Enantioselective electrophilic trifluoromethylation of β-keto esters with Umemoto reagents induced by chiral nonracemic guanidines†‡

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Received 14th May 2009, Accepted 9th June 2009
First published as an Advance Article on the web 10th July 2009
DOI: 10.1039/b909641h

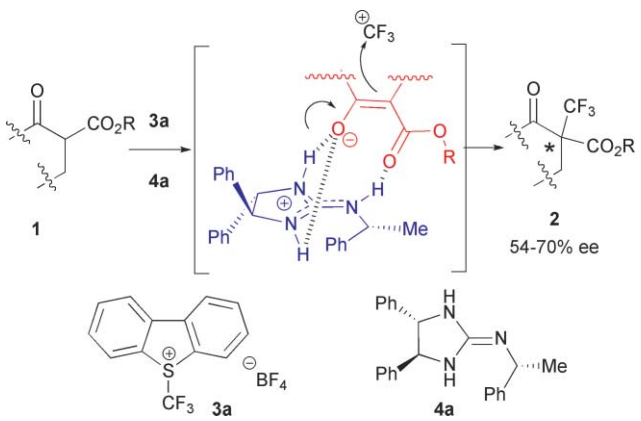
Chiral nonracemic guanidines act as Brønsted bases to generate guanidinium enolates for the enantioselective electrophilic trifluoromethylation of β-keto esters by means of *S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate (Umemoto reagent) with good enantioselectivity of 60–70% range. Despite the fact that the ees are still improvable, the model reported in this work could spark the imagination of chemists to design new chiral bases to improve the stereochemical outcome.

Introduction

It is nowadays evident that fluorinated molecules play a crucial role in the pharmaceutical, agrochemical, and materials fields.[1] Parallel to the significant progresses in modern fluoro-organic chemistry, two main branches of enantioselective synthesis that are organocatalysis and organometallic catalysis have permitted the asymmetric synthesis of chiral chemicals featuring a fluorinated stereogenic centre. The interest in enantiopure fluorinated molecules has increased spectacularly in the last few years and several approaches are now well documented.[2] Research in organo-fluorine chemistry has already provided successful results for the enantioselective transfer of "F^+", F^- and CF_3^- often with very high stereoselectivities. Indeed, enantioselective electrophilic fluorination to which our two groups have amply contributed has been achieved with the aid of chiral electrophilic fluorinating agents as well as by transition-metal catalysts and organocatalysts with excellent enantioselectivities, routinely in the range 90–99%.[3–5] On the other hand, a single example of enantioselective nucleophilic fluorination was reported by Bruns and Haufe consisting of the Jacobsen's (salen)chromium chloride complex mediated ring-opening of *meso*-epoxides with silver fluoride with up to 72% ee.[6] As for enantioselective trifluoromethylation, only the nucleophilic version has been successfully conducted; several reports mention high enantioselectivities, reaching 94% from ketones.[7,8] However, the asymmetric electrophilic trifluoromethylation has clearly been under investigated or was perhaps unsuccessful.[9] The pioneering work of Umemoto in 1994 led to the synthesis of an α-trifluoromethylated ketone in 20% yield and 45% ee by the reaction of a potassium enolate of ethyl phenyl ketone with *S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate (Umemoto reagent, **3a**), with the aid of a stoichiometric amount of chiral borepin featuring a binaphthol scaffold.[10] Since 1994, no progress was made in the field until the communication by one of us (D. C.) in 2006 in which methyl 1-indanone-2-carboxylate reacted with the Umemoto reagent in the presence of hydroquinine to give the expected trifluoromethylated product in 53% yield with 71% ee.[11] However, except these sporadic data, no deepened study of the reaction has been conducted. In connection with our studies on the development of a new methodology for the asymmetric synthesis of fluoro-organic compounds,[3,4] we herein disclose our new advances towards the enantioselective electrophilic trifluoromethylation reaction.

Results and discussion

The chiral guanidine base **4a** is found to give optically active trifluoromethylated products **2** with a quaternary carbon centre by reaction of β-keto esters **1** with Umemoto reagent **3a** in good enantioselectivity (Scheme 1).



Scheme 1 Enantioselective electrophilic trifluoromethylation of β-keto esters with Umemoto reagent induced by chiral nonracemic guanidine.

Chiral nonracemic guanidine bases are widely utilized in versatile asymmetric organic transformations[12,13] such as Michael reactions, Henry reactions, Diels–Alder reactions and more;

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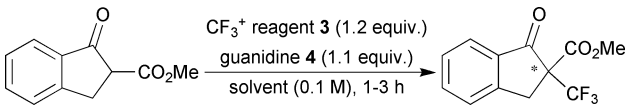
† Dedicated to Dr. Teruo Umemoto on the occasion of his 60th birthday.

‡ Electronic supplementary information (ESI) available: ^1H, ^{13}C and ^{19}F NMR spectra and chiral HPLC analyses. See DOI: 10.1039/b909641h

Table 1 Optimization of the reaction conditions; solvent, temperature, chiral guanidine **4** and CF_3^+ reagent **3**



1a **2a**

Entry	Solvent	Temp.	3	4	Yield[a] (%)	Ee[b] (%)
1	THF	rt	**3a**	**4a**	66	16
2	1,4-dioxane	rt	**3a**	**4a**	73	26
3	DMF	rt	**3a**	**4a**	85	7
4	CH_3CN	rt	**3a**	**4a**	83	20
5	Toluene	rt	**3a**	**4a**	3	27
6	CH_2Cl_2	rt	**3a**	**4a**	57	41
7	CH_2Cl_2	–80 °C	**3a**	**4a**	58	57
8	CH_2Cl_2/hexane= 1/2	–80 °C	**3a**	**4a**	58	63
9	CH_2Cl_2/CH_3CN= 4/3	–80 °C	**3a**	**4a**	61	52
10	$CHCl_3$	rt	**3a**	**4a**	65	43
11	$CHCl_3$	0 °C	**3a**	**4a**	64	45
12	$CHCl_3$	–40 °C	**3a**	**4a**	76	65
13	$CHCl_3$/toluene= 1/1	–40 °C	**3a**	**4a**	34	65
14	$CHCl_3/CH_2Cl_2$= 1/1	–80 °C	**3a**	**4a**	63	70
15	CCl_4	rt	**3a**	**4a**	29	54
16	CCl_4	–15 °C	**3a**	**4a**	15	41
17	CCl_4/CH_2Cl_2= 1/1	–40 °C	**3a**	**4a**	59	64
18	$ClCH_2CH_2Cl$	rt	**3a**	**4a**	61	41
19	$CHCl_3$	rt	**3a**	**4b**	25	0
20	$CHCl_3$	–40 °C	**3a**	**4c**	41	49
21	$CHCl_3/CH_2Cl_2$= 1/1	–80 °C	**3a**	**4c**	32	37
22	$CHCl_3$	–40 °C	**3a**	**4d**	55	59
23	$CHCl_3/CH_2Cl_2$= 1/1	–80 °C	**3a**	**4d**	41	54
24	$CHCl_3$	–40 °C	**3a**	**4e**	65	57
25	$CHCl_3/CH_2Cl_2$= 1/1	–80 °C	**3a**	**4e**	45	63
26	$CHCl_3$	–40 °C	**3a**	**4f**	50	38
27	$CHCl_3/CH_2Cl_2$= 1/1	–80 °C	**3a**	**4f**	36	28
28	$CHCl_3/CH_2Cl_2$= 1/1	–80 °C	**3b**	**4a**	38	63
29	$CHCl_3/CH_2Cl_2$= 1/1	–80 °C	**3c**	**4a**	16	51

[a] Isolated yield of analytically pure product. [b] Determined by chiral HPLC.

however, successful examples of electrophilic trifluoromethylation are not known so far. We considered evaluating the enantioselective electrophilic trifluoromethylation of β-keto esters **1** with the aid of chiral guanidine bases. Chiral guanidines were expected both to generate the guanidinium enolates of β-keto esters and to coordinate the substrate through H-bonding for an excellent transfer of stereochemical information (Scheme 1). Among several types of chiral nonracemic guanidines that have been developed,[12] we chose the Ishikawa chiral guanidine **4a** for initial investigations,[13] due to the easiness of the preparation. Commercially available Umemoto reagent **3a**[14] was selected as CF_3^+ source. Table 1 summarizes the results obtained for the trifluoromethylation of methyl 1-indanone-2-carboxylate (**1a**) with **3a** in various solvents and in the range of temperatures from –80 °C to rt. It is clear that solvents of high polarity are effective for the reaction providing high yields of **2a** within one hour albeit with low ees (Table 1, entries 1–4). Toluene is not suitable for the reaction most likely because **3a** is not soluble in this solvent (entry 5). Inversely, chlorinated solvents appeared to be a good compromise between yield and ee values. Mixtures of chlorinated solvents slightly increased ees as also observed when running the reactions at lower temperatures (entries 6–18).

Next, a series of chiral nonracemic guanidines **4b–f** were synthesized (Fig. 1)[12b] and shown to provide enantioselective

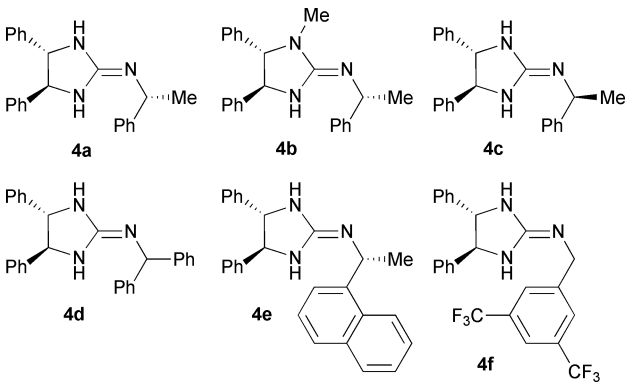
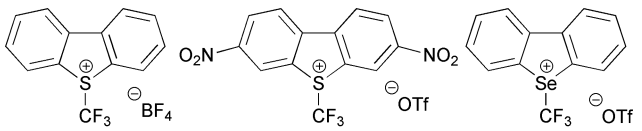


Fig. 1 Structures of chiral guanidines **4a–f**.

trifluoromethylation with Umemoto reagent **3a** (entries 20–27) except for the mono *N*-methyl-substituted guanidine **4b** (entry 19). The suppression of one H-bonding from the imidazolidine ring system dramatically affects the stereochemical outcome of the trifluoromethylation, which supports the transition state structure illustrated in Scheme 1. Chiral guanidines **4a–f** feature the common 1,2-diphenylethylenediamine subunit and are distinguishable by the primary amine employed for the construction of the imino residue. Interestingly, the same major enantiomer of **2a** was

obtained whatever the chiral guanidine used. Nevertheless, the additional stereogenic centre on the acyclic part of the guanidines still plays a role since the ee values with **4a** and **4c** are quite different (entries 12, 14 and 20, 21). Sterically more encumbered guanidines **4d** or **4e** did not provide superior ee values nor the use of the less basic guanidine **4f** (entries 22–27). The reactivity of guanidinium enolates generated from **1a** and **4a** was studied with different Umemoto reagents **3b–c** (Fig. 2) in order to find a suitable match between the nucleophilicity of the enolate and the electrophilicity of the trifluoromethylating agent (entries 28–29). The electrophilic power of Umemoto reagents is strongly influenced by the electronegativity of the chalcogens and aromatic substituents; the power order was determined to be **3c**<**3a**<**3b**.[8a] The selenophenium salt **3c** is not appropriate since **2a** could be isolated in only 16% yield (entry 29). The most reactive reagent **3b** gave lower results (entry 28). It is worth noting that **3a** is also the most easily synthesized reagent.

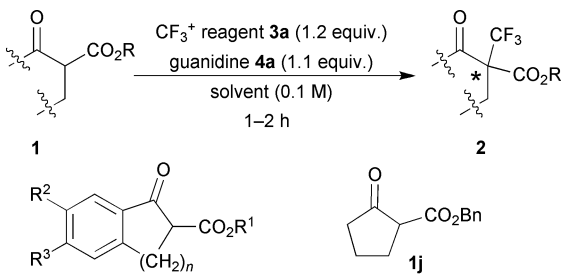


3a **3b** **3c**

Fig. 2 Structures of Umemoto reagents **3a–c**.

Table 2 shows substrates screened using optimized reaction conditions. In the indanone series, higher steric bulk for the ester moiety did not secure a better enantiodiscrimination; the methyl ester provided the best result in this study (55–70% ees, entries 1–7). In the tetralone series, ee values (54–65% ees) were in the same range as indanone derivatives but the yields of trifluoromethylation were low although the starting β-keto esters could be easily recovered (entries 8 and 9). The same can be done for product **2j** from benzyl cyclopentanone 2-carboxylate (**1j**) (entry 10).

Table 2 Substrate scope for enantioselective electrophilic trifluoromethylation



1 **2** **1j**

1a: R^1=Me, R^2=R^3=H, *n*=1 **1f**: R^1=Me, R^2=R^3=OMe, *n*=1
1b: R^1=Et, R^2=R^3=H, *n*=1 **1g**: R^1=Me, R^2=H, R^3=Br, *n*=1
1c: R^1=Bn, R^2=R^3=H, *n*=1 **1h**: R^1=Me, R^2=R^3=H, *n*=2
1d: R^1=*t*Bu, R^2=R^3=H, *n*=1 **1i**: R^1=CH_2CF_3, R^2=R^3=H, *n*=2
1e: R^1=CH_2CF_3, R^2=R^3=H, *n*=1

Entry	1	Solvent	Temp.	2	Yield[a] (%)	Ee[b] (%)
1	**1a**	$CHCl_3/CH_2Cl_2$= 1/1	–80 °C	**2a**	63	70
2	**1b**	$CHCl_3/CH_2Cl_2$= 1/1	–80 °C	**2b**	59	67
3	**1c**	$CHCl_3$	–40 °C	**2c**	56	63
4	**1d**	$CHCl_3$	–40 °C	**2d**	57	55
5	**1e**	$CHCl_3$	–40 °C	**2e**	49	66
6	**1f**	$CHCl_3$	–40 °C	**2f**	67	58
7	**1g**	$CHCl_3$	–40 °C	**2g**	64	58
8	**1h**	$CHCl_3$	–40 °C	**2h**	9 (90[c])	65
9	**1i**	$CHCl_3$	–40 °C	**2i**	20 (37[c])	54
10	**1j**	$CHCl_3$	–40 °C	**2j**	22 (61[c])	62

[a] Isolated yield of analytically pure product. [b] Determined by chiral HPLC. [c] Based on recovered starting β-keto esters.

The absolute configuration of the newly generated stereogenic centre in **2a** was tentatively assigned to be *S* deduced from the similar circular dichroic (CD) data and the sign of $[\alpha]_D$ values with those of a methyl analogue, methyl 2-(methyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate.[15] The sign of the $[\alpha]_D$ value of **2a** is positive and the CD spectra of (+)-**2a** shows a positive Cotton effect for the n→π * transition at about 320 nm. And if this is the case, the transition state in Fig. 3 can explain the *S*-enantioselectivity in the reaction based on the discussion in Table 1 (entries 19–27) with the literature observation (Fig. 3).[13] Determination of the absolute stereochemistry of **2** based on the X-ray crystallographic analysis of the derivative of **2** is under investigation.

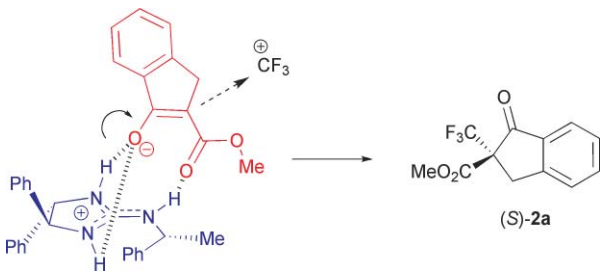


Fig. 3 Proposed transition state of (*S*)-**2a**.

Conclusions

In summary, we have investigated the direct enantioselective electrophilic trifluoromethylation to construct a quaternary carbon centre, a most formidable goal of fluorine chemistry. Despite the fact that the ees are still improvable, the model reported in this work could spark the imagination of chemists to design new chiral bases to improve the stereochemical outcome. Further optimization of chiral guanidines[12,13] in combination with novel electrophilic trifluoromethylating agents[16] for this reaction should offer a straightforward way for achieving high enantioselectivity. We are working in this direction and a catalytic version of this procedure is also under exploration.

Experimental

General

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Solvents were transferred *via* syringe and were introduced into the reaction vessels through a rubber septum. All of the reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel (60-F254). The TLC plates were visualized with UV light and 7% phosphomolybdic acid or *p*-anisaldehyde in ethanol/heat. Column chromatography was carried out on a column packed with

silica gel 60 N spherical neutral size 63–210 μm. The ^{1}H-NMR (200 MHz), ^{13}C NMR (50.3 MHz) and ^{19}F-NMR (188 MHz) spectra for solution in $CDCl_3$, were recorded on a Varian Gemini-200. ^{13}C NMR (150.9 MHz) spectra were recorded on a BRUKER 600 UltraShield^{TR}. Chemical shifts (δ) are expressed in ppm downfield from internal TMS or $CHCl_3$. Mass spectra were recorded on a SHIMADZU GCMS-QP5050A (EI-MS) and SHIMAZU LCMS-2010EV (ESI-MS and APCI-MS). Infrared spectra were recorded on a JASCO FT/IR-200 spectrometer. HPLC analyses were performed on a JASCO PU-2080 Plus or SHIMADZULC-2010A HT using 4.6 × 250 mm CHIRALPAK AD-H, CHIRALCEL OJ-H or CHIRALCEL OD-H. Optical rotations were measured on a HORIBA SEPA-300. CD spectra were measured on a JASCO J-800.

Typical procedure for the enantioselective trifluoromethylation of β-keto ester (in $CHCl_3$). To a stirred solution of β-keto ester **1a** (10 mg, 0.0526 mmol) in $CHCl_3$ (0.5 ml, 0.1 M) was added chiral guanidine **4a** (19.8 mg, 0.0579 mmol), and stirred for 10 min at room temperature and 5 min at –40 °C. The reagent **3a** (21.5 mg, 0.0631 mmol) was added, and stirred for 1 h at –40 °C. Then sat. NH_4Cl aq was added, extracted by AcOEt (3 ml × 3). The solvent was evaporated, and the residue was purified by column chromatography on silica gel (benzene) to give **2a** (10.3 mg, 76%, 65% ee) as a pale yellow oil.

Typical procedure for the enantioselective trifluoromethylation of β-keto ester (in $CHCl_3$/CH_2Cl_2). To a stirred solution of β-keto ester **1a** (10 mg, 0.0526 mmol) in $CHCl_3/CH_2Cl_2$= 1/1 (0.5 ml, 0.1 M) was added chiral guanidine **4a** (19.8 mg, 0.0579 mmol), and stirred for 10 min at room temperature and 5 min at –80 °C. The reagent **3a** (21.5 mg, 0.0631 mmol) was added, and stirred for 2 h at –80 °C. Then sat. NH_4Cl aq was added, and extracted by AcOEt (3 ml × 3). The solvent was evaporated, and the residue was purified by column chromatography on silica gel (benzene) to give **2a** (8.6 mg, 63%, 70% ee) as a pale yellow oil.

Methyl 2-(trifluoromethyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (2a). $[\alpha]_D^{25}$ +5.18° (c 0.257 in $CHCl_3$, 70% ee); CD ($CHCl_3$) λ_{ext} 332.0 nm (Δε +0.412), 322.0 (+0.512), 296.6 (+0.726), 270.2 (+0.156) ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (d, *J*= 7.4 Hz, 1H), 7.73–7.65 (m, 1H), 7.54–7.41 (m, 2H), 3.78 (s, 3H), 3.75, 3.59 (AB quartet, *J*= 17.5 Hz, 2H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$): δ –69.2 (s, 3F) ppm; ^{13}C NMR (150.9 Hz, $CDCl_3$) δ 192.82, 165.60, 151.65, 136.28, 134.36, 128.50, 126.30, 125.60, 123.47 (q, *J*= 282 Hz), 63.05 (q, *J*= 26.3 Hz), 53.56, 34.16 ppm; IR (KBr) 2968 (C-H), 1756 (COOMe), 1719 (CO), 1316–1163 (CF_3) cm^{-1}; MS (APCI) *m/z* 257 (M^--H); HRMS (EI) Calcd for $C_{12}H_9F_3O_3$ $[M]^+$: 258.0504, found: 258.0504; HPLC (CHIRALCEL OD-H, hexane:2-propanol= 99:1, 1.0 ml/min, 254 nm, t_R= 10.8 min (minor isomer), 14.3 min (major isomer)).

Ethyl 2-(trifluoromethyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (2b). The reaction of **1b** (10 mg, 0.0490 mmol) with chiral guanidine **4a** (18.4 mg, 0.0539 mmol) and **3a** (20.0 mg, 0.0588 mmol) in $CHCl_3/CH_2Cl_2$= 1/1 (0.5 ml, 0.1 M) at –80 °C gave **2b** (7.9 mg, 59%, 67% ee) as a pale yellow oil. $[\alpha]_D^{25}$ +44.33° (c 0.200 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (d, *J*= 7.8 Hz, 1H), 7.72–7.64 (m, 1H), 7.54–7.41 (m, 2H), 4.25 (q, *J*= 7.1 Hz, 2H), 3.74, 3.58 (AB quartet, *J*= 17.7 Hz, 2H), 1.24 (t, *J*=7.1 Hz) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ –69.1 (s, 3F) ppm; ^{13}C NMR (150.9 Hz, $CDCl_3$) δ 192.97, 165.10, 151.68, 136.20, 134.41, 128.44, 126.27, 125.53, 123.51 (q, *J*= 281 Hz), 63.10 (q, *J*= 26.1 Hz), 62.81, 34.16, 13.82 ppm; IR (NaCl) 2986 (C-H), 1756 (COOEt), 1727 (CO), 1303–1158 (CF_3) cm^{-1}; MS (EI) *m/z* 272 (M^+), 227 (M^+-OCH_2CH_3), 199 (M^+-$COOCH_2CH_3$); HRMS (EI) Calcd for $C_{13}H_{11}F_3O_3$ $[M]^+$: 272.0660, found: 272.0660; HPLC (CHIRALCEL OD-H, hexane:2-propanol= 99:1, 1.0 ml/min, 254 nm, t_R= 8.9 min (minor isomer), 11.6 min (major isomer)).

Benzyl 2-(trifluoromethyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (2c). The reaction of **1c** (10 mg, 0.0376 mmol) with chiral guanidine **4a** (14.1 mg, 0.0414 mmol) and **3a** (15.3 mg, 0.0451 mmol) in $CHCl_3$ (0.34 ml, 0.1 M) at –40 °C gave **2c** (7.1 mg, 56%, 63% ee) as a pale yellow oil. $[\alpha]_D^{25}$ +25.60° (c 0.193 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (d, *J*=7.8 Hz, 1H), 7.71–7.63 (m, 1H), 7.51–7.44 (m, 2H), 7.40–7.21 (m, 5H), 5.25, 5.18 (AB quartet, *J*=12.9 Hz, 2H), 3.72, 3.57 (AB quartet, *J*=17.7 Hz, 2H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ –69.0 (s, 3F) ppm; ^{13}C NMR (150.9 Hz, $CDCl_3$) δ 192.71, 164.96, 151.59, 136.24, 134.61, 134.38, 128.59, 128.48, 128.44, 127.72, 126.27, 125.57, 123.47 (q, *J*=282 Hz), 68.03, 63.14 (q, *J*=26.1 Hz), 34.11 ppm; IR (NaCl) 3067 (Ar-H), 3036 (Ar-H), 2955 (C-H), 1758 (COOBn), 1726 (CO), 1302–1158 (CF_3) cm^{-1}; MS (EI) *m/z* 334 (M^+), 243 (M^+-$CH_2C_6H_5$), 227 (M^+-$OCH_2C_6H_5$), 199 (M^+-$COOCH_2C_6H_5$); HRMS (EI) Calcd for $C_{18}H_{13}F_3O_3$ $[M]^+$: 334.0817, found: 334.0785; HPLC (CHIRALCEL OD-H, hexane:2-propanol= 99:1, 1.0 ml/min, 254 nm, t_R= 17.0 min (minor isomer), 20.9 min (major isomer)).

***tert*-Butyl 2-(trifluoromethyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (2d).** The reaction of **1d** (10 mg, 0.0431 mmol) with chiral guanidine **4a** (16.2 mg, 0.0474 mmol) and **3a** (17.6 mg, 0.0517 mmol) in $CHCl_3$ (0.45 ml, 0.1 M) at –40 °C gave **2d** (7.4 mg, 57%, 55% ee) as a white solid. $[\alpha]_D^{25}$ +17.25° (c 0.220 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82 (d, *J*=7.6 Hz, 1H), 7.70–7.62 (m, 1H), 7.52–7.39 (m, 2H), 3.69, 3.54 (AB quartet, *J*= 17.7 Hz, 2H), 1.43 (s, 9H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ –69.0 (3F) ppm; ^{13}C NMR (150.9 Hz, $CDCl_3$) δ 193.38, 164.05, 151.68, 135.98, 134.60, 128.31, 126.20, 125.38, 123.59 (q, *J*=281 Hz), 84.26, 63.82 (q, *J*=26.0 Hz), 34.23, 27.66 ppm; IR (KBr) 2978 (C-H), 2934 (C-H), 1753 (COO^tBu), 1720 (CO), 1324–1146 (CF_3) cm^{-1}; MS (APCI) *m/z* 299 (M^--H); HRMS (EI) Calcd for $C_{15}H_{15}F_3O_3$ $[M]^+$: 300.0973, found: 300.0964; HPLC (CHIRALCEL OD-H, hexane 100, 0.5 ml/min, 254 nm, t_R= 25.1 min (minor isomer), 27.1 min (major isomer)).

2,2,2-Trifluoroethyl 2-(trifluoromethyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (2e). The reaction of **1e** (10 mg, 0.0387 mmol) with chiral guanidine **3a** (14.5 mg, 0.0426 mmol) and **4a** (15.8 mg, 0.0465 mmol) in $CHCl_3$ (0.40 ml, 0.1 M) at –40 °C gave **2e** (6.2 mg, 49%, 66% ee) as a pale yellow oil. $[\alpha]_D^{25}$ +32.22° (c 0.167 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85 (d, *J*=7.8 Hz, 1H), 7.75–7.67 (m, 1H), 7.56–7.44 (m, 2H), 4.74–4.39 (m, 2H), 3.75, 3.63 (AB quartet, *J*= 17.8 Hz, 2H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ –69.4 (s, 3F), –73.7 (t, *J*= 7.9 Hz) ppm; ^{13}C NMR (150.9 Hz, $CDCl_3$) δ 191.69, 163.83, 151.33, 136.59, 134.01, 128.76, 126.32, 125.79, 123.15 (q, *J*=281 Hz), 122.22 (q, *J*=278 Hz), 62.88 (q, *J*=26.4 Hz), 61.37 (q, *J*=37.4 Hz), 34.00 ppm; IR (KBr) 1772 (COO^tBu), 1733 (CO), 1317–1169 (CF_3) cm^{-1}; MS (APCI) *m/z* 349 (M^++Na); HRMS (EI) Calcd for $C_{14}H_{13}F_3O_5$

[M]$^+$: 326.0378, found: 326.0397; HPLC (CHIRALCEL OD-H, hexane:2-propanol= 99.5:0.5, 1.0 ml/min, 254 nm, t_R= 15.7 min (minor isomer), 24.4 min (major isomer)).

Methyl 2-(trifluoromethyl)-2,3-dihydro-5,6-dimethoxy-1-oxo-1H-indene-2-carboxylate (2f). The reaction of **1f** (10 mg, 0.0400 mmol) with chiral guanidine **4a** (15.0 mg, 0.0440 mmol) and **3a** (16.3 mg, 0.0480 mmol) in $CHCl_3$ (0.40 ml, 0.1 M) at –40 °C gave **2f** (8.5 mg, 67%, 58% ee) as a white solid. $[\alpha]_D^{25}$ +52.40° (c 0.227 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20 (s, 1H), 6.91 (s, 1H), 4.00 (s, 3H), 3.92 (s, 3H), 3.78 (s, 3H), 3.64, 3.47 (AB quartet, *J*=17.5 Hz, 2H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ –69.3 (s, 3F) ppm; ^{13}C NMR (150.9 Hz, $CDCl_3$) δ 191.16, 165.88, 156.80, 150.25, 147.57, 127.12, 123.59 (q, *J*=281 Hz), 106.94, 105.35, 63.36 (q, *J*=26.1 Hz), 56.46, 56.20, 53.49, 33.81 ppm; IR (KBr) 3082 (Ar-H), 3020 (Ar-H), 2955 (C-H), 1756 (COOMe), 1715 (CO), 1323–1154 (CF_3), cm^{-1}; MS (EI) *m/z* 318 (M^+), 287 (M^+-OCH_3), 259 (M^+-$COOCH_3$); HRMS (EI) Calcd for $C_{14}H_{13}F_3O_5$ [M]$^+$: 318.0715, found: 318.0737; HPLC (CHIRALCEL AD-H, hexane:2-propanol= 90:10, 1.0 ml/min, 254 nm, t_R= 12.4 min (major isomer), 15.2 min (minor isomer)).

Methyl 5-bromo-2-(trifluoromethyl)-2,3-dihydro-1-oxo-1H-indene-2-carboxylate (2g). The reaction of **1g** (10 mg, 0.0372 mmol) with chiral guanidine **4a** (14.0 mg, 0.0409 mmol) and **3a** (15.2 mg, 0.0446 mmol) in $CHCl_3$ (0.37 ml, 0.1 M) at –40 °C gave **2g** (8.0 mg, 64%, 58% ee) as a pale yellow solid. $[\alpha]_D^{25}$ +58.84° (c 0.220 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71–7.67 (m, 2H), 7.62–7.57 (m, 1H), 3.79 (s, 3H), 3.74, 3.56 (AB quartet, *J*=18.0 Hz, 2H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ –69.2 (s, 3F) ppm; ^{13}C NMR (150.9 Hz, $CDCl_3$) δ 191.58, 165.17, 153.05, 133.18, 132.30, 132.02, 129.69, 126.64, 123.25 (q, *J*=282 Hz), 63.09 (q, *J*=26.4 Hz), 53.70, 33.73 ppm; IR (KBr) 2966 (C-H), 1755 (COOMe), 1724 (CO), 1327–1157 (CF_3), cm^{-1}; MS (APCI) *m/z* 337, 335 (M^+-H); HRMS (EI) Calcd for $C_{14}H_{13}F_3O_5$ [M]$^+$: 337.9588, found: 337.9608; HPLC (CHIRALCEL OD-H, hexane:2-propanol= 99:1, 1.0 ml/min, 254 nm, t_R= 12.5 min (major isomer), 14.5 min (minor isomer)).

Methyl 2-(trifluoromethyl)-1,2,3,4-tetrahydro-1-oxonaphthalene-2-carboxylate (2h). The reaction of **1h** (10 mg, 0.0490 mmol) with chiral guanidine **4a** (18.4 mg, 0.0539 mmol) and **3a** (20.0 mg, 0.0588 mmol) in $CHCl_3$ (0.50 ml, 0.1 M) at –40 °C gave **2h** (1.2 mg, 9%, 65% ee) as a colorless oil. $[\alpha]_D^{25}$ –90.91° (c 0.127 in $CHCl_3$, 59% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10 (d, *J*=7.8 Hz, 1H), 7.56–7.49 (m, 1H), 7.39–7.32 (m, 1H), 7.23 (d, *J*=7.4 Hz, 1H), 3.76 (s, 3H), 3.06–2.99 (m, 2H), 2.88–2.78 (m, 1H), 2.55–2.39 (m, 1H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ –68.7 (s, 3F) ppm; ^{13}C NMR (150.9 Hz, $CDCl_3$) δ 186.97, 165.75, 142.07, 134.32, 131.34, 128.69, 128.39. 127.26, 123.79 (q, *J*=284 Hz), 61.94 (q, *J*=24.1 Hz), 53.57, 27.68, 25.03 ppm; IR (KBr) 3013 (Ar-H), 2962 (C-H), 2936 (C-H), 1750 (COOMe), 1700 (CO), 1308–1173 (CF_3) cm^{-1}; MS (EI) *m/z* 272 (M^+), 213 (M^+-$COOCH_3$); HRMS (EI) Calcd for $C_{13}H_{11}F_3O_3$ [M]$^+$: 272.0660, found: 272.0655; HPLC (CHIRALCEL OD-H, hexane:2-propanol= 99:1, 1.0 ml/min, 254 nm, t_R= 10.2 min (major isomer), 11.5 min (minor isomer)).

2,2,2-Trifluoroethoxy 2-(trifluoromethyl)-1,2,3,4-tetrahydro-1-oxonaphthalene-2-carboxylate (2i). The reaction of **1i** (10 mg, 0.0367 mmol) with chiral guanidine **4a** (13.8 mg, 0.0404 mmol) and **3a** (15.0 mg, 0.0441 mmol) in $CHCl_3$ (0.37 ml, 0.1 M) at –40 °C gave **2i** (2.5 mg, 20%, 54% ee) as a colorless oil. $[\alpha]_D^{25}$ –47.92° (c 0.060 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10 (d, *J*=9.0 Hz, 1H), 7.58–7.50 (m, 1H), 7.40–7.33 (m, 1H), 7.27–7.23 (m, 1H), 4.74–4.39 (m, 2H), 3.09–3.02 (m, 2H), 2.90–2.79 (m, 1H), 2.62–2.47 (m, 1H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ –68.5 (s, 3F), –73.8 (t, *J*= 7.9 Hz, 3F) ppm; ^{13}C NMR (150.9 Hz, $CDCl_3$) δ 186.09, 164.23, 141.84, 134.62, 131.18, 128.72, 128.56, 127.46, 123.48 (q, *J*=284 Hz), 122.12 (q, *J*=278 Hz), 61.83 (q, *J*=24.4 Hz), 61.32 (q, *J*=37.3 Hz), 27.52, 24.75 ppm; IR (KBr) 1763 (COOMe), 1698 (CO), 1308–1168 (CF_3) cm^{-1}; MS (ESI) *m/z* 363 (M^++Na); HRMS (EI) Calcd for $C_{14}H_{13}F_3O_5$ [M]$^+$: 340.0534, found: 340.0540; HPLC (CHIRALCEL OD-H, hexane:2-propanol= 99.5:0.5, 0.5 ml/min, 254 nm, t_R= 34.7 min (major isomer), 38.3 min (minor isomer)).

Benzyl 2-oxocyclopentanecarboxylate (2j). The reaction of **1j** (10 mg, 0.0458 mmol) with chiral guanidine **4a** (13.8 mg, 0.0504 mmol) and **3a** (15.0 mg, 0.0550 mmol) in $CHCl_3$ (0.46 ml, 0.1 M) at –40 °C gave **2j** (2.9 mg, 22%, 62% ee) as a colorless oil. $[\alpha]_D^{25}$ +30.47° (c 0.053 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5H), 5.26, 5.17 (AB quartet, *J*=12.3 Hz, 2H), 2.64–2.34 (m, 4H), 2.11-1.98 (m, 2H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ –68.6 (s, 3F) ppm; ^{13}C NMR (150.9 Hz, $CDCl_3$) δ 205.01, 165.34, 134.55, 128.70, 128.63, 127.95, 123.38 (q, *J*=281 Hz), 68.05, 63.05 (q, *J*=26.1 Hz), 38.23, 30.65, 19.29 ppm; IR (NaCl) 3067 (Ar-H), 3035 (Ar-H), 2964 (C-H), 1769 (COOBn), 1747 (CO), 1300–1196 (CF_3) cm^{-1}; MS (EI) *m/z* 286 (M^+); HRMS (EI) Calcd for $C_{14}H_{13}F_3O_3$ [M]$^+$: 286.0817, found: 286.0800; HPLC (CHIRALCEL OJ-H, hexane:2-propanol= 99.5:0.5, 1.0 ml/min, 205 nm, t_R= 22.7 (major isomer), 25.5 (minor isomer)).

Acknowledgements

This work was supported by a Joint Project JSPS - CNRS to NS and DC, as well as by KAKENHI (to NS, 21390030), by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology Japan (to NS, 19020024). We thank Dr K. Adachi, Daikin Industries Ltd. for the generous gift of the Umemoto reagents.

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