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Fluorous chiral bisoxazolines. Synthesis and applications to an asymmetric allylic alkylation

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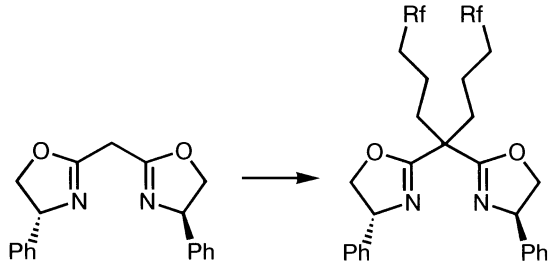
Abstract—The easily accessible fluorous bisoxazolines **3a**–**b** bearing two fluorous ponytails are efficient ligands in the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate with carbonucleophiles in benzotrifluoride or CH_2Cl_2, enantioselectivities of up to 95% being obtained. The ligand is easily separated from the reaction mixture by simple extraction with a fluorous solvent.

There is a growing interest in the use of non-usual solvents such as fluorous solvents[1–6] or ionic liquids[7,8] in organometallic catalysis. These new media can offer the possibility of cleaner technology for the chemical industry, as well as to promote reactions with other selectivities.

In order to prepare ligand systems and catalysts soluble in fluorous solvent, as well as in supercritical CO_2 ($scCO_2$), the attachment of long perfluoroalkyl chains to conventional ligands has been widely used. However, despite the growing number of articles on fluorous chemistry, there have been relatively few reports on the preparation and applications of fluorous chiral ligand systems in organometallic catalysis or in $scCO_2$. Literature examples using fluorous solvents include the epoxydation of alkenes with fluorous chiral salen manganese complexes,[9–11] the asymmetric alkylation of aldehydes with fluorous BINOL titanium alkoxides,[12–15] the hydrogen transfer reaction using iridium complexes of fluorous diimines and diamines,[16,17] the hydrolytic kinetic resolution of terminal epoxides in the presence of fluorous chiral Co(salen) complexes,[18] and more recently the ruthenium-catalyzed hydrogenation of dimethyl itaconate[19] and the Heck reaction[20] using fluorous chiral BINAP complexes, and the palladium-alkylation of prochiral allylic acetates in the presence of fluorous analogues of MOP.[21,22]

In $scCO_2$, highly efficient and enantioselective catalysis was performed using fluorous ligands in hydrogenation of imines and hydroformylation of alkenes.[23–26]

Chiral bisoxazolines and their applications in asymmetric catalysis have been the subject of extensive research during the last decade.[27] These ligands show excellent enantioselectivities for a wide range of reactions, including allylic alkylation, cyclopropanation, Diels–Alder reaction, ene reaction, allylic oxidation, and hydrocyanation of aldehydes. We thought that it would be interesting to prepare chiral fluorous bisoxazolines in



Scheme 1. *Reagent and conditions:* NaH (3 equiv.), DMF, then *n*-$C_8F_{17}(CH_2)_3$-I **2a** for **3a**, or *n*-$C_{10}F_{21}(CH_2)_3$I **2b** for **3b** (2.3 equiv.), 80°C, 16 h.

Keywords: asymmetric alkylation; fluorous bisoxazolines; palladium catalyst.

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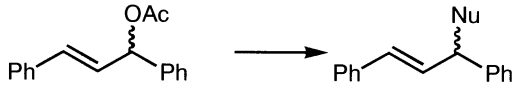
order to test their potentiality in asymmetric catalysis in fluorous solvents and $scCO_2$. We report herein the synthesis of two fluorous bisoxazolines and their preliminary evaluation in asymmetric allylic alkylation.

The synthesis of the fluorous bisoxazolines was investigated taking into account the accessibility of the starting bisoxazolines and the necessity to introduce the fluorous ponytails far from the coordination sites. The direct attachment of two $C_8F_{17}CH_2CH_2CH_2-$ or a $C_{10}F_{21}CH_2CH_2CH_2-$ groups to the bisoxazoline structure was performed via the condensation of the bisoxazoline **1** with the corresponding fluorous alkyl iodide **2a** or **2b** (2.3 equiv.) in the presence of NaH (3 equiv.) in DMF at 80°C (Scheme 1). The two fluorous bisoxazoline ligands **3a** and **3b** were obtained as solids in 47 and 34% chemical yields, respectively, after column chromatography.[28]

The partition coefficients for ligands **3a** and **3b** between FC-72 and two organic solvents (CH_2Cl_2 and toluene) were found to be 0.16 and 0.25, and 0.42 and 0.67, respectively. As expected, these new ligands show a certain affinity for organic solvents, due to their relatively low fluorine content (52.70 and 55.96, respectively) and also their polarity.

In order to investigate the potentiality of these ligands in asymmetric catalysis, we first carried out the asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate **4** (Scheme 2). The results obtained are summarized in Table 1.



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Scheme 2. *Reagents and conditions*: **4** (1 equiv.), nucleophile (3 equiv., see Table 1), BSA (2 equiv.)+KOAc (0.1 equiv.), or NaH (2 equiv.), $[Pd(C_3H_5)Cl]_2$ (5%), **3** (10%).

The reaction of **4** (1 equiv.) with dimethyl malonate (3 equiv.) using **3a** (10 mol%) and $[Pd(C_3H_5)Cl]_2$ (5 mol%) in the presence of NaH in THF gave the alkylated product at room temperature in 47% yield after 40 h with an enantioselectivity of 78% (Table 1, entry 1). However when the reaction was performed in CH_2Cl_2 or in benzotrifluoride (BTF) the transformation was quantitative after 8 and 20 h, respectively, affording the alkylated product with an enantioselectivity of up to 94 and 90%, respectively (Table 1, entries 2 and 3). These values are as high as those obtained using non-fluorous bisoxazolines in usual organic solvents.[29–31]

Performing the reaction in the presence of bis(trimethylsilyl)acetamide (BSA, 2 equiv.) and potassium acetate (10.1 equiv.) instead of NaH gave both higher activities and enantioselectivities. In CH_2Cl_2 or BTF, enantioselectivites of up to 94 and 92% were obtained, the transformation being practically quantitative (Table 1, entries 4 and 6). Lowering the amount of palladium to 1% gave the same enantioselectvity, 95% ee in CH_2Cl_2 and 91% ee in benzotrifluoride (Table 1, entries 5 and 7), although the yields are lower. However, a higher yield was obtained when the reaction was performed under these conditions at 50°C, but with a lower enantioselectivity (Table 1, entry 8). Even using 2% palladium gave, at 50°C, an enantioselectivity of 88% (Table 1, entry 9). However the use of THF as the solvent gave lower activity (31% conversion after 46 h) but the same enantioselectivity (90% ee) (Table 1, entry 10). Next we investigated the asymmetric allylic alkylation using other carbonucleophiles. Reaction of **4** with dimethyl methylmalonate or dimethyl acetamidomalonate gave the expected alkylated compounds in 93 and 83% yields, and with 90 and 93% ee, respectively (Table 1, entries 11 and 12).

We then used **3b** (10 mol%) and $[Pd(C_3H_5)Cl]_2$ (5 mol%) as the catalyst in the reaction of dimethyl malonate with acetate **4** in CH_2Cl_2. Enantioselectivity of up to 94% was obtained using bis(trimethylsilyl)acetamide (BSA, 2 equiv.) and potassium acetate (10.1 equiv.), or

Table 1. Asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate **4**

Entry	Ligand	Nucleophile	Base	Solvent	T (°C)	Pd (mol%)	t (h)	Yield (%)[a]	ee (%)[a] (config.)
1	**3a**	$CH_2(CO_2Me)_2$	NaH	THF	25	5	40	47	78 *(S)*
2	**3a**	$CH_2(CO_2Me)_2$	NaH	CH_2Cl_2	25	5	8	98	94 *(S)*
3	**3a**	$CH_2(CO_2Me)_2$	NaH	BTF	25	5	20	100	90 *(S)*
4	**3a**	$CH_2(CO_2Me)_2$	BSA/KOAc	CH_2Cl_2	25	5	24	89	94 *(S)*
5	**3a**	$CH_2(CO_2Me)_2$	BSA/KOAc	CH_2Cl_2	25	1	96	53	95 *(S)*
6	**3a**	$CH_2(CO_2Me)_2$	BSA/KOAc	BTF	25	5	40	93	92 *(S)*
7	**3a**	$CH_2(CO_2Me)_2$	BSA/KOAc	BTF	25	1	136	45	91 *(S)*
8	**3a**	$CH_2(CO_2Me)_2$	BSA/KOAc	BTF	50	1	72	81	87 *(S)*
9	**3a**	$CH_2(CO_2Me)_2$	BSA/KOAc	BTF	50	2	24	100	88 *(S)*
10	**3a**	$CH_2(CO_2Me)_2$	BSA/KOAc	THF	25	5	46	31	90 *(S)*
11	**3a**	$CH_3CH(CO_2Me)_2$	BSA/KOAc	CH_2Cl_2	25	5	24	93	90 *(R)*
12	**3a**	$AcNHCH(CO_2Me)_2$	BSA/KOAc	CH_2Cl_2	25	5	90	83	93 *(R)*
13	**3b**	$CH_2(CO_2Me)_2$	BSA/KOAc	CH_2Cl_2	25	5	25	97	94 *(S)*
14	**3b**	$CH_2(CO_2Me)_2$	NaH	CH_2Cl_2	25	5	16	100	94 *(S)*

[a] Determined by HPLC analysis (column Chiralpak AD, 0.40×25 cm).

NaH as the base, the transformation being quantitative (Table 1, entries 13 and 14).

We tried to recycle the palladium-catalyst using a two-phase system CH_2Cl_2-FC-72. However all attempts were unsuccessful, due to the precipitation of black palladium. So we turned our attention to an easy extraction of the fluorous ligand and its reuse. When the reaction was performed in CH_2Cl_2, the solution was evaporated, and the residue was extracted with perfluorous solvent FC-72 (3×2 mL). Evaporation of the solvent gave the ligand in approximatively 70% yield (non optimized). This ligand was reused in a new alkylation reaction of **4** with dimethyl malonate in the presence of $[Pd(C_3H_5)Cl]_2$ (5 mol%), bis(trimethylsilyl)acetamide (BSA, 2 equiv.) and potassium acetate (0.1 equiv.); the corresponding alkylated product was obtained with an enantioselectivity up to 98%.

In conclusion, fluorous chiral bisoxazolines were easily prepared from the corresponding non-fluorous ligands. They gave enantioselectivities as high as their non-fluorous analogues in the palladium-catalyzed alkylation of allylic substrates, although the activity seemed lower. The applications of these ligands in other reactions, as well as their uses in $scCO_2$ are currently under intense investigation and will be published in due course.

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28. **3a**: mp = 68–70°C; $[\alpha]_D^{20} = -34.7$ (*c* 0.3, $C_6H_5CF_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.61–1.64 (m, 4H), 2.03–2.13 (m, 8H), 4.17 (dd, $J = 8.3$ Hz, $J = 8.3$ Hz, 2H), 4.68 (dd, $J = 9.6$ Hz, $J = 8.3$ Hz, 2H), 5.27 (dd, $J = 9.6$ Hz, $J = 8.3$ Hz, 2H), 7.16–7.21 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 15.9 (CH_2), 31.5 (t, $J_{CF} = 22.3$ Hz, CH_2), 33.3 (CH_2), 46.5 (CH_2), 70.0 (CHC_6H_5), 75.6 (OCH_2), 110–120 (m, CF_2), 127.0, 128.1, 129.1, 142.4 (C_6H_5), 168.2 (C=N); ^{19}F (282.4 MHz, $CDCl_3$): −126.9 (m, 4F), −124.0 (m, 4F), −123.4 (m, 4F), −122.4 (m, 12F), −114.7 (m, 4F), −81.7 (t, $J_{FF} = 9.2$ Hz, 6F). Anal. calcd. for $C_{41}H_{28}F_{34}N_2O_2$: C, 40.15; H, 2.30. Found: C, 40.19; H, 2.38.
3b: mp = 78–80°C; $[\alpha]_D^{20} = -25.1$ (*c* 0.2, $C_6H_5CF_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.61–1.64 (m, 4H), 2.08–2.14 (m, 8H), 4.08 (dd, $J = 8.4$ Hz, $J = 8.4$ Hz, 2H), 4.60 (dd, $J = 9.6$ Hz, $J = 8.4$ Hz, 2H), 5.18 (dd, $J = 9.6$ Hz, $J = 8.4$ Hz, 2H), 7.16–7.27 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 15.8 (CH_2), 31.5 (t, $J_{CF} = 22.3$ Hz, CH_2), 33.1 (CH_2), 46.4 (CH_2), 70.0 (CHC_6H_5), 75.6 (OCH_2), 110–120 (m, CF_2), 127.0, 128.1, 129.2, 142.3 (C_6H_5), 168.2 (C=N); ^{19}F (282.4 MHz, $CDCl_3$): −126.7 (m, 4F), −123.9 (m, 4F), −123.2 (m, 4F), −122.2 (m, 20F), −114.5 (m, 4F), −81.4 (t, $J_{FF} = 10.3$ Hz, 6F). Anal. calcd. for $C_{45}H_{28}F_{42}N_2O_2$: C, 37.89; H, 1.98. Found: C, 38.15; H, 1.92.
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