ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: I. Baglai, M. leeman, K. Wurst, B. kaptein, R. M. Kellogg and W. Noorduin, *Chem. Commun.*, 2018, DOI: 10.1039/C8CC06658B.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C8CC06658B

Journal Name

COMMUNICATION

The Strecker Reaction coupled to Viedma Ripening: A Simple Route to Highly Hindered Enantiomerically Pure Amino Acids

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Iaroslav Baglai,[a] Michel Leeman,[b] Klaus Wurst,[c] Bernard Kaptein,[d] Richard M. Kellogg,[b] and Willem L. Noorduin*,[a]

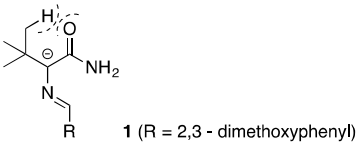
The Strecker reaction is broadly used for the preparation of α-amino acids. However, control of enantioselectivity remains challenging. We here couple the Strecker reaction to Viedma ripening for the absolute asymmetric synthesis of highly sterically hindered α-amino acids. As proof-of-principle, the enantiomerically pure α-amino acids tert-leucine and 1-adamantylglycine were obtained.

Even after more than one and a half centuries since discovery, the Strecker reaction[1] remains one of the simplest and most powerful methods to synthesize α-amino acids both in the laboratory and also in origin of life scenarios.[2] However, the classical Strecker reaction gives racemates. In general, two strategies have been developed to obtain enantioselectivity by means of an asymmetric Strecker reaction.[3] One is the nucleophilic addition of cyanide to a protected imine; this entails use of stoichiometric amounts of a chiral auxiliary/protecting group.[4] The second strategy relies on chiral catalysts for the enantioselective cyanation of a protected achiral imine.[5] Despite tremendous progress over the years, both approaches still require protecting groups and chiral reagents that need to be removed after the reaction.

A virtually quantitative, catalyst or protecting group free, alternative route to enantiomerically pure α-amino acids may be offered by a combination of the classical Strecker reaction and attrition-enhanced deracemization (Viedma Ripening) - a tantalizingly simple process to convert a racemate to a desired single enantiomer.[6] In short, the solid phase of a slurry is completely converted via racemization in the liquid phase into a desired handedness by a continuous dissolution/recrystallization process.

Viedma ripening relies on two prerequisites: *a*) the compound must crystallize as a racemic conglomerate, *i.e.* a mechanical mixture of enantiomeric crystals, and *b*) the enantiomers must interconvert in the liquid phase. In other words, a *racemizable conglomerate* is essential. However, suitable racemization conditions are often not obvious. Furthermore, conglomerate formation remains unpredictable and statistically occurs only for 5-10% of chiral organic compounds.[7] Consequently, each type of compound requires careful design to fulfill the requirements for Viedma ripening.

Viedma ripening has been used successfully to access enantiomerically pure phenylglycines. Recently, Kawasaki et al have reported deracemization by Viedma ripening of two protected α-aminonitriles and their conversion to phenylglycine derivatives.[8] Although elegant, this approach does not allow systematic search for conglomerate precursors of α-amino acids with a side chain of choice. This is possible with our previously developed amide-based approach, which involves imine formation. Libraries of imines are prepared that can be searched for conglomerates.[9] However, this approach fails for analogous imine derivatives of highly hindered amino acids. In an explorative study, we could not find suitable base-catalyzed racemization conditions for the model compound **1** (Supporting Information). We attribute this to steric hindrance ("Newman Rule of Six"),[10] which prevents planarity and resonance stabilization of the carbanion as illustrated in Scheme 1. These results highlight that a different approach needs to be developed for deracemization towards sterically hindered amino acids.



1 (R = 2,3 - dimethoxyphenyl)

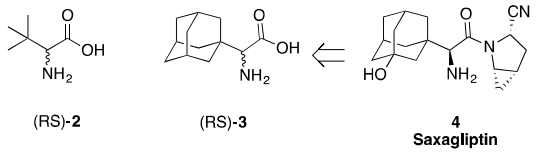
Scheme 1. Newman Rule illustration.

Here we introduce a flexible Strecker-based strategy for absolute asymmetric synthesis of α-amino acids. Specifically, we focus on structurally challenging α-amino acids bearing quaternary alkyl α-substituents. These are highly desired components for many pharmaceutical target compounds[11] and chiral catalysts.[12] To demonstrate the proof-of-principle, we target two prototypical and commercially relevant representatives of highly sterically hindered unnatural amino acids, *tert*-leucine **2** and 1-adamantylglycine **3**, neither of which is attainable by the previously developed routes. Enantiomerically pure *tert*-leucine, which produces strong conformational effects, is widely used in the synthesis of modified

[a] AMOLF, Science Park 104, 1098 XG Amsterdam, The Netherlands.
[b] Syncom BV,Kadijk 3, 9747 AT Groningen, The Netherlands.
[c] University of Innsbruck, Innrain 80-82, A-6020 Innsbruck, Austria.
[d] InnoSyn BV, PO Box 1090, 6160 BB Geleen, The Netherlands.
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

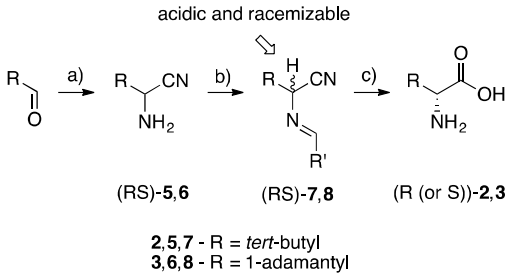
View Article Online
DOI: 10.1039/C8CC06658B

peptides.[13] The S-enantiomer of 1-adamantylglycine is a key building block for the antidiabetic drug Saxagliptin **4** (Scheme 2).[14]



Scheme 2. The target molecules **2,3** and Saxagliptin **4**.

Our approach offers several advantages: a) racemic α-aminonitriles **5**,**6** are readily accessible; b) simple Schiff condensation with aromatic aldehydes directly provides libraries of α-aminonitriles imines **7**,**8** readily subject to base catalyzed racemization; this library may be searched for conglomerates; and c) the small, electron withdrawing, nitrile group reduces steric hindrance around the chiral proton in **7**,**8** (Scheme 3).



Scheme 3. Schematic illustration of the methodology. [a] NH_3/HCN; [b] X-Ar-CHO; the substituents "**R's**" used for libraries of imines **7** and **8** are given in Tables S1 and S2 (Supporting Information), respectively; [c] 1) conglomerate identification; 2) attrition of suspension with DBU and (S) or (R) seed; 3) acidic hydrolysis.

We demonstrate our approach for the synthesis of enantiomerically pure *tert*-leucine **2**. The Strecker reaction with commercially available pivaldehyde readily yields α-aminonitrile **5**. Subsequent reaction of **5** with a selection of benzaldehydes creates a library of imines **7**. Unfortunately, all these imines **7** are poorly crystalline and highly soluble solids or even oils, thus making any type of crystallization induced enantiomeric transformation (CIET)[15] nearly impossible. This poor crystallinity can be attributed to the lack of hydrogen bonds in the compounds **7**. To overcome this, we enhance the π-π stacking in the crystal structures using naphthaldehydes instead of benzaldehydes for library preparation. Indeed, we find that all naphthalene-substituted imines **7** are nicely crystalline.

A nonlinear optical technique, Second Harmonic Generation (SHG), may be used to indicate the absence of a center of symmetry in the crystals and, consequently, potential presence of a conglomerate as conglomerates crystallize in a chiral (non-centrosymmetric) space group from racemates.[16] Screening of the prepared library of 8 representatives for conglomerate behavior using SHG and X-Ray Diffraction (XRD) allows tentative identification of **7a**,**b** as conglomerates (Figure 1; see also Table S1, Supporting Information).

Enantiomerically pure (*R*)-**7a** rapidly racemizes in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in various solvents (Fig. S1, Supporting Information), demonstrating the anticipated higher acidity of nitriles **7** compared to the corresponding amide derivatives **1**. Both compounds are readily deracemized by grinding a slurry of **7a** or **7b** (1.0 g) in methanol (10 mL) using 0.3 equivalents of DBU as a base at 20°C. For both compounds, an initial solid phase with an enantiomeric excess (*ee*) of ≈ 5% (R-enantiomer) completely converts into an enantiomerically pure solid phase of (*R*)-**7a** and (*R*)-**7b**, respectively, within 16 hours of grinding. For compound **7a**, chosen for detailed investigation, the deracemization can be completed within 8 hours and directed to either enantiomer by addition of 25 mol % of the desired enantiomer to the solid phase (Figure 1). Subsequent stepwise hydrolysis of either (*R*)- or (*S*)-**7a** with hydrochloric acid proceeds with complete preservation of the chirality, giving enantiomerically pure (*R*)- or (*S*)-*tert*-leucine (*ee* > 99%), respectively, in virtually quantitative yield.

To demonstrate the scope of this approach, we deracemize an even more bulky 1-adamantylglycine **3** precursor. A Strecker reaction with 1-adamantyl aldehyde provides α-aminonitrile **6**. Subsequently, reaction of **6** with a selection of benzaldehydes yields a library of 24 α-aminonitrile imines **8** (Table S2, Supporting Information). In this case, all representatives **8** are nicely crystalline products, probably owing the presence of the rigid adamantane moiety. We identify derivatives **8a**,**b** (Figure 2) as conglomerates using SHG and XRD. However, from further studies we conclude that compound **8b** crystallizes as an unstable polymorph under deracemization conditions (Fig. S7, Supporting Information), making it unsuitable for a robust process. Compound **8a**, on the other hand, is a stable conglomerate. A slurry of **8a** (1.0 g) in acetonitrile (10 mL) deracemizes readily on grinding in the presence of 0.3 equivalents of DBU. Within 16 hours at 20°C, an initial solid phase with an *ee* of ≈ 10% (*S*-enantiomer) completely converts into an enantiomerically pure solid phase in virtually quantitative yield. As expected, the deracemization can be directed to either enantiomer by starting with a small excess of the desired enantiomer in the solid phase[6] (Figure 2).

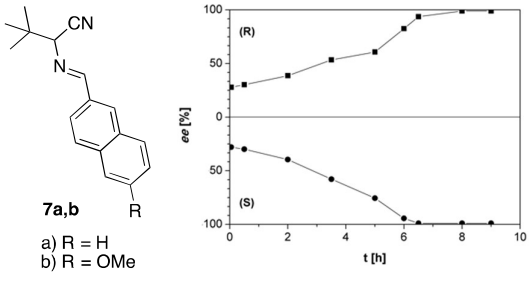


Figure 1. Identified conglomerates **7a**,**b** (*left*). Deracemization of **7a** (*right*) (0.1 g solid/1.0 mL of 4% (*v/v*) DBU in methanol).

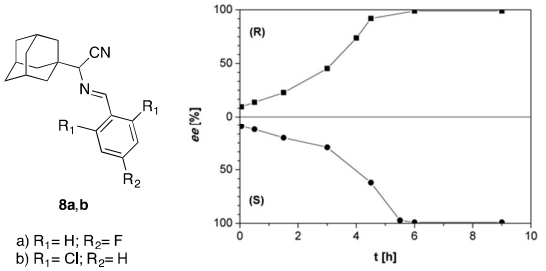


Figure 2. Deracemization of the identified conglomerate 8a (0.1 g solid/1.0 mL of 2% (*v/v*) DBU in acetonitrile).

View Article Online
DOI: 10.1039/C8CC06658B

Finally, stepwise hydrolysis of (*S*)-**8a** with hydrochloric acid provides the corresponding (*S*)-1-adamantylglycine hydrochloride (*S*)-**2**·HCl in nearly quantitative yield and with complete retention of stereochemistry at the chiral center (*ee* > 99%).

In summary, we here introduce a methodology to access *essentially quantitatively* enantiomerically pure highly sterically hindered α-amino acids with a handedness of choice. Our approach combines the advantages of both the classical Strecker reaction and Viedma ripening and bypasses any chiral additives (only a seed of the desired enantiomer is used to direct the deracemization). Importantly, we show how both the physical (crystallinity) and chemical (acidity) properties can be optimized by simple modifications of the chemical structure, while still preserving the target moiety. Access to libraries is essential both for discovery of conglomerates and modification of physicochemical properties. Although this typically requires the synthesis of *ca*. 10-15 library entries, this initial work is rewarded by a final process that is robust and extremely simple to execute. Often expensive resolving agents, protecting groups or chiral catalysts required for asymmetric Strecker syntheses are unnecessary. Only simple condensation chemistry is involved together with the use of mineral acids and water. We employ mild attrition for the deracemization. Potentially, temperature cycling[17] or other attrition methods such as homogenization[18] may also be used as alternatives. A small amount of either enantiomer can be used to direct the deracemization to the desired handedness, acting as a template for amplification, thus making it unnecessary to develop independent processes or catalysts for each enantiomer. Finally, we foresee that this simple and sustainable methodology can readily be extended to other sterically demanding as well as unhindered α-amino acids.

This work was supported by AMOLF funds for Topsector-related research. We are grateful to the analytical department at Syncom BV for carrying out the analyses. We thank Marko Kamp for his assistance with the SHG measurements and Hinco Schoenmaker for building the experimental setup.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 A. Strecker, *Ann. Chem. Pharm.* 1850, **75,** 27–45.
2 J. L. Bada, *Chem. Soc. Rev.* 2013, **42,** 2186.
3 (a) H. Gröger, *Chem. Rev.* 2003, **103,** 2795–2827. (b) J. Wang, X. Liu, X. Feng, *Chem. Rev.* 2011, **111,** 6947–6983.
4 (a) W. H. J. Boesten, J.-P. G. Seerden, B. De Lange, H. J. A. Dielemans, H. L. M. Elsenberg, B. Kaptein, H. M. Moody, R. M. Kellogg, Q. B. Broxterman, *Org. Lett.* 2001, **3,** 1121–1124. (b) L. Shu, P. Wang, *Org. Process Res. Dev.* 2008, **12,** 298–300; c) J. T. Kuethe, D. R. Gauthier, G. L. Beutner, N. Yasuda, *J. Org. Chem.* 2007, **72,** 7469–7472.
5 (a) S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature* 2009, **461,** 968–970. (b) S. Saravanan, A. Sadhukhan, N. H. Khan, R. I. Kureshy, S. H. R. Abdi, H. C. Bajaj, *J. Org. Chem.* 2012, **77,** 4375–4384. (c) M. Shibasaki, M. Kanai, T. Mita, *Org. React.* 2008, **70,** 3–40.
6 (a) C. Viedma, *Phys. Rev. Lett.* 2005, **94,** 65504. (b) P. S. M. Cheung, J. Gagnon, J. Surprenant, Y. Tao, H. Xu, L. A. Cuccia, *Chem. Comm.*, 2008, 987-989. (c) W. L. Noorduin, T. Izumi, A. Millemaggi, M. Leeman, H. Meekes, W. J. P. Van Enckevort, R. M. Kellogg, B. Kaptein, E. Vlieg, D. G. Blackmond, *J. Am. Chem. Soc.* 2008, **130,** 1158–1159. (d) C. Viedma, J. E. Ortiz, T. de Torres, T. Izumi, D. G. Blackmond, *J. Am. Chem. Soc.*, 2008, **130,** 15274–15275. (e) S.V. Tsogoeva, S. Wei, M. Freund, M. Mauksch, *Angew. Chem. Int. Ed.* 2009, **48,** 590-594. (f) W. L. Noorduin, W. J. P. Van-enckevort, H. Meekes, B. Kaptein, R. M. Kellogg, J. C. Tully, J. M. McBride, E. Vlieg, *Angew. Chem. Int. Ed.* 2010, **49,** 8435–8438. (g) L.-C. Sögütoglu, R. E. Steendam, H. Meekes, E. Vlieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* 2015, **44,** 6723–6732.
7 (a) G. Levilain, G. Coquerel, *CrystEngComm* 2010, **12,** 1983–1992. (b) A. Otero-de-la-roza, B. H. Cao, I. K. Price, J. E. Hein, E. R. Johnson, *Angew. Chem. Int. Ed.* 2014, **53,** 7879–7882.
8 (a) E. J. Corey, M. J. Grogan, *Org. Lett.* 1999, **1,** 157–160; (b) T. Kawasaki, N. Takamatsu, S. Aiba, Y. Tokunaga, *Chem. Comm.* 2015, **51**, 14377-14380; (c) S. Aiba, N. Takamatsu, T. Sasai, Y. Tokunaga, T. Kawasaki, *Chem. Comm.* 2016, **52**, 10834-10837; (d) S. Miyagawa, K. Yoshimura, Y. Yamazaki, N. Takamatsu, T. Kuraishi, S. Aiba, Y. Tokunaga, T. Kawasaki, *Angew. Chem. Int. Ed.* 2017, **56,** 1055–1058. (e) N. Takamatsu, S. Aiba, T. Yamada, Y. Tokunaga, T. Kawasaki, *Chem. - A Eur. J.* 2018, **24,** 1304–1310.
9 (a) M. van der Meijden, M. Leeman, E. Gelens, W. Noorduin, H. Meekes, W. van Enckevort, B. Kaptein, E. Vlieg, R. Kellogg, *Org. Process Res. Dev.* 2009, **13,** 1195–1198. (b) P. Wilmink, C. Rougeot, K. Wurst, M. Sanselme, M. Van Der Meijden, W. Saletra, G. Coquerel, R. M. Kellogg, *Org. Process Res. Dev.* 2015, **19,** 302–308.
10 M. S. Newman, *J. Am. Chem. Soc.* 1950, **72,** 4783–4786.
11 (a) A. Arasappan, S. Venkatraman, A. I. Padilla, W. Wu, T. Meng, Y. Jin, J. Wong, A. Prongay, V. Girijavallabhan, F. George Njoroge, *Tetrahedron Lett.* 2007, **48,** 6343–6347. (b) Y. S. Tsantrizos, *Acc Chem Res* 2008, **41,** 1252–1263.
12 R. P. Reddy, G. H. Lee, H. M. L. Davies, *Org. Lett.* 2006, **8,** 3437–3440.
13 (a) F. Formaggio, C. Baldini, V. Moretto, M. Crisma, B. Kaptein, Q. B. Broxterman, C. Toniolo, *Chem. - A Eur. J.* 2005, **11,** 2395–2404. (b) A. S. Bommarius, M. Schwarm, K. Drauz, *J. Mol. Catal. - B Enzym.* 1998, **5,** 1–11.
14 (a) B. Gallwitz, *IDrugs* 2008, **11,** 906–917. (b) D. J. Augeri, J. A. Robl, D. A. Betebenner, D. R. Magnin, A. Khanna, J. G. Robertson, A. Wang, L. M. Simpkins, P. Taunk, Q. Huang, S.-P. Han, B. Abboa-Offei, M. Cap, L. Xin, L. Tao, E. Tozzo, G. E. Welzel, D. M. Egan, J. Marcinkeviciene, S. Y. Chang, S. A. Biller, M. S. Kirby, R. A. Parker, L. G. Hamann, *J. Med. Chem.* 2005, **48,** 5025–5037. (c) J. Dong, Y. Gong, J. Liu, X. Chen, X. Wen, H. Sun, *Bioorg. Med. Chem.* 2014, **22,** 1383–1393. Note that the hydroxylated 4-position in the adamantane is not chiral.
15 K. M. J. Brands, A. J. Davies, *Chem. Rev.* 2006, **106,** 2711-2733.
16 (a) A. Galland, V. Dupray, B. Berton, S. Morin-Grognet, M. Sanselme, H. Atmani, G. Coquerel, *Cryst. Growth Des.* 2009, **9,** 2713–2718. (b) F. Simon, S. Clevers, V. Dupray, G. Coquerel, *Chem. Eng. Technol.* 2015, **38,** 971–983.
17 (a) Z. El-Hachemi, J. Crusats, J. M. Ribó, S. Veintemillas-Verdaguer, *Cryst. Growth Des.* 2009, **9,** 4802–4806. (b) Z. El-Hachemi, J. Crusats, J. M. Ribó, J. M. McBride, S. Veintemillas-Verdaguer, *Angew. Chem. Int. Ed.* 2011, **50,** 2359–2363. (c) C. Viedma, P. Cintas, *Chem. Commun.* 2011, **47,** 12786. (d) K. Suwannasang, A. E. Flood, C. Rougeot, G. Coquerel, *Cryst. Growth Des.* 2013, **13,** 3498–3504. (e) W. W. Li, L. Spix, S. C. A. De Reus, H. Meekes, H. J. M. Kramer, E. Vlieg, J. H. Ter Horst, *Cryst. Growth Des.* 2016, **16,** 5563–5570. (f) G. M. Maggioni, M. P. Fernandez-Ronco, M. van der Meijden, R. M. Kellogg, M. Mazzotti, *CrystEngComm.* 2018, **20,** 3828-3838.
18 M. Iggland, M. P. Fernández-Ronco, R. Senn, J. Kluge, M. Mazzotti, *Chem. Eng. Sci.* 2014, **111,** 106–111.

View Article Online
DOI: 10.1039/C8CC06658B

Journal Name

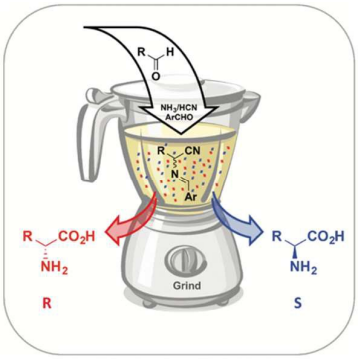
COMMUNICATION

The Strecker Reaction coupled to Viedma Ripening: A Simple Route to Highly Hindered Enantiomerically Pure Amino Acids

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Iaroslav Baglai,[a] Michel Leeman,[b] Klaus Wurst,[c] Bernard Kaptein,[d] Richard M. Kellogg,[b] and Willem L. Noorduin*,[a]



www.rsc.org/

A methodology based on a combination of the classical Strecker reaction, simple Schiff condensation and Viedma ripening (attrition induced deracemization) permits access to highly sterically α-amino acids in high enantiomeric excess and yield. This approach, unaided by chiral additives or protecting groups, allows obtainment of the handedness of choice by seeding with a small amount of enantiomerically pure crystals of the desired enantiomer.

[a] AMOLF, Science Park 104, 1098 XG Amsterdam, The Netherlands.
[b] Syncom BV,Kadijk 3, 9747 AT Groningen, The Netherlands.
[c] University of Innsbruck, Innrain 80-82, A-6020 Innsbruck, Austria.
[d] InnoSyn BV, PO Box 1090, 6160 BB Geleen, The Netherlands.
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x