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COMMUNICATIONS

Published on Web 04/27/2007

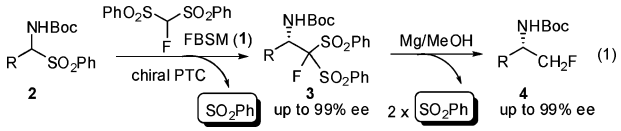
Cinchona Alkaloid-Catalyzed Enantioselective Monofluoromethylation Reaction Based on Fluorobis(phenylsulfonyl)methane Chemistry Combined with a Mannich-type Reaction

Satoshi Mizuta, Norio Shibata,* Yosuke Goto, Tatsuya Furukawa, Shuichi Nakamura, and Takeshi Toru*

Department of Applied Chemistry, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

Received March 3, 2007; E-mail: nozshiba@nitech.ac.jp; toru@nitech.ac.jp

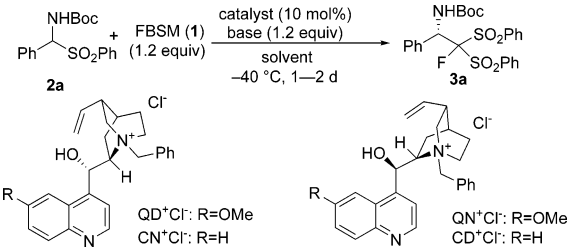
Enantiocontrolled synthesis of fluorine-containing organic molecules is extremely important in the field of medicinal chemistry and material science.[1] Enantioselective fluorination and fluoromethylation reactions are especially attractive for this purpose because nonfluorinated prochiral substrates can be directly transformed to chiral fluoroorganic compounds with controlled absolute configuration by these methods.[2] Significant progress has been made in the development of asymmetric fluorination reactions in recent years;[2] however, direct enantioselective fluoromethylation remains a challenge.[2b−d,3,4] There are several reports on the stereocontrolled nucleophilic additions of fluoromethyl groups to imines, and the majority of them have been accomplished using chiral auxiliaries.[2b,4] Prakash et al. showed the fluoride anion catalyzed diastereoselective nucleophilic trifluoromethylation of optically active *N*-*tert*-(butanesulfinyl) imines using $TMSCF_3$ in 2001.[4a−c] Hu and co-workers successively demonstrated the diastereoselective difluoromethylation as well as the monofluoromethylation reactions of the *N*-*tert*-(butanesulfinyl) imines using $LiCF_2SO_2Ph$ or $LiCFHSO_2Ph$.[4d,e] These nucleophilic additions of fluoromethyl groups to the chiral imines offer chiral, nonracemic α-fluoromethyl amines of biological interest;[5] however, the corresponding enantioselective reactions have been elusive until now in our knowledge. We recently found 1-fluorobis(phenylsulfonyl)methane (FBSM, **1**) to be a synthetic equivalent of a fluoromethide species under the Tsuji−Trost allylic alkylation conditions, which provided the palladium-catalyzed asymmetric allylic monofluoromethylation reaction with high enantiocontrol.[6a] In connection with our studies on the development of new methodology for asymmetric synthesis,[2f,g,6] herein we disclose an unprecedented catalytic enantioselective monofluoromethylation reaction of in situ generated prochiral imines with **1** in the presence of a chiral phase transfer catalyst (PTC). The methodology consists of two consecutive steps, the Mannich-type reaction and reductive desulfonylation. The quaternary ammonium salts derived from cinchona alkaloids are found to be effective for chiral induction to the process. The key feature of our strategy is the effective use of phenylsulfonyl groups throughout the sequence of transformations that provide efficient access to enantiomerically enriched α-monofluoromethylated amines.



Initially, we studied the nucleophilic addition of FBSM (**1**) to *N*-Boc α-amido sulfone **2** by applying the conditions developed by Ricci et al.[7] for the Mannich reaction[8] of malonates with α-amido sulfones[7,8] since the in situ generation of *N*-Boc imines from the corresponding α-amido sulfones[8g] via desulfonylation would be suitable for the reaction with an unstable anion of **1**. FBSM (**1**) was added to a mixture of **2a** and 1.2 equiv of K_2CO_3 in toluene in the presence of a catalytic amount of *N*-benzylquinidinium chloride (QD^+Cl^-) at −40 °C. However, even after 2 days of stirring, a large amount of the starting material was detected by TLC analysis, with a trace of addition product (Table 1, run 1). The reaction was then attempted using aqueous K_2CO_3 or Cs_2CO_3 as base, but the results were not improved (runs 2 and 3). To our delight, the use of $CsOH·H_2O$ afforded the desired addition product **3a** in 72% with 92% ee (run 4). A considerable difference in asymmetric induction was noticed between ammonium salts derived from quinine, quinidine, cinchonine, and cinchonidine, and quinidine was the most effective (runs 4−7). Better enantioselectivity was observed in CH_2Cl_2 (run 8), and the optimal enantiocontrol was observed by lowering the temperature to −80 °C (run 10). The amount of catalyst can be reduced to 5 mol % without any loss of enantioselectivity (run 11).

With these optimized conditions established, the scope of the reaction in terms of substrates was investigated (Table 2). We find that QD^+Cl^- is an extremely general catalyst for the asymmetric

Table 1. Optimization of Bases, Quaternary Ammonium Salts, and Solvents in the Reaction of α-Amido Sulfone **2a** with FBSM (**1**)[a]

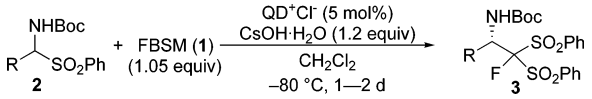


run	catalyst	base	solvent	temp (°C)	yield (%)	ee (%)
1	QD^+Cl^-	K_2CO_3	toluene	−40	trace	
2	QD^+Cl^-	K_2CO_3(aq)	toluene	−40	trace	
3	QD^+Cl^-	Cs_2CO_3	toluene	−40	trace	
4	QD^+Cl^-	$CsOH·H_2O$	toluene	−40	72	92
5	QN^+Cl^-	$CsOH·H_2O$	toluene	−40	40	0
6	CD^+Cl^-	$CsOH·H_2O$	toluene	−40	91	0
7	CN^+Cl^-	$CsOH·H_2O$	toluene	−40	22	13
8	QD^+Cl^-	$CsOH·H_2O$	CH_2Cl_2	−40	83	90
9	QD^+Cl^-	$CsOH·H_2O$	toluene	−80	trace	
10	QD^+Cl^-	$CsOH·H_2O$	CH_2Cl_2	−80	72	97
11[b]	QD^+Cl^-	$CsOH·H_2O$	CH_2Cl_2	−80	79	97

[a] All of the reaction was performed on 0.086 mmol scale of **2a**. The absolute stereochemistry of **3a** was determined to be *S* after chemical derivatization (see Supporting Information). [b] 5 mol % of catalyst was used.

10.1021/ja071509y CCC: $37.00

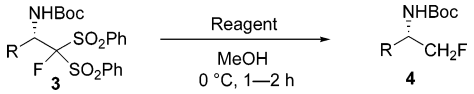
Table 2. Scope of the Enantioselective Monofluoromethylation[a]



entry	2	R	3	yield (%)	ee (%)
1	**2a**	Ph	**3a**	92	96
2[b]	**2b**	*m*-Cl−C_6H_4	**3b**	98	97[c]
3	**2c**	*p*-Cl−C_6H_4	**3c**	94	87[c]
4	**2d**	*p*-MeO−C_6H_4	**3d**	88	95[c]
5	**2e**	2-naphthyl	**3e**	96	90[c]
6	**2f**	2-furyl	**3f**	81	93[d]
7	**2g**	$PhCH_2CH_2$	**3g**	85	90[d]
8	**2h**	$Me(CH_2)_6$	**3h**	95	95[d]
9[e]	**2i**	*c*-C_6H_{11}	**3i**	80	98[d]
10	**2j**	*i*-Pr	**3j**	93	99[d]
11[e]	**2k**	*t*-Bu	**3k**	70	96[d]

[a] All of the reaction was performed on 0.35 mmol scale of **2**. [b] 10 mol % of catalyst was used. [c] The absolute stereochemistry was tentatively determined by comparing the optical rotation with that of **3a**. [d] The stereochemistry was not determined. [e] The reaction was carried out at −40 °C.

Table 3. Reductive Desulfonylation of **3**



entry	3 (ee)	reagent	4	yield (%)	ee (%)
1	**3a** (96)	Mg	**4a**	84	95[a]
2	**3b** (97)	Mg	**4b**	82	96[b]
3	**3c** (87)	Mg	**4c**	88	83[b]
4	**3d** (95)	Mg	**4d**	80	93[b]
5	**3e** (90)	Mg	**4e**	85	89[b]
6	**3f** (93)	Mg	**4f**	81	92[c]
7	**3g** (90)	Mg	**4g**	87	90[c]
8	**3h** (95)	Mg	**4h**	83	96[c]
9	**3i** (98)	Mg	**4i**	87	98[c]
10	**3j** (99)	Mg	**4j**	75	99[c]
11	**3k** (96)	Mg	**4k**	26 (74[d])	96[c]
12[e]	**3a** (92)	Na(Hg), Na_2HPO_4	**4a**	92	92[a]

[a] The absolute configuration of **4a** was determined to be *S* after chemical derivatization (see Supporting Information). [b] The absolute stereochemistry was tentatively determined by comparing the optical rotation with that of **4a**. [c] The absolute stereochemistry was not determined. [d] Based on the recovered starting material. [e] Performed at −20 to −10 °C.

reaction of **1** with a broad range of aryl α-amido sulfones **2a**−**f**, including a heteroaryl group, and functional groups such as chloro and methoxy were tolerated in the reaction. The desired products **3a**−**f** were obtained in high yields with up to 97% ee (entries 1−6). It should be mentioned that alkyl α-amido sulfones **2g**−**j** that have enolizable protons also gave good reactivities and enantioselectivities: the corresponding *N*-Boc α-fluorobisphenylsulfonyl amines **3g**−**j** were produced in high yields with excellent enantioselectivities of 90−99% (entries 7−10). High enantioselectivity was also achieved with a sterically hindered α-amido sulfone **2k** (96% ee, entry 11).

With a range of enantiomerically enriched *N*-Boc α-fluorobisphenylsulfonyl amines **3** in hand, we were now in a position to investigate the reductive desulfonylation of **3** to complete the sequence of enantioselective monofluoromethylation. A simple one-step removal of the two phenylsulfonyl groups from **3a**−**k** was affected under Mg/MeOH conditions to afford the corresponding monofluoromethylated amines **4a**−**k** in high yields (Table 3). The desulfonylation of **3k** gave only incomplete conversion, which is presumably due to the steric bulk of the *tert*-butyl group (entry 11). The substituents on the aryl groups, furanyl, and alkyl chains were well tolerated, and the enantiomeric excesses of the starting α-fluorobisphenylsulfonyl amines **3a**−**k** were nearly maintained during the desulfonylation reaction. The desulfonylation of **3** was also possible using Na(Hg)/Na_2HPO_4 in MeOH to give **4** (entry 12).

In conclusion, we have described the first catalytic enantioselective fluorobisphenylsulfonylmethylation of in situ generated imines from α-amido sulfones under the combination of Mannich-type conditions with FBSM chemistry.[9] The α-fluorobisphenylsulfonylmethylated amines were converted to α-monofluoromethyl amines by reductive desulfonylation. Application to the synthesis of biologically important molecules is currently under investigation via the FBSM/Mannich strategy.

Acknowledgment. Support was provided by JSPS KAKENHI (19390029, 17590087) and by Japan Science & Technology (JST).

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The reaction of **2a** using 1-fluoro(phenylsulfonyl)methane (CH_2FSO_2Ph) in place of FBSM (**1**) under the same condition did not give the corresponding product. More basic conditions might be needed.

JA071509Y