VIP Asymmetric Synthesis

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Desymmetrization-like Catalytic Enantioselective Fluorination of Malonates and Its Application to Pharmaceutically Attractive Molecules**

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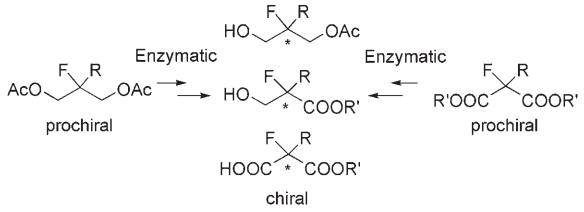
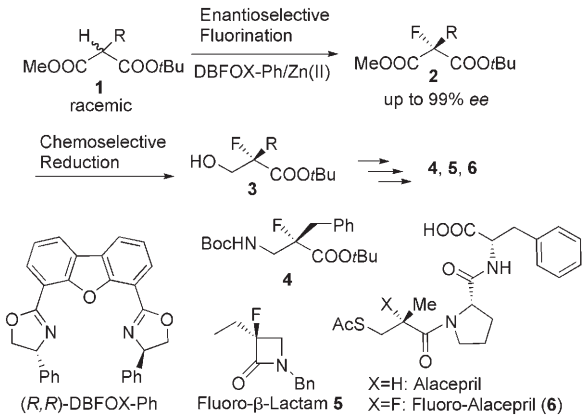
Optically active organofluorine compounds are attractive in both modern pharmaceutical chemistry and materials science,[1] especially the simple chiral vicinal fluorohydrins that are employed as important building blocks in the synthesis of polyfunctional bioactive molecules.[2] Fluorinated malonates with a fluorine atom at a quaternary carbon center are a class of versatile and important monofluorinated chiral synthons[2] utilized in the synthesis of liquid crystals,[3] antitumor agents,[4] enzyme inhibitors,[5] antiviral agents,[6a] antibiotics,[6b] and anti-Alzheimer agents.[6c] A variety of enantioselective syntheses of fluorinated compounds have been developed for the elaboration of optically active fluorinated malonates, as well as their synthetic equivalents such as vicinal fluorohydrins and fluorinated half hydroxy esters.[2] These approaches include the enzymatic desymmetrization of substituted 2-fluoromalonic diesters, 2-fluoropropane-1,3-diols, and 2-fluoro-1,3-diacetoxypropane derivatives, which lead in each case to similar 2-fluorinated synthons (Scheme 1).[2,7] These microbial transformations are more practical than the chemical approaches[8] for obtaining the target compounds; unfortunately, the resulting enantioselectivity is highly dependent on the substrate and thus significantly limits the applicability of this process.



Scheme 1. Enzymatic desymmetrization approach for the synthesis of simple fluorinated synthons.

We have recently reported a highly enantioselective fluorination[9] of β-keto esters and oxindoles catalyzed by Box–Ph/$Cu(OTf)_2$ or DBFOX–Ph/$Ni(ClO_4)_2$ (Box = bisoxazoline, Tf = triflate, DBFOX = 4,6-dibenzofurandiyl-2,2′-bisoxazoline.[9a,b] In response to the limitations associated with the use of microbial desymmetrization for the preparation of chiral fluorinated malonates and hydroxy esters, we have now extended our protocol to the desymmetrization-like enantioselective fluorination of malonates **1** and herein show that a DBFOX–Ph/$Zn(OAc)_2$ complex is an effective catalyst to give the optically active 2-fluorinated malonates **2** with very high enantioselectivity (up to 99% *ee*). The 2-fluoromalonates **2** can be selectively converted into 2-fluorinated hydroxy esters **3**. The synthetic utility of the method was demonstrated by the syntheses of pharmaceutically attractive compounds, namely, chiral fluorinated α-benzyl-β-alanine **4**, fluorinated β-lactam **5,** and fluoro-alacepril (**6**); Scheme 2. The synthesis of an HIV-1 protease inhibitor was also achieved through the chemoselective ester–amide exchange reaction of chiral malonates **2**.

Diastereoselective fluorination of malonates has been reported by Fukumoto and co-workers.[8b–d] L-Menthylphenyl esters of malonates were fluorinated with fluoropyridinium triflate in high yield with moderate diastereoselectivities by



Scheme 2. Desymmetrization-like approach for the synthesis of **2** and its application to pharmaceutically attractive molecules.

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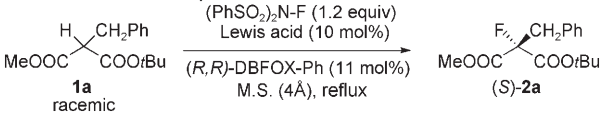
using lithium hexamethyldisilazane (LiHMDS). Kaneko and co-workers also reported that fluorination of chiral 5-substituted 1,3-oxazine-4,6-dione derivatives proceeded diastereoselectively to give the 5-fluorooxazinediones, which were readily transformed to optically pure fluoromalonic acids.[8e] Sodeoka and co-workers reported the enantioselctive fluorination of lactones and lactams, which were catalyzed by chiral palladium(II)–bisphosphine complexes.[10] However, there are no reports of the enantioselective fluorination of malonates.[9–12] In contrast to β-keto esters, malonates are nearly symmetrical and less acidic. Therefore, improvement of the reactivity and discrimination of the two ester moieties are necessary to achieve high enantiocontrol.

We first attempted the fluorination of racemic 2-benzyl-*tert*-butyl methyl malonate (**1a**) with *N*-fluorobenzenesulfonimide (NFSI) under the reported conditions for enantioselective fluorination of β-keto esters, namely, in the presence of $Ni(ClO_4)_2{\cdot}6H_2O$ in CH_2Cl_2 (Table 1).[9a] The

Table 1: Desymmetrization-like catalytic enantioselective fluorination of racemic malonate **1a**: optimization of reaction conditions.[a]



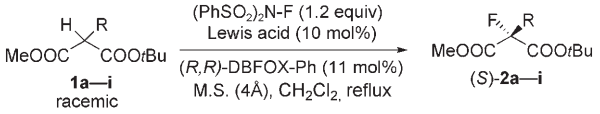
Entry	Lewis acid	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	48	97	89
2	$Ni(OAc)_2{\cdot}4H_2O$	CH_2Cl_2	48	90	86
3	$Mg(ClO_4)_2$	CH_2Cl_2	48	62	7
4	$Mg(OTf)_2$	CH_2Cl_2	48	59	0
5	$Zn(SbF_6)_2$	CH_2Cl_2	36	59	69
6	$Zn(OTf)_2$	CH_2Cl_2	36	94	87
7	$Zn(OAc)_2$	CH_2Cl_2	15	90	98
8	$Zn(OAc)_2$	toluene	24	71	96
9	$Zn(OAc)_2$	Et_2O	62	52	68
10	$Zn(OAc)_2$	EtOH	62	49	86
11[d]	$Zn(OAc)_2$	CH_2Cl_2	90	47	59

[a] The reaction of **1a** with NFSI was carried out in the presence of Lewis acid (10 mol%), (*R*,*R*)-DBFOX–Ph (11 mol%), and M.S. (4 Å) in solvent under reflux. The absolute stereochemistry of **2a** was assigned to be *S* by derivatization, see Scheme 7 for details. [b] Yields of isolated products. [c] Determined by HPLC on a chiral stationary phase. [d] The reaction was carried out in the absence of MS (4 Å). M.S. = molecular sieves.

(S)-2-fluoro-2-benzyl-*tert*-butyl methyl malonate (**2a**) was obtained in excellent yield and high enantioselectivity (Table 1, entry 1; 97% yield and 89% *ee*). The conditions described for the enantioselective fluorination of oxindoles ($Ni(OAc)_2{\cdot}4H_2O$ in CH_2Cl_2[9a]) also gave good results (Table 1, entry 2; 90% yield and 86% *ee*). These enantioselectivities are acceptable, but not excellent when compared with the enantioselective fluorination of β-keto esters and oxindoles. Optimization experiments for both the Lewis acid and the solvent were carried out to improve the enantioselectivity of the transformation (Table 1, entries 3–7). $Zn(OAc)_2$ was found to be very effective for the desymmetrization-like enantioselective fluorination of malonates. Thus, the use of NFSI, DBFOX–Ph (11 mol%), and $Zn(OAc)_2$ (10 mol%) in CH_2Cl_2 at reflux became the standard conditions for our desymmetrization-like enantioselective fluorination reaction of malonates (Table 1, entry 7; 90% yield and 98% *ee*). Dichloromethane was determined to be a suitable solvent after screening the reaction with several different solvents (Table 1, entries 8–10), and molecular sieves (4 Å) were indispensable for achieving high enantiocontrol (Table 1, entry 11).

With the conditions now optimized, the scope of the desymmetrization-like fluorination reaction was investigated in terms of the range of substrates that could be tolerated (Table 2). The $Zn(OAc)_2$/DBFOX–Ph combination is

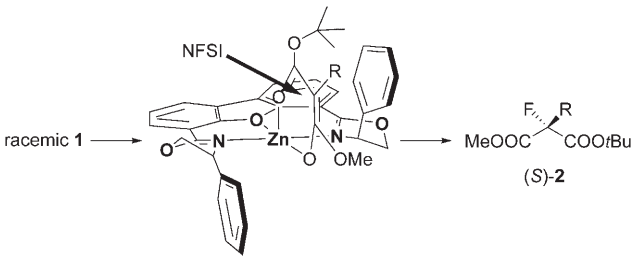
Table 2: Desymmetrization-like catalytic enantioselective fluorination of racemic malonates **1a–i**.[a]



Entry	**1**	R	*t* [h][b]	Yield [%][b,c]	*ee* [%][b,d]
1	**1a**	CH_2Ph	15 (48)	90 (97)	98 (89)
2	**1b**	Et	24 (32)	94 (76)	96 (94)
3	**1c**	Me	24 (36)	90 (81)	99 (95)
4	**1d**	Bu	36 (62)	93 (69)	99 (94)
5	**1e**	Ph	24 (48)	95 (96)	99 (93)
6	**1f**	OPh	15 (48)	85 (52)	98 (91)
7	**1g**	SPh	24	81	90
8	**1h**	NPht	18	91	93
9	**1i**	NPht(4-Br)	24	93	97

[a] The reaction of **1** with NFSI was carried out in the presence of $Zn(OAc)_2$ (10 mol%), (*R*,*R*)-DBFOX–Ph (11 mol%), and M.S. (4 Å) in CH_2Cl_2 under reflux unless otherwise indicated. The absolute configuration of **2c** was determined by comparing the optical rotation of the alcohol derivative of **2c** with that of the known (*S*)-ethyl 2-fluoro-3-hydroxy-2-methylpropanoate, and the stereochemistry of the other malonates **2** were tentatively assumed to be the same by analogy (see, the Supporting Information for details). [b] The data given in parentheses are the results using $Ni(ClO_4)_2{\cdot}6H_2O$ instead of $Zn(OAc)_2$ for the reaction. [c] Yields of isolated products. [d] Determined by HPLC on a chiral stationary phase or by GC analysis. NPht = *N*-phthaloyl, NPht(4-Br) = *N*-4-bromophtaloyl.

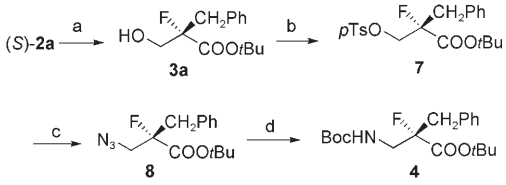
extremely general for the enantioselective fluorination of a broad range of malonates **1a–i** and is compatible with a wide range of functional groups such as alkyl, aryl, oxygen, sulfur, and amino substitutions. The desired products (*S*)-**2a–i** were obtained in high yields, with excellent enantioselectivities of up to 99% *ee* (Table 2, entries 1–9). Significantly, the best conditions reported for the fluorination of β-keto esters, namely, $Ni(ClO_4)_2$/DBFOX–Ph,[9a] produced fluorinated malonates with lower enantioselectivities of about 90% *ee* (Table 2, entries 1–6; the results are given in parentheses). To our knowledge, this is the first example of the enantioselective fluorination[9–12] of malonates **1** to provide chiral 2-fluorinated malonates **2** and this sequence surely serves as a potential non-enzymatic strategy for the desymmetrization of malonates. The stereochemistry of the resulting fluoromalonates **2**, can easily be explained by the directional approach of the fluorinating agent (NSFI) from the less hindered *Si* face of the complex formed between the substrates, a Zn^{II} ion, and DBFOX–Ph (Scheme 3). This was explained previously for



Scheme 3. Transition–state structure for the DBFOX–Ph/Zn^{II} catalyzed enantioselective fluorination of malonates **1** to (*S*)-**2**.

the fluorination reaction of β-keto esters, which was catalyzed by Ni^{II}/DBFOX–Ph.[9a]

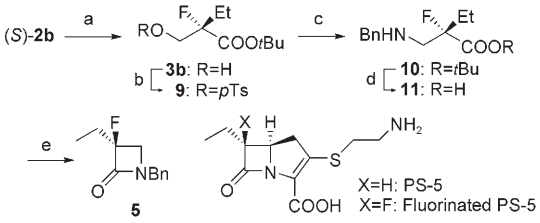
In the described transformation, the observed chemical yields and enantioselectivities are excellent and the resulting chiral 2-fluorinated malonates **2** are potentially versatile starting materials for the synthesis of biologically important compounds. In this context, a synthetic application of these malonates for producing pharmaceutically attractive molecules was investigated. The first of our targets was the transformation of **2a** to fluorinated α-benzyl-β-alanine **4** (Scheme 4). Chemoselective reduction of (*S*)-**2a** into **3a** was



Scheme 4. Reagents and conditions: a) $LiAl(OtBu)_3H$ (5.0 equiv), THF, −78 °C to RT, 1 h, 89%; b) *p*-TsCl (1.2 equiv), pyridine, $CHCl_3$, 0 °C to RT, 12 h, 90%; c) NaN_3 (3.0 equiv), DMF, 80 °C, 24 h, 95%; d) Pd/C, H_2, AcOEt, Boc_2O, (1.5 equiv), RT, 2 h, 95%. Ts = 4-toluenesulfonyl, DMF = *N*,*N*-dimethylformamide, Boc = *tert*-butoxycarbonyl.

examined by using diisobutylaluminum hydride, $LiAlH_4$, or $LiAl(OtBu)_3H$.[13] After optimization of the conditions (see Table S1 in the Supporting Information), the best result was achieved when using five equivalents of $LiAl(OtBu)_3H$ in THF at −78 °C, then warming to room temperature giving **3a** in 89% yield. The OH moiety of **3a** was then protected using *p*-TsCl and pyridine in $CHCl_3$ to give **7** in 90% yield. Nucleophilic azidation of **7** with NaN_3 (95% yield) and subsequent hydrogenolysis under H_2 atmosphere in the presence of Pd/C and Boc_2O in AcOEt afforded the fluoro-α-benzyl-β-alanine target **4** in 95% yield (Scheme 4).

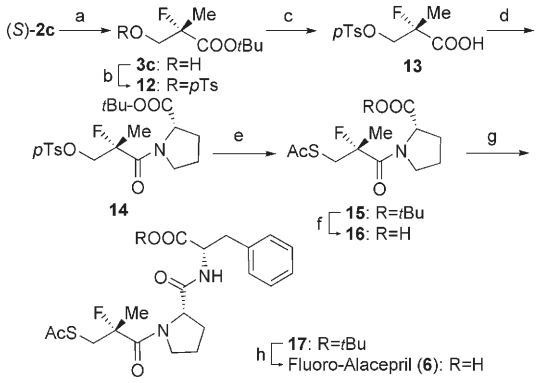
The utility of 2-fluorinated malonates was next demonstrated by synthesizing a 3-fluorinated β-lactam[5a,b,14] (Scheme 5). Chemoselective reduction of the malonate (*S*)-**2b** with the $LiAl(OtBu)_3H$ procedure mentioned above gave **3b** (80% yield). Subsequent tosylation afforded **9** (85% yield), which underwent nucleophilic amination using benzylamine to give the β-amino acid derivative **10** (72% yield). Removal of the *tert*-butyl ester from **10** with TFA followed by intramolecular cyclization by the Mukaiyama procedure[15] afforded the fluorinated β-lactam **5** in 70% yield. This lactam



Scheme 5. Reagents and conditions: a) $LiAl(OtBu)_3H$ (5.0 equiv), THF, −78 °C to RT, 1 h, 80%; b) *p*-TsCl (1.2 equiv), pyridine, $CHCl_3$, 0 °C to RT, 12 h, 85%; c) $BnNH_2$ (10.0 equiv), $NaHCO_3$ (3.0 equiv), toluene, 80 °C, 72 h, 72%; d) TFA (5.0 equiv), CH_2Cl_2, 0 °C to RT, 3 h, 87%; e) 2-chloro-1-methylpyridinium iodide (1.1 equiv), triethylamine (3.0 equiv), CH_2Cl_2, RT, 6 h, 70%. Bn = benzyl, TFA = trifluoroacetic acid.

could be a useful synthon for the synthesis of a fluorinated analogue of the antibiotic PS-5.[16]

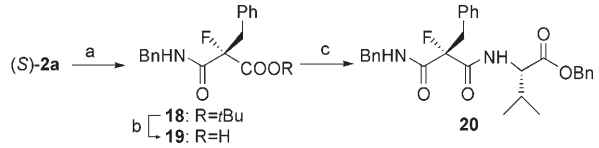
The synthesis of fluoro-alacepril was then examined. Alacepril is an orally active antihypertensive angiotensin-converting enzyme (ACE) inhibitor, which was synthesized in 1978[17] and launched in Japan in 1988, along with captopril. Structurally, alacepril is characterized as a tripeptide-like compound consisting of L-phenylalanine, L-proline, and 3-mercapto-(2*S*)-methylpropionic acid. Captopril and alacepril both possess a 2-methyl unit with *S* configuration, which is indispensable for their ACE inhibitor activities.[18] We were therefore interested in the previously unknown fluoro-alacepril as a non-epimerized isostere of alacepril.[19] The total synthesis of (*S*)-fluoro-Alacepril was accomplished in eight steps starting from chiral malonate (*S*)-**2c**, based on the strategy outlined in Scheme 6. Optically active 2-fluoromalonate (*S*)-**2c** was treated with $LiAl(OtBu)_3H$ in THF (85% yield) followed by tosylation using *p*-TsCl and pyridine in $CHCl_3$ to give **12** (81% yield). The L-proline-containing



Scheme 6. Reagents and conditions: a) $LiAl(OtBu)_3H$ (5.0 equiv), THF, −78 °C to RT, 1 h, 85%; b) *p*-TsCl (1.2 equiv), pyridine, $CHCl_3$, 0 °C to RT, 12 h, 81%; c) TFA (5.0 equiv), CH_2Cl_2, 0 °C to RT, 3 h, 90%; d) L-proline *tert*-butyl ester (1.05 equiv), EDCI (1.2 equiv), HOBt (1.2 equiv), diisopropylethylamine (2.0 equiv), CH_2Cl_2, 0 °C to RT, 24 h, 67%; e) NaH (3.0 equiv), CH_3COSH (3.0 equiv), DMF, 0 °C to 80 °C, 4 h, 77%; f) TFA (5.0 equiv), CH_2Cl_2, 0 °C to RT, 3 h, 95%; g) L-Phe-O*t*Bu (1.0 equiv), EDCI (1.3 equiv), HOBt (1.3 equiv), triethylamine (2.5 equiv), CH_2Cl_2, 0 °C to RT, 5 h, 82%; h) TFA (6.0 equiv), CH_2Cl_2, RT, 16 h, 73%. EDCI = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole.

compound **14** was derived from **12** after removal of the *tert*-butyl ester with TFA, followed by coupling to L-Pro-O*t*Bu under standard peptide coupling conditions. Nucleophilic substitution of CH_3COSNa to give **15** followed by TFA cleavage of the resulting *tert*-butyl ester gave **16**. Subsequent coupling to L-phenylalanine *tert*-butyl ester and TFA treatment afforded fluoro-alacepril (**6**) in good overall yield.

Finally, the optically active fluorinated retroamide isostere **20** was synthesized. Compound **20** is an HIV-1 protease inhibitor that was prepared by Welch and co-workers from enantiomerically pure 3-fluoro-2-azetidinones by a ring-opening reaction.[5a,b,20] However, the synthesis requires multiple-step transformations including diastereoselective fluorination of 2-azetidinones. The fluorinated malonate (*S*)-**2a** can be transformed into fluorinated retroamide isostere **20** in only three steps via unsymmetrical ester-amide **18** (Scheme 7). Chemoselective ester–amide exchange



Scheme 7. Reagents and conditions: a) $Zr(OtBu)_4$ (0.5 equiv), HOAt (0.5 equiv), $BnNH_2$ (1.0 equiv), toluene, 60 °C, 24 h, 55 %; b) TFA (10.0 equiv), CH_2Cl_2, RT, 3 h, 74 %; c) L-Val-OBn (1.0 equiv), HOBt (1.0 equiv), DCC (1.0 equiv), *N*-methylmorpholine (1.0 equiv), THF, 0 °C to RT, 24 h, 77 %. DCC = 1,3-dicyclohexylcarbodiimide, HOAt = 1-hydroxy-azobenzotriazole.

reaction[21] of (*S*)-**2a** successfully proceeded in the presence of $Zr(OtBu)_4$ to give **18** in good yield. The chemoselectivity observed is thought to result from the bulkier *tert*-butyl group compared to the methyl ester moiety. Subsequent treatment of **18** with TFA gave the acid **19**. Finally, the coupling of **19** with L-Val-OBn proceeded smoothly when effected by DCC with HOBt treatment to afford the target HIV-1 protease inhibitor **20** (77 % yield).

In conclusion, we have described the first highly enantioselective fluorination of malonates catalyzed by DBFOX–Ph and $Zn(OAc)_2$. This desymmetrization-like approach for the preparation of fluorinated chiral building blocks showed higher enantioselectivity and generality than the corresponding enzymatic approaches.[7] The 2-fluoromalonates **2** can be easily converted into the corresponding chiral fluorinated hydroxy esters **3** by chemoselective reduction with $LiAl(OtBu)_3H$. The 2-fluoromalonates **2** can also be converted into the unsymmetrical ester-amides by an chemoselective ester–amide exchange reaction. All the derivatives are valuable starting materials for the preparation of pharmaceutically attractive molecules,[2–5] and we have demonstrated the preparation of fluorinated β-amino acids and β-lactams. The total syntheses of the ACE inhibitor fluoro-alacepril and the HIV-1 protease inhibitor fluorinated retroamide isostere were also accomplished.

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