ChemPubSoc Europe

DOI: 10.1002/ejoc.201501551

EurJOC European Journal of Organic Chemistry

Communication

Organic Methodology

Rh^{III}-Catalyzed C–H Allylation of Amides and Domino Cycling Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones with *N*-Bromosuccinimide

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Abstract: A Rh^{III}-catalyzed C–H allylation of electron-deficient arenes, heteroarenes, and alkenes at room temperature was developed with allyl bromide. The reaction was carried out in diethyl ether without dehydration, and C–H activation was assisted by the directing anionic nitrogen of the aniline-derived amide. Following the allylation, a domino cycling synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones with *N*-bromosuccinimide (NBS) through intramolecular aminobromination of the introduced double bond was achieved.

Introduction

The allyl group is one of the prominent structural motifs in many bioactive natural products,[1] and allylic intermediates can be conveniently transformed to other functionalized products.[2] Therefore, allylation of organic compounds has attracted much attention. For instance, the classic Claisen rearrangement of allyl, aroyl, or acrylate esters[3] and Friedel–Crafts allylation of electron-rich arenes[4] are useful in rapidly accessing a variety of allylarenes. However, poor regio- and stereoselectivity, low yield, harsh conditions, and narrow substrate scope have limited the application of these reactions. In order to avoid these deficiencies, transition-metal-catalyzed allylation has been developed, including decarboxylative allylation,[5] preactivated C–C cross coupling,[6] and, the most attractive, direct C–H allylation. In the cases of electron-deficient arenes such as polyfluoroarenes, allylation can be performed by Pd or Cu catalysis with the assistance of a base,[7] otherwise, directing groups have to be used. The directing-group-assisted C–H allylation can expand to a wider range of arenes as well as olefins. The reaction consists of three basic protocols: (1) allene insertion into the C–M bond;[8] (2) C–C coupling with α or γ selectivity;[9–11] (3) β-LG (LG: leaving group) elimination following olefin insertion[12] with γ-selectivity.[13–17] However, these protocols have several drawbacks. For instance, all the reported reactions have been performed in anhydrous solvents, and very few can be conducted at room temperature. Furthermore, only three examples are applicable to both arenes and olefins.[8a,9,13d] In the case of the third protocol mentioned above, allyl halides are no longer the appropriate allyl electrophiles because of either low activity[7b,7c,13a,14] or severe α-olefination isomerization.[18,19]

We have developed a new allylation. It can be conducted at room temperature with commercial solvents and is also applicable to both aroyl- and acrylamide substrates. Moreover, the allyl sources are not restricted to carbonates, esters, or alcohols, but allyl halides can also be used.

Aminohalogenation of olefins is one of the most fundamental and useful reactions in organic chemistry,[20] which can produce versatile building blocks for chemical synthesis, in particular in the preparation of drugs,[21] and the domino cycling synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones through intramolecular aminobromination of the corresponding allyl products was achieved without extra catalyst.

Results and Discussion

We started by examining the reaction between *N*-(3,4,5-trimethoxyphenyl)benzamide (**1a**) and allyl bromide (**2a**). C–H activation selectively occurred at the *ortho* position of the aroyl ring, and allylation product **3a** was isolated. No byproducts derived from β-H elimination or α-olefination isomerization of **3a** were detected. The influence of different catalysts was evaluated, and $[Cp^*RhCl_2]_2$ showed the best activity with a yield of 45 % when AgOAc in acetonitrile was added (Table 1, entries 1–4). Next, a range of solvents were screened: diethyl ether was the best with a yield of 73 % for **3a** (Table 1, entry 9). Silver salts (Table 1, entries 9–13) were also examined, and those with non-coordinating anions showed no activity, which indicates the importance of the coordination effect of the anion. To our surprise, raising the temperature to 40 °C led to a lower yield of **3a** (50 %) (Table 1, entry 14), and using an anhydrous solvent did not improve the yield (Table 1, entry 15). Moreover, oxygen did not retard the reaction (Table 1, entry 16). We tested both the steric and electronic effects of anilines (Table 1, entry 17–20), and **1a** seemed to produce the best yield.

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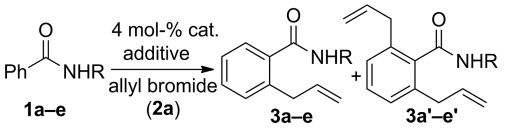
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201501551.

Table 1. Optimization of the reaction conditions.[a,b]

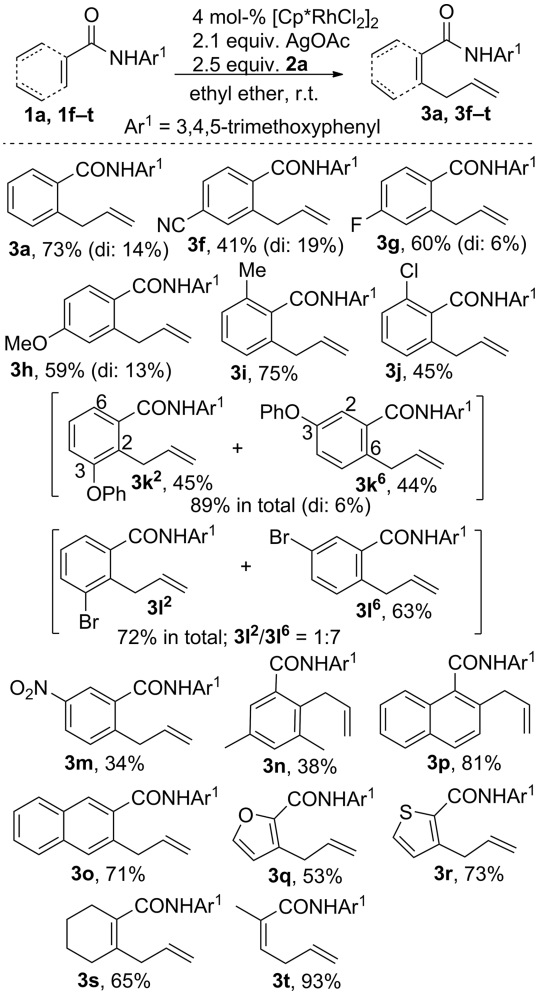


Entry	Catalyst R = Ar^1 = 3,4,5-trimethoxyphenyl, **1a**	Additive	Solvent	Yield (%) **3**	 **3′**
1	$[Cp^*RhCl_2]_2$	AgOAc	MeCN	45	6
2	$[Cp^*IrCl_2]_2$	AgOAc	MeCN	<10	–
3	$[(p\text{-cymene})RuCl_2]_2$	AgOAc	MeCN	–	–
4	$PdCl_2$	AgOAc	MeCN	–	–
5	$[Cp^*RhCl_2]_2$	AgOAc	MeOH	14	7
6	$[Cp^*RhCl_2]_2$	AgOAc	THF	56	8
7	$[Cp^*RhCl_2]_2$	AgOAc	PhMe	15	–
8	$[Cp^*RhCl_2]_2$	AgOAc	DCE	12	–
9	$[Cp^*RhCl_2]_2$	AgOAc	Ether	73	14
10	$[Cp^*RhCl_2]_2$	AgOBz	Ether	51	13
11	$[Cp^*RhCl_2]_2$	AgOTf	Ether	43	–
12	$[Cp^*RhCl_2]_2$	$AgBF_4$	Ether	<10	–
13	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Ether	–	–
14[c]	$[Cp^*RhCl_2]_2$	AgOAc	Ether	50	10
15[d]	$[Cp^*RhCl_2]_2$	AgOAc	Ether	66	13
16[e]	$[Cp^*RhCl_2]_2$	AgOAc	Ether	69	14
	R				
17[f]	Phenyl, **1b**			59	13
18[f]	2,4,6-trimethylphenyl, **1c**			–	–
19[f]	4-methylphenyl, **1d**			61	10
20[f]	4-fluorophenyl, **1e**			53	11

[a] Unless otherwise noted, the reactions were carried out at room temperature with **1a**–**e** (0.2 mmol, 1 equiv.), **2a** (42 μL, 2.5 equiv.), additive (2.1 equiv.), and catalyst (4 mol-%) in solvent (5 mL) for 12 h. [b] Isolated yield. [c] 40 °C. [d] Anhydrous solvent. [e] No O_2. [f] The same conditions as those for entry 9.

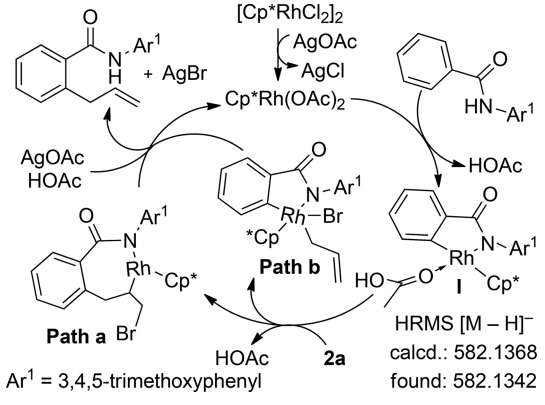
Furthermore, we explored the influence of various allyl sources (allyl halides **2a**–**c**, esters **2d**–**h**, and carbonate **2i**; see Table S1). The tested allyl electrophiles were all active, and allyl iodide **2b** gave the best result with a yield of 77 %. Noticeably, allyl halides are not suitable for the previously published metal-catalyzed C–H allylation, except for some C_{sp2}–C_{sp3} coupled examples[11] and organometallic reagents,[22] as they suffer from either low activity[7b,7c,13a,14] or severe α-olefination isomerization.[18,19] The yield of our reaction was affected by both the coordinating and the leaving abilities of the functional groups in the allyl electrophiles. Since **2a** can lead to a higher yield than that achieved with allyl acetate (**2d**), it most likely performs allylation directly, rather than forming an allyl ester intermediate. In view of both the availability and price of allyl halides, **2a** was chosen as the allyl electrophile, despite the higher yield with **2b**. Thus, the following optimized conditions were chosen: diethyl ether as solvent, room temperature, 4 mol-% $[Cp^*RhCl_2]_2$ as catalyst, and 2.1 equiv. AgOAc as additive.

With the optimized reaction conditions in hand, the scope and limitations of the reaction with respect to amides were investigated (Scheme 1). Gratifyingly, this reaction enabled the selective *ortho*-allylation of various benzamides to generate the corresponding products in yields from 34 % to 93 %. Notably, the reaction can tolerate different substituents on the starting benzamides such as methoxy, halogen, cyano, and nitro. And these groups could be subjected to further chemical transformations. However, electron-withdrawing groups seemed to retard the reaction, especially the nitro group (34 %). In addition, the lower yield (38 %) of **3n** indicated the effect of steric hindrance. For substrate **1l** containing an electron-withdrawing group at the 3-position, the allylation preferred the 6-position relative to the 2-position. But for **1m**, the substitution was only observed at the 6-position because of the stronger electron-withdrawing ability of the nitro group. However, the allylation of **1k** showed no regioselectivity. This indicates the role of the electronic effect. It is noteworthy that moderate yields were obtained for heterocycles such as furan and thiophene. Moreover, this reaction is also suitable for acrylamides that lead to the corresponding 1,4-diene skeletons in high yields. No by-products, such as conjugated alkene moieties, were isolated.



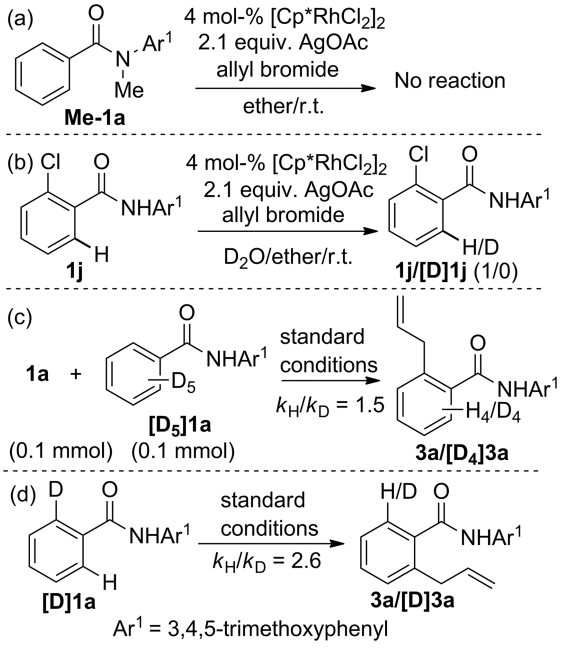
Scheme 1. Reaction scope of amides. General conditions: The reactions were carried out at room temperature using **1a** and **1f**–**t** (0.4 mmol), **2a** (84 μL, 2.5 equiv.), AgOAc (140.2 mg, 2.1 equiv.), and $[Cp^*RhCl_2]_2$ (9.9 mg, 4 mol-%) in Et_2O (10 mL) for 12 h. Isolated yield. "**3a**, 73 % (di, 14 %)" means the isolated yield of the monoallylated product **3a** is 73 % and the ^1H NMR spectroscopic yield of diallylated product is 14 %. The diallylated products of **1l**–**n** and **1o** were not observed. The ratio of $\mathbf{3l^2}$ to $\mathbf{3l^6}$ was determined by ^1H NMR spectroscopy.

A possible mechanism for the allylation of aroyl- and acrylamides by allyl bromide is proposed in Scheme 2 on the basis of control experiments and the detected intermediates. The catalytic cycle is initiated by amide-directed *ortho*-C–H activation to form intermediate **I**, which carries a five-membered metallic ring. The directing group is most likely an anionic nitrogen, as **Me-1a** showed no activity under the same conditions [Scheme 3(a)]. Furthermore, the formation of **I** is irreversible, since no deuterated **1j** was isolated when D_2O was added [Scheme 3(b)]. The structure of **I** is supported by its ESI-HRMS data (with molecular peak at $[M - H]^-$, m/z = 582.1342) and ^1H NMR spectroscopic data (showing the loss of the NH hydrogen and only four hydrogen atoms on the aroyl ring; see Figure S1 in the Supporting Information). Additionally, C–H activation might be the rate-determining step of the reaction, as the intermolecular deuterium isotopic effect was observed to be 1.5 [Scheme 3(c)] and the intramolecular isotopic effect was 2.6 [Scheme 3(d)]. Then the double bond of allyl bromide might be inserted into the C–Rh bond in **I**,[23] followed by β-Br elimination to afford the desired product, **3a**. The β-Br elimination should be facilitated by the existence of AgOAc[24] (Path a, Scheme 2); however, oxidative addition of the C–Br bond to Rh is also a possible pathway for the reaction (Path b, Scheme 2).

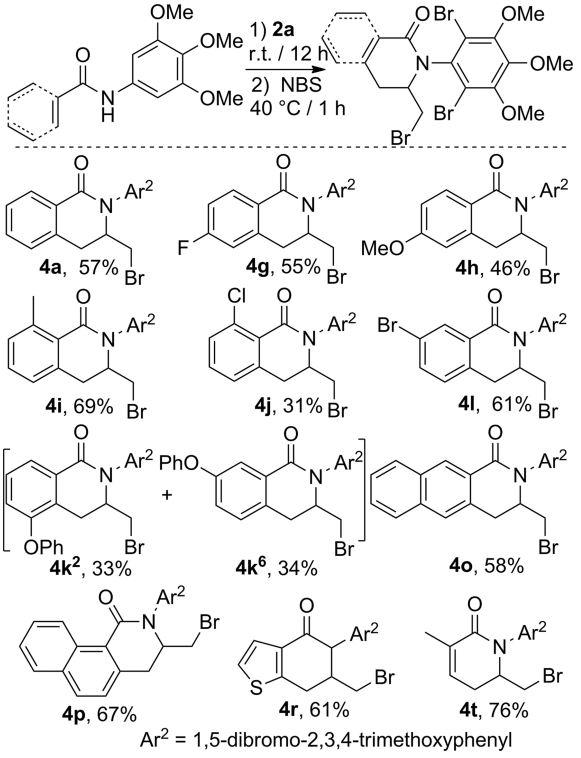


Scheme 2. Proposed mechanism.

Considering the useful aminohalogenation and versatile transformations of allylic intermediates,[25,26] we tried using *N*-bromosuccinimide (NBS) for the domino synthesis of heterocycles. The conditions were optimized as shown in Table S2. To our delight, we were able to prepare 3,4-dihydroisoquinolin-1(2*H*)-ones from the corresponding amides in a one-pot reaction. These compounds belong to one of the most important families of heterocycles and frequently appear as the core framework in bioactive compounds.[27,28] Since the C–F coupling constants provide more information on the structure, the structure of compound **4g** was confirmed by 2DNMR spectroscopy (COSY, HSQC & HMBC, Figures S5–S7). However, bromination took place at the original aniline ring as well, which might be ascribed to the presence of electron-donating groups. The domino synthesis was proved to be applicable to both aroyl- and acrylamides (Scheme 4). However, it is not suitable for substrates **1b**, **1d**, and **1e**, unless anhydrous solvent is used for the cyclization.



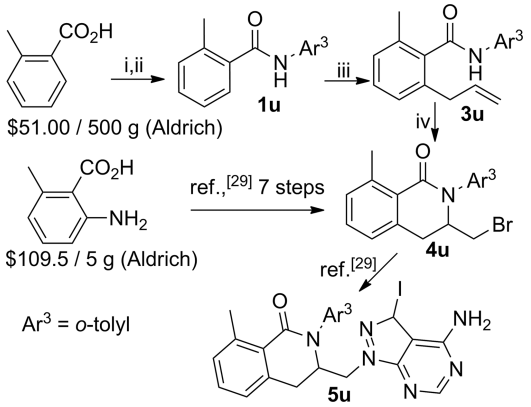
Scheme 3. Mechanistic investigation.



Scheme 4. Reaction scope of 3,4-dihydroisoquinolin-1(2*H*)-one. The details of the reaction are in the Supporting Information (Part VII).

Bicyclic compound **5u** has been demonstrated to be useful for inhibiting phosphatidyl inositol-3 kinase (P13 kinase). The activity of P13 kinase is associated with lots of diseases, including but not limited to cancer and inflammatory disease.[29] Compound **4u**, previously prepared from the expensive starting material 6-methylanthranilic acid in seven steps,[29] is the key intermediate for the synthesis of **5u**. Now, by means of the

allylation and NBS cyclization strategy, we are able to prepare **4u** in 21 % isolated yield from cheap 2-methyl-benzoic acid in four steps. In this reaction, only 1.1 equiv. NBS was added to avoid bromination of the aniline ring (Scheme 5).



Scheme 5. The synthesis of **5u**. Reagents and conditions: (i) $SOCl_2$, CH_2Cl_2, reflux, 4 h; (ii) NEt_3, 1 equiv. 2-toluidine, 0–25 °C, 4 h; (iii) 4 mol-% $[Cp^*RhCl_2]_2$, 2.1 equiv. AgOAc, 2.5 equiv. allyl bromide, Et_2O, room temperature, 12 h; (iv) 1.1 equiv. NBS, anhydrous Et_2O, 40 °C, 1 h.

Conclusions

We have developed a Rh^{III}-catalyzed allylation of both aroyl- and acrylamides in commercial solvents, and moderate to good yields can be obtained at room temperature. Allyl halides are the best allyl reagents. The reaction can tolerate a broad range of substituents such as halogens and heterocycles. On the basis of this straightforward allylation, one-pot domino cycling synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones has also been achieved.

Experimental Section

Typical Procedure for Allylation of Amides: A 25 mL flask was charged with substrate **1a**–**t** (0.40 mmol, 1.0 equiv.), $[Cp^*RhCl_2]_2$ (9.9 mg, 0.016 mmol, 4 mol-%), AgOAc (140.2 mg, 0.84 mmol, 2.1 equiv.), diethyl ether (10 mL), and **2a** (84 μL, 1 mmol, 2.5 equiv.) in air. The flask was capped, and the reaction mixture was stirred for 12 h at room temperature. Then CH_2Cl_2 (2 mL) was added into the flask to dissolve potential organic precipitates. The mixture was filtered, and the precipitate was washed with CH_2Cl_2 (2 mL × 3). The filtrate was then concentrated in a rotary evaporator under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using EtOAc/hexane as the eluent.

Typical Procedure for Preparing Heterocycles 4a, 4g, 4h–l, 4o, 4p, 4r, 4t Based on the Allylation: After the general procedure for allylation (0.4 mmol), CH_2Cl_2 (2 mL) was added into the flask to dissolve potential organic precipitates. The mixture was filtered, and the precipitate was washed with CH_2Cl_2 (2 mL × 3). The filtrate was concentrated in a rotary evaporator under reduced pressure, and NBS (249.2 mg, 1.4 mmol, 3.5 equiv.) and solvent (5 mL) were added to the flask. After that, the flask was capped and submerged into a preheated 40 °C oil bath for 1 h. After cooling to room temperature, the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography using EtOAc/hexane (1:30) as the eluent.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^1H NMR and ^{13}C NMR spectra for all key intermediates and final products.

Acknowledgments

We gratefully acknowledge the National Basic Research Program of China (2013CB922101), the National Natural Science Foundation of China (21271102, 21472086, and 21531004), and the Natural Science Foundation of Jiangsu Province (BK20130054).

Keywords: Allylation · C–H activation · Heterocycles · Synthetic methods

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Received: December 10, 2015
Published Online: February 22, 2016

