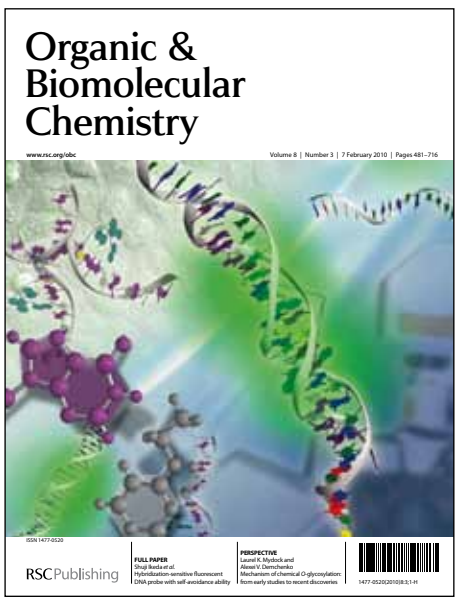
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: N. Shibata, T. Nishimine, N. Shibata, E. Tokunaga, K. Kawada, T. Kagawa, J. L. Acena, A. E. Sorochinsky and V. A. Soloshonok, *Org. Biomol. Chem.*, 2013, DOI: 10.1039/C3OB42425A.



Dynamic Article Links ►
View Article Online
DOI: 10.1039/C3OB42425A

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Asymmetric Mannich reaction between (*S*)-*N*-(*tert*-butanesulfinyl)-3,3,3-trifluoroacetaldimine and malonic acid derivatives. Stereodivergent synthesis of (*R*)- and (*S*)-3-amino-4,4,4-trifluorobutanoic acids

Norio Shibata,*[a] Takayuki Nishimine,[a] Naoyuki Shibata,[a] Etsuko Tokunaga,[a] Kosuke Kawada,[b] Takumi Kagawa,[b] José Luis Aceña,[c] Alexander E. Sorochinsky[c,d,e] and Vadim A. Soloshonok*[c,d]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Inorganic as well as organic base catalysis was found to be effective for diastereoselective Mannich additions of malonic acid derivatives to (S_S)-*N*-(*tert*-butanesulfinyl)-3,3,3-trifluoroacetaldimine. In the presence of catalytic amounts of inorganic bases, *n*-BuLi or DMAP, the reaction gives the corresponding (R,S_S)-β-aminomalonates in good yield and with diastereoselectivity up to 9/1 dr. On the contrary, phosphazene bases favour the formation of the (S,S_S)-diastereomer with selectivities as high as 99/1. Simple choosing of appropriate base catalyst for the Mannich addition reaction allowed to obtain enantiomerically pure either (*R*)- or (*S*)-configured 3-amino-4,4,4-trifluorobutanoic acids after hydrolysis and decarboxylation of the corresponding β-aminomalonates.

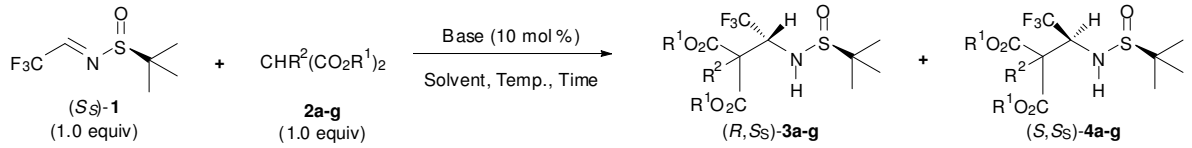
Introduction

The diastereoselective Mannich reaction of chiral ester enolates or chiral imines and related compounds with the corresponding achiral counterparts has become an efficient and powerful strategy allowing access to chemically and biologically important β-amino acids and their derivatives.[1] Since chiral trifluoromethyl imines are good electrophiles owing to the electron-withdrawing effect of the CF_3 group, there are several reports on their Mannich reactions with ester enolate nucleophiles.[2] According to this strategy, LiCl/Et_3N-assisted Mannich reaction of chiral Ni(II) complex of glycine Schiff base with *N*-*p*-methoxyphenyl imine derived from trifluoroacetaldehyde has been used by Soloshonok et al. for the synthesis of α,β-diamino-β-(trifluoromethyl)carboxylic acid in high yield and with excellent diastereoselectivity.[3] Additionally, the Mannich reaction of the chlorotitanium enolate of (α-benzyloxy)acetyl 2-oxazolidinone with the *N*-Cbz imine of trifluoropyruvate was explored by Zanda et al. in asymmetric preparation of α-(trifluoromethyl)-β-hydroxyaspartic acid.[4] The Mannich reaction of diastereomeric mixtures of oxazolidines derived from trifluoroacetaldehyde and (*R*)-phenylglycinol with ethyl trimethylsilyl ketene acetal, studied by Huguenot and Brigaud, was shown to afford the corresponding β-amino ester derivatives with moderate diastereoselectivity.[5] After chromatographic separation and removal of the chiral auxiliary, the major isomer gave rise to enantiopure (*R*)-3-amino-4,4,4-trifluorobutanoic acid. Lately, examples of highly diastereoselective Mannich reactions were represented by addition of ester enolates to trifluoromethyl imines bearing an *N*-sulfinyl group as the chiral auxiliary. An efficient procedure involving the addition of the chlorotitanium enolate of *tert*-butyl acetate to the enantiomerically pure *N*-*p*-toluenesulfinyl imine of ethyl trifluoropyruvate was applied by Zanda et al. to the asymmetric synthesis of (*S*)- and (*R*)-α-(trifluoromethyl)aspartic acids in good yield and excellent diastereoselectivity.[6] Addition of a Reformatsky reagent to α-aryl(alkyl)-α-(trifluoromethyl)-*N*-*tert*-butanesulfinyl amino acetals as stable precursors of the corresponding trifluoromethyl ketimines was further utilized by Grellepois for the elaboration of β-alkyl(aryl)-β-(trifluoromethyl)-β-amino acid derivatives in good yields and high diastereoselectivities.[7] Nitro-Mannich reaction, which involves the nucleophilic addition of nitroalkanes to trifluoromethyl α,β-unsaturated *N*-*tert*-butanesulfinyl ketimines was carried out readily in the presence of catalytic amounts of anhydrous potassium carbonate by Liu et al. to give the corresponding adducts diastereoselectively in high yields.[8] Conversions of the resulting trifluoromethyl β-nitroamines to α-(trifluoromethyl)-α,β-diamino acids was also demonstrated.

Recently, (S_S)-*N*-(*tert*-butanesulfinyl)-3,3,3-trifluoroacetaldimine (S_S)-**1** was introduced as a multifunctional chiral synthon for the potencial preparation of a great variety of organic compounds containing the biologically important α-(trifluoromethyl)amino moiety.[9] In particular, (S_S)-**1** has been successfully employed for the asymmetric Reformatsky reaction[10] as well as reactions with enolates to give adducts with good to high level of diastereoselectivity.[11] Subsequent deprotection of the addition adducts under acidic conditions produced the free α-trifluoromethyl amino derivatives without any sign of racemization. Importantly, the synthesis of (S_S)-**1** as a pure *E*-isomer can be performed on industrial scale, thus providing a significant incentive for systematic study of its chemistry and synthetic applications.[10] To continue developing practical methods for constructing fluorinated β-amino acids we have

View Article Online
DOI: 10.1039/C3OB42425A

Table 1 Mannich reaction between dialkyl malonates **2** and imine (S_S)-**1** using inorganic bases or *n*-BuLi as catalysts[a]



R^1 = Et, R^2 = H (**a**), R^1 = Me, R^2 = H (**b**), R^1 = *i*-Pr, R^2 = H (**c**), R = *t*-Bu, R^2 = H (**d**), R^1 = Bn, R^2 = H (**e**), R^1 = Et, R^2 = F (**f**), R^1= Et, R^2 = Me (**g**)

Entry	malonate	base	Solvent (0.3 M)	Temp. (°C)	Time (h)	Yield (%)[b]	dr (R,S_S)/(S,S_S)[c]
1	**2a**	K_2CO_3	toluene	rt	12	84	75/25
2	**2a**	Cs_2CO_3	toluene	rt	12	80	71/29
3	**2a**	KO*t*-Bu	toluene	rt	12	87	76/24
4	**2a**	NaO*t*-Bu	toluene	rt	12	96	75/25
5[d]	**2a**	K_2CO_3	toluene	rt	24	83	48/52
6	**2a**	*n*-BuLi	toluene	rt	3	85	86/14
7	**2a**	*n*-BuLi	toluene	–78	2	88	89/11
8[e]	**2a**	*n*-BuLi	toluene	–78	2	88	89/11
9	**2a**	LiHMDS	toluene	–78	2	95	88/12
10	**2a**	*n*-BuLi	THF	–78	3	82	80/20
11	**2a**	*n*-BuLi	Et_2O	–78	2	78	88/12
12[f]	**2a**	*n*-BuLi	toluene	–78	5	85	87/13
13[g]	**2a**	*n*-BuLi	toluene	–78	1	83	89/11
14	**2a**	*n*-BuLi	toluene (0.2 M)	–78	3	61	87/13
15	**2a**	*n*-BuLi	toluene	–78	0.25	94	89/11
16[h]	**2a**	*n*-BuLi	toluene	–78	0.25	98	90/10
17	**2b**	*n*-BuLi	toluene	–78	0.25	99	92/8
18	**2c**	*n*-BuLi	toluene	–78	0.25	98	86/14
19	**2d**	*n*-BuLi	toluene	–78	0.25	99	58/42
20	**2e**	*n*-BuLi	toluene	–78	0.25	99	95/5
21	**2f**	*n*-BuLi	toluene	–78	0.25	84	79/21
22	**2g**	*n*-BuLi	toluene	–78	0.25	80	84/16

[a] The reactions of (S_S)-**1** (1 equiv) with dialkyl malonates **2** (1 equiv) were performed in the corresponding solvent (0.3 M) in the presence of base (10 mol %). [b] Isolated total yield of both diastereomers. [c] Determined by ^{19}F NMR analysis. [d] 20 mol % of 18-crown-6 was added to the reaction mixture. [e] 1.2 equiv of LiCl was added to the reaction mixture. [f] 5 mol % of *n*-BuLi was used. [g] 20 mol % of *n*-BuLi was used. [h] 1.2 equiv of imine (S_S)-**1** were used.

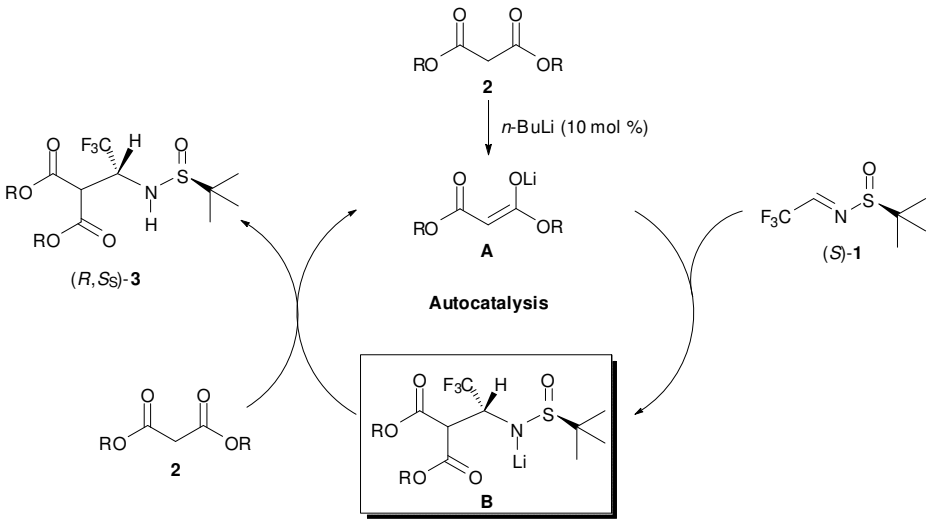
explored a new asymmetric approach *via* the Mannich-type reactions between (S_S)-**1** and derivatives of malonic acid followed by decarboxylation of one of the carboxylic groups.[12] Operational simplicity of this approach would render it a highly attractive alternative to the existing methods toward enantiomerically pure 3-amino-4,4,4-trifluorobutanoic acids. We report herein a full account of our study concerning the asymmetric base-catalyzed malonates addition to (S_S)-**1** giving access to β-amino acid precursors.

Results and Discussion

Mannich addition of dialkyl malonates 2 to *N*-(*tert*-butanesulfinyl)-3,3,3-trifluoroacetaldimine (S_S)-1 in the presence of inorganic bases or *n*-BuLi as catalysts

Our investigation of the asymmetric direct Mannich reaction was begun with the addition of diethyl malonate **2a** to the imine (S_S)-**1** in toluene in the presence of 10 mol % of K_2CO_3 or Cs_2CO_3. These reactions required 12 h at room temperature to go to completion giving rise to the desired addition product as a mixture of (R,S_S)-**3a** and (S,S_S)-**4a** diastereomers. While K_2CO_3 afforded the addition product in 84% yield and 75/25 dr in favor of the (R,S_S)-**3** isomer, the use of the Cs_2CO_3 lowered the stereoselectivity of the reaction to 71/29 dr (Table 1, entries 1 and 2). The shown effect may be related to the size of the cation in the solution. Other bases tested in the reaction such as KO*t*-Bu and NaO*t*-Bu resulted in similar level of diastereoselectivity as compared to K_2CO_3 (entries 3 and 4). However, in both cases the yields were higher than 87%. Interestingly, the use of 18-crown-6 ether in conjunction with catalytic amounts of K_2CO_3 provided the opposite ratio of diastereomers, however low dr was observed (entry 5). Changing the counterion from potassium and sodium to lithium by using malonate enolate prepared in advance with 10 mol % of *n*-BuLi allowed to improve the result of the Mannich reaction. After stirring the reaction mixture for 3 h at room temperature the addition product was isolated in 85% yield with significant increase in diastereoselectivity to 86/14 dr (entry 6). Temperature control experiments showed that the diastereoselectivity was sensitive to temperature and the highest 89/11 dr and chemical yield of 88% could be obtained at –78 °C (entry 7). The addition of LiCl as additive to the reaction catalyzed by *n*-BuLi did not modify the result (entry 8). If a catalytic amount of LiHMDS was employed as base for pregeneration of lithium malonate enolate the mixture of diastereomers was formed with improving yield without affecting the diastereoselectivity significantly (entry 9). THF and Et_2O were also examined as solvents for this reaction, but lower yield and diastereoselectivity were observed in both cases (entries 10 and 11). Further optimization of the reaction conditions focused on several factors such as amount of catalyst, concentration of reagents and reaction time, to reveal that using 10 mol % of *n*-BuLi for pregeneration of malonate-derived enolate was required

View Article Online
DOI: 10.1039/C3OB42425A



Scheme 1 Autocatalytic reaction of dialkyl malonates **2** with imine (S_S)-**1** in the presence of catalytic amount of *n*-BuLi

to ensure the best yields and selectivities in toluene at –78 ºC within 0.25 h (entries 12-15). Under these optimized conditions, the addition adduct was obtained in 98% isolated yield and 90/10 dr (entry 16). Increasing the amount of base did not improve either yield or diastereoselectivity (entry 13). Interestingly, the alkyl group of dialkyl malonates was found to have a substantial effect on the stereoselectivity. Excellent yield and a slightly improved diastereoselectivity was observed for the addition of dimethyl and dibenzyl malonates **2b,e** when compared to the diethyl malonate **2a** (entries 17 and 20). When diisopropyl and di-*tert*-butyl malonates **2c,d** were employed for the reaction, excellent yield could still be obtained, however a significant drop in diastereoselectivity to 86/14 and 58/42 dr was observed (entries 18 and 19). The diethyl malonates **2f,g** having fluorine or methyl substituent at the α-position also reacted with imine (S_S)-**1** giving the Mannich adducts in satisfying yield and diastereoselectivity ranging from 79/21 to 84/16 (entries 21 and 22).

Taking into account the experimental results, the behavior of *n*-BuLi as a catalyst in the Mannich addition reaction could be explained by an autocatalytic process (Scheme 1). The first step involves deprotonation of dialkyl malonate **2** with *n*-BuLi. The resulting malonate-derived enolate **A** then reacts with the imine (S_S)-**1** to form the lithium sulfinamide intermediate **B**. The latter is sufficiently basic to deprotonate a new molecule of dialkyl malonate **2** thus providing the sulfinamide (R,S_S)-**3** and regenerating the malonate-derived enolate **A** to re-enter the catalytic cycle.

Assignment of the configuration of the major diastereomer (R,S_S)-**3a** was done after hydrolysis to the corresponding known β-(trifluoromethyl)-β-alanine of (*R*) absolute configuration which had (+)-sign of rotation.[5,13] The resulting stereochemistry revealed that the asymmetric induction in the Mannich-type reaction of imine (S_S)-**1** with dialkyl malonates **2** catalyzed by inorganic bases or *n*-BuLi matches to that of the reactions of non-fluorinated *N*-*tert*-butanesulfinyl and *N*-*p*-toluenesulfinyl imines with ester and malonate enolates.[1b-e] Thus, this stereoselectivity could be rationalized by the six/four-membered bicyclic chelated transition state **TS 1** (Fig. 1) similar to proposed by Davis et al. and Ellman et al., were both the sulfinyl oxygen and imine nitrogen are coordinated to the metal.[14] The suggestion of four-membered chelate ring presented in transition state **TS 1** is in accord with previously published crystal structure of lithium azaenolates derived from carboxylic acid amides.[15] Due to chelation of the metal with the sulfinyl oxygen, enolate approach occurs from opposite to the bulky *tert*-butyl group *Re* face of the imine delivering (R,S_S) addition product. It should be emphasized that this mechanism is different from addition of organometallic and Reformatsky reagents as well as enolates to imine (S_S)-**1** which proceeded via a non-chelated transition state model affording predominantly (S,S_S) diastereomers.[9b,c,10] The crucial role of the metal ion for realization of high stereoselectivity has been proved by addition of diethyl malonate **2a** in the presence of 18-crown-6 ether effectively breaking up the chelation (Table 1, entry 5). Under these conditions (R,S_S)-**3a** and (S,S_S)-**4a** diastereomers were formed in almost 1:1 ratio. Considering the sterically congested structure of the bicyclic chelated **TS 1**, the size of the chelating metal might be of great importance in its stabilization. One may assume that Li could be a better fit in both six- and four-membered chelated rings leading to more stable **TS 1** and higher stereochemical outcome.

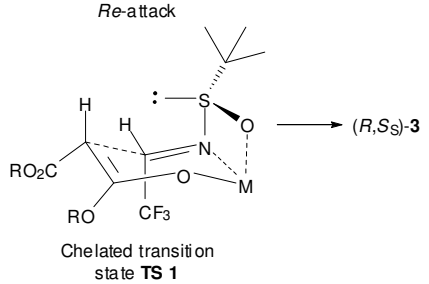


Fig. 1 Transition state model for the Mannich reaction between imine (S_S)-**1** and dialkyl malonates **2** catalyzed by inorganic bases or *n*-BuLi.

Mannich addition of dialkyl malonates 2 to *N*-(*tert*-butanesulfinyl)-3,3,3-trifluoroacetaldimine (S_S)-1 in the presence of organic bases as catalysts

View Article Online
DOI: 10.1039/C3OB42425A

The success in achieving high level of diastereoselectivity in the *n*-BuLi-catalyzed asymmetric Mannich reaction between dialkyl malonates **2** and imine (S_S)-**1** led us to explore organic bases as catalysts with the goal of inverting the stereochemical outcome of these reactions. In this case no preformation of malonate enolate would be required for preparation of addition adducts. We have found that the reaction of imine (S_S)-**1** with diethyl malonate **2a** in the presence of 10 mol % of Et_3N took place at a relatively slow rate at room temperature to give, however, the desired addition products as a mixture of (R,S_S)-**3a** and (S,S_S)-**4a** diastereomers in 69/31 dr and 14% combined yield within 12 h (Table 2, entry 1). With the aim to improve the yield and ratio of diastereomers we revisited the reaction catalyzed by Et_3N with other organic bases. We found that synthetically meaningful chemical yield (87%) and diastereomeric ratio (88/12) can be obtained in the reactions catalyzed by DMAP at room temperature for 48 h (entry 2). The ester group of malonate also affected the asymmetric induction under DMAP-catalyzed reaction. While dimethyl malonate **2b** provided yield and diastereoselectivity comparable to that observed for the diethyl ester **2a**, the use of more sterically demanding di-*tert*-butyl malonate **2c** produced noticeably lower yield and diastereoselectivity (entries 3 and 4). The addition reaction with diethyl malonate **2a** catalyzed by sterically hindered, non-nucleophilic *N*,*N*-diisopropylethylamine (Hünig's base) occurred at higher rate within 24 h but, most surprisingly, gave the ratio of diastereomers (R,S_S)-**3a** and (S,S_S)-**4a**, which was opposite to that we observed in the Et_3N and DMAP-catalyzed reactions (entry 5). Inversion of the diastereoselectivity by simply changing of base implied the involvement of two competitive reaction pathways. With these results in hand, we set for ourselves a goal of preparing the diastereomer (S,S_S)-**4a** as the major product in a synthetically meaningful yield by reasonable choice of the catalyst. Taking advantage of commercial availability of numerous quite strong and non-nucleophilic bases (Fig. 2) we were in position to study their effect on rate and diastereoselectivity of the reactions between imine (S_S)-**1** and dialkyl malonates **2**.

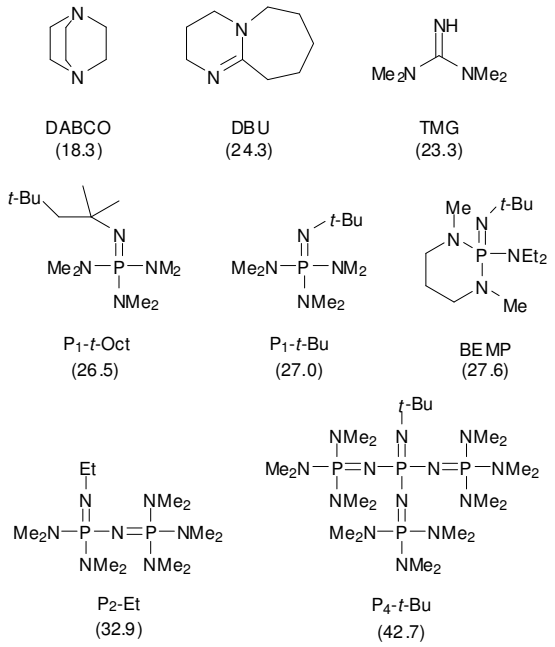


Fig. 2 Structures of strong, non-nucleophilic organic bases (pK_{BH} values in acetonitrile in parentheses[16])

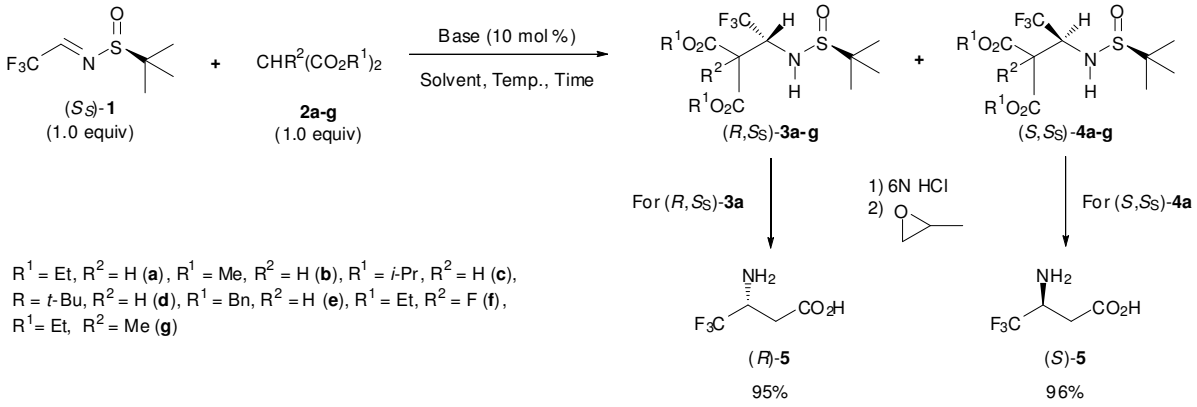
The reactions in the presence of the catalytic strong organic nitrogen bases DBU and TMG allowed complete conversion of the starting materials in 12 h. However, the observed ratio of diastereomers still favoring product (S,S_S)-**4a** was lower than in the Hünig's base-catalyzed reaction (Table 2, entries 7 and 8). In the presence of 10 mol % of DABCO, which is less basic than DBU and TMG, the reaction was sluggish and low yield of Mannich adduct was obtained (entry 6). This finding showed that DBU and TMG facilitated the nucleophilic attack, but did not affect the structure of the transition state essentially. In an attempt to improve these results, highly reactive "naked" enolates were generated by deprotonation of **2a** using a catalytic amount of phosphazene bases.[17] A series of reactions in the presence of 10 mol % of P_1, P_2, and P_4 phosphazene bases in toluene at room temperature showed a noticeable increase in the ratio of diastereomers (S,S_S)-**4a** and (R,S_S)-**3a** to synthetically meaningful 94/6 in the case of P_1-*t*-Oct (entries 9-13). The solvent effect was also examined for the P_1-*t*-Oct-catalyzed reaction. In DMF, (S,S_S)-**4a** was produced as the major product in a similar diastereoselectivity and yield (entry 14). Using THF and CH_2Cl_2 as solvents gave comparable diastereoselectivity but low chemical yields (entries 15 and 16). Furthermore, when the reaction was performed in MeOH the diastereoselectivity was decreased substantially (entry 17). The impact of temperature on diastereoselectivity and yield of phosphazene bases-catalyzed Mannich reactions was examined next. Lowering the temperature to –78 ^{o}C led to an improvement in diastereoselectivity up to 98/2–99/1 dr (entries 18-22). The best result was observed with P_2-Et which was found to promote the addition of diethylmalonate **2a** in 84% yield and with 99/1 dr. To verify the efficacy of the optimization procedure, the Mannich addition was performed on various malonate esters **2b-g** using the best experimental conditions. Dialkyl malonates **2b**-**e** cleanly reacted with imine (S_S)-**1** to afford the desired Mannich products generally with good yield and excellent diastereoselectivity

View Article Online
DOI: 10.1039/C3OB42425A

(≥98/2 dr) (entries 23-26). A sole exception was dibenzyl malonate **2e** which gave the product in lower diastereoselectivity but without deteriorating yield. It should be mention that diethyl 2-fluoromalonate **2f** was also tolerated under relatively basic reaction conditions affording the Mannich product in excellent yield and diastereoselectivity (entry 27). In fact, a single diastereoisomer was observed for these cases by crude ^{19}F NMR analysis. Methyl-substituted diethyl malonate **3g** gave the Mannich adduct with a quaternary carbon atom in excellent 99/1 dr (entry 28). However, the yield of Mannich adduct was diminished to 22% probably because of steric hindrance.

It is noteworthy that major diastereomers (R,S_S)-**3** and (S,S_S)-**4** could be purified by column chromatography. Further one-step hydrolysis and decarboxylation under reflux in 6N HCl was performed on Mannich products to furnish the corresponding β-amino acids (R)-**5** and (S)-**5** in enantiomerically pure form. Yield of 95-96% was obtained under these convenient conditions. The absolute stereochemistry of the products (R)-**5** and (S)-**5** has been determined by comparison of their chiroptical properties with the literature data.[5,13] The configurations of the major diastereomers **3** and **4** were therefore assigned as (R,S_S) and (S,S_S) correspondingly.

Table 2 Mannich-type reaction between dialkyl malonates **2** and imine (S_S)-**1** in the presence of organic bases as catalysis[a]



R^1 = Et, R^2 = H (**a**), R^1 = Me, R^2 = H (**b**), R^1 = *i*-Pr, R^2 = H (**c**), R = *t*-Bu, R^2 = H (**d**), R^1 = Bn, R^2 = H (**e**), R^1 = Et, R^2 = F (**f**), R^1 = Et, R^2 = Me (**g**)

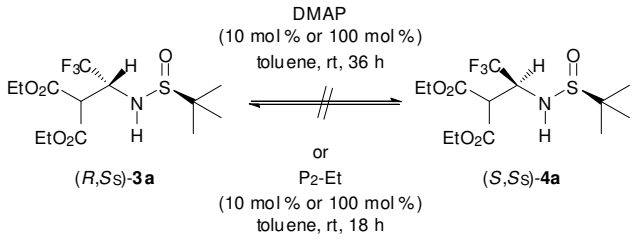
Entry	Malonate	Base	Solvent (0.3 M)	Temp. (°C)	Time (h)	Yield (%)[b]	dr (R,S_S)/(S,S_S)[c]
1	**2a**	Et_3N	toluene	rt	12	14	69/31
2	**2a**	DMAP	toluene	rt	48	87	88/12
3	**2a**	DMAP	toluene	rt	48	85	88/12
4	**2a**	DMAP	toluene	rt	48	67	80/20
5	**2a**	*i*-Pr_2EtN	toluene	rt	24	47	20/80
6	**2a**	DABCO	toluene	rt	12	33	34/66
7	**2a**	DBU	toluene	rt	12	62	25/75
8	**2a**	TMG	toluene	rt	12	82	39/61
9	**2a**	P_1-*t*-Oct	toluene	rt	12	71	6/94
10	**2a**	P_1-*t*-Bu	toluene	rt	12	73	9/91
11	**2a**	BEMP	toluene	rt	12	76	12/88
12	**2a**	P_2-Et	toluene	rt	12	80	7/93
13	**2a**	P_4-*t*-Bu	toluene	rt	12	65	7/93
14	**2a**	P_1-*t*-Oct	DMF	rt	12	70	6/94
15	**2a**	P_1-*t*-Oct	THF	rt	12	43	9/91
16	**2a**	P_1-*t*-Oct	CH_2Cl_2	rt	12	61	9/91
17	**2a**	P_1-*t*-Oct	MeOH	rt	12	67	13/87
18	**2a**	BEMP	toluene	–78	25	59	2/98
19	**2a**	P_1-*t*-Oct	toluene	–78	24	70	2/98
20	**2a**	P_1-*t*-Bu	toluene	–78	22	32	2/98
21	**2a**	P_2-Et	toluene	–78	24	72	1/99
22[d]	**2a**	P_2-Et	toluene	–78	24	84	1/99
23	**2b**	P_2-Et	toluene	–78	24	85	2/98
24	**2c**	P_2-Et	toluene	–78	24	89	>1/99
25	**2d**	P_2-Et	toluene	–78	24	73	>1/99
26	**2e**	P_2-Et	toluene	–78	24	78	8/92
27	**2f**	P_2-Et	toluene	–78	24	98	>1/99
28	**2g**	P_2-Et	toluene	–78	24	22	1/99

[a] The reactions of (S_S)-**1** (1 equiv) with dialkyl malonates **2** (1 equiv) were performed in the corresponding solvent (0.3 M) in the presence of base (10 mol %). [b] Isolated total yield of both diastereomers. [c] Determined by ^{19}F NMR analysis. [d] 1.2 equiv of imine (S_S)-**1** were used.

To determine whether the (R,S_S)-**3a** and (S,S_S)-**4a** products were formed under kinetic or thermodynamic control, they were subjected to treatment with DMAP and phosphazene P_2-Et under the reaction conditions. However, attempts to isomerize diastereomer (R,S_S)-**3a** in the presence of 10 or 100 mol % of DMAP or phosphazene P_2-Et in toluene at room temperature failed and it was recovered in 90-95% yield (Scheme 2). Retro-Mannich products were not also observed either by NMR analysis of the reaction mixtures or following separation of the product. Similar results were noted for (S,S_S)-**4a** with the same

View Article Online
DOI: 10.1039/C3OB42425A

bases combinations. These data indicated a kinetically controlled addition of dialkyl malonates to imine (S_S)-**1** leading preferentially to (R,S_S)-**3** or (S,S_S)-**4** depending on the organic base employed.



Scheme 2 Stability of diastereomers (R,S_S)-**3a** and (S,S_S)-**4a** under basic reaction conditions.

To explain the observed results one can reasonably suggest that diastereoselectivity of organic base-catalyzed Mannich reactions of dialkyl malonates **2** with imine (S_S)-**1** is determined by the competing of two transition states. Apparently, in the presence of DMAP addition of dialkyl malonates in their enol forms occurred via a proton-mediated six/four-membered bicyclic chelated transition state **TS 2** (Fig. 3) similar to transition state **TS 1** (Fig. 1) proposed for the Mannich reaction catalyzed by inorganic bases or *n*-BuLi affording predominantly (R,S_S) diastereomers. The opposite sense of stereoinduction observed for phosphazene-catalyzed addition of dialkyl malonates **2** was attributed to the formation of "naked" enolates due to the noncoordinating phosphazene counterion. Thus, the "naked" caracter of phosphazene enolates precludes the formation of the chelated transition state and addition was suggested to proceed *via* a non-chelated transition state **TS 3** (Fig. 3). In transition state **TS 3** enolates preferably added to the imine from the less hindered *Si*-face to afford (S,S_S) major diastereomer. Previously, steric arguments were already used to explain stereochemical preference for addition of organometallic reagents and ketone-derivative enolates to weakly coordinating imine (S_S)-**1**.

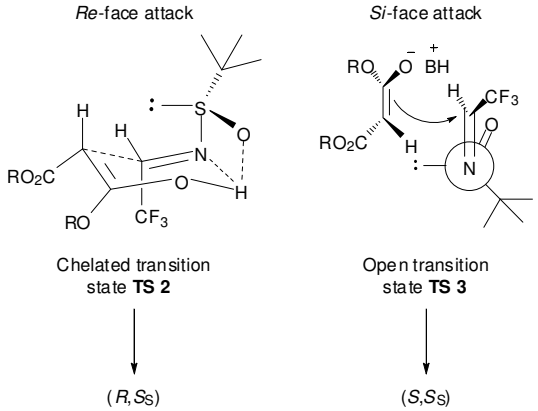


Fig. 3 Transition state models for the Mannich-type reaction between imine (*S*)-**1** and dialkyl malonates **2** catalyzed by organic bases.

Conclusions

Inorganic as well as organic bases promote the catalytic asymmetric Mannich addition of dialkyl malonates to (S_S)-*N*-(*tert*-butanesulfinyl)-3,3,3-trifluoroacetaldimine. These reactions can be applied to a wide range of dialkyl malonates and lead to highly stereoselective synthesis of either (R,S_S)- or (S,S_S)-β-aminomalonates in good yield. Especially high diastereoselectivity was attained using "naked"-enolates generated with phosphazene bases. The β-aminomalonates obtained were further applied in the synthesis of valuable 3-amino-4,4,4-trifluorobutanoic acids **5** in both (*R*)- and (*S*)-configurations. The described base-catalyzed asymmetric synthesis is the shortest and most direct approach to 3-amino-4,4,4-trifluorobutanoic acids.

Experimental

General methods

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 reactions were monitored by TLC on 0.25 mm Merck aluminum plates, silica gel 60, F_{254}. The TLC plates were visualized with UV light and 7% phosphomolybdic acid or $KMnO_4$ in water followed by brief heating. Column chromatography was carried out on a column packed with silica gel 60N spherical neutral size 63-210 μm. The ^{1}H-NMR (300 MHz), ^{13}C-NMR (75.5 MHz) and ^{19}F-NMR (282 MHz) spectra for solution in $CDCl_3$ or CD_3OD were recorded on a Varian Mercury 300. Chemical shifts (δ) are expressed in ppm and referenced to the internal TMS (^{1}H) and $CFCl_3$ (^{19}F). Mass spectra were recorded on a SHIMAZU LCMS-2010EV (ESI-MS). Optical rotations were measured on a HORIBA SEPA-300. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer.

(*R*)-Diethyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (3a). General Procedure.

(a) To a solution of diethyl malonate **2a** (0.30 mmol; 45.5 μl) in dry toluene (1.0 ml), *n*-BuLi (1.15 M in Hexane, 0.03 mmol; 26.1 μl) was added with stirring at –78 ºC. After 10 min at –78 ºC imine (S_S)-**1** (0.36 mmol; 72.4 mg) was added dropwise. Stirring was continued at –78 ºC for 15 min, then the reaction was quenched with saturated NH_4Cl (3.0 ml), followed by H_2O (10.0 ml) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with diethyl ether (3 × 10 ml). The combined organic layers were washed with brine (15 ml), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. After purification by chromatography on silica-gel (Hexane/EtOAc = 4/1), **3a** (106.5 mg, 98.2%) was obtained as a colorless oil; $[\alpha]_D^{25}$ +71.9 (*c* 1.48, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 9H), 1.29 (t, J = 6.9 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 3.81 (d, J = 3.0 Hz, 1H), 4.21 (q, J = 6.9 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 4.47 (dqd, J = 3.0, 6.6, 9.3 Hz, 1H), 5.59 (d, J = 9.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.6, 22.2, 49.5, 56.8, 58.6 (q, J = 31.6 Hz), 62.2, 63.1, 124.1 (q, J = 282.1 Hz), 165.1, 167.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ –75.6 (d, J = 6.6 Hz); IR (NaCl): 3328, 2984, 1747, 1469, 1263, 1182, 1130, 1092, 878, 461 cm^{-1}; MS (ESI): m/z = 384.1 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{13}H_{22}F_3NNaO_5S$: ($M+Na^+$): 384.1068, found: 384.1068.

(b) To a solution of diethyl malonate **2a** (0.3 mmol; 45.5 μl) and DMAP (0.03 mmol; 3.7 mg) in dry toluene (1.0 ml), imine (*S*)-**1** (0.30 mmol; 60.4 mg) was added with stirring at room temperature. After 48 h the solvent was removed under reduced

View Article Online
DOI: 10.1039/C3OB42425A

pressure. Purification by chromatography on silica-gel (Hexane/EtOAc = 4/1) gave **3a** (94.6 mg, 87.3%) as colorless oil; $[\alpha]_D^{25}$ +68.5 (*c* 1.13, $CHCl_3$).

(*R*)-Dimethyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (3b). Colorless oil; $[\alpha]_D^{25}$ +78.9 (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 9H), 3.83 (s, 3H), 3.86 (d, *J* = 3.9 Hz, 1H), 3.88 (s, 3H), 4.53–4.41 (m, 1H), 5.55 (d, *J* = 9.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.3, 49.4, 53.1, 53.8, 56.9, 58.8 (q, *J* = 31.6 Hz), 124.1 (q, *J* = 282.1 Hz), 165.6, 167.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ –75.7 (d, *J* = 7.9 Hz); IR (NaCl): 3479, 3298, 2960, 1738, 1438, 1360, 1264, 1174, 1130, 1090, 929, 472 cm^{-1}; MS (ESI): m/z = 356.6 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{11}H_{18}F_3NNaO_5S$: $(M+Na^+)$: 356.0755, found: 356.0770.

(*R*)-Diisopropyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (3c). Colorless oil; $[\alpha]_D^{25}$ +65.4 (*c* 0.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 9H), 1.29 (d, *J* = 6.0, 6H), 1.33 (d, *J* = 6.0 Hz, 6H), 3.75 (d, *J* = 2.7 Hz, 1H), 4.48 (dqd, *J* = 2.7, 7.8, 7.8 Hz, 1H), 5.15 (sept, *J* = 6.3 Hz, 1H), 5.16 (sept, *J* = 6.3 Hz, 1H), 5.62 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.3, 21.3, 21.4, 21.6, 22.3, 49.7, 56.8, 58.4 (q, *J* = 31.5 Hz), 70.1, 71.4, 124.3(q, *J* = 282.1 Hz), 164.7, 167.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ –75.6 (d, *J* = 7.1 Hz); IR (NaCl): 3289, 2984, 1730, 1469, 1375, 1263, 1181, 1101, 920, 489; MS (ESI): m/z = 412.6 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{15}H_{26}F_3NNaO_5S$: $(M+Na^+)$: 412.1381, found: 412.1394.

(*R*)-Di-*tert*-butyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (3d). Colorless oil; $[\alpha]_D^{25}$ +61.0 (*c* 2.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 9H), 1.50 (s, 9H), 1.53 (s, 9H), 3.64 (d, *J* = 2.4 Hz, 1H), 4.43 (dqd, *J* = 2.4, 7.9, 8.7 Hz, 1H), 5.56 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.4, 27.7, 27.8, 50.8, 56.9, 58.1 (q, *J* = 30.4 Hz), 83.4, 84.5, 124.5 (q, *J* = 282.7 Hz), 164.3, 166.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ –75.5 (d, *J* = 7.9 Hz); IR (NaCl): 3288, 2980, 1724, 1459, 1370, 1263, 1175, 1094, 845, 488 cm^{-1}; MS (ESI): m/z = 440.5 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{17}H_{30}F_3NNaO_5S$: $(M+Na^+)$: 440.1694, found: 440.1693.

(*R*)-Dibenzyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (3e). Colorless oil; $[\alpha]_D^{25}$ +49.1 (*c* 1.39, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (s, 9H), 3.93 (d, *J* = 2.7 Hz, 1H), 4.52 (dqd, *J* = 3.0, 7.8, 9.3 Hz, 1H), 5.14-5.27 (m, 4H), 5.54 (d, *J* = 9.0 Hz, 1H), 7.26-7.41 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.3, 50.0, 56.9, 58.8 (q, *J* = 31.6 Hz), 68.1, 68.9, 124.1 (q, *J* = 282.1 Hz), 128.5, 128.5, 128.5, 128.6, 128.6, 128.8, 134.3, 134.6, 164.9, 167.1; ^{19}F NMR (282 MHz, $CDCl_3$): δ –75.4 (d, *J* = 7.9 Hz); IR (NaCl): 3296, 2960, 1751, 1457, 1345, 1263, 1173, 1089, 698, 467; MS (ESI): m/z = 508.3 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{23}H_{26}F_3NNaO_5S$: $(M+Na^+)$: 508.1381, found: 508.1394.

(*R*)-Diethyl 2-fluoro-2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (3f). Colorless oil; $[\alpha]_D^{25}$ +79.4 (*c* 1.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (s, 9H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 4.15 (d, *J* = 10.2 Hz, 1H), 4.31-4.48 (m, 4H), 4.81-4.94 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.6, 13.7, 22.2, 57.6, 61.5 (dq, *J* = 20.5, 30.6 Hz), 63.7, 64.4, 93.3 (d, *J* = 208.5 Hz), 123.0 (q, *J* = 283.2 Hz), 162.3, 162.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ –71.3 (dd, *J* = 7.1, 9.9 Hz), –179.0 (dq, *J* = 9.9, 22.3 Hz); IR (NaCl): 3304, 2985, 1780, 1472, 1256, 1166, 1094, 1046, 882, 644; MS (ESI): m/z = 402.7 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{13}H_{21}F_4NNaO_5S$: $(M+Na^+)$: 402.0974, found: 402.0989.

(*R*)-Diethyl 2-methyl-2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (3g). Colorless oil; $[\alpha]_D^{25}$ +82.1 (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 6.9 Hz, 3H), 1.60 (s, 3H), 4.26-4.33 (m, 4H), 4.48 (dq, *J* = 9.6, 7.5 Hz, 1H), 5.06 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.6, 18.3, 18.4, 22.3, 55.9, 57.2, 62.5, 62.7 (q, *J* = 29.9 Hz), 62.8, 124.4 (q, *J* = 283.8 Hz), 168.8, 169.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ –69.0 (d, *J* = 6.8 Hz); IR (NaCl): 3312, 2984, 1742, 1470, 1245, 1180, 1097, 1018, 863, 417; MS (ESI): m/z = 398.4 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{14}H_{24}F_3NNaO_5S$: $(M+Na^+)$: 398.1225, found: 398.1249.

(*S*)-Diethyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (4a). General Procedure.

To a solution of diethyl malonate **2a** (0.30 mmol; 45.5 µl) in dry toluene (1.0 ml), P_2-Et (0.03 mmol; 10.0 µl) was added with stiring at –78 ºC. After 10 min at –78 ºC imine (S_S)-**1** (0.36 mmol; 72.4 mg) was added dropwise. Stirring was continued at –78 ºC for 24 h, then the reaction was quenched with saturated NH_4Cl (3.0 ml), followed by H_2O (10.0 ml) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with diethyl ether (3 × 10 ml). The combined organic layers were washed with brine (15 ml), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. After purification by chromatography on silica-gel (Hexane/EtOAc = 4/1), **4a** (91.1 mg, 84.0%) was obtained as a colorless oil; $[\alpha]_D^{25}$ +20.1 (*c* 1.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 3.81 (d, *J* = 3.6 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.47 (dqd, *J* = 3.6, 7.2, 10.8 Hz, 1H), 5.08 (d, *J* = 10.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.7, 13.7, 22.3, 50.2, 57.2, 58.3 (q, *J* = 32.1 Hz), 62.1, 62.6, 123.9 (q, *J* = 284.3 Hz), 165.5, 166.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ –74.0 (d, *J* = 7.2 Hz); IR (NaCl): 3294, 2984, 1733, 1471, 1263, 1181, 1130, 1092, 882, 493 cm^{-1}; MS (ESI): m/z = 384.5 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{13}H_{22}F_3NNaO_5S$: $(M+Na^+)$: 384.1068, found: 384.1052.

(*S*)-Dimethyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (4b). Colorless oil; $[\alpha]_D^{25}$ +18.5 (*c* 0.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 9H), 3.78 (s, 3H), 3.81 (s, 3H), 3.87 (d, *J* = 3.9 Hz, 1H), 4.48 (dqd, *J* = 3.9, 7.2, 10.8 Hz, 1H), 5.03 (d, *J* = 10.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.3, 50.0, 53.1, 53.3, 57.3, 58.4 (q, *J* = 31.5 Hz), 123.9 (q, *J* = 283.8 Hz), 166.0, 167.1; ^{19}F NMR (282 MHz, $CDCl_3$): δ –74.0 (d, *J* = 7.2 Hz); IR (NaCl): 3472, 3331, 2959, 1749, 1438, 1365, 1263, 1173, 1131, 1086, 424 cm^{-1}; MS (ESI): m/z = 356.5 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{11}H_{18}F_3NNaO_5S$: $(M+Na^+)$: 356.0755, found: 356.0757.

(*S*)-Diisopropyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (4c). Colorless oil; $[\alpha]_D^{25}$ +14.5 (*c* 0.97, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (s, 9H), 1.25-1.31 (m, 12H), 3.75 (d, *J* = 3.3 Hz, 1H), 4.46 (dqd, *J* = 3.3, 7.2, 10.8 Hz, 1H), 5.04 (sept, *J* = 6.3 Hz, 1H), 5.12 (sept, *J* = 6.3 Hz, 1H), 5.14 (d, *J* = 10.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.3, 21.3, 21.4, 21.4, 22.4, 50.5, 57.3, 58.2 (q, *J* = 32.1 Hz), 70.0, 70.7, 124.1 (q, *J* = 283.0 Hz), 165.1, 166.3; ^{19}F NMR (282 MHz,

View Article Online
DOI: 10.1039/C3OB42425A

$CDCl_3$): δ –74.0 (d, *J* = 7.2 Hz); IR (NaCl): 3324, 2983, 1742, 1469, 1375, 1264, 1183, 1130, 908, 496 cm^{-1}; MS (ESI): m/z = 412.6 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{15}H_{26}F_3NNaO_5S$: ($M+Na^+$): 412.1381, found: 412.1386.

(*S*)-Di-*tert*-butyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (4d). White solid, Mp = 93–94 ºC; $[\alpha]_D^{25}$ +7.5 (*c* 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 9H), 1.47 (s, 9H), 1.49 (s, 9H), 3.65 (d, *J* = 3.3 Hz, 1H), 4.36-4.41 (m, 1H), 5.13 (d, *J* = 10.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.6, 27.6, 27.7, 51.5, 57.3, 58.0 (q, *J* = 31.0 Hz), 83.2, 83.7, 124.3 (q, *J* = 284.4 Hz), 164.7, 166.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ –74.0 (d, *J* = 7.9 Hz); IR (KBr): 3324, 2987, 1733, 1458, 1368, 1265, 1151, 1082, 985, 619 cm^{-1}; MS (ESI): m/z = 440.6 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{17}H_{30}F_3NNaO_5S$: ($M+Na^+$): 440.1694, found: 440.1681.

(*S*)-Dibenzyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]malonate (4e). Colorless oil; $[\alpha]_D^{25}$ +3.3 (*c* 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (s, 9H), 3.93 (d, *J* = 3.3 Hz, 1H), 4.49 (dqd, *J* = 3.3, 7.2, 10.8 Hz, 1H), 4.97 (d, *J* = 10.8 Hz, 1H), 5.10-5.25 (m, 4H), 7.21-7.37 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.3, 50.5, 57.3, 58.4 (q, *J* = 32.1 Hz), 68.1, 68.3, 123.9 (q, *J* = 284.3 Hz), 128.3, 128.5, 128.6, 128.7, 128.7, 128.8, 134.2, 134.3, 165.3, 166.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ –73.9 (d, *J* = 7.2 Hz); IR (NaCl): 3337, 2960, 1746, 1457, 1344, 1263, 1220, 1170, 1129, 1088, 698, 465 cm^{-1}; MS (ESI): m/z = 508.4 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{23}H_{26}F_3NNaO_5S$: ($M+Na^+$): 508.1381, found: 508.1378.

(*S*)-Diethyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]-2-fluoromalonate (4f). Colorless oil; $[\alpha]_D^{25}$ +0.9 (*c* 1.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 9H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 3.99 (d, *J* = 11.1 Hz, 1H), 4.19-4.40 (m, 4H), 4.79-4.97 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.7, 13.7, 22.3, 57.4, 61.3 (dq, *J* = 19.9, 31.0 Hz), 63.5, 63.7, 93.7 (d, *J* = 211.3 Hz), 123.0 (q, *J* = 284.9 Hz), 162.5 (d, *J* = 24.9 Hz), 162.8 (d, *J* = 24.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ –69.7 (dd, *J* = 6.9, 8.7 Hz), –179.8 (dq, *J* = 8.7, 23.7 Hz); IR (NaCl): 3286, 2985, 1771, 1472, 1254, 1166, 1094, 1046, 881, 492 cm^{-1}; MS (ESI): m/z = 402.5 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{13}H_{21}F_4NNaO_5S$: ($M+Na^+$): 402.0974, found: 402.0988.

(*S*)-Diethyl 2-[(*S*)-1-(*tert*-butanesulfinamido)-2,2,2-trifluoroethyl]-2-methylmalonate (4g). Colorless oil; $[\alpha]_D^{25}$ +6.2 (*c* 0.57, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.56 (d, *J* = 1.5 Hz, 3H), 4.17-4.30 (m, 4H), 4.57-4.59 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.7, 13.7, 17.2, 22.5, 56.6, 57.1, 62.2, 62.3, 62.6 (q, *J* = 29.9 Hz), 124.3 (q, *J* = 285.5 Hz), 168.5, 168.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ –67.4 (d, *J* = 7.2 Hz); IR (NaCl): 3470, 3286, 2984, 1740, 1469, 1252, 1184, 1155, 1097, 734, 417 cm^{-1}; MS (ESI): m/z = 398.6 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{14}H_{24}F_3NNaO_5S$: ($M+Na^+$): 398.1225, found: 398.1217.

(*R*)-3-Amino-4,4,4-trifluorobutanoic acid (5). General Procedure.

A solution of **3a** (1.0 mmol; 361.4 mg) in 6N HCl (3.0 ml) was refluxed for 12 h. The reaction mixture was brought to room temperature and the aqueous layer was extracted with diethyl ether (3 × 5.0 ml). The aqueous layer was concentrated under reduced pressure to dryness. The resulting solid was treated with propylene oxide (3.0 ml) and stirred for 1 h at room temperature. Precipitate was filtered off and washed with hexane (2 × 3.0 ml) to provide (*R*)-**5** (149.4 mg, 95%) as a white solid: mp 174–175 ºC; $[\alpha]_D^{25}$ +24.4 (*c* 1.05, 6N HCl); ^1H NMR (300 MHz, CD_3OD): δ 2.49 (dd, *J* = 9.6, 16.5 Hz, 1H), 2.71 (dd, *J* = 3.6, 16.5 Hz, 1H), 3.81-3.91 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD): δ 35.2, 51.8 (q, *J* = 30.4 Hz), 127.0 (q, *J* = 280.5 Hz), 173.7; ^{19}F NMR (282 MHz, CD_3OD): δ –77.1 (d, *J* = 7.1 Hz); IR (KBr): 2894, 2724, 2132, 1620, 1526, 1381, 1133, 902, 655; MS (ESI): m/z = 158.0 $[M+H]^+$; HRMS (ESI) Calcd for $C_4H_7F_3NO_2$: ($M+H^+$): 158.0429, found: 158.0427.

(*S*)-3-Amino-4,4,4-trifluorobutanoic acid (5). This compound was synthesized according to procedure for (*R*)-**5** starting from **4a** on 2.50 mmol scale; yield 376.9 mg (96%); white solid; $[\alpha]_D^{25}$ –25.9 (*c* 1.02, 6N HCl).

Acknowledgements

We thank IKERBASQUE, Basque Foundation for Science, and the Basque Government (SAIOTEK S-PE12UN044) for generous financial support.

Notes and references

[a] *Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan. Fax: +81-52-735-5442; Tel: +81-52-735-7543; E-mail: nozshiba@nitech.ac.jp*
[b] *Research Laboratory, TOSOH F-TECH, Inc., 4988 Kaisei-cho, Shunan, Yamaguchi 746-0006, Japan.*
[c] *Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU, 20018 San Sebastián, Spain. Fax: +34 943-015270; Tel: +34 943-015177; E-mail: vadym.soloshonok@ehu.es*
[d] *IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain*
[e] *Institute of Bioorganic Chemistry & Petrochemistry, National Academy of Sciences of Ukraine, Murmanska 5, 02094 Kyiv, Ukraine.*

† Electronic Supplementary Information (ESI) available: Copies of NMR spectra for all compounds obtained. See DOI: 10.1039/b000000x/

1 (*a*) M. Liu and M. P. Sibi, *Tetrahedron*, 2002, **58**, 7991–8035; (*b*) M.-A. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600–3740; (*c*) F. Ferreira, C. Botuha, F. Chemla and A. Pérez-Luna, *Chem. Soc. Rev*., 2009, **38**, 1162–1186; (*d*) P. Zhou, B. C. Chen and F. A. Davis, *Tetrahedron*, 2004, **60**, 8003–8030; (*e*) D. Morton and R. A. Stockman, *Tetrahedron*, 2006, **62**, 8869–8905; (*f*) J. L. Aceña, A. Simón-Fuentes and S. Fustero, *Curr. Org. Chem*., 2010, **14**, 928–949; (*g*) K. Mikami, S. Fustero, M. Sánchez-Roselló, J. L. Aceña, V. A. Soloshonok and A. E. Sorochinsky, *Synthesis*, 2011, 3045–3079; (*h*) A. Viso, R. F. de la Pradilla, M. Tortosa, A. García and A. Flores, *Chem. Rev.*, 2011, **111**, PR1–PR42.
2 J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev*., 2011, **111**, 455–529.
3 V. A. Soloshonok, D. V. Avilov, V. P. Kukhar, L. Van Meervelt and N. Mischenko, *Tetrahedron Lett.*, 1997, **38**, 4671–4674.
4 P. Bravo, S. Fustero, M. Guidetti, A. Volonterio and M. Zanda, *J. Org. Chem*., 1999, **64**, 8731–8735.
5 F. Huguenot and T. Brigaud, *J. Org. Chem.*, 2006, **71**, 2159–2162.
6 F. Lazzaro, M. Crucianelli, F. De Angelis, M. Frigerio, L. Malpezzi, A. Volonterio and M. Zanda, *Tetrahedron: Asymmetry*, 2004, **15**, 889–893.
7 F. Grellepois, *J. Org. Chem.*, 2013, **78**, 1127−1137.
8 F. Zhang, Z.-J. Liu and J.-T. Liu, *Org. Biomol. Chem.*, 2011, **9**, 3625–3628.
9 (*a*) S. D. Kuduk, C. N. D. Marco, S. M. Pitzenberger and N. Tsou, *Tetrahedron Lett*., 2006, **47**, 2377–2381; (*b*) V. L. Truong, M. S. Ménard and I. Dion, *Org. Lett*., 2007, **9**, 683–685; (*c*) V. L. Truong and V. J. Y. Pfeiffer, *Tetrahedron Lett*., 2009, **50**, 1633–1635; (*d*) H. Zhang, Y. Li, W. Xu, W. Zheng, P. Zhou and Z. Sun, *Org. Biomol.*

View Article Online
DOI: 10.1039/C3OB42425A

Chem., 2011, **9**, 6502–6505; (*e*) G.-V. Röschenthaler, V. P. Kukhar, I. B. Kulik, M. Y. Belik, A. E. Sorochinsky, E. B. Rusanov and V. A. Soloshonok, *Tetrahedron Lett.*, 2012, **53**, 539–542; (*f*) K. V. Turcheniuk, K. O. Poliashko, V. P. Kukhar, A. B. Rozhenko, V. A. Soloshonok and A. E. Sorochinsky, *Chem. Commun.*, 2012, **48**, 11519–11521; (*g*) Y. Liu, J. Liu, Y. Huang and F.-Q. Ling, *Chem. Commun.*, 2013, **49**, 7492–7494.

10 H. Mimura, K. Kawada, T. Yamashita, T. Sakamoto and Y. Kikugawa, *J. Fluorine Chem.*, 2010, **131**, 477–486.

11 (*a*) H. Mei, Y. Xiong, J. Han and Y. Pan, *Org. Biomol. Chem.*, 2011, **9**, 1402–1406; (*b*) M. V. Shevchuk, V. P. Kukhar, G.-V. Röschenthaler, B. S. Bassil, K. Kawada, V. A. Soloshonok and A. E. Sorochinsky, *RSC Adv.*, 2013, **3**, 6479–6484.

12 N. Shibata, T. Nishimine, N. Shibata, E. Tokunaga, K. Kawada, T. Kagawa, A. E. Sorochinsky and V. A. Soloshonok, *Chem. Commun.*, 2012, **48**, 4124–4126.

13 (*a*) V. A. Soloshonok, A. G. Kirilenko, N. A. Fokina, I. P. Shishkina, S. V. Galushko, V. P. Kukhar, V. K. Svedas and E. V. Kozlova, *Tetrahedron: Asymmetry*, 1994, **5**, 1119–1126; (*b*) P. Davoli, A. Forni, C. Franciosi, I. Moretti and F. Prati, *Tetrahedron: Asymmetry*, 1999, **10**, 2361–2371; (*c*) Y. Ishida, N. Iwahashi, N. Nishizono and K. Saigo, *Tetrahedron Lett.*, 2009, **50**, 1889–1892.

14 (*a*) F. A. Davis, T. Reddy and R. E. Reddy, *J. Org. Chem.*, 1992, **57**, 6387–6389; (*b*) T. Fujisawa, Y. Kooriyama and M. Shimizu, *Tetrahedron Lett.*, 1996, **37**, 3881–3884; (*c*) T. P. Tang and J. A. Ellman, *J. Org. Chem.*, 2002, **67**, 7819–7832.

15 (*a*) T. Maetzke and D. Seebach, *Organometallics*, 1990, **9**, 3032–3037; (*b*) T. Maetzke, C. P. Hidber and D. Seebach, *J. Am. Chem. Soc.*, 1990, **112**, 8248–8250.

16 (*a*) R. Schwesinger, C. Hasenfratz, H. Schlemper, L. Walz, E. M. Peters, K. Peters and H. G. von Schnering, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1361–1363; (*b*) R. Schwesinger and H. Schlemper, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 1167–1169.

17 (*a*) Y. Kondo, in *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; T. Ishikawa, Ed.; John Wiley & Sons, Ltd: 2009; pp 145–185; (*b*) A. Solladié-Cavallo, T. Liptaj, M. Schmitt and A. Solgadi, *Tetrahedron Lett.*, 2002, **43**, 415–418; (*c*) J.-S. Fruchart, G. Lippens, C. Kuhn, H. Gras-Masse and O. Melnyk, *J. Org. Chem.*, 2002, **67**, 526–532; (*d*) J.-S. Fruchart, H. Gras-Masse, O. Melnyk, D. T. Fox and R. G. Bergman, *Tetrahedron Lett.*, 2003, **44**, 2243; (*e*) K. J. Kolonko and H. J. Reich, *J. Am. Chem. Soc.*, 2008, **130**, 9668–9669.