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Ligand-dependent stereoselective Suzuki–Miyaura cross-coupling reactions of β-enamido triflates

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Letter

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Abstract

The stereoselective Suzuki–Miyaura cross-coupling of (*Z*)-β-enamido triflates is demonstrated. Depending on the nature of the ligand in the palladium catalyst, either retention or inversion of the configuration during the synthesis of β,β-diaryl-substituted enamides is observed. Thus, the method provides synthetic access to both isomers of the target enamides from (*Z*)-β-enamido triflates.

Introduction

Enamides are substrates of high value in organic synthesis [1,2]. Their multifacial reactivity has been explored in asymmetric alkylations [3], hydroalkynylations [4], trifluoromethylcyanations [5], heterocycle synthesis [6], asymmetric acylations [7], hydroborations [8], hydrogenations [9], etc. They are also important pharmacophores, which display a range of cytotoxic, antifungal, or antibiotic properties [10-12]. Modern stereoselective syntheses leading to highly substituted enamides include cross-coupling of vinyl (pseudo)halides or organoboron compounds [13], hydroamidation of alkynes [14-16], ynamide functionalization [17-19], or isomerization of *N*-allyl amides [20], but still possess drawbacks, especially for stereoselective synthesis of tri- and tetrasubstituted enamides.

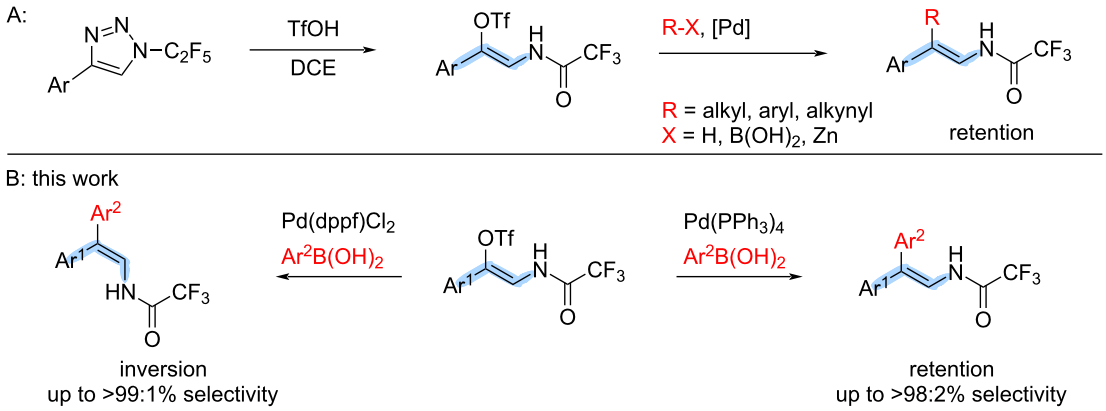
Recently, we have reported a triflic acid-mediated reaction of *N*-fluoroalkyl-1,2,3-triazoles leading to (*Z*)-β-enamido triflates [21] and Lewis acid-mediated reaction to (*Z*)-β-enamido fluorides [22] and halovinyl imidoyl halides [23]. In addition, Li and co-workers extended the scope of accessible (*Z*)-β-enamido triflates by denitrogenative reaction of *N*1-*H*-1,2,3-triazoles in the presence of acyl halides and sodium triflate [24]. These enamido triflates and halides were found to undergo cross-cou-

pling reactions with retention of configuration on the double bond and served as valuable starting materials for the synthesis of functionalized β,β-disubstituted enamides (Scheme 1A) [21,23].

In the last decade, only a few reports describing isomerization of the double bond of vinyl (pseudo)halides during the Suzuki coupling have been published [25-29]. Typically, inversion of configuration occurs on substrates containing a double bond in conjugation with an electron-withdrawing group, such as the carbonyl group in enones [27,30]. We hypothesized that (*Z*)-β-enamido triflates could, during the Suzuki cross-coupling, undergo isomerization of the double bond, similarly to enones, and thus serve as starting materials to either (*E*) or (*Z*)-isomers of enamides depending on the conditions used. Here we present a study of the effect of ligand on the stereoselective outcome of the Suzuki cross-coupling reaction of various (*Z*)-β-enamido triflates (Scheme 1B).

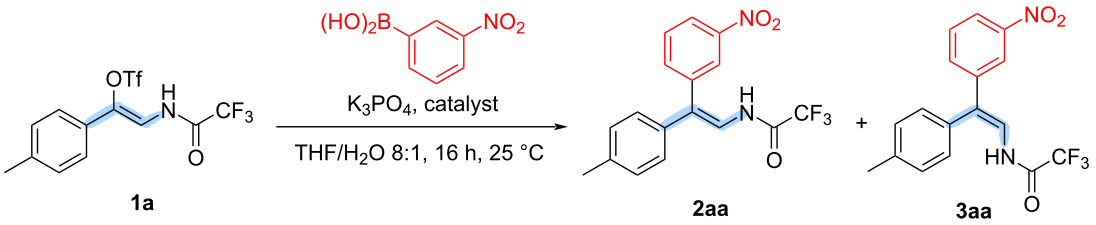
Results and Discussion

We initiated our study by examining the Suzuki cross-coupling of vinyl triflate **1a** and 3-nitrophenylboronic acid. First, the influence of the catalyst on the stereoselective outcome of the reaction was studied (Table 1). The use of $Pd(PPh_3)_4$ resulted in



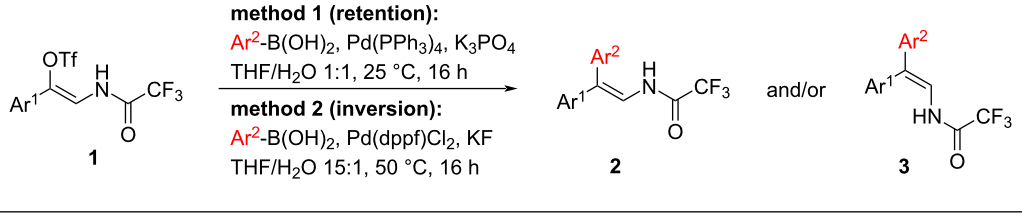
Scheme 1: A: Synthesis of (*Z*)-β-enamido triflates and subsequent stereoselective cross-coupling reactions. B: Ligand-controlled stereoselective synthesis of β,β-diaryl-substituted enamides.

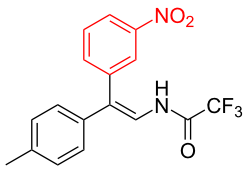
Table 1: The effect of different catalysts on product yields and ratios.



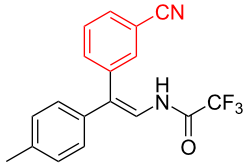
Entry	Catalyst (10 mol %)	Yield (%)[a]	**2aa/3aa**
1	**$Pd(PPh_3)_4$**	**70**	**93:7**
2	$PdCl_2(PPh_3)_2$	80	81:19
3	2-(2'-di-*tert*-butylphosphine)biphenylpalladium(II) acetate	42	83:17
4	Pd(*t*-$Bu_3P)_2$	46	48:52
5	Pd(dtbpf)Cl_2	66	33:67
6	**Pd(dppf)Cl_2**	**70**	**29:71**
7	$Pd(acac)_2$	34	24:76
8	$Pd(dba)_2$	23	22:78
9	$Pd(OAc)_2(PPh_3)_2$	11	18:82

[a]Combined ^{19}F NMR yield of **2aa** and **3aa** using $PhCF_3$ as an internal standard.

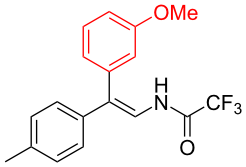




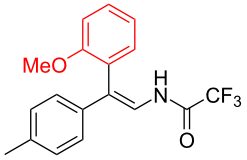
method 1: **2aa/3aa**, 97:3[a], 90%[b], **2aa** (71%)[c]
method 2: **2aa/3aa**, 26:74[a], 95%[b], **3aa** (57%)[c]



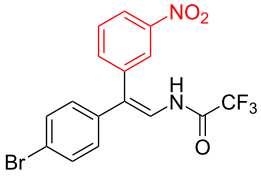
method 1: **2ab/3ab**, >98:2[a], 76%[b], **2ab** (53%)[c]
method 2: **2ab/3ab**, 26:74[a], 81%[c], **3ab** (46%)[c]



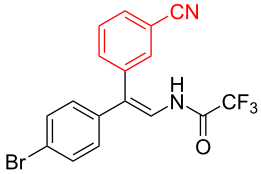
method 1: **2ac/3ac**, >98:2[a], 80%[b], **2ac** (61%)[c]
method 2: **2ac/3ac**, 18:82[a], 69%[b], **3ac** (26%)[c,d]



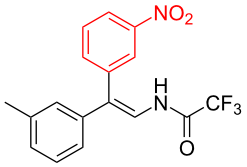
method 1: **2ad/3ad**, 94:6[a], 95%[b], **2ad** (60%)[c]
method 2: **2ad/3ad**, 31:69[a], 96%[b], **3ad** (29%)[c]



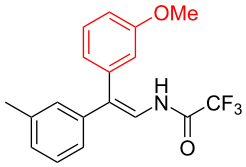
method 1: **2ba/3ba**, >98:2[a], 74%[b], **2ba** (20%)[c]
method 2: **2ba/3ba**, 35:65[a], 41%[b], **3ba** (19%)[c]



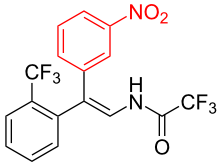
method 1: **2bb/3bb**, >98:2[a], 52%[b], **2bb** (28%)[c]
method 2: **2bb/3bb**, 34:66[a], 60%[b], **3bb** (32%)[c]



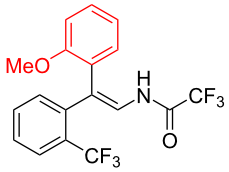
method 1: **2ca/3ca**, >98:2[a], 85%[b], **2ca** (50%)[c]
method 2: **2ca/3ca**, 34:66[a], 72%[b], **3ca** (8%)[c]



method 1: **2cc/3cc**, >98:2[a], 78%[b], **2cc** (43%)[c]
method 2: **3cc** not formed



method 1: **2da/3da**, 83:17[a], 60%[b], **2da** (25%)[c]
method 2: **2da/3da**, 20:80[a], 50%[b], **3da** (33%)[c]



method 1: **2dd/3dd**, 85:15[a], 90%[b], **2dd** (45%)[c]
method 2: **2dd/3dd**, <1:99[a], 65%[b], **3dd** (44%)[c]

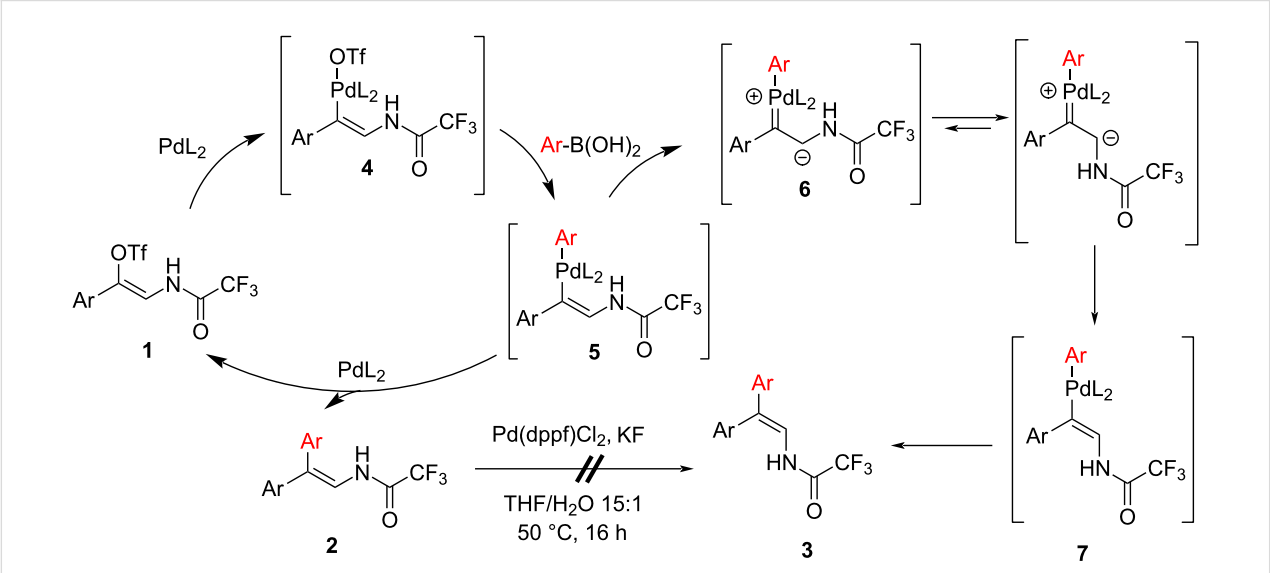
Scheme 2: Substrate scope of the Suzuki coupling leading to enamides **2** and **3**. [a]Ratio determined by ^{19}F NMR; [b]yield determined by ^{19}F NMR using $PhCF_3$ as an internal standard; [c]isolated yield; [d]isolated as a mixture of isomers *E*/*Z* = 64:36.

the formation of isomeric products **2aa** and **3aa** in a 93:7 ratio (Table 1, entry 1). Other catalysts led to significant loss of stereoselectivity on the double bond (Table 1, entries 2–9). When Pd(dppf)Cl_2 was employed, isomeric product **3aa** was preferentially formed (**2aa**/**3aa**, 29:71, Table 1, entry 6). Although other catalysts, such as Pd(acac)$_2$, Pd(dba)$_2$, and Pd(OAc)$_2$(PPh_3)$_2$ showed good selectivity to inversion product **3aa**, the products were formed in low yields (Table 1, entries 7–9). Further screening of the solvent and the base led to the identification of Pd(PPh_3)$_4$ (10 mol %), arylboronic acid (1 equiv), K_3PO_4 (2 equiv) in THF/H_2O 1:1 as ideal conditions providing enamides **2aa** and **3aa** in a 93:7 ratio in 90% ^{19}F NMR yield (Table S1 in Supporting Information File 1).

The optimized conditions were applied to the scope study. Substituted phenylboronic acids and vinyl triflates led to the formation of enamides **2** with high stereoselectivity and in good to high NMR yields (Scheme 2). However, isolated yields were found to be lower due to the decomposition of the formed enamides **2** during column chromatography on silica gel. A moderate loss of stereochemistry was observed only in cases of bulky *ortho*-substitution of either arylboronic acid or vinyl triflate (**2ad**, **2da**, and **2dd**). Alkylboronic acids were found to be unreactive even after prolonged reaction time (**1a** with *n*-hexylboronic acid, 60 h, rt).

Next, conditions for the formation of isomeric products were optimized. Screening the reaction conditions identified Pd(dppf)Cl_2 (10 mol %), arylboronic acid (1.2 equiv), KF (2 equiv) in THF/H_2O 15:1 at 50 °C as a system affording the best obtained ratio and yield in favor to product **3aa** (Table S2 in Supporting Information File 1). Subsequently the optimized conditions for preferential formation of **3** were used in the scope study and in all cases, isomeric products **3** formed preferentially (Scheme 2). The highest selectivity in favor to enamide **3** was noted in the Suzuki coupling of vinyl triflate **1d** bearing a 2-trifluoromethylphenyl group which gave enamides **3da** (**2da**/**3da**, 20:80) and **3dd** (**2dd**/**3dd**, <1:99). It is worth mentioning that the reaction of vinyl triflate **1c** with 3-methoxyphenylboronic acid led to full decomposition of the starting material. The stereochemistry of the double bond in compounds **2** and **3** was determined by 2D ROESY NMR analysis showing interaction between the alkenyl hydrogen and *ortho*-hydrogens on the aryl rings.

Based on previously proposed mechanisms of isomerization in Suzuki cross-coupling reactions, we suggest the following explanation for the observed isomerization [25,29] (Scheme 3). In the first step, vinyl triflate undergoes oxidative addition to give complex **4**, which subsequently transmetalates with arylboronic acid to form palladium complex **5**. In the case of Pd(PPh_3)$_4$, reductive elimination occurs to give enamide **2**. However, using catalysts with very bulky ligands, such as Pd(dppf)Cl_2 causes the tautomerization of complex **5** [30] to zwitterionic carbene **6** which can now isomerize through the C–C bond rotation to the thermodynamically more stable palladium complex **7**, followed by reductive elimination to enamide **3**. A possible isomerization of enamides **2** or **3** in the presence of a catalyst was ruled out because the treatment of **2ca** under conditions leading to inversion of the configuration did not affect the ratio between the resulting enamides.



Scheme 3: Proposed mechanisms for the formed Suzuki coupling retention products **2** and inversion products **3**.

Conclusion

In conclusion, the stereoselective outcome of the Suzuki cross-coupling of vinyl triflates **1** with arylboronic acids was found to be catalyst dependent. The use of $Pd(PPh_3)_4$ led to the selective formation of enamides **2** with retention of configuration of the double bond. Reactions with other catalysts provided significant losses of stereoselectivity on the double bond. When $Pd(dppf)Cl_2$ was used, enamides **3** with inversion of the configuration of the double bond were formed preferably. Both conditions were applied to a range of arylboronic acids and (*Z*)-β-enamido triflates.

Supporting Information

Supporting Information File 1

Experimental part, optimization, compound characterization, and copies of NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-179-S1.pdf]

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