Trifluoromethylation

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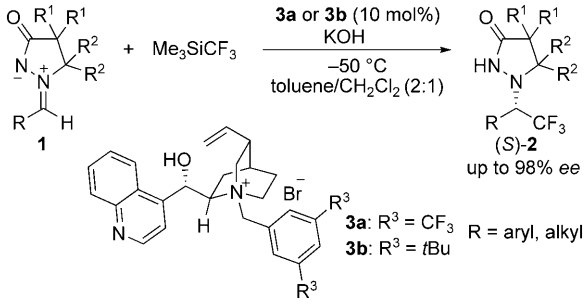
Catalytic Enantioselective Trifluoromethylation of Azomethine Imines with Trimethyl(trifluoromethyl)silane**

*Hiroyuki Kawai, Akihiro Kusuda, Shuichi Nakamura, Motoo Shiro, and Norio Shibata**

Although the first report on the nucleophilic trifluoromethylation of carbonyl compounds using tetrabutylammonium fluoride by Prakash and Olah[1,2] was reported over 20 years ago, the enantioselective nucleophilic trifluoromethylation using trimethyl(trifluoromethyl)silane, Me_3SiCF_3, remains a challenge in fluoroorganic chemistry. Although a variety of methodologies for catalytic asymmetric reactions are now available in modern organic synthesis, chiral auxiliary based diastereoselective trifluoromethylation[3] is still the most widely applied approach in the field of fluorine chemistry with enantioselective catalysis remaining a big challenge.[4,5] Our research group has recently devised such processes using a catalyst system comprised of bromide salts of cinchona alkaloids and tetramethylammonium fluoride (TMAF); aryl alkyl ketones can be efficiently converted into the corresponding trifluoromethylated alcohols in high yields and with enantioselectivities up to 94% *ee*.[6] As for nucleophilic trifluoromethylation of imines or their equivalents, however, only classical diastereoselective approaches using chiral auxiliaries have been reported,[7,8] and no examples of an enantioselective variant has been reported, despite the potential usefulness and wide applicability of enantiomerically pure trifluoromethylated amines in the syntheses of pharmaceuticals and agrochemicals.[9] We disclose herein the first enantioselective trifluoromethylation of imine equivalents, azomethine imines **1**, with Me_3SiCF_3 (Scheme 1).



Scheme 1. Enantioselective trifluoromethylation of azomethine imines **1**.

Given our success with enantioselective trifluoromethylation of carbonyl compounds,[6] we anticipated that imines would perform with similar effectiveness as substrates in the enantioselective trifluoromethylation reaction under our catalytic protocol. We observed, however, that conventional imines such as *N*-tosylimines were poor substrates from both a reactivity and selectivity point of view under our reported and modified reaction conditions. Work on the mechanistic details of the present reaction led us to realize that the observed insufficient selectivity may have resulted from the size and flexibility in conformation of the *N*-tosylimines. Low conversion might be attributed to the poor nucleophilicity of the generated sulfonamide intermediates towards Me_3SiCF_3. A substrate for trifluoromethylation is usually required to generate a species which is sufficiently nucleophilic to attack Me_3SiCF_3 in the autocatalytic process.[2a] These prerequisites allowed us to employ azomethine imines **1** as a family of sterically demanding imine equivalents with a constrained conformation, which were expected to react with the CF_3 anion stereoselectively to generate species having suitable autocatalytic activity. The catalytic scenario in the presence of a chiral phase transfer catalyst (PTC) is presented in Scheme 2. Azomethine imines are well-known partners of asymmetric 1,3-cycloaddition reaction with olefins or alkynes for achieving heterocycle formation under mild reactions conditions;[10] however, reports of simple nucleophilic addition to azomethine imines are not available.

We started our investigation with the reaction of an azomethine imine **1a**, derived from benzaldehyde, with Me_3SiCF_3 in the presence of chiral ammonium bromide **3a**, and screened a broad range of additives (Table 1). First, our original reaction conditions[6] for enantioselective trifluoromethylation of ketones were tested. A catalytic amount of TMAF was added to a mixture of **1a** and two equivalents of Me_3SiCF_3 in CH_2Cl_2 in the presence of a catalytic amount of *N*-3,5-bis(trifluoromethylbenzyl)cinchoninium bromide (**3a**) at −40 °C; the product was obtained in a 12% yield with a 28% *ee* (Table 1, entry 1). The reaction was next attempted using *t*BuOK at −40 °C, and trifluoromethylated adduct **2a** was formed in 70% *ee*, albeit in low yield (Table 1, entry 2). This preliminary result encouraged us to investigate other combinations in an attempt to improve enantioselectivity (Table 1, entries 3–7). After screening several additives, the enantioselectivity was increased to 77% *ee* by the use of KOH, but the yield was still low at 11% (Table 1, entry 5). We

[*] H. Kawai, A. Kusuda, Dr. S. Nakamura, Prof. N. Shibata
Department of Frontier Materials, Graduate School of Engineering
Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya 466-8555 (Japan)
Fax: (+81) 52-735-5442
E-mail: nozshiba@nitech.ac.jp
Dr. M. Shiro
Rigaku Corporation
3-9-12 Mastubara-cho, Akishima, Tokyo 196-8666 (Japan)

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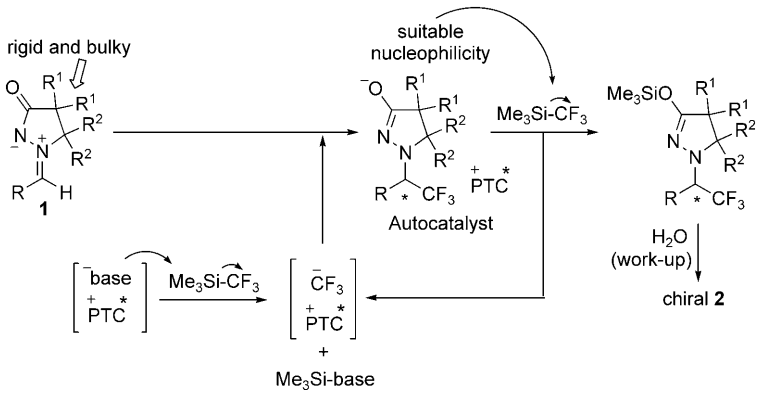
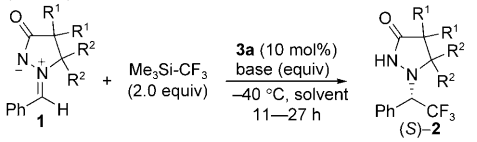


Scheme 2. Autocatalytic scenario of chiral phase transfer catalyst (PTC) catalyzed trifluoromethylation of azomethine imines **1** with Me_3SiCF_3.

Table 1: Optimization of additives for enantioselective trifluoromethylation catalyzed by **3a**.[a]



1a: $R^1 = R^2 = H$
1b: $R^1 = Me$, $R^2 = H$
1c: $R^1 = H$, $R^2 = Me$

2a: $R^1 = R^2 = H$
2b: $R^1 = Me$, $R^2 = H$
2c: $R^1 = H$, $R^2 = Me$

Entry	1	Base (equiv)	Solvent	Yield [%]	*ee* [%][b]
1[c]	**1a**	TMAF (0.2)	CH_2Cl_2	12	28
2[c]	**1a**	*t*BuOK (0.2)	CH_2Cl_2	15	70
3[c]	**1a**	NaOH (0.2)	CH_2Cl_2	7	71
4[c]	**1a**	PhOK (0.2)	CH_2Cl_2	18	74
5	**1a**	KOH (0.2)	CH_2Cl_2	11	77
6	**1a**	$CsOH·H_2O$ (0.2)	CH_2Cl_2	14	75
7	**1a**	CsF (0.2)	CH_2Cl_2	7	75
8[d]	**1a**	KOH (1.5)	CH_2Cl_2	57	75
9[d]	**1a**	KOH (6.0)	CH_2Cl_2	73	75
10[d]	**1a**	KOH (6.0)	toluene/CH_2Cl_2	67	77
11[d]	**1b**	KOH (6.0)	toluene/CH_2Cl_2	85	85
12[d]	**1c**	KOH (6.0)	toluene/CH_2Cl_2	76	89
13[d,e]	**1c**	KOH (6.0)	toluene/CH_2Cl_2	80	91
14[e,f]	**1c**	KOH (6.0)	toluene/CH_2Cl_2	94	90
15[d,g]	**1c**	KOH (6.0)	toluene/CH_2Cl_2	82	87

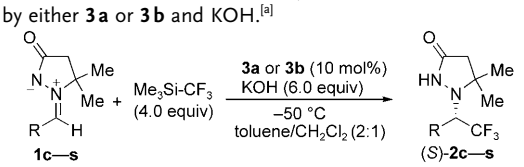
[a] The reaction of **1** with Me_3SiCF_3 (2.0 equiv) was carried out in the presence of **3a** (10 mol%) and base in solvent (CH_2Cl_2 or toluene/CH_2Cl_2 = 2:1) at −40 °C, unless otherwise noted. [b] Determined by HPLC methods using a Chiralcel OJ-H column. [c] The reaction mixture was cooled to −40 °C and warmed to −20 °C over a 2 h time period. [d] Me_3SiCF_3 (10 equiv) was used. [e] The reaction was carried out at −50 °C. [f] Me_3SiCF_3 (4 equiv) was used. [g] Catalyst **3b** (10 mol%) was used instead of **3a**.

believe that the low conversion is probably because of the instability of Me_3SiCF_3 and poor solubility of KOH in the reaction solution. We therefore used a large excess of Me_3SiCF_3 (10 equiv) and KOH (1.5 equiv) to ensure high conversion of azomethine imine, and the yield was improved to 57% without any loss of enantioselectivity (Table 1, entry 8). Additional improvement was observed in the presence of six equivalents of KOH to give **2a** in 73% with 75% *ee* (Table 1, entry 9). In a mixed solvent system, toluene/CH_2Cl_2 (2:1), the *ee* value was slightly increased to 77% *ee* (Table 1, entry 10). Having established the viability of enantioselective trifluoromethylation of azomethine imine **1a** under the chiral phase transfer conditions, we next turned our attention to a fine-tuning of the azomethine imine structure (Table 1, entries 11 and 12). Steric hindrance around the nitrogen atoms of **1b–c** was found to be necessary for achieving high enantiocontrol, and *ee* values up to 89% were obtained when the 5,5-dimethyl derivative **1c** was used as a substrate (Table 1, entry 12). Lowering the reaction temperature to −50 °C allowed the enantioselectivity of the CF_3 adduct **2c** to reach as high as 91% *ee* (Table 1, entry 13). The amount of Me_3SiCF_3 could be reduced to four equivalents without a significant change to either the yield or enantioselectivity (Table 1, entry 14); therefore, the optimum conditions required the use of 5,5-dimethyl azomethine imine **1c**, 10 mol% of the ammonium bromide **3a**, four equivalents of Me_3SiCF_3 with an excess of KOH in toluene/CH_2Cl_2 (Table 1, entry 14). The sterically demanding *tert*-butyl ammonium bromide **3b** also proved to be an almost equally effective catalyst, affording **2c** in 82% yield with 87% *ee* (Table 1, entry 15).

With optimized reaction conditions, several families of azomethine imines differing in the nature of the R groups were submitted to the action of our trifluoromethylation system to explore the scope of the chiral ammonium bromide **3a** or **3b**/KOH catalyst. The best results of such reactions are collected in Table 2. High chemical yields and high enantioselectivities, in the 90% range, were obtained in all cases, with these being almost independent of the functional groups such as alkyl, sterically demanding alkyl, halogen-containing, and methoxy moieties, as well as the positions of the substituents on the aromatic ring (Table 2, entries 1–12). For other aromatic analogues bearing bulky naphthyl groups, we obtained the CF_3 products **2o–q** in high yields with enantioselectivities ranging from 90 to 93% (Table 2, entries 13–15). Cinnamyl- and alkyl-substituted azomethine imines **1r** and **1s** are also suitable substrates for **3b**/KOH-catalyzed asymmetric trifluoromethylation, although the enantioselectivities were somewhat low at 79% and 71% *ee*, respectively (Table 2, entries 16 and 17). To the best of our knowledge, these are the first examples of enantioselective trifluoromethylation of imines or their equivalents. The absolute stereochemistry of the newly generated stereocenter in **2n** was determined by X-ray crystallographic analysis and the stereochemistry of other trifluoromethylated amines **2** was tentatively assumed by analogy (Figure 1a).

To understand the high enantioselectivity observed for the present reaction catalyzed by the bromide salts of cinchona alkaloids **3**, we postulated a transition-state structure for the production of (*S*)-**2c** catalyzed by **3** generated from the results of X-ray crystallographic analyses of **2n** and **3a** (Figure 1a–c). The X-ray crystallographic analysis of **3a** indicated that the cinchona alkaloid exists in an open conformation.[11] The free hydroxy group in **3** captures the substrate **1c**, presumably by intermolecular hydrogen-bond formation to the oxygen atom

Table 2: Enantioselective trifluoromethylation of **1** with Me_3SiCF_3 catalyzed by either **3a** or **3b** and KOH.[a]



Entry	1	R	3	*t* [h]	2	Yield [%]	*ee* [%]
1	**1c**	Ph	**3a**	17	**2c**	94	90
2[b]	**1d**	2-MeC_6H_4	**3a**	20	**2d**	86	88
3	**1e**	3-MeC_6H_4	**3b**	6	**2e**	72	94
4	**1f**	4-MeC_6H_4	**3b**	8	**2f**	87	90
5	**1g**	3-$MeOC_6H_4$	**3b**	3	**2g**	73	92
6	**1h**	4-$MeOC_6H_4$	**3b**	8	**2h**	84	95
7	**1i**	4-*i*PrC_6H_4	**3b**	6	**2i**	84	96
8	**1j**	4-*t*BuC_6H_4	**3b**	3	**2j**	88	98
9	**1k**	3,4-$Me_2C_6H_3$	**3b**	9	**2k**	89	88
10	**1L**	4-FC_6H_4	**3b**	12	**2L**	89	89
11[b]	**1m**	4-ClC_6H_4	**3b**	9	**2m**	81	86
12[b]	**1n**	4-BrC_6H_4	**3b**	9	**2n**	85	83
13[b]	**1o**	1-naphthyl	**3b**	18	**2o**	74	93
14	**1p**	2-naphthyl	**3b**	4	**2p**	95	90
15[c]	**1q**	6-MeO-2-naphthyl	**3a**	8	**2q**	90	90
16[b]	**1r**	$C_6H_4CH{=}CH$	**3b**	9	**2r**	78	79
17[d]	**1s**	cyclohexyl	**3b**	7	**2s**	85	71

[a] The reaction of **1** with Me_3SiCF_3 (4.0 equiv) was carried out in the presence of **3** (10 mol%) and KOH (6.0 equiv) in toluene/CH_2Cl_2 (2:1) at −50 °C unless otherwise noted. The *ee* values were determined by HPLC methods using a Chiralcel OJ-H, AD-H, or OD-H column. [b] The reaction mixture was cooled to −50 °C and warmed to −40 °C over a 2 h time period. [c] Me_3SiCF_3 (6.0 equiv) and 30 mol% of **3a** were used. The reaction was carried out at −40 °C in CH_2Cl_2. [d] The reaction mixture was cooled to −70 °C and warmed to −60 °C over a 2 h time period.

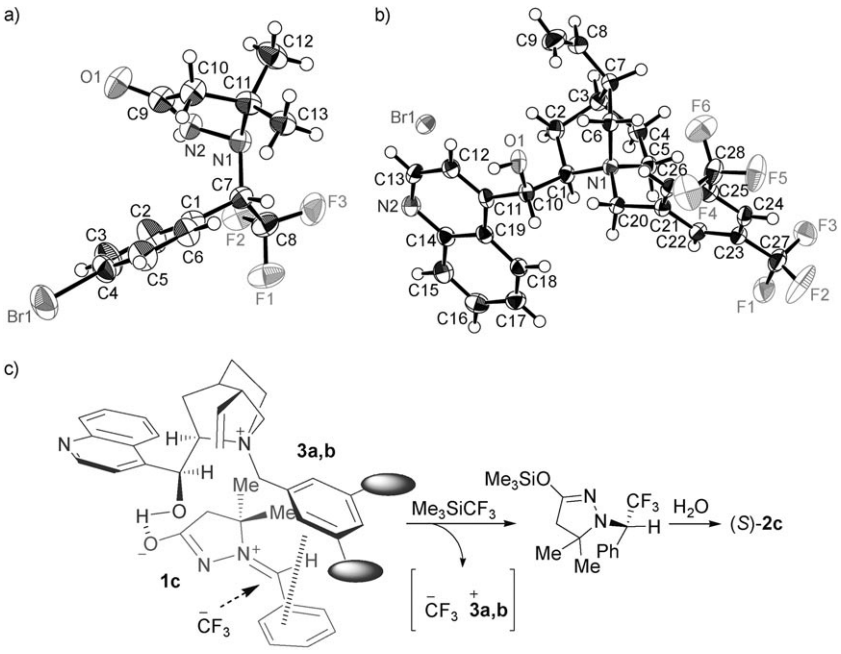
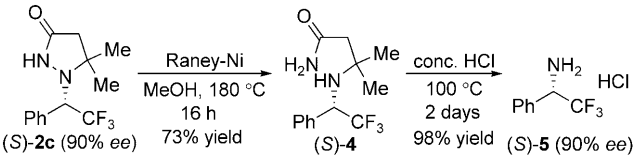


Figure 1. a) X-ray crystallographic analysis of (*S*)-**2n**. Thermal ellipsoids at 50% probability.[12] b) X-ray crystallographic analysis of **3a**. Thermal ellipsoids at 50% probability.[12] c) Proposed transition-state model for the conversion of **1c** into (*S*)-**2c**.

in **1c**. Sterically demanding dimethyl substituents on **1c** should be located in the space between the quinuclidine ring and either the bulky CF_3 or *t*Bu group on the benzene ring of **3**. The aromatic π–π interactions between **1c** and **3** would assist in the stabilization of the transition-state structure in which the CF_3 anion approaches from the *Si* face of **1c**; the *Re* face is effectively blocked by the bulky parts of the benzyl substituent in **3** (Figure 1c).

Final removal of the protective group of amines proceeded uneventfully even though there are no examples of this type of amines which have been successfully deprotected. Thus, treatment of the amine **2c** with Raney-Ni in MeOH at 180 °C and subsequent acid treatment led to the trifluoromethylated amine (*S*)-**5** in high yield without any loss of enantiopurity (Scheme 3).



Scheme 3. Removal of the protecting group of **2c** to generate the trifluoromethylated amine **5.**

In summary, we have developed the first enantioselective trifluoromethylation of imine equivalents with Me_3SiCF_3. The use of azomethine imines **1** was key for the success in the present reaction. By employing bromide salts of cinchona alkaloids and KOH as chiral catalysts, we have efficiently reacted a wide range of azomethine imines **1** and Me_3SiCF_3 to provide pharmaceutically important trifluoromethylated amines **2** in very good enantiomeric excess. Asymmetric monofluoromethylation and difluoromethylation reactions, as well as conventional cyanation and nitroaldol reactions of azomethine imines are under investigation based on this strategy.

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[12] CCDC 738896 ((*S*)-**2n**) and 738896(**3a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi.

