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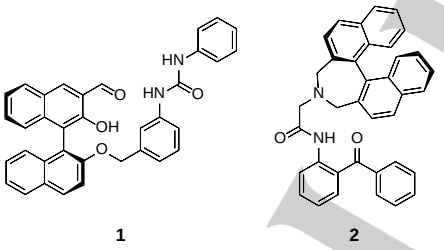
Hydrogen Bond Assisted *L* to *D* Conversion of α-Amino Acids

Rui Fu, Soon Mog So, Alan J. Lough, and Jik Chin*

Abstract: *L* to *D* conversion of unactivated α-amino acids was achieved by solubility-induced diastereomer transformation (SIDT). Ternary complexes of an α-amino acid with 3,5-dichlorosalicylaldehyde and a chiral guanidine (derived from corresponding chiral vicinal diamine) were obtained in good yield as diastereomerically pure imino acid salt complexes and were hydrolysed to obtain enantiopure α-amino acids. Combination of DFT computation, NMR spectroscopy, and crystal structure provide detailed insight into how two types of strong hydrogen bonds assist in rapid epimerization of the complexes that is essential for SIDT.

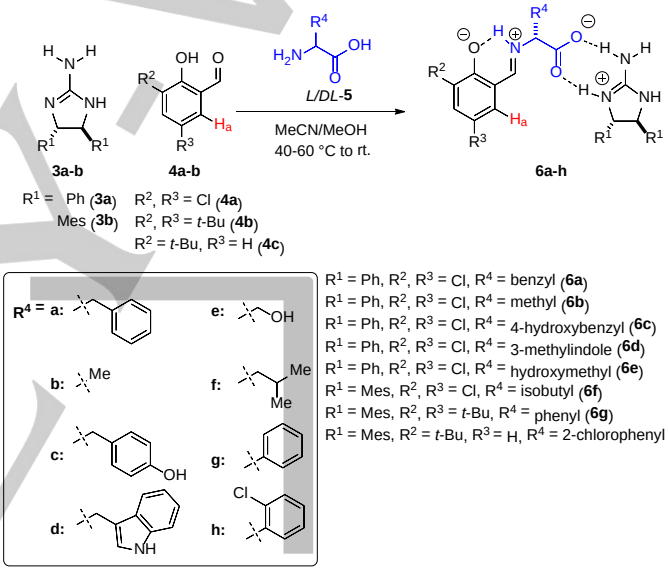
There has been much interest in developing efficient methods for the synthesis of *D*-amino acids. They are common building blocks to many pharmaceuticals such as saxagliptin[1] (antidiabetic), tadalafil[2] (erectile dysfunction), clopidogrel[3] (heart disease) and cycloserine[4] (antibiotic). In addition, *D*-amino acids are of considerable interest in the rapidly growing field of unnatural peptide-based drugs such as telaprevir[5] (antiviral), degarelix[6] (prostate cancer), and carfilzomib[7] (multiple myeloma). Many interesting chemical[8] and biological[9] methods have been developed for making *D*-amino acids. Chemical processes include Strecker synthesis,[10] hydrogenation,[11] transamination,[12] alkylation,[13] arylation,[14] and alcoholysis[15] reactions. We reported stereoselective organic (**1**)[19] and cobalt-based[20] receptors for *L* to *D* conversion of α-amino acids. More recently, Soloshonok and co-workers reported elegant designs of highly stereoselective nickel-based receptors (**2**)[21] for deracemisation of a wide variety of natural and unnatural α-amino acids.



1 **2**

Figure 1. Examples of stereoselective receptors for *L* to *D* conversion of α-amino acids.

Despite recent advances in stereoselective molecular recognition and synthesis of α-amino acids, biological[16, 17] and chemical[18] resolutions remain the most widely used methods for bulk production of *D*-amino acids. However, such methods suffer from reduced yields (< 50%) and poor substrate diversity. A more general solution that is both operationally simple and economically feasible would be beneficial for the industrial production of *D*-amino acids. In principle, highly stereoselective receptors (**1**, **2**) may be useful for efficient *L* to *D* conversion of amino acids.[19,21] However it is challenging to design such receptors that are generally applicable for a wide variety of natural and unnatural amino acids. Here we report deracemisation or *L* to *D* conversion of amino acids by using solubility differences between two diastereomeric salts of amino acids for continuous and complete transformation of one diastereomer to the other. We introduce the term SIDT (solubility-induced diastereomer transformation) instead of using CIDT (crystallization-induced diastereomer transformation)[22] or SOAT (second-order asymmetric transformation).[23]



Scheme 1. Substrates for SIDT strategy of *L* to *D* conversion and deracemisation. Mes = 1,3,5-trimethylphenyl.

The term CIDT is misleading because crystallization is not required for diastereomer transformation as it is for enantiomer transformation (CIET, crystallization-induced enantiomeric transformation) where conglomerate crystals[22,24] are required. It has also been pointed out that the term SOAT has been incorrectly translated[22] from German and can be confused with kinetic order.[23] In SIDT, one diastereomer that is below saturation is in rapid equilibrium with the other that is above saturation. This results in continuous transformation of the more soluble diastereomer to the less soluble diastereomer. SIDT can theoretically provide double the yield of classical resolutions and does not require the development of stereoselective receptors. It has been a challenge to rapidly racemise free unactivated amino acids due to the weak acidity of the α-carbon hydrogen. Here we show how two types of strong hydrogen bonds can be used in concert to deracemise unactivated amino acids by SIDT under mild reaction conditions (Scheme 1). The same method can be used to convert readily available *L*-amino acids to *D*-amino acids.

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In a typical experiment, a solution of *L*-phenylalanine, 3,5-dichlorosalicylaldehyde (**4a)** and (*S,S*)-**3a** in acetonitrile was stirred at 40 °C for 5 hours (Scheme 1). The clear solution cooled to room temperature and stirred for another 20 hours for SIDT to take place. The precipitated imino acid salt ((*S,S*)-*D*-**6a**) was filtered (83% yield, > 99:1 dr). Stirring the mixture for an additional 2 days resulted in 90% yield. Addition of *(S,S)-D*-**6a** to acetonitrile with 3% (v/v) conc. HCl resulted in hydrolysis of the imino acid

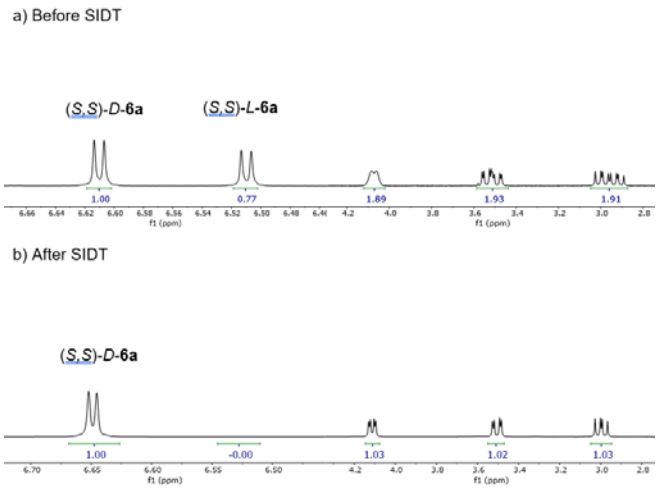

Figure 2. a) Partial ^{1}H NMR ($CDCl_3$) of a mixture of phenylalanine imine salt complexes (prior to SIDT) showing H_a belonging to (*S,S*)-*D*-**6a** and (*S,S*)-*L*-**6a**. The α-proton and methylene protons of phenylalanine are shown on the right. b) Partial ^{1}H NMR ($CDCl_3$) of the phenylalanine imine salt complex after SIDT.

salt and precipitation of the *D*-amino acid hydrochloride salt (>98% ee). **3** and **4** can be recovered and recycled without the need for chromatographic purification by evaporating the above filtrate and stirring with 0.5 M HCl (precipitation of **4**) followed by basification of the filtrate (precipitation of **3**).

Table 1. SIDT of imino acid complexes (**6**)

Entry	Substrate	Guanidine	Product	Yield (%)[a]	d.r.[b]
1	*L*-**5a**	(*S,S*)-**3a**	(*S,S*)-*D*-**6a**	83	>99:1
2	*L*-**5b**	(*S,S*)-**3a**	(*S,S*)-*D*-**6b**	64	>99:1
3	*L*-**5c**	(*S,S*)-**3a**	(*S,S*)-*D*-**6c**	92	>99:1
4	*L*-**5d**	(*S,S*)-**3a**	(*S,S*)-*D*-**6d**	91	98:2
5	*L*-**5e**	(*S,S*)-**3a**	(*S,S*)-*D*-**6e**	78	>99:1
6	*L*-**5f**	(*S,S*)-**3b**	(*S,S*)-*D*-**6f**	71	>99:1
7	*DL*-**5f**	(*R,R*)-**3b**	(*R,R*)-*L*-**6f**	70	>99:1
8	*DL*-**5g**	(*R,R*)-**3b**	(*R,R*)-*L*-**6g**	78	>99:1
9	*DL*-**5h**	(*R,R*)-**3b**	(*R,R*)-*L*-**6h**	73	97:3

[a] Isolated yield of imino acid complex. [b] d.r. values were determined by ^{1}H NMR analysis of isolated imino acid complexes.

The ratio of concentrations of *(S,S)-D*-**6a** and *(S,S)-L*-**6a** can be determined from ^{1}H NMR by integrating the H_a signals (Scheme 1) of the two diastereomeric salts. There is about equal concentrations of *(S,S)-L*-**6a** and *(S,S)-D*-**6a** in the initial reaction mixture after heating at 40 °C for 5 h (Figure 1a). After SIDT, the H_a signal due to *(S,S)-L*-**6a** has essentially disappeared (Figure 1b). Interestingly, the H_a signals for *(S,S)-D*-**6a-e** appear downfield of corresponding *(S,S)-L*-**6a-e** signals. Furthermore, *(S,S)-D*-**6a-e** are less soluble than corresponding *(S,S)-L*-**6a-e**.

This general and unified approach for sensing *D*- and *L*-amino acids as well as for converting *L*-amino acids to *D*-amino acids is unprecedented. In case of **5f**, the solution failed to yield precipitates during attempts at SIDT using **3a** and **4a**. However, using a different guanidine **3b** with **4a**, we were able to achieve *L* to *D* conversion of **5f** (Table 1, entry 6) and deracemisation of racemic **5f**. (Table 1, entry 7). SIDT was also successful in our system using α-arylglycines as substrates (Table 1, entries 8-9). However, due to the increased activation of the α-carbon by the α-aryl group, decarboxylation was observed when the electron-withdrawing 3,5-dichlorosalicylaldehyde (**4a**) was used. Upon switching to 3,5-di-*tert*-butylsalicylaldehyde (**4b**) and 3-*tert*-butylsalicylaldehyde (**4c**), we were able to obtain the diastereomeric salts of *L*-phenylglycine (Table 1, entry 8) and *L*-2-chlorophenylglycine (Table 1, entry 9) from their racemic mixtures in 78% and 73% yields, respectively. Both *L* to *D* conversion of tryptophan and deracemisation of 2-chlorophenylglycine are of industrial interest as they are the unnatural amino acids found in tadalafil and clopidogrel, respectively.

It is worth noting that the sense of stereoselectivity remains the same for **3b** as for **3a**. Thus the H_a signal for *(S,S)-D*-**6f** is downfield that of *(S,S)-L*-**6f** and *(S,S)-D*-**6f** is less soluble than *(S,S)-L*-**6f**. In addition to the H_a signal, other ^{1}H NMR signals can be used to determine the ratio of concentrations of *(S,S)-D* -**6a-f** and *(S,S)-L*-**6a-f** (Supporting Information). There is excellent agreement between the concentration ratios obtained from integration of H_a signals and other ^{1}H NMR signals. Thus, our system allows for simultaneous deracemisation and determination of diastereomeric purity.

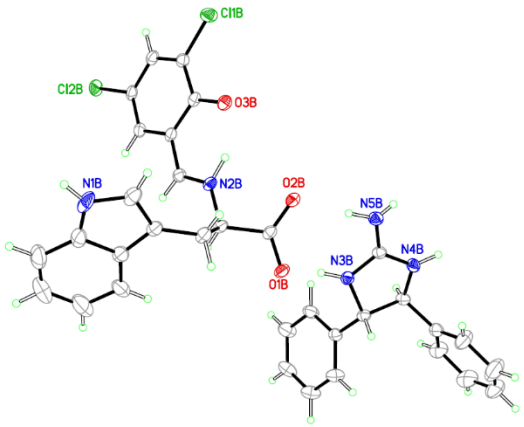

Figure 3. X-ray crystal structure of *(S,S)-D*-**6d**.

One of the main conditions for a successful SIDT is that racemisation be faster than crystallization. There are two special types of strong hydrogen bonds in our system (Scheme 1) that appear to play important roles in the rapid racemisation. The first is the resonance-assisted hydrogen bond (RAHB)[25] between the

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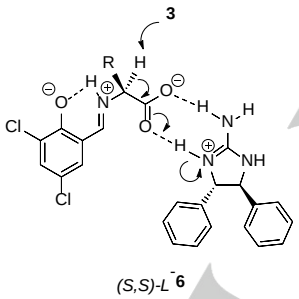
phenolic oxygen and the imine nitrogen and the second is the charged double-hydrogen bond between the carboxylate and the guanidinium groups. Insight into the role of the hydrogen bonds in speeding up the racemisation may be obtained from our crystallographic and computational studies discussed below.

Figure 3 shows the crystal structure of *(S,S)-D*-**6d**. Interestingly, the hydrogen involved in the RAHB is attached to the imine nitrogen and hydrogen bonded to the phenolic oxygen. Computation also shows that *(S,S)-D*-**6d** is more stable when the proton is attached to the imine nitrogen than when it is attached to the phenolic oxygen. If the two chloro- substituents in *(S,S)-D*-**6d** are removed, computation then shows that the hydrogen is favored to be on the phenolic oxygen rather than the imine nitrogen (See Supporting Information). It appears that the phenolic group in *(S,S)-D*-**6d** is sufficiently electron deficient for the proton to prefer the imine nitrogen over the phenolic oxygen. This is consistent with our NMR studies as the proton is observed to be significantly more downfield (15 ppm) than in other compounds when the proton is on the phenolic oxygen (13 ppm). The positive charge on the imine nitrogen in *(S,S)-D*-**6d** may acidify the α-proton of the imino acid. This is corroborated by our observation that deuteration of the α-carbon of phenylalanine occurs more rapidly with 3,5-dichlorosalicylaldehyde (**4**) than with salicylaldehyde.

In order to gain more insight into our rapid racemisation, we carried out DFT computation of our imino acid ion pair complex (**6**) at the B3LYP/6-31G* level of theory. In general, base catalysts are needed for racemisation of amino acids. In our case, neutral guanidine (**3**) can play this role. However, computation indicates that there may be an additional general acid catalysis coming from the guanidinium group in the ion pair complex (Figure 4).

a)



(S,S)-L-**6**

b)

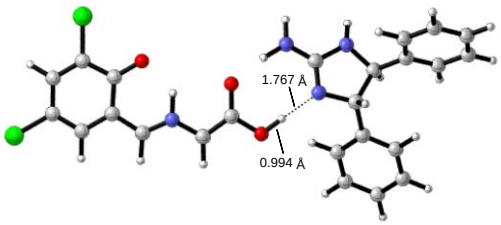


Figure 4. a) Proposed concerted general acid/base catalysis for racemisation. b) Computed structure of an anionic glycine imino acid salt complex with an α-proton deprotonated. (B3LYP/6-31G* level of theory)

The carboxylate group in our ion pair complex is not basic enough to deprotonate the guanidinium counter ion. However, computation reveals that once the α-proton is removed with a base, the carboxylate group becomes basic enough to deprotonate the guanidinium. Computation of the complex was started as the carboxylate guanidinium salt. After minimisation, the proton has transferred from the guanidinium nitrogen to the carboxylate oxygen. The distance between the proton and nitrogen is 1.767 Å while the distance between the proton and oxygen is 0.994 Å (Figure 4b). Thus, removal of proton from the α-position is expected to be concerted with proton transfer from the guanidinium to the carboxylate group in the ion pair complex. This is in accordance with Jencks' "libido-rule" and matching-pK_a requirement for general acid/base catalysis.[26] Pre-association between the carboxyl group and the guanidium group by charge assisted hydrogen bonding would allow efficient proton transfer at the transition state resulting in general acid catalysis. This proposed dual general acid/base catalysis for amino acid racemisation represents the first of its kind. Interestingly, racemisation is more rapid with our system in less polar solvents like acetonitrile where tight ion pairs would form. This contrasts with other systems where racemisation is faster in more polar solvents like water or alcohol.

CIDT[22] and SOAT[27] are two terms that explain the same phenomenon. The process involves rapid equilibration between diastereomers in solution. One of the diastereomer continuously crystallizes out resulting in diastereomer transformation to give one diastereomer crystals. It has been suggested that this process is based on serendipity and cannot be rationally designed. To quote Brands and Davies,[22] "a CIDT can only become viable when the diastereomers crystallize as a eutectic mixture". Similarly, Soloshonok[27] points out that "SOAT is essentially a serendipitous approach resulting from rather complex and multifactorial interplay of numerous chemical/steric/physical properties". However, classic diastereomer resolution depends only on the solubility difference of the diastereomers and crystallization is not required. Thus, diastereomer transformation should not require crystallization. Rapidly equilibrating diastereomers in solution resulting in supersaturation of one diastereomer should result in continuous precipitation of that diastereomer resulting in diastereomer transformation. Theoretical yield of diastereomer resolution is 50% while that of diastereomer transformation is 100%. This phenomenon that we call SIDT should be less dependent on serendipity and allow a more general approach for rational design.

In conclusion, we have demonstrated that organic SIDT can be used for deracemisation of free, unprotected amino acids without the need for developing stereoselective receptors. A single system consisting of **3** and **4** can be used to achieve *L* to *D* conversion or deracemisation and detect the *D/L* ratio of a variety of amino acids in a unified way. X-ray and computational data indicate that two special types of strong hydrogen bonds are involved in facilitating rapid racemisation of amino acids which is crucial for SIDT. Excellent diastereoselectivity (up to >99:1 dr) is observed with the same sense of stereoselectivity for our substrates and subsequent hydrolysis of the imino acid salts results in enantiopure amino acids (up to >98% ee). This organic system can be recycled without the need for chromatographic purification as in metal based systems. Overall, our operationally simple method offers an attractive strategy towards the synthesis of *D*-amino acids — a useful entry point into a variety of biologically active molecules.

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Keywords: amino acids • SIDT • deracemisation • computation • general acid/base catalysis

[1] A. Daugan, P. Grondin, C. Ruault, A. C. Le Monnier de Gouville, H. Coste, J. M. Linget, J. Kirilovsky, F. Hyafil, R. Labaudinièret, *J. Med. Chem.* **2003**, *46*, 4533–4542.

[2] 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, et al., *J. Med. Chem.* **2005**, *48*, 5025–5037.

[3] J. M. Herbert, D. Frehel, E. Vallee, G. Kieffer, D. Gouy, Y. Berger, J. Necciari, G. Defreyn, J. P. Maffrand, *Cardiovasc. Drug Rev.* **1993**, *11*, 180–198.

[4] F. A. Kuehl, F. J. Wolf, N. R. Trenner, R. L. Peck, E. Howe, B. D. Hunnewell, G. Downing, E. Newstead, K. Folkers, R. P. Buhs, et al., *J. Am. Chem. Soc.* **1955**, *77*, 2344–2345.

[5] A. D. Kwong, R. S. Kauffman, P. Hurter, P. Mueller, *Nat. Biotechnol.* **2011**, *29*, 993–1003.

[6] J. Anderson, *Future Oncol.* **2009**, *5*, 433−443

[7] M. L. Khan, A. K. Stewart, *Future Oncol.* **2011**, *7*, 607−612

[8] S. M. So, H. Kim, L. Mui, J. Chin, *Eur. J. Org. Chem.* **2012**, 229–241.

[9] a) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer, T. Zelinski, *Angew. Chem Int. Ed.* **2004**, *43*, 788–824. b) M. A. T. Blaskovich, *J. Med. Chem.* **2016**, *59*, 10807–10836.

[10] a) M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* **1996**, *118*, 4910-4911. b) J. Wang, X. Liu, X. Feng, *Chem. Rev.* **2011**, *111*, 6947-6983. c) S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature* **2009**, *461*, 968-970. d) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358-15374.

[11] a) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106-112. b) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998-2007. c) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029-3070. d) M. J. Burk, *J. Am. Chem. Soc.* **1991**, *113*, 8518-8519. e) D. Pena, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2002**, *124*, 14552-14553. f) M. Van den Berg, R. M. Haak, A. J. Minnaard, A. H. M. De Vries, J. G. De Vries, B. L. Feringa, Adv. Synth. Catal. 2002, 344, 1003-1007. g) M. T. Reetz, J.-A. Ma, R. Goddard, *Angew. Chem. Int. Ed.* **2005**, *44*, 412-415. h) Y. Liu, K. Ding, *J. Am. Chem. Soc.* **2005**, *127*, 10488-10489. i) C. Zhu, T. Akiyama, *Adv. Synth. Catal.* **2010**, *352*, 1846-1850.

[12] a) X. Xiao, Y. Xie, C. Su, M. Liu, Y. Shi, *J. Am. Chem. Soc.* **2011**, *133*, 12914-12917. b) S. Bandyopadhyay, W. Zhou, R. Breslow, *Org. Lett.* **2007**, *9*, 1009-1012. c) K. R. Knudsen, S. Bachmann, K. A. Jorgensen, *Chem. Commun.* **2003**, *20*, 2602-2603. d) S. Bachmann, K. R. Knudsen, K. A. Jorgensen, *Org. Biomol. Chem.* **2004**, *2*, 2044-2049. e) A. Hjelmencrantz, U. Berg, *J. Org. Chem.* **2002**, *67*, 3585-3594.

[13] a) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506-517. b) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415. c) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107*, 5656-5682. d) S. Kobayashi, R. Yazaki, K. Seki, Y. Yamashita, *Angew. Chem. Int. Ed.* **2008**, *47*, 5613-5615. e) Y.-J. Chen, K. Seki, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2010**, *132*, 3244-3245.

[14] a) D. J. Leonard, J. W. Ward, J. Clayden, *Nature* **2018**, *562*, 105–109. b) J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs, J.-Q. Yu, *Science* **2014**, *343*, 1216-1220.

[15] a) J. Hang, S.-K. Tian, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 12696-12697. b) Y. Ishii, R. Fujimoto, M. Mikami, S. Murakami, Y. Miki, Y. Furukawa, *Org. Process Res. Dev.* **2007**, *11*, 609-615. c) H. S. Rho, S. H. Oh, J. W. Lee, J. Y. Lee, J. Chin, C. E. Song, *Chem. Commun.* **2008**, *10*, 1208-1210. d) S. H. Oh, H. S. Rho, J. W. Lee, J. E. Lee, S. H. Youk, J. Chin, C. E. Song, *Angew. Chem. Int. Ed.* **2008**, *47*, 7872-7875. e) T. Honjo, S. Sano, M. Shiro, Y. Nagao, *Angew. Chem. Int. Ed.* **2005**, *44*, 5838-5841. f) J. Liang, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 3154-3155. g) A. Peschiulli, C. Quigley, S. Tallon, Y. K. Gun'ko, S. J. Connon, *J. Org. Chem.* **2008**, *73*, 6409-6412. h) A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Mueller, J. Lex, *Angew. Chem. Int. Ed.* **2005**, *44*, 807-811. i) D. Seebach, G. Jaeschke, Y. M. Wang, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2395-2396. j) K. Gottwald, D. Seebach, Tetrahedron 1999, 55, 723. k) D.Seebach, G. Jaeschke, K. Gottwald, K. Matsuda, R. Formisano, D. A. Chaplin, M. Breuning, G. Bringmann, Tetrahedron 1997, 53, 7539.

[16] I.G. Fotheringham, P. P. Taylor, J. L. Ton (Monsanto Co.), US5728555, **1998** [*Chem. Abstr.***1999**, *128*, 216437].

[17] a) K. Yasukawa, R. Hasemi, Y. Asano, *Adv. Synth. Catal.* **2011**, *353*, 2328–2332. b) O. May, S. Verseck, A. Bommarius, K. Drauz, *Org. Process Res. Dev.* **2002**, *6*, 253–257.

[18] a) G. J. Roff, R. C. Lloyd, N. J. Turner, *J. Am. Chem. Soc.* **2004**, *126*, 4098–4099. b) W. Liu, S. Laneman, D. J. Ager, P. P. Taylor (Great Lakes Chemical Corp.), WO 01/62948A2, **2001** [*Chem. Abstr*. **2001**,*135*, 209968].

[19] a) H. Park, M. K. Kwan, A. Lee, S. Ham, W. Nam, J. Chin, *J. Am. Chem. Soc.* **2007**, *129*, 1518–1519. b) S. M. So, K. Moozeh, A. J. Lough, J. Chin, *Angew. Chem. Int. Ed.* **2014**, *53*, 829–832. c) K. Moozeh, S. M. So, A. J. Lough, J. Chin, *Angew. Chem. Int. Ed.* **2015**, *54*, 9381–9385.

[20] J. Chin, S. S. Lee, K. J. Lee, S. Park, D. H. Kim, *Nature* **1999**, *401*, 254–257.

[21] a) V. A. Soloshonok, T. K. Ellis, H. Ueki, T. Ono, *J. Am. Chem. Soc.* **2009**, *131*, 7208–7209. b) R. Takeda, A. Kawamura, A. Kawashima, T. Sato, H. Moriwaki, K. Izawa, K. Akaji, S. Wang, H. Liu, J. L. Aceña, et al., *Angew. Chem. Int. Ed.* **2014**, *53*, 12214–12217. c) S. Zhou, J. Wang, X. Chen, J. L. Aceña, V. A. Soloshonok, H. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 7883–7886. d) Y. Nian, J. Wang, S. Zhou, S. Wang, H. Moriwaki, A. Kawashima, V. A. Soloshonok, H. Liu, *Angew. Chem. Int. Ed.* **2015**, *54*, 12918–12922. e) J. Han, T. T. Romoff, H. Moriwaki, H. Konno, Vadim A. Soloshonok, *ACS Omega* **2019**, *4*, 18942−18947 f) K. D. Klika, A. Wzorek, V. A. Soloshonok, *Chirality*, **2018**, *30*, 1054-1066.

[22] K. M. J. Brands, A. J. Davies, *Chem. Rev*. **2006**, *106*, 2711−2733.

[23] M. M. Jamison, E. E. Turner, *J. Chem. Soc.*, **1942**, 437–440

[24] B. Kaptein, W. L. Noorduin, H. Meekes, W. J. P. Enckevort, R. M. Kellogg, E. Vlieg, Angew. Chem. Int. Ed. 2008, 47, 7226-7229.

[25] P. Gilli, V. Bertolasi, V. Ferretti, G. Gilli, *J. Am. Chem. Soc.* **2000**, *122*, 10405-10417

[26] W. P. Jencks, *J. Am. Chem. Soc.* **1972**, *94*, 4731–4732.

[27] a) R. Takeda, A. Kawashima, J. Yamamoto, T. Sato, H. Moriwaki, K. Izawa, H. Abe, V. A. Soloshonok, *ACS Omega* **2018**, *3*, 9729-9737. b) R. Takeda, A. Kawamura, A. Kawashima, T. Sato, H. Moriwaki, K. Izawa, H. Abe, V. A. Soloshonok, *Org. Biomol. Chem.* **2018**, *16*, 4968-4972.

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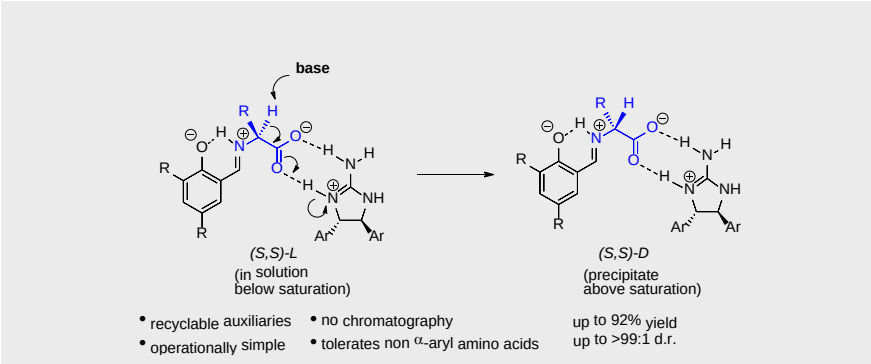

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Hydrogen Bond Assisted *L* to *D* Conversion of α-Amino Acids