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Solvent-Controlled, Tunable β-OAc and β-H Elimination in Rh(III)-Catalyzed Allyl Acetate and Aryl Amide Coupling via C−H Activation

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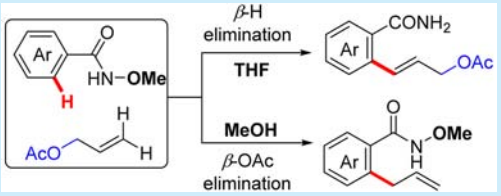
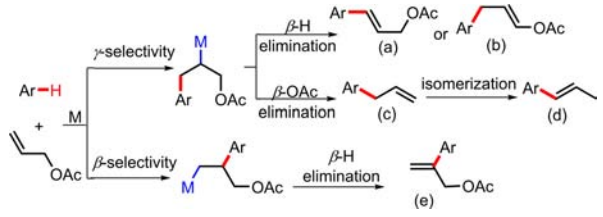
Supporting Information

ABSTRACT: The Heck reaction between arenes and allyl acetate has led to cinnamyl derivatives and allyl products depending on the regioselectivity of β-elimination. The regioselectivity can be controlled by the solvent in the Rh(III)-catalyzed arene−allyl acetate coupling via C−H activation: (1) in THF, cinnamyl derivatives via β-H elimination were generated; (2) in MeOH, allyl products via β-OAc elimination were produced. Both routes have advantages such as excellent γ-selectivity toward allyl acetate, good to excellent yields, and broad substrate scope.



Arene−alkene coupling is one of the most commonly used and well-developed reactions in organic synthesis,[1,2] among which dehydrogenative cross-coupling by C−H activation of arenes is the most convenient and economical strategy because it avoids prefunctionalization.[3−5] The coupling-partner alkenes have been expanded from electron-deficient alkenes to aliphatic olefins and styrenes, whereas allyl esters still remain challenging because of the lack of fine-tunability of issues such as (i) metal-selective insertion (internal vs terminal), (ii) divergence of β-elimination (β-OAc vs β-H), and (iii) competitive regioselectivity in β-elimination (allylic vs styrenyl) (Scheme 1).[6−11] Gratefully, a breakthrough in

Scheme 1. Oxidative Heck Reaction between Arenes and Allyl Acetate



selective β-H elimination has been achieved by the pioneering work on Pd catalysis (Scheme 1a).[7,8] However, high temperature and excess arene are needed for all of the reactions because of the absence of directing groups. Moreover, the regioselectivity on the arenes is quite low except for special arenes[8] such as thiophene. In terms of selective β-OAc elimination (Scheme 1c,d[9]), some effective reactions under Rh,[10] Ru,[11] and other metal catalysis[12] have been published. Nonetheless, how to tune the regioselectivity of β-elimination through simple manipulation of the reaction conditions has not been reported yet.

Solvents are known to play very important roles in chemical processes. Significant influences have been disclosed in regioselectivity,[13] stereoselectivity,[14] structural control,[15] physical properties,[16] and so on. Herein we report solvent-tunable β-elimination in Rh(III)-catalyzed coupling of arenes and allyl esters, which is based on amide-directed C−H activation. By solvent control, different selectivity in β-elimination has been reached: (1) in THF, cinnamyl derivatives by β-H elimination were isolated; (2) in MeOH, allylation products by β-OAc elimination were obtained. Both pathways share the advantages such as excellent γ-selectivity toward allyl acetate, good to excellent yields, and broad substrate scope. Moreover, both products are of high value in organic synthesis and biochemical studies.[17−19]

To optimize the reaction conditions, our study was initiated by using amide **1a** and allyl acetate as the model substrates (Table 1). First, different catalysts were examined with MeOH as the solvent and AgOAc as the additive. Both $[Cp^*RhCl_2]_2$ and $[(\eta^6\text{-cymene})RuCl_2]_2$ led to **4a** with excellent β-OAc elimination, and the former could give rise to yields of up to 99% (entries 1 and 3). However, $Cp^*CoI_2(CO)$ was inactive (entry 2). Then the effect of different solvents was investigated (entries 4−13). An additional product **3aa** was generated by β-H elimination in solvents other than MeOH or MeCN. The newly formed alkenyl group adopts the *E*-type conformation, as confirmed by ^1H NMR spectroscopy. Furthermore, **1a** exhibited excellent selectivity toward the γ-site of allyl acetate. The −N(H)OMe group behaves as an internal oxidant here. THF was the best solvent for the formation of **3aa** (entry 10), but $[(\eta^6\text{-cymene})RuCl_2]_2$ was inactive in THF (entry 13). Additives were also screened. Ag_2CO_3 was found to be slightly better than AgOAc (entry 14 and Table S1). When the catalyst loading was increased to 3 mol %, the yield of **3aa** was improved to 67% (entry 15). Notably, the addition of 4 Å molecular sieves improved both the yield and selectivity, which

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Table 1. Optimization of the Reaction Conditions[a]

entry	catalyst	solvent	additive	yield (%)[b] 3aa	4a
1	$[Cp^*RhCl_2]_2$	MeOH	AgOAc	0	99
2[c]	$Cp^*CoI_2(CO)$	MeOH	AgOAc	0	0
3[c]	$[(\eta^6\text{-cymene})\ RuCl_2]_2$	MeOH	AgOAc	0	79
4	$[Cp^*RhCl_2]_2$	MeCN	AgOAc	0	88
5	$[Cp^*RhCl_2]_2$	DCE	AgOAc	17	69
6	$[Cp^*RhCl_2]_2$	DCM	AgOAc	<10	27
7	$[Cp^*RhCl_2]_2$	PhMe	AgOAc	28	62
8	$[Cp^*RhCl_2]_2$	DMF	AgOAc	23	66
9	$[Cp^*RhCl_2]_2$	DMSO	AgOAc	<10	43
10	$[Cp^*RhCl_2]_2$	THF	AgOAc	46	19
11	$[Cp^*RhCl_2]_2$	1,4-dioxane	AgOAc	22	<10
12	$[Cp^*RhCl_2]_2$	Et_2O	AgOAc	32	<10
13[c]	$[(\eta^6\text{-cymene})\ RuCl_2]_2$	THF	AgOAc	0	12
14	$[Cp^*RhCl_2]_2$	THF	Ag_2CO_3	49	15
15[c]	$[Cp^*RhCl_2]_2$	THF	Ag_2CO_3	67	19
16[d]	$[Cp^*RhCl_2]_2$	THF	Ag_2CO_3	74	18
17	$[Cp^*RhCl_2]_2$	MeOH	Ag_2CO_3	0	98

[a]Unless otherwise noted, the reactions were carried out in refluxing solvent (2 mL) containing **1a** (33.0 mg, 0.2 mmol), **2a** (45 μL, 2.5 equiv), catalyst (1.5 mol %), and additive (20 mol %) for 12 h. [b]Isolated yields. [c]Using 3 mol % catalyst. [d]Using 3 mol % catalyst and 60 mg of 4 Å molecular sieves.

might be attributed to the removal of generated MeOH (entry 16). In MeOH, Ag_2CO_3 performed as well as AgOAc (entry 17). Therefore, Ag_2CO_3 was finally chosen as the additive in the solvent-controlled reaction. Of note, the reaction is water-sensitive but not air-sensitive.

Different allyl electrophiles were screened as well (Tables 2 and S3). The activity of those allyl reagents varied with the

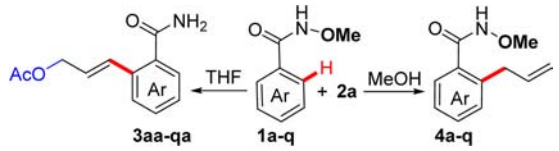
Table 2. Scope of Allyl Resources

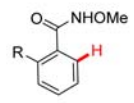
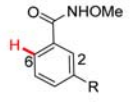
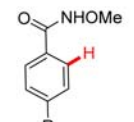
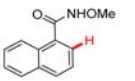
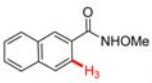
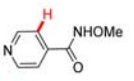
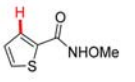
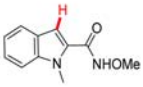
	allyl resources: 			
R	OAc, **2a**	OBz, **2b**	$OCOCF_3$, **2c**	OCO_2Me, **2d**
R	OTf, **2e**		$OPO(OEt)_2$, **2f**	Br, **2g**

leaving group. In THF, **2a** was the only suitable candidate, affording a 74% yield. However, the reaction could not proceed through β-H elimination with **2e**–**g** (Table S3, entries 5–7). In MeOH, all of the tested allyl reagents were active. **2e** gave a yield lower than 10%, but **2a** and **2d** were able to yield **4a** almost quantitatively. Therefore, **2a** was chosen to explore the reactivities of different amides.

With the optimized conditions in hand, amides bearing varying functional groups were investigated (Table 3). To our delight, the solvent-dependent reaction can tolerate not only substituents such as halogens and PhO– but also those such as cyano, nitro, oximido, and heterocycles. In THF, all of the substrates preferred β-H rather than β-OAc elimination, although the selectivity was not ideally perfect. Furthermore, they all exhibited excellent selectivity toward the γ-site of allyl acetate. The yields are moderate to good but comparatively

Table 3. Scope of Amides[a]



	substrate	R	yield (%) 3(THF)[b] (3/4)	4(MeOH)
1		Me, **1a**	**3aa**, 74 (4/1)	**4a**, 98
2		OMe, **1b**	**3ba**, 69 (5/2)	**4b**, 98
3		Cl, **1c**	**3ca**, 59 (3/1)	**4c**, 98
4		F, **1d**	**3da**, 57 (3/1)	**4d**, 81
5		NO_2, **1e**	**3ea**, 46 (4/1)	**4e**, 63
6[c]		OPh, **1f**	**3fa**, 69 (2/1)	**4f**, 96
7		COOMe, **1g**	**3ga**, 67 (5/1)[d] *E*/*Z* >10/1	**4g**, 89
8		NO_2, **1h**	**3ha**, 48 (3/1)[d] *E*/*Z* = 2/1	**4h**, 83
9		H, **1i**	**3ia**, 71 (6/1)	**4i**, 70
10		OMe, **1j**	**3ja**, 81 (9/1)	**4j**, 66
11		CN, **1k**	**3ka**, 65 (2/1) *E*/*Z* = 10/1	**4k**, 78
12		CHNOMe, **1l**	**3la**, 67 (3/1) *E*/*Z* = 15/1	**4l**, 73
13		**1m**	**3ma**, 61 (9/1)	**4m**, 97
14		**1n**	**3na**, 91 (7/1)	**4n**, 97
15		**1o**	**3oa**, 32 (9/1) *E*/*Z* = 5/1	**4o**, 56
16		**1p**	**3pa**, 35 (15/2) *E*/*Z* = 10/1	**4p**, 47
17		**1q**	**3qa**, 0[e]	**4q**, 39

[a]The optimized standard conditions were used. [b]Ratios were determined by ^1H NMR spectroscopy. [c]**3fa**^{6}/**3fa**^{2} = 2/1; **4f**^{6}/**4f**^{2} = 4/5. [d]36 h. [e]No reaction.

lower for the electron-deficient substrates (e.g., **1e** and **1h**) and for the substrates containing a heterocycle (e.g., **1o** and **1p**). Notably, the –N(H)OMe group serves as not only a directing group but also an internal oxidant. Once reduced to a primary amine, it loses the directing function, thereby avoiding the follow-up alkenylation. Because of steric hindrance, **1f**–**h** preferred the alkenylation at the 6-position. Additionally, *Z*-isomer products were observed in the cases of electron-deficient substrates, especially those containing electron-withdrawing groups at the *meta* position. The *Z*-isomer products could be transformed to corresponding *E* isomers by prolonging the reaction time.

In MeOH, all of the substrates exhibited an exclusive preference for β-OAc elimination, and good to excellent yields were obtained. However, **1p** and **1q** led to **4p** and **4q**, respectively, in only moderate yields because of double-bond α-

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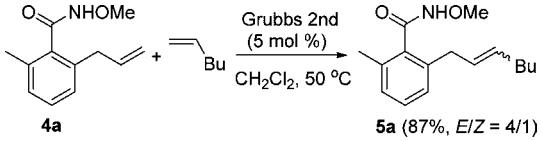
isomerization of the allylation products. Those terminal allyl products can be further transformed to substituted alkenes through olefin metathesis[20] (Scheme 2).

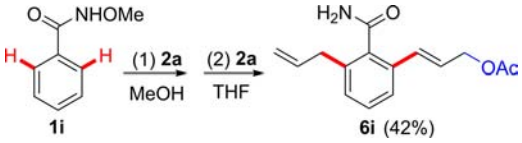
Scheme 2. Substituted Alkenes Derived from Allylation Products through Olefin Metathesis



4a **5a** (87%, *E*/*Z* = 4/1)

On the basis of this solvent-dependent approach, not only the products of single β-OAc or β-H elimination but also those products obtained by both types of eliminations can be produced. For example, **6i** could be prepared by cascade alkenylation in a one-pot reaction (Scheme 3).

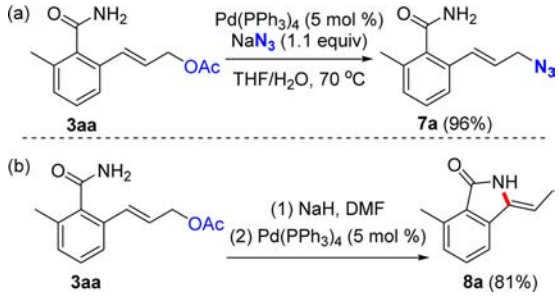
Scheme 3. One-Pot Preparation of 6i



1i **6i** (42%)

We tested further transformations of the two types of solvent-tunable reaction products. **3aa** could lead to azide-substituted olefin product **7a** (Scheme 4a) and 3-methyleneisoindolin-1-one derivative **8a** (Scheme 4b) under the catalysis of $Pd(PPh_3)_4$ based on the Tsuji–Trost reaction.[19] **4a** could be transformed to 3,4-dihydroisoquinolin-1(2*H*)-one derivatives **9aa–ac** when halogenated reagents were used;[21] products **9** also could be prepared in one pot using **1a** as the starting material (Table 4).

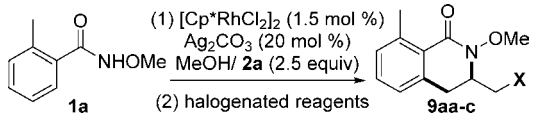
Scheme 4. Transformations of 3aa



3aa **7a** (96%) **3aa** **8a** (81%)

To understand the mechanism behind this interesting reaction, some control experiments were conducted. Since **Me-1i** was not reactive in either MeOH or THF (Scheme S6), the Rh(III) catalyst should be directed by the anionic nitrogen to activate the *ortho* C–H bond to generate **I**, as shown in Scheme 5. Furthermore, H/D scrambling was observed at the *ortho* site next to the amide group of the products when **1h** reacted in MeOD or THF/D_2O (Schemes S7 and S8), and thus, the C–H bond activation is reversible. The kinetic isotope effect was measured as 2.1 in MeOH and 1.8 in THF, respectively (Scheme S9), so the C–H bond activation is the rate-determining step in both solvents. The double bond of allyl acetate inserts into the C–Rh bond in **I** to give **II**.[10−12] Then the reaction proceeds in different pathways depending on the solvent: (1) in THF, the reaction prefers to produce **3ia** through β-H elimination; (2) in MeOH, the reaction entirely goes through β-OAc elimination. The difference might be caused by solvents that affect the coordination sphere of the Rh center in **II** as well as the stability of the intermediates **III** and **IV** after β-elimination.

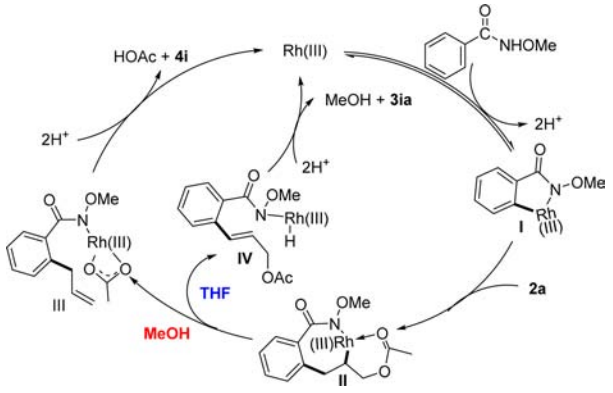
Table 4. One-Pot Synthesis of Dihydroisoquinolinones



1a **9aa-c**

X	halogenated reagents	**9**, yield (%)
Cl	NCS	**9aa**, 45
Br	NBS	**9ab**, 78
I	NIS	**9ac**, 86

Scheme 5. Proposed Mechanism



In conclusion, solvent-tunable β-elimination in Rh(III)-catalyzed coupling of arenes and allyl acetate through C–H activation has been realized: (1) in THF, cinnamyl derivatives by β-H elimination were generated; (2) in MeOH, allyl products by β-OAc elimination were obtained. Both routes lead to good to excellent yields with broad substrate scope under mild conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01566.

Experimental procedures and full characterization details, including ^1H and ^{13}C NMR and HRMS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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