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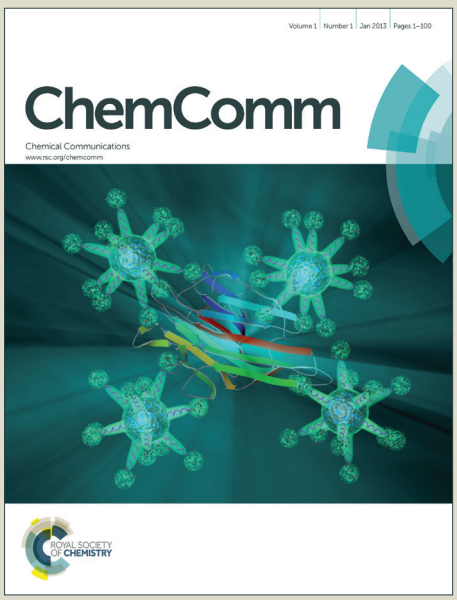

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ARTICLE TYPE

Pd-Catalyzed Highly Regio-, Diastereo-, and Enantioselective Allylic Alkylation of α-Fluorophosphonate

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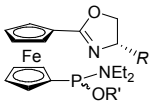
Highly efficient Pd-catalyzed asymmetric allylic alkylation reaction of ethyl 2-fluoro-2-(diethoxyphosphoryl)acetate with monosubstituted allylic substrates has been developed, affording corresponding α-fluorophosphonates with two chiral centers in high regio-, diastereo- and enantio-selectivities The usefulness of the products in organic synthesis has been demonstrated.

Phosphonates as phosphate mimics have enormous significance in the studies of biology, materials science and so on.[1] Compared to the non-fluorinated analogues, α-fluoro alkylphosphonates are better mimics of natural phosphates,[2] because they reduced the disparity in physical properties between alkylphosphonates and phosphates, leading to isosteric, isopolar and isoacidic analogues of biological phosphate.[2b,3] To date, α-fluoro alkylphosphonates have found wide applications in biomedical studies.[4] In these compounds the stereochemistry of the α-carbon has great impact on the biological activity as the interaction with chiral biological molecules such as enzymes.[5,2a] So far, the asymmetric electrophilic fluorination is the only strategy to construct optical active α-fluoroalkylphosphonates.[6] α-Carbanion of α-fluorophosphonates, easily produced from the corresponding phosphonate esters by deprotonation or halogen/metal exchange reactions,[7] has widely been used as a versatile intermediate to prepare functionalized α-fluorophosphonates.[8,2c] However, the report using this strategy in asymmetric way was scarce, in spite of a few chiral reagent controlled cases.[9] We have been involved in the Pd-catalyzed asymmetric allylic alkylation (AAA) reaction for many years, realizing high enantioselectivity in the reactions of different kind of nucleophiles.[10] We envisioned that α-carbanion of α-fluorophosphonates might be the suitable nucleophile in Pd-catalyzed AAA reaction though the presence of fluorine atom has a great influence on the reactivity of carbanions.[11] To date only a few reports realized Pd-catalyzed AAA reaction with fluorinated enol ethers and carbonates,[12e,f] monofluoro-bis(phenylsulfonyl)methane,[12d] and Pd-catalyzed asymmetric decarboxylative allylation of α-fluoro-β-ketoesters and fluorinated enol carbonates,[12a-c] providing products with chiral center installed on nucleophiles or allyl subunit. There has been no report to construct chiral centers both on the fluorinated-nucleophile and allyl unit under Pd-catalyzed conditions[12,13]. In this paper, we would report our results of the Pd-catalyzed AAA of ethyl 2-fluoro-2-(diethoxyphosphoryl)acetate with monosubstituted allyl reagents, providing ethyl 2-allyl-2-fluoro-2-(diethoxyphosphoryl)acetates with two chiral centers in high regio-, diastereo- and enantio-selectivities. The usefulness of the protocol is demonstrated by transformation of the products into some other chiral 2-fluorophosphonates.

Initially, ethyl 2-fluoro-2-(diethoxyphosphoryl)acetate **1** and cinnamyl carbonate **2a** were subjected to the reaction in the presence of the catalyst derived from $[Pd(C_3H_5)Cl]_2$ (2.5 mol %) and (S_c, R_{phos}, R_a)- SIOCPhox **L3** (5 mol%), using Cs_2CO_3 as a base in THF at 25 °C. The reaction afforded the product in poor yield with lower diastereoselectivity but high regio- and enantioselectivities (Table 1, entry 1). To improve the yield and diastereoselectivity, the reaction parameters were investigated (Table 1).



R = H, (R_{phos},R_a)-**L1**
R = H, (R_{phos},S_a)-**L2**
R = ^{i}Pr, (S_c,R_{phos},R_a)-**L3**
R = ^{i}Pr, (S_c,S_{phos},S_a)-**L4**
R = ^{i}Pr, (S_c,R_{phos},S_a)-**L5**
R = ^{i}Pr, (S_c,S_{phos},R_a)-**L6**

L1, L3, L6: R' = (*R*)-2'-hydroxy-1,1'-binaphthyl-2-yl
L2, L4, L5: R' = (*S*)-2'-hydroxy-1,1'-binaphthyl-2-yl

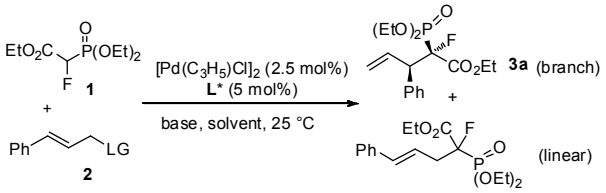
Figure 1. The structure of SIOCPhox ligands **L1-L6**

It was found that the yield was still poor using different bases in THF (Table 1, entries 1-4). In the case of DABCO and K_2CO_3, inferior ee values were provided (entries 2 and 4) and other bases such as DIPEA, DBU, LiOAc, KO^{t}Bu, CsF, LDA and LiHMDS gave trace product (not shown in table). The screen of the solvents showed that poor yield was given again when the reaction proceeded in $MeOCH_2CH_2OMe$ (DME). In MeCN and CH_2Cl_2 , only trace product was observed (not shown in table 1). However, the yield increased to 18% with excellent regio- and enantio-selectivities and moderate diastereoselectivity if the reaction ran in low polar solvent, toluene (entry 6). The yield increased greatly to 63% with excellent regio-, diastereo- and enantio-selectivities when non polar solvent hexane was used (entry 7). The major diastereomer of **3a** was *syn*-configuration (Ph *vs* $PO(OEt)_2$) determined via X-ray analysis of its derivatives (*vide infra*).

Based on our previous studies and understanding about SIOCPhox ligands,[10] the different combination of chiral elements of the ligand showed the great impact on the reaction. Thus, SIOCPhox ligands with different combination of chiral elements were tested in hexane (Fig. 1, Table 1, entries 8-12). The reaction

afforded the product in high yield, but the regio-, diastereo- and enantio-selectivities were much lower when (R_{phos}, R_a)-SIOCPhox **L1** was the ligand (entry 8) while the yield, regio- and diastereo-selectivities were moderate but the enantioselectivity was good and the configuration was reversed if **L2** was used (entry 9). However, the yield and regioselectivity were moderate but the diastereo- selectivity and enantioselectivity were good using **L5** as ligand (entry 10). Only trace product was observed when **L4** and **L6** were used (not shown in table). The examination of the leaving group (LG) of allyl substrate **2** revealed that the enantioselectivity was kept excellent for **3** while the yields were lower with other leaving groups (entry 10 *vs* entries 13-16). The yield was 78% if the ratio of **1**/**2** was switched from 1/1.5 to 2/1 (entry 7 *vs* entry 15).

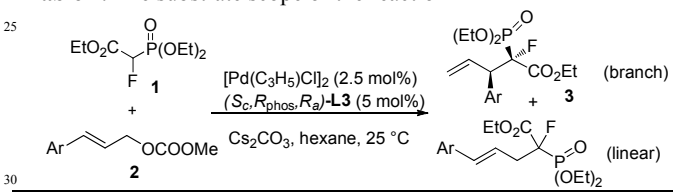
Table 1. Optimization of Parameters for the Reaction of **1** with **2**[a]



Entry	L*	solvent	LG(**2**)	Yield (%)[b]	b/l[c]	dr[c]	Ee (%)[d]
1	**L3**	THF	OCO_2Me(**2a**)	10	10:1	3.3:1	90
2[e]	**L3**	THF	OCO_2Me(**2a**)	10	10:1	2:1	98
3[f]	**L3**	THF	OCO_2Me(**2a**)	8	8:1	2:1	89
4[g]	**L3**	THF	OCO_2Me(**2a**)	8	6:1	2:1	97
5	**L3**	DME	OCO_2Me(**2a**)	8	>20:1	2:1	91
6	**L3**	Toluene	OCO_2Me(**2a**)	18	>20:1	4:1	99
7	**L3**	Hexane	OCO_2Me(**2a**)	63	>20:1	>20:1	99
8	**L1**	Hexane	OCO_2Me(**2a**)	98	10:1	14:1	88
9	**L2**	Hexane	OCO_2Me(**2a**)	34	3:1	8:1	-80
10	**L5**	Hexane	OCO_2Me(**2a**)	42	3:1	10:1	94
11	**L3**	Hexane	OAc(**2k**)	37	>20:1	>20:1	99
12	**L3**	Hexane	Cl(**2l**)	29	15:1	>20:1	98
13	**L3**	Hexane	$OPO(OEt)_2$(**2m**)	36	15:1	>20:1	99
14	**L3**	Hexane	OBoc(**2n**)	39	12:1	>20:1	79
15[h]	**L3**	Hexane	OCO_2Me(**2a**)	78[i]	>20:1	>20:1	99

[a] Reaction was carried out at 25 °C, Molar ratio of **1**/**2**/$[Pd(C_3H_5)Cl]_2$/**L**/Cs_2CO_3 =100:150:2.5:5:120. [b] Yields of **3a** are based on **1**, determined by crude ^{1}H NMR using mesitylene as the internal standard. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. [e] DABCO as base. [f] K_3PO_4 as base. [g] K_2CO_3 as base. [h] Molar ratio of **1**/**2**/$[Pd(C_3H_5)Cl]_2$/**L**/base =200:100:2.5:5:240. [i] Yield of **3a** is based on **2a**,

Table 2. The substrate scope of the reaction[a]



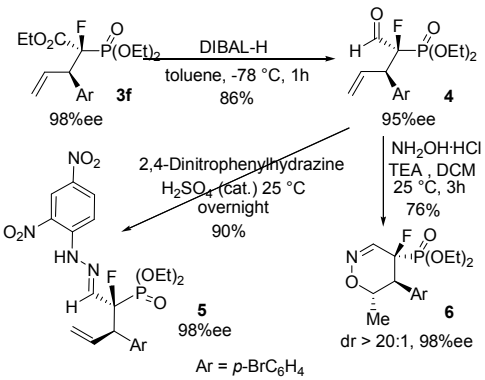
Entry	Ar(**2**)	**3**,Yield (%)[b]	b/l[c]	dr[c]	Ee (%)[d]
1	Ph(**2a**)	**3a**, 75	>20:1	>20:1	99
2	*p*-MeC_6H_4(**2b**)	**3b**, 69	14:1	17:1	98
3	*p*-$MeOC_6H_4$(**2c**)	**3c**, 75	7:1	>20:1	92
4	o-$MeOC_6H_4$(**2d**)	**3d**, 75	10:1	>20:1	97
5	*p*-ClC_6H_4(**2e**)	**3e**, 85	10:1	>20:1	97
6	*p*-BrC_6H_4(**2f**)	**3f**, 85	10:1	20:1	98
7	*p*-$CF_3C_6H_4$(**2g**)	**3g**, 72	10:1	>20:1	90
8	m-$MeOC_6H_4$(**2h**)	**3h**, 68	10:1	>20:1	96
9	*m*-ClC_6H_4(**2i**)	**3i**, 77	10:1	16:1	96
10	1-naphthyl(**2j**)	**3j**, 81	16:1	>20:1	95

[a] Reaction was carried out at 25 °C, Molar ratio of **1**/**2**/$[Pd(C_3H_5)Cl]_2$/**L3**/Cs_2CO_3 =200:100:2.5:5:400. [b] Isolated yields of **3** are based on **2**. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.

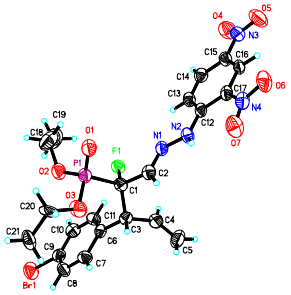
Under the optimized reaction conditions, the scope of the substrates was examined (Table 2). It can be seen that a wide range of aryl substituted allyl carbonates **2** were suitable for the reaction, affording the products in good to high yields with high regio-, diastereo- and enantio-selectivities (Table 2). The diastereoselectivity was excellent for all allyl substrates **2** with either electron-donating or electron-withdrawing substituent on phenyl ring but the regioselectivity was sensitive to the substituent on aryl group of carbonates **2**. Compared to **2a**, the regioselectivity was lower with any substituent on the phenyl ring of carbonates **2** (Table 2, entries 2-10 *vs* 1), the lowest b/l ratio of 7:1 being afforded for **2c** with *p*-$MeOC_6H_4$ as substituent in allyl carbonate (entry 3). The enantioselectivity was slightly changed with different substituents on phenyl ring of carbonates **2**. A little bit lower ees were given for **2c** and **2g** with methoxyl or trifluromethyl on *para*-position of phenyl ring (entries 3 and 7).

To show the utility of our methodology, the transformations of the highly functionalized allylation products were performed. The reduction of allylated product **3f** with DIBAL-H in THF failed to obtain desired product, instead, alkene product was detected from NMR via the elimination of diethyl phosphate. However, aldehyde **4** was afforded if **3f** was treated with DIBAL-H in Toluene, which was converted to hydrazone **5** without changes in the diastereo- and enantioselectivities when treated with 2,4-dinitrophenylhydrazine (Scheme 1). The absolute configuration of product **5** was assigned as (1*R*, 2*R*) by X-ray analysis of its

single crystal (Scheme 2). Accordingly, the absolute configuration of allylation product **3f** was (1*R*, 2*R*). When the aldehyde **4** was treated with hydroxylamine hydrochloride, it afforded a cyclic product **6** with high diastereoselectivity (Scheme 1), which could undergo various functional transformations to provide other optical active derivatives of α-fluoroalkylphosphonate.



Scheme 1. Transformations of the Reaction Products.



Scheme 2. ORTEP Diagram of X-ray Diffraction Structure of Product **5**

In conclusion, we have achieved Pd-catalyzed AAA of α-fluoroalkylphosphonate with monosubstituted allylic substrates, providing products with two chiral centers in high yields with excellent regio-, diastereo-, and enantioselectivities. The resulting products contain two adjacent stereogenic centers and three functional groups that can be easily elaborated to more complex products. Further investigations to extend the reaction scope and applications of this methodology in organic synthesis are in progress.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and analysis data for new compounds. CIF file of **5**, CCDC 992890. ^{1}H, ^{13}C NMR and HPLC spectra of compounds **3a-3i**, **4-6**. See DOI: 10.1039/b000000x/

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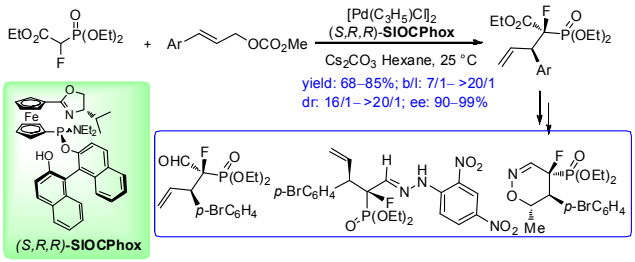

α-Fluorophosphonates with two chiral centers have been synthesised in high diastereo- and enatioselectivites via Pd-catalyzed asymmetric allylic alkylation reaction of ethyl 2-fluoro-2-(diethoxyphosphoryl)acetate with monosubstituted allylic substrates. The transformation of functional groups were also demonstrated.