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Diastereoselective Synthesis of Aliphatic α,α-Difluoro-β^3-Amino Esters via a Sonocatalyzed Reformatsky Reaction

Taryn L. March,[†] Martin R. Johnston,[†] and Peter J. Duggan*[,‡]

School of Chemical and Physical Sciences, Flinders University, SA 5042, Australia, and CSIRO Materials Science and Engineering, Bag 10, Clayton South, Victoria 3169, Australia

peter.duggan@csiro.au

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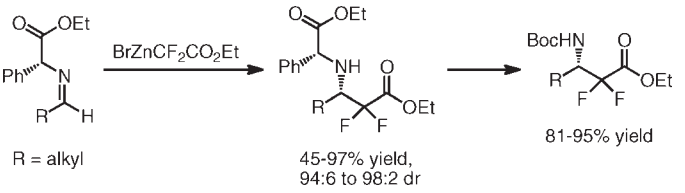
ABSTRACT



(*R*)-2-Phenylglycine ethyl ester was found to be a cheap and effective auxiliary for the preparation of aliphatic α,α-difluoro-β^3-amino esters via a Reformatsky reaction performed under sonication conditions. The products were obtained in good to high yield and ≥96:4 dr, thus providing a new stereoselective route to this under-represented class of compounds. A facile one-pot removal of the phenylglycine moiety and concomitant Boc protection subsequently afforded the corresponding Boc-protected β^3-amino esters in excellent yield.

The ability to effect novel changes in the bioactivity and physicochemical properties of a compound through the inclusion of fluorine is well-known.[1] α-Fluorinated β^3-amino acids in particular continue to attract interest for their use as tools in peptide conformational studies[2] and as enzyme inhibitors,[3] while they are also direct precursors to the biologically important β-lactams.[4]

We recently reported an enantioselective tandem conjugate addition−fluorination approach to α-fluoro-β^3-amino esters which can be extended to the synthesis of α,α-difluoro-β^3-amino esters;[5] however, the most efficient and versatile routes to α,α-difluoro-β^3-amino acids typically employ a building block approach.[6] The introduction of a CF_2 synthon with Reformatsky reactions involving imines[4f,g,7] or imine-type substrates[8] together with ethyl bromodifluoroacetate is among the most popular. The majority of these literature reports focus primarily on the use of imines derived from aromatic aldehydes, with high yields and excellent dr values generally obtained. Aliphatic imines, however, are notably more difficult to work with

[†] Flinders University.
[‡] CSIRO Materials Science and Engineering.

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because of their instability and hence receive much less attention; the limited examples that do appear in the literature often suffer from poor to moderate yields and unsatisfactory dr values. The lack of progress in this area is surprising considering that the side chains of most naturally occurring amino acids are aliphatic in nature. The highly stereoselective but moderate yielding Honda–Reformatsky reaction[4c,d,9] is among the most promising; however, it requires a rhodium catalyst and diethyl zinc. We desired a more general method for the preparation of aliphatic α,α-difluoro-β^3-amino acids that was applicable to a wide variety of substrates, uses only simple and readily available reagents, and is amenable to large-scale synthesis. Our efforts toward extending the Reformatsky reaction to the successful preparation of these compounds are reported herein.

Application of the Reformatsky methodology to the synthesis of α,α-difluoro-β^3-amino acids presents two immediate problems, namely, the relative unreactivity of imines (cf. carbonyl compounds) and the instability of the Reformatsky reagent $BrZnCF_2CO_2Et$, which is typically generated in refluxing THF yet rapidly decomposes under these conditions.[10] The application of ultrasound, which has long been used as a tool in organic synthesis[11]—and indeed the Reformatsky reaction itself[12]—offered a solution to both problems: first, sonication of the reaction mixture can greatly enhance the reactivity of poor electrophiles in the Reformatsky reaction when compared to standard reflux conditions,[13] and second, the $BrZnCF_2CO_2Et$ species is relatively stable when generated under ultrasonic conditions, extending its half-life.[4b] While ultrasound has been successfully used in Reformatsky reactions involving either imines or ethyl bromodifluoroacetate alone, its use for reactions employing both reagents together for the preparation of α,α-difluoro-β^3-amino esters is previously unreported.

Amines derived from the chiral pool represent the most common chiral auxiliaries employed in this type of Reformatsky reaction, and amino acid derivatives capable of forming highly chelated transition states, such as those based on (*R*)-phenylglycinol, generally give the highest degree of asymmetric induction.[4f,6,8,14] Given that enantiopure sources of phenylglycinol can be prohibitively expensive on a large scale, the cheaper (*R*)-phenylglycine methyl ester was chosen as an alternative. The susceptibility of phenylglycine derivatives to epimerize at the α-carbon often precludes their use as chiral auxiliaries; however, they previously have been reported to show extremely high stereocontrol in organometallic enolate condensations[15] and Barbier-type allylations.[16]

Using isovaleraldehyde as a model substrate, (*E*)-phenylglycine imine **3**[17] was prepared in quantitative yield using anhydrous Na_2SO_4 as a desiccant. The mixture was filtered and the crude imine subsequently added to a THF solution of $BrZnCF_2CO_2Et$ (**4**), which was preprepared via the addition of ethyl bromodifluoroacetate to a sonicating suspension of zinc and catalytic I_2. After 15 min of sonication followed by acidic workup, ^1H NMR analysis of the crude reaction mixture revealed the desired β-amino ester was present as a 96:4 mixture of diastereomers (Table 1, entry 1). The major isomer, tentatively assigned the (*S*) configuration at C3 in line with analogous phenylglycine systems,[4f,6,8,13a,14] was subsequently isolated in 53% yield after chromatography. Importantly, no cyclized β-lactam product, which is commonly produced during the Reformatsky reaction, was evident in the spectrum of the crude material. Increasing the reaction time to 30 min and decreasing the amount of ethyl bromodifluoroacetate from 2 to 1.5 equiv improved the yield to 64%. The dr was unchanged after this prolonged reaction period, attesting to the configurational stability of the phenylglycine moiety under these relatively mild reaction conditions. Reactant concentration appeared to have a negligible effect on the reaction outcome.

As shown in Table 1, performing the experiment with other typical Reformatsky solvents such as diethyl ether and toluene resulted in inferior yields and diastereomeric ratios. Surprisingly, the traditionally poorer solvents DCM and acetonitrile gave results almost comparable to THF, while the use of DMSO and DMF resulted largely in decomposition. Under the same reaction conditions, the use of the more common (*R*)-phenylglycinol auxiliary

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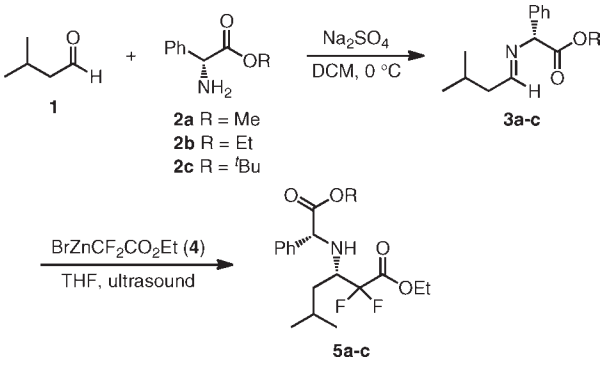
Table 1. Reaction of Phenylglycine-Derived Imines with Reformatsky Reagent **4** in Various Solvents[a]



entry	R	solvent	product	yield (%)[b]	dr[c]
1	Me	THF[d]	**5a**	53	96:4
2	Me	THF	**5a**	64	96:4
3	Me	diethyl ether	**5a**	45	80:20
4	Me	1,4-dioxane	**5a**	19	95:5
5	Me	toluene	**5a**	21	75:25
6	Me	DCM	**5a**	52	86:14
7	Me	MeCN	**5a**	47	85:15
8	Me	DMSO	**5a**	trace	
9	Me	DMF	**5a**	25	59:41
10	Et	THF	**5b**	72	96:4
11	^{t}Bu	THF	**5c**	48	86:14

[a] Reaction stoichiometry: aldehyde (1.0 mmol), amine (1.0 mmol), Zn 3.0 mmol), I_2 (0.2 mmol), $BrCF_2CO_2Et$ (1.5 mmol). [b] Isolated yield from **2**. [c] Determined from crude reaction mixture by integration of the ^{1}H NMR esonances due to α-proton of phenylglycine moiety. [d] 2 equiv of $BrCF_2CO_2Et$ used, sonicated for 15 min.

furnished the corresponding β-amino ester in only 9% yield. This was largely a result of poor imine formation, even with prolonged reaction times.

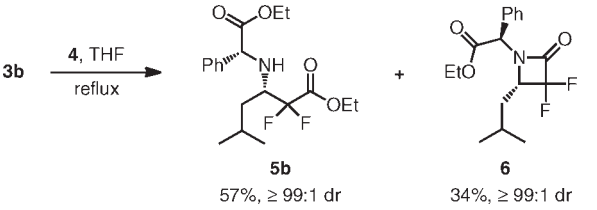
During these experiments, the transesterified product (**5b**) was continually evident in small quantities (10−15%) in the ^{1}H NMR spectra of the crude material. To eliminate this problem, both the *tert*-butyl and ethyl ester of (*R*)-phenylglycine were used in the Reformatsky reaction (entries 10 and 11). While the *tert*-butyl ester gave a disappointing 48% yield and 86:14 dr, use of the ethyl ester gave a yield of 72% and excellent dr of 96:4.

With the ethyl ester of (*R*)-phenylglycine providing superior results, a one-pot reaction that did not involve preformation of the Reformatsky reagent was investigated. This furnished the desired β-amino ester in a similar 71% yield, although the dr dropped to 82:18. One possible explanation for this drop may involve isomerization of the imine double bond by ultrasound before attack of the organozinc species; addition to the (*Z*)-imine would result in the (3*R*) isomer.

It was also of interest to determine if the incorporation of Lewis acids into the reaction mixture would enhance the dr for the addition of **4** to imine **3b**; however, the inclusion of 1 equiv of $ZnBr_2$, $BF_3 \cdot OEt_2$, or $TiCl_4$ to the reaction mixture led to dr values of 71:29, 60:40, and 57:43, respectively. This is likely caused by a disruption of the highly chelated transition state postulated to be responsible for the high stereoselectivity seen in this type of Reformatsky reaction;[18] an open transition state would result in indiscriminate attack by the Reformatsky reagent, affording a mixture of isomers.

Lastly, as a comparison to traditional Reformatsky conditions the imine **3b** was added to **4** in refluxing THF (Scheme 1). This resulted in an undesirable 63:37 mixture of β-amino ester (**5b**) and β-lactam (**6**), which were isolated in 57 and 34% yields, respectively.

Scheme 1. Preparation of **5b** under "Classical" Reflux Conditions



Application of the sonocatalyzed Reformatsky reaction to C-alkyl imines derived from a range of aldehydes generally produced pleasing results (Table 2), with a high degree of diastereoselectivity obtained for each β-amino ester. Yields were typically between 66 and 76% with imines bearing simple linear or branched alkyl chains, while β-amino ester **7e** was obtained in 97% yield from 4-pentenal. The sterically hindered cyclohexyl derivative **7d** was obtained in a lower 46% yield, although almost exclusively as a single isomer. For imines derived from heteroatom-functionalized aldehydes (entries 7−9), reaction conditions were modified slightly to counter the increased sensitivity of these substrates. Phthalimide **7f** was obtained in a synthetically useful 45% yield with the use of a 2:1 diethyl ether/THF mixed solvent system, which had no negative impact on the diastereoselectivity of the reaction. The TBSO group was found to be relatively unstable under sonicating conditions; however, by adding the imine to **4** (preprepared using sonication) and simply stirring the mixture at rt, **7g** and **7h** could be obtained in 53 and 60% yields, respectively. It was also found that scaling the preparation of **7g** and **7h** up to gram quantities had minimal impact on yield or dr.

Removal of the phenylglycine moiety with concomitant Boc protection was achieved in excellent yield under standard hydrogenolysis conditions using Pearlman's catalyst (Table 3). With crystalline samples of the Reformatsky adducts (**5a**−**c**, **7a**−**h**) unavailable for X-ray crystallographic analysis, a comparison of the optical rotations of

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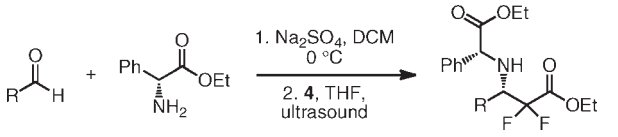
Table 2. Application of the Sonocatalyzed Reformatsky Reaction Conditions to Imines Derived from Aliphatic Aldehydes



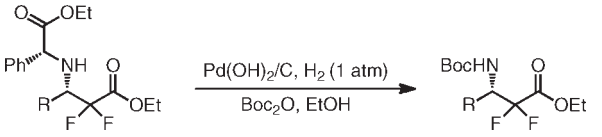
entry	R	product	yield (%)[a]	dr[b]
1	^{i}Bu	**5b**	72	96:4
2	^{i}Pr	**7a**	66	98:2
3	$CH_3(CH_2)_6$	**7b**	70	94:6
4	$Ph(CH_2)_2$	**7c**	75	96:4
5	$^{c}C_6H_{11}$	**7d**	46	98:2
6	$CH_2{=}CH(CH_2)_2$	**7e**	97	97:3
7	$phthal(CH_2)_3$	**7f**	45[c]	96:4
8	$TBSO(CH_2)_3$	**7g**	53[d]	96:4
9	$TBSO(CH_2)_2$	**7h**	60[d]	96:4

[a] Isolated yield from the aldehyde. [b] Determined from crude reaction mixture by integration of the ^{1}H NMR resonances due to α-proton of phenylglycine moiety. [c] Diethyl ether/THF (2:1) used as the solvent. [d] Magnetic stirring used upon addition of imine.

known compounds (**8b** and **8e**) was performed. While the magnitude of the rotations for **8b** ($[\alpha]^{20}_D = -5$; lit.[14b] $[\alpha]^{22}_D = -13.9$) and **8e** ($[\alpha]^{20}_D = -3$; lit.[9] $[\alpha]^{23}_D = -10.9$) was significantly smaller than those reported previously, the sign of the rotation supports the assigned (3*S*) stereochemistry of the products.

The stereochemical purity of a selection of Boc-protected amino esters (**8a**,**c**,**d**) was analyzed using the method of James and Bull[19] following Boc cleavage with TFA. The method involves the in situ derivatization of the crude amine with 2-formylphenylboronic acid and (*S*)-BINOL and integration of the two diastereomeric imino protons present in the ^{1}H NMR spectrum of the mixture, found in the region of 8.2−8.7 ppm. In the case of the amine derived from **8d**, a dr for the imine of 96:4 was obtained. Other substrates subjected to the same treatment displayed partial overlap of key resonances; however, crude estimates based on these spectra generally put dr values of the in situ

Table 3. Removal of the Phenylglycine Auxiliary under Hydrogenolysis Conditions and Concomitant Boc Protection



entry	R	product	isolated yield (%)
1	^{i}Bu	**8a**	93
2	^{i}Pr	**8b**	82
3	$CH_3(CH_2)_6$	**8c**	95
4	$Ph(CH_2)_2$	**8d**	88
5	$TBSO(CH_2)_3$	**8e**	81
6	$TBSO(CH_2)_2$	**8f**	95

formed imines to be between 90:10 and 95:5 (see Supporting Information).

In conclusion, we have developed a highly stereoselective sonocatalyzed Reformatsky reaction using inexpensive (*R*)-phenylglycine ethyl ester as a chiral auxiliary for the preparation of aliphatic α,α-difluoro-β^3-amino esters with dr ≥ 96:4. The reaction proceeds in good yield without the need for additional catalysts or additives and is compatible with sensitive functional groups. The Reformatsky adducts are easily deprotected under standard conditions and reprotected as the Boc derivatives to give substrates amenable to further functionalization.

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Supporting Information Available. Experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds, as well as experimental details and spectra for er determination of β-amino esters. This material is available free of charge via the Internet at http://pubs.acs.org.