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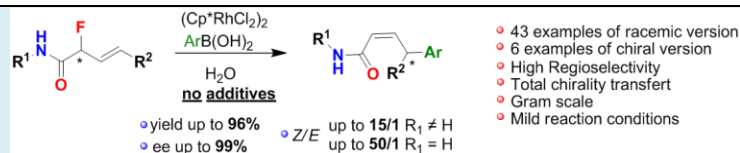
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Rhodium (III) Catalyzed Regioselective and Enantiospecific Allylic Arylation in Water by β -Fluorine Elimination of the Allylic Fluoride: toward the Synthesis of *Z*-alkenyl-unsaturated amides.

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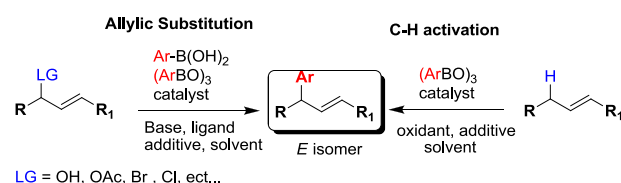


ABSTRACT: A direct coupling of arylboronic acids with allylic fluorides was carried out in water without additives using a rhodium (III) catalyst $(Cp^*RhCl_2)_2$. The transformation proceeded with excellent γ -selectivity to afford major allyl-aryl coupling products (*Z*) γ -substituted α,β -unsaturated amides. The reactions of α -chiral allylic fluorides took place with excellent α -to- γ chirality transfer to give allylated arenes with a stereogenic center at the benzylic and allylic position.

The development of original molecular architectures is still a major challenge for the organic chemist community. New criteria have been added to this challenge during the 21st century, such as ecological friendly processes with atoms economy; it is obvious that catalytic processes are extremely demanded and developed to meet this challenge. However, despite the high ecological and economic demand, the major catalytic processes are still developed under drastic conditions (toxic organic solvents, additives oxidants, bases, acids ...). To overcome these drawbacks, the development of catalytic reactions in water¹ is one of the solutions to this problem, provided that the selected substrates and catalysts are compatible with water. Alkenes are an integral part of the most widely used organic compounds in the chemical industry and are present in a large number of bioactive molecules. Although the synthesis of *E*-alkenes is well established, the synthesis of *Z*-alkenes² is less depicted because of their low thermodynamic stability. Thus, the synthesis of *Z*-alkenes is a challenge and an important goal for synthetic chemists. To overcome the Wittig reaction,³ which is the most general method of formation of *Z*-alkenes. Many different catalytic reactions have been developed, such as semi-hydrogenation of alkynes,⁴ stereospecific cross-coupling reactions,⁵ terminal-to-internal olefin isomerization⁶ and *Z*-selective cross-metathesis.⁷ Among the catalytic reactions, which make it possible to obtain a functionalized olefin, are the transition-metal catalyzed allylic substitutions with unstabilized carbon nucleophiles. Various approaches have been studied to allow allylic arylation using arylborane reagents with either prefunctionalized olefins⁸⁻¹⁰ (bearing an appropriate leaving group) or nonfunctionalized olefins¹¹ (Scheme 1). In all cases, these methods described previously give *E*-aryls alkenes. Regarding the prefunctionalized olefins, the allylic arylations were carried out according to two well-established mechanisms, either via the $(\pi$ -allyl) metal intermediates¹² or a regioselective carbometallation of the allylic alkene followed by a β -acetoxy elimination group

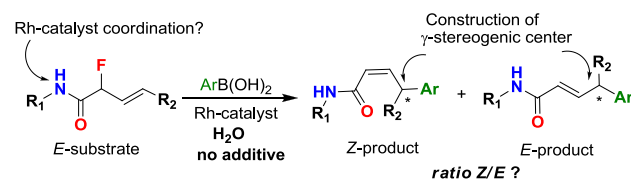
rather than β -hydride elimination.¹³ Recently, we have described a Pt(0) catalyzed allylic substitution process of α -fluoroenamides. The use of a soft nucleophile (amine) allowed us to generate an *E*-alkene via a $(\pi$ -allyl) metal intermediate¹⁴ no coordination was observed in this case. On the other hand, other metals such as rhodium can bond to the nitrogen atom of the amide to form amide-rhodium complexes. These complexes have been observed recently in allylation reactions via C-H activation.¹⁵ Knowing the potential for coordination that the amide function of our fluoroenamide substrates can have with the metallic atom of the catalyst, we thought that by using a boronic acid (hard nucleophile), we could easily and selectively obtain *Z*-arylated alkenes. Rhodium has been selected as transition metal because it is one of the metals that have been proven to coordinate with heteroatoms.

Scheme 1. Strategies to Accomplish of Allylic Arylations States of art



No allylic arylation with allylic fluorides has been reported at this date

This Work: Allylic Arylation from Allylic Fluoride via β -F elimination

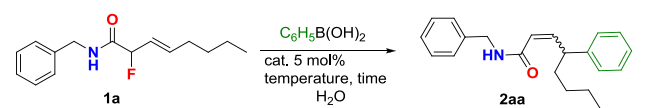


The challenge for us is to answer different questions: How could we orient the selectivity in favor of the thermodynamically less stable *Z*-isomer? How to avoid a second addition of aryl-boronics on the α,β -unsaturated amide formed? How could we get total regioselectivity? Is there a transfer of chirality if we start from a chiral compound?

Here we report an unprecedented catalytic process that allows generating both the γ stereocenter and the *Z*-olefin in one step via the creation of a Csp²-Csp³ bond (Scheme 1).

Initially, α -fluoroamide **1a** was examined as an allylating agent for phenylboronic acid in the presence of a variety of catalysts in water (Table 1). A control reaction conducted in the absence of catalyst with phenylboronic acid as a nucleophile, demonstrate that transformation is only induced by the presence of the catalyst (Table 1, entry 1). Although the reaction hardly proceeded with rhodium (I) catalysts (entries 2-5), the yield was greatly improved with a catalytic amount of rhodium (I) catalyst (entry 6). On the other hand, a significant quantity of the product resulting from the β -H elimination was observed. The same result was observed using a rhodium (II) catalyst but with an increased ratio in favor of the *Z*-isomer (entry 7). Using rhodium trichloride no reaction was observed (entry 8). But, the use of the rhodium (III) (Cp**RhCl*₂)₂ complex allowed us to obtain the product with excellent yield and a high *Z/E* ratio in favor of the *Z* isomer (entry 9). What must be noted is the absence of the product resulting from the β -H elimination. By lowering the temperature, we observed a decrease of the ratio *Z/E* (entries 10-11). No significant improvement in the *Z/E* ratio was observed at 100 °C.

Table 1. Screening of Rhodium catalysts^a



entry	catalyst	T °C (time)	yield %	<i>Z/E</i> ratio
1	-	80 (16h)	N. R	-
2	(<i>S,S</i>)-Et-DUPHOS-Rh	80 (1h)	<10 +SM	2.1:1
3	Rh(COD) ₂ BF ₄	80 (1h)	<10 +S.M	2.6:1
4	RhCl(PPh ₃) ₃	80 (1h)	N.R.	-
5	[RhCl(COD)] ₂	80 (1h)	<5 +S.M	1.5:1
6	[Rh(OH)(COD)] ₂	80 (1h)	40 ^a	1.7:1
7	Rh ₂ (OOCCH ₃) ₄	80 (1h)	32 ^c	2.6:1
8	RhCl ₃	80 (1h)	NR	-
9	(Cp* <i>RhCl</i> ₂) ₂	80 (3h)	94 ^a	4.4:1
10	(Cp* <i>RhCl</i> ₂) ₂	40 (24h)	80 ^c	1.6:1
11	(Cp* <i>RhCl</i> ₂) ₂	25 (72h)	87 ^c	1:1

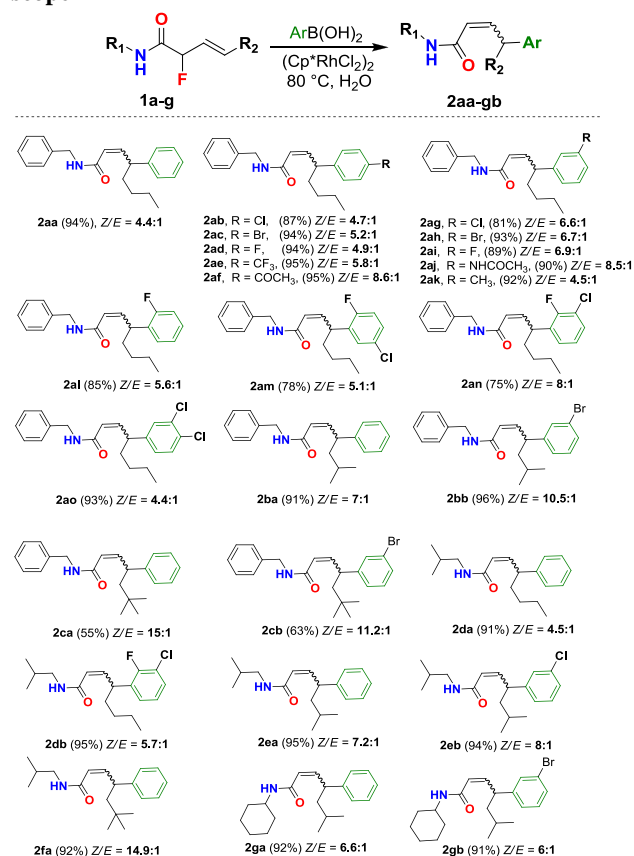
^a Reaction conditions: **1a** (0.4 mmol), PhB(OH)₂ (0.8 mmol), catalyst 5 mol %, H₂O (1 mL). ^b Isolated yield. ^c Yields determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as internal standard.

Recently, the Sanford group¹⁶ has described the preparation of (Cp**RhCl*₂)₂ in situ in 2-propanol from RhCl₃ and the pentamethylcyclopentadiene (Cp**H*). We have tested these conditions in the presence of compound **1a** and phenylboronic acid and no formation of desired product was observed. This lack of reactivity was confirmed using commercial

(Cp**RhCl*₂)₂. However, the association of RhCl₃ and (Cp**H*) in water allowed to obtain the arylated product. This result clearly shows that the catalyst (Cp**RhCl*₂)₂ can be generated in situ in water and the use of isopropanol instead of water inhibits the reaction. Other organic solvents (THF, Dioxane, MeOH, and toluene) had the same inhibition effect.¹⁷ The reactions afforded exclusively the γ -substitution products.

To generalize those conditions, a series of substituted *N*-benzylamide (**1a**, **1b**, and **1c**) were examined with Arylboronic acid, mono or di-substituted arylboronic acids bearing both electron-withdrawing and electron-donating groups (Cl, Br, F, CF₃, COCH₃, NHCOCH₃, Me), in both the para, meta and ortho positions. The desired products **2ab** to **2bb** were obtained in good yield (75-95%) and a high *Z/E* selectivity (4.4/1 to 10.5/1). Using other boronic acids having substituents in the ortho position such as 2-bromo phenylboronic acid and 2,6-dimethyl phenyl boronic acid no reaction was observed using the substrate **1a** presumably due to steric effects. On the other hand, the product yield decreased only for the product **2ca** in 55% yield (R₂ = CH₂*t*Bu), but with an excellent *Z/E* ratio 15:1 (Scheme 2). By contrast, the combination of (R₂ = CH₂*t*Bu) with 3-bromophenylboronic acid gives only a ratio of 11.3/1 in favor of *Z* for the product **2cb** in 63% yield.

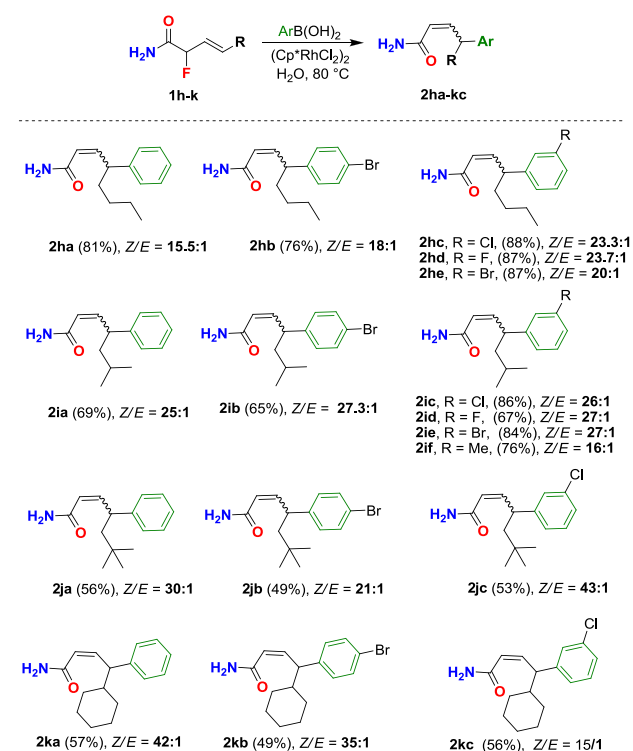
Scheme 2. Investigation of the secondary amide substrates scope^{a,b,c}



^a Reaction conditions: **1a** (1 equiv), ArB(OH)₂ (2 equiv), (Cp**RhCl*₂)₂ 4-5 mol %, H₂O (C = 0.2-0.6 M) see supporting information. ^b Isolated yield. ^c ratio *Z/E* determined by ¹H NMR analysis of the crude reaction.

We showed that the reaction is sensitive to the electronic and steric effects of the aryl boronic acids and the substituent R_2 in γ -position of **1**, but also by the nature of the substituent R_1 of the amide as shown in the results for a series N-isobutyl amide (**1d-1f**) and cyclohexyl amide **1g** (Scheme 2). The desired products **2da-2gb** were obtained in good yield (91-95%) and good ratio Z/E (4.5/1 to 14.9/1). On the other hand, the reactivity is better in the most sensitive case ($R_2 = \text{CH}_2\text{tBu}$) since the product **2fa** (92%) is obtained after 15h of reaction while for the product **2ca** the reaction is not complete after the same reaction time. It is important to note that for the amides derived from anilines, a decrease in reactivity was observed at long reaction times (14 h) and with a low Z/E ratio in favor of the Z isomer. Based on these results, we then investigated the case of primary amides to study the influence of a non-substituent amide on the reactivity and the stereoselectivity of the reaction. A series of primary α -fluoroamide substrates **1h-1k** has been studied with a variety of phenylboronic acid, affording the corresponding products **2ha-2ka** in moderate to good yield (up to 81%) and an excellent Z/E ratio (15.5/1 to 43/1) (Scheme 3). Finally, we investigated other arylboronic acids bearing either electron-withdrawing or electron-donating groups (3-Cl, 3-Br, 3-F, 3-Me, and 4-Br). The desired products **2hb-2kc** were obtained in 49-88% yield and with an excellent Z/E ratio (15/1 to 43/1) (Scheme 3).

Scheme 3. Investigation of the primary amide substrates scope^{a,b,c}



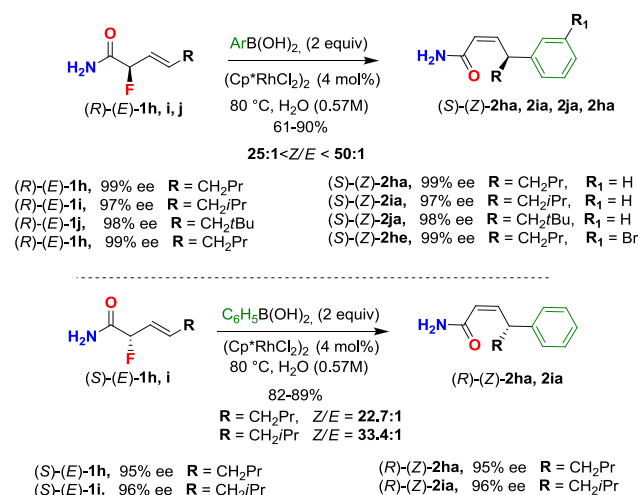
^a Reaction conditions: **1a** (1 equiv), ArB(OH)_2 (2 equiv), $(\text{Cp}^*\text{RhCl}_2)_2$ 4-5 mol %, H_2O (C = 0.3-0.8 M) see supporting information. ^b Isolated yield of Z -product. ^c ratio Z/E determined by ^1H NMR analysis of the crude reaction.

The coordination of nitrogen rather than carbonyl has been demonstrated. No reaction occurs when the amide is replaced with an ester. On the other hand, with a tertiary amide (morpholine) the reaction occurs moderately in favor of the isomer E .¹⁷ The origin of (Z)-stereoselectivity and regioselectivity can be explained by coordination of the rhodium catalyst with amide N -atom and the formation of the five-membered rhodacycle intermediate followed by β -fluorine elimination (Scheme 6).

For these considerations, we chose to study the stereospecificity of the reaction with chiral allylic fluorides bearing a primary amide moiety.¹⁸

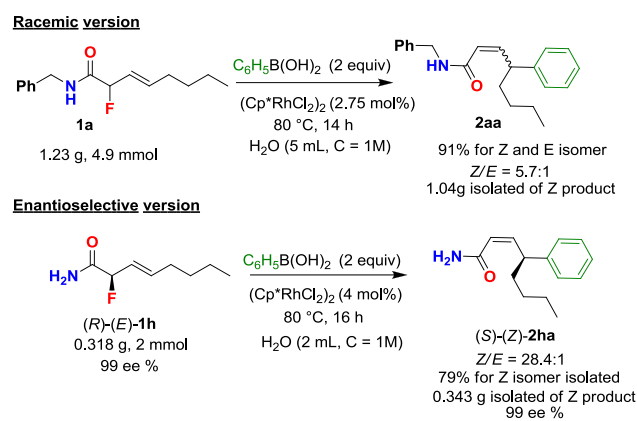
The reaction of the (R)-(E)-**1h** (99% ee), which has a γ - CH_2Pr substituent, with phenylboronic acid in the presence $(\text{Cp}^*\text{RhCl}_2)_2$ gave (S)-(Z)-**2ha** (99% ee), indicating that the allyl-aryl coupling with an α -chiral allylic fluorides took place with excellent α -to- γ position chirality transfer. The reaction of (R)-(E)-**1i** and (R)-(E)-**1j**, which has respectively γ - CH_2iPr and γ - CH_2tBu substituents, with phenylboronic acid gave (S)-(Z)-**2ia** (97% ee) and (S)-(Z)-**2ja** (98% ee), suggesting that the efficiency of the chirality transfer is not significantly influenced by the steric demand of the γ -substituent (Scheme 4). Similarly, when using the 3-bromophenylboronic acid the chirality transfer in the arylation of the (R)-(E)-**1h** (99% ee), is not affected, the (S)-(Z)-**2he** is obtained with excellent ee 99%. This transfer of chirality was confirmed starting from chiral allylic fluorides of S -configuration (Scheme 4).

Scheme 4. Arylation of the Chiral allylic Fluorides



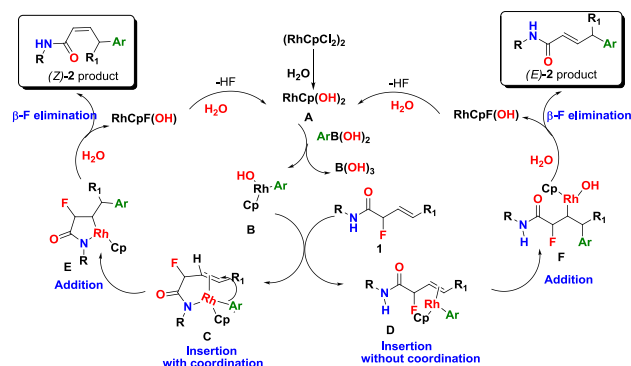
Subsequently, we conducted large-scale reactions of the Rh (III) catalyzed fluorinated alkene arylation method to demonstrate the practicality and operational simplicity of this methodology. This large-scale process was performed in racemic, and stereospecific versions giving high yield, good Z/E ratio and 99% ee (Scheme 5).

Scheme 5. Large-Scale allylic Arylations



Based on the above experimental results, we propose a simplified mechanistic model for the formation of the *Z*-arylated and *E*-arylated products, shown in (Scheme 6). $(\text{Cp}^*\text{RhCl}_2)_2$ reacts with H_2O to produce the active rhodium species **A**, which would react with arylboronic acid to form the arylrhodium (III) intermediate **B**. Subsequently, **B** forms with the allylic fluoride **1** the complex **C** (major) after deprotonation and coordination of the nitrogen atom. The complex **C** then undergoes regioselective C-C double bond insertion into the arylrhodium bond to form a five-membered rhodacycle **E**. Finally, β -fluorine elimination rather than β -hydride elimination from **E** affords coupling product (*Z*)-**2** and regenerates **A** to close the catalytic cycle.

Scheme 6. Proposed catalytic cycle.

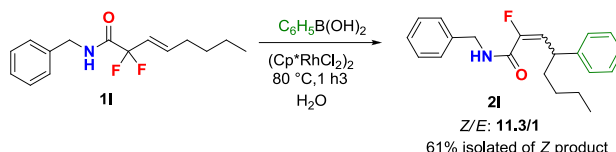


The formation of the *E*-arylated product can be explained by the formation of the non-coordinated complex **D**, which then undergoes a regioselective insertion of the double bond C-C in the aryl-rhodium bond to form the complex **F**. The latter then undergoes a *syn* β -fluorine elimination to form (*E*)-**2** and regenerates **A**. At this stage, no precedent for β -fluorine elimination from allyl fluoride in the presence of rhodium catalyst has been reported in the literature.¹⁹ It is important to note that for our substrates, the β -fluorine elimination process is very

fast compared to β -acetoxy elimination as shown by NMR spectra (see details for Supporting Information S24).

Similarly, the β -fluorine elimination is not impacted by the presence of a second fluorine at the gem position, and the *Z/E* isomer ratio is even higher (see details for Supporting Information S66). This example is the first described from the gem-difluoro alkenes catalysis with Rh(III) (Scheme 7). The only examples in the literature dealing with the case of gem-difluoroalkenes have been studied in the presence of catalysts based on Co (III), Mn (I or 0)²⁰ and copper(I).²¹

Scheme 7. Allylic Arylations of gem-difluorenamides



Finally, the functionalization of compound **2ac** under the conditions of stille coupling at high temperature showed the high *Z* double bond stability, no isomerization was observed.¹⁷

In summary, we have established a highly efficient, green and sustainable protocol for rhodium(III)-catalyzed γ -selective and stereospecific reaction between functionalized allylic fluoride and arylboronic acids, which gave α,β -unsaturated amides with a high *Z* selectivity and a γ stereogenic center *via* the creation of a Csp²-Csp³ bond.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org>.

General information, experimental procedures, characterization data and NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

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