Organic Process Research & Development

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Attrition Induced Deracemisation of 2-Fluorophenylglycine

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S *Supporting Information*

ABSTRACT: By search of a library of closely related structures, two conglomerate imines of the amide of 2-fluorophenylglycine have been discovered and unambiguously characterized. One conglomerate is formed on reaction with benzaldehyde and the other on reaction with 4-Br-benzaldehyde. The crystal structures of both have been determined. Both deracemise on grinding of the crystals under conditions whereby racemisation in solution can occur. Deracemisation of the former compound is hampered both by hydrate formation and formation of a polymorph. In contrast the latter deracemises efficiently. Hydrolysis of the enantiomerically pure (*R*)-imine to enantiomerically pure (*R*)-2-fluorophenylglycine proceeds smoothly. Either the (*R*)- or the (*S*)-enantiomer of the imine can be produced at will by seeding.

INTRODUCTION

Near total deracemisation of several racemisable conglomerates has been achieved by means of the recently discovered technique of attrition induced by grinding of the crystals.[1,2] The best studied procedure involves contact between solid conglomerate and liquid under near equilibrium conditions; continuous racemisation occurs in solution while the growing crystals are subjected to attrition by grinding induced by stirring with glass beads. Once a chiral imbalance has been achieved either by primary nucleation in solution of one of the enantiomers of the conglomerate (stochastic) or by deliberate seeding or adding specific impurities, continuous mechanical attrition of the crystals and secondary nucleation ensure complete deracemisation. Various models have been developed to explain this process, which was first demonstrated with inorganic sodium chlorate and bromate by Viedma (these types of deracemisation process are also referrred to as Viedma ripening).[3]

With regard to practical applicability, attrition-induced deracemisation has been used to prepare enantiomerically pure naproxen,[4] and it has also been employed as an alternative to diastereomeric resolution in the synthesis of the commercial drug (*S*)-clopidogrel **1**, which contains (*S*)-2-chlorophenylglycine **2** as the chiral component. Deracemisation was achieved via crystalline imine **3**, which is a readily racemisable conglomerate (Scheme 1a).[5−8] The deracemisation of the racemate of **1** has been studied in depth including details of the growth of the crystals.[9] Related principles have also been applied to nonracemisable conglomerates including a conglomerate salt of the commercial drug esomeprazole.[10]

RESULTS

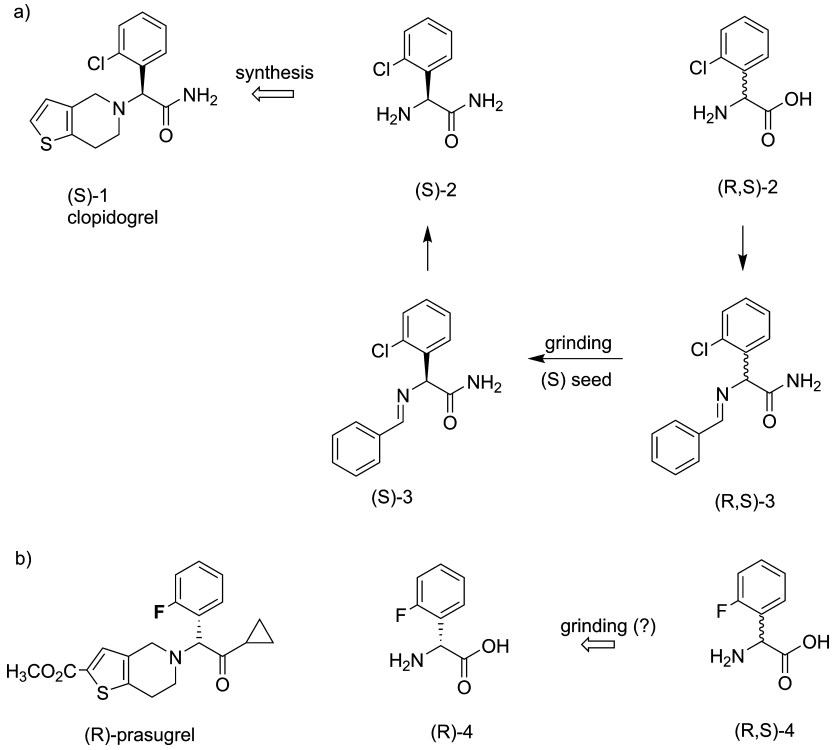
In view of the successful clopidogrel synthesis, we were interested whether this method would lend itself readily to the preparation of other racemisable amino acids, especially those of potential pharmacological interest. Extension to 2-F-phenylglycine **4**, using essentially the technique applied for **2**, is an obvious step motivated by, for example, reports of use of **4** as a side chain of antibiotics,[11] hepatitis C virus inhibitors,[12] and investigation for use in artificial sweeteners (Scheme 1b).[13] Particularly interesting is prasugrel (Effient, Scheme 1b), a second generation antiplatelet drug approved for use in both Europe and the United States in 2009. This contains as chiral unit a segment that could be obtained in principle from **4**.[14] Prasugrel, illustrated as the (*R*)-enantiomer in Scheme 1b, is marketed as the racemate although effects due to chirality have been reported.[15]

A possible route to **4**, illustrated for the (*R*)-enantiomer, is shown in Scheme 2. Based on previous experience, if racemic imine **6** forms a conglomerate, deracemisation, induced by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), will occur on attrition (the direction of deracemisation via the achiral carbanion derived on deprotonation of **6** can be determined by seeding), and hydrolysis under acidic conditions should provide enantiomerically pure **6**, which, dependent on absolute configuration, can be hydrolysed to either (*S*)- or (*R*)-**4**. However, theory and practice sometimes do not go hand-in-hand.

Received: November 10, 2014
Published: December 12, 2014

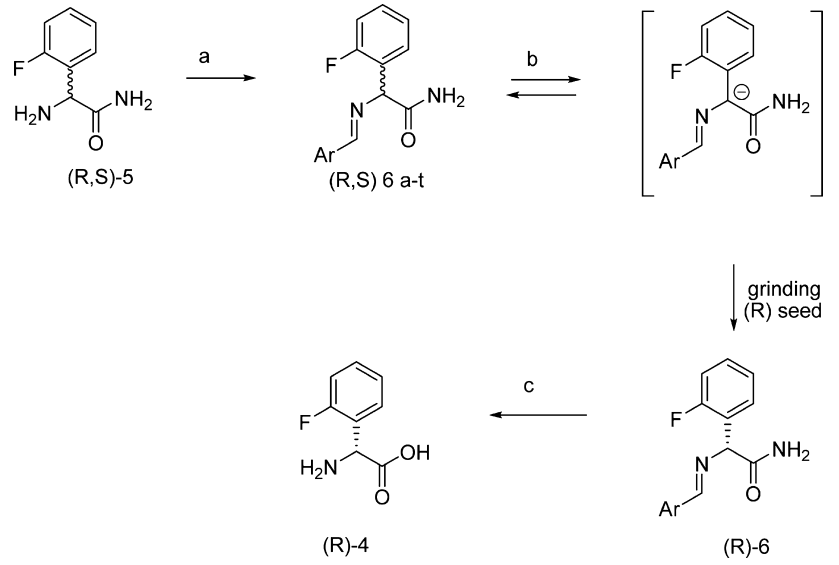
DOI: 10.1021/op500352m
Org. Process Res. Dev. 2015, 19, 302−308

Scheme 1. (a) The known route to the intermediate used for the preparation of clopidogrel; (b) Structure of (*R*)-2-fluorophenylglycine 4 (illustrated) and (*R*)-prasugrel[a]



[a]Grinding could deliver equally well (*S*)-**4**.

Scheme 2. (a) ArCHO; (b) Select conglomerate/DBU; (c) HCl/H_2O



A conglomerate must be found. In our experience, there are no structural guidelines for discovery of conglomerates. This is regrettable. Certain families, such as helicenes and salts, seem to have a relatively higher population, and in general one should expect at least 10% occurrence of conglomerates in a library of structurally related compounds.[16] A series of racemates of imines **6** (Ar = phenyl (**a**), 2-methoxyphenyl (**b**), 2-chlorophenyl (**c**), 4-methylphenyl (**d**), 4-methoxyphenyl (**e**), 3-chlorophenyl (**f**), 2,4-dichlorophenyl (**g**), 2-bromophenyl (**h**), 4-trifluoromethylphenyl (**i**), pentafluorophenyl (**j**), 4-bromophenyl (**k**), 1- (**l**) and 2-naphthyl (**m**), 3,4-dimethoxyphenyl (**n**), 2,3-dimethoxyphenyl (**o**), 3,5-dimethoxylphenyl (**p**), 2-fluorophenyl (**q**), 2,5-dimethylphenyl (**r**), and 2,3-dimethyl-4-methoxyphenyl (**s**)) was prepared.[17] These were rapidly scanned using second harmonic generation (SHG) techniques. Both the theory and the practice of this remarkably useful, simple, and quick process have been described.[18a,b]

Strongly positive responses were obtained for **6a,g,i,k** (20% of the library). Weakly or moderately positive responses were found for **6e,h,p,s**. A positive SHG response indicates a high probability—but not an absolute guarantee—that the compound is a conglomerate. Further characterisation including the

DOI: 10.1021/op500352m
Org. Process Res. Dev. 2015, 19, 302−308

determination of the crystal structures of those conglomerates used for deracemisation was performed for verification (see further).

Initial qualitative experiments indicated that **6a**, obtained from cheap benzaldehyde, deracemised on attrition. This compound was chosen for further characterisation. Unfortunately single crystals of **6a** suitable for a crystal structure determination could not be obtained although the crystallization as a conglomerate forming system (in the $P2_1$ space group) was confirmed by (i) its deracemization, (ii) the perfect matching of the XPRD patterns of racemic mixture and pure enantiomer (Figure 1), and (iii) the resolution of the structure

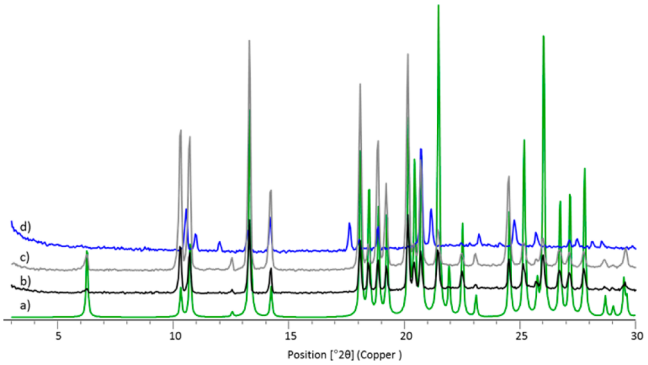


Figure 1. XPRD patterns of the (a) calculated conglomerate of **6a**, (b) racemic mixture of **6a**, (c) pure enantiomer of **6a**, and (d) racemic mixture of **3**.

using the high similarity existing between the two experimental XRPD patterns of the imines **6a** and **3**. The procedure for the crystal structure determination and the crystallographic data are described in the Supporting Information. The melting point of enantiomerically pure **6a** is 117.5 °C, whereas that of the racemate is 113.2 °C. This melting point difference is appreciably less than the 15−20 °C commonly observed for conglomerates.[16]

The molecules are connected as ribbons with the expected hydrogen bonding between the amide and carbonyl groups (Figure 2). The length of the hydrogen bonds is 2.0 Å. The unsubstituted aromatic rings interact in the (001) plane via $\pi-\pi$ stacking (dashed green lines), whereas the fluorinated rings stack along the *b*-axis (dashed blue lines). The distances between the rings are, respectively, 3.97 and 3.84 Å.

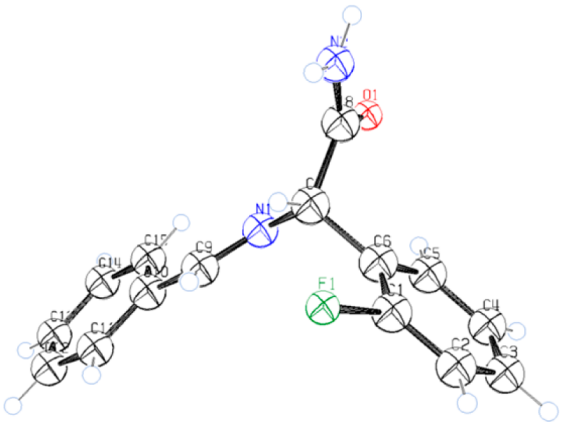


Figure 2. Asymmetric unit of **6a**.

If **6a** was allowed to stand in acetonitrile unprotected from air and humidity, it readily converted to a new form, which crystallized nicely. A single crystal was obtained although the material was relatively unstable. Structural analysis revealed that this was the monohydrate **6a**·H_2O, which crystallizes in the centrosymmetric $P2_1/c$ space group. The molecular structure is shown in Figure 3, and the hydrogen bonding scheme and packing are illustrated in the Supporting Information).

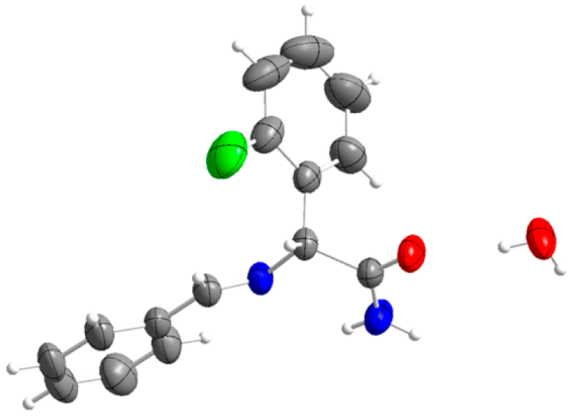


Figure 3. Asymmetric unit of monohydrate **6a**·H_2O.

This material has a significantly different (nonconglomerate) structure (space group $P2_1/c$) wherein the molecules are linked via infinite homochiral ribbons and each water molecule forms three hydrogen bonds to three different imines. The $\pi-\pi$ stacking of the aromatic groups now involves cross stacking between unsubstituted and fluorinated phenyl groups.

On heating at 80 °C or stirring for 3 days in acetonitrile at room temperature, **6a**·H_2O is converted entirely to the anhydrous conglomerate **6a**, which is clearly the thermodynamically more stable phase near ambient temperature in an anhydrous medium.

Initial attempts at deracemisation of **6a** by grinding led to the isolation of enantiomerically pure material but in low and not reproducible yield. As described in the Introduction, deracemisation can be performed at room temperature under near-equilibrium conditions, although for preparative purposes we prefer to use a saturated, entirely homogeneous solution held at higher temperature, which is then cooled using temperature programming together with attrition provided by glass beads moved by a magnetic stirring bar.[5a,20] We assume, but have not proved, that the mechanism is essentially the same as for the isothermal process.

To optimise the process, the solubility of **6a** in various solvents was measured (Supporting Information). On the basis of these measurements, the nonprotic solvent acetonitrile was chosen as best, although the relatively high solubility leads to retention of considerable material in the liquid phase at the end of the reaction. Protic solvents like ethanol were not used owing to the possibility of cyclisation via addition of the amide to the imine functionality.[1] *tert*-Butyl methyl ether (TBME) was the solvent of choice for washing because of the very low solubility of **6a**.

From the solubility measurements (Supporting Information), it is clear that the solubility of **6a** increases greatly with temperature in dry acetonitrile. One may calculate that 2.45 g (9.57 mmol) of **6a** will dissolve in 5 g of acetonitrile at 50 °C. A saturated solution was prepared by dissolving 2.45 g (9.57

DOI: 10.1021/op500352m
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Table 1. Deracemisation of 6k

entry	scale	solvent (volume)	yield	ee	product configuration	seeded with	cooling speed(°C/min)
1	106 mg	MeCN (0.21 mL)	n.d.[a]	99%	S	none	0.05 °C
2	1 g	MeCN (1.96 mL)	21.5%	98%	R	none	0.05 °C
3	3 g	MeCN (5.89 mL)	57%	97%	R	none	0.05 °C
4	3 g	MeCN (5.8 mL)	57%	94%	R	R	0.1 °C
5	1 g	*n*-PrCN (1.96 mL)	58%	96%	S	S	0.1 °C
6	1 g	2-MeBuCN (1.96 mL)	66%	99%	S	S	0.1 °C
7	8 g	2-MeBuCN (15.7 mL)	80%	99%	S	S	0.1 °C

[a]Not determined.

mmol) **6a** in 5 g acetonitrile and heating the solution to 52−53 °C and then adjusting the temperature to exactly 50 °C. Glass beads (5 g), a magnetic stirring bar, and DBU (0.425 g, 2.80 mmol) were added, and the solution was cooled to 25 °C at a rate of 5 °C/h with vigourous stirring. Stirring was continued for 30 min, and the solid was filtered, washed with TBME, and dried. There was obtained 1.06 g pure **6a** (4.14 mmol, 43% yield) with an e.e. >97% as determined by HPLC. From the solubility data, one calculates that, at equilibrium at 25 °C, 1.92 g (7.5 mmol) of **6a** (78% yield) should precipitate. This discrepancy is cause for concern.

Attempts to improve matters were unrewarding. Lowering the amount of DBU led to lower conversions. Care was also necessary to ensure that the hydrate **6a**·H_2O did not form at cost of the overall conversion. Despite all of these precautions, as well as deliberate seeding, in an unpredictable manner, occasional problems were also encountered with the formation of what appears to be a new solid phase, which contaminated the product and which could not be identified further.

Would another conglomerate work better? Attempts to deracemise **6g**, the imine formed with 2,4-dichlorobenzaldehyde, and a conglomerate as suggested by SHG results, were unsuccessful. Repetition of the SHG measurements again led to a strong positive signal, which strongly indicates that **6g** is indeed a conglomerate. An enantiomerically pure seed was not available to help start possible deracemisation. The imine **6i** formed from reaction with trifluoromethylbenzaldehyde is also a conglomerate as suggested by SHG results. Unfortunately this compound was highly soluble in virtually every solvent examined and deracemisation could not be accomplished. Other compounds with moderately positive SHG responses were not investigated although it is possible that one or more of these could be a conglomerate.

In dramatic contrast to the disappointing results described above imine **6k**, formed from reaction with 4-bromobenzaldehyde, deracemised cleanly and quickly. Details are summarised in Table 1. Deracemisations were performed analogously to the procedure described for **6a**.

The experiments reported in entries 1−3 of Table 1 were orientational. DBU was used as a base (0.3 equiv). The solution immediately developed a yellow colour on addition of DBU. In initial experiments, problems were encountered with the formation of a yellow solid along the walls of the reaction vessel. This solid also attached to the glass beads. Although this solid contained nearly enantiomerically pure **6k**, DBU was also present, and it racemised on dissolution in methylene chloride. After some experimentation it was found that relative gentle stirring so that solvent did not splash was sufficient. The stirring was less vigourous than that used in ref 4. The use of TBME, in which **6k** is nearly insoluble, as rinsing solvent led to isolation of very clean, virtually enantiomerically pure **6k**. From these three orientational experiments without deliberate seeding, it appears that deracemisation is stochastic (twice R and once S).

Experiments 4−7 involve the use of seed material. As expected, the absolute configuration of seed determines that of the product. Excessive solubility was a problem, and in experiments 5−7 less polar solvents were used in the hope of lowering the solubility. Experiment 7 represents the optimal result in which 2-methylbutyronitrile, a chiral solvent employed in a racemic composition, was used. The solubility of **6k** in butyronitrile and 2-methylbutyronitrile is definitely less than in acetonitrile although exact measurement has not been carried out.

There was in our opinion uncertainty with regard to the absolute configuration of **4**. In the literature values of $[\alpha]_D$ of +45.3° and +108° (in 1 N HCl) are given for what is thought to be the (*S*) enantiomer.[21] Unambiguous chiral HPLC data (more trustworthy than rotations in our experience) were unavailable. The melting point of the racemate of **6k** is 129 °C and that of the pure enantiomer 135 °C. As for **6a** this difference is rather small for a conglomerate.[16] To resolve any uncertainty, the crystal structure of a sample of enantiomerically pure **6k** was determined in the chiral space group $P2_1$. The material crystallized cleanly, and the structures of the imine **6k** and of the racemate were determined. To be sure that there was no twinning, the structures of both enantiomerically pure material and racemate were determined; the structures were identical. On the basis of the Flack parameter, the absolute configuration of **6k** was established to be *R*. The crystal structure is illustrated in Figure 4. The crystal structure of a single crystal from the racemic mixture was also resolved and was the same as the crystal structure of the pure enantiomer, the product crystallizing as a conglomerate. The hydrogen bonding scheme of **6k** is much different from that for 6a and is illustrated in Figure 4. In contrast to **6a**, where strong hydrogen bonds are formed in a chain-like manner between the amide groups, the weak hydrogen bonds of **6k** include also the imine nitrogen atom leading to a nine-membered ring system with two hydrogen bonds, which prolongates along the *b*-axis. The hydrogen bond lengths are around 2.23 Å for N(1)−H−O(1A) and 2.35 Å for N(1)−H−N(2B), respectively. This different (relative to **6a**) hydrogen bonding scheme, which leads also to infinite ribbons, is responsible that no $\pi-\pi$ interactions develop within a ribbon, but that the ribbons are stacked together in a zipper-like manner by pairwise $\pi-\pi$ interactions between fluorinated and brominated rings along the *a*-axis, forming a layered structure.

Enantiomerically pure **6k** was hydrolysed with HCl/acetone to form the amide **5** as HCl salt, which was hydrolysed further with 6 N HCl (two steps were used to prevent reaction with benzaldehyde freed upon hydrolysis of the imine, a complication known to occur with (*S*)-**3**[5a] on hydrolysis) to

DOI: 10.1021/op500352m
Org. Process Res. Dev. 2015, 19, 302−308

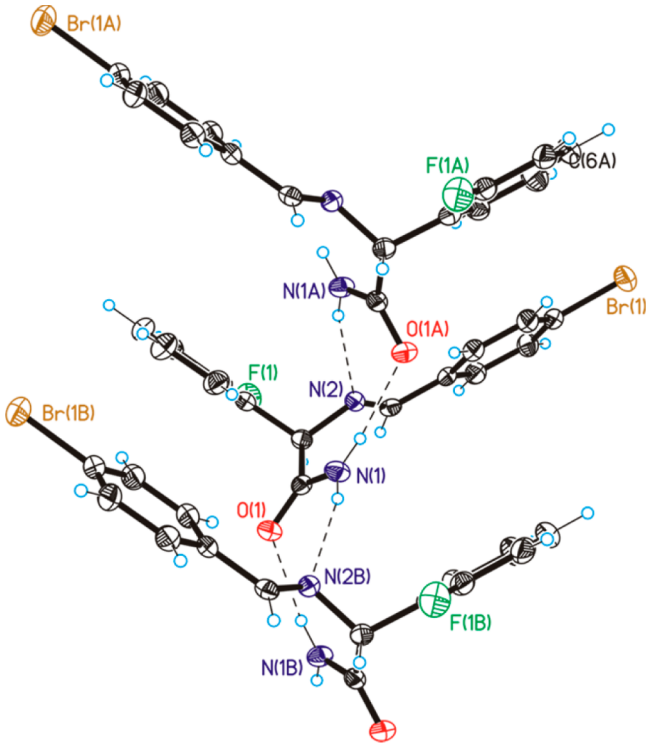


Figure 4. Hydrogen bonding scheme of **6k** along the *b*-axis.

provide the amino acid **4** as HCl salt in 90% yield and 99% ee (Scheme 3).

There is no reason to expect inversion of configuration on hydrolysis so **4**·HCl obtained from **6k** may be assigned the (*R*) absolute configuration. Retention time data for the enantiomers of **4** are given in the Supporting Information.

CONCLUSIONS

The procedure described here should be more broadly applicable to amino acids and related structures. The approach used in this paper involves a search for suitable conglomerates by means of the reversible formation of families/libraries of derivatives that are crystalline. Although this approach is well-suited to the chemical properties of amino acid amides, there are other chemical possibilities. For example, hydrates, salts, and cocrystals are also possible sources of derivatives that can be formed reversibly with certain compounds depending on structure and properties.

Rapid identification of high probability candidates is readily accomplished by means of scanning by SHG. If possible, it is better to prepare a large enough library to ensure that several conglomerate structures are available for investigation owing to the fact that, just as for preferential crystallization, not every conglomerate has properties suitable for the experimental conditions. Compound **6k** was not part of the original small library that we prepared and was only discovered once the size of the library had been essentially doubled. Further structural characterisation of promising candidates, including unambiguous proof of conglomerate structure, should be carried out. Moreover, the examination of solubility characteristics is also needed as well as investigations of the potential for formation of extra crystalline phases, i.e., polymorphs, solvates, racemic compounds, etc., and general stability of the crystals. For detailed studies of the compound types described here, knowledge of the acidity of the chiral centre is necessary. DBU is an excellent base for the examples studied so far, although for less acidic amino acid derivatives more powerful bases might be necessary. Investigation of the base catalysed racemisation is also necessary to ensure, for example, that tautomerisation to isomeric structures does not take place.

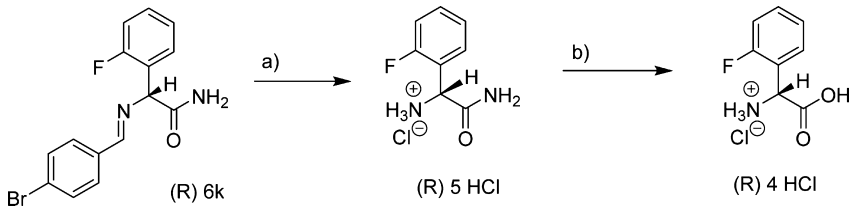
The protocol described in this paper for attrition induced deracemisation, with due consideration of the various factors mentioned, should be more broadly applicable, especially for amino acids. An obvious challenge for application of this technique for larger scale production is the development of suitable apparatus. It is therefore encouraging to note that technology for attrition induced deracemisation with the potential for scale-up has recently been described.[21]

EXPERIMENTAL SECTION

Preparation of (±)-2-(2-Fluorophenyl)glycine Methyl Ester Hydrochloride. A batch of 2-fluorophenylglycine (10 g, 59.1 mmol, 1.0 equiv) was suspended in methanol (MeOH, 60 mL) under an N_2 atmosphere. The flask was cooled in an ice/water bath, and $SOCl_2$ (5.8 mL, 79.9 mmol, 1.35 equiv) was added dropwise using an injection pump (20 mL/h), and the yellow solution was stirred at ambient temperature overnight. The MeOH (30 mL) was evaporated from the resulting suspension under reduced pressure, and the yellow/white suspension was transferred to a glass filter using TBME (300 mL) and washed with further TBME (4 × 50 mL) and dried to afford 12.57 g (97% yield) of the methyl ester hydrochloride as a white solid with a chemical purity of 95% (215 nm) as indicated by HPLC-MS. ^{1}H NMR (300 MHz, CD_3OD) δ 7.61−7.44 (m, 2H), 7.36−7.23 (m, 2H), 5.42 (s, 1H), 3.83 (s, 3H); MS: (ESI$^+$) Calculated mass $[M + H]^+$ $C_9H_{10}FNO_2$ 184.0777 found: 184.0.

Preparation of 2-Amino-2-(2-fluorophenyl)acetamide 5. The 2-fluorophenylglycine methyl ester hydrochloride (12.54 g, 57.2 mmol) was dissolved in an aqueous ammonia solution (25% w/w, 66 mL) and stirred overnight at ambient temperature. The solution was transferred to a separation funnel using a minimal amount of water and extracted with dichloromethane (DCM) (25 × 20 mL) and with 10% MeOH/DCM (4 × 25 mL). The organic phases were dried with sodium sulfate, filtered, and concentrated in vacuo to yield a

Scheme 3. (a) HCl/acetone; (b) HCl/H_2O



DOI: 10.1021/op500352m
Org. Process Res. Dev. 2015, 19, 302−308

yellow/white solid, which was washed with TBME to afford a white solid (5.634 g, 59% yield) with a chemical purity of 96% (215 nm) and 87% (254 nm) by HPLC-MS. An additional 183 mg of crystalline amide **5** was later retrieved from the standing TMBE wash, increasing the yield to 60%. ^{1}H NMR (300 MHz, CD_3OD) δ 7.49−7.40 (m, J = 26.3 Hz, 1H), 7.37−7.27 (m, 1H), 7.21−7.05 (m, 2H), 4.73 (s, 1H); MS: (ESI$^+$) Calculated mass $[M + H]^+$ $C_8H_9FN_2O$ 169.0780 found: 169.0. Compound **5** is highly soluble in water and somewhat difficult to isolate. An alternative isolation procedure involves concentration of the reaction mixture followed by stripping with toluene three times. The residue is then washed three times with isopropyl alcohol and twice with MeOH. The solids are removed by filtration to give **5** in 89% yield and purity equivalent to that described above.

Preparation of (±)-2-((4-Bromobenzylidene)amino)-2-(2-fluorophenyl)acetamide (6k). The following procedure is representative for all imines **6**. Portions of **5** (5.63 g, 33.5 mmol, 1.0 equiv), *p*-bromobenzaldehyde (6.81 g, 37.0 mmol, 1.1 equiv), and sodium sulfate (7.76 g, 54.6 mmol, 1.63 equiv) were combined in DCM (50 mL) and stirred overnight under an N_2 atmosphere. The suspension was heated with a hot water bath and filtered, the residue was rinsed with hot DCM (3 × 50 mL), and the combined DCM layers were concentrated in vacuo to afford a yellow/white solid. The product was washed with TBME (3 × 50 mL) to afford **6k** as a white solid (10.0 g, 89% yield) with a chemical purity of 97% (215 nm) and 97% (254 nm) by HPLC-MS. ^{1}H NMR (300 MHz, CD_3OD) δ 8.35 (s, 1H), 7.69 (bdd, J = 49.1, 8.6 Hz, 4H), 7.53 (dd, J = 15.0, 1.8 Hz, 1H), 7.40−7.30 (m, 1H), 7.24−7.08 (m, 2H), 5.37 (s, 1H); MS: (ESI$^+$) Calculated mass $[M + H]^+$ $C_{15}H_{12}BrFN_2O$ 335.0198/337.0178 found: 334.8/336.9.

For **6a**, which was also deracemised in initial experiments, ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (s, 1H), 7.06−7.3 (m, 3H), 7.40−7.48 (m, 4H), 7.76−7.78 (m, 2H), 8.29 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 69.43, 115.56−115.85 (d, J = 21.9 Hz), 124.45−124.50 (d, J = 3.5 Hz), 125.88, 126.07, 128.41, 128.59, 129.41−129.46 (d, J = 3.7 Hz) 129.63−129.74 (d, J = 8.3 Hz), 131.48, 135.22, 158.85−162.12 (d, J = 247.5 Hz, 163.68, 173.94. MS: (ESI$^+$) Calculated mass for $C_{15}H_{13}FN_2O$= 256.15 [M + H} found 257.15 [M + H]. Elem. Anal. Calc for $C_{15}H_{13}FN_2O$ C 70.30; H 5.11; N 10.93; found C 70.04; H 5.12; N 10.91.

Preparation of (*R*)-6k. *Method A.* A portion of (±)-**6k** (3.0 g, 9.0 mmol, 1.0 equiv) was combined with glass beads (borosilicate, 2 mm, 4.65 g) and MeCN (5.8 mL). A portion of 1,8-diazabicycloundec-7-ene (0.40 mL, 2.70 mmol, 0.3 equiv) was added under N_2 atmosphere, and the suspension was stirred at medium speed while heating to 70 °C. The clear orange solution was then cooled to 20 °C at 0.1 °C/min using a Huber ministat and seeded with R-enantiomer crystals at 65, 60, and 55 °C. At 20 °C, the yellow suspension was filtered on a glass filter (pore 4) using TBME and washed of all yellow color with additional TBME to afford a white solid (6.35 g, including glass beads, 1.70 g, corrected 57% yield). Chiral HPLC (Chiralpak IA, heptane/EtOH 80/20, 0.7 mL/min @ 263 nm) revealed an ee of 94% for the *R*-enantiomer.

Preparation of (*S*)-6k. *Method B.* A portion of (±)-**6k** (1.0 g, 3.0 mmol, 1.0 equiv) was combined with glass beads (borosilicate, 2 mm, 1.56 g) and *i*-PrCN (1.96 mL). A portion of diazabicycloundec-7-ene (0.134 mL, 0.90 mmol, 0.3 equiv) was added under N_2 atmosphere, and the suspension was stirred at medium speed while heating to 70 °C. The clear orange solution was then cooled to 20 °C at 0.1 °C/min using a Huber ministat and seeded with *S*-enantiomer crystals at 67 °C, and twice more after 30 min intervals, the last seed was added at 57.7 °C. At 20 °C, the yellow suspension was filtered on a glass filter (pore 4) using TBME (75 mL) and washed of all yellow color with additional TBME (10 mL) to afford a white solid (2.14 g, including glass beads, 0.58 g, corrected (58% yield). Chiral HPLC (Chiralpak IA, heptane/EtOH 80/20, 0.7 mL/min @ 263 nm) revealed an ee of 96% for the *S*-enantiomer.

Preparation of (*S*)-6k. *Method C.* A portion of (±)-**6k** (1.0 g, 3.0 mmol, 1.0 equiv) was combined with glass beads (borosilicate, 2 mm, 1.56 g) and 2-methylbutyronitrile (1.96 mL). A portion of 1,8-diazabicycloundec-7-ene (0.134 mL, 0.90 mmol, 0.3 equiv) was added under N_2 atmosphere, and the suspension was stirred at medium speed while heating to 75 °C. The clear orange solution was then cooled to 20 °C at 0.1 °C/min using a Huber ministat and seeded with *S*-enantiomer crystals at 74, 73, 72, and 71 °C. At 20 °C, the yellow suspension was filtered on a glass filter (pore 4) using TBME and washed of all yellow color with additional TBME to afford a white solid (2.21 g, including glass beads, 0.66 g, corrected (66% yield). Chiral HPLC (Chiralpak IA, heptane/EtOH 80/20, 0.7 mL/min measured at 263 nm) revealed an ee of 99% for the *S*-enantiomer.

A larger scale preparation was carried out using method C. A portion of (±)-**6k** (8.0 g, 3.0 mmol, 1.0 equiv) was combined with glass beads (borosilicate, 2 mm, 12.4 g) and 2-methylbutyronitrile (15.7 mL). A portion of 1,8-diazabicycloundec-7-ene (1.08 mL, 7.2 mmol, 0.3 equiv) was added under N_2 atmosphere, and the suspension was stirred at medium speed while heating to 75 °C. The clear orange solution was then cooled to 20 °C at 0.1 °C/min using a Huber ministat and seeded with *S*-enantiomer crystals at 74, 73, 72, and 71 °C. At 20 °C, the yellow suspension was filtered on a glass filter (pore 4) using TBME and washed with additional TBME (3×), the solid was dried in vacuo to afford a white solid (18.78 g, including glass beads, 6.39 g, corrected (80% yield). Chiral HPLC (Chiralpak IA, heptane/EtOH 80/20, 0.7 mL/min measured at 263 nm) revealed an ee of 99% for the *S*-enantiomer.

Preparation of (*R*)-2-Amino-2-(2-fluorophenyl)-acetamide ((*R*)-5·HCl). Imine (*R*)-**6k** (1.59 g, 4.75 mmol) was dissolved in acetone (85 mL) with 4.3 g glass beads and stirred while aqueous HCl (37% ww, 0.46 mL) was added. The solution immediately became cloudy and was stirred for 1 h at rt. The white solid in suspension was decanted from the glass beads with acetone (50 mL) and filtered. The solid was washed with further acetone (2 × 50 mL) and dried in vacuo to afford 0.88 g (90%) of a white solid. ^{1}H NMR (300 MHz, cd3od) δ 7.60−7.47 (m, 1H), 7.37−7.22 (m, 1H), 5.22 (bd, J = 1.9 Hz, 1H); MS: (ESI$^+$) MS: (ESI$^+$) Calculated mass $[M + H]^+$ $C_8H_9FN_2O$ = 169.0780 found: 169.2.

Preparation of (*R*)-2-Amino-2-(2-fluorophenyl)acetic Acid-4. Amide **5**·hydrochloride (0.88 g, 4.29 mmol) was suspended in aqueous HCl (6 M, 10.6 mL) and refluxed for 2 h. The resulting solution was cooled to room temperature, where a suspension formed again. The solvent was removed in vacuo and the yellow/white solid stripped with toluene. The solid was then suspended in MeOH and filtered over glass (pore 4). The filtrate was concentrated to afford a white solid, 1.11 g of material that was enantiomerically pure as established by HPLC but which was not purifed further. Chiral HPLC

DOI: 10.1021/op500352m
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(CHIROBIOTIC TAG, H_2O, 1 mL/min measured at 217 nm) revealed an ee of 98+%; retention time (*R*) enantiomer 6.5 min, retention time (*S*) enantiomer 11 min. ^{1}H NMR (300 MHz, CD_3OD) δ 7.59−7.46 (m, 1H), 7.37−7.21 (m, 1H), 5.29 (s, 1H).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and mass spectra for experiments with **6k** and **6a** together with (chiral) HPLC traces and summary of SHG measurements for **6a**−**s**. XPRD data for **6a**, solubility data for **6a**, crystal structure data for **6a**, **6k**, and **6**·H_2O. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research carried out by M.v.d.M. and W.S. has received funding from the European Community's Seventh Framework Programme under grant agreement n° NMP4-SL-2008-214340, project RESOLVE.

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DOI: 10.1021/op500352m
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