was studied with alkyne **2a** (Table 2). Delectably, electron-donating (Me, OMe, OBn) as well as electron-withdrawing (CF_3, F, Cl and Ph) groups were well tolerated at the *para* position of the benzamide, furnishing the corresponding allenes **3b–3h** in good yields. 2,4-Dimethylbenzamide afforded the corresponding allene **3i** in 72% yield. Substitutions at the *ortho*-position of the benzamide furnished the products **3j–3o** in good yields of up to 79%. The structure of C-2 allenylated benzamide was confirmed by performing single crystal X-ray diffraction studies of **3l**. While 2-thiophene carboxamide yielded the product **3p** in 32% yield, 2-pyridyl carboxamide failed to provide the corresponding product **3q** probably due to the chelation with the metal catalyst and rendering the catalytic complex inactive. Next, the scope of various substituted propargyl alcohols was probed with benzamide **1a**. Diverse substitutions on the phenyl ring of the propargylic alcohol were well tolerated to afford the corresponding allenes **3r–3w** in good yields (61–82%). Naphthyl and 2-thiophenyl substituted propargyl alcohols were also found to be suitable for providing **3x** and **3y** in 75% and 58% yields, respectively. Diversification of the aliphatic groups on the carbon 3 of the allene was

Table 2 Scope of C-2 allenylation[a]

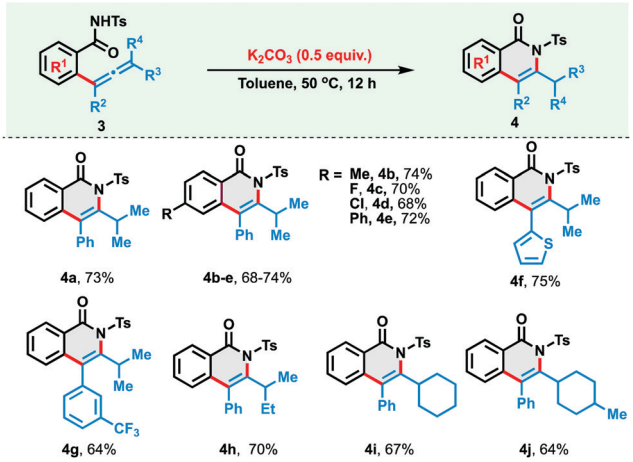


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), KPF_6 (30 mol%), NaOAc (0.2 mmol), DCE (1 mL), 70 °C for 10 h. [b] Reaction performed with 1.0 g of **1a**.

compatible as the corresponding products **3z–3ad** were obtained in good yields 68–78%. To our delight, the current protocol also allowed for the late stage modification of natural products like *R*-(−)-carvone, raspberry ketone and ethisterone to the corresponding allene derivatives **3ae**-**3ag** in good yields. Additionally, when 1 g of the amide **1a** was reacted with 0.838 g of alkyne **2a** under our standard conditions, 1.29 g of the allene **3a** was obtained in 66% yield.

Delectably, allenes **3** could be effortlessly converted into the corresponding isoquinolone derivatives **4** under basic conditions leading to formal 1,2-annulation products (Table 3). Allene **3a** on treatment with 0.5 equiv. of K_2CO_3 in toluene furnished **4a** in 73% yield. With these results in hand, we probed the scope of this transformation employing allenylamides **3** bearing diverse substituents on both the amide fragment as well as on the allene moiety. A variety of structurally diversely functionalized isoquinolones **4b–4j**,

Table 3 Base mediated annulation[a]

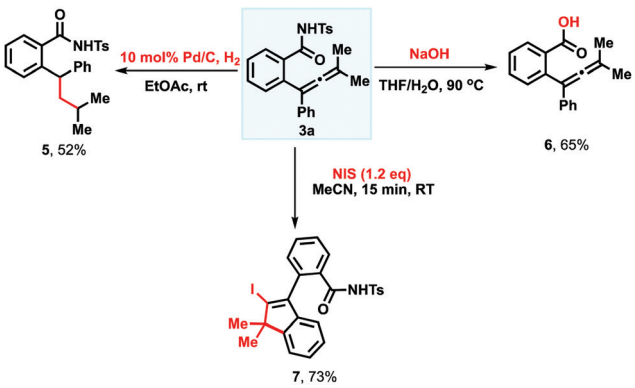


[a] Reaction conditions: **3** (0.15 mmol), K_2CO_3 (0.075 mmol), toluene (0.75 mL), 50 °C for 12 h.

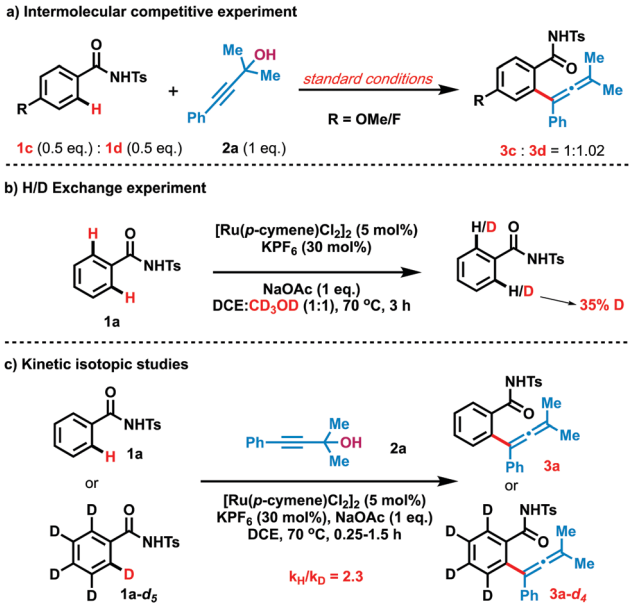
having substituents at various positions were obtained in moderate to good yields 64–75%.

Subsequently, we carried out further functionalizations to probe the synthetic utility of C-2 allenylated benzamide **3a** (Scheme 2). Allene **3a** on catalytic hydrogenation delivered the alkane derivative **5** in 52%. Allenoic acid **6** was obtained in 65% yield under base mediated hydrolysis. Interestingly, when the allenylated product **3a** was treated with *N*-iodosuccinimide,[15] a chemoselective iodocarbocyclization was observed resulting in the formation of the substituted 2-iodoindene **7** in 73% yield.

An intermolecular competition experiment between electronically variant *p*-substituted benzamides **1c** and **1d** with propargyl alcohol **2a** (Scheme 3a) was carried out and no notable preference was observed for the formation of **3c** or **3d**. This indicated that C–H activation might proceed *via* concerted-metalation-deprotonation pathway. A substantial amount of deuterium incorporation (35%) was observed at the *ortho*-position of benzamide **1a** when subjected to standard conditions with MeOH-*d4* in the absence of **2a** (Scheme 3b). This indicates that alkyne insertion is preceded by reversible coordination and C–H activation. Kinetic isotopic studies



Scheme 2 Synthetic utility of **3a**.



Scheme 3 Mechanistic studies.

(Scheme 3c) depict a mild k_H/k_D ratio of 2.3 indicating that C–H activation might be involved in the rate-determining step of the reaction.[16]

Based on the above experimental observations and preceding literature, we propose the following plausible mechanism (see Supporting Information). The nitrogen atom of benzamide **1** coordinates with ruthenium catalyst **I** and undergoes *ortho*-metalation to form a five-membered ruthenacycle intermediate **II**, which coordinates with the propargyl alcohol **2** to generate intermediate **III**. A subsequent regioselective migratory insertion of the alkyne onto the Ru–carbon bond of **III** gives seven-membered metallacycle intermediate **IV**. β-Hydroxy elimination from intermediate **IV** then affords the *ortho*-allenylated benzamide **3a** and the ruthenium hydroxy species which undergoes water elimination regenerating the active catalyst **I**.

In summary, we have successfully demonstrated C–H bond allenylation of benzamides with propargyl alcohols using a readily available ruthenium catalyst. Furthermore, the afforded allenylamides could be conveniently converted to the corresponding isoquinolone derivatives under basic conditions. In addition, the high functional group tolerance, scalability and synthetic utility of the developed protocol along with the mechanistic insights emphasized the application of such types of catalytic transformations. The formation of water as the sole byproduct adds to the value of the protocol from a sustainability point of view.

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Conflicts of interest

There are no conflicts to declare.

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