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A highly enantioselective alkene methoxycarbonylation enables a concise synthesis of (*S*)-Flurbiprofen

Gavin J. Harkness,[a] and Matthew L. Clarke*[a]

Abstract: A highly enantioselective synthesis of (*S*)-Flurbiprofen methyl ester in two steps from commercially available 4-bromo-2-fluoro-1,1'-biphenyl is shown. [$PdCl_2$((*S*)-Xylyl-Phanephos)] catalyst is used to accomplish both Grignard cross-coupling and the highly enantioselective intermolecular methoxycarbonylation reaction.

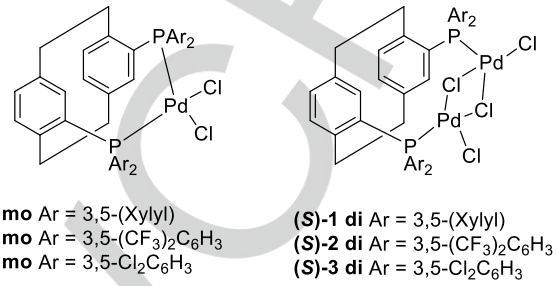
Introduction

Flurbiprofen is one of the "profen" anti-inflammatories and is widely sold as a racemate.[1] However, some applications, including those that are expanding commercially, require a single enantiomer form of Flurbiprofen.[1b-c, 2] The enantiomers of Flurbiprofen do not undergo significant inversion *in vivo*.[1a, 1c, 3] Catalytic asymmetric syntheses of enantiomerically enriched Flurbiprofen are relatively rare and generally have some problems that would prevent scale-up; such as requiring quite a large number of steps and reagents that are generally not preferred at large scale.[4] It has long been recognised that direct conversion of alkenes to branched carboxylic acid derivatives is potentially a more attractive procedure for making various products,[5] including various profen type drugs have been made in this way industrially as racemates.[5b, 6]

Hydroxycarbonylation and methoxycarbonylation of vinyl arenes has been a very challenging reaction to develop,[5e-f, 7] most likely due to difficulties with simultaneous control of enantio- and regioselectivity.[5g-i, 8] Palladium catalysts derived from certain Phanephos ligands[9d] represent leading catalysts for intermolecular enantioselective alkene carbonylation (Figure 1).[9a-c] [Pd_2Cl_4(F_{24}-Phanephos)] dimer,[9b] **2 di**, was found to be an especially suitable catalyst for the methoxycarbonylation of styrene (typically around 80 % e.e. and near perfect regioselectivity). Other phanephos ligands tend to give similar enantioselectivities between 70 and 90 % in the methoxycarbonylation of styrene but with no regiocontrol. In order to study the use of this catalyst system in the synthesis of a real target, we have investigated the catalytic synthesis of (*S*)-Flurbiprofen, and report these results here.

Results and Discussion

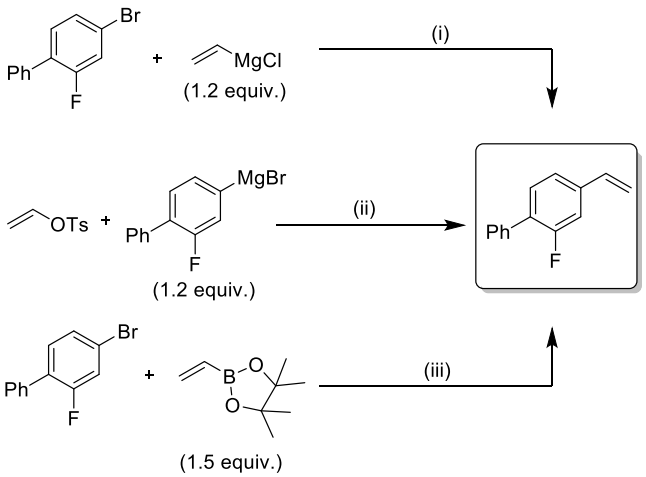
We first required reliable access to the vinyl arene, 3-fluoro-4-phenylstyrene. This could be made by a Pd-catalysed cross-coupling of vinyl magnesium bromide with 4-bromo-2-fluoro-1,1'-biphenyl exploiting the same class of Pd-Phanephos catalysts that are used in carbonylation. However, low yields as well as forcing conditions made us seek an alternative synthesis (Scheme 1 (i)). We felt a preferable synthesis might make use of a vinyl electrophile and a more stable aromatic Grignard reagent.[10] Indeed, large scale syntheses of vinyl arenes from vinyl chloride have been carried out before.[11] We found that vinyl tosylate, readily available by the decomposition of tetrahydrofuran[12], was an easier to handle vinyl electrophile than gaseous but cheap vinyl chloride/bromide, and could be cross-coupled with 2-fluoro-1,1'-biphenyl magnesium bromide with good efficiency in the presence of 1 mol% **(*S*)-1 mo** or **(*R*)-2 mo** (Scheme 1 (ii) and Table 1). To the best of our knowledge, this is the first example of vinyl tosylate being used in a Grignard cross-coupling reaction.



(*S*)-1 mo Ar = 3,5-(Xylyl)
(*S*)-2 mo Ar = 3,5-$(CF_3)_2C_6H_3$
(*S*)-3 mo Ar = 3,5-$Cl_2C_6H_3$

(*S*)-1 di Ar = 3,5-(Xylyl)
(*S*)-2 di Ar = 3,5-$(CF_3)_2C_6H_3$
(*S*)-3 di Ar = 3,5-$Cl_2C_6H_3$

Figure 1. Pd-Phanephos catalysts for the hydroxy- / methoxycarbonylation of alkenes.



Scheme 1. Three routes for the synthesis of vinyl arene, 3-fluoro-4-phenylstyrene. Reaction conditions: (i) 1 mol% ***rac*-1 mo**, 2-MeTHF, 80 °C, 89 h, 44 % yield; (ii) 1 mol% **(*S*)-1 mo**, 2-MeTHF, 20 °C, 17 h, up to 99 % yield, *see Table 1*; (iii) 1 mol% ***rac*-1 mo**, K_2CO_3 (3 equiv.), dioxane/H_2O, 101 °C, 17 h, 59 % isolated yield.

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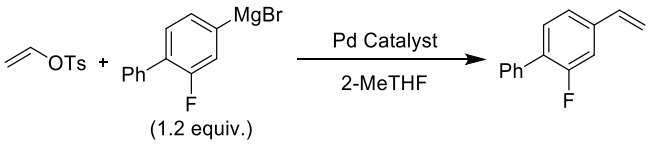
Isolation of pure product was complicated by the very apolar, soluble nature of the product and the homocoupling and hydrolysis by-products, 3',3''-difluoro-[1,1';4',1'';4'',1''']quarterphenyl and 2-fluorobiphenyl (Table 1, Entries 2 and 6). However, we felt that these inert impurities could likely be removed from the final product. An alternative route involving an adaptation of the Suzuki reaction of 4-bromo-2-fluoro-1,1'-biphenyl with vinylboronic acid pinacol ester[13] gave, after chromatography, pure alkene in 59 % yield using ***rac*-1 mo** (Scheme 1 (iii)), which was used to initially investigate the carbonylation reactions.

Table 1. Pd-Phanephos-catalysed Grignard cross-coupling of vinyl tosylate with 2-fluoro-4-biphenylylmagnesium bromide.

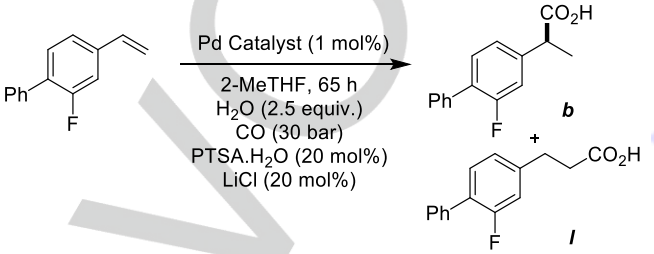


Entry[a]	Catalyst	Catalyst Loading (mol%)	T (° C)	t (h)	Conversion[b] (%)	Product[b] (%)
1	**(*S*)-1 mo**	1	20	17	> 99	99[c]
2[d][e]	**(*S*)-1 mo**	1	20	17	> 99	[90][f]
3	**(*S*)-1 mo**	0.25	20	4 20	83 > 99	78 83
4	**(*S*)-1 mo**	0.1	50	3	> 99	65
5[g]	**(*R*)-2 mo**	1	20	19	> 99	82
6[d][g][h]	**(*R*)-2 mo**	1	20	17	> 99	[79][i]

[a] Reactions were carried out on the scale of vinyl tosylate (0.50 mmol), Grignard reagent (0.60 mmol in 2-MeTHF, molarity determined by titration before use), 2-MeTHF (1.0 mL) in Schlenk flasks under argon, unless otherwise noted. [b] Conversions and yields were determined by ^{1}H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets]. [c] Average yield of 13 experiments (t 17-21 h) = 92 %, see Table S2, entries 1-14. [d] No internal standard. [e] 0.76 mmol scale. [f] 90 % yield isolated with 2-fluorobiphenyl impurity; total product obtained = 68 %. [g] 0.25 mmol scale. [h] Reaction performed in a sealed microwave vial with crimp cap. [i] 79 % yield isolated with 2-fluorobiphenyl impurity; total product obtained = 63 %.

In previous work on hydroxycarbonylation and methoxycarbonylation of styrene[9a, 9b], $[Pd_2Cl_4(F_{24}\text{-Phanephos})]$ dimer, **2di**, was clearly identified as the best catalyst for this type of process in terms of productivity, rate, and due to giving very high regioselectivity. It was therefore examined and compared to other Pd-Phanephos catalysts in the hydroxycarbonylation of 3-fluoro-4-phenylstyrene (Table 2). It is clear that, F_{24}-Phanephos catalysts give the best results in hydroxycarbonylation of 3-fluoro-4-phenylstyrene. High yields, as well as excellent regioselectivity towards the branched isomer were observed. In contrast to previous studies, the monomeric palladium complex **(*R*)-2 mo** gave higher enantioselectivity than the dipalladium complex **(*R*)-2 di**. The level of enantioselectivity using **(*R*)-2 di** is significantly lower than that observed with styrene (~ 80 % e.e.). Monomeric $[PdCl_2((S)\text{-Xylyl-Phanephos})]$, **(*S*)-1 mo**, gave slightly higher enantioselectivity but low yield. All of the acid products could be isolated in pure form by simple acid-base extraction.

Table 2. Synthesis of Flurbiprofen by enantioselective hydroxycarbonylation using Pd-Phanephos catalysts.

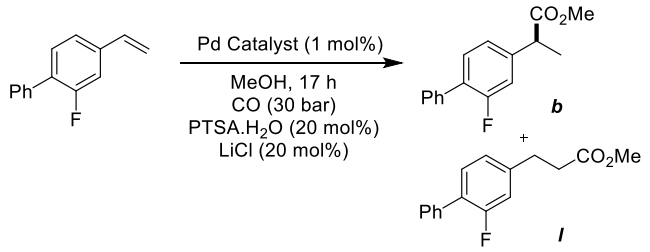


Entry[a]	Catalyst	T (° C)	Product[b] (%)	b/l[c]	e.e.[d] (%)
1[e][f]	**(*S*)-1 mo**	80	14 [6]	0.50	56
2[f]	**(*S*)-1 mo**	80	21 [13]	0.73	55
3	**(*S*)-1 mo**	60	14 [10]	0.96	72
4	**(*R*)-2 mo**	60	97 [69]	79	47
5	**(*R*)-2 di**	60	91 [69]	55	42

[a] Reactions were carried out on the scale of vinyl arene (0.25 mmol) in 2-MeTHF (750 µL) and according to table, equation and ESI, unless otherwise noted. [b] Conversions and yields were determined by ^{1}H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets after acid-base extraction]. [c] b/l ratio determined by ^{1}H NMR. [d] Enantiomeric excess determined by chiral HPLC. (*S*)-configured catalysts give (*S*)-configured product and *vice versa*. [e] Reaction performed in 2-butanone. [f] 17 h.

While the results with the F_{24}-Phanephos catalysts (Table 2, Entries 4 and 5) are reasonably good in the context of this challenging reaction, the moderate enantioselectivity was not sufficient to be synthetically useful. We therefore checked to see if methoxycarbonylation could deliver any improvements (Table 3). In all our previous work, methoxycarbonylation and hydroxycarbonylation of a given alkene have tended to give fairly similar regioselectivity and enantioselectivity. The results in Table 3 were therefore surprising for several reasons. Most catalysts show very disappointing activity with only $[PdCl_2((S)\text{-Xylyl-Phanephos})]$, **(*S*)-1 mo**, yielding any considerable product, with methanol as solvent. On top of this, **(*S*)-1 mo** was found to show excellent enantioselectivity (Table 3, Entries 1-7); this exceeds the selectivity observed with other styrene derivatives in previous work.[9a,b]

Table 3. Synthesis of prodrug Flurbiprofen methyl ester by enantioselective methoxycarbonylation using Pd-Phanephos catalysts.

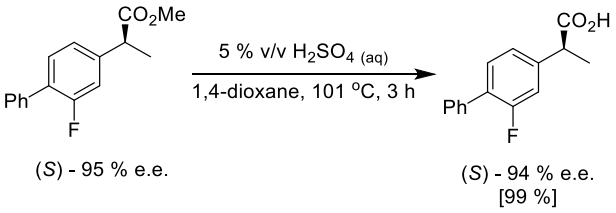


Entry[a]	Catalyst	T (° C)	Product[b] (%)	b/l[c]	e.e.[d] (%)
1	**(*S*)-1 mo**	60	98	1.17	91
2[e]	**(*S*)-1 mo**	60	> 99	1.37	93
3[e][f]	**(*S*)-1 mo**	60	59	1.27	92
4[g]	**(*S*)-1 mo**	45	83 [78]	1.31	95
5	**(*S*)-1 mo**	40	81 [71]	1.39	95
6[h]	**(*S*)-1 mo**	40	61	1.54	96
7[e]	**(*S*)-1 mo**	40	81	1.63	96
8[i][j]	**(*S*)-1 mo**	40	0	-	-
9[j][k]	**(*S*)-1 mo**	40	0	-	-
10[j][l]	**(*S*)-1 mo**	40	0	-	-
11	**(*S*)-1 mo**	20	14	1.69	98
12	**(*S*)-1 di**	40	27	1.62	96
13	**(*R*)-2 mo**	40	8	> 100	51
14[i]	**(*R*)-2 mo**	40	7	> 100	58
15[i]	**(*R*)-2 di**	40	10	> 100	40
16	**(*R*)-3 mo**	40	6	2.78	83
17	**(*R*)-3 di**	40	8	3.38	74

[a] Reactions were carried out on the scale of vinyl arene (0.25 mmol) in MeOH (750 µL) and according to table, equation and ESI, unless otherwise noted. [b] Conversions and yields were determined by ^{1}H NMR using 1-methylnaphthalene as an internal standard [yield of isolated product in square brackets], this includes regioisomerically pure branched products 39 % (entry 4), 32 % (entry 5). [c] b/l ratio determined by ^{1}H NMR. [d] Enantiomeric excess determined by chiral HPLC. (*S*)-configured catalysts give (*S*)-configured product and *vice versa*. [e] 70 bar CO. [f] No PTSA.H_2O. [g] 1 mmol scale. [h] $Al(OTf)_3$ (20 mol%) as acid. [i] 2-MeTHF solvent. [j] 10 equiv. MeOH. [k] 2-butanone solvent. [l] PhMe as solvent.

Isolation of pure branched ester (95 % e.e.) was possible by column chromatography, albeit in only moderate yields due to the lower regioselectivity of the reactions using **(*S*)-1 mo**. Increasing CO pressure increased regioselectivity to branched ester, but not considerably (Table 3, Entries 2 and 7). The low yields using F_{24}-Phanephos catalysts **(*R*)-2 mo/di** are likely due to an unfavourable electronic effect retarding some part of the cycle to a much greater degree here than is observed with styrene itself. Consistent with this, the essentially isosteric phanephos based catalysts **(*R*)-3 mo/di** with *meta* dichlorophenyl groups also gave low yields relative to Xylyl-Phanephos catalyst **(*S*)-1 mo**. Since enantioselection is a subtle event, the increases in enantioselectivity with this substrate, while striking, represent very small energy differences, but do reveal that this substrate is very nicely matched to the chiral pocket in the Pd/ phanephos catalysts. We have previously found that the concentration of methanol is significant to both productivity and selectivity in methoxycarbonylations. Neat methanol is beneficial for productivity in previous work.[9] Here this case is even more extreme, with other solvents using methanol as a reagent giving no product at all. This is not likely due to incompatibility in these solvents, since toluene, Me-THF and butanone have all given some product formation in carbonylation of another substrate using these catalysts.[9c] In addition, successful reactions in methanol tend to be accompanied by the formation of palladium black, while the reactions in Table 3, entries 8-10 were homogeneous solutions. It is quite likely that the active catalyst did not form in these solvents under these conditions. Some time ago we adopted the use of PTSA and LiCl as convenient solid sources of acid and chloride;[5c] this also gives better results when compared to the use of HCl, MsOH (inactive under these conditions) or $Al(OTf)_3$ (Table 3, entry 7 and ESI Table S-4)

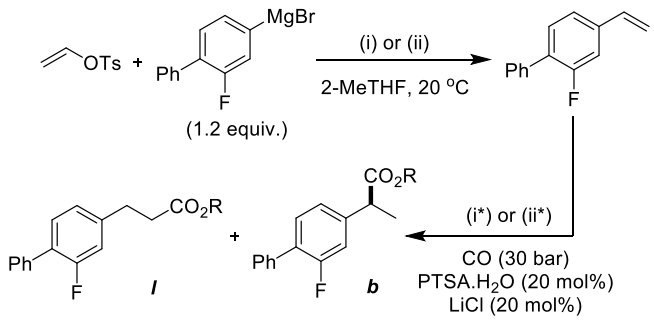
The highly enantioenriched Flurbiprofen methyl ester obtained was then subjected to acid-catalysed hydrolysis to (*S*)-Flurbiprofen in near quantitative yield and without any considerable loss in enantioselectivity (Scheme 2).[1a]



Scheme 2. Acid hydrolysis of enantio-enriched Flurbiprofen methyl ester to desired Flurbiprofen without any significant loss in enantioselectivity. Yield of isolated product in square bracket.

Attempts were made to try to couple the two processes of cross-coupling and carbonylation together in a tandem manner, re-using the catalyst.[5b, 6c-f] Unfortunately, a one-pot process involving hydroxycarbonylation failed to give any considerable product and returned unreacted vinyl arene. Cannula filtration between the two steps improved yields, with 50 % product detected (21 % isolated product) over the two steps. Similar issues were encountered with one-pot cross-coupling -

methoxycarbonylation, with the overall yield of pure branched isomer over the two steps not exceeding 17 % (*see ESI*).



Scheme 3. Synthesis of Flurbiprofen and prodrug Flurbiprofen methyl ester from vinyl tosylate. Reaction conditions: (i) **Cross-coupling**: **(*R*)-2 mo** (1 mol%), 19 h, > 99 % conversion, 73 % yield; (i*) **Hydroxycarbonylation**: Reaction mixture quenched with H_2O (5 equv.), filtered by cannula, H_2O (5 equiv.) added to filtrate prior to reaction, 60 °C, 65 h, 69 % conversion, 69 % yield – Total isolated product from vinyl tosylate = 21 %, b:l = 6.08, e.e. = 41 % (*R*), R = H. (ii) **Cross-Coupling**: **(*S*)-1 mo** (1 mol%), 17 h, > 99 % conversion, 90 % yield isolated with 2-fluorobiphenyl impurity; total product obtained = 68 %; (ii*) **Methoxycarbonylation**: Isolated mixture re-charged with **(*S*)-1 mo** (1 mol%), MeOH, 40 °C, 17 h, 73 % conversion, 68 % yield – Total isolated product from vinyl tosylate = 40 %, b:l = 1.50, e.e. = 96 % (*S*), this includes regioisomerically pure branched product 17 %, R = Me.

Conclusions

A highly enantioselective synthesis of (*S*)-Flurbiprofen methyl ester in two steps from commercially available 4-bromo-2-fluoro-1,1'-biphenyl has been achieved. [$PdCl_2$((*S*)-Xylyl-Phanephos)], catalyst **(*S*)-1 mo** was used to accomplish both the novel Grignard cross-coupling of vinyl tosylate and the intermolecular methoxycarbonylation of vinyl arene. Significantly higher enantioselectivity is observed in the methoxycarbonylation of this substrate than styrene.

Experimental Section

Example procedure of methoxycarbonylation of 3-fluoro-4-phenylstyrene, **Table 3**, Entry 5:

Lithium chloride (2.1 mg, 0.05 mmol), *para*-toluenesulfonic acid monohydrate (9.5 mg, 0. 50 mmol) and [$PdCl_2$((*S*)-Xylyl-Phanephos)] (2.2 mg, 0.0025 mmol) were weighed into a microwave vial equipped with a magnetic stirrer bar. The vial was sealed with a crimp cap and flushed with argon for 30 minutes. 3-fluoro-4-phenylstyrene (49.6 mg, 0.25 mmol) and 1-methylnaphthalene (30 µL, 0.21 mmol, internal standard) were added to a flame dried Schlenk flask under an inert atmosphere. Degassed methanol (750 µL) was then added to the Schlenk flask to make a solution. A t_0 sample (approximately 10 µL) was taken and analysed by ^{1}H NMR (to calibrate the ratio of internal standard to starting material). The solution containing the alkene and internal standard was added to the microwave vial *via* syringe. The crimp cap was pierced with two needles and quickly placed into an autoclave which had previously been placed under an argon atmosphere, before being opened under a flow of argon. The autoclave was sealed, purged three times with CO and then pressurised to 30 bar. The autoclave was then placed in an oil bath at 40 °C for 17 hours with constant stirring. Upon cooling to room temperature, the pressure was released slowly into a well-ventilated fume cupboard. The mixture was analysed by taking a sample, diluting in $CDCl_3$, and analysing by ^{1}H NMR to assess the ratio between SM and desired product, as well as regioselectivity. Solvent was removed under reduced pressure and purification *via* column chromatography on silica gel (eluent petroleum ether:EtOAc, 100:0 to 90:10) gave branched methyl 2-(2-fluoro-biphenyl-4-yl)-propionate (20.7 mg, 32 %) as a white crystalline solid, linear methyl 3-(2-fluoro-biphenyl-4-yl)-propionate (3.6 mg, 6 %) as a colourless oil and a mixture of both regioisomers (21.3 mg, 33 %) as a colourless oil. The enantiomeric excess was determined by HPLC, using a Chiracel OJ column, 250 x 4.6 mm, 10 µm, 0.5 mL min^{-1}, 95:5 hexane : iso-propanol, t_R[(-)-*R*] = 23 min, t_R[(+)-*S*] = 27 min, t_R[linear] = 46 min.

Methyl 2-(2-fluoro-biphenyl-4-yl)-propionate: m.p. 39-40 °C {Lit.[14] 40 °C}; δ_H (500 MHz, $CDCl_3$): 7.56-7.51 (2H, m, $C_{Ar}H$), 7.48-7.33 (4H, m, $C_{Ar}H$), 7.17-7.09 (2H, m, $C_{Ar}H$), 3.77 (1H, q, *J* = 7.2, -C*H*CH_3), 3.71 (3H, s, -OCH_3), 1.54 (3H, d, *J* = 7.2, -CHCH_3); δ_F (376 MHz, $CDCl_3$): -117.6; δ_C (125 MHz, $CDCl_3$): 174.6 (CO_2CH_3), 159.8 (d, *J* = 248.3, C_{Ar}F), 141.9 (d, *J* = 7.7, C_{Ar}), 135.6 (C_{Ar}), 131.0 (d, *J* = 3.9, C_{Ar}H), 129.1 (2C, d, *J* = 2.9, C_{Ar}H), 128.6 (2C, C_{Ar}H), 128.0 (d, *J* = 13.6, C_{Ar}), 127.8 (C_{Ar}H), 123.7 (d, *J* = 3.3, C_{Ar}H), 115.4 (d, *J* = 23.6, C_{Ar}H), 52.4 (-OCH_3), 45.1 (-CHCH_3) 18.6 (-CHCH_3); m/z HRMS (ESI$^+$) $C_{16}H_{16}FO_2$ ([M+H]$^+$) requires 259.1129; found 259.1126 (-1.2 ppm). Anal. Calcd for $C_{16}H_{15}FO_2$: C, 74.40; H, 5.85; Found: C, 74.51; H, 5.99. These data are consistent with those reported in literature.[15] $[\alpha]_D^{20}$ = + 46.2 (c = 1.00, $CHCl_3$, e.e. = 95 % (*S*)) {lit.[1a] $[\alpha]_D^{20}$ = - 39.2 (c = 1.50, $CHCl_3$, e.e. = 76 % (*R*))}.

Methyl 3-(2-fluoro-biphenyl-4-yl)-propionate: ν_{max} (ATR) 1732 (s), 1485 (w), 1416 (m), 1265 (w) 1196 (m), 1153 (m), 1126 (m), 827 (w), 766 (s); δ_H (500 MHz, $CDCl_3$): 7.56-7.52 (2H, m, $C_{Ar}H$), 7.47-7.42 (2H, m, $C_{Ar}H$), 7.40-7.33 (2H, m, $C_{Ar}H$), 7.06 (1H, dd, *J* = 7.8, 1.7, $C_{Ar}H$), 7.02 (1H dd, *J* = 11.5, 1.7, $C_{Ar}H$), 3.70 (3H, s, -OCH_3), 3.00 (2H, t, *J* = 7.8, $C_{Ar}CH_2$) 2.68 (2H, t, *J* = 7.8, $C_{Ar}CH_2CH_2$); δ_F (376 MHz, $CDCl_3$): -118.2; δ_C (125 MHz, $CDCl_3$): 173.2 (CO_2CH_3), 159.8 (d, *J* = 248.0, C_{Ar}F), 142.2 (d, *J* = 7.7, C_{Ar}), 135.8 (C_{Ar}), 130.8 (d, *J* = 3.9, C_{Ar}H), 129.0 (2C, d, *J* = 3.0, C_{Ar}H), 128.5 (2C, C_{Ar}H), 127.7 (C_{Ar}H), 127.0 (d, *J* = 13.5, C_{Ar}), 124.4 (d, *J* = 3.2, C_{Ar}H), 116.0 (d, *J* = 22.8, C_{Ar}H), 51.9 (-OCH_3), 35.4 ($C_{Ar}CH_2CH_2$), 30.4 ($C_{Ar}CH_2CH_2$); m/z HRMS (ESI$^+$) $C_{16}H_{15}FO_2Na^+$ ([M+Na]$^+$) requires 281.0948; found 281.0944 (-1.4 ppm).

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Keywords: Palladium • Asymmetric Catalysis • Carbonylation • Hydroesterification • Hydroxycarbonylation

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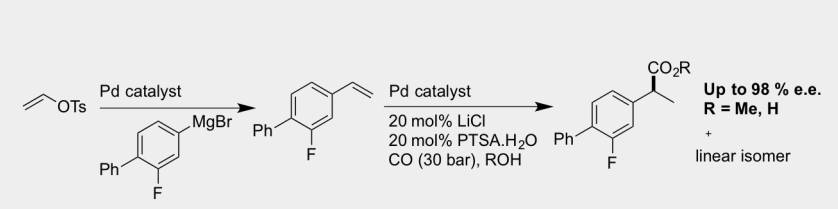

An enantioselective synthesis of (S)-Flurbiprofen is described: The same type of Pd complex has been found to be useful in making the vinyl arene substrate, and as catalyst for a highly enantioselective alkene carbonylation.

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Palladium catalysis

*Gavin J. Harkness Matthew L. Clarke**

Page No. – Page No.

A highly enantioselective alkene methoxycarbonylation enables a concise synthesis of (*S*)-Flurbiprofen