Synthesis of compounds containing α-aryl quaternary carbon centers

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Abstract
Acrylates **3** were synthesized following a known procedure using a Brønsted acid catalyst, and were converted into the O-allylated products **4** in high yields. The O-allylated products **4** undergo a Claisen rearrangement in refluxing DMF for 6–24 hours, affording compounds **5** with α-aryl quaternary carbon centers in high yields.

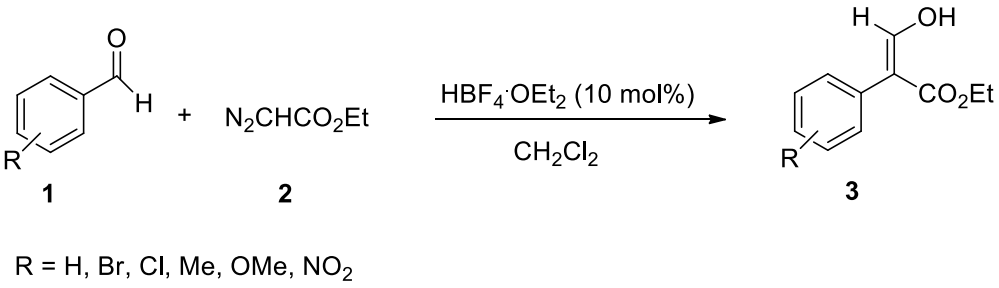
Keywords: Arylhydroxyacrylates, quaternary carbon, Claisen rearrangement

Introduction

The development of catalytic, enantioselective methods for the construction of α-aryl quaternary carbon centers represents a daunting challenge in organic chemistry. Excellent reviews have been published on this topic.[1,2] The formation of α-aryl quaternary carbon centers, present in a growing number of biologically active natural products and pharmaceutical agents, poses a unique challenge due to the steric congestion encountered during the C–C bond formation process. Generally, a quaternary aryl carbon center is formed using strongly basic lithium arenes.[2,3] The aryl anion, while quite reactive, suffers from being unstable to air, non-catalytic, and potentially tedious and expensive when used on larger scales. Furthermore, when used stereoselectively, the aryl anion must attack a stereogenic electrophile. Because most inexpensive electrophiles are prochiral, this approach requires using an additional chiral auxiliary to block the *re*- or *si*-face of the prochiral electrophile. Additionally, sp^2-hybridized electrophiles, such as carbonyls and imines, usually lack tertiary carbons. To circumvent this problem, the nucleophile must undergo an S_N2 attack at a tertiary bound carbon or undergo Michael-type addition. These considerations make arylhydroxyacrylates **3** (Scheme 1) attractive

alternatives, because their α-carbon is tertiary, hence allowing for the possibility of asymmetric synthesis under phase transfer catalysis conditions.[4]

Our group was successful in the development of a novel reaction involving the formation of arylhydroxyacrylates **3** in high yields from aromatic aldehydes **1** and ethyl diazoacetate (EDA) **2** in the presence of a Brønsted acid catalyst (Scheme 1).[5a] Herein, we describe a Claisen rearrangement process for generating α-aryl quaternary carbon centers from 3-allyloxy-2-arylacrylates **4**, made from arylhydroxyacrylates **3** (Scheme 2). Although Claisen rearrangements have been used previously for making quaternary carbon centres[6–8], the use of Claisen rearrangements to afford α-aryl quaternary carbon centers is very rare. In fact, the only example we were able to find is an asymmetric Pd Lewis acid-catalyzed Meerwein-Eschenmoser-Claisen rearrangement[9] involving the rearrangement of 2-amino allyl vinyl ethers into oxindoles bearing an α-aryl quaternary center.



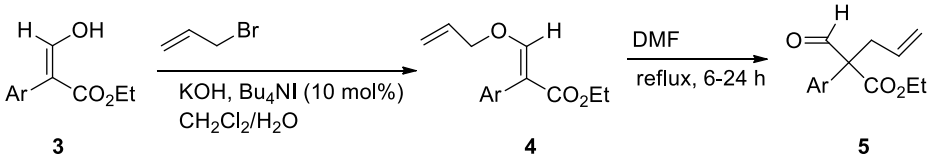
Scheme 1. Synthesis of α-arylhydroxyacrylates **3**.

Results and Discussion

Our initial approach for the construction of an α-aryl quaternary carbon starting from arylhydroxyacrylates **3** involved direct alkylation of the enolate of **3** with an alkyl halide. Alkylation with bases such as solid or aqueous KOH gives exclusive O-alkylation (Scheme 2), whilst the attempted alkylation with solid or aqueous NaOH only gave a small amount of C-alkylated product (ca 20% with allyl iodide). We believe that O-alkylation is much more favored since the high degree of conjugation present in the acrylate **3**, preserved in O-alkylation, is however disrupted in C-alkylation. We have screened various electrophiles for the reaction [allyl iodide, allyl bromide, ethyl iodide, 4-(trifluoromethoxy)benzyl bromide] and solvents (toluene, dichloromethane, THF); all reactions with KOH under any conditions provided exclusively the O-alkylated product. In the case of using NaOH, increasing the polarity of the solvent by using THF resulted in even lower amounts of C-alkylated product. An electrophile with a softer leaving group (allyl iodide instead of allyl bromide) resulted only in a slightly greater yield (by 5%) of C-alkylated product. However, we realized that the O-allyl vinyl ethers were suitable

candidates for a Claisen rearrangement that would afford an indirect C-alkylation leading to the desired α-aryl quaternary carbon. (Scheme 2, Table 1).

The O-alkylation of acrylates **3** was carried out in dichloromethane using allyl bromide under phase transfer catalysis conditions (using either Bu_4NI or Bu_4NBr) and aqueous or solid KOH as base. Reactions carried out in the absence of a phase transfer catalyst resulted in very low yields of product. The attempted alkylation with *n*-butyl lithium in dry THF provided complex mixtures of products.



3, 4, 5	Ar
a	C_6H_5
b	4-MeC_6H_4
c	2,4-$Cl_2C_6H_3$
d	4-$MeOC_6H_4$
e	4-FC_6H_4
f	5-Br-2-$MeOC_6H_3$
g	4-*t*-BuC_6H_4

Scheme 2. Phase transfer catalyzed O-alkylation of ethyl 2-aryl-3-hydroxyacrylates **3** followed by Claisen rearrangement of ethyl 3-allyloxy-2-arylacrylates **4** affording ethyl 2-aryl-2-formyl-2-pent-4-enoates **5**.

Table 1. Yields of ethyl 3-allyloxy-2-arylacrylates **4** and ethyl 2-aryl-2-formyl-2-pent-4-enoates **5**

4, **5**	Ar	**4** Yield[a] [%]	**5** Yield[a] [%]
a	C_6H_5	71	89
b	4-MeC_6H_4	80	85
c	2,4-$Cl_2C_6H_3$	82	69
d	4-$MeOC_6H_4$	66	88
e	4-FC_6H_4	65	55
f	5-Br-2-$MeOC_6H_3$	72	90
g	4-*t*-BuC_6H_4	84	91

[a]Isolated yields.

The Claisen rearrangement of the allyl vinyl ethers **4** (Scheme 2) was performed in refluxing DMF for 6–24 h. The products were isolated by column chromatography in good to moderate yields (Table 1), and were identified and characterized by ^1H and ^{13}C NMR, as well as HRMS. NMR studies (NOESY experiment) showed *E*-stereochemistry of the double bond, presumably due to steric hindrance between the oxygen of the allyl vinyl ether and the carbonyl oxygen of the ester.

For the Claisen rearrangement products, as summarized in Table 1, the yields are mostly very good. In most cases, the crude reaction mixture was 90–95% pure and could be used without further purification for further synthetic work. We did notice, however, a slight decomposition of the product upon purification with flash chromatography to the deformylated product, presumably due to the high steric strain present in the α-aryl quaternary carbon. The Claisen rearrangement was carried out in DMF as solvent due to the lower conversion to product for most of the substrates **4** if a lower boiling solvent such as xylenes was used. For example, under refluxing xylenes, the conversion of substrate **4c** into product **5c** was only about 40%; with DMF, the conversion was considerably higher at 74% (NMR yield). However, in the case of substrate **4b** xylenes could be used successfully as a solvent, with a more simplified work-up consisting of simply evaporating the solvent at reduced pressure (1 Torr), yielding the product in high purity (95%) without any further purification.

It appears that there is a considerable electronic effect on the amount of conversion to product, since the lowest yields appear to occur when electronegative elements are present in the aromatic ring. For example, the lowest yields occur for the conversion of **4c** into **5c** and **4e** into **5e** (Table 1, 69% and 55% respectively). Conversely, one would expect that a methoxy group in the *ortho* position would lead to a reduced yield due to steric hindrance in the chair-like transition state **5f** (Table 1), however the Claisen rearrangement proceeded smoothly to afford the product in 90% yield. Clearly, electronic effects seem to play a larger role than steric effects for determining how far to completion the reaction is able to proceed.

We believe that the highly functionalized Claisen rearrangement products **5** could prove to be powerful building blocks for the synthesis of molecules bearing α-aryl quaternary carbon centers. The aldehyde, ester and allyl functional groups are easily converted into intermediates, which could be useful precursors for the synthesis of a wide variety of molecules including natural products such as the spirooxindole horsfiline.[10]

Conclusions

We have developed a general procedure for making α-aryl quaternary carbons in two steps from arylhydroxyacrylates. The overall reaction sequence starting from a benzaldehyde and EDA (Scheme 1) and leading in two further steps via the O-allyl enol ether to the Claisen rearrangement product (Scheme 2) is an atom economic process for the synthesis of compounds bearing α-aryl quaternary carbons. The synthesis of chiral quaternary carbon centers from O-allylated substrates via the asymmetric Claisen rearrangement is currently under investigation.

Experimental Section

General. All ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 300 spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz) at room temperature in $CDCl_3$. Analytical thin layer chromatography was

performed using EMD Chemicals TLC Glass plates, Silica Gel 60 F254. Flash column chromatography was performed using Biosolve 60 Å (0.032–0.063 mm) silica gel.
All reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use.

Synthesis of (*Z*)-ethyl 2-aryl-3-hydroxyacrylates. (*Z*)-ethyl 3-hydroxy-2-phenylacrylate[5a-e] **3a**, (*Z*)-ethyl 3-hydroxy-2-(*p*-tolyl)acrylate[5a,c-e] **3b**, (*Z*)-ethyl 2-(2,4-dichlorophenyl)-3-hydroxyacrylate **3c**, (*Z*)-ethyl 3-hydroxy-2-(4-methoxyphenyl)acrylate[5a,c-e] **3d**, (*Z*)-ethyl 2-(4-fluorophenyl)-3-hydroxyacrylate[5c-e] **3e**, (*Z*)-ethyl 2-(5-bromo-2-methoxyphenyl)-3-hydroxy-acrylate[5e] **3f**, and (*Z*)-ethyl 2-(4-(*tert*-butyl)phenyl)-3-hydroxyacrylate[5b] **3g** were synthesized using our published procedure.[5a]
(*Z*)-Ethyl 2-(2,4-dichlorophenyl)-3-hydroxyacrylate (3c). 2,4-Dichlorobenzaldehyde (3.4 g, 19.43 mmol) was dissolved in CH_2Cl_2 (100 mL) under N_2, followed by addition of $HBF_4{\cdot}OEt_2$ (0.26 mL, 1.94 mmol), and the reaction mixture was cooled to –78°C. Ethyl diazoacetate (2.42 mL, 23.03 mmol) was then added dropwise *via* syringe at this temperature over a period of 15 min. The reaction mixture was allowed to stir at –78°C for a period of 4 h, at which time the mixture was warmed to room temperature and quenched by the addition of H_2O (60 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), the combined organic extracts were dried over Na_2SO_4 and the mixture was concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, elution gradient: 0 to 8% Et_2O/pentane) to afford **3c** as a yellow oil (3.2 g, 62%). HRMS: 261.0092 [calcd. for $C_{11}H_{10}Cl_2O_3$ (M+H): 261.0085]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.05 (d, *J* = 12.7 Hz, 1H), 7.4 (s, 1H), 7.3–7.1 (m, 3H), 4.25 (q, *J* = 7.0 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 163.5, 134.1, 132.9, 131.5, 129.2, 127.5, 126.9, 105.6, 60.9, 14.0.

Synthesis of (*E*)-ethyl-3-(allyloxy)-2-aryacrylates (4). General procedure
Ethyl 2-aryl-3-hydroxyacrylate **3** (1.0–5.0 mmol) was dissolved in freshly distilled dichloromethane (5–10 mL) under nitrogen. Bu_4NI (0.1 equiv.), allyl bromide (1.2 equiv.), and potassium hydroxide (10 equiv.) were added, and the reaction mixture was stirred at room temperature until completion of the reaction was confirmed by NMR. The reaction was quenched by adding saturated NH_4Cl, and the aqueous layer was extracted with diethyl ether (2 × 25 mL). The organic extracts were combined and dried over Na_2SO_4. The organic layer was then passed through a silica plug and the solvent was removed by rotary evaporation. Pure product was isolated by column chromatography (5–10% ethyl acetate in pentane) and identified by ^{1}H NMR. ^{1}H, ^{13}C NMR and HRMS were applied to characterize the new compounds.
(*E*)-Ethyl 3-(allyloxy)-2-phenylacrylate (4a). Yellow oil. HRMS: 233.1169 [calcd. for $C_{14}H_{16}O_3$ (M+H): 233.1177]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.45-7.30 (m, 5H), 5.92 (m, 1H), 5.4 (d, *J* = 17.4 Hz, 1H), 5.3 (d, *J* = 10.5 Hz, 1H), 4.53 (d, *J* = 4.0 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 157.6, 132.7, 132.4, 130.2, 127.6, 126.9, 119.3, 111.9, 74.9, 60.2, 14.3.

(*E*)-Ethyl 3-(allyloxy)-2-(*p*-tolyl)acrylate (4b). Yellow oil. HRMS: 247.1358 [calcd. for $C_{15}H_{18}O_3$ (M+H): 247.1363]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.37–7.22 (m, 4H), 5.95 (m, 1H), 5.4 (d, *J* = 18.8 Hz, 1H), 5.35 (d, *J* = 10.5 Hz, 1H), 4.53 (d, *J* = 5.1 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 157.5, 136.5, 132.6, 129.7, 129.3, 127.7, 118.6, 111.9, 74.9, 60.2, 21.2, 14.4.

(*E*)-Ethyl 3-(allyloxy)-2-(2,4-dichlorophenyl)acrylate (4c). Yellow oil. HRMS: 301.0472 [calcd. for $C_{14}H_{14}Cl_2O_3$ (M+H): 301.0398]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 2.6 Hz, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.27–7.17 (m, 2H), 5.86 (m, 1H), 5.35 (d, *J* = 12.5 Hz, 1H), 5.3 (d, *J* = 4.4 Hz, 1H), 4.52 (d, *J* = 4.2 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 166.6, 158.7, 135.2, 133.8, 133.0, 132.1, 130.7, 130.2, 129.1, 119.0, 109.3, 75.1, 60.4, 14.2.

(*E*)-Ethyl 3-(allyloxy)-2-(4-methoxyphenyl)acrylate (4d). Yellow oil. HRMS: 263.1260 [calcd. for $C_{15}H_{18}O_4$ (M+H): 263.1283]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.33 (m, 2H), 6.92 (m, 2H), 5.93 (m, 1H), 5.4 (d, *J* = 17.9 Hz, 1H), 5.3 (d, *J* = 10.4 Hz, 1H), 4.52 (d, *J* = 5.4 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 157.1, 132.5, 131.2, 129.5, 124.9, 118.7, 113.8, 111.5, 74.8, 60.2, 55.1, 14.3.

(*E*)-Ethyl 3-(allyloxy)-2-(4-fluorophenyl)acrylate (4e). Yellow oil. HRMS: 253.1237 [calcd. for $C_{14}H_{15}FO_3$ (M+H): 251.1083]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 4.0 Hz, 1H), 7.36 (m, 2H), 7.05 (m, 2H), 5.90 (m, 1H), 5.35 (d, *J* = 14.7 Hz, 1H), 5.3 (d, *J* = 5.4 Hz, 1H), 4.53 (d, *J* = 5.4 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H) . ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 163.3, 158.2, 132.3, 131.8, 128.5, 118.9, 114.7, 111.0, 75.0, 60.3, 14.3.

(*E*)-Ethyl 3-(allyloxy)-2-(5-bromo-2-methoxyphenyl)acrylate (4f). Yellow oil. HRMS: 341.0120 [calcd. for $C_{15}H_{17}BrO_4$ (M+H): 341.0388]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.39–7.28 (m, 2H), 6.77 (d, *J* = 8.7 Hz, 1H), 5.93 (m, 1H), 5.32 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 9.6 Hz, 1H), 4.48 (d, *J* = 5.4 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 157.8, 156.4, 134.2, 132.4, 131.4, 124.2, 118.6, 112.4, 112.1, 108.0, 74.8, 60.1, 55.6, 14.3.

(*E*)-Ethyl 2-(4-*t*-butylphenyl)-3-(allyloxy)acrylate (4g). Yellow oil. HRMS: 289.1797 [calcd. for $C_{18}H_{24}O_3$ (M+H): 289.1803]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.41–7.35 (m, 4H), 5.93 (m, 1H), 5.38 (d, *J* = 18.9 Hz, 1H), 5.32 (d, *J* = 10.8 Hz, 1H), 4.54 (d, *J* = 5.4 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.36 (s, 9H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 157.8, 149.5, 132.5, 129.5, 128.3, 124.5, 118.7, 111.6, 74.9, 60.2, 34.4, 31.2, 14.3.

Synthesis of ethyl 2-formyl-2-arylpent-4-enoates 5. General procedure

(*E*)-Ethyl-3-(allyloxy)-2-arylacrylate **4** (1.0–5.0 mmol) was dissolved in anhydrous DMF (5–10 mL) under nitrogen. The reaction mixture was then refluxed for 6–24 hours (until completion of the reaction was confirmed by TLC), cooled to room temperature and diluted with water. The aqueous layer was extracted two times with diethyl ether. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residual DMF was removed by azeotropic distillation with xylenes. The pure product was isolated by column

chromatography (5–10% ethyl acetate in pentane) and identified by ^{1}H NMR. ^{1}H, ^{13}C NMR and HRMS were applied to characterize the new compounds.

Ethyl 2-formyl-2-phenylpent-4-enoate (5a). Light yellow oil. HRMS: 233.1000 [calcd. for $C_{14}H_{16}O_3$ (M+H): 233.1177]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.95 (s, 1H), 7.44–7.23 (m, 5H), 5.76 (m, 1H), 5.13 (d, *J* = 18 Hz, 1H), 5.07 (d, *J* = 9.9 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.14 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.88 (dd, *J* = 8.1, 13.8 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.3, 170.6, 135.0, 132.6, 129.0, 128.5, 127.8, 119.1, 65.6, 61.6, 37.5, 14.0.

Ethyl 2-formyl-2-*p*-tolylpent-4-enoate (5b). Yellow oil. HRMS: 247.1346 [calcd. for $C_{15}H_{18}O_3$ (M+H): 247.1334]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.28–7.12 (m, 4H), 5.75 (m, 1H), 5.15 (d, *J* = 18.3 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.12 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.88 (dd, *J* = 8.1, 13.8 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 196.3, 170.8, 137.9, 132.8, 130.0, 129.0, 127.4, 118.9, 65.3, 61.5, 36.5, 20.8, 14.0.

Ethyl 2-(2,4-dichlorophenyl)-2-formylpent-4-enoate (5c). Yellow oil. HRMS: 301.0397 [calcd. for $C_{14}H_{14}Cl_2O_3$ (M+H): 301.0398]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.32 (s, 1H), 7.72 (s, 1H), 7.44–7.28 (m, 2H), 5.75 (m, 1H), 5.2-5.1 (m, 2H), 4.25 (q, *J* = 7.1, 2H), 3.10 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.94 (dd, *J* = 7.2, 14.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 198.0, 169.9, 134.6, 134.5, 133.9, 131.1, 130.5, 127.3, 119.9, 64.0, 61.9, 37.7, 13.9.

Ethyl 2-formyl-2-(4-methoxyphenyl)pent-4-enoate (5d). Yellow oil. HRMS: 263.1284 [calcd. for $C_{15}H_{18}O_4$ (M+H): 263.1283]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.28–6.86 (m, 4H), 5.80 (m, 1H), 5.13 (d, *J* = 18.6 Hz, 1H), 5.08 (d, *J* = 9.9 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.10 (dd, *J* = 6.3, 13.8 Hz, 1H), 2.87 (dd, *J* = 7.8, 13.8 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1, 170.9, 159.2, 132.7, 128.8, 126.8, 119.0, 114.4, 64.9, 61.5, 55.4, 36.5, 14.0.

Ethyl 2-(4-fluorophenyl)-2-formylpent-4-enoate (5e). Yellow oil. HRMS: 251.1072 [calcd. for $C_{14}H_{15}FO_3$ (M+H): 251.1083]. ^{1}H NMR (300MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.28–7.07 (m, 4H), 5.73 (m, 1H), 5.20-5.05 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.11 (dd, *J* = 6.6, 14.1 Hz, 1H), 2.88 (dd, *J* = 7.8, 14.1 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.0, 170.5, 160.5, 132.3, 130.7, 129.2, 116.1, 115.8, 65.0, 61.8, 36.8, 14.0.

Ethyl 2-(5-bromo-2-methoxyphenyl)-2-formylpent-4-enoate (5f). Yellow oil. HRMS: 347.0244 [calcd. for $C_{15}H_{17}BrO_4$ (M+Li): 346.9698]. ^{1}H NMR δ: 10.1 (s, 1H), 7.42–7.31 (m, 2H), 6.75 (d, *J* = 8.7 Hz, 1H), 5.77 (m, 1H), 5.15-5.05 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.00 (dd, *J* = 6.6, 13.8 Hz, 1H), 2.80 (dd, *J* = 7.8, 13.8 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H) . ^{13}C NMR δ: 197.8, 170.6, 155.5, 132.0, 130.8, 128.7, 128.0, 119.1, 113.4, 112.6, 68.0, 61.2, 55.7, 36.5, 14.0.

Ethyl 2-(4-tert-butylphenyl)-2-formylpent-4-enoate (5g). Yellow oil. HRMS: 289.1809 [calcd. for $C_{18}H_{24}O_3$ (M+H): 289.1804]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.42 (d, *J* = 6.7 Hz, 2H), 7.18 (d, *J* = 6.7 Hz, 2H), 5.90 (m, 1H), 5.15 (d, *J* = 18.9 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.15 (dd, *J* = 6.3, 14.1 Hz, 1H), 2.86 (dd, *J* = 8.1, 13.8 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.2, 170.8, 151.0, 132.8, 131.8, 126.8, 126.4, 119.3, 65.2, 61.5, 36.5, 34.4, 31.1, 14.0.

References

1. (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, *3*, 369. (b) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001,** *40*, 4591. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (d) Douglas, C. J.; Overman, L. E. *PNAS* **2003**, *101*, 5363.
2. Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105.
3. Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis* Wiley-VCH: Weinheim, 2005.
4. For a recent overview on the scope of phase transfer catalyzed reactions see: Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679.
5. (a) Dudley, M. E.; Morshed, M. M.; Brennan, C. L.; Islam, M. S.; Ahmad, M. S.; Atuu, M-R.; Branstetter, B.; Hossain, M. M. *J. Org. Chem.* **2004**, *69*, 7599. For other procedures for making arylhydroxyacrylates see: (b) Schmittel, M.; Ammon, H. *Eur. J. Org. Chem.* **1998**, *5*, 785. (c) Xiao, F.; Liu, Y.; Wang, J. *Tetrahedron Lett.* **2007**, *48*, 1147. (d) Benito-Garagorri, D.; Wiedermann, J.; Pollak, M.; Mereiter, K.; Kirchner, K. *Organometallics* **2007**, *26*, 217. (e) Atuu, M. R.; Mahmood, S. J.; S. J.; Laib, F.; Hossain, M. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3091.
6. Nubbemeyer, U. *Synthesis* **2003**, *7*, 961.
7. Castro, M. *Chem. Rev.* **2004**, *104*, 2939.
8. Abraham, L.; Korner, M.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 3647.
9. Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162.
10. Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027.