ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 6751

Received 24th March 2014,
Accepted 4th May 2014

DOI: 10.1039/c4cc02158d

www.rsc.org/chemcomm

Pd-catalyzed highly regio-, diastereo-, and enantioselective allylic alkylation of α-fluorophosphonates†

Ying Huang,[b] Qing-Song Zhang,[a] Ping Fang,*[a] Tie-Gen Chen,[a] Jun Zhu[b] and Xue-Long Hou*[a]

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 a wide range of applications in biomedical studies.[4] In these compounds the stereochemistry of the α-carbon has a great impact on the biological activity due to the interaction with chiral biological molecules such as enzymes.[5,2a] So far, the asymmetric electrophilic fluorination is the only strategy to construct optically active α-fluoroalkylphosphonates.[6] The 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 an asymmetric way is 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 kinds of nucleophiles.[10] We envisioned that the α-carbanion of α-fluorophosphonates might be the suitable nucleophile in Pd-catalyzed AAA reaction though the presence of the 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 the chiral center installed on nucleophiles or the allyl subunit. There has been no report on the construction of chiral centers both on the fluorinated-nucleophile and the allyl unit under Pd-catalyzed conditions.[12,13] In this communication, we report our results of the Pd-catalyzed AAA of ethyl 2-fluoro-2-(diethoxyphosphoryl)acetate using mono-substituted 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).

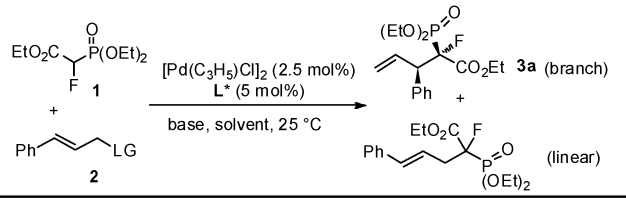
It was found that the yield was still poor using different bases in THF (Table 1, entries 1–4). In the case of DABCO and K_2CO_3, inferior ee values were obtained (entries 2 and 4) and other bases such as DIPEA, DBU, LiOAc, KO^{t}Bu, CsF, LDA and LiHMDS gave trace amounts of product (not shown in the table). The screening of the solvents showed that poor yield was obtained again when the reaction proceeded in $MeOCH_2CH_2OMe$ (DME) (entry 5). In MeCN and CH_2Cl_2, only trace amounts of product were observed (not shown in Table 1). However, the yield increased to 18% with excellent regio- and enantio-selectivities and moderate diastereo-selectivity if the reaction ran in low polar solvent, toluene (entry 6).

[a] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. E-mail: xlhou@sioc.ac.cn, pfang@sioc.ac.cn*

[b] *State Key Laboratory of Physical Chemistry of Solid Surfaces Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China*

† 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**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc02158d

Table 1 Optimization of parameters for the reaction of **1** with **2**[a]

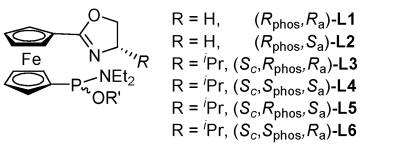


Entry	L*	Solvent	LG(2)	Yield[b] (%)	b/l[c]	dr[c]	ee[d] (%)
1	**L3**	THF	OCO_2Me(**2a**)	10	10 : 1	3.3 : 1	90
2[e]	**L3**	THF	OCO_2Me(**2a**)	10	10 : 1	2 : 1	98
3[f]	**L3**	THF	OCO_2Me(**2a**)	8	8 : 1	2 : 1	89
4[g]	**L3**	THF	OCO_2Me(**2a**)	8	6 : 1	2 : 1	97
5	**L3**	DME	OCO_2Me(**2a**)	8	>20 : 1	2 : 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**.

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** had *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 had a great impact on the reaction. Thus, SIOCPhox ligands with different combinations of chiral elements were tested in hexane (Fig. 1, Table 1, entries 7–10). 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 used as 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 when **L5** was used as a ligand (entry 10). Only trace amounts of product were observed when **L4** and **L6** were used (not shown in the table). The examination of the leaving group (LG) of allyl substrate **2** revealed that the

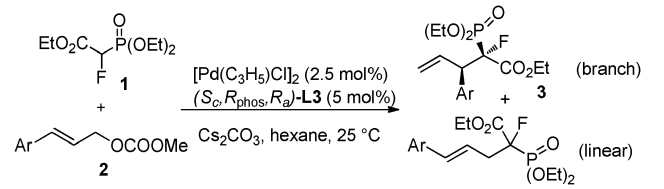


R = H, (R_{phos},R_a)-**L1**
R = H, (R_{phos},S_a)-**L2**
R = ^{i}Pr, (S_c,R_{phos},R_a)-**L3**
R = ^{i}Pr, (S_c,S_{phos},S_a)-**L4**
R = ^{i}Pr, (S_c,R_{phos},S_a)-**L5**
R = ^{i}Pr, (S_c,S_{phos},R_a)-**L6**

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

Fig. 1 The structure of SIOCPhox ligands **L1–L6**.

Table 2 The substrate scope of the reaction[a]



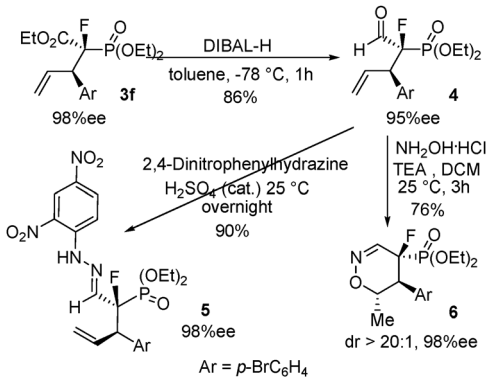
Entry	Ar(2)	3, Yield[b] (%)	b/l[c]	dr[c]	ee[d] (%)
1	Ph(**2a**)	**3a**, 75	>20 : 1	>20 : 1	99
2	*p*-MeC_6H_4(**2b**)	**3b**, 69	14 : 1	17 : 1	98
3	*p*-$MeOC_6H_4$(**2c**)	**3c**, 75	7 : 1	>20 : 1	92
4	*o*-$MeOC_6H_4$(**2d**)	**3d**, 75	10 : 1	>20 : 1	97
5	*p*-ClC_6H_4(**2e**)	**3e**, 85	10 : 1	>20 : 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 : 240. [b] Isolated yields of **3** are based on **2**. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.

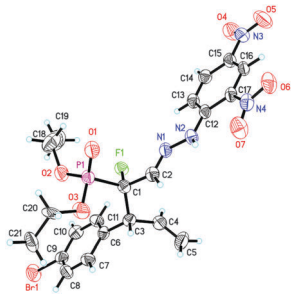
enantioselectivity was kept excellent for **3a** while the yields were lower with other leaving groups (entry 10 *vs.* entries 11–14). The yield was 78% if the ratio of **1**/**2** was switched from 1/1.5 to 2/1 (entry 7 *vs.* entry 15).

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 substituents on the phenyl ring but the regioselectivity was sensitive to the substituent on the 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 a substituent in allyl carbonate (entry 3). The enantioselectivity was slightly changed with different substituents on the phenyl ring of carbonates **2**. A little bit lower ees were obtained for **2c** and **2g** with methoxyl or trifluromethyl on the *para*-position of the 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 give the desired product, instead, an alkene product was detected using NMR *via* the elimination of diethyl phosphate. However, aldehyde **4** was obtained 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



Scheme 1 Transformations of the reaction products.



Scheme 2 ORTEP diagram of the X-ray diffraction structure of product **5**.

transformations to provide other optical active derivatives of α-fluoroalkylphosphonate.

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.

This work was financially supported by the Major Basic Research Development Program (2010CB833300), National Natural Science Foundation of China (21121062, 21302205, 21032007), Chinese Academy of Sciences and the Technology Commission of Shanghai Municipality. This communication is dedicated to Professor Chang Tao Qian on the occasion of his 80th birthday.

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