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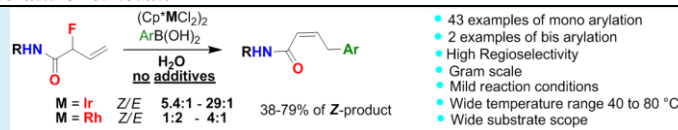
Iridium (III) catalyzed Z-selective Allylic Arylation of α -fluoro but-1-enoic acid amides via β -F-elimination in Water

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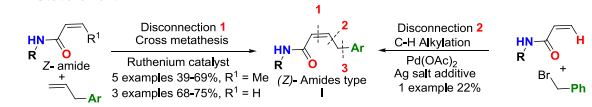
ABSTRACT: Allylic arylation of α -fluoro but-1-enoic acid amides with arylboronic acids was carried out in water by comparing the catalytic activity of iridium(III) and rhodium (III). Ir(III) has shown a strong superiority over Rh(III) to give allyl-aryl coupling products with excellent stereoselectivity in favor of the Z isomer. The origin of high stereoselectivity is perhaps because of the a coordination of iridium Ir-N or Ir-O.

The allylic arylation is an versatile reaction for the creation of a $Csp^2(Ar)-Csp^3$ bond.¹⁻⁵ Different metals were used in this reaction. Among these metals, iridium, which has demonstrated its reactivity in many transformations⁶ was rarely during allylic arylation.⁷ In addition, during allylic arylations, the products obtained possess olefins with a predominant *E* stereochemistry. Although the synthesis of *E*-alkenes is well established, the synthesis of *Z*-alkenes is less represented, particularly from an allylic substitution process. The direct synthesis of γ -aryl-(*Z*)- α,β -unsaturated amides of type **I** remains a major challenge. The synthesis of these compounds was accomplished either through a cross metathesis reaction of acrylamides⁸ (disconnection 1) or via assisted C-H alkylation⁹ (disconnection 2) (Scheme 1a). Recently, our group reported the first $(Cp^*Rh(III)Cl_2)_2$ catalyzed allylic arylation in water. This reaction occurred regioselectively at the γ position of the α -fluoro but-1-enoic acid amides of type **A** to produce γ -substituted- α,β -unsaturated amides with high *Z* selectivity (Scheme 1b).¹⁰ During this study we observed that reactivity and stereoselectivity were controlled by the coordination effect of the amide and the steric effect of the substituent **R** of the double bond. During this study, the role of **R** substituent of the double bond is essential. This role of the **R** substituent is so decisive that its absence resulted in deterioration of the *Z/E* ratio (Scheme 1c).

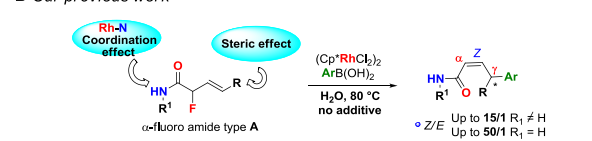
Herein, we report the synthesis of (*Z*)- α,β -unsaturated amides **I** from α -fluoro but-1-enoic acid amides of type **B** via *Z*-selective allylic arylation catalyzed by $(Cp^*Ir(III)Cl_2)_2$ (disconnection 3) (Scheme 1d). To compensate for the absence of the steric effect, we decided to focus our work on the coordination effect of the metal used in the catalyst by comparing the catalytic activity of $(Cp^*IrCl_2)_2$ and $(Cp^*RhCl_2)_2$. Iridium(III) has been described as a harder and stronger Lewis acid than rhodium(III) due to the relativistic contraction of iridium. This difference in the Lewis acid character of iridium compared to rhodium influences the catalytic activity of the two complexes **AM1** and **AM2**, which have a different reactivity on α -fluoro but-1-enoic

Scheme 1. Strategies for Synthesis of (*Z*)- α,β -unsaturated amides

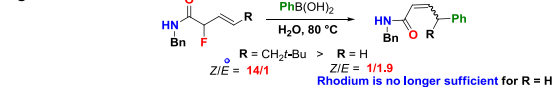
A- State of art



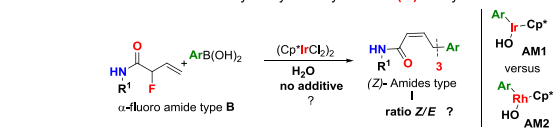
B-Our previous work



C



D- Present Work : Z-selective Allylic Arylation by Iridium (III) catalysis in water via β -F elimination

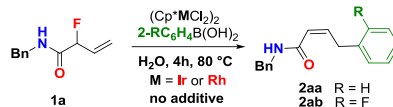


acid amides of type **B**. The metals ($M = Rh, Ir$) have different modes of **M-N** and **M-O** coordination with amides.¹¹

To verify the postulate, we probed the reaction conditions for allylic arylation catalyzed by rhodium and iridium on the secondary amide **1a** with phenylboronic acid in water and without additives (Table 1). As anticipated, the desired transformation has proven to be highly efficient and the nature of the metal appeared to have a considerable effect on the stereoselectivity of the product. Indeed, the reaction with iridium favored *Z*-isomer **Z-2aa** (*Z/E* = 6.6:1), while with rhodium provided a mixture of isomers (*Z/E* = 1:1.9) (entries 2, 3). In the reaction with rhodium, we observed the bis-arylation product of resulting from the 1,4 addition of phenyl boronic acid onto **2aa**. On the

other hand, when 1 eq of boronic acid is used, no bis-arylation product was observed with the Rh(III) catalyst (see [SI](#) for details [S7](#)). This secondary product was not formed with iridium.

Table 1. First comparison studies between Ir and Rh^a

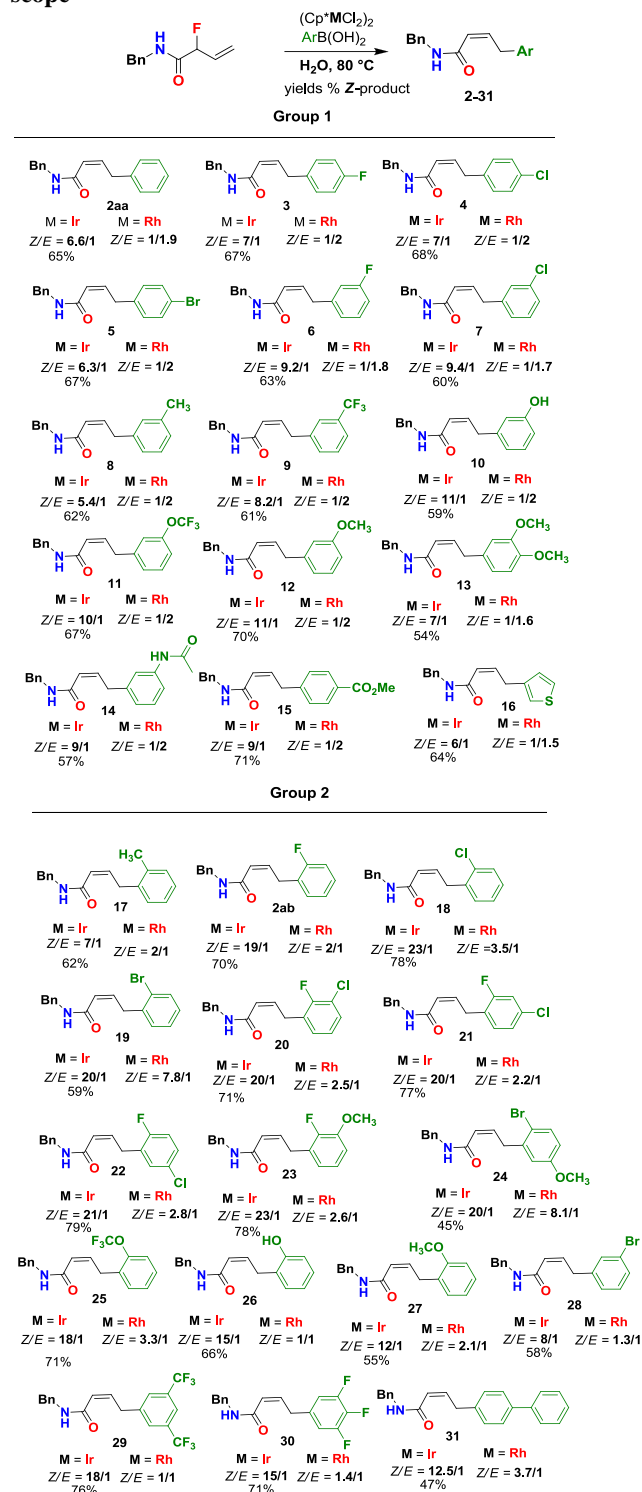


entry	Catalyst (mol%)	R	yield (%) ^{b, c}	Z/E
1	-	H	N. R	-
2	(Cp*RhCl ₂) ₂	H	59 ^b	1:1.9
3	(Cp*IrCl ₂) ₂	H	60 ^c	6.6:1
4	(Cp*RhCl ₂) ₂	F	96 ^b	2:1
5	(Cp*IrCl ₂) ₂	F	70 ^c	19:1
6	(Cp*IrCl ₂) ₂ ^d	F	72 ^c	19:1
7 ^e	(Cp*IrCl ₂) ₂	F	72 ^c	19:1

^a Reaction conditions: **1a** (0.5 mmol), **ArB(OH)₂** (1 mmol), catalyst 4 mol %, H₂O (1 mL). ^b Yields of Z+E isomers determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as internal standard. ^c Yield of isolated Z-product. ^d catalyst 10 mol %. ^e Premixed catalyst and water (C = 0.1 M) at 80 °C for 40 min followed by addition **1a** and **ArB(OH)₂**

To check whether the difference in stereoselectivity is sensitive to the substituents of the arylboronic acid, the reaction was performed with arylboronic acid containing a fluoro substitution at the ortho position. Employing Rh(III) catalyst produced the product **2ab** with 2:1 Z/E ratio, whereas the reaction with Ir(III) gave **2ab** with an excellent Z/E ratio of 19:1 (entries 4, 5). Increase in the catalyst loading (entry 6) as well as the premixing of the catalyst in water¹² before adding the catalyst and the substrates did not alter the Z/E ratio (entry 7). It is important to note that the β-fluorine elimination process is very fast and stereoselective compared to β-acetoxy elimination as shown by NMR (see [SI](#) for details [S8-9](#)). However, the reaction did not work at all in CH₃CN, toluene, THF, DMSO, HFIP and iPrOH (see [SI](#) for details [S10](#)). We also established a kinetic profile of the Ir(III) catalyzed reaction (4 mol%) of **1a** with 2-fluorophenylboronic acid over a period of 28h (see [SI](#) for details [S11-12](#)). This profile clearly shows that at a temperature of 80 °C the ratio (Z/E = 19:1) remains constant up to 4h and that beyond this time we observe an erosion of the Z/E ratio up to 14:1. Performing the reaction with 1, 2 and 3 mol% of Ir(III) catalyst in the reaction of **1a** and 2-fluorophenylboronic acid, formation of the Z isomer is predominant (see [SI](#) for [S13](#)). The Z/E ratio increases by lowering the temperature but requires a long time of 24 hours. These interesting results show that this iridium catalyzed arylation reaction can be carried out over a wide temperature range (see [SI](#) for details of the boronic acid (2F, 2Cl and 2Br) [S14-19](#)). For the rest of the study, we chose the temperature 80 °C with a short time of 4 hours. Taking into account the notable difference in stereoselectivity observed in the first two examples between the catalysts (Cp*IrCl₂)₂ and (Cp*RhCl₂)₂, we explored the reaction of allylic arylation with different arylboronic acids. These results can be classified into two groups ([Scheme 2](#)). In the first group, all substituted or disubstituted aryl boronic acids in the *meta* and *para* position (F, Cl, CH₃, CF₃, OH, OCF₃, NHCOCH₃, CO₂CH₃) except 3-bromophenylboronic acid were used as reactants. The Z-products (**2aa**, **3-16**) were obtained with a yield varying between 57-72%.

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

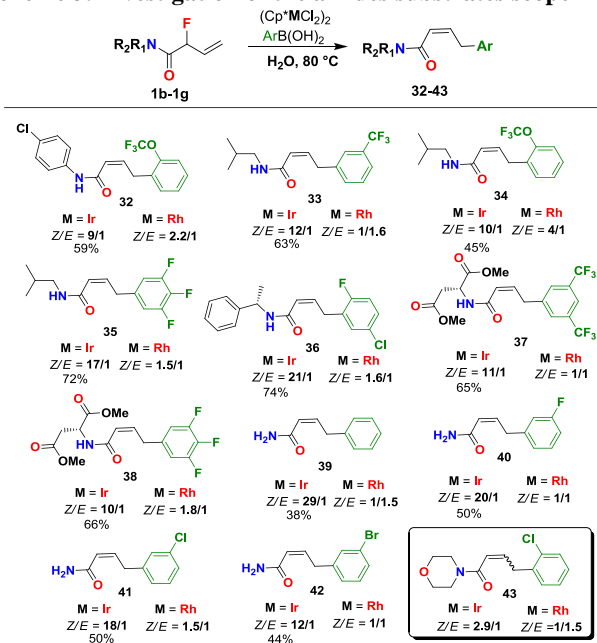


^a Reaction conditions: **1a** (1 eq), **ArB(OH)₂** (2 eq), catalyst 4-5 mol %, H₂O (C = 0.52 M) see [SI](#). ^b Isolated yield of Z-product. ^c ratio Z/E determined by ¹H NMR analysis of the crude reaction.

The second group contains aryl boronic acids substituted at the ortho and the arylation products (**2ab**, **17-27**) were obtained with the iridium catalyst with a Z/E ratio varying between 7:1 and 20:1. In the second group, the case of di and trisubstituted compounds **29** and **30** is particularly noted, which are obtained

with high *Z/E* ratio in comparison with the monosubstituted compounds **9** and **6** of the first group. The superiority of iridium (*Z/E* = 9: 1 to 29: 1) over rhodium (*Z/E* = 1: 1.6 to 2.2: 1) has been confirmed with other secondary and primary fluorinated amides **1b-1g** (Scheme 3). The *Z*-products (**32-42**) were obtained with a yield varying between 38-74%. It is worth noting that when 4-pyridylboronic acid is used in the presence of iridium (III) no reaction was observed, the starting product remains unchanged. Presumably, pyridylboronic acid breaks the Ir-amide bond and deactivates the catalyst.

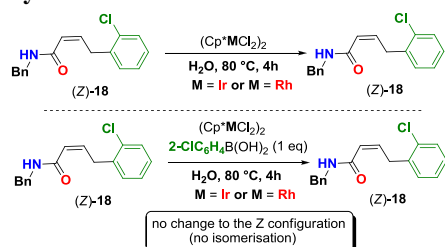
Scheme 3. Investigation of the amides substrates scope^{a,b,c}



^a Reaction conditions: **1b-1g** (1 eq), **ArB(OH)₂** (2 eq), catalyst 4-5 mol %, H₂O (C = 0.35-0.97 M) see supporting information. ^b Isolated yield of *Z* product. ^c ratio *Z/E* determined by 1 H NMR analysis of the crude reaction.

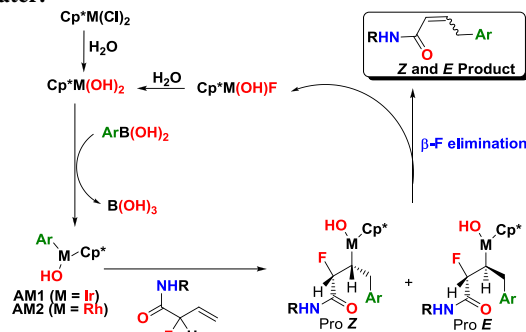
It is important to note the case of tertiary amide **43**, the use of a hindered aryl boronic and despite the absence of NH, iridium gave the product with *Z* olefin as a major isomer (*Z/E* = 2.9:1) while rhodium gave the product with *E* olefin as a major isomer (*Z/E* = 1:1.7). This demonstrates that an Ir-O type coordination cannot be ruled out.

Scheme 4. Isomerization Studies with catalysts and with or without arylboronic



Interestingly, the *Z* configuration of isolated product (*Z*) was found to be unaltered upon exposure to the iridium or rhodium catalysis procedure with or without arylboronic acid, thereby excluding a post arylation isomerization process (Scheme 4) (see SI for details S20-21).

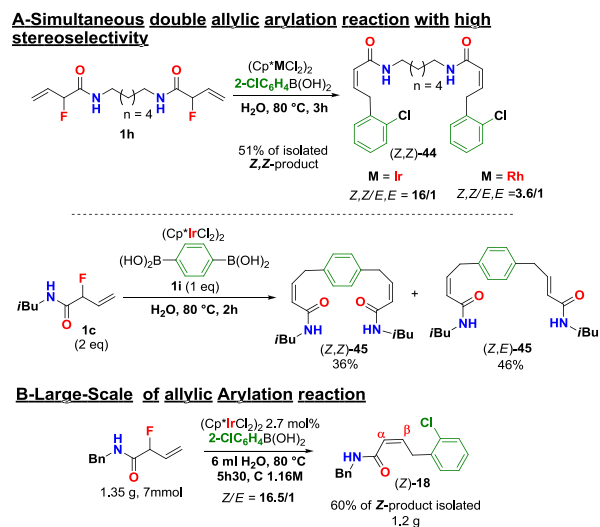
Scheme 5. Plausible mechanism for *Z*-Allylic Arylation in water.



We assume that after transmetalation, the insertion of the aryl metal is done after η^2 -coordination of the C-C double bond on the cation. This step is assisted by the coordination of the N or O atom or without coordination, which are only different rotamers of the same structure. The migratory insertion thus leading to the intermediate pro*Z* and pro*E*. β -F-elimination^{13,14} from the pro*Z* and pro*E* intermediates leads to the product *Z* and *E* olefins respectively. At this stage, the preference for the formation of the *Z*-olefin from the reaction with **AM1** (M= Ir) is not clear. The theoretical and experimental investigations to elucidate the difference in formation of *Z* and *E* olefin products with the iridium and rhodium catalysts used is under investigation.¹⁵

The fact that we obtain the *Z* olefin, we believe that a π -metal-allyl intermediate is a less possibility, although recently such a *Z* olefin was obtained via π -metal-allyl intermediate starting from a *Z* olefin.^{16,17} **AM1** and **AM2** lead to different isomer ratio. In an attempt to explain this difference, we performed reactions with both catalysts simultaneously. The results obtained from seven significant examples indicate a drop in the *Z/E* ratio, but remains in favor of the *Z* isomer, which shows that the iridium is better in the presence of rhodium. This result indicates that the catalytic activity of the two arylmetals **AM1**(Ir) and **AM2** (Rh) is very different (see SI for details S22-23).

Scheme 6. The bis allylic arylation and large-scale reaction



This reaction is also effective in the biarylation of the bis amide **1h** and with a substrate a substrate having two boronic acid sites **1i** (Scheme 6A). In both cases, we were able to obtain and isolate new molecular architectures (*Z,Z*-**44**, (*Z,Z*)-**45** and (*Z,Z*)-**45** with satisfactory yields. These two examples show the robustness of this arylation reaction in water, which is also demonstrated by the gram-scale reaction of **1a**, and 2-chlorophenylboronic acid. The desired (*Z*)-**18** acrylamide was obtained in 65% yield (Scheme 6B). The synthetic transformations via functionalisation of α and β positions of compound **18** were carried out. (see SI for details S45-49 and S213-233).

In summary, we established Ir-catalyzed selective reaction between functionalized allylic fluoride and arylboronic acids to obtain unsaturated *Z*-amides via the creation of a Csp²-Csp³ bond. In this study, we have demonstrated the superiority of the Ir(III) catalyst over Rh(III) in the formation of the product.

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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