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C–H Activation |*Hot Paper*|

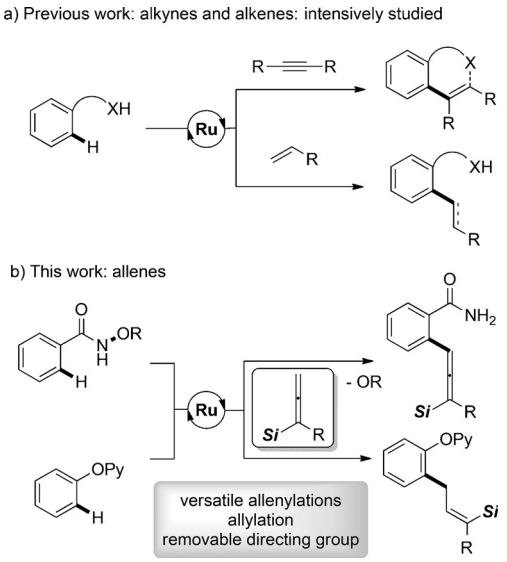
Ruthenium(II)-Catalyzed C–H Functionalizations with Allenes: Versatile Allenylations and Allylations

Sachiyo Nakanowatari and Lutz Ackermann*[a]

Abstract: Ruthenium(II)-catalyzed direct C–H functionalization of aromatic compounds with allenes was achieved under exceedingly mild reaction conditions to yield trisubstituted allenes. The reactions of *N*-methoxybenzamides proceeded smoothly in an isohypsic fashion at ambient temperature with high chemo- and regioselectivity, thereby providing a versatile means of accessing trisubstituted allenes. Detailed mechanistic studies were suggestive of a kinetically relevant C–H metalation step, which occurs by the assistance of a carboxylate moiety; this also set the stage for unprecedented C–H allylations with removable directing groups in a step-economical fashion.

Introduction

During the last decades, allenes have attracted the interest of many chemists due to their unique structural and electronic features. The allene moiety is present in a number of natural products, pharmaceutical compounds, and materials;[1–3] furthermore, allenes are particularly valuable precursors[4] in organic synthesis.[5] However, despite their importance, the use of allenes in the field of the transition-metal-catalyzed C–H activation[6] is underdeveloped, whereas alkynes and alkenes have been actively studied for catalytic C–H functionalizations.[7] Indeed, achieving chemo-, regio-, and diastereoselectivity[8] in C–H functionalizations with allenes is particularly difficult. An early example of C–H functionalization with allenes was reported by Krische in 2009, in which a cationic iridium catalyst was used to yield allylated arenes.[9] Thereafter, the use of allenes in tandem cyclizations,[10] annulations,[11] allylations,[12] dienylations,[13] and allenylations[14] has been developed through aromatic C–H bond activation by exploiting rhodium, rhenium, or palladium catalysis. However, to the best of our knowledge, an economically favorable[15] ruthenium-catalyzed C–H functionalization[16] with allenes has so far proven to be elusive. Within our research on sustainable C–H activation,[17] we now report a novel ruthenium(II)-catalyzed C–H functionalization with *gem*-disubstituted allenylsilanes to achieve aromatic C–H allenylation as well as an unprecedented allylation of an aromatic compound with a removable directing group (Scheme 1).



Scheme 1. Ruthenium(II)-catalyzed C–H functionalization by insertion into unsaturated C–C bonds.

Results and Discussion

Optimization studies

We commenced our studies on the envisioned ruthenium-catalyzed C–H bond functionalization with allenes by probing various Lewis basic directing groups. We selected the *gem*-disubstituted silylallene **2a** with the expectation that allenes would preferentially react at the terminal position due to the steric repulsion between the substituents on the allene and the ruthenium complex, thereby ensuring a predictable regioselectivity.[9,11h,12,14] Also, we expected that the silyl substituents would enhance the inherent reactivity of the allenes. To our delight, we found that ruthenium complexes were indeed capable of catalyzing the desired allenylation reaction[14] of *N*-methoxybenzamide (**1a**) by an isohypsic C–H functionalization strategy

[a] *S. Nakanowatari, Prof. Dr. L. Ackermann*
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
E-mail: Lutz.Ackermann@chemie.uni-goettingen.de

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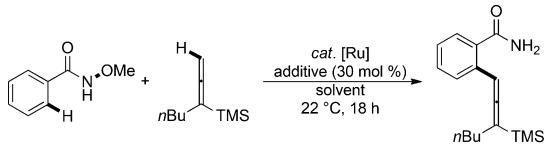
Table 1. Optimization of C–H bond allenylation of amide **1a**.[a]

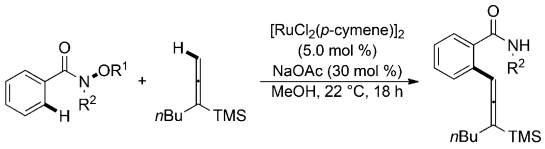


1a **2a** **3aa**

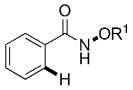
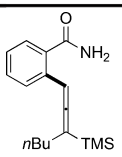
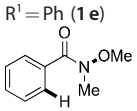
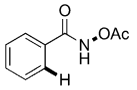
Entry	[Ru]	Additive	Solvent	Yield [%]
1	$RuCl_3·(H_2O)_n$	NaOAc	MeOH	–
2	$[Cp^*RuCl_2]_n$	NaOAc	MeOH	26
3	$[RuCl_2(benzene)]_2$	NaOAc	MeOH	58
4	$[RuBr_2(p\text{-cymene})]_2$	NaOAc	MeOH	52
5	**$[RuCl_2(p\text{-cymene})]_2$**	**NaOAc**	**MeOH**	**75**
6	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	MeOH	77[b]
7	$[Ru(OAc)_2(p\text{-cymene})]$	–	MeOH	24
8	$[Ru(OAc)_2(p\text{-cymene})]$	NaOAc	MeOH	41
9	$[Ru(OAc)_2(p\text{-cymene})]$	KCl	MeOH	46
10	$[RuCl(OAc)(p\text{-cymene})]$	–	MeOH	–
11	$[RuCl(OAc)(p\text{-cymene})]$	NaOAc	MeOH	65
12	$[RuCl_2(p\text{-cymene})]_2$	–	MeOH	3[c]
13	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	MeOH/H_2O (20:1)	75
14	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	DCE	34
15	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	PhMe	5[c]
16	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	MeOH	56[d]
17	–	NaOAc	MeOH	–

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.53 mmol), [Ru] (10 mol%), additive (30 mol%), solvent (3.0 mL), 22 °C, 18 h, under N_2, yields of isolated products. [b] With 0.75 mmol of allene **2a**. [c] Conversion determined by ^1H NMR spectroscopy with CH_2Br_2 as the internal standard. [d] At 0 °C.

Table 2. Influence of the amide **1** substitution pattern.[a]



1 **2a** **3**

Entry	**1**	Yield of **3** [%]
	 **1**	 **3aa**
1	R^1 = Me (**1a**)	**3aa**: 75
2	R^1 = Et (**1b**)	**3aa**: 71
3	R^1 = *i*Pr (**1c**)	**3aa**: 8[b]
4	R^1 = *t*Bu (**1d**)	–
5	R^1 = Bn (**1f**)	**3aa**: 18[b]
6	R^1 = Ph (**1e**)	**3aa**: 5[b]
7	 **1g**	–
8	 **1h**	–

[a] Reaction conditions: **1** (0.50 mmol), **2a** (0.53 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol%), NaOAc (30 mol%), MeOH (3.0 mL), 22 °C, 18 h, under N_2, yields of isolated products. [b] Conversion determined by ^1H NMR spectroscopy with CH_2Br_2 as the internal standard.

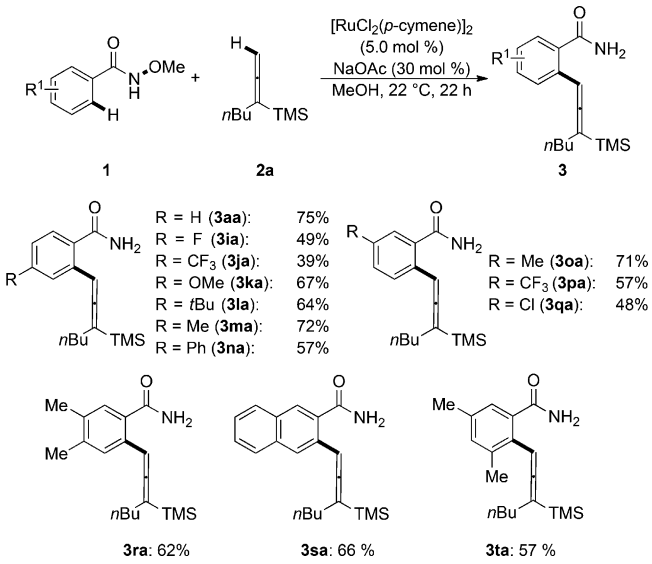
(Table 1 and Tables SI1 and SI2, Supporting Information).[18] Among a set of representative ruthenium complexes, $[RuCl_2(p\text{-cymene})]_2$ catalyzed the reaction to deliver the desired product **3aa** in the highest yield (Table 1, entries 1–5). The well-defined ruthenium(II) biscarboxylate complex $[Ru(OAc)_2(p\text{-cymene})]$[19] delivered a moderate yield of product **3aa**, even when NaOAc or KCl[20] were used as additives (entries 7–9). $[RuCl(OAc)(p\text{-cymene})]$[21] did not furnish the desired product **3aa**, but the catalytic activity could be restored through the addition of NaOAc (entries 10 and 11). After testing a variety of cocatalytic additives and solvents, we found that acetates and protic solvents proved to be superior, and optimal results were obtained with NaOAc and MeOH (entries 12–15). The reaction proceeded smoothly under exceedingly mild reaction conditions of 22 °C;[22] in fact, the catalyst was also operative at 0 °C (entry 16). In the absence of a ruthenium complex, the substrates **1a** and **2a** did not react (entry 17).

Subsequently, we examined the influence of the substituents on the *N*-alkoxyl moiety (Table 2). *N*-Methoxy- and *N*-ethoxy-substituted amides **1a** and **1b** reacted with comparable conversion (Table 2, entries 1 and 2). Amides with a more hindered benzyl or *iso*-propyl group reacted sluggishly (entries 3 and 5), and substrates with phenyl or *tert*-butyl groups did not participate in the C–H activation reaction (entries 4 and 6), probably due to unfavourable steric interactions. Similarly, no conversion was observed with the tertiary Weinreb benzamide (**1g**, entry 7), which suggests that the coordination by an anionic amide is essential. The amides that bear other potential leaving groups, such as acetyl (entry 8), pivaloyl, *tert*-butyloxycarbonyl, or benzoyl substituents, were found to be ineffective.

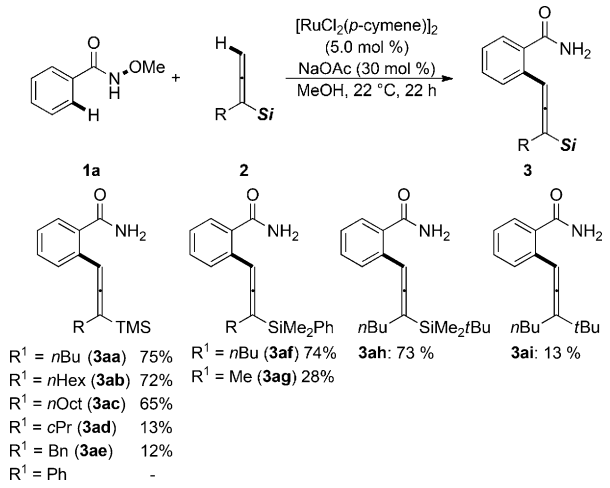
Substrate scope

To evaluate the versatility of the ruthenium(II)-catalyzed process, the optimized reaction conditions were applied to variously substituted *N*-methoxybenzamides **1i–t** (Scheme 2). Accordingly, high yields of the desired allenylated products **3ia–na** were obtained with electron-rich substituents, whereas electron-deficient aromatic compounds **1** proved to be more challenging. Amides with *meta*-methyl, *meta*-trifluoromethyl, or *meta*-chloro substituents (**1o–q**) furnished a single isomer through the functionalization at the less sterically encumbered C–H bond. The disubstituted amide **1r** and the naphthoic amide **1s** also underwent the C–H functionalization process with excellent site-selectivity. Notably, the hindered di-*meta*-substituted aromatic compound **1t** delivered the desired product **3ta** with high catalytic efficacy.

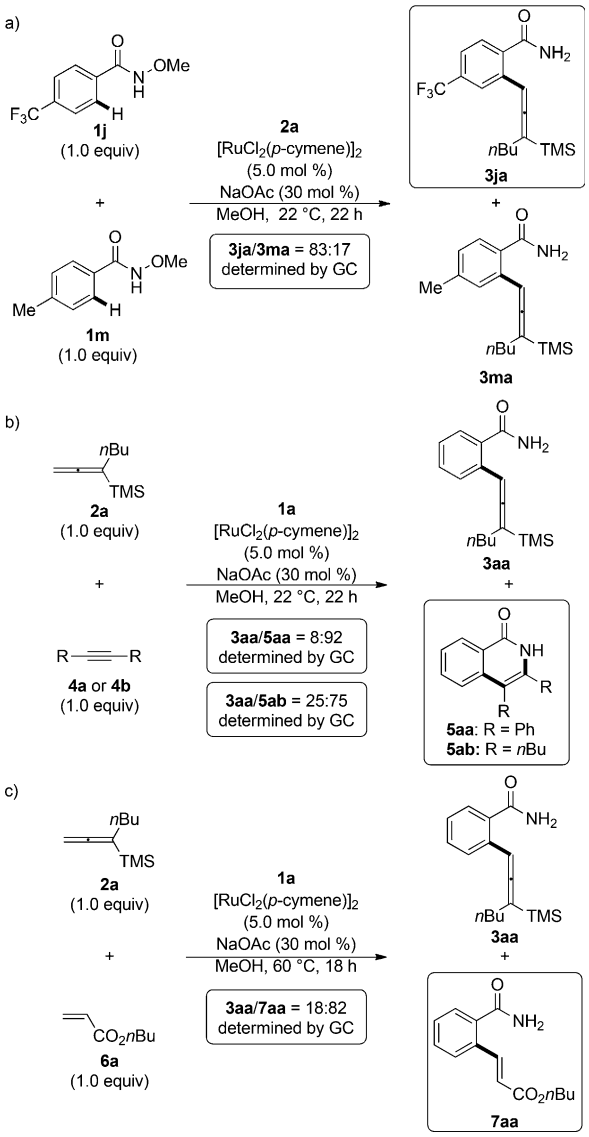
Subsequently, differently decorated allenes **2b–i** were subjected to the optimized reaction conditions (Scheme 3). Under the mild reaction conditions, a variety of silylated *gem*-disubstituted allenes reacted to give products **3ab–ai**, despite the bulk of the silyl groups. We observed that the reactivity of the allenes was strongly influenced by the substituents on the



Scheme 2. Scope of ruthenium(II)-catalyzed allenylation: *N*-methoxyarylamides **1**.



Scheme 3. Scope of ruthenium(II)-catalyzed allenylation: allenes **2**.



Scheme 4. Intermolecular competition experiments.

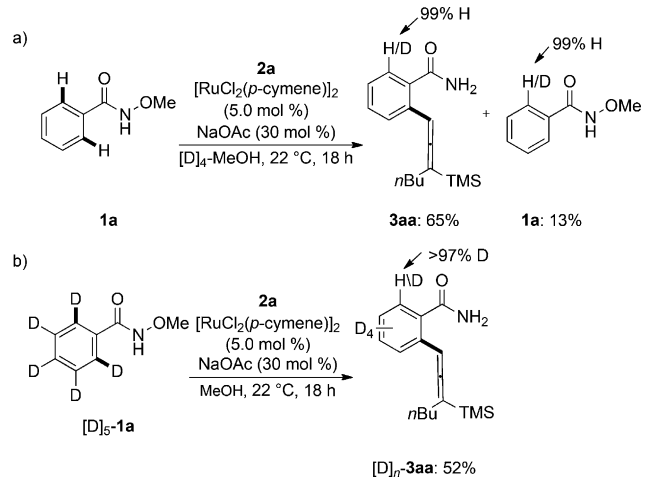
allene. Allenes **2b**, **2c**, **2f**, and **2h** reacted to give the desired products **3ab**, **3ac**, **3af**, and **3ah** in high yields, whereas allene substrates **2** that contained methyl, cyclopropyl, benzyl, or phenyl groups reacted rather sluggishly. Monosubstituted allenes furnished less satisfactory results.[23]

Mechanistic studies

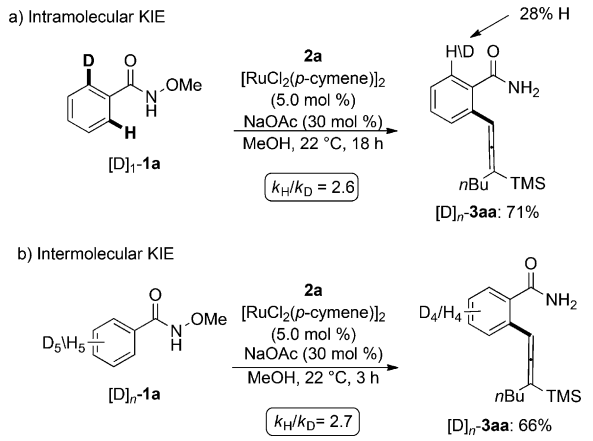
Given the unique regio- and site-selectivity features of our ruthenium(II) catalyst, we sought to delineate its mode of action. To this end, we performed intermolecular competition experiments. When a mixture of amides **1j** and **1m** was exposed to the ruthenium-catalyzed allenylation conditions, we observed that the more electron-poor benzamide **1j** reacted preferentially, which could be rationalized in terms of the higher kinetic acidity of the C–H bond in benzamide **1j** (Scheme 4a). Competition experiments between allene **2a** and phenyl- or butyl-disubstituted alkynes **4a** or **b**, as well as alkene **6a** reflected the challenges that are associated with C–H functionalizations using allenes **2**, such that the alkyne or alkene reacted preferentially over the allene (Scheme 4b and c).

To further corroborate the reaction mechanism, a set of experiments with isotopically labeled compounds were conducted (Scheme 5 and 6). In reactions that were carried out in deuterated solvent [D_4]MeOH or with isotopically labeled substrate [D_5]**1a**, we did not observe an H/D exchange, which is suggestive of an irreversible C–H bond metalation step. In agreement with these findings, intra- and intermolecular kinetic isotope effects (KIE) were determined to be 2.6 and 2.7, respectively. KIEs of this magnitude were indicative[24] of a kinetically relevant C–H ruthenation step.

On the basis of our mechanistic studies, we propose that the ruthenium(II)-catalyzed C–H functionalization with allenes

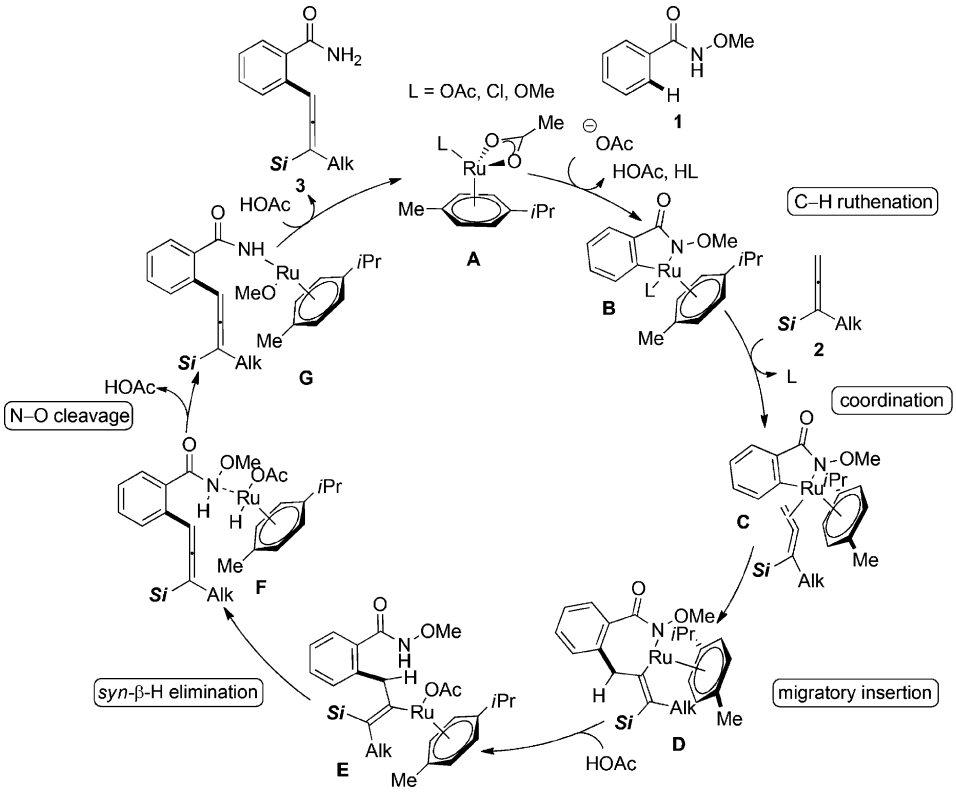


Scheme 5. Ruthenium(II)-catalyzed allenylation with isotopically labeled compounds.



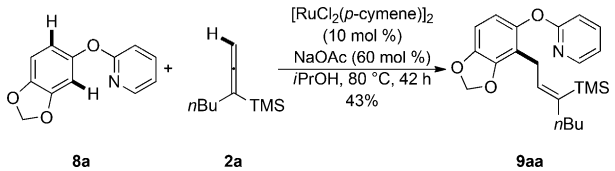
Scheme 6. Kinetic isotope effect (KIE) study.

2 is initiated through the coordination of acetate complex **A** with the nitrogen of benzamide **1**, which is followed by a kinetically relevant, carboxylate-assisted[25] C–H metalation to form ruthenacycle **B** (Scheme 7). After the isohypsic C–H activation, intermediate **B** is coordinated by allene **2** (intermediate **C**);[26] subsequent migratory insertion yields the 7-membered intermediate **D**, which undergoes protonation (intermediate **E**) followed by *syn*-β-H elimination to give intermediate **F**. Thereafter, oxidative insertion of the N–O bond in intermediate **F** leads to intermediate **G**, which is protonated to allow liberation of the product **3** and regenerates the active ruthenium(II) catalyst **A**.



Scheme 7. Proposed catalytic cycle.

Finally, we were pleased to find that the ruthenium(II) catalyst $[RuCl_2(p\text{-cymene})]_2$ was not limited to oxidative allenylation reactions, but it also proved applicable for hydroarylations of allene **2a** with 2-phenoxypyridine[27] **8a**, which contains a removable directing group (Scheme 8). Preliminary optimization studies showed that the use of *i*PrOH as the solvent was beneficial for a highly regio- and site-selective allylation of phenol derivative **8a**.



Scheme 8. Ruthenium(II)-catalyzed hydroarylation with allene **2a**.

Conclusion

We have developed the unprecedented ruthenium(II)-catalyzed intermolecular direct arene functionalization reaction with al-

lenes through C–H activation. The key to the success of these reactions was the use of a highly active ruthenium(II) carboxylate catalyst, which set the stage for direct C–H functionalizations under exceedingly mild reaction conditions. With *N*-methoxybenzamides, the direct allenylation occurred in an isohypsic fashion at ambient temperature with high regioselectivity and functional group tolerance. Mechanistic studies were supportive of a kinetically relevant carboxylate-assisted C–H ruthenation step. The broadly applicable ruthenium(II) catalyst also enabled an unprecedented C–H allylation of an aromatic compound that contained a removable directing group.

Experimental Section

Representative procedure for ruthenium(II)-catalyzed C–H functionalization of benzamides with allenylsilanes

$[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol%), NaOAc (12.3 mg, 30 mol%), *N*-methoxybenzamide (**1a**, 75.5 mg, 0.50 mmol), MeOH (3.0 mL), and allene **2a** (89 mg, 0.53 mmol) were placed into a 25 mL Schlenk tube that was equipped with a septum and placed under N_2. The reaction mixture was stirred at 22 °C for 22 h. After evaporation of the solvents and the unreacted allene in vacuo, the crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 8:1) to afford the desired product **3aa**.

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Keywords: allenes · allenylation · amides · C–H Activation · ruthenium

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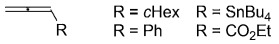

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