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Enantioselective Horner–Wadsworth–Emmons reaction for the asymmetric synthesis of α-fluoro-α,β-unsaturated esters

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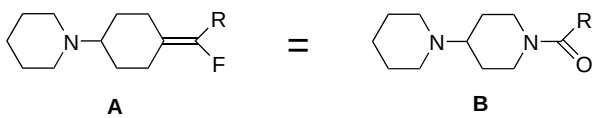
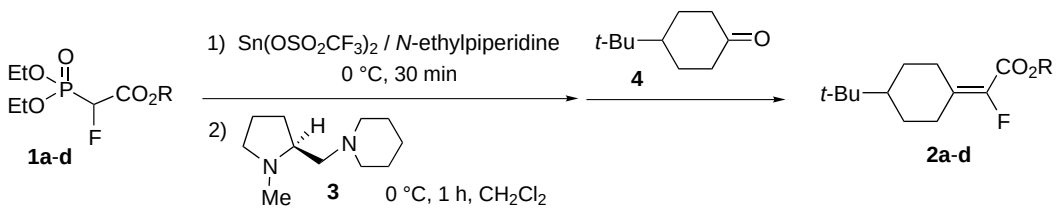
Abstract—The enantioselective Horner–Wadsworth–Emmons reaction of 2-fluoro-2-diethylphosphonoacetates with σ-symmetric prochiral 2-substituted-1,3-dioxan-5-ones and 4-substituted-cyclohexanones was investigated by employing $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine in the presence of an external chiral ligand, (*S*)-(−)-1-methyl-2-(1-piperidinomethyl)pyrrolidine. A chiral α-fluoro-α,β-unsaturated ester was obtained in up to 80% ee.

The Horner–Wadsworth–Emmons (HWE) reaction provides an important method for the synthesis of α,β-unsaturated esters, α,β-unsaturated ketones, and other conjugated systems.[1] Much effort has been made to develop asymmetric HWE reactions of chiral phosphonates, phosphonamides, and phosphonamidates.[2–7] Recently, enantioselective HWE reactions of achiral phosphonates have been performed by utilizing an external chiral source.[8–10] Taking into account the importance of biologically active molecules containing fluorine atoms, we have envisioned a highly enantioselective HWE reaction for the preparation of α-fluoro-α,β-unsaturated esters.[11,12] It is well known that a fluoroolefin unit is available as an amide bond substitute mimicking both steric and electronic features of the peptide bond.[13] Therefore, the fluoroolefinic moieties involving an axis of chirality must be a new attractive research subject for drug design. Specifically, fluoroolefin amide isosteres **A** can be exploited for the 4-substituted-piperidinocarbonyl moieties **B**.[14,15] In previous papers we have reported a new reaction mode for the HWE reaction using $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine to obtain excellent stereoselectivity (*E*/*Z*) in the reactions of phosphonates and aryl alkyl ketones.[16–18] Herein we wish to describe enantioselective HWE reactions of 2-fluoro-2-diethylphosphonoacetates **1a–d** with σ-symmetric prochiral cyclic ketones **4–7**, employing $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine in the presence of an external chiral ligand, (*S*)-(−)-1-methyl-2-(1-piperidinomethyl)pyrrolidine (**3**).[19,20] To the best of our knowledge, our result is the first example of an enantioselective HWE reaction for the asymmetric synthesis of α-fluoro-α,β-unsaturated esters.





Scheme 1.

Keywords: Horner–Wadsworth–Emmons reactions; asymmetric synthesis; fluorine and compounds; α-fluoro-α,β-unsaturated esters; Wittig reactions.

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Table 1. Enantioselective HWE reactions of 2-fluoro-2-diethylphosphonoacetates **1a–d** with 4-*tert*-butylcylcohexanone (**4**) in the presence of chiral diamine **3**[a]

Entry	Phosphonate	Temperature (°C)	Time (h)	Yield (%) of **2a–d**[b]	Ee (%) of **2a–d**[c]
1	**1a**	−40	40	97	68[d]
2	**1a**	−60	40	54	57
3	**1b**	−40	40	92	70 (a*S*)
4	**1b**	−78	40	40	78 (a*S*)
5	**1c**	−40	23	44	74[d]
6	**1d**	−40	40	20	76[d]

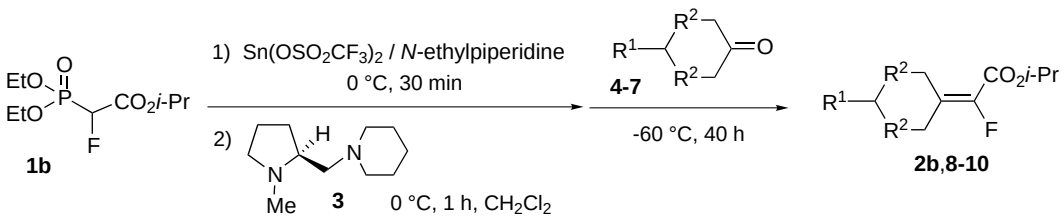
[a] **1**/$Sn(OSO_2CF_3)_2$/*N*-ethylpiperidine/**3**/**4** (1.4:1.7:1.5:2:1).
[b] Isolated yields.
[c] Determined by HPLC (CHIRALCEL OD, hexane–2-propanol) analysis.
[d] Absolute configuration was not determined.

First, enantioselective HWE reactions of 2-fluoro-2-diethylphosphonoacetates **1a–d** with a prochiral 4-*tert*-butylcyclohexanone (**4**) in the presence of a chiral diamine **3** were examined (Scheme 1). Quantitative alkaline hydrolysis of a commercially available fluorinating building-block, ethyl 2-fluoro-2-diethylphosphonoacetate **1a**, followed by condensation with 2-propanol, dicyclohexylmethanol, and 2-methyl-2-propanol, employing 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC·HCl) and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 furnished the corresponding achiral phosphonates **1b–d** in 86–100% yields.

As shown in Table 1, the presence of an ester moiety with proper bulkiness in molecule **1** is related to obtaining either appropriate yields or enantioselectivity of α-fluoro-α,β-unsaturated esters **2**. A lower reaction temperature was found to lead to increase in the enantiomeric excess (ee) values of **2b** to some degree, but the yield was considerably decreased (Table 1, entries 3 and 4). However, a lower reaction temperature does not tend to improve both the yield and enantioselectivity of **2a** (Table 1, entries 1 and 2). The ee values of **2a–d** were determined to be 57–78% by chiral-stationary-phase HPLC analysis (Daicel Chiralcel OD, hexane/2-propanol). The stereochemistry of **2b** was established as a*S* by its chemical conversion to **11a** (vide infra). These results suggest that **1b** is a most promising phosphonate for the desirable enantioselective HWE reaction.

Subsequently, we investigated the enantioselective HWE reaction and found it to work well for other σ-symmetric prochiral cyclic ketones **5–7**. 2-Substituted-1,3-dioxan-5-ones **6** and **7** were readily synthesized from 2-hydroxymethyl-2-nitro-1,3-propanediol and 1,2,3-propanetriol, respectively, by the literature methods.[21–23] An 80% ee was achieved by the HWE reaction of **1b** and **6** (Table 2, entry 3, Scheme 2). The absolute configurations of **2b** and **8–10** were confirmed by chemical conversion to known alcohols **11a–d**, followed by a comparison of their retention times in the chiral-stationary-phase HPLC analysis with those of **11a–d** derived from diastereomerically pure esters **12a–d**, as shown in Scheme 3. X-Ray crystallographic analysis was performed in order to determine the stereochemistry of **12a**,**b** (Fig. 1) and **12c**,**d** (Fig. 2).[24,25]

In a typical procedure, *N*-ethylpiperidine (229 μL, 1.42 mmol) was added to a stirred suspension of $Sn(OSO_2CF_3)_2$ (670 mg, 1.61 mmol) and isopropyl 2-fluoro-2-diethylphosphonoacetate (**1b**) (341 mL, 1.33 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0°C under argon. The mixture was stirred at 0°C for 30 min and (*S*)-(−)-1-methyl-2-(1-piperidinomethyl)pyrrolidine (**3**) (381 mg, 1.90 mmol) was added to the solution. After 1 h at 0°C, a solution of ketone **6** (150.3 mg, 0.95 mmol) in CH_2Cl_2 (5 mL) was slowly added at −60°C. After being stirred at −60°C for 40 h under argon, the reaction mixture was poured into H_2O (10 mL) and then extracted with $CHCl_3$ (3×30 mL). To the $CHCl_3$ extract was added *n*-hexane (90 mL) and the mixture was submitted to filtration through a silica gel short column. The filtrate was evaporated in vacuo to afford a crude product, which was purified by chromatography on a silica gel column eluted with *n*-hexane–AcOEt (25:1) to obtain α-fluoro-α,β-unsaturated ester **9** (195 mg, 79%, 80% ee) as colorless needles.



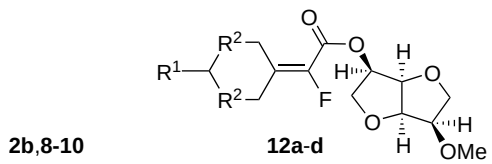
4,**2b**: R^1 = *t*-Bu, R^2 = CH_2; **5**,**8**: R^1 = Ph, R^2 = CH_2; **6**,**9**: R^1 = *t*-Bu, R^2 = O; **7**,**10**: R^1 = Ph, R^2 = O

Scheme 2.

Table 2. Enantioselective HWE reactions of isopropyl 2-fluoro-2-diethylphosphonoacetate **1b** with ketones **4**–**7** in the presence of chiral diamine **3**[a]

Entry	Ketone	Product	Yield (%)[b]	Ee (%)
1	**4**	**2b**	88	78 (a*S*)[c]
2	**5**	**8**	40	66 (a*S*)[d]
3	**6**	**9**	79	80 (a*R*)[c]
4	**7**	**10**	39	60 (a*R*)[d]

[a] **1b**/Sn(OSO$_2$CF$_3$)$_2$/*N*-ethylpiperidine/**3**/ketone (1.4:1.7:1.5:2:1).
[b] Isolated yields.
[c] Determined by HPLC (CHIRALCEL OD, hexane–2-propanol) analysis.
[d] Determined by HPLC (CHIRALCEL OD, hexane–ethanol) analysis.



a: R^1 = *t*-Bu, R^2 = CH$_2$, **b**: R^1 = Ph, R^2 = CH$_2$,
c: R^1 = *t*-Bu, R^2 = O, **d**: R^1 = Ph, R^2 = O

Scheme 3.

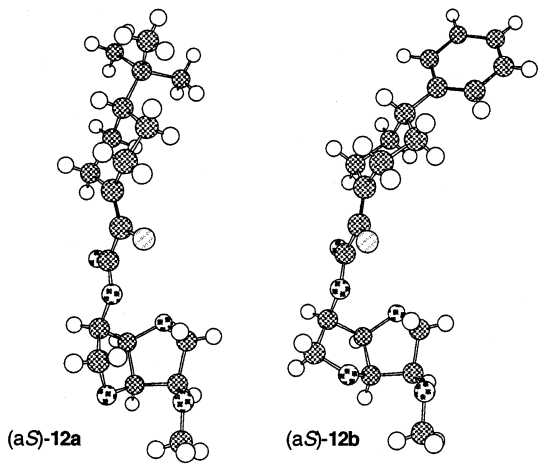


Figure 1. Computer-generated drawing of (a*S*)-**12a** and (a*S*)-**12b**.

In conclusion, the methodology described herein provides an enantioselective route to α-fluoro-α,β-unsaturated esters through the HWE reaction with an external chiral source.

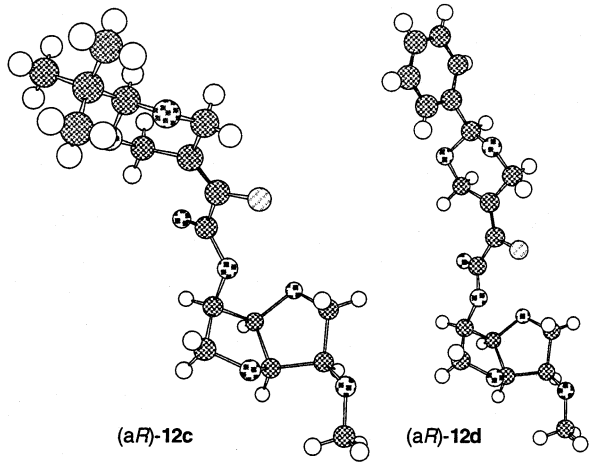


Figure 2. Computer-generated drawing of (a*R*)-**12c** and (a*R*)-**12d**.

Acknowledgements

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24. The crystallographic data of **12a–d** are as follows. (a*S*)-**12a**: $C_{19}H_{29}O_5F$, $M=356.43$, monoclinic, $P2_1$, $a=11.261(1)$ Å, $b=6.2628(7)$ Å, $c=13.613(2)$ Å, $\beta=111.518(6)°$, $V=893.1(2)$ Å^3, $Z=2$, $D_{calcd}=1.325$ g/cm^3. (a*S*)-**12b**: $C_{21.50}H_{27.40}O_{5.70}F$, $M=396.05$, monoclinic, C2, $a=15.1818(9)$ Å, $b=6.1809(3)$ Å, $c=41.780(2)$ Å, $\beta=96.630(1)°$, $V=3894.3(3)$ Å^3, $Z=8$, $D_{calcd}=1.351$ g/cm^3. (a*R*)-**12c**: $C_{17}H_{25}O_7F$, $M=360.38$, orthorhombic, $P2_12_12_1$, $a=6.3789(3)$ Å, $b=10.6456(5)$ Å, $c=26.063(1)$ Å, $V=1769.9(1)$ Å^3, $Z=4$, $D_{calcd}=1.352$ g/cm^3. (a*R*)-**12d**: $C_{19}H_{21}O_7F$, $M=380.37$, monoclinic, $P2_1$, $a=9.367(1)$ Å, $b=8.4542(8)$ Å, $c=12.159(1)$ Å, $\beta=111.196(2)°$, $V=897.7(2)$ Å^3, $Z=2$, $D_{calcd}=1.407$ g/cm^3.
25. Details of diastereoselective HWE reactions for the synthesis of **12a–d** will be published as part of a forthcoming paper.