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Development of the first Suzuki-Miyaura cross-coupling for the formation of alkylfluorostilbenes and studies of the *E/Z*- isomerization *of (2-bromo-2-fluorovinyl)-benzene derivatives*

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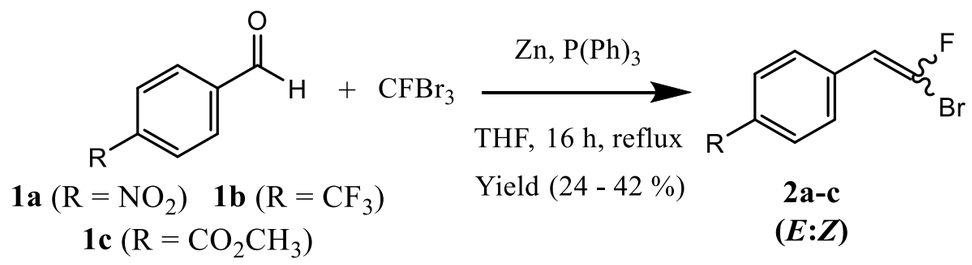
Objectives

Development of new methodologies for the synthesis of fluoro-organic compounds have gained great interest during the past decades, especially for applications in the fields of medical chemistry and agrochemistry. Introduction of fluorine atoms can drastically enhance biological properties such as bioavailability, lipophilicity, half-time and absorption [1]. The aim of this thesis research is to develop the first Suzuki-Miyaura reaction leading to alkylfluorostilbenes. Different reaction parameters like temperature and nature of the catalyst have been investigated and a scope of the reaction has been realized. Subsequently, isomerism-studies were performed.

1. Synthesis of starting materials

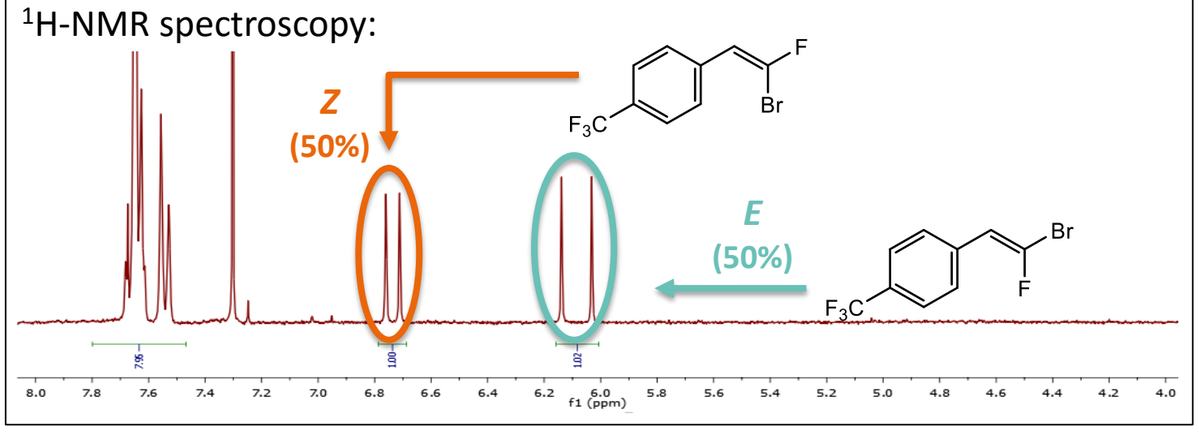
(E/Z)-(2-bromo-2-fluorovinyl)-benzene derivatives were obtained through a Wittig reaction starting from the corresponding aldehyde.



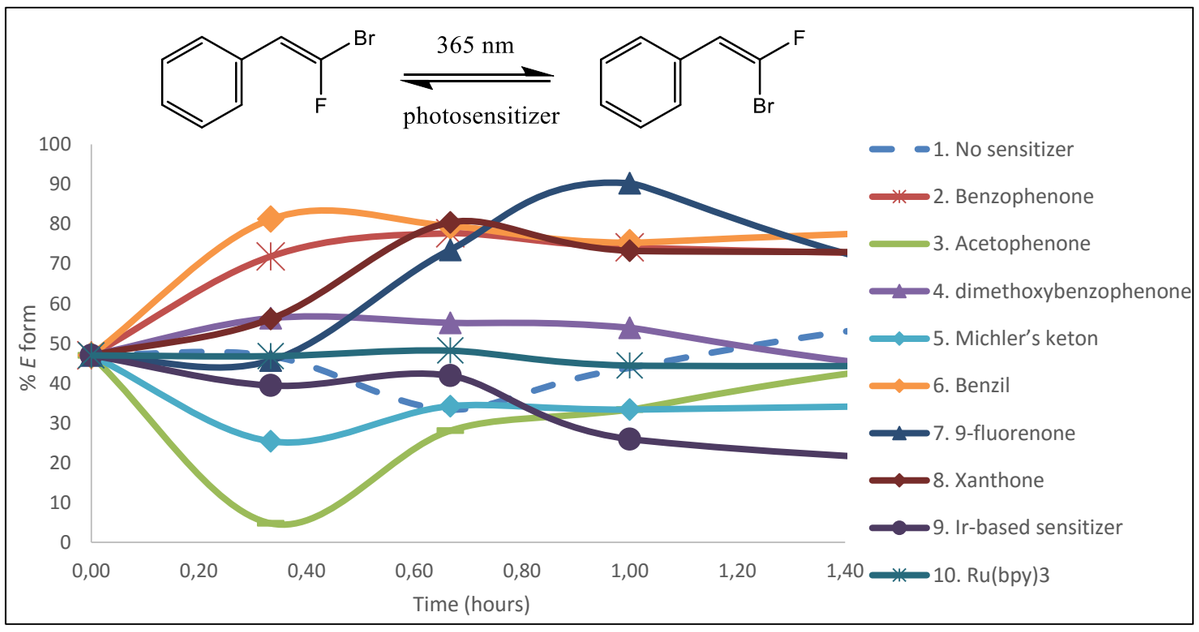
1a (R = NO_2) **1b** (R = CF_3) **1c** (R = CO_2CH_3)

2a-c (***E*:*Z***)

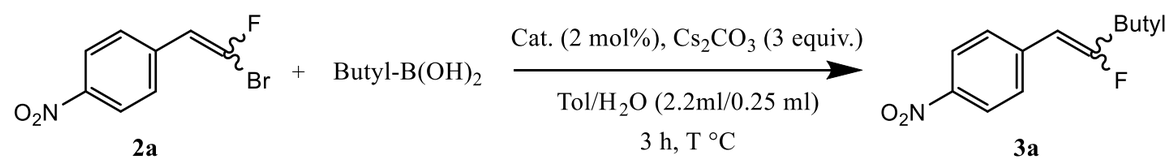
^{1}H-NMR spectroscopy:



2. Isomerization



3. Optimization of the Suzuki-Miyaura

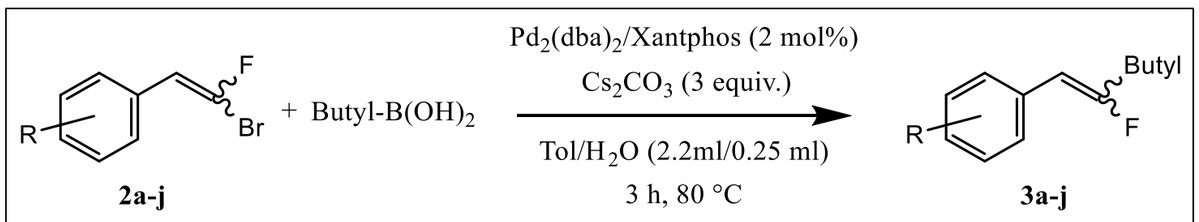


2a **3a**

Entry[a]	catalyst	2a (*E*:*Z*)[b]	T °C	3a (*E*:*Z*)[b]	Yield (%)
1	$PdCl_2$dppF	46:54	RT	-	-
	Pd_2dba_3/Xantphos			-	-
2	$PdCl_2$dppF	46:54	60	55:45	51[c]
	Pd_2dba_3/Xantphos			52:48	29[c]
3	$PdCl_2$dppF	46:54	80	55:45	97[d]
	Pd_2dba_3/Xantphos			49:51	99[d]
4	$PdCl_2$dppF	87:13	80	17:83	93[d]

a) All the reactions were performed under inert atmosphere. b) The *E*:*Z*-ratio was determined from ^{1}H-NMR spectroscopy, thanks to characteristic doublets of the vinylic proton around 6 ppm. c) An internal standard was added to calculate NMR yields. d) isolated yields were obtained after purification of the product by column chromatography on silica gel.

4. Scope of the Suzuki-Miyaura reaction



2a-j **3a-j**

Entry[a]	-R	2 (*E*:*Z*)[b]	3 (*E*:*Z*)[b]	Yield (%)[d]
a	-*p*-NO_2	46:54	48:52	99
b	-*p*-H	47:53	46:54	81
c	-*p*-OCH_3	48:52	41:59	96
d	-*p*-CF_3	50:50	53:47	95
e	-*p*-CO_2CH_3	45:55	46:54	89
g	-*p*-Cl	47:53	46:54	88
h	-*p*-CH_3	49:51	49:51	96
i	-*o*-OCH_3	41:59	40:60	81
j	-*m*-NO_2	53:48	49:51	99

Conclusion

The first Suzuki-Miyaura cross-coupling reaction with (*E*/*Z*)-(2-bromo-2-fluorovinyl)-benzene derivatives and alkylboronic acids as coupling partners was developed with yields above 80% and maintaining excellent stereoselectivity. Regarding the isomerization reaction, 2 photosensitizers (benzil and 9-fluorenone) show promising results and further studies are still ongoing in the laboratory to obtain a robust protocol.

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Reference: [1] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. Luis Aceña, V. A. Soloshonok, K. Izawa and H. Liu, "Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II−III Clinical Trials of Major Pharmaceutical Companies, …" *Chem. Rev.*, vol. 116, p. 422–518, 2016.