A Stereoselective Suzuki Cross-Coupling Strategy for the Synthesis of Ethyl-Substituted Conjugated Dienoic Esters and Conjugated Dienones

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Abstract: A stereoselective approach towards ethyl-substituted conjugated dienoic esters and dienones utilising a Suzuki cross-coupling reaction has been achieved. In addition, a method for their conversion into the corresponding ethyl ketones is presented.

Key words: cross-coupling, dienoic esters, Suzuki reaction, stereoselective, triflate

Conjugated dienoic esters and conjugated dienones **1** (Figure 1) are useful building blocks for organic synthesis, being precursors for prominent structural features of a number of natural products, including carotenoids.[1]

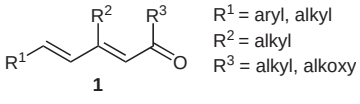
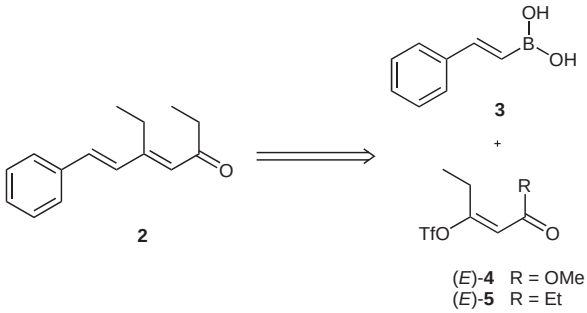


Figure 1 Alkyl-substituted dienoic esters (only *E*,*E* isomer shown for simplicity)

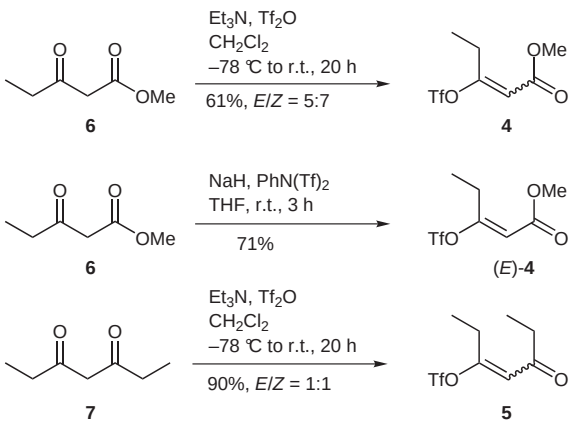
The unsubstituted and methyl-substituted compounds (R^2 = H, Me) can be easily prepared by aldol reaction, though care has to be taken to establish the correct stereochemistry across the double bonds. Other possibilities include the utilisation of Wittig-type,[2] Horner–Wadsworth–Emmons-type,[3] or Julia-type[4] olefination strategies for the formation of the double bonds. However, all these reactions suffer from a sometimes insufficient degree of stereocontrol and low reaction yields in the case of bulkier side chains. To the best of our knowledge, Suzuki cross-coupling strategies involving vinyl triflates have not been applied in the synthesis of ethyl-substituted dienoic ester and dienone derivatives, though there are a number of examples of other cross-coupling reactions, namely Heck and Stille reactions, in the synthesis of retinal and analogues.[5] In this paper we present a novel stereoselective approach towards conjugated dienoic esters featuring a Suzuki cross-coupling reaction.[6] In addition, we present a synthesis of 5-ethyl-7-phenylhepta-4,6-dien-3-one (**2**) by cross-coupling of a ketone-derived vinyl triflate and a versatile synthetic strategy for the conversion of the corresponding dienoic ester into the ketone **2**. The synthetic strategy for **2** is summarised in Scheme 1.



Scheme 1 Retrosynthetic analysis of 5-ethyl-7-phenylhepta-4,6-dien-3-one (**2**)

Thus, **2** can be formed by reaction of inexpensive commercially available (*E*)-2-phenylvinylboronic acid (**3**) and vinyl triflate precursor **4** or **5**. The ester derivative **4** was first synthesised starting from 3-oxopentanoic acid methyl ester (**6**) following a literature precedence on a very similar system[7] using triethylamine and trifluoromethanesulfonic anhydride, which provided the product in a combined yield of 61% in a 5:7 ratio in favour of the undesired *Z* isomer (*Z*)-**4** (Scheme 2). The isomers could be separated by column chromatography. When sodium hydride and *N*-phenylbis(trifluoromethanesulfonimide)[8] were utilised, the desired *E* isomer (*E*)-**4** could be obtained exclusively in a yield of 71%.

Unknown ketone derivative **5** was obtained from heptane-3,5-dione (**7**) using trifluoromethanesulfonic anhydride and triethylamine in a combined yield of 90% as a 1:1 mixture of both isomers. The isomers could also be separated by column chromatography, but the *E* isomer (*E*)-**5** decomposed rapidly.



Scheme 2 Synthesis of vinyl triflates **4** and **5**

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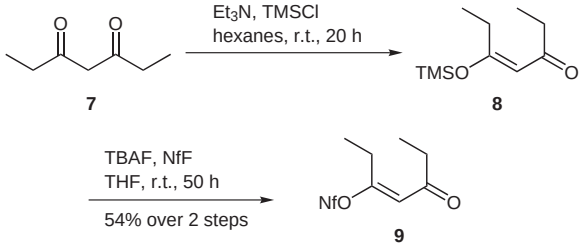
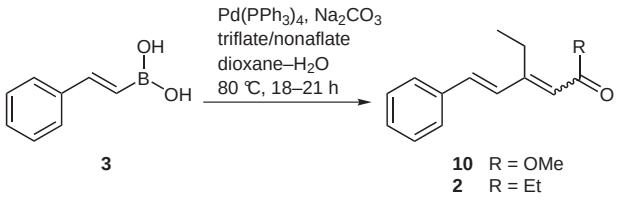
As the desired triflate isomer (*E*)-**5** could not be isolated due to its latent lability, a nonaflate analogue was prepared as these are also known to be potent leaving groups in cross-coupling reactions.[9] Starting from heptane-3,5-dione (**7**), the corresponding trimethylsilyl ether **8** was synthesised using triethylamine und trimethylsilyl chloride in hexanes.[10] Ether **8** was then transformed into nonaflate **9** by addition of tetrabutylammonium fluoride and nonaflate fluoride[9a] yielding the desired product in 54% yield over both steps as a single stereoisomer (Scheme 3).



Scheme 3 Synthesis of vinyl nonaflate **9**

The three triflates (*E*)-**4**, (*Z*)-**4** and **5** and nonaflate **9** were then employed in a Suzuki reaction[6] using standard conditions [$Pd(PPh_3)_4$, Na_2CO_3, dioxane–H_2O].[11] The results are summarised in Table 1.

Table 1 Results of the Cross-Coupling Reaction[a]



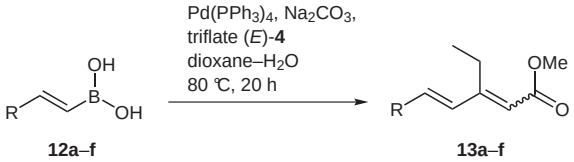
Reactant	Yield	*E*:*Z* ratio
(*E*)-**4**/(*Z*)-**4** (5:7)	72%	5:7
(*E*)-**4**	77%	pure *E*
(*Z*)-**4**	81%	pure *Z*
(*E*)-**5**	64%	1:1
(*E*)-**9**	no reaction	–

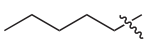
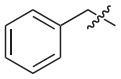
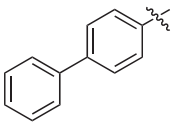
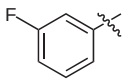
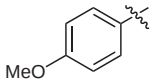
[a] Reaction conditions: $Pd(PPh_3)_4$ (0.04 equiv), Na_2CO_3 [2 M in H_2O; 1.5 equiv], boronic acid (1.0 equiv), triflate/nonaflate (1.0 equiv), dioxane (2 mL/mmol), 80 °C, 18–21 h.

The reaction of ester derivatives (*E*)-**4** and (*Z*)-**4** proceeded uneventfully. When the crude mixture of isomers was subjected to the cross-coupling conditions, the same ratio of product isomers was obtained in a combined yield of 72%. When the pure isomers, (*E*)-**4** and (*Z*)-**4**, were employed the corresponding esters (*E*)-**10** and (*Z*)-**10** were formed in 77% and 81% yields, respectively, and no signs of the other isomer were detected. When ketone derivative **5** was used under the same reaction conditions, dienone **2** was formed in a yield of 64%, but with complete loss of the stereochemical information across the double bond conjugated to the ester, possibly due to a pronounced configurational lability of triflate **5** under the reaction conditions. Gratifyingly, the products were again separable by column chromatography. Nonaflate **9** did not provide any product.

To explore the scope and limitations of the Suzuki approach to conjugated dienoic acid esters, a series of commercially available vinylboronic acid derivates was employed under the standard conditions. The results are summarised in Table 2.

Table 2 Cross-Coupling of Boronic Acids **12** with Vinyl Triflate (*E*)-**4**[a]



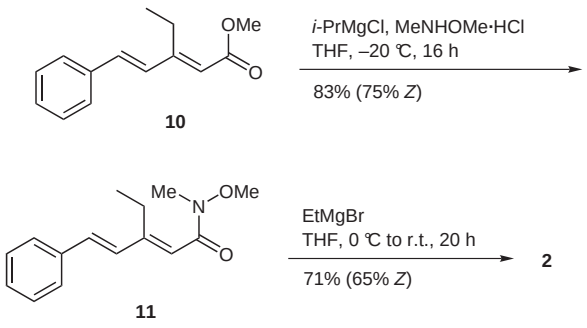
R	Yield (*E* + *Z*)	*E*/*Z* ratio
 **12a**	77%	9:1
 **12b**	83%	19:1
 **12c**	53%	9:1
 **12d**	71%	19:1
 **12e**	86%	3:1
 **12f**	38%	19:1

[a] Reaction conditions: $Pd(PPh_3)_4$ (0.04 equiv), Na_2CO_3 [2 M in H_2O; 1.5 equiv], boronic acid (1.0 equiv), triflate (*E*)-**4** (1.0 equiv), dioxane (2 mL/mmol), 80 °C, 20 h.

When (*E*)-1-heptenylboronic acid (**12a**) was subjected to the standard conditions, the desired product (*E*)-**13a** was obtained in a satisfactory combined yield of 77% along with approximately 10% of the *Z* isomer. The reason for this partial isomerisation could not be resolved; explanations are the possible potential configurational lability of the vinyl triflate **4** or a base-catalyzed isomerisation of the reaction product. Steric interactions contribute to these findings. When (*E*)-2-cyclohexylvinylboronic acid (**12b**) was employed, conjugated dienoic ester **13b** could be

isolated in a yield of 83% with a *E*/*Z* ratio of about 19:1. Boronic acids **12c** and **12d** gave similar results, the yield being 83% for **13c** and 71% for **13d**, respectively, with *E*/*Z* ratios in the same range as in the first two cases. The heteroatom-substituted aromatic systems **12e** and **12f** proved to be more difficult substrates in this reaction. When (*E*)-2-(fluorophenyl)vinylboronic acid (**12e**) was used, the desired product **13e** could be obtained in a yield of 86%, but with a moderate *E*/*Z* ratio of 3:1. A possible explanation could be the electron-withdrawing aromatic fluorine substituent that also requires a lowered electron-density in the conjugated olefinic bonds, possibly facilitating base-catalysed isomerisation of the terminal double bond. In contrast, when (*E*)-2-(4-methoxyphenyl)vinylboronic acid (**12f**) as employed, the reaction showed an improved *E*/*Z* ratio of 19:1 under standard conditions, but a lower reaction yield of 38%. Substantial amount of boronic acid **12f** could be reisolated from the reaction mixture, indicating a slower reaction in this special case. This finding can be attributed to the fact that the Suzuki reaction requires electrophilic attack on the formed palladium intermediate, which is slower due to the electron-donating properties of the aromatic methoxy substituent.

With these results in hand, we studied the conversion of conjugated esters (*E*)-**10** and (*Z*)-**10** into the desired ketone **2**. To achieve the transformation, we relied upon the two-step strategy which is summarised in Scheme 4.



Scheme 4 Synthesis of (*E*)-**2** and (*Z*)-**11** (shown for *E* isomer, yields for *Z* isomer in parentheses)

The esters were first transformed into the corresponding Weinreb amides[12] in 83% (*E* isomer) and 75% (*Z* isomer) yields with complete retention of the double-bond stereochemistry. The amides were then subjected to a Grignard reaction using ethylmagnesium bromide[13] which provided the stereoisomeric ketones (*E*)-**2**[14] and (*Z*)-**2**[15] in 71% and 65% yields, respectively. Again, this transformation did not lead to a substantial degree of isomerisation of the double-bond geometry.

In conclusion, the Suzuki cross-coupling approach tolerates a wide variety of vinylboronic acid derivatives and provides the desired conjugated dienoic esters in good to excellent yields and stereoselectivities. Thus, this strategy provides a novel versatile entry into this class of substances which is difficult to synthesise by other methods.

In addition, we were able to prepare both stereoisomers of 5-ethyl-7-phenylhepta-4,6-dien-3-one (**2**) using two different approaches. Direct Suzuki cross-coupling of (*E*)-phenylvinylboronic acid **3** with ketone-derived triflate **5** provided a separable 1:1 mixture of isomers in a yield of 64%, thus enabling us to produce (*E*)-**2** and (*Z*)-**2** in a yield of 32%. Further transformations using conjugated dienoic ester derivative **10** led to the formation of (*Z*)-**2** in a yield of 39% over three steps starting from (*Z*)-**4**. The corresponding *E* isomer could be obtained in a yield of 45%.

References and Notes

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(11) **Representative Experimental Procedure**: Na_2CO_3 (1.15 g, 10.8 mmol, 1.5 equiv) was dissolved in H_2O (5.4 mL) under an argon atmosphere. (*E*)-Trifluoromethanesulfonyloxy-pent-2-enoic acid methyl ester [(*E*)-**4**; 1.89 g, 7.20 mmol, 1.0 equiv] and (*E*)-2-phenylvinylboronic acid (**3**; 1.08 g, 7.20 mmol, 1.0 equiv) in dioxane (16 mL) were added. The solution was degassed, $Pd(PPh_3)_4$ (333 mg, 0.29 mmol, 0.04 equiv) was added and the mixture was heated to 80 °C for 20 h. After cooling, the reaction was quenched with H_2O (75 mL). Et_2O (80 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (3 × 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexanes–Et_2O, 19:1) yielding (*E*)-**10** as a yellow oil (1.20 g, 5.55 mmol, 77%).

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(14) Spectroscopic data for (*E*)-**2**: R_f = 0.65 (hexanes–Et_2O, 9:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.3 Hz, 3 H, CH_3CH_2C=C), 1.23 (t, *J* = 7.5 Hz, 3 H, CH_3CH_2CO), 2.60 (q, *J* = 7.3 Hz, 2 H, CH_3CH_2C=C), 2.95 (q, *J* = 7.5 Hz, 2 H, CH_3CH_2CO), 6.27 (s, 1 H, C=CHCO), 6.76 (d, *J* = 16.2 Hz, 1 H, PhC=CH), 7.07 (d, *J* = 16.2 Hz, 1 H, PhCH=C), 7.32–7.45 (m, 3 H, ArH), 7.51–7.62 (m, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.2 (CH_3), 14.1 (CH_3), 21.1 (CH_2), 37.8 (CH_2), 123.0 (CH), 125.6 (CH), 127.0 (CH), 127.4 (CH, CAr), 128.6 (CH), 128.7 (CH, CAr), 130.9 (CH, CAr), 134.6 (CH), 136.5 (C, CAr), 156.5 (C), 201.3 (C). IR (film on KBr): 3031 (w), 2973 (m), 2935 (w), 2876 (w), 1677 (m), 1615 (w), 1577 (m), 1466 (w), 1448 (w), 1391 (w), 1172 (w), 1125 (m), 1040 (m), 962 (m), 836 (w), 750 (m), 691 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 214 (73) [M^+], 199 (30), 185 (100), 157 (32), 141 (43), 129 (54), 115 (41), 91 (32). HRMS: *m*/*z* calcd for $C_{15}H_{18}O$: 214.1358; found: 214.1357. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.15; H, 8.44.

(15) Spectroscopic data for (*Z*)-**2**: R_f = 0.58 (hexanes–Et_2O, 9:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.3 Hz, 3 H, CH_3CH_2C=C), 1.13 (t, *J* = 7.5 Hz, 3 H, CH_3CH_2CO), 2.39–2.45 (m, 2 H, CH_3CH_2C=C), 2.44–2.50 (m, 2 H, CH_3CH_2CO), 6.02 (s, 1 H, C=CHCO), 6.76 (d, *J* = 16.2 Hz, 1 H, PhC=CH), 7.17–7.30 (m, 3 H, ArH), 7.45–7.50 (m, 2 H, ArH), 8.27 (d, *J* = 16.7 Hz, 1 H, PhCH=C). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.1 (CH_3), 13.9 (CH_3), 26.8 (CH_2), 37.8 (CH_2), 123.0 (CH), 125.9 (CH), 127.0 (CH), 128.5 (CH, CAr), 128.6 (CH), 128.7 (CH, CAr), 130.9 (CH, CAr), 135.3 (CH), 136.8 (C, CAr), 154.4 (C), 202.0 (C). IR (film on KBr): 2973 (m), 2936 (w), 2876 (w), 1676 (m), 1615 (m), 1579 (m), 1449 (w), 1375 (w), 1199 (w), 1127 (m), 1040 (w), 973 (m), 753 (w), 691 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 214 (29) [M^+], 185 (100), 141 (17), 129 (34), 115 (20), 91 (12). HRMS: *m*/*z* calcd for $C_{15}H_{18}O$: 214.1358; found: 214.1354. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.44; H, 8.43.