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Highly Selective Mild Stepwise Allylation of *N*-Methoxybenzamides with Allenes

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Supporting Information

ABSTRACT: An efficient Rh(III)-catalyzed stepwise ortho allylation of *N*-methoxybenzamides **1** with polysubstituted allenes is reported. This C−H functionalization involving allenes is conducted under very mild conditions (−20 °C or room temperature) and compatible with ambient air and moisture, and it can be applied to terminal or internal allenes with different synthetically attractive functional groups. Highly efficient axial chirality transfer has been realized, yielding optically active lactones.

Transition-metal-catalyzed C−H bond functionalization for hydroarylation of C−C multiple bonds has emerged as a powerful, distinct, and atom-economical method for the construction of C−C bonds from cheap and readily available chemicals in organic synthesis.[1] Despite the fact that much attention has been paid to hydroarylation of alkenes[2] and alkynes[3] via C−H bond functionalization in recent years, these reactions generally require a high temperature (often >100 °C).[1,4−6] However, such reports on the reactions of allenes are very limited.[7,8] Because of the high reactivity of allenes,[9] we envisioned that such reactions with allenes may be realized at ambient temperature with accommodation of different functional groups. However, in reality, the limited number of reports in this area (four) demonstrated that this is not true: in 2009, Krische and co-workers[7a] reported a carboxamide-group-directed hydroarylation reaction via a cationic Ir-catalyzed oxidative addition with the C−H bond, with subsequent insertion of 1,1-dimethylpropadiene and reductive elimination to afford monoallylation products of arenes; in 2010, Cramer[7b,c] and Kuninobu[7d] independently reported Rh- and Re-catalyzed cyclization reactions of imines via C−H bond functionalization, allene insertion, and cyclic allylation to afford aminoindane derivatives. These reactions all require high temperatures (115−120 °C); furthermore, it should be noted that only terminal allenes have been applied and that no stepwise double allylation with allenes has been realized. Thus, it still remains a challenge to control the regio- and stereoselectivity when polysubstituted allenes are involved. We envisioned a catalytic protocol for controlled stepwise double allylation[10,11] with allenes under mild conditions with high regio- and stereoselectivity with the possibility of axial chirality transfer of the allenes.

Very recently, the groups of Fagnou and Glorius reported the Rh(III)-catalyzed C−H activation of *N*-methoxybenzamide (**1a**)[12] for coupling with alkynes[12b] and alkenes,[12c] respectively, at 60 °C. In these reactions, the methoxy group on the nitrogen functions as an oxidant and is removed in the final products. We showed interest in the Rh(III)-catalyzed C−H fuctionalization involving allenes. After screening, we found that the Rh-catalyzed hydroarylation reaction of **1a** with 3-butyl-1,2-heptadiene (**2a**) with 30 mol % CsOAc and using 2 mol % $[Cp^*RhCl_2]_2$ as the catalyst in toluene at *room temperature* afforded the monoallylation product **3aa** in 55% yield together with a 7% yield of the diallylation product **4aa** [entry 1 in Table S1 in the Supporting Information (SI)], and no cyclization product was observed; this indicated a fast protonolysis, which is different from what has been reported.[12b,c] Some of the well-established directing groups (Figure 1)[13−15] failed to initiate such reactions. After optimization,[16] we were glad to observe that the reaction could even be conducted at −20 °C in $MeOH/H_2O$, where the yield of **3aa** was further improved to 82% with a very high **3aa**/**4aa** selectivity (>20/1) (Table S1, entry 7); these were defined as the standard conditions.

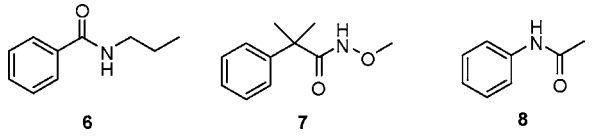

Figure 1. Directing groups screened.

With the optimized reaction conditions in hand, the scope of the hydroarylation reaction of allenes via C−H functionalization of arenes was demonstrated with a variety of differently substituted *N*-methoxybenzamides (**1a−i**) and allenes (**2a−g**). Gratifyingly, moderate to good yields for the allylation of arenes were generally obtained for most of the substrates (Table 1). The reaction provided the monoallylation products **3** when substrates **1** bearing either an electron-donating substituent such as 4-OMe (**1c**), 4-Bu^t (**1d**), 2-OMe (**1f**), or 2,4-dimethyl (**1i**) or an electron-withdrawing group such as 4-Br (**1b**), 2-I (**1e**), 3-CF_3 (**1g**), or 2-Cl-4-Br (**1h**) were employed. Using *N*-methoxy-3-trifluoromethylbenzamide (**1g**) under the standard conditions afforded the monoallylation product **3ga** exclusively in 81% yield, and no diallylation product was observed (entry 7). Carbon−halogen bonds were smoothly tolerated, affording the corresponding C−H functionalization products **3ba**, **3ea**, and **3ha** (entries 2, 5, and 8). When *N*-methoxy-1-naphthylformamide (**1j**) was employed in the reaction, the C−H bond at the 2-position was selectively activated to afford

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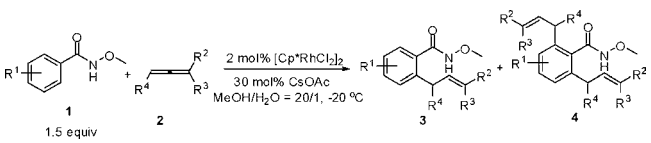
Table 1. Rh(III)-Catalyzed C−H Monoallylation of *N*-Methoxybenzamides 1 with Allenes 2[a]



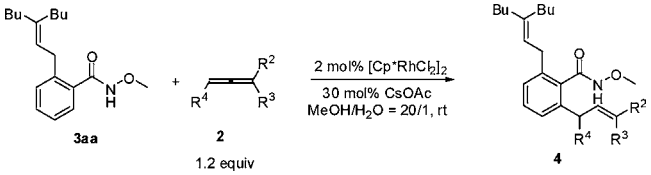
entry	Ar (1)	R^2/ R^3/R^4 (2)	yield (%)[b] 3	4	3/4[b]
1	Ph (**1a**)	Bu/Bu/H (**2a**)	77 (**3aa**)	4	20/1
2	4-BrPh (**1b**)	**2a**	72 (**3ba**)	5	15/1
3	4-MeOPh (**1c**)	**2a**	71 (**3ca**)	6	12/1
4	4-^{t}BuPh (**1d**)	**2a**	74 (**3da**)	5	17/1
5[c]	2-IPh (**1e**)	**2a**	69 (**3ea**)	–[d]	–
6[c]	2-MeOPh (**1f**)	**2a**	76 (**3fa**)	–[d]	–
7	3-CF_3Ph (**1g**)	**2a**	81 (**3ga**)	–[d]	–
8[c]	2-Cl-4-BrPh (**1h**)	**2a**	65 (**3ha**)	–[d]	–
9[c]	2,4-Me_2Ph (**1i**)	**2a**	82 (**3ia**)	–[d]	–
10	α-naphthyl (**1j**)	**2a**	81 (**3ja**)	–[d]	–
11	2-benzofuran (**1k**)	**2a**	73 (**3ka**)	–[d]	–
12	Ph (**1a**)	Bu/Ph/H (**2b**)	62 ((*Z*)-**3ab**)	2	32/1
13	Ph (**1a**)	Bu/*p*-tolyl/H (**2c**)	56 ((*Z*)-**3ac**)	2	30/1
14	Ph (**1a**)	Pr/Pr/MOM (**2d**)	90 (**3ad**)	–[d]	–
15[e]	Ph (**1a**)	−$(CH_2)_5$−/ CH_2OH (**2e**)	58 (**3ae**)	2	31/1
16	Ph (**1a**)	Me/Me/ CH_2CO_2Et (**2f**)	53 (**3af**)	–[d]	–
17	Ph (**1a**)	−$(CH_2)_5$−/ CH_2O-allyl (**2g**)	77 (**3ag**)	–[d]	–
18[f,g]	Ph (**1a**)	Bu/Bu/H (**2a**)	76 (**3aa**)	–	–

[a]The reaction was conducted with **1** (0.45 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (0.006 mmol), CsOAc (0.09 mmol), MeOH (2 mL), and H_2O (0.1 mL) at −20 °C, unless mentioned otherwise. [b]The yields of **3** are isolated yields. The yields of **4** and the **3**/**4** ratios were determined by ^{1}H NMR analysis of the crude products. [c]The reaction was conducted at room temperature. [d]No diallylation product was observed. [e]The reaction was conducted at 0 °C. [f]**2a** (6.1081 g), **1a** (1.5 equiv), and Rh catalyst (0.4 mol %) were used. [g]The product was directly isolated by silica gel flash column chromatography.

the corresponding product **3ja** in 81% yield (entry 10), no reaction occurred with the C−H bond at the 8-position of the naphthyl skeleton. Moreover, treatment of 2-benzofuran derivative **1k** with **2a** cleanly provided the 3-position allylation product **3ka** in 73% yield (entry 11). When 3-phenyl-1,2-heptadiene (**2b**) and 3-*p*-tolyl-1,2-heptadiene (**2c**) were used as the substrates, the reaction afforded the monoallylation products (*Z*)-**3ab** and (*Z*)-**3ac** as single stereoisomers in isolated yields of 62 and 56%, respectively, as determined by NOESY analysis[17] (entries 12 and 13). Intriguingly, when internal allenes **2d**−**f** with different functionalities were treated with **1a**, the corresponding hydroarylation products **3ad**−**af** were obtained in moderate to excellent yields, with the reaction occurring exclusively at the less substituted C=C bond; the ether group of **2d** (entry 14), the hydroxyl group of **2e** (entry 15), and the ester group of **2f** (entry 16), remained untouched. Moreover, with allyl 4,4-pentamethylene-2,3-butadienyl ether (**2g**) as the substrate, the reaction exclusively took place at the less substituted C=C bond of the allene moiety, with no reaction occurring at the allylic C=C bond (entry 17). Gladly, a large-scale reaction of **1a** and **2a** using just 0.4 mol % Rh catalyst afforded **3aa** in 76% yield (entry 18). Regretfully, tetrasubstituted allenes failed to undergo this reaction.

We further examined the reaction of monoallylation product **3aa** with a second molecule of allene **2** to provide the diallylation product at room temperature (Table 2). Interestingly, the reaction of **3aa** with **2b** again afforded (*Z*)-**4ab** as a single isomer in 57% yield, as determined by NOESY analysis.[17]

Table 2. Synthesis of Diallylation Products

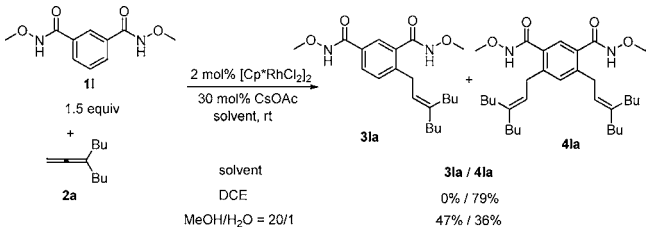


entry	R^2/ R^3/R^4 (2)	isolated yield of **4** (%)
1	Bu/Bu/H (**2a**)	98 (**4aa**)
2	Bu/Ph/H (**2b**)	57 ((*Z*)-**4ab**)
3[a]	Pr/Pr/MOM (**2d**)	87 (**4ad**)
4	−$(CH_2)_5$−/CH_2OH (**2e**)	84 (**4ae**)
5	−$(CH_2)_5$−/CH_2O-allyl (**2g**)	68 (**4ag**)

[a]The reaction was conducted in DCE instead of MeOH/H_2O.

Reaction of bisamide substrate **1a** with allene **2a** in dichloroethane (DCE) afforded only the diallylation product **4la** in 79% yield, while a mixture of **4la** and the monoallylation product **3la** was obtained in MeOH/H_2O (Scheme 1); no 2-position C−H cleavage product was observed in these reactions. However, the reaction of *N*-methoxy-4-(pyridin-2-yl)benzamide (**1m**) was very slow and afforded a mixture of at least three products (see SI).

Scheme 1. Reactions of Bisamide Substrate 1l with 2a



In addition, the reaction of **3aa** with **2e** in DCE smoothly afforded the hydroarylation product **4ae** in 84% yield under the standard conditions (Table 2, entry 4). Subsequent lactonization by direct addition of 2.0 equiv of TsOH·H_2O[18] to the reaction mixture with stirring for another 100 min easily afforded bicyclic lactone **5ae** in 83% yield (eq 1). Moreover, treatment of **3aa** with 1.5 equiv of *N*-iodosuccinimide (NIS) in MeCN/H_2O afforded the seven-membered ring product **9aa** in 68% yield through an electrophilic cyclization process (eq 2).[9j] Finally, highly efficient chirality transfer was realized with the optically active allenols (*S*)-(−)-**2h**/**2i** and (*R*)-(+)-**2h**/**2i**, which afforded the optically active bicyclic lactones (*R*)-**5** and (*S*)-**5**, respectively, after the subsequent lactonization (Scheme 2).

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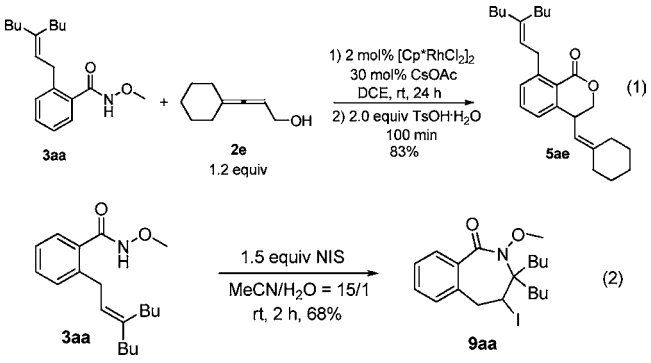
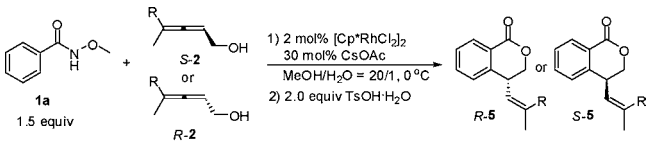
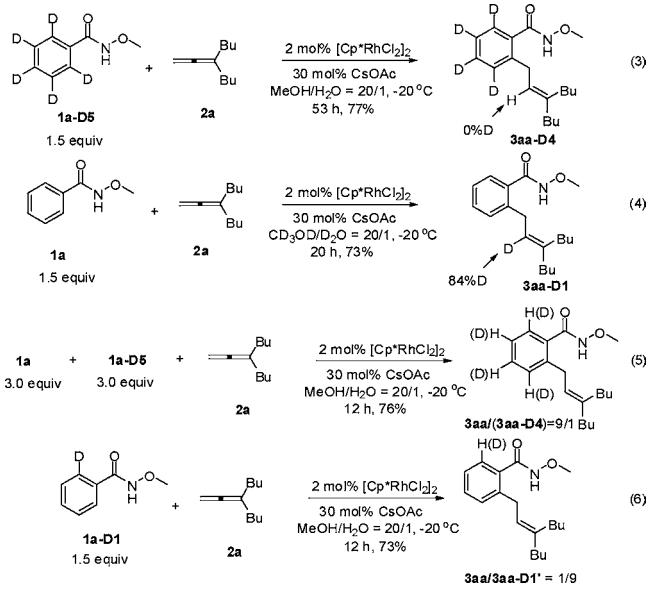


Scheme 2. Axial Chirality Transfer Reactions



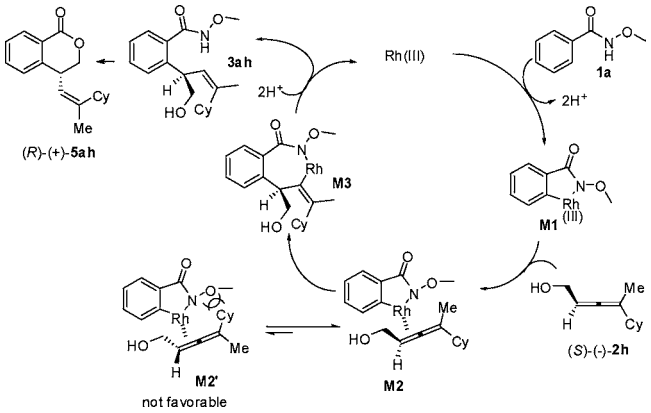
R	2	ee value of 2	5	yield	ee value of 5
Cy	(*S*)-(-)-**2h**	99%	(*R*)-(+)-(*Z*)-**5ah**	70%	99%
Cy	(*R*)-(+)-**2h**	97%	(*S*)-(-)-(*Z*)-**5ah**	67%	97%
$BnCH_2$	(*S*)-(-)-**2i**	99.7%	(*R*)-(+)-(*Z*)-**5ai**	56%	99.7%
$BnCH_2$	(*R*)-(+)-**2i**	99.7%	(*S*)-(-)-(*Z*)-**5ai**	54%	99.6%

To probe the reaction mechanism, substrate **1a-D5** was subjected to the reaction with **2a** under the standard conditions and smoothly afforded the product **3aa-D4** in 77% yield, with no deuterium incorporation on the C═C bond (eq 3).



Treatment of **1a** with **2a** using a CD_3OD/D_2O as the solvent gave the product **3aa-D1** in 73% yield, with 84% deuterium incorporation at the olefinic position (eq 4).[19] An intermolecular kinetic isotope effect (KIE) experiment was performed by treating 3.0 equiv of **1a**, 3.0 equiv of **1a-D5**, and 1.0 equiv of **2a** under the standard conditions. The KIE was determined to be k_H/k_D = 9/1[19] (eq 5), indicating that the C−H bond cleavage process should be the rate-determining step. The intramolecular KIE was also determined to be k_H/k_D = 9/1[19] by treatment of **1a-D1** with **2a** (eq 6), providing additional evidence regarding the reactions.

Scheme 3. Proposed Mechanism



On the basis of this evidence, a plausible mechanism for this reaction is proposed, as shown in Scheme 3 using **1a** and (*S*)-(−)-**2h** as the substrates. The first step of the transformation should be arene electrophilic rhodation of **1a** to provide cyclic intermediate **M1**. This would be followed by coordination with the less-substituted C═C bond and mild insertion of this C═C bond to afford C(sp^2)−Rh intermediate **M3**, which would explain the regioselectivity.[20] Finally, facile protonolysis with in situ-generated H^+ would yield the product **3ah** and regenerate the catalyst; this may be explained by the possible steric interaction between the Me and MeO groups caused by the reductive C−N bond formation of **M3**. The steric interaction shown in **M2** and **M2′** may explain the observed *Z*/*E* stereoselectivity and axial chirality transfer of the allenes.

In conclusion, we have developed a Rh(III)-catalyzed hydroarylation reaction of allenes that proceeds via C−H bond functionalization and allene insertion.[21] These reactions can be run at −20 °C or rt and are compatible with ambient air and moisture. Moreover, the reactions are applicable to a wide range of both arenes and allenes with different functionalities and should be useful for atom-economical preparation of mono- or diallylated arenes. Furthermore, chiral products could be synthesized from axially chiral allenes through a chirality transfer process. Further studies in this area are being carried out in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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