Stereoselective Deuteration

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Catalytic Stereoinversion of L-Alanine to Deuterated D-Alanine**

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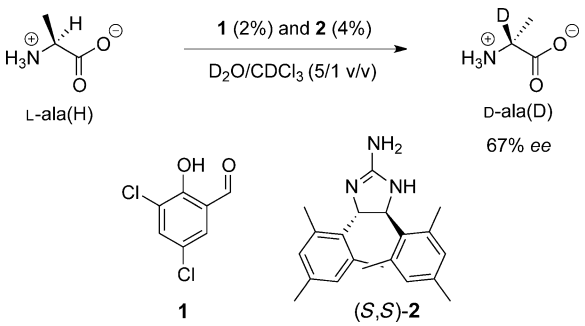
Abstract: *A combination of an achiral pyridoxal analogue and a chiral base has been developed for catalytic deuteration of* L*-alanine with inversion of stereochemistry to give deuterated* D*-alanine under mild conditions (neutral pD and 25 °C) without the use of any protecting groups. This system can also be used for catalytic deuteration of* D*-alanine with retention of stereochemistry to give deuterated* D*-alanine. Thus a racemic mixture of alanine can be catalytically deuterated to give an enantiomeric excess of deuterated* D*-alanine. While catalytic deracemization of alanine is forbidden by the second law of thermodynamics, this system can be used for catalytic deracemization of alanine with deuteration. Such green and biomimetic approach to catalytic stereocontrol provides insights into efficient amino acid transformations.*



Scheme 1. Catalytic stereoselective deuteration of L-alanine to deuterated D-alanine using a pyridoxal analogue (**1**) and a chiral base (**2**).

Catalytic conversion of L-amino acids to D-amino acids is a topic of considerable interest in biology and chemistry.[1] Although L-amino acids dominate nature, D-alanine, D-serine, D-proline, D-aspartic acid, and D-glutamic acid all have biological functions and are produced from their corresponding L-amino acids enzymatically.[2] Chemists have been interested in making D-amino acids as they are building blocks for making small-molecule pharmaceuticals.[3] There is much interest in developing green and efficient methods for modifying amino acids without the use of activating or protecting groups.[4] Furthermore, stereoselective deuteration of amino acids and drugs is a topic of considerable current interest.[5] Preliminary studies in stereoselective recognition of amino acids[6] and L to D conversion of amino acids[7] led us to investigate their catalytic transformations with deuteration. Here we show a proof-of-principle of how alanine can be catalytically deuterated stereoselectively under mild conditions without the use of any protecting groups (Scheme 1).

In a typical experiment, **1** (0.1 M) and (*S*,*S*)-**2** (0.2 M) were dissolved in $CDCl_3$ (0.2 mL) and vigorously stirred with 1 mL of a 1 M solution of L-alanine or D-alanine in D_2O (Scheme 1). ^1H NMR of the D_2O layer shows that the α-proton quartet of alanine disappears and the methyl signal of alanine collapses from a doublet to a singlet. With the above catalyst loading of 2% for **1** and 4% for (*S*,*S*)-**2**, the half-life for deuteration of D-alanine in the D_2O layer at neutral pD is about 15 min at ambient temperature. Deuteration of L-alanine is about five times slower with a half-life of about 75 min.

Remarkably, both L-alanine and D-alanine give predominantly deuterated D-alanine at 90% deuteration. For example, when L-alanine is reacted for 4 h under the present condition, deuteration is about 87% complete (Figure 1, Table 1) and the D/L ratio of the deuterated alanine is about 5:1 (67% *ee*). To determine the D to L ratio of this solution, the water layer was first separated from the chloroform layer

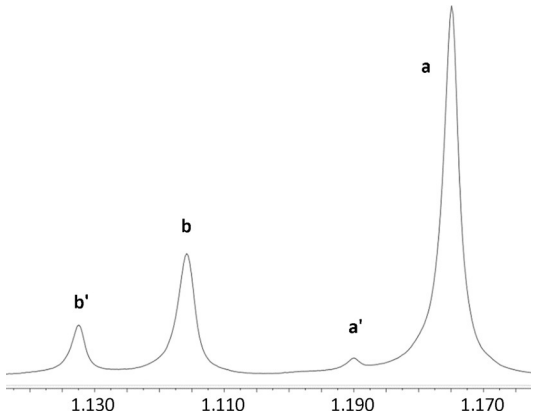


Figure 1. Signals in the ^1H NMR spectrum for the alanine salt methyl group after extracting the D_2O layer with $CDCl_3$ as described in the text. a) Deuterated D-alanine salt. b) Deuterated L-alanine salt. b′) Doublet signal of the initial non-deuterated L-alanine salt partially hidden under (b). a′) Doublet signal of non-deuterated D-alanine salt partially hidden under (a).

Table 1: Catalytic deuteration of L-ala as described in the text.

Reaction time	% Deuteration of Ala in D_2O	D/L ratio of *S*,*S*-(D)-**3**	D/L ratio of *S*,*S*-(L)-**4**
4 h	87%	5/1	7.5/1
72 h	99%	1/1	1.5/1

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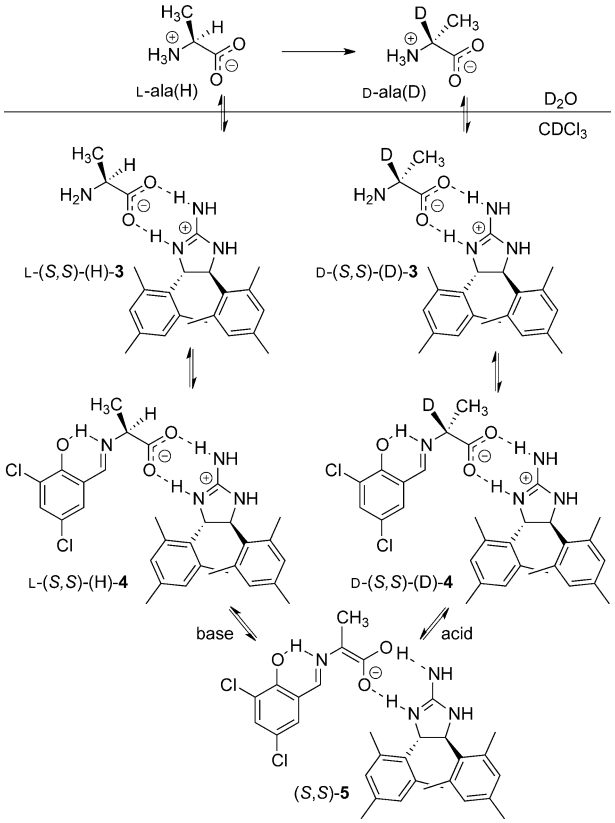
and extracted with a fresh solution of $CDCl_3$ that contains (*S*,*S*)-**2** but not **1**. The chiral guanidine by itself, (*S*,*S*)-**2**, does not racemize alanine under our conditions and is useful for extraction of alanine from the water to the chloroform layer by formation of the diastereomeric amino acid salts (**3**, Scheme 2). This extraction step is non-stereoselective. The two diastereomeric salts give distinct ^{1}H NMR signals for determination of the D/L ratio of alanine. The signals of the methyl groups of deuterated D-ala and L-ala salts appear at 1.03 (signal (a); Figure 1) and 1.08 ppm (b), respectively. We also observe half of the doublet signal (b′) owing to the starting alanine salt that has not been deuterated. The other half of the doublet is hidden under peak (b) and was corrected in calculating the D/L ratio of deuterated alanine. Half of the doublet signal (a′) due to D-alanine that is not deuterated is also visible although very small.

When L-alanine is reacted for three days instead of 4 h under the present conditions, the D/L ratio of deuterated alanine in the water layer is close to equilibrium at 1:1 (Table 1). The drop in the D/L ratio (5:1 to 1:1) is due to catalytic racemization of deuterated D-alanine.

In case of catalytic deuteration of D-alanine with **1** and (*S*,*S*)-**2**, deuteration is about 95% complete in 90 min under the condition to give deuterated D-alanine preferentially with a D/L ratio of about 5:1. Thus deuteration of L-alanine takes place more slowly with inversion of stereochemistry while deuteration of D-alanine takes place more rapidly with retention of stereochemistry. This system can also be used for deracemization of racemic mixtures of alanine to give deuterated D-alanine.



Scheme 2. Proposed mechanism for catalytic conversion of L-alanine to deuterated D-alanine.

Scheme 2 shows the proposed mechanism for catalytic deuteration of L-alanine with **1** and (*S*,*S*)-**2**. At neutral pH L-alanine is in the water layer as the zwitterionic form. The basic and highly hydrophobic guanidine ((*S*,*S*)-**2**) effectively extracts L-alanine from the D_2O layer to the $CDCl_3$ layer where it forms the amino acid salt (**3**). The amino acid salt is in equilibrium with the imino acid salt (**4**), which deprotonates (**5**) and then deuterates to give the two diastereomeric imino acid salts (D-(*S*,*S*)-(D)-**4** and L-(*S*,*S*)-(D)-**4**). The imino acid salts are in equilibrium with the two diastereomeric amino acid salts (D-(*S*,*S*)-(D)-**3** and L-(*S*,*S*)-(D)-**3**). In the final step, deuterated alanine is released back to the water layer. The D/L ratio of the two imino acid salts (D-(*S*,*S*)-(D)-**4** and L-(*S*,*S*)-(D)-**4**), and the two amino acid salts (D-(*S*,*S*)-(D)-**3** and L-(*S*,*S*)-(D)-**3**) can be monitored by ^{1}H NMR spectroscopy (Figure 1).

Apart from monitoring the D/L ratio of alanine in the D_2O layer by extraction (Figure 1), we also separated and monitored the $CDCl_3$ layer of the catalytic system after 20 min of vigorous stirring. For example, a ^{1}H NMR spectrum (Supporting Information, Figure S26) shows the chloroform layer of the catalytic system for deuteration of L-alanine immediately after (top) and 3 h after (bottom) separation from the water layer. Deuteration of alanine trapped in the separated chloroform layer (Supporting Information, Figure S26 top) is almost complete within the time (15 min) it takes to prepare and run the NMR sample. Since only about 4% of alanine is trapped in the chloroform layer, the half-life for deuteration of the trapped alanine in the separated $CDCl_3$ layer should roughly be about 3 min (4% of 75 min). The D/L ratio of the deuterated amino acid salts (D-(*S*,*S*)-(D)-**3** and L-(*S*,*S*)-(D)-**3**) in Scheme 2 is about 4.2:1 (Supporting Information, Figure S26 top right), corresponding to 62% *ee*. Thus the chloroform layer is rapidly generating enantiomeric excess of deuterated D-alanine from L-alanine within minutes (Supporting Information, Figure S26 top). When this chloroform layer is in contact with the water layer, amino acid exchange takes place between the two layers resulting in an increase in enantiomeric excess of deuterated D-alanine within hours (Figure 1) in the water layer. Not surprisingly, the ratios of methyl signals in Figure 1 closely resemble those in the Supporting Information, Figure S26 top right.

When the above chloroform layer is kept separated from the water layer for 3 h, the D/L ratio of the deuterated amino acid salts (D-(*S*,*S*)-(D)-**3** and L-(*S*,*S*)-(D)-**3**) goes down from 4.2:1 and reaches equilibrium at 1:1 (Supporting Information, Figure S26 bottom right). This is due to catalytic racemization of deuterated D-alanine trapped in the NMR tube. The D/L ratio of the imino acid salt (D-(*S*,*S*)-(D)-**4** plus D-(*S*,*S*)-(H)-**4** and L-(*S*,*S*)-(D)-**4** plus L-(*S*,*S*)-(H)-**4**) reaches equilibrium at about 1.5:1 (Supporting Information, Figure S26 bottom left) as determined by the ratio of the imine hydrogen signals at 7.72 ppm (D-(*S*,*S*)-(D)-**4** plus D-(*S*,*S*)-(H)-**4**) and 7.69 ppm (L-(*S*,*S*)-(D)-**4** plus L-(*S*,*S*)-(H)-**4**). Our NMR data (Supporting Information, Figure S26) indicates that the stablilities in $CDCl_3$ of the two diastereomeric amino acid salts (Table 1) are about the same (1:1) while for the imino acid salts, D-

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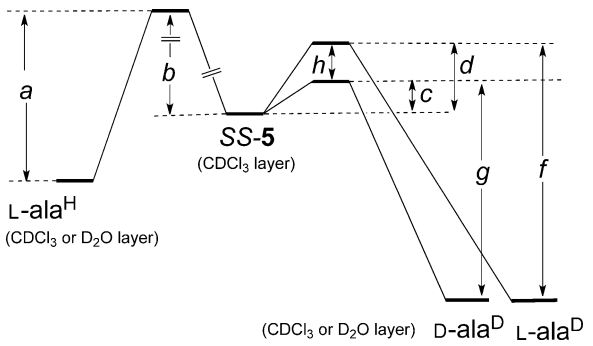
(*S*,*S*)-(D)-**4** is slightly more stable than L-(*S*,*S*)-(D)-**4** (1.5:1). There appears to be some stereoselective interaction between the guanidyl and salicyl groups in the imino acid salt (**4**). It is interesting that the kinetic stereoselectivity (5:1) is considerably greater than the thermodynamic stereoselectivity (1.5:1). Table 1 shows that even at 4 h as at 72 h, the diastereomeric ratio of the imino acid salt (7.5:1) is greater than that of the amino acid salt (5:1) by a factor of 1.5.

The results are quite different if we carry out the above experiment with L-alanine in H_2O (Supporting Information, Figure S27) instead of D_2O. Unlike in D_2O, there is no enantiomeric excess of D-alanine in H_2O at any point in time. Immediately after separating the two layers, the CD_3Cl layer shows that the amino acid salt ratio (D-(*S*,*S*)-(H)-**3**/L-(*S*,*S*)-(H)-**3**) is about 0.87:1 (Supporting Information, Figure S27 top). After 3 h of separation of the chloroform layer, the amino acid salt ratio is about 1:1 while the imino acid salt ratio is about 1.5:1 favoring the D form (Supporting Information, Figure S27 bottom). In comparing the experiments in D_2O and H_2O, the results are very different initially (Supporting Information, Figure S26 vs S27 top) but similar at 3 h (Supporting Information, Figure S26 vs S27 bottom). Initially, there is equilibrium overshoot (net L to D conversion) in the D_2O experiment but not in the H_2O experiemnt. At 3 h, both the H_2O and the D_2O experiments reach the same thermodynamic equilibrium (same D/L ratios of the imino acid salts (1.5:1) and the amino acid salts (1:1)).

It is interesting that we observe catalytic L to D conversion of alanine in D_2O (Figure 1; Supporting Information, Figure S26). This could not take place in H_2O (Supporting Information, Figure S27 top) since it would violate the principle of microscopic reversibility to have net directional catalysis (that is, more efficient L to D than D to L). Furthermore, it would go against the second law of thermodynamics to go beyond racemization to enantiomeric excess of D-alanine in H_2O with a catalyst since that would represent decreasing entropy without change in enthalpy. In our case, significant kinetic isotope effect allows catalytic L to D conversion of alanine to take place in D_2O.

The deuteration of L-alanine takes place more rapidly if **1** is used with (*R*,*R*)-**2** instead of (*S*,*S*)-**2**. The half-life for deuteration of L-alanine when (*R*,*R*)-**2** is used with **1** is about 15 min in contrast to about 75 min when (*S*,*S*)-**2** is used with **1** under our experimental conditions. However we do not observe net L to D conversion of alanine if we use (*R*,*R*)-**2** instead of (*S*,*S*)-**2**. We observe deuteration of L-alanine with retention of configuration when (*R*,*R*)-**2** is used with **1**. Similarly, we observe deuteration of D-alanine with retention of configuration when (*S*,*S*)-**2** is used with **1**. This can be explained by using an energy diagram (Scheme 3) for catalytic deuteration of L-alanine (L-ala^H, Scheme 3) to give deuterated D-alanine (D-ala^D) and deuterated L-alanine (L-ala^D). The starting material and products in Scheme 3 may be regarded to be in the chloroform layer or the D_2O layer.

The energy diagram is consistent with all our experimental results but is not drawn to scale. The intermediate ((*S*,*S*)-**5**, Scheme 2) deuterates stereoselectively to give D-ala^D over L-ala^D as depicted by the energy difference *h* in Scheme 3. The selectivity can be seen experimentally as amino acid salt ratios



Scheme 3. Energy diagram for deuteration of L-ala^H.

in $CDCl_3$ (Supporting Information, Figure S26 top right). The two products equilibrate slowly due to kinetic isotope effect and eventually reach equilibrium ratio of 1:1 as depicted by equal energies of the two products (Scheme 3). This can also be seen experimentally to be about 1:1 amino acid salt ratio in $CDCl_3$ as determined by integration of the ^1H NMR peaks (Supporting Information, Figure S26 bottom right). Note that the imino acid salt ratio is not 1:1 at equilibrium (Supporting Information, Figure S26 bottom left) as there is some stereoselectivity for formation of the diastereomeric imino acid salts. Conversion of the starting material to products is downhill since there is much more D_2O than H_2O in the experiment. D-ala^D should dedeuterate more rapidly than L-ala^D ($f > g$) as shown in Scheme 3. It follows that D-ala^H should deprotonate more rapidly than L-ala^H. In agreement, we observe that (*S*,*S*)-**2** is more reactive for deprotonating D-alanine than L-alanine. Indeed, the relative rate of deprotonation of D-ala^H and L-ala^H with (*S*,*S*)-**2** should be essentially equal to the relative rate of deuteration of (*S*,*S*)-**5** to give D-ala^D and L-ala^D (given by *h* in Scheme 3). When the experiment is carried out with H_2O instead of D_2O (Supporting Information, Figure S27), there cannot be enantiomeric excess of the product (D-ala^H) since it would be equal in energy as the starting material (L-ala^H) unlike in Scheme 3.

If (*R*,*R*)-**2** is used instead of (*S*,*S*)-**2** as catalyst, intermediate (*R*,*R*)-**5** would form and preferentially give L-ala^D over D-ala^D in symmetry with Scheme 3, and therefore not result in net L to D conversion of alanine. Thus, deuteration of L-alanine with (*R*,*R*)-**2** and **1** should take place with retention of configuration in agreement with the experiment.

The only previous examples for obtaining catalytic stereoselective deuteration of amino acids is with enzymes. Alanine[8] and proline[9] racemases have been shown to deuterate amino acids streoselectivity. It is remarkable that our simple system provides greater stereoselectivity (67 % *ee*) than the enzymic systems (< 20 % *ee*) for deuteration of alanine or proline. In the enzymic studies, CD spectroscopy was used to determine the enantiomeric excess of D-amino acids. While detailed NMR studies are readily accessible with both enantiomers of the catalyst in our system ((*S*,*S*)-**2** and (*R*,*R*)-**2**), it would be technically difficult to do similar studies with enzymes. Highly efficient chemoenzymatic catalytic L to D conversion of amino acids under non-equilibrium conditions using oxidation and reducing agents have been reported.[10]

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1 or (*S*,*S*)-**2** by itself does not catalyze deuteration or racemization of alanine under our experimental condition but together they represent the most efficient non-enzymic system for catalytic racemization of alanine and other amino acids. We do not observe deuteration of alanine if we replace (*S*,*S*)-**2** in our experiment with DBU. Less hydrophobic bases like DBU does not work in our system because it cannot extract alanine to the chloroform layer. Indeed alanine extracts DBU to the water layer instead. Similarly, we do not observe deuteration of alanine when (*S*,*S*)-**2** is replaced with triethylamine or tetrabutylammonium hydroxide. Triethylamine is a weaker base than (*S*,*S*)-**2** and tetrabutylammonium hydroxide is quenched by neutral alanine. In contrast, (*S*,*S*)-**2** is not fully quenched by neutral alanine. Some (*S*,*S*)-**2** in the chloroform layer exists as the amino acid salt and some as the neutral form.

3,5-dichlorosalicylaldehyde (**1**) was chosen as a pyridoxal mimic. Both aldehydes are electron deficient and both aldehydes have intramolecular resonance assisted hydrogen bonds. The rate of deuteration of alanine decreases about 50 fold if **1** is replaced with salicylaldehyde in our experiment. The deuteration reaction slows even further if **1** is replaced with benzaldehyde or 2-pyridinealdehyde. Combination of two weak forces (electronic and H-bonding) for the aldehyde together with a strongly basic and hydrophobic guanidine provides enormous rate-acceleration for the racemization reaction at neutral pH and ambient temperature.

To study the scope of our racemization reaction, we investigated 18 natural amino acids. The concentration of the amino acids was lowered to 0.2 M, 0.1 M or 0.05 M in D_2O (1 mL) to accommodate the solubility of all amino acids. 12 of the amino acids (ala, thr, trp, phe, met, glu, gly, gln, asn, ser, lys, leu) were fully deuterated at the α-position within a few hours. Valine and isoleucine did not deuterate appreciably under our conditions presumably due to steric effects. Proline did not deuterate because the secondary amine does not form the imine with **1**. Cysteine can form the imine with **1** but the side chain thiol group adds to the imine and prevents deuteration. Arginine and histidine did not extract well and did not deuterate appreciably. The solubility of tyrosine in water is too low for our studies.

Above amino acids that can be catalytically racemized may be considered for catalytic deracemization. For example, phenylalanine can be catalytically deracemized (Supporting Information, Figures S27–S29) with comparable extent and same sense of stereoselectivity as for alanine deracemization.

Our mixture of **1** and **2** is the most efficient non-enzymic catalytic system for racemization of alanine reported to date. Racemization takes place within minutes at neutral pH and 25 °C with just a few percent catalyst loading. In most cases, non-enzymatic racemization of amino acids are carried out under basic conditions and/or elevated temperatures (100 °C).[11] This is also the first non-enzymic catalytic system for L to D conversion of alanine in D_2O. It is interesting to compare stereoselective deuteration and alkylation of amino acids. Chemists have developed catalytic systems for stereoselective alkylation of amino acids to make unnatural amino acids.[12] Various ketones and aldehydes were used as pyridoxal analogues to irreversibly activate *tert*-butyl amino esters. Chiral-phase transfer catalysts were used to obtain impressive stereoselective alkylation of the activated amino esters under highly basic conditions. In contrast, alanine racemase or our system consisting of **1** and **2** can efficiently catalyze stereoselective deuteration of unprotected and unactivated amino acids under mild conditions by reversible formation of imine intermediates. It is interesting that our simple system (**1** and **2**) provides greater stereoselectivity (67 % *ee*) than alanine racemase (< 20 % *ee*) for deuteration of alanine. Lessons learned from the catalytic deuteration may be applicable to catalytic alkylation of amino acids in the future. The stereoselectivity is expected to become higher as the size of the reactant is increased from deuterium to carbon-based electrophiles for alkylation reactions.

Experimental Section

General procedures for amino acid racemization: Mesitylguanidine ((*R*,*R*) or (*S*,*S*),40 μmol), and 3,5-dichlorosalicylaldehyde (20 μmol) in $CDCl_3$ (0.2 mL) was vigorously mixed with a D_2O (or H_2O) solution (1 mL) of alanine (L- or D-, 1000 μmol). The reaction mixture was stirred vigorously at room temperature for times specified herein.

To determine the D to L ratio of alanine, the D_2O/H_2O layer of the above reaction mixtures were separated after 4 h. The water layer was extracted with mesitylguanidine (40 μmol) in $CDCl_3$ (0.7 mL). The ^1H NMR of the solution was taken to determine the ratio of amino acid salts.

K.M. and S.S. contributed equally to experiments.

Keywords: amino acids · catalysis · deuteration · stereoinversion · stereoselectivity

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[1] S. M. So, H. Kim, L. Mui, J. Chin, *Eur. J. Org. Chem.* **2012**, 229–241.
[2] a) T. Yoshimura, M. Goto, *FEBS J.* **2008**, *275*, 3527–3537; b) M. E. Tanner, *Acc. Chem. Res.* **2002**, *35*, 237–246.
[3] S. Martínez-Rodríguez, A. I. Martinez-Gomez, F. Rodriguez-Vico, J. M. Clemente-Jimenez, F. J. LasHeras-Vazquez, *Chem. Biodiversity* **2010**, *7*, 1531–1548.
[4] a) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479; b) R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem. Int. Ed.* **2008**, *47*, 2876–2879; *Angew. Chem.* **2008**, *120*, 2918–2921; c) K. Ishihara, *Tetrahedron* **2009**, *65*, 1085–1109.
[5] T. G. Gant, *J. Med. Chem.* **2014**, *57*, 3595–3611.
[6] J. Chin, S. S. Lee, K. J. Lee, S. Park, D. H. Kim, *Nature* **1999**, *401*, 254–257.
[7] a) H. Park, K. M. Kim, 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; *Angew. Chem.* **2014**, *126*, 848–851; c) R. Takeda, A. Kawamura, A. Kawashima, T. Sato, H. Moriwaki, K. Izawa, K. Akaji, S. Wang, H. Liu, J. L. Aceña, V. A. Soloshonok, *Angew. Chem. Int. Ed.* **2014**, *53*, 12214–12217; *Angew. Chem.* **2014**, *126*, 12410–12413; d) A. E. Sorochinsky, J. L. Acena, H. Moriwaki, T. Sato, V. Soloshonok, *Amino Acids* **2013**, *45*, 1017–1033; e) A. E. Sorochinsky, H. Ueki, J. L. Acena, T. K. Ellis, H. Moriwaki, T. Sato, V. A. Soloshonok, *Org. Biomol. Chem.* **2013**, *11*, 4503–4507; f) A. E. Sorochinsky, H. Ueki, J. L. Acena, T. K. Ellis, H. Moriwaki, T. Sato, V. A. Soloshonok, *J. Fluorine Chem.* **2013**,

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152, 114 – 118; g) V. A. Soloshonok, H. Ueki, J. L. Moore, T. K. Ellis, *J. Am. Chem. Soc.* **2007**, *129*, 3512 – 3513.
[8] a) M. A. Spies, J. J. Woodward, M. R. Watnik, M. D. Toney, *J. Am. Chem. Soc.* **2004**, *126*, 7464 – 7475; b) M. A. Spies, D. Toney Michael, *J. Am. Chem. Soc.* **2007**, *129*, 10678 – 10685.
[9] G. J. Cardinale, R. H. Abeles, *Biochemistry* **1968**, *7*, 3970 – 3978.
[10] N. J. Turner, *Curr. Opin. Chem. Biol.* **2010**, *14*, 115 – 121.
[11] R. Yoshioka, *Top. Curr. Chem.* **2007**, *269*, 83 – 132.
[12] a) T. Ooi, K. Maruoka, *Aldrichimica Acta* **2007**, *40*, 77 – 86; b) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506 – 517; c) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518 – 525; d) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414 – 12415.

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