Iridium-catalyzed regio- and enantioselective allylic alkylation of fluorobis(phenylsulfonyl)methane†

Wen-Bo Liu,[a] Sheng-Cai Zheng,[b] Hu He,[a] Xiao-Ming Zhao,*[b] Li-Xin Dai[a] and Shu-Li You*[a]

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Highly regio- and enantioselective allylic alkylation of fluorobis-(phenylsulfonyl)methane (FBSM) has been realized by [Ir(COD)Cl]$_2$/phosphoramidite, affording enantiopure fluorobis-(phenylsulfonyl)methylated compounds bearing a terminal alkene, which could be converted to monofluoro-methylated ibuprofen in just two steps without loss of the optical purity (95% ee).

Fluoroorganic compounds have exhibited unique physical, chemical and biological properties.[1] As a consequence, the development of efficient methodology for the synthesis of organofluorine compounds has attracted considerable attention in organic synthesis, pharmaceutical chemistry and material sciences.[1,2] Various fluorination reactions have been documented,[3,4] and among these, fluoroalkylation reactions represent a straightforward and powerful method to construct fluorine-containing molecules. Their asymmetric versions are particularly attractive and useful in medicinal chemistry.[3,4] In this context, compounds with a monofluoromethyl unit are of great importance with regards to isostere-based drug design.[5] Notably, with the significant pioneering studies by Shibata and Toru,[6] Hu,[7] Prakash and Olah,[8] monofluoro-bisphenylsulfonylmethane (FBSM) has been demonstrated successfully as a synthetic equivalent of CH_2F. Particularly, palladium-catalyzed asymmetric allylic alkylation of FBSM with symmetrical allylic substrates was realized, providing the access to monofluorinated ibuprofen.[6a,9] In connection with our research interest in iridium-catalyzed allylic alkylation reactions,[10,11] we envisioned iridium complexes could be utilized for allylic alkylation of FBSM with 1,3-unsymmetrical allylic substrates to afford the enantiopure fluorobis(phenylsulfonyl)methylated compounds bearing a terminal alkene, which would enable the subsequent transformation more atom economical and efficient. Here, we report the highly regio- and enantioselective iridium-catalyzed allylic alkylation of fluorobis(phenylsulfonyl)methane and the synthesis of monofluorinated ibuprofen and naproxen as a demonstration of the utility of the current methodology.

At the outset, we utilized a well-developed iridium catalytic system including [Ir(COD)Cl]$_2$ and **1a** as the catalyst (Fig. 1). In the presence of 2 mol% of [Ir(COD)Cl]$_2$, 4 mol% of **1a** and 1.1 equivalents of Cs_2CO_3, reaction of FBSM (**3a**) with allylic carbonate **2a** in DCM for 12 h gave a mixture of **4aa** and **5aa** in 92% yield with high levels of both branch-selectivity (88/12) and enantioselectivity of **4aa** (93% ee) (entry 1, Table 1). Encouraged by these results, various bases were examined. As listed in Table 1, several inorganic bases such as K_3PO_4, NaH and KOAc, all led to good branch-selectivity and enantioselectivity, except for Li_2CO_3 (entries 2–5, Table 1). In addition, the reaction proceeded smoothly with organic bases such as urotropine, DABCO, BSA, quinine, though not DBU (entries 6–10, Table 1). To our great delight, the use of excess Cs_2CO_3 (2.2 equiv.) increased greatly the regioselectivity, branched product **4aa** was formed exclusively with excellent enantioselectivity (94% ee) (entry 11, Table 1). After testing different solvents such as $CDCl_3$, THF, ether, toluene and CH_3CN, DCM was found to be the optimal solvent (entries 11–17, Table 1).

Under the conditions listed in entry 11, Table 1, different chiral ligands were evaluated, and the results are summarized in Table 2. Phosphoramidite ligands **1b** and **1c**, varying the substituents on the amine moiety, afforded the products in slightly lower yields but with excellent ees (entries 1–3, Table 2). Unfortunately, ligands **1d** and **1f** were not effective for the reaction (entries 4 and 6, Table 2). The reaction with **1e**, a diastereoisomer of **1a**, led to the product in a lower yield with decreased selectivity, indicating the match of chiralities in (S,S,S_a)-**1a** (entry 5, Table 2). Interestingly, Phox ligand **1g** could also give **4aa** in moderate yield with 82% ee (entry 7, Table 2).

Under the optimized reaction conditions [2 mol% of [Ir(COD)Cl]$_2$, 4 mol% of **1a**, 250 mol% of Cs_2CO_3, DCM at rt], the generality of Ir-catalyzed allylic alkylation of fluorobis-(phenylsulfonyl)methane was examined. As summarized in Table 3, aryl allylic carbonates **2b–f** with electron-donating groups such as *p*-OMe, *m*-OMe, *p*-Me and *p*-^{t}Bu on the phenyl ring all gave excellent yields with 91–95% ee (entries 2, 3, 5 and 6, Table 3). The *ortho*-methoxy phenyl substrate **2d** can also be tolerated but with moderate enantioselectivity (**4ad**, 86% yield, 70% ee, entry 4, Table 3). The unfavorable *ortho* substituent effect is in agreement with the previous

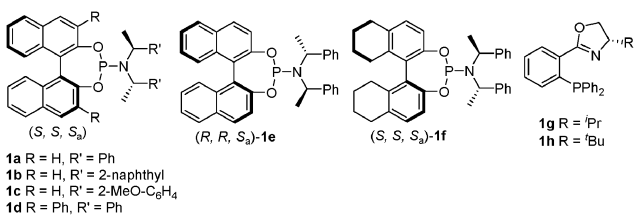

Fig. 1 Chiral ligands **1a–g**.

[a] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China. E-mail: slyou@mail.sioc.ac.cn; Fax: (+86) 21-54925087*
[b] *Department of Chemistry, Tongji University, 1239 Siping Lu, Shanghai 200092, China. E-mail: xmzhao08@mail.tongji.edu.cn*

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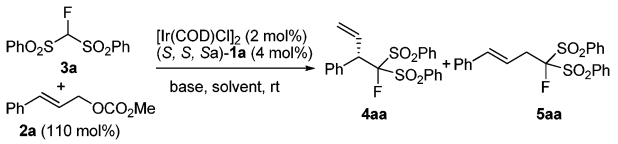
Table 1 Optimizing reaction conditions for Ir-catalyzed allylic alkylation of FBSM[a]



Entry	Base[b]	Solvent	*t*/h	Yield (%)	**4aa**/**5aa**[c]	ee[d] (%)
1	Cs_2CO_3	DCM	12	92	88/12	93
2	Li_2CO_3	DCM	72	Trace	—	—
3	K_3PO_4	DCM	17	77	85/15	93
4	NaH	DCM	40	28	87/13	93
5	KOAc	DCM	36	44	85/15	90
6	Urotropine	DCM	72	30	84/16	91
7	DABCO	DCM	48	57	93/7	92
8	DBU	DCM	48	Trace	—	—
9	BSA	DCM	18	91	82/18	94
10	Quinine	DCM	24	93	88/12	90
11	Cs_2CO_3	DCM	10	89	>99/1	94
12	Cs_2CO_3	DCE	16	56	>99/1	95
13	Cs_2CO_3	$CDCl_3$	10	87	>99/1	90
14	Cs_2CO_3	THF	24	18	95/5	89
15	Cs_2CO_3	Et_2O	22	22[e]	>99/1	—
16	Cs_2CO_3	Toluene	24	14[e]	>99/1	—
17	Cs_2CO_3	MeCN	72	*NR*[f]	—	—

[a] *Reaction conditions*: 2 mol% of $[Ir(COD)Cl]_2$, 4 mol% of (*S*,*S*,*Sa*)-**1a**, 110 mol% of **2a** and **3a** (0.1 M) at rt. [b] 110 mol% for entries 1–10; 220 mol% for entries 11–17. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Determined by chiral HPLC analysis (Chiralcel OD-H column). [e] NMR yield. [f] *NR* = no reaction.

Table 2 Screening the chiral ligands[a]

Entry	Ligand	*t*/h	Yield (%)	**4aa**/**5aa**	ee (%)
1	**1a**	10	89	>99/1	94
2	**1b**	22	61	>99/1	92
3	**1c**	12	76	>99/1	95
4	**1d**	48	*NR*	—	—
5	**1e**	48	42	89/11	65
6	**1f**	48	*NR*	—	—
7	**1g**	16	48	>99/1	82
8	**1h**	72	*NR*	—	—

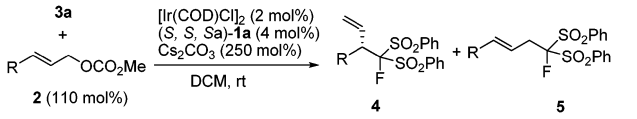
[a] *Reaction conditions*: as listed in entry 11, Table 1.

iridium-catalyzed asymmetric allylic substitution reactions.[10b,c] Allylic carbonates **2g–i** bearing electron-withdrawing groups (*m*-Cl, *p*-Br and *p*-CF_3) were tolerated well to furnish the fluorobis(phenylsulfonyl)methylated products in moderate yields with high regio- and enantioselectivities (entries 7–9, Table 3).

The reaction of 6-methoxynaphthyl allylic carbonate with **3a** underwent well to afford **4aj** in 94% yield with 93% ee (entry 10, Table 3). Reaction of 2-thienyl substituted allylic carbonate **2k** led to **4ak** in a lower yield mainly due to the decomposition of the substrate under the reaction conditions (entry 11, Table 3). Aliphatic allylic carbonates **2l** and **2m** were both suitable substrates (entries 12 and 13, Table 3). Notably, when the steric bulky nucleophile $HCF(SO_2\text{-}1\text{-naphthyl})_2$ (**3b**) was used, **4ba** was smoothly obtained in moderate yield with excellent selectivity (entry 14, Table 3).

To determine the absolute configuration of the product, the enantiopure bromo-containing compound **4ah** was obtained

Table 3 The substrate scope[a]



Entry	R	*t*/h	**4** (%)	**4**/**5**[b]	ee[c] (%)
1[d]	C_6H_5	10	**4aa**, 89 (79)	>99/1	94 (>99)
2	4-$MeOC_6H_4$	12	**4ab**, 95	99/1	95
3	3-$MeOC_6H_4$	10	**4ac**, 91	95/5	91
4	2-$MeOC_6H_4$	24	**4ad**, 86	>99/1	70
5	4-MeC_6H_4	10	**4ae**, 94	97/3	94
6	4-^{t}BuC_6H_4	10	**4af**, 96	97/3	95
7[e]	3-ClC_6H_4	48	**4ag**, 41	>99/1	94
8[d]	4-BrC_6H_4	17	**4ah**, 66 (54)	>99/1	92 (>99)
9	4-$CF_3C_6H_4$	40	**4ai**, 60	>99/1	91
10	6-MeO-2-naphthyl	15	**4aj**, 94	>99/1	93
11	2-Thienyl	14	**4ak**, 28	>99/1	96
12	(*E*)-1-Propenyl	5	**4al**, 52	84/16	75
13	Me	8	**4am**, 92	87/13	89
14[f]	C_6H_5	13	**4ba**, 42	>99/1	90

[a] *Reaction conditions*: 2 mol% of $[Ir(COD)Cl]_2$, 4 mol% of (*S*,*S*,*Sa*)-**1a**, 250 mol% of Cs_2CO_3, 110 mol% of **2** and 100 mol% **3** (0.1M) in DCM at rt. [b] Determined by ^1H NMR of the crude reaction mixture. [c] The ee of **4** was determined by chiral HPLC analysis. [d] Values in parenthesis were those obtained after recrystallization. [e] Under reflux. [f] $HCF(SO_2\text{-}1\text{-naphthyl})_2$ was used.

by recrystallization. An X-ray crystallographic analysis (see ESI†) of enantiopure **4ah** disclosed the absolute configuration as *S* (Fig. 2). The stereochemistry of the current reaction with (S,S,S_a)-**1a** parallels that of our previous studies.[10a,c]

To test the practicality of the current methodology, a gram scale reaction was carried out for allylic carbonate **2f**. To our delight, the reaction proceeded smoothly and **4af** was obtained in 97% yield and 94% ee (Scheme 1). To explore the synthetic utility of the products obtained here, the sulfonyl groups of **4af** were removed by treatment with activated magnesium in methanol, and subsequent oxidation with $RuCl_3$ led to **6af**.[12] Both enantiomers of **4af** were converted to the mono-fluorinated ibuprofen in high yields without loss of the optical purity.[13] The highly shortened synthetic route (two *vs.* four steps) is likely due to that the desulfonyl conditions, Mg/MeOH, could be tolerated by the isolated terminal alkene in product **4**, but not the conjugated double bond.[6a] Notably, the $RuCl_3$ oxidation is not suitable for the synthesis of mono-fluorinated naproxen, which was successfully synthesized by dihydroxylation, oxidation with sodium periodate, and then Pinnick oxidation[14] (Scheme 2).

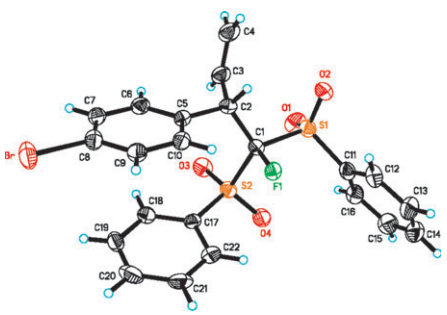
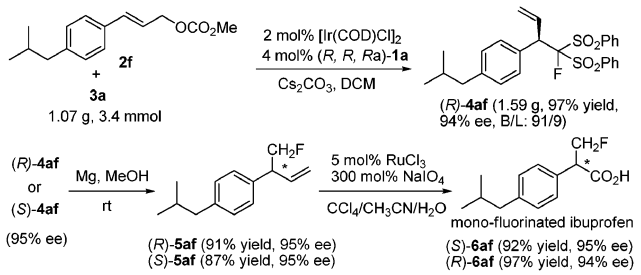
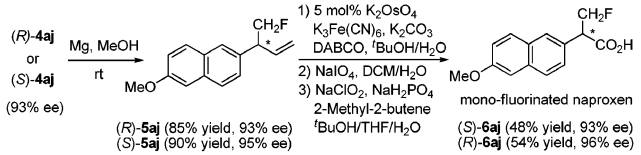


Fig. 2 X-Ray structure of (*S*)-**4ah** (thermal ellipsoids are set at 30% probability).



Scheme 1 A gram-scale synthesis and practical synthesis of enantiopure monofluorinated ibuprofen.



Scheme 2 Synthesis of monofluorinated naproxen.

In summary, we found that $[Ir(COD)Cl]_2$/phosphoramidite **1a** is an efficient catalytic system for highly regio- and enantioselective allylic alkylation of fluorobis(phenylsulfonyl)methane. The monofluoromethylated products could be transformed to the fluorobis(phenylsulfonyl)methylated ibuprofen family in a highly efficient manner.

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