NJC

Cite this: *New J. Chem.*, 2011, **35**, 2614–2621

www.rsc.org/njc

PAPER

Asymmetric synthesis of chiral trifluoromethylated heliotridane *via* highly catalytic asymmetric Friedel–Crafts alkylation with β-trifluoromethylated acrylates and pyrroles†‡

Yiyong Huang,[ab] Satoru Suzuki,[a] Guokai Liu,[a] Etsuko Tokunaga,[a] Motoo Shiro[c] and Norio Shibata*[a]

Received (in Montpellier, France) 22nd June 2011, Accepted 15th August 2011
DOI: 10.1039/c1nj20550a

Chiral Ph-dbfox (Ph-dbfox = (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline))/Zn(NTf$_2$)$_2$ catalyzed enantioselective Friedel–Crafts reactions of β-CF$_3$ acrylates with pyrroles and indoles have been investigated, which afforded the corresponding chiral trifluoromethyl pyrrole and indole derivatives in high yields (90–99%) with a range of 66–99% ee values. With the aid of the chiral adduct of the asymmetric Friedel–Crafts reaction, the chiral trifluoromethylated heliotridane has been successfully constructed in good total yield.

Introduction

It is well known that fluorinated organic compounds have some pharmaceutical superiority over their non-fluorinated analogues.[1] They have similar compatibility to the enzyme receptor because of similarity in size and shape. On the other hand, the C–F bond (485 kJ mol^{-1}) is much stronger than the C–H bond (416 kJ mol^{-1}). So the fluorinated compounds show higher metabolic stability. In addition, the incorporation of fluorine(s) into pharmaceuticals can increase lipophilicity (especially with the trifluoromethyl group), membrane permeability, and the binding capability to the target molecules. The importance can be reflected in that around 20% of new drugs contain fluorine(s) and more than 30% of crop protection agents are organofluorine compounds.[2] Furthermore, according to a most up-to-date survey, 138 fluorine-containing drugs have received FDA approval for human diseases and 33 are currently in use for veterinary applications.[3] Therefore, recent investigations focus on the introduction of fluorine atoms and perfluoroalkyl groups into molecules of known bioactive compounds to improve their properties. Importantly, it is now a common practice in drug discovery to study fluoro-analogues of parent compounds under development.[4] For example, a remarkable CF$_3$ group effect was observed when Danishefsky's group sought for drug candidates. In Fig. 1, it was found that when the *C*12-methyl group of compound 9,10-dehydro-dEpoB was replaced with a trifluoromethyl functionality, termed fludelone, a dramatic improvement in terms of therapeutic index ensued. In addition, fludelone is markedly less toxic than the parent compound.[5]

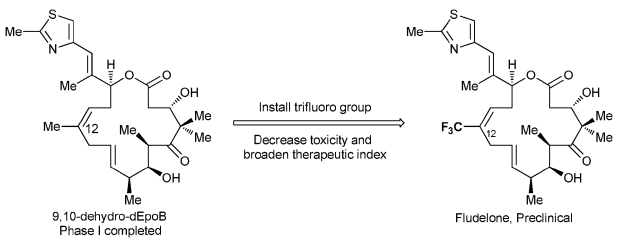


Fig. 1 9,10-Dehydro-dEpoB and its trifluoromethyl analogue.

Among various types of organo-fluorine molecules,[6] chiral substances in which a trifluoromethyl (CF$_3$) group and heteroatom are attached to an asymmetric carbon center have been popularly studied and many strategies have been available to construct them due to some unique biological and pharmaceutical activities in recent years.[7] However, the work to construct chiral trifluoromethylated compounds with a CF$_3$ group at an all-C tertiary or quaternary chiral carbon center without any heteroatom substituent remains challenging.[8] In Fig. 2, several of this type of important compounds of biological interest are listed. Consequently, the development of efficient and convenient synthetic methods for such molecules has been highly required. In our previous studies,

[a] *Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan. E-mail: nozshiba@nitech.ac.jp; Fax: +81 52-735-5442; Tel: +81 52-735-7543*
[b] *College of Chemistry and Chemical Engineering, Central South University, Changsha 410083, China*
[c] *Rigaku Corporation, 3-9-12 Matsubara-cho, Akishima, Tokyo 196-8666, Japan*

† We briefly communicated this work in 2010.[23] In the present paper, we describe in full the results of our highly catalytic asymmetric Friedel–Crafts alkylation.

‡ Electronic supplementary information (ESI) available: General experimental procedures, ^{1}H, ^{13}C and ^{19}F NMR spectra for all crossed products, characterisation data for all new products. CCDC 758056. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1nj20550a

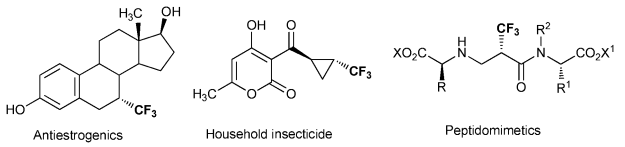


Fig. 2 Chiral trifluoromethylated compounds of biological interest.

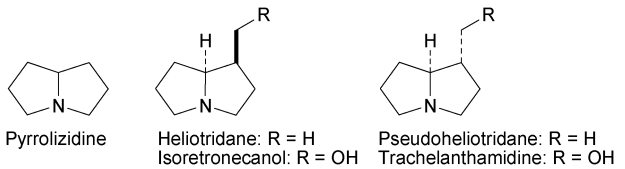


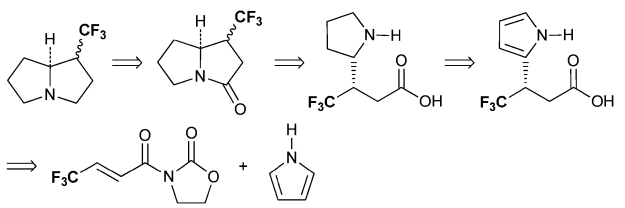
Fig. 3 Pyrrolizidine alkaloids.

we reported enantioselective electrophilic trifluoromethylation of β-keto esters with Umemoto's reagent in the presence of a stoichiometric amount of chiral non-racemic guanidines to access trifluoromethylated products with a quaternary carbon center.[9] Continuing this work, we present herein a new strategy to generate chiral compounds bearing a CF_3 group at a quaternary chiral carbon center without any heteroatom. Most importantly, we can apply the chiral adduct to the synthesis of chiral trifluoromethylated heterocyclic compounds.

Nitrogen-containing heterocycles are omnipresent in natural products and biologically active compounds. Among them, the pyrrolizidine alkaloids of heliotridane and pseudoheliotridane represent a diverse group of natural products.[10] Considerable effort has been directed toward the synthesis of these compounds because of their interesting pharmacological properties (cytotoxic, antimitotic immunostimulatory, and anticancer).[11] Fluorine-containing heterocyclic compounds play an important role in drug and pesticide design. Though much attention was drawn in the synthesis of fluorinated heterocycles,[12] no information on the synthesis of fluorinated heliotridane and pseudoheliotridane is available in the literature. We assumed that trifluoromethylated heliotridane or pseudoheliotridane (Fig. 3) by alternating the CH_3 group with a CF_3 group would have potentially interesting pharmacological properties.

In this context, a novel retrosynthetic proposal to access chiral trifluoromethylated heliotridane and/or pseudoheliotridane is illustrated in Scheme 1. Our approach is based on the catalytic asymmetric Friedel–Crafts reaction of *N*–H pyrrole with the β-CF_3 acrylate. Thus, the asymmetric Friedel–Crafts reaction between pyrroles and β-CF_3 acrylates needed to be fully explored in the arena of total syntheses of the optically active trifluoromethylated heliotridane or pseudoheliotridane.

The organo- and organometal-catalytic asymmetric Friedel–Crafts reactions as a versatile C–C bond formation approach



Scheme 1 Retrosynthetic analysis of chiral trifluoromethylated heliotridane and pseudoheliotridane.

have been widely explored in the last few decades.[13] In particular, this methodology is a topic of great interest in the application of selectively constructing enantioenriched compounds bearing a CF_3 group at stereogenic centers by using prochiral trifluoromethylated substrates as building blocks, which is an indirect asymmetric trifluoromethylation strategy. Since Jørgensen's group documented the novel catalytic enantioselective Friedel–Crafts reactions of 3,3,3-trifluoropyruvate with pyrroles, furans and thiophenes to obtain various chiral hydroxy-trifluoromethyl ethyl esters in 2000,[14] many groups in the world have devoted to the asymmetric Friedel–Crafts reaction studies to construct various chiral trifluoromethylated compounds.

Recently, employing chiral BINOL-derived phosphoric acids as chiral Brønsted acid catalysts in the asymmetric Friedel–Crafts reaction to obtain various enantioenriched trifluoromethylated tertiary alcohols was reported by two groups. Ma's group[15] utilized ethyl 4,4,4-trifluoroacetoacetate, ethyl trifluoropyruvate and 2,2,2-trifluoroacetophenone as electrophiles, but Akiyama's group[16] used methyl 3,3,3-trifluoropyruvate. They both have obtained good results for the asymmetric Friedel–Crafts reaction of indoles. However, when they attempted to apply the optimized conditions to the reaction with *N*–H pyrroles, a low level of enantioselectivity was observed. Very recently, Bolm's group developed a highly chiral phosphoric acid catalyzed enantioselective Friedel–Crafts reaction of *N*-Boc-protected ethyl trifluoropyruvate imine with indoles to afford a wide variety of quaternary indole-derived α-amino acids.[17] In the meantime, organometallic-catalyzed asymmetric Friedel–Crafts reactions based on chiral trifluoromethylated products were also presented. Pedro's group developed the enantioselective Friedel–Crafts reaction of β-trifluoromethyl-α,β-unsaturated ketones with indoles by using chiral BINOL-type Zr(IV) complexes. Unfortunately, the reaction didn't work well with pyrrole (55% ee).[8k] Feng's group described the chiral *N*,*N*′-dioxide–zinc(II) complexes catalyzed asymmetric Friedel–Crafts alkylation between ethyl trifluoropyruvate and indoles.[18] In 2011, Lu's group described an highly enantioselective alkylation of trifluoroethylidene malonates with indoles catalyzed by copper(II)-bis (oxazoline) complexes, but only 16% ee was obtained when reacting with *N*–H pyrrole. Furthermore, they applied the chiral indole derivatives to the transformation of some optically pure trifluoromethyl-substituted alkylated indole derivatives with potentially interesting bioactivities.[8l] Additionally, the chiral copper(I)[19] and Yb(III)[20] catalysts were for the first time employed in the asymmetric Friedel–Crafts reaction for the preparation of chiral trifluoromethylated compounds by another two groups.

Obviously, in the previous literature, most of the electrophiles were focused on the trifluoroacetyl compounds[7a] or their imine derivatives,[21] whereas the use of trifluoromethylated α,β-unsaturated carbonyl compounds as electrophiles is less studied. In addition, while the indole nucleophiles have been intensively investigated in the enantioselective Friedel–Crafts reaction, the utility of pyrrole nucleophiles in this context remains relatively unexplored and less successful.[22] Bidentate Michael acceptors of compound **1** are β-trifluoromethylated acrylates bearing an achiral auxiliary as an alternative

acceptor moiety capable of chelating to a chiral metal complex and can be transformed into the trifluoromethylated carboxylic acid.[23] We anticipated that compound **1** would be excellent nucleophile acceptor candidates in the asymmetric Friedel–Crafts reaction. Herein, we reported our full studies on the chiral Lewis acid catalyzed enantioselective Friedel–Crafts reaction of pyrroles and indoles with β-trifluoromethylated acrylates **1**.†

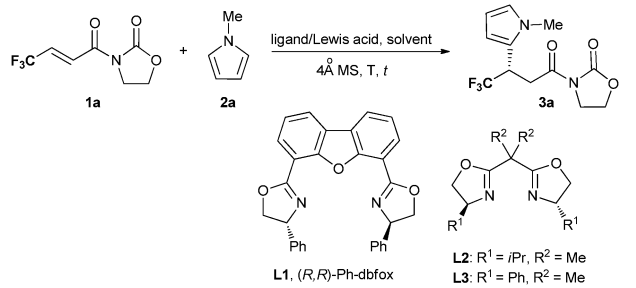
Results and discussion

A chiral bisoxazoline ligand of Ph-dbfox (Ph-dbfox = (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline)) has proven to be an excellent ligand in many asymmetric reactions by our group.[24] Thus, Ph-dbfox was chosen as the chiral ligand in the preliminary studies.

Our investigation began by examining the Lewis acid screening. The model reaction was performed in CH_2Cl_2 at room temperature employing substrates **1a** and *N*-methyl pyrrole **2a**. Surprisingly, no reaction occurred with either $Cu(OTf)_2$ or $Cu(NTf_2)_2$ as Lewis acids (Table 1, entries 1 and 2). Then we turned our attention to the zinc salts. The reaction did not proceed in the presence of $Zn(OAc)_2$ (Table 1, entry 3). Low yield and ee were observed when $Zn(OTf)_2$ was used (Table 1, entry 4). The ee could be improved to 75% by using $Zn(ClO_4)_2{\cdot}6H_2O$ (Table 1, entries 5) or $Zn(NTf_2)_2$ (Table 1, entry 6). However, $Zn(NTf_2)_2$ shows higher rate enhancement compared with $Zn(ClO_4)_2{\cdot}6H_2O$. So $Zn(NTf_2)_2$ was used as the metal salt for further studies. The use of bisoxazoline ligand **L2** or **L3** in combination with $Zn(NTf_2)_2$ led to no further improvement of enantioselectivity (Table 1, entries 7 and 8). The subsequent solvent screening revealed that CH_2Cl_2 is the best choice of solvent. In order to improve the ee value, the Friedel–Crafts reaction was carried out at low temperatures. To our delight, lower temperature afforded a higher ee value. The improvement of 89% ee was observed at −40 °C, albeit a longer reaction time was needed (Table 1, entry 12). Further improvement of the enantioselectivity excess to 96% was obtained at −60 °C (Table 1, entry 13). The best ee up to 98% could be restored at −75 °C at the expense of higher catalyst loading and concentration (Table 1, entry 14).

According to the optimized conditions of entry 13 in Table 1, we investigated the substrates scope of a wide variety of pyrroles **2** (Table 2). The asymmetric Friedel–Crafts reaction of *N*–H pyrrole **2b** with **1a** provided (*S*)-**3b** in 96% yield and 98% ee (Table 2, entry 2). The ee value could be further improved to 99% at −75 °C. To the best of our knowledge, this has been so far the best ee value obtained for the Friedel–Crafts reaction with *N*–H pyrrole.[25] Various protecting groups on the pyrrole nitrogen were well tolerated. A decrease in enantiomeric excess was observed as the length of the *N*-alkyl substituent of the pyrrole was increased (Table 2, entries 3–5). It is probably due to an increase in steric effects of the protecting group. Pyrrole **2e** proceeded with similar ee to pyrrole **2f** for the same steric hindrance (Table 2, entry 6). Additionally, the presence of electron-withdrawing and high steric hindrance groups on the pyrrole nitrogen resulted in a decrease in enantioselectivity and

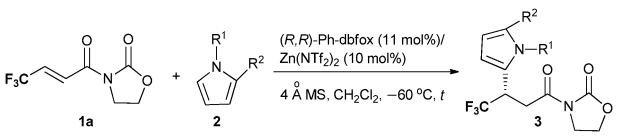
Table 1 Optimization of the asymmetric Friedel–Crafts reaction between β-CF_3 acrylate **1a** and *N*-methyl pyrrole **2a**[a]



Entry	Lewis acid	Ligand	Solvent	T/°C	t/h	Yield (%)[b]	ee (%)[c]
1	$Cu(OTf)_2$	**L1**	CH_2Cl_2	20	24	Trace	ND
2	$Cu(NTf_2)_2$	**L1**	CH_2Cl_2	20	24	Trace	ND
3	$Zn(OAc)_2$	**L1**	CH_2Cl_2	20	24	Trace	ND
4	$Zn(OTf)_2$	**L1**	CH_2Cl_2	20	24	40	38
5	$Zn(ClO_4)_2$[e]	**L1**	CH_2Cl_2	20	4	86	75
6	$Zn(NTf_2)_2$	**L1**	CH_2Cl_2	20	2	96	75
7	$Zn(NTf_2)_2$	**L2**	CH_2Cl_2	20	2	92	69
8	$Zn(NTf_2)_2$	**L3**	CH_2Cl_2	20	2	90	55
9	$Zn(NTf_2)_2$	**L1**	Toluene	20	6	93	60
10	$Zn(NTf_2)_2$	**L1**	Et_2O	20	6	91	72
11	$Zn(NTf_2)_2$	**L1**	$CHCl_3$	20	2	90	70
12	$Zn(NTf_2)_2$	**L1**	CH_2Cl_2	−40	12	98	89
13	$Zn(NTf_2)_2$	**L1**	CH_2Cl_2	−60	24	96	96
14[d]	$Zn(NTf_2)_2$	**L1**	CH_2Cl_2	−75	24	96	98

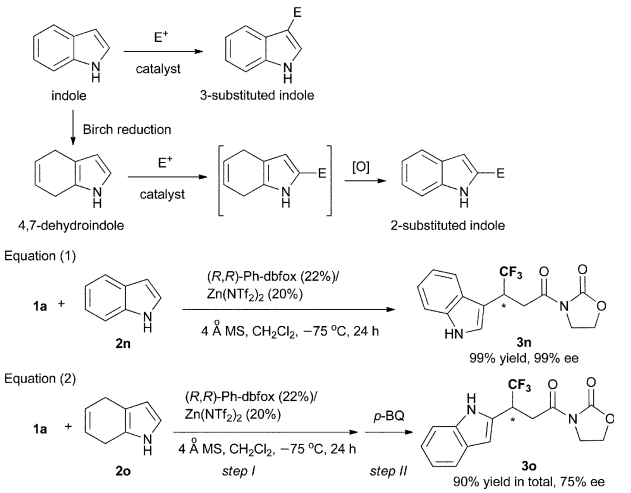
[a] Unless noted, all reactions are performed at 0.10 M in substrate **1a** and 0.50 M in substrate **2a**, with 10 mol% catalyst loading in 0.5 mL of solvent. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC; ND = not determined. [d] Reaction was performed at 0.20 M in substrate **1a**, with 0.25 mL of solvent and 20 mol% catalyst was used. [e] Hexahydrate was used.

Table 2 Substrates scope of pyrrole nucleophiles[a]



Entry	R^1	R^2	**2**	**3**	t/h	Yield (%)[b]	ee (%)[c]
1	Me	H	**2a**	**3a**	24	96 (96)	96 (98)
2	H	H	**2b**	**3b**	24	96 (97)	98 (99)
3	Et	H	**2c**	**3c**	24	97 (96)	94 (96)
4	*n*-Pr	H	**2d**	**3d**	24	95 (96)	93 (95)
5	*n*-Bu	H	**2e**	**3e**	36	95 (95)	94 (95)
6	Allyl	H	**2f**	**3f**	48	94 (90)	98 (99)
7	Bn	H	**2g**	**3g**	48	93	85
8[d]	Ph	H	**2h**	**3h**	48	94	87
9	H	Me	**2i**	**3i**	24	96 (96)	88 (97)
10	H	Et	**2j**	**3j**	24	96 (98)	84 (92)
11	Me	Me	**2k**	**3k**	24	97 (97)	87 (94)
12	Me	Et	**2l**	**3l**	24	99 (99)	70 (88)
13	Me	Bn	**2m**	**3m**	48	95 (95)	66 (76)

[a] Unless noted, all reactions are performed at 0.10 M in substrate **1a** and 0.50 M in substrate **2**, with 10 mol% catalyst loading in 0.5 mL of solvent. [b] Isolated yields. Data in brackets are obtained at −75 °C with 20 mol% catalyst loading at 0.2 M. [c] Determined by chiral HPLC. Data in brackets are obtained at −75 °C with 20 mol% catalyst loading at 0.2 M. [d] Reaction was performed at −20 °C.



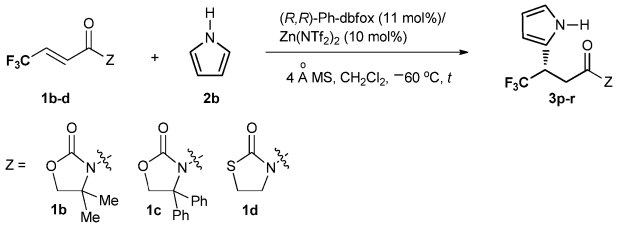
Scheme 2 Asymmetric F–C reaction between β-CF_3 acrylate **1a** and indoles.

reactivity (Table 2, entries 7 and 8). In the case of pyrrole **2h**, a higher temperature up to −20 °C was needed to complete the reaction. The introduction of Me and Et groups at the 2-position of **2b** resulted in lower ee of 88% and 84% respectively (Table 2, entries 9 and 10). A similar sense of asymmetric induction was disclosed by using *N*-methylpyrrole **2a** and its 2-position derivatives. Increasing the steric requirements of the substituents at the 2-position of *N*-methylpyrrole from H (96% ee, Table 2, entry 1) to Me (87% ee, Table 2, entry 11), Et (70% ee, Table 2, entry 12), and Bn (66% ee, Table 2, entry 13) resulted in gradual reduction of ee. Furthermore, as the results shown in brackets in Table 2, all ee values could be improved by using the reaction conditions of entry 14 in Table 1, with a lower temperature to −75 °C albeit higher catalyst loading (20%) and concentration (0.2 M). Especially for the asymmetric Friedel–Crafts reactions of 2-substituted pyrroles, the improvement of enantioselectivity was much more obvious.

Subsequently, the optimized conditions of entry 14 in Table 1 were utilized in the asymmetric Friedel–Crafts reaction of **1a** with indole and 4,7-dihydroindole. Whereas the locus of nucleophilicity of pyrroles is at C-2, it resides at C-3 for the indoles. Initial examination of the indole **2n** was encouraging. 3-Substituted indole **3n** was furnished with excellent levels of selectivity (99% ee) and in nearly quantitative yield (Scheme 2, eqn (1)). Although C-2 substituted indoles were impossible to be directly generated in this Friedel–Crafts reaction, we solved this problem by using the reported strategy: 4,7-dihydroindole **2o** could be employed as a 2,3-disubstituted pyrrole nucleophile, and easily transformed into the corresponding indole product by aromatization with *p*-benzoquinone (*p*-BQ) oxidation.[26] Taking advantage of this property, 2-substituted indole **3o** was successfully accessed in 90% yield with 75% ee through two steps (Scheme 2, eqn (2)).

A subsequent survey of nucleophile acceptors revealed that different substituents on the 4-position of the achiral template play a key role in the reactivity and selectivity. When the acceptor **1b** with two methyl groups is introduced, the reaction with *N*–H pyrrole completed in 79% ee after 24 h

Table 3 Survey of nucleophile acceptors[a]



Entry	Acceptor	3	*t*/h	Yield (%)[b]	ee (%)[c]
1	**1b**	**3p**	24	95	79
2	**1c**	**3q**	48	NR	ND
3	**1d**	**3r**	48	97	95

[a] All reactions are performed at 0.10 M in substrates **1b–d** and 0.50 M in substrate **2b**. [b] Isolated yields. [c] Determined by chiral HPLC.

(Table 3, entry 1). No reaction occurred even at RT by changing the methyl groups of **1b** to phenyl groups (Table 3, entry 2). Compared to nucleophile acceptor **1a**, **1d** bearing achiral auxiliary of thiazolidinone was also examined to display 97% yield and 95% ee after 48 h (Table 3, entry 3). These inferior results well proved that nucleophile acceptor **1a** was the best candidate in our studies.

The plausible mechanism is illustrated in Fig. 4: initially, 1,4-addition of a pyrrole nucleophile to a β-trifluoromethylated α,β-unsaturated carbonyl compound **A**, followed by enantioselective protonation of the resulting transient enolate **B** to generate product **3b** and the chiral catalyst. The absolute configuration of **3b** was determined to be *S* by the comparison of its optical rotation after derivatization to (*S*)-**4** (Scheme 4). The sample of (*R*)-**4** was synthesized in a different way and its absolute stereochemistry was determined by X-ray crystallographic analysis of **3s** (CCDC 758056, Scheme 3). To account for the stereochemistry of the asymmetric Friedel–Crafts reaction, a plausible transition-state model is depicted in Fig. 4. The acrylate coordinates in a bidentate fashion to the catalyst metal center which adopts a six-member-planar geometry and the nucleophilic pyrrole approaching the less shielded *Re* face of the olefin β-carbon leads to the formation of the major stereoisomer.

To demonstrate the synthetic utility of this Friedel–Crafts reaction methodology, we carried out the synthesis of

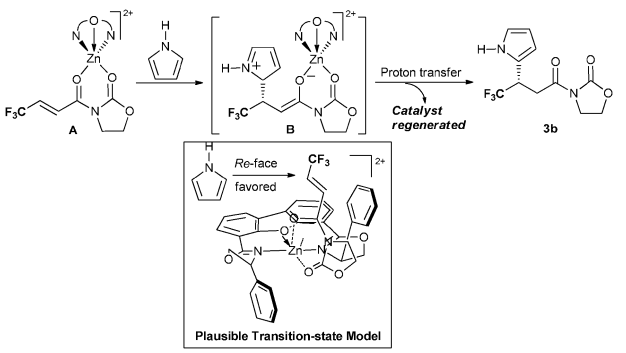
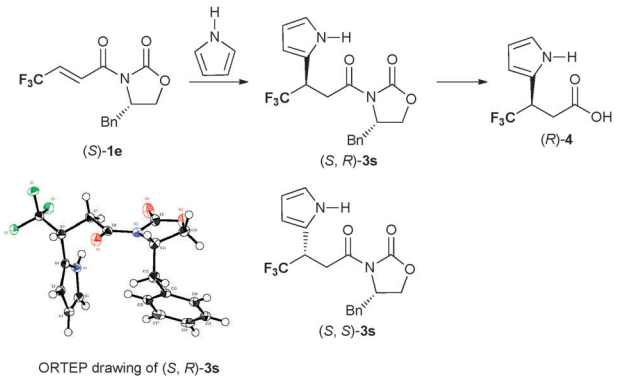
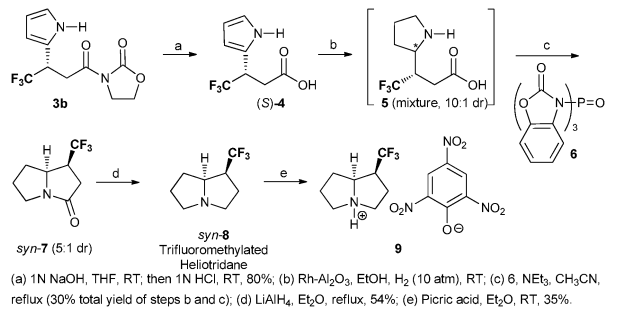


Fig. 4 Assumed catalytic cycle and working model for the stereoinduction.



Scheme 3 Total synthesis of trifluoromethylated heliotridane picrate **9**.



Scheme 4 Synthesis of (*R*)-**4** from (*S*)-**1e** *via* (*S*, *R*)-**3s** (see ESI‡ for details) and X-ray crystallographic analysis of (*S*, *R*)-**3s** (CCDC 758056).

unreported trifluoromethylated heliotridane by using the Friedel–Crafts reaction adduct (*S*)-**3b** as an important chiral building block (Scheme 4). The scale-up synthesis of compound (*S*)-**3b** (1.0 g, 3.6 mmol) in the presence of 1 mol% of the chiral Ph-dbfox/$Zn(NTf_2)_2$ catalyst at −60 °C was achieved with the *ee* value up to 98%. With (*S*)-**3b** in hand, the first transformation into the corresponding carboxylic acid (*S*)-**4** proceeded well in 80% yield. Rhodium-catalyzed hydrogenation of (*S*)-**4** afforded the diastereomeric mixture of 2-pyrrolidine carboxylic acid **5** (dr = 10 : 1) in quantitative yield in the presence of H_2 (10 atm) at room temperature. Without further purification, **5** was successfully cyclized to the trifluoromethylated hexahydropyrrolizin-3-one *syn*-**7** (30%) and *anti*-**7** (5%) in the presence of tris(1,3-dihydro-2-oxobenzoxazolin-3-yl) phosphine oxide **6** when heated under reflux in acetonitrile. The initial trial of DCC instead of **6** as a cyclization reagent proved ineffective. A volatile trifluoromethylated heliotridane *syn*-**8** was obtained in 54% yield by using $LiAlH_4$ reduction of *syn*-**7** in ether, which was finally fixed as picrate **9** by mixing with picric acid in ether.

The stereochemistry of the major isomer *syn*-**7** was identified by ^{19}F NMR and 2D ^1H NMR (^1H-^1H COSY) spectra (Fig. 5, see also ESI‡). In the case of ^{19}F NMR spectra, the chemical shift value of −71.1 ppm in a lower magnetic field for compound *syn*-**7** due to the steric deshielding effect indicates a *trans* arrangement of *C5*-H and the CF_3 group.[27] However, another diastereomer with –67.9 ppm belongs to the *anti* isomer. It should be mentioned that these two diastereomers of compound **7** could be separated by column chromatography. The stereochemistry of compound *syn*-**7** was further supported by 2D ^1H NMR (^1H-^1H COSY) spectra. For compound *syn*-**7**, a strong cross peak was observed between the bridgehead proton and the adjacent proton attached to the quaternary carbon in the five-membered cyclic hexahydropyrrolizinone due to the *cis*-substitution, while compound *anti*-**7** showed a much weaker cross peak between the corresponding protons.

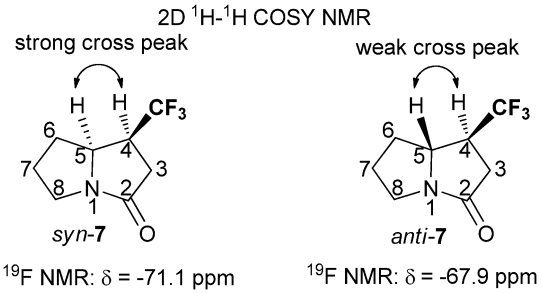


Fig. 5 NMR studies of compound **7**.

Conclusions

In summary, we have developed a novel strategy to obtain various chiral pyrroles, 2-substituted and 3-substituted indole derivatives bearing a CF_3 group at a quaternary chiral carbon center without any heteroatom. This chiral $Zn(NTf_2)_2$-catalyzed enantioselective Friedel–Crafts reaction not only showed high reactivity and enantioselectivity for the commonly studied indole and *N*-protected nucleophiles, but also for the challenging *N*–H pyrrole substrates (up to 99% ee). To the best of our knowledge, this is the best result for the asymmetric Friedel–Crafts reaction with *N*–H pyrrole. The plausible reaction mechanism and stereochemistry were illustrated. Significantly, this methodology enabled the rapid total synthesis of unreported chiral trifluoromethylated heliotridane. The structures of these compounds were intensively determined by using NMR studies. The pharmacological properties of **8** and other catalytic asymmetric reactions with β-trifluoromethylated acrylates are currently being studied.

Experimental section

General

All reactions were performed in oven-dried glassware under a nitrogen atmosphere, except where noted. Chemicals and solvents were purchased from commercial suppliers and used as received, except as follows. Dichloromethane, THF, ether, and toluene were dried by passing through an activated column. All reactions were monitored by TLC, or ^{19}F NMR. TLC analysis was performed by illumination with a UV lamp (254 nm), staining with I_2, or PMA [phosphomolybdic acid (5 g) in ethanol (100 ml)] and heating. The column of flash chromatography was packed with silica-gel (60N spherical neutral size 63–210 μm) as the stationary phase. ^1H NMR (600 MHz) spectra were recorded on a Bruker Avance 600 instrument in $CDCl_3$ (7.26), or CD_2Cl_2 (5.24), and chemical shifts were measured relative to a residual solvent peak. Chemical shifts (δ) are expressed in ppm

downfield from internal TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, m = multiplet, br = broad), coupling constant(s) and integration. ^{13}C NMR (150.9 MHz) spectra were recorded on a Bruker Avance 600 instrument. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of $CDCl_3$ (77.23), or CD_2Cl_2 (53.73) as an internal standard. ^{19}F NMR (188 MHz) was recorded on a Varian Mercury 200 instrument using $CFCl_3$ (0) as an internal standard. HPLC analysis was performed on a JASCO U-2080 plus using 4.6 × 250 mm CHIRALPAK OD-H or CHIRALCEL AD-H column. Optical rotations were measured on a HORIBA SEPA-300. Infrared spectra were recorded on a JASCO FT/IR-200 spectrometer. Mass spectra were recorded on a SHIMADZU GCMS-QP5050A or SHIMADZU LCMS-2010EV. High resolution mass spectra (HRMS) (EI+) were obtained from the Mass Spectrometry Laboratory, Nagoya Institute of Technology, Nagoya.

General catalytic procedure for the Friedel–Crafts reactions

To a dried 10 mL test tube was added appropriate Lewis acid and 1.1 equiv. of the (*R*,*R*)-Ph-dbfox ligand. Under a N_2 atmosphere, dry solvent was introduced, followed by stirring at RT for 1 h. 4 Å MS and β-CF_3 acrylates were added at RT, then the solution of pyrroles in the same solvent was injected by a syringe at the reaction temperature. While some Friedel–Crafts products have the same polarity as the starting material on TLC, the reaction would be monitored by ^{19}F NMR. After the starting material was consumed, the residue was directly subjected to the silica-gel column chromatography to afford the title product.

4,4-Dimethyl-3-[4,4,4-trifluoro-3-(1*H*-pyrrol-2-yl)-butyryl]-oxazolidin-2-one (3p)

Under a N_2 atmosphere, to 10 mol% (0.005 mmol) of catalyst complex $Zn(NTf_2)_2$/(*R*,*R*)-Ph-dbfox prepared as described above in 0.2 mL CH_2Cl_2 was sequentially added 4 Å MS (15.0 mg), β-CF_3 acrylate **1b** (11.8 mg, 0.050 mmol), and the solution of pyrrole **2a** (17.0 mg, 0.250 mmol) in 0.05 mL CH_2Cl_2. The mixture was stirred at −60 °C for 24 h, then passed through a plug of silica gel using a 2 : 1 ratio of petroleum ether and ethyl acetate to afford the title compound (14.5 mg, 95%) as a white solid. The enantiomeric purity was determined by HPLC analysis as 79% ee; Chiralcel OD-H, *n*-hexane/*i*-PrOH = 70/30, flow rate 0.5 mL min^{-1}, λ = 232 nm, τ_{min} = 10.9 min, τ_{maj} = 12.1 min; $[\alpha]_D^{25}$ = +22.6 (*c* = 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ = 8.43 (br s, 1H), 6.76–6.75 (m, 1H), 6.17–6.16 (m, 2H), 4.19–4.12 (m, 1H), 4.00 (ddd, *J* = 1.2 Hz, 8.4 Hz, 21.6 Hz, 1H), 3.67 (dd, *J* = 9.6 Hz, 16.8 Hz, 1H), 3.38 (dd, *J* = 4.8 Hz, 16.8 Hz, 1H), 1.54 (s, 3H), 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 150.9 MHz): δ = 170.6, 154.0, 126.1 (q, *J* = 279.3 Hz), 123.7, 118.4, 108.6, 108.2, 75.3, 60.7, 39.4 (q, *J* = 29.7 Hz), 36.5, 24.7, 24.5; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = −70.2 (d, *J* = 9.2 Hz, 3F); IR (KBr): 3383.5, 1772.3, 1695.1, 1397.2, 1350.9, 1327.8, 1279.5, 1263.2, 1244.8, 1185.0, 1163.8, 1127.2, 1102.1, 1076.1, 1033.7, 926.6, 889.9, 797.4, 759.8, 736.7, 718.3, 687.5 cm^{-1}; mp = 123–124 °C; HRMS calcd. for $C_{13}H_{15}F_3N_2O_3^+$ 304.1035, found 304.1005.

3-[4,4,4-Trifluoro-3-(1*H*-pyrrol-2-yl)-butyryl]-thiazolidin-2-one (3r)

Under a N_2 atmosphere, to 10 mol% (0.005 mmol) of catalyst complex $Zn(NTf_2)_2$/(*R*,*R*)-Ph-dbfox prepared as described above in 0.2 mL CH_2Cl_2 was sequentially added 4 Å MS (15.0 mg), β-CF_3 acrylates **1d** (11.2 mg, 0.050 mmol), and the solution of pyrrole **2a** (17.0 mg, 0.250 mmol) in 0.05 mL CH_2Cl_2. The mixture was stirred at −60 °C for 48 h, then passed through a plug of silica gel using a 2 : 1 ratio of petroleum ether and ethyl acetate to afford the title compound (14.2 mg, 97%) as a white solid. The enantiomeric purity was determined by HPLC analysis as 95% ee; Chiralcel AD-H, *n*-hexane/*i*-PrOH = 80/20, flow rate 0.5 mL min^{-1}, λ = 232 nm, τ_{maj} = 25.8 min, τ_{min} = 37.1 min; $[\alpha]_D^{25}$ = −7.0 (*c* = 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ = 8.41 (br s, 1H), 6.74 (t, *J* = 1.2 Hz, 1H), 6.16–6.15 (m, 2H), 4.16–4.00 (m, 1H), 4.11 (dt, *J* = 1.2 Hz, 7.2 Hz, 2H), 3.60 (ddd, *J* = 1.2 Hz, 10.2 Hz, 18.0 Hz, 1H), 3.38 (dd, *J* = 3.0 Hz, 18.0 Hz, 1H), 3.26 (dt, *J* = 1.2 Hz, 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150.9 MHz): δ = 173.0, 169.5, 126.1 (q, *J* = 279.5 Hz), 124.1, 118.3, 108.7, 107.9, 46.9, 39.1 (q, *J* = 29.0 Hz), 36.7, 25.1; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = −70.1 (d, *J* = 9.0 Hz, 3F); IR (KBr): 3370.9, 1707.6, 1682.6, 1408.7, 1364.4, 1309.4, 1259.3, 1162.9, 1131.1, 1110.8, 1098.3, 735.7 cm^{-1}; mp = 104–105 °C; HRMS calcd. for $C_{11}H_{11}F_3N_2O_2S^+$ 292.0493, found 292.0468.

(*S*)-4,4,4-Trifluoro-3-(1*H*-pyrrol-2-yl)-butylic acid (4)

To a solution of (*S*)-**3b** (98% ee, 110.0 mg, 0.40 mmol) in THF was added 1 N NaOH (aq., 0.80 mL, 0.80 mmol). After stirring at RT for 1 h, 1 N HCl (aq.) was slowly added to adjust the pH value of the reaction mixture to 1–2. Compound (*S*)-**4** (66.2 mg, 80%) was isolated as a solid by flash column chromatography using a 3 : 1 ratio of petroleum ether and ethyl acetate as the eluent. $[\alpha]_D^{25}$ = +17.3 (*c* = 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ = 8.26 (br s, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.18–6.16 (m, 2H), 3.96–3.91 (m, 1H), 3.01 (dd, *J* = 4.2 Hz, 10.8 Hz, 1H), 2.88 (dd, *J* = 9.6 Hz, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.9 MHz): δ = 176.1, 125.8 (q, *J* = 279.5 Hz), 123.2, 118.8, 108.9, 108.1, 39.7 (q, *J* = 29.3 Hz), 33.8; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = −70.7 (s, 3F); IR (KBr): 3470.3, 3119.3, 1719.2, 1660.4, 1560.1, 1418.4, 1363.4, 1293.0, 1272.8, 1181.2, 1164.8, 1035.6, 993.2, 930.5, 859.1, 810.9, 680.8 cm^{-1}; mp = 70–71 °C; HRMS calcd. for $C_8H_8F_3NO_2^+$ 207.0507, found 207.0513.

(4*S*,5a*S*)-4-Trifluoromethyl-hexahydropyrrolizin-2-one (*syn*-7)

To a 10 mL test tube was added **4** (66.0 mg, 0.40 mmol), 5% of Rh–Al_2O_3 (8 mg), and 4 mL of EtOH. The resulting mixture was put into an autoclave, and purged with H_2 (10 atm). After stirring at RT for 24 h, the solution was filtered through Celite, and the solvent was evaporated *in vacuo* to provide the 2-pyrrolidine carboxylic acid as a white solid. Without further purification, the compound obtained was heated under reflux with the phosphine oxide **6** (186 mg, 0.41 mmol) and triethyl

amine (0.2 mL, 1.43 mmol) in 10 mL acetonitrile. After 6 h, the resulting solution was concentrated, then subjected to column chromatography using ether as the eluent. The faster running fraction of a colourless oil was determined as the *syn* isomer (23.0 mg, 30%), while the lower fraction of a slightly yellow oil was the *anti* isomer (4.0 mg, 5%). $[\alpha]_D^{25} = +26.0$ ($c = 0.35$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 3.95$ (dt, $J = 6.6$ Hz, 9.0 Hz, 1H, 5-H), 3.59 (dt, $J = 8.4$ Hz, 11.4 Hz, 1H, 8-H), 3.13–3.09 (m, 1H, 8′-H), 2.91 (dd, $J = 10.2$ Hz, 16.2 Hz, 1H, 3-H), 2.87–2.79 (m, 1H, 4-H), 2.67 (dd, $J = 9.0$ Hz, 16.2 Hz, 1H, 3′-H), 2.21–2.15 (m, 2H, 6-H, 7-H), 2.12–2.04 (m, 1H, 7′-H), 1.50–1.43 (m, 1H, 6′-H); ^{13}C NMR ($CDCl_3$, 600 MHz): $\delta = 171.1$, 126.1 (q, $J = 276.6$ Hz), 60.9 (d, $J = 3.2$ Hz), 44.8 (q, $J = 29.1$Hz), 41.3, 35.2 (d, $J = 2.26$ Hz), 31.6, 26.6; ^{19}F NMR ($CDCl_3$, 188 MHz): $\delta = -71.1$ (d, $J = 6.6$ Hz, 3F); IR (neat): 2976.6, 2884.9, 1782.9, 1702.8, 1428.0, 1343.2, 1270.9, 1166.7, 1123.3, 1085.7, 688.5 cm^{-1}; HRMS calcd. for $C_8H_{10}F_3NO$ 193.0714, found 193.0756.

(4*S*,5a*R*)-4-Trifluoromethyl-hexahydropyrrolizin-2-one (*anti*-7)

$[\alpha]_D^{25} = +24.0$ ($c = 0.3$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 4.04$–4.00 (m, 1H, 5-H), 3.57 (dt, $J = 8.4$ Hz, 11.4 Hz, 1H, 8-H), 3.23–3.15 (m, 1H, 4-H), 3.14–3.10 (m, 1H, 8′-H), 2.93 (dd, $J = 10.2$ Hz, 17.4 Hz, 1H, 3-H), 2.64 (dd, $J = 4.8$ Hz, 17.4 Hz, 1H, 3′-H), 2.22–2.17 (m, 1H, 7-H), 2.06–1.98 (m, 1H, 7′-H), 1.96–1.92 (m, 1H, 6-H), 1.75–1.67 (m, 1H, 6′-H); ^{13}C NMR ($CDCl_3$, 600 MHz): $\delta = 172.0$, 126.5 (q, $J = 278.5$ Hz), 61.1, 41.3, 38.3 (q, $J = 28.5$ Hz), 33.9, 29.7, 26.4; ^{19}F NMR ($CDCl_3$, 188 MHz): $\delta = -67.8$ (d, $J = 6.6$ Hz, 3F); IR (neat): 2926.5, 1779.0, 1684.4, 1484.0, 1428.0, 1392.4, 1294.0, 167.0, 1178.3, 1150.3, 1126.2, 1103.1, 760.8 cm^{-1}; MS (ESI, m/z): 216.100 ($M + Na^+$); HRMS calcd. for $C_8H_{10}F_3NO$ 193.0714, found 193.0698.

Trifluoromethylated heliotridane (8)

Under a N_2 atmosphere, to a solution of *syn*-**7** (20.0 mg, 0.104 mmol) in ether (2.0 mL) was added $LiAlH_4$ (15.8 mg, 0.416 mmol) directly at 0 °C. After stirring at 35 °C for 6 h, the solution was cooled to RT before $Na_2SO_4{\cdot}10H_2O$ (135.0 mg, 0.416 mmol) was slowly added to the reaction mixture. The resulting solution was stirred at RT overnight. The solvent was removed by a steady stream of N_2 to obtain slightly yellow oil **8** (10.0 mg, 54% yield). $[\alpha]_D^{25} = +20.3$ ($c = 0.3$, Et_2O); ^1H NMR (CD_2Cl_2, 600 MHz): $\delta = 3.41$–3.38 (m, 1H, 5-H), 3.04–3.01 (m, 1H, 2-H), 2.83 (dt, $J = 10.2$ Hz, 6.6 Hz, 1H, 8-H), 2.54 (dt, $J = 9.6$ Hz, 6.6 Hz, 1H, 2′-H), 2.46 (dt, $J = 10.2$ Hz, 6.6 Hz, 1H, 8′-H), 2.35–2.29 (m, 1H, 4-H), 2.06–2.00 (m, 1H, 3-H), 1.96–1.85 (m, 2H, 6-H, 3′-H), 1.80–1.73 (m, 1H, 7-H), 1.72–1.65 (m, 1H, 7′-H), 1.54–1.49 (m, 1H, 6′-H); ^{13}C NMR (CD_2Cl_2, 600 MHz): δ = 128.1 (q, $J = 277.2$ Hz), 64.8(d, $J = 2.3$ Hz), 54.7, 54.1, 49.6 (q, $J = 26.1$ Hz), 32.2, 27.7 (d, $J = 2.1$ Hz), 26.1; ^{19}F NMR (CD_2Cl_2, 188 MHz): $\delta = -70.1$ (d, $J = 9.2$ Hz, 3F); HRMS calcd. for $C_8H_{12}F_3N$ 179.0922, found 179.0941.

Trifluoromethylated heliotridane picrate (9)

To a solution of **8** (10.0 mg, 0.056 mmol) in 1 mL ether was added the solution of picric acid (20.0 mg, 0.056 mmol) in 1 mL ether. After stirring for 1 h at RT, the precipitate was filtered as the target compound **9** (8.0 mg, 35% yield). $[\alpha]_D^{25} = -5.8$ ($c = 0.6$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 8.88$ (s, 2H, Ar–H), 4.50–4.47 (m, 1H, 5-H), 4.15–4.12 (m, 1H, 2-H), 3.80 (dt, $J = 12.0$ Hz, 7.2 Hz, 1H, 8-H), 3.16–3.12 (m, 1H, 8′-H), 3.06 (dt, $J = 10.8$ Hz, 6.0 Hz, 1H, 2-H), 2.81–2.75 (m, 1H, 4-H), 2.54–2.46 (m, 2H, 6-H, 3-H), 2.38–2.32 (m, 1H, 7-H), 2.21–2.14 (m, 1H, 7′-H), 2.05–2.00 (m, 1H, 6′-H); ^{13}C NMR ($CDCl_3$, 600 MHz): $\delta = 162.3$, 141.6, 128.6, 126.7, 125.2 (q, $J = 277.7$ Hz), 67.0 (d, $J = 2.4$ Hz), 55.6, 54.9, 48.7 (q, $J = 29.5$ Hz), 30.8, 26.7, 25.0; ^{19}F NMR ($CDCl_3$, 188 MHz): $\delta = -70.0$ (d, $J = 6.6$ Hz, 3F); IR (KBr): 1716.3, 1637.3, 1557.2, 1489.7, 1434.8, 1329.7, 1276.7, 1162.9, 111.8 cm^{-1}; mp = 181–183 °C; MS (ESI, m/z): 212.200 ($M + Na^+$); anal. calcd. (%) for $C_{14}H_{15}F_3N_4O_7$ C, 41.18; H, 3.70; N, 13.72; found C, 41.22; H, 3.90; N, 13.60%.

Acknowledgements

This study was financially supported in part by Grants-in-Aid for Scientific Research (21390030, 22106515, Project No. 2105: Organic Synthesis Based on Reaction Integration). We also thank the Asahi Glass Foundation.

Notes and references

1 (*a*) *Fluorine in Medicinal Chemistry and Chemical Biology*, ed. I. Ojima, Wiley-Blackwell, Oxford, 2009; W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (*b*) K. Mikami, Y. Itoh and M. Yamanaka, *Chem. Rev.*, 2004, **104**, 1.
2 (*a*) A. Togni, *Adv. Synth. Catal.*, 2010, **352**, 2689; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
3 *Fluorine in Medicinal Chemistry and Chemical Biology*, ed. I. Ojima, Wiley-Blackwell, West Sussex, 2008, p. 1.
4 (*a*) K. L. Kirk, *J. Fluorine Chem.*, 2006, **127**, 1013; (*b*) L. K. Kirk, *Curr. Top. Med. Chem.*, 2006, **6**, 1529.
5 R. M. Wilson and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2010, **49**, 6032.
6 (*a*) *Organofluorine Compounds: Chemistry Applications*, ed. T. Hiyama, Springer, New York, 2000; (*b*) D. Cahard, X.-H. Xu, S. Couve-Bonnaire and X. Pannecoucke, *Chem. Soc. Rev.*, 2010, **39**, 558.
7 P. V. Ramachandran, in *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions*, American Chemical Society Symposium Series No. 746, American Chemical Society, Washington, DC, 2000. For selected reviews, see: (*a*) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455; (*b*) G. Valero, X. Companyó and R. Rios, *Chem.–Eur. J.*, 2011, **17**, 2018; (*c*) T. Konno, *Curr. Org. Synth.*, 2010, **7**, 455; (*d*) Y. Zheng and J.-A. Ma, *Adv. Synth. Catal.*, 2010, **352**, 2745; (*e*) N. Shibata, S. Mizuta and H. Kawai, *Tetrahedron: Asymmetry*, 2008, **19**, 2633.
8 For direct trifluoromethylation, see: (*a*) T. Umemoto and K. Adachi, *J. Org. Chem.*, 1994, **59**, 5692; (*b*) V. Petrik, J.-A. Ma and D. Cahard, http://www.usc.es/congresos/ecsoc/10/ECSOC10.htm, poster a034, 2006; (*c*) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 10875; (*d*) A. E. Allen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 4986; (*e*) T. Furukawa, T. Nishimine, E. Tokunaga, K. Hasegawa, M. Shiro and N. Shibata, *Org. Lett.*, 2011, **13**, 3972; (*f*) E. Magnier, J.-C. Blazejewski, M. Tordeux and C. Wakselman, *Angew. Chem., Int. Ed.*, 2006, **45**, 1279; (*g*) Y. Macé, B. Raymondeau, C. Pradet, J.-C. Blazejewski and E. Magnier, *Eur. J. Org. Chem.*, 2009, 1390; (*h*) C. Urban, F. Cadoret, J.-C. Blazejewski and E. Magnier, *Eur. J. Org. Chem.*, 2011, 4862.For using trifluoromethylated building blocks: (*i*) K. Uneyama, *J. Fluorine Chem.*, 1999, **97**, 11; (*j*) T. Konno,

T. Tanaka, T. Miyabe, A. Morigaki and T. Ishihara, *Tetrahedron Lett*., 2008, **49**, 2106; (*k*) G. Blay, I. Fernández, M. C. Muñoz, J. R. Pedro and C. Vila, *Chem.–Eur. J*., 2010, **16**, 9117; (*l*) L.-L. Wen, Q.-L. Shen, X.-L. Wan and L. Lu, *J. Org. Chem*., 2011, **76**, 2282.

9 S. Noritake, N. Shibata, Y. Nomura, Y.-Y. Huang, A. Matsnev, S. Nakamura, T. Toru and D. Cahard, *Org. Biomol. Chem*., 2009, **7**, 3599.

10 (*a*) A. Numata and T. Ibuka, In *The Alkaloids*, ed. A. Brossi, Academic Press, San Diego, 1987, p. 193; (*b*) M. Ikeda, T. Sato and H. Ishibashi, *Heterocycles*, 1988, **27**, 1465; (*c*) T. Hudlicky, G. Seoane, J. D. Price and K. G. Gadamasetti, *Synlett*, 1990, 433; (*d*) W.-M. Dai, Y. Nagao and E. Fujita, *Heterocycles*, 1990, **30**, 1231; (*e*) D. J. Robins, *Nat. Prod. Rep*., 1993, **10**, 487; (*f*) S.-H. Kim, S.-I. Kim, S. Lai and J.- K. Cha, *J. Org. Chem*., 1999, **64**, 6771.

11 (*a*) A. R. Mattocks, *The Chemistry and Toxicology of Pyrrolizidine Alkaloids*, Academic Press, London, 1986; (*b*) A. D. Elbein and R. J. Molyneux, In *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Wiley, New York, 1987.

12 For books on fluorinated heterocyclic compounds, see: (*a*) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, ed. V. A. Petrov, John Wiley & Sons, New Jersey, 2009; (*b*) *Fluorinated Heterocycles*, in *Fluorinated Heterocycles*, ed. A. G. Andrei and L. K. Kirk, ACS Symposium Series, 2009.

13 *Catalytic Asymmetric Friedel–Crafts Alkylations*, ed. M. Bandini and A. Umani-Ronchi, Wiley-VCH, Weinheim, 2009, pp. 1–301. For recent reviews on catalytic asymmetric Friedel-Crafts reactions, see: (*a*) M. Bandini, A. Melloni and A. Umani-Ronchi, *Angew. Chem., Int. Ed*., 2004, **43**, 550; (*b*) T. B. Poulsen and K. A. Jøgensen, *Chem. Rev*., 2008, **108**, 2903; (*c*) V. Terrasson, R. M. de Figueiredo and J. M. Campagne, *Eur. J. Org. Chem*., 2010, 2635.

14 W. Zhuang, N. Gathergood, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem*., 2001, **66**, 1009.

15 (*a*) T. Wang, G.-W. Zhang, Y. Teng, J. Nie, Y. Zheng and J.-A. Ma, *Adv. Synth. Catal*., 2010, **352**, 2773; (*b*) J. Nie, G.-W. Zhang, L. Wang, D.-H. Zheng, Y. Zheng and J.-A. Ma, *Eur. J. Org. Chem*., 2009, 3145.

16 W. Kashikura, J. Itoh, K. Mori and T. Akiyama, *Chem.–Asian J*., 2010, **5**, 470.

17 R. Husmann, E. Sugiono, S. Mersmann, G. Raabe, M. Rueping and C. Bolm, *Org. Lett*., 2011, **13**, 1044.

18 Y.-H. Hui, W.-L. Chen, W.-T. Wang, J. Jiang, Y.-F. Cai, L.-L. Lin, X.-H. Liu and X.-M. Feng, *Adv. Synth. Catal*., 2010, **352**, 3174.

19 C. Wolf and P. Zhang, *Adv. Synth. Catal*., 2011, **353**, 760.

20 G. Grach, A. Dinut, S. Marque, J. Marrot, R. Gil and D. Prim, *Org. Biomol. Chem*., 2011, **9**, 497.

21 For the enantioselective Friedel–Crafts reaction of trifluoromethyl imines, see ref. 17; for the diastereoselective Friedel–Crafts reaction of trifluoromethyl imines, see: (*a*) F. Lazzaro, A. Gissot, M. Crucianelli, F. De Angelis, L. Bruché and M. Zanda, *Lett. Org. Chem*., 2005, **2**, 235; (*b*) M. Abid, L. Teixeira and B. Török, *Org. Lett*., 2008, **10**, 933; (*c*) A. E. Sorochinsky and V. A. Soloshonok, *J. Fluorine Chem*., 2010, **131**, 127.

22 M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed*., 2009, **48**, 9608; M. Zeng and S.-L. You, *Synlett*, 2010, 1289.

23 Y.-Y. Huang, E. Tokunaga, S. Suzuki, M. Shiro and N. Shibata, *Org. Lett*., 2010, **12**, 1136.

24 (*a*) D. S. Reddy, N. Shibata, T. Horikawa, S. Suzuki, S. Nakamura, T. Toru and M. Shiro, *Chem.–Asian J*., 2009, **4**, 1411; (*b*) D. S. Reddy, N. Shibata, J. Nagai, S. Nakamura and T. Toru, *Angew. Chem., Int. Ed*., 2009, **48**, 803; (*c*) D. S. Reddy, N. Shibata, J. Nagai, S. Nakamura, T. Toru and S. Kanemasa, *Angew. Chem., Int. Ed*., 2007, **47**, 164; (*d*) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru and S. Kanemasa, *Angew. Chem., Int. Ed*., 2005, **44**, 4204.

25 Selected examples of the asymmetric Friedel–Crafts reaction of *N*–H pyrrole: (*a*) G. Blay, I. Fernández, A. Monleón, J. R. Pedro and C. Vila, *Org. Lett*., 2009, **11**, 441; (*b*) B. M. Trost and C. Miller, *J. Am. Chem. Soc*., 2008, **130**, 2438; (*c*) D. A. Evans and K. R. Fandrick, *Org. Lett*., 2006, **8**, 2249; (*d*) G.-L. Li, G. B. Rowland, E. B. Rowland and J. C. Antilla, *Org. Lett*., 2007, **9**, 4065.

26 (*a*) Q. Kang, X.-J. Zheng and S.-L. You, *Chem.–Eur. J*., 2008, **14**, 3539; (*b*) M. Zeng, Q. Kang, Q.-L. He and S.-L. You, *Adv. Synth. Catal*., 2008, **350**, 2169; (*c*) Y.-F. Sheng, G.-Q. Li, Q. Kang, A.-J. Zhang and S.-L. You, *Chem.–Eur. J*., 2009, **15**, 3351.

27 R. William and J. R. Dolbier, *Guide to Fluorine NMR for Organic Chemistry*, John Wiley & Sons, New Jersey, 2009, p. 1.