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Dibromohydantoins as halogen bond (XB) donors: a route toward the introduction of chirality in halogen bonded systems †

Irène Nicolas,^a Olivier Jeannin,^a Delphine Pichon,^a and Marc Fourmigué^{*a}

Abstract

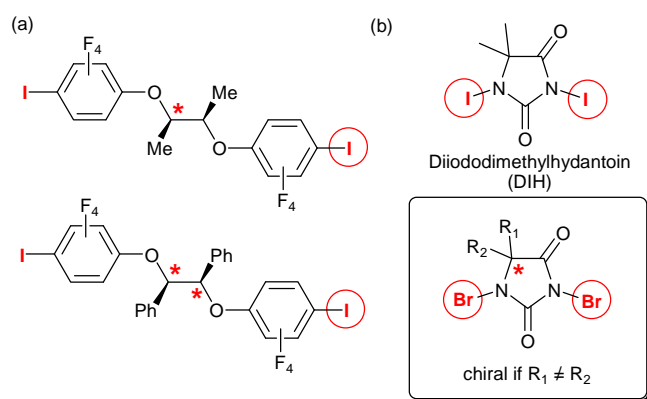
N,N'-dibromohydantoins, known as electrophilic bromination reagents, are successfully used here as halogen bond (XB) donors, as demonstrated in their crystalline adducts with *para*-substituted pyridines acting as halogen bond acceptors. 1:1 adducts of the achiral 5,5-dimethyl-N,N'-dibromohydantoin (DBH) are crystallized with methylisonicotinate, 4-trifluoromethylpyridine and 4-cyanopyridine while both nitrogen atoms of pyrazine are engaged in halogen bonding in the 2:1 adduct (DBH)₂•(pyrazine). A strengthening of the XB interaction between the imidic N–Br group of DBH and the pyridinic nitrogen atom is observed with the more electron rich pyridines with the order: Py–CO₂Me > Py–CF₃ > Py–CN > pyrazine. Chiral hydantoins and their N,N'-dibromo derivatives are obtained in good yields from different amino acids (phenylglycine, phenylalanine, valine and leucine). The ability of such enantiopure N-iodoimides derivatives to act as halogen-bond donors is demonstrated in the 1:1 methylisonicotinate adduct with (*S*)-5-isobutyl-N,N'-dibromohydantoin.

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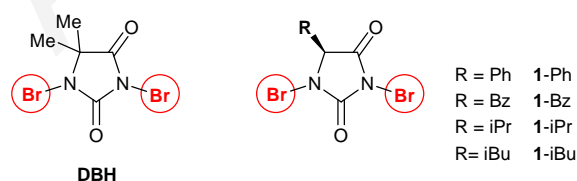
Introduction

The formation of chiral supramolecular assemblies is an attractive challenge in the context of crystal engineering,^{1,2} It most often relies on the use of different intermolecular interactions such as metal coordination, hydrogen bonding³ or π - π interactions.⁴ By comparison, the use of halogen bonding⁵ (XB) as a crystal engineering tool in the formation of chiral, eventually helical structures has been only rarely mentioned, albeit XB has been also recently established as a powerful intermolecular interaction for the elaboration of complex supramolecular architectures.^{6,7,8,9} One of the earliest examples is the resolution of racemic 1,2-dibromohexafluoropropane through co-crystallisation with (-)-sparteine hydrobromide into supramolecular helices stabilised by C-Br \cdots Br⁻ XB interactions.¹⁰ Halogen bonds can be also associated with hydrogen bonding, for example in chiral amines,^{3b} ammonium salts¹¹ or sulfinamides.¹² Chirality has been introduced in conducting halogen bonded tetrathiafulvalenium salts, through chiral counter ions¹³ or chiral iodinated TTF themselves.¹⁴ One can also mention chiral nematic phases from halogen-bonded, bent-core achiral mesogen,¹⁵ host-guest compounds involving octafluorodiiodobutane,¹⁶ asymmetrical porphyrin derivatives,¹⁷ or chiral anion recognition.¹⁸ In order to favour the formation of intrinsically chiral structures based on halogen bond interactions, we are currently investigating neutral iodinated spacers with a built-in chirality and recently described ditopic halogen bond donors derived from chiral diols (Scheme 1a).¹⁹ Their crystallisation with halide anions as halogen bond acceptors afforded helical halogen bonded anionic chains. Looking for more compact but still chiral ditopic halogen bond donors, we turned our attention to N-iodoimides derivatives, known to act powerful halogen bond donors.²⁰ For example, N-iodosuccinimide,^{21,22} or N-iodosaccharin,²³ originally used as electrophilic iodinating agents can be efficiently engaged in XB systems, for example with pyridines of various Lewis base character.²⁴ In the same vein, N,N'-diodo-dimethylhydantoin (DIH) has found many uses in organic synthesis as halogenating agents²⁵ or as catalysts.²⁶ It can also act as a powerful halogen bond donor with both an imidic and an amidic N-I halogen bond donor groups (Scheme 1b). We have recently demonstrated, in the halogen bonded adducts of DIH with pyridines, an anti-cooperativity property: while the most basic pyridines were able to co-crystallize with DIH into bis-adducts where both iodine atoms are indeed involved in XB interactions, the less basic ones led to monoadducts involving only the imidic N-I moiety.²⁷



Scheme 1 (a) Chiral ditopic XB donors reported from chiral diols.¹⁹ (b) Diodo- and dibromohydantoin.

The hydantoin core offers another attractive feature associated with the substitution pattern at 5-position. Two methyl groups are found in the prototypical dimethylhydantoin and its diiodo derivative diiododimethylhydantoin (DIH) but the presence of two different substituents at the 5-position affords indeed a chiral hydantoin (Scheme 1b). Many of them have been in fact reported in the literature for therapeutic applications,²⁸ most of them derived from natural amino acids. On the other hand, the corresponding N,N'-dihalo derivatives of such *chiral* hydantoin were only scarcely mentioned. Chiral dichloro hydantoin are mentioned as a chlorenium source in asymmetric chlorolactonization reactions,²⁹ while dibromo derivatives were only mentioned as racemic mixtures as CCl₄-soluble halogenating agents.³⁰ Chiral N,N'-diodo derivatives are still unknown. In the following, we have explored the preparation of four different chiral N,N'-dibromohydantoin derivatives (**1-R** in Scheme 2) and their association, together with that of achiral 5,5-dimethyl-N,N'-dibromo derivative DBH, with pyridines of various Lewis base character. We were able to isolate single crystalline phases from the association of DBH with electron-poor pyridines such as 4-cyanopyridine, 4-trifluoromethylpyridine and methylisonicotinate. Among the chiral dibromohydantoin prepared here, the **1-iBu** dibromohydantoin derived from leucine was also successfully co-crystallized, in a 1:1 stoichiometry, with methylisonicotinate.



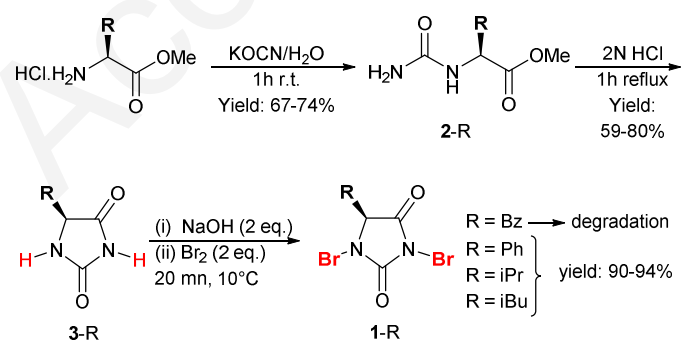
Scheme 2 Dibromohydantoin investigated with pyridines as XB acceptors.

Results and discussion

Syntheses

The main synthetic route toward chiral hydantoins is based on the formation of an urea **2-R** from the starting amino acid methyl ester (Scheme 3). Further cyclization to the desired hydantoins **3-R** can be then performed, either under acidic³¹ or basic conditions.³² This second step is often difficult because affected by racemisation problems. As shown in Scheme 3, we have use here the methylester derivatives of four different amino acids, phenylglycine (R = Ph), phenylalanine (R = Bz), valine (R = iPr) and leucine (R = iBu). The ureido intermediates **2-R** were formed in good yields (67 to 74 %) from the reaction of the amino acid methylester hydrochloride with potassium cyanate in water at room temperature.³³ Being aware of the racemisation problems reported earlier, an optimization of the cyclization conditions was conducted on the phenylalanine ureido derivative (R = Bz). Conducting the cyclization step in basic medium with sterically hindered amines such as DMAP or NEt₃ as reported, led however to the racemised hydantoins, as shown by HPLC. A similar optimization of the cyclisation step, but under acidic conditions, has been also reported by Dakin et al,^{31b} by varying the experimental conditions (nature, concentration of acid and reaction time) and monitoring the optical activity of the final hydantoin product. Based on this study, we used 2N HCl and a minimum reflux time, allowing for a complete conversion of the four different ureas **2-R** to the corresponding hydantoins **3-R** (in 59-89% yields) while maintaining the initial optical purity.

The next dibromination step was performed as described elsewhere³⁴ for achiral hydantoins, by neutralization of **3-R** with two equiv. KOH and reaction with dibromine at 10°C. The dibromohydantoins **1-R** were obtained in excellent yields (90-94%) but only with R = Ph, iPr and iBu, while 5-benzylhydantoin **3-Bz** was degraded under these conditions.



Scheme 3 Synthetic path to the chiral dibromohydantoins.

Halogen bonding in the pyridine adducts

The co-crystallisation of achiral DBH with the electron-rich pyridines such as pyridine itself, 4-picoline, or 4-dimethylaminopyridine did not afford the expected adducts. Bromine-free dimethylhydantoin was recovered. With picoline, we could only isolate crystals of 4-methylpyridinium bromide. On the other hand, the pyridines substituted in *para* position with electron-withdrawing substituents ($-\text{CN}$, $-\text{CF}_3$, $-\text{CO}_2\text{Me}$) afforded systematically a 1:1 adduct (Fig. 1), despite the presence of two equivalents pyridine in the solution before crystallisation by vapour diffusion.

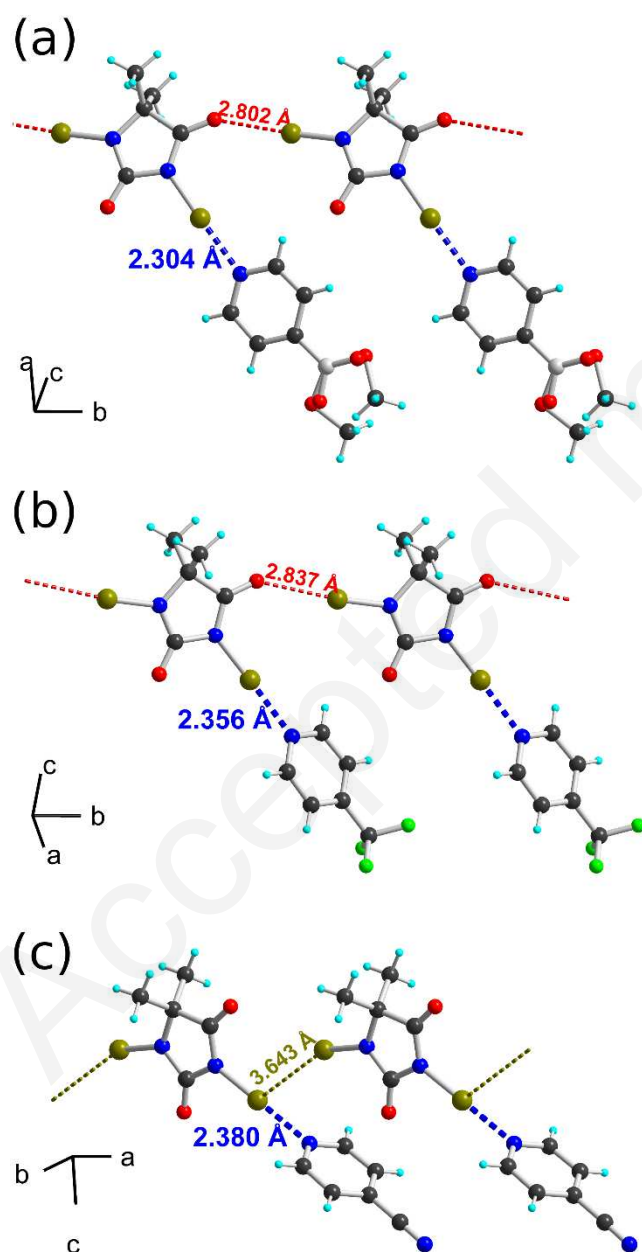


Fig. 1. Detail of the halogen bond interactions in the 1:1 adducts between DBH and respectively (a) methyisonicotinate, (b) 4-trifluoromethylpyridine and (c) 4-cyanopyridine.

DBH•[Py-CO₂Me] crystallises in the triclinic system, space group $P\bar{1}$, with one halogen-bonded monoadduct in general position in the unit cell (Fig. 1a). The imidic bromine atom is halogen bonded to the nitrogen atom of methylisonicotinate while the other bromine atom in amidic position is halogen bonded to one oxygen atom of a neighbouring molecule. Note the disorder of the ester group on two positions with a 75:25 distribution. Relevant bond distances for these two intermolecular interactions are collected in Table 1, and compared with the sum of the van der Waals radii (r_X , r_Y) of interacting atoms (X, Y) to define a so-called reduction ratio (RR), i.e. $d(X\cdots Y)/(r_X + r_Y)$.

DBH•[Py-CF₃] crystallises in the monoclinic system, space group $P2_1/c$ with one XB monoadduct in general position in the unit cell (Figure 1b). Intermolecular interactions parallel those observed above with a strong $Br\cdots N_{Py}$ interaction involving the imidic bromine atom and a weaker $Br\cdots O$ interaction with the amidic bromine atom.

The situation is slightly different in DBH•[Py-CN]. It crystallises in the monoclinic system, space group $C2/m$ with the XB adduct located on a mirror plane containing the hydantoin core while the cyanopyridine is perpendicular to this plane. This adduct crystallises with one 1,2-dichloroethane molecule, located on a $2/m$ position, hence the exact formulation $DBH\cdot[Py-CN]\cdot(ClH_2C-CH_2Cl)_{0.5}$. Furthermore, besides the strong $Br\cdots N_{Py}$ halogen bond involving the imidic bromine atom, the other amidic bromine atom is not halogen bonded to an oxygen atom as observed above with Py-CO₂Me and Py-CF₃, but is almost at van der Waals contact with a neighbouring bromine atom. The corresponding reduction ratio for this $Br\cdots Br$ interaction amounts indeed to 0.985.

At last, the pyrazine adduct involves two DBH molecules for one pyrazine, located in an inversion centre. Halogen bonding $Br\cdots N$ interactions involve the imidic bromine atom while the amidic bromine is bonded to the oxygen atom of a neighbouring DBH molecule (Fig. 2).

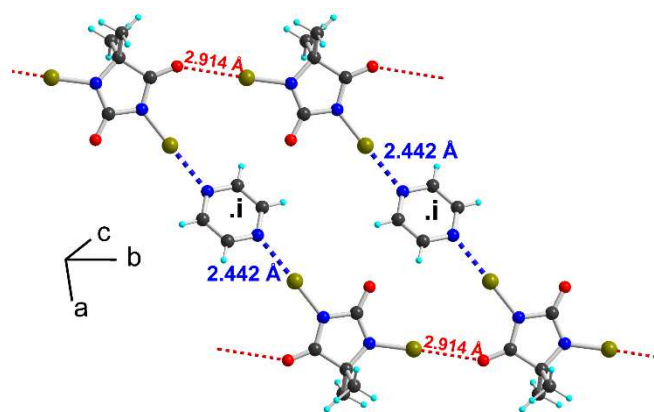


Fig. 2 Detail of the halogen bond interactions (blue and red dotted lines) in the adduct (DBH)₂•Pyrazine.

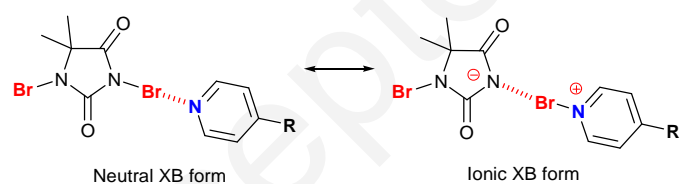
Table 1 Relevant bond distances involving the imidic and amidic bromide atoms of the dibromohydantoin DBH and the chiral 1-iBu in their pyridines (or pyrazine) adducts. The reduction ratio (RR, see text for definition) are based on Bondi's values of van des Waals radii, $r_{\text{Br}} = 1.85 \text{ \AA}$, $r_{\text{N}} = 1.55 \text{ \AA}$, $r_{\text{O}} = 1.52 \text{ \AA}$.

Lewis base	Intramol. dist. N–Br _{imidic} (Å)	Br _{imidic} •••N _{Py} dist. (Å)	RR(BrN)	Intramol. dist. N–Br _{amidic} (Å)	Br _{amidic} •••Y dist. (Å)	RR(BrY)
With DBH:						
Pyrazine	1.890(6)	2.442(8)	0.718	1.847(4)	2.914(4), Y = O	0.865
Py–CN	1.917(7)	2.380(7)	0.700	1.832(6)	3.643(6), Y = Br	0.985
Py–CF ₃	1.908(4)	2.356(4)	0.693	1.850(3)	2.837(2), Y = O	0.842
Py–CO ₂ Me	1.932(7)	2.304(8)	0.678	1.849(4)	2.802(4), Y = O	0.831
With 1-iBu:						
Py–CO ₂ Me	1.930(3)	2.306(3)	0.678	1.850(3)	2.898(3)	0.860
With DIH:^a						
	N–I _{imidic} (Å)	I _{imidic} •••N _{Py} (Å)	RR(IN)	N–I _{amidic} (Å)	I _{amidic} •••O	RR(IN)
Py–CO ₂ Me	2.137(6)	2.398(6)	0.679	2.051(5)	2.720(4)	0.777

^a see Ref 27

The evolution of the halogen bond distances with the nature of the Lewis base XB acceptor is particularly interesting to discuss here. We first note that the stronger XB interaction involves the imidic bromine atom, as already observed in the analogous diiodohydantoin analog.²⁷ The interaction is particularly strong, with RR values in the range 0.68–0.72. Also, the interaction is stronger, i.e. the reduction ratio RR is smaller, with the more electron rich pyridines. The observed ranking, Py–CO₂Me > Py–CF₃ > Py–CN > Pyrazine is fully consistent with our own earlier observations with diiodohydantoin adducts,²⁷ as well as with other pK_B scales established for examples with diiodine (I₂) as XB donor.³⁵ The XB interaction also affects the dibromohydantoin itself as the intramolecular N–Br_{imidic} distance increases as the bromine is

involved in the strongest XB. Another interesting feature is the fact that the second, amidic bromine atom is not halogen bonded to a second pyridine (despite an excess of pyridine in the crystallisation process) but is halogen bonded to the carbonyl oxygen atom of a neighboring DBH molecule. This behaviour was already encountered with diodohydantoin (DIH) faced with these electron poor pyridines.²⁷ It is associated to a strong polarization of the XB adduct following the setting of the strongest XB through the imidic bromine atom (Scheme 4). The partial negative charge which delocalizes on the DBH moiety deactivates the second amidic bromine atom while it increases simultaneously the negative charge of the carbonyl oxygen atoms. Last but not least, a comparison of the strength of the halogen bond, within the bromo and iodo adducts of methylisonicotinate, that is DBH•[Py-CO₂Me] and DIH•[Py-CO₂Me] can be obtained from the comparison of the reduction ratios. As shown in Table 1, the RR(Br,N) and RR(I,N) are essentially the same, 0.678 vs. 0.679, in contradiction to the general rule that states that halogen bonding is systematically stronger with iodine than with bromine. A similar behaviour has been mentioned by Rissanen et al.³⁶ in the halonium–pyridine [Py–X–Py]⁺ cations,^{37,38} where the reduction ratio for the N•••Br bonds (0.63) is even smaller than for the N•••I bonds (0.65). This striking result tends to indicate that the XB(I) > XB(Br) rule only holds for "normal", i.e. relatively weak halogen bonds. In the extreme situations mentioned above, the halogen bonds exhibit a sizeable covalent character, and the covalent bond strengths for N–I and N–Br bonds are indeed in reverse order, N–Br (67 kcal mol⁻¹) > N–I (38 kcal mol⁻¹).



Scheme 4 Polarization on the XB adduct DBH•[Py-R].

As mentioned in the Introduction, the interest of such diodo- or dibromohydantoins also lies in their ability to potentially provide chiral, enantiopure ditopic halogen bond donors. For that purpose, the chiral hydantoins **3-R** derived from (*S*)-phenylglycine (R = Ph), phenylalanine (R = Bz), valine (R = iPr) and leucine (R = iBu) were prepared and the corresponding dibromo derivatives **1-R** were isolated with, as substitution pattern on the 5 position, one hydrogen and one R group, R = Ph, iPr and iBu. Note that **1-Bz** could not be isolated under these conditions. Our first attempts to co-crystallise the three novel chiral

halogen bond donors with different pyridines afforded a crystalline phase from the association of the **1-iBu** with methylisonicotinate, formulated as $[\mathbf{1-iBu}] \cdot [\text{Py-CO}_2\text{Me}]$. It crystallises in the orthorhombic system, chiral space group $P2_12_12_1$, with one adduct in general position in the unit cell (Fig. 3). The halogen bonded motifs parallels those observed above with the achiral DBH, with the imidic bromine atom engaged in XB with the pyridinic nitrogen while the other amidic bromine atom links to the carbonyl oxygen atom of a neighbouring molecule by translation along the *b* axis. The structural characteristics of the strongest $\text{Br} \cdots \text{N}_{\text{Py}}$ XB interaction (Table 1) are very close to those observed within the adduct of achiral DBH with the same Lewis base, methylisonicotinate, but the secondary $\text{Br} \cdots \text{O}$ interaction is notably weakened (2.898 Å instead of 2.802 Å). It is associated with a lowered directionality, with the Br atom lying 1.31 Å above the basal plane defined by the neighbouring heterocycle along *b*, while within the adduct of achiral DBH, this bromine atom is only at 0.36 Å above the basal plane of the neighbouring molecule.

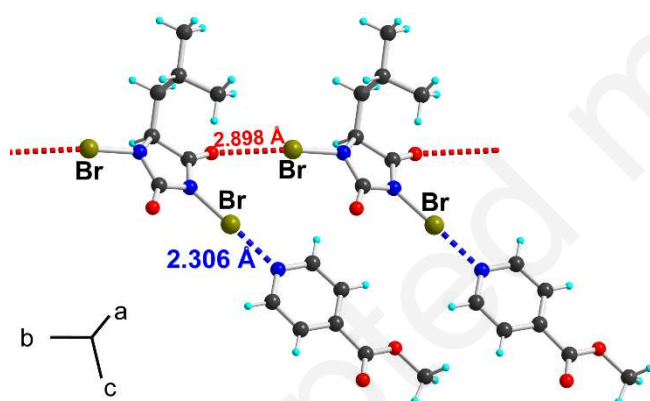


Fig. 3 Detail of the halogen bond interactions in the $[\mathbf{1-iBu}] \cdot [\text{Py-CO}_2\text{Me}]$ adduct.

In conclusion, we have demonstrated that *N,N'*-dibromohydantoin derivatives can act as strong halogen bond donors, comparable indeed to the corresponding iodo derivatives. At variance with them however, the reactivity of dibromohydantoin hinders the isolation of Lewis base adducts with the most electron rich pyridines (pyridine, 4-picoline, 4-dimethylaminopyridine) but allows for the isolation of XB adducts with the pyridines bearing electron-withdrawing substituents (CO_2Me , CF_3 , CN) or with pyrazine, with only the imidic bromine atom engaged in the XB interaction with the pyridinic nitrogen atom. The isolation of the chiral *N,N'*-dibromo hydantoin **1-R** ($R = \text{Ph}$, *iPr*, *iBu*) opens many perspectives in crystal engineering, for the elaboration of chiral networks, as demonstrated here by a first

pyridine adduct involving the (*S*)-5-isobutyl-*N,N'*-dibromohydantoin **1**-iBu and methyl isonicotinate.

Experimental

General. ^1H and ^{13}C spectra were collected on a BRUKER AV 300 (^1H : 300 MHz, ^{13}C : 75,5 MHz). Chemical shifts δ are expressed in part per million (ppm), vs. the deuterated solvent used as reference, such as d^6 -DMSO (^1H NMR δ 2.50 ppm, ^{13}C NMR δ 128.06 ppm). The following abbreviations were used to describe signal multiplicity: bs broad singlet, s singlet, d doublet, t triplet, q quadruplet, m multiplet, dd doublet of doublet, ddd doublet of doublet of doublet. Analytical thin layer chromatography was performed with MACHEREY-NAGEL 60F254 plates (Silica on aluminum foil 60F254, 60/20 mm) and the plates were revealed by Ninhydrin solution and read with UV fluorescence at 254 nm. Chiral HPLC was performed on a Varian Prep Star 218 equipped with Photodiodes Varian Pro Star 330. An analytical Chiracel® OD-H (4,6x250 mm, 5 μm) column was used with as eluent an hexane/isopropanol mixture, at 1 mL.min $^{-1}$ flow with solutions of 5 mg sample for 500 μL isopropanol. Absolute optical rotations $[\alpha]_D$ were determined on a Perkin Elmer 341 polarimeter using the Na line at 589 nm according to $[\alpha]_D = \frac{\alpha_{exp}}{l \times c}$ where is α_{exp} is the observed rotation angle, l the length of optical path (10 cm) and c the concentration (in g.mL $^{-1}$).

General procedure for the preparation of the chiral ureas (2-R). In a 100 mL flask, the aminoester hydrochloride (2 g) is dissolved in water (170 equiv.) and KOCN (1.02 equiv.) is added. The mixture is stirred for one hour at room temperature.

2-Ph. L-Phenylglycine methyl ester hydrochloride (2 g, 9.92 mmol), KOCN (845 mg, 1.02 eq), H₂O (7 mL, 170 equiv.). The white precipitate is filtered and washed with cold water, and then dried over KOH in vacuum. Yield: 1.47 g (71 %). M.p. 136-137 °C. ^1H NMR (DMSO- d_6 , 300 MHz) δ 3.62 (s, 3H, COOCH₃), 5.25 (d, $^3J = 6,0$ Hz, 1H, CH α), 5.69 (ls, 2H, NH₂), 6.86 (d, $^3J = 9\text{Hz}$, 1H, NH), 7.36 (m, 5H, H_{Ar}). ^{13}C NMR (DMSO- d_6 , 75.5 MHz) δ 52.57 (COOCH₃), 57.12 (CH α), 127.66 (C_{Ar}), 128.52 (C_{Ar para}), 129.17 (C_{Ar}), 137.99 (C_{Ar}), 158.18 (COOCH₃), 172.54 (CONH). HPLC (Eluent: Hexane/Isopropanol 80:20) $\tau_R = 8.376$ min. $[\alpha]_D$ ($c = 9.9 \cdot 10^{-4}$ g mL $^{-1}$, EtOH) = +147.5°.

2-Bz. L-Phenylalanine methyl ester hydrochloride (2 g, 9.97 mmol), KOCN (753 mg, 1.02 eq), H₂O (30 mL, 170 equiv.). The solution is extracted with AcOEt. The organic phases are dried over Na₂SO₄, filtered and concentrated under reduced pressure. Yield: 1.36 g (67 %). M.p. 102-103 °C. ¹H NMR (DMSO-d₆, 300 MHz) δ 2.92 (qd, ³J₁ = 13.7 Hz, ³J₂ = 6.8 Hz, 2H, Ph-CH₂), 3.60 (s, 3H, COOCH₃), 4.38 (td, ³J₁ = 8.1 Hz, ³J₂ = 5.6 Hz, 1H, CHα), 5.63 (bs, 2H, NH₂), 6.28 (d, ³J = 8.2 Hz, 1H, NH), 7.25 (m, 5H, H_{Ar}). ¹³C NMR (DMSO-d₆, 75.5 MHz) δ 38.06 (Ph-CH₂), 52.10 (COOCH₃), 54.33 (CHα), 126.97 (C_{Ar para}), 128.70 (C_{Ar}), 129.58 (C_{Ar}), 137.60 (C_{Ar}), 158.41 (COOCH₃), 173.51 (CONH). HPLC (Eluent Hexane/Isopropanol 80:20) τ_R = 8.584 min. [α]_D (c = 1.06.10⁻³ g.mL⁻¹, EtOH) = +28.3°.

2-iPr. L-Valine methyl ester hydrochloride (2 g, 13 mmol), KOCN (973 mg, 1.02 equiv.), H₂O (36 mL, 170 equiv.). The solution is extracted with AcOEt. The organic phases are dried over Na₂SO₄, filtered and concentrated under reduced pressure. Yield 1.63 g (74 %). M.p. 99-100 °C. ¹H NMR (DMSO-d₆, 300 MHz) 0.85 (t, ³J = 7.2 Hz, 6H, 2CH₃), 1.96 (m, 1H, CH(CH₃)₂), 3.63 (s, 3H, COOCH₃), 4.05 (dd, ³J₁ = 8.8 Hz, ³J₂ = 5.5 Hz, 1H, CHα), 5.61 (ls, 2H, NH₂), 6.29 (d, ³J = 8.8 Hz, 1H, NH). ¹³C NMR (DMSO-d₆, 75.5 MHz) δ 18.27 (CH(CH₃)₂), 19.43 (CH(CH₃)₂), 30.83 (CH(CH₃)₂), 51.92 (COOCH₃), 58.0 (CHα), 158.86 (COOCH₃), 173.64 (CONH). HPLC (Eluent Hexane/Isopropanol 90:10) τ_R = 10.8 min. [α]_D (c = 1.11.10⁻³ g.mL⁻¹, EtOH) = -6.30°.

2-iBu. L-Leucine methyl ester hydrochloride (2 g, 12 mmol), KOCN (1.26 g, 1.02 equiv.), H₂O (47 mL, 170 eq). The solution is extracted with AcOEt. The organic phases are dried over Na₂SO₄, filtered and concentrated under reduced pressure. Yield 1.53 g (68 %). M.p. 67-68 °C. ¹H NMR (DMSO-d₆, 300 MHz) δ 0.87 (2d, ³J₁ = 6.7 Hz, ³J₂ = 6.6 Hz, 6H, 2CH₃), 1.43 (t, ³J = 7.5 Hz, 2H, CH₂), 1.61 (m, 1H, CH(CH₃)₂), 3.61 (s, 3H, COOCH₃), 4.14 (q, ³J = 7.7 Hz, 1H, CHα), 5.55 (bs, 2H, NH₂), 6.30 (d, ³J = 8.2 Hz, 1H, NH). ¹³C NMR (DMSO-d₆, 75.5 MHz) δ 21.95 (CH(CH₃)₂), 23.19 (CH(CH₃)₂), 24.71 (CH(CH₃)₂), 41.24 (CH₂) 51.21 (COOCH₃), 52.07 (CHα), 158.63 (COOCH₃), 174.71 (CONH). HPLC (Eluent Hexane/Isopropanol 90:10) τ_R = 10.381 min. [α]_D (c = 1.03.10⁻³ g mL⁻¹, EtOH) = -17.47°.

General procedure for the preparation of the chiral hydantoins (3-R). The above prepared ureas **2-R** are suspended in 2N HCl and stirred at reflux for one hour.^{31b}

3-Ph. With **2-Ph** (504.6 mg, 2.4 mmol) and HCl 2N (10 mL, 8.3 eq). The filtered residue is washed with cold water and dried under vacuum over KOH. Yield: 250 mg (59 %). M. p. 177-178 °C (Litt^[31a] 177-178 °C). ¹H NMR (DMSO-d₆, 300 MHz) δ 5.16 (s, 1H, CH), 7.37 (m, 5H, H_{Ar}), 8.39 (ls, 1H, CONH), 10.78 (ls, 1H, CONHCO). ¹³C NMR (DMSO-d₆, 75.5 MHz) δ (ppm) : 61.64 (CH α), 127.15 (C_{Ar}), 128.69 (C_{Ar} *para*), 129.10 (C_{Ar}), 136.50 (C_{Ar}), 157.94 (CONH), 174.64 (NHCONH). HPLC (Eluent Hexane/Isopropanol 80:20) τ_R = 15 min (ee 99.7 %). $[\alpha]_D$ (c = 0.98.10⁻³ g mL⁻¹, EtOH) = +103.06° (Litt^[39]: +112°, c = 0.20 g.mL⁻¹, EtOH).

3-Bz. With **2-Bz** (1.013 g, 4.6 mmol) and HCl 2N (19 mL, 8.3 equiv.). The solution is extracted with AcOEt. The combined organic phases are dried over Na₂SO₄, filtered and concentrated to dryness. Yield: 764 mg (87 %). M.p. 175-176 °C (Litt. ^[30a] 187-189 °C). ¹H NMR (DMSO-d₆, 300 MHz) δ 2.93 (m, 2H, CH₂), 4.33 (td, ³J₁ = 3 Hz, ³J₂ = 6 Hz, 1H, CH), 7.25 (m, 5H, H_{Ar}), 7.90 (ls, 1H, CONH), 10.41 (ls, 1H, CONHCO). ¹³C NMR(DMSO-d₆, 75.5 MHz) δ 36.89 (CH₂), 58.84 (CH), 127.09 (C_{Ar} *para*), 128.52 (C_{Ar}), 130.17 (C_{Ar}), 136.09 (C_{Ar}), 157.56 (CONH), 175.61 (NHCONH). HPLC (Eluent Hexane/Isopropanol 80:20) τ_R = 8.536 min (ee 99.8 %). $[\alpha]_D$ (c = 0.97.10⁻³ g mL⁻¹, EtOH) = -98.97° (Litt^[40] -96°; c = 0.20 g.mL⁻¹, EtOH).

3-iPr. With **2-iPr** (1.047 g, 6.0 mmol) and HCl 2N (30 mL, 8.3 equiv.). The solution is extracted with AcOEt. The combined organic phases are dried over Na₂SO₄, filtered and concentrated to dryness. Yield: 688 mg (81 %). M. p. 131-132 °C (Litt. ^[31a] 144-146 °C). ¹H NMR (DMSO-d₆, 300 MHz) δ 0.80 (d, ³J = 6 Hz, 3H, CH₃), 0.94 (d, ³J = 6 Hz, 3H, CH₃), 1.98 (m, 1H, CH(CH₃)₂), 3.90 (dd, ³J₁ = 3 Hz, ³J₂ = 6 Hz, 1H, CH α), 7.89 (ls, 1H, CONH), 10.55 (ls, 1H, CONHCO). ¹³C NMR (DMSO-d₆, 75.5 MHz) δ 16.30 (CH(CH₃)₂), 18.99 (CH(CH₃)₂), 29.99 (CH(CH₃)₂), 63.19 (CH α), 158.26 (CONH), 175.87 (NHCONH). HPLC (Eluent Hexane/Isopropanol 90:10) τ_R = 10.541 min (ee 100 %). $[\alpha]_D$ (c = 1.08.10⁻³ g mL⁻¹, EtOH) = -94.44° (Litt. ^[40] - 94°, c = 0.20 g.mL⁻¹, EtOH)

3-iBu. With **2-iBu** (1.002 g, 5.3 mmol) and HCl 2N (32 mL, 8.3 equiv.). The filtered residue is washed with cold water and dried under vacuum over KOH. Yield: 674 mg (81%). M.p. 213-214 °C (Litt. ^[31a] 213-214 °C). ¹H NMR (DMSO-d₆, 300 MHz) δ 0.88 (2d, ³J₁ = 6.6 Hz, ³J₂ = 4.8 Hz, 6H, 2CH₃), 1.45 (m, 2H, CH₂), 4.00 (ddd, ³J₁ = 9.3 Hz, ³J₂ = 4.5 Hz, ³J₃ = 1.4 Hz,

1H, CH α), 8.00 (ls, 1H, CONH), 10.57 (ls, 1H, CONHCO). ¹³C NMR (DMSO-d₆, 75.5 MHz) δ 21.89 (CH(CH₃)₂), 23.58 (CH(CH₃)₂), 24.58 (CH(CH₃)₂), 41.24 (CH₂), 56.54 (CH α), 157.88 (CONH), 176.95 (NHCONH). HPLC (Eluent Hexane/Isopropanol 90:10) τ_R = 9.088 min (ee: 99 %). $[\alpha]_D$ (c = 1.07.10⁻³ g.mL⁻¹, EtOH) = -78.5°.

General procedure for the preparation of the N,N'-dibromohydantoins (1-R). In a 100 mL flask, hydantoin 3-R (200 mg) is suspended in water (111 equiv.) and the suspension cooled to 10°C. NaOH (1N in water, 2 equiv.) is added and the mixture stirred until complete dissolution. The flask is covered to work in the dark and Br₂ (2 equiv.) is added dropwise. After stirring for 20 min at 10°C, the resulting precipitate is filtered, washed with cold water and dried in vacuum over KOH.

1-Ph. With 3-Ph (195 mg, 0.92 mmol), NaOH 1N (2 mL, 2 mmol), H₂O (2 mL, 0.11 mol, 111 equiv.) and Br₂ (102 μ L, 2 mmol, 2 equiv.). Yield: 304 mg (Yield 91%). M. p. 108-109 °C. ¹H NMR (ACN-d₃, 300 MHz) δ 5.24 (s, 1H, CH α), 7.60 (m, 5H, H_{Ar}). ¹³C NMR (ACN-d₃, 75.5 MHz) δ 71,69 (CH α), 127,84 (C_{Ar}), 129,15 (C_{Ar}), 129,77 (C_{Ar para}), 132,48 (C_{Ar}), 154,45 (CONBr), 168,69 (NBrCONBr). Elem. Anal. Calcd for C₉H₆Br₂N₂O₂ (M = 333.967 g mol⁻¹) C, 32.37; H, 1.81; N, 8.39%. Found: C, 32.52; H, 2.41; N, 8.44%. $[\alpha]_D$ (c = 1,12.10⁻³ g.mL⁻¹, EtOH) = + 66.1°.

1-Bz. With 3-Bz (205 mg, 1 mmol), NaOH 1N (2.1 mL, 2.1 mmol, 2 eq), H₂O (2.1 mL, 0.12 mol, 111 eq) and Br₂ (108 μ L, 2.1 mmol, 2 eq). The reaction failed to provide tractable material.

1-iPr. With 3-iPr (200 mg, 1.4 mmol), NaOH (2.8 mL, 2.8 mmol, 2 eq), H₂O (2.8 mL, 0.16 mol, 111 eq) and Br₂ (144 μ L, 2.8 mmol, 2 equiv.). Yield 450 mg (94 %). M. p. 114-115 °C. ¹H NMR (ACN-d₃, 300 MHz) δ 0.96 (d, ³J = 6.9 Hz, 3H, CH₃), 1.09 (d, ³J = 7.0 Hz, 3H, CH₃), 2.26 (qd, ³J₁ = 7,0 Hz, ³J₂ = 3.2 Hz, 1H, CH(CH₃)₂), 4.13 (dd, ³J = 3.2 Hz, 1H, CH). ¹³C NMR (ACN-d₃, 75.5 MHz) δ 15.82 (CH(CH₃)₂), 16.45 (CH(CH₃)₂), 29.52 (CH(CH₃)₂), 72.68 (CH), 154.89 (CONBr), 169.36 (NBrCONBr). Elem. Anal. Calcd. for C₆H₈Br₂N₂O₂ (M = 297.895 g mol⁻¹) C, 24.03; H, 2.69; N, 9.34. Found: C, 24.74; H, 3.19; N, 9.65 %. $[\alpha]_D$ (c = 1.10⁻³ g.mL⁻¹, EtOH) = -16.0°.

1-iBu. With **3-iBu** (205 mg, 0.7 mmol), NaOH (2.6 mL, 2.6 mmol, 2 equiv.), H₂O (2.6 mL, 0.14 mol, 111 equiv.) and Br₂ (131 μ L, 2.6 mmol, 2 equiv.). The mixture is stirred at 10°C after Br₂ addition for only 10 min. Yield: 198 mg (90 %). M. p. 100-101 °C. ¹H NMR (ACN-d₃, 300 MHz) 0.92 (d, ³J = 6.6 Hz, 3H, CH₃), 0.98 (d, ³J = 6.6 Hz, 3H, CH₃), 1.72 (m, 2H, CH₂), 4.24 (t, ³J = 5.5 Hz, 1H, CH). ¹³C NMR (ACN-d₃, 75.5 MHz) δ (ppm): 21.63 (CH(CH₃)₂), 21.99 (CH(CH₃)₂), 23.94 (CH(CH₃)₂), 38.43 (CH₂), 66.90 (CH), 154.77 (CONBr), 170.47 (NBrCONBr). $[\alpha]_D$ (c = 9.6·10⁻⁴ g·mL⁻¹, EtOH) = -8.3°.

Synthesis of the adducts.

DBH•[Py-CN]. DBH (15 mg, 5.25 10⁻⁵ mol) was dissolved in 1,2-dichloroethane (2 mL). 4-Cyanopyridine (15 mg, 15.75 10⁻⁵ mol) was added. The solution was filtered to remove non-dissolved particles and poured in a Durham tube. Crystals were obtained by vapor diffusion method. Hexane was used as precipitant. The sample was left to 2°C during 8 days in the dark. White crystals were obtained. M. p. 148°C. ¹H NMR (300 MHz, DMSO-d₆) δ 8.81 (dd, J = 1.6 and 4.5 Hz, 2H, H_{Ar}), 7.67 (d, J = 1.6 and 4.5 Hz, 2H, H_{Ar}), 1.39 (s, 6H, CH₃). Elem. Anal. Calcd for C₁₁H₁₀Br₂N₄O₂ (M = 387.917 g mol⁻¹): C, 33.87; H, 2.58; N, 14.36 %. Found: C, 33.99; H, 2.44; N, 14.37 %.

DBH•[Py-CF₃]. DBH (15 mg, 5.25 10⁻⁵ mol) and 4-trifluoromethylpyridine (30 μ L, 15.75 10⁻⁵ mol) were dissolved in dichloromethane (4 mL). The solution was filtered to remove non-dissolved particles. The solution was left to evaporate during 8 days in the dark at room temperature. White crystals were obtained. M. p. 196°C. ¹H NMR (300 MHz, DMSO-d₆) δ 8.96 – 8.79 (m, 2H), 7.79 (m, 2H), 1.31 – 0.97 (m, 6H). Elem. Anal. Calcd. for C₁₁H₁₀Br₂F₃N₃O₂ (M = 433.02 g mol⁻¹): C, 30.51; H, 2.33; N, 9.70 %. Found: C, 30.50; H, 2.64; N, 11.18 %.

DBH•[Py-CO₂Me]. DBH (15 mg, 5.25 10⁻⁵ mol) was dissolved in chlorobenzene (2 mL). 4-Methylisonicotinate (21 μ L, 15.75 10⁻⁵ mol) was added. The solution was filtered to remove non-dissolved particles and poured in a Durham tube. Crystals were made by vapor diffusion method. Hexane was used as precipitant. The sample was left at 2°C during 8 days in the dark. White crystals were obtained. M.p. 134°C. ¹H NMR (300 MHz, acetonitrile-d₃) δ 8.79 (dd, J = 4.4 Hz and 1.6 Hz, 2H, H_{Ar}), 7.86 (dd, J = 4.4 Hz and 1.6 Hz, 2H, H_{Ar}), 3.94 (s, 3H,

COOCH₃), 1.39 (s, 6H, 2xCH₃). Elem. Anal. Calcd. for C₁₂H₁₃Br₂N₃O₄ (M = 423.061 g mol⁻¹): C, 35.77; H, 2.67; N, 9.63 %. Found: C, 34.23; H, 3.04; N, 9.94 %.

(DBH)₂(pyrazine). DBH (15 mg, 5.25 10⁻⁵ mol) was dissolved in CH₂Cl₂ (2 mL). Pyrazine (21 μL, 15.75 10⁻⁵ mol) was added. The solution was filtered to remove non-dissolved particles and poured in a Durham tube. Crystals were made by vapor diffusion method. Hexane was used as precipitant. The sample was left at 2°C during 8 days in the dark. White crystals were obtained. M. p. 159°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.66 (s, 4H, H_{Ar}), 1.50 (s, 12H, CH₃). Elem. Anal. Calcd. for C₁₄H₁₆Br₄N₆O₄ (M = 651.936 g mol⁻¹): C, 25.79; H, 2.47; N, 12.89 %. Found: C, 25.97; H, 2.44; N, 12.71 %.

[1-*i*Bu]•[Py-CO₂Me]. 1-*i*Bu (15 mg, 4.78 10⁻⁵ mol) was dissolved in 1,2-dichloroethane (2 mL). 4-Methylisonicotinate (17 μL, 9.56 10⁻⁵ mol) was added. The solution was filtered to remove non-dissolved particles and poured in Durham tube. Crystals were made by vapor diffusion method. Hexane was used as precipitant. The sample was left to 2°C during 8 days in the dark. White crystals were obtained. M.p. 97-98°C. Elem. Anal. Calcd. for C₁₄H₁₇Br₂N₃O₄ (M = 451.115 g mol⁻¹): C, 37.28; H, 3.80; N, 9.31 %. Found: C, 37.80; H, 3.86; N, 9.44 %.

Crystallography. X-ray crystal structure collections were performed on an APEXII Bruker-AXS diffractometer equipped with a CCD camera and a graphite-monochromated Mo-K α radiation source ($\lambda = 0.71073 \text{ \AA}$). Details of the structural analyses are summarized in Table 2. Absorption corrections were performed with SADABS. Structures were solved by direct methods using the SIR97 program,⁴¹ and then refined with full-matrix least-squares methods based on F² (SHELXL-97)⁴² with the aid of the WINGX program.⁴³ All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions. Crystallographic data were deposited as CCDC 1509929: DBH•[Py-CN]•(C₂H₄Cl₂)_{0.5}; CCDC 1509930: (DBH)₂•Pyrazine; CCDC 1509931: DBH•[Py-CO₂Me]; CCDC 1509932: [1-*i*Bu]•[Py-CO₂Me] and CCDC 1509933: DBH•[Py-CF₃].

Table 2 Crystallographic data

	(DBH) ₂ • Pyrazine	DBH•[Py–CN]• (C ₂ H ₄ Cl ₂) _{0.5}	DBH• [Py–CF ₃]	DBH• [Py–CO ₂ Me]	[1-iBu]• [Py–CO ₂ Me]
Formula	C ₇ H ₈ Br ₂ N ₃ O ₂	C ₁₂ H ₁₂ Br ₂ ClN ₄ O ₂	C ₁₁ H ₁₀ Br ₂ F ₃ N ₃ O ₂	C ₁₂ H ₁₃ Br ₂ N ₃ O ₄	C ₁₄ H ₁₇ Br ₂ N ₃ O ₄
FW (g.mol ⁻¹)	325.98	439.53	433.04	423.07	451.12
System	triclinic	monoclinic	monoclinic	triclinic	orthorhombic
Space group	P-1	C2/m	P2 ₁ /c	P-1	P2 ₁ 2 ₁ 2 ₁
<i>a</i> (Å)	7.7140(4)	8.6301(5)	9.4108(4)	6.1692(8)	6.5779(5)
<i>b</i> (Å)	8.0925(4)	7.7579(7)	7.9826(3)	7.9700(10)	7.9462(5)
<i>c</i> (Å)	9.1626(4)	23.769(2)	19.9558(10)	15.743(2)	32.486(2)
α (deg)	64.045(3)	90.00	90.00	88.236(5)	90.00
β (deg)	81.550(4)	98.599(4)	97.418(2)	81.458(5)	90.00
γ (deg)	85.532(4)	90.00	90.00	85.411(5)	90.00
<i>V</i> (Å ³)	508.65(4)	1573.5(2)	1486.59(11)	762.90(17)	1698.0(2)
<i>T</i> (K)	150(2)	150(2)	150(2)	150(2)	150(2)
<i>Z</i>	2	2	4	2	4
<i>D</i> _{calc} (g.cm ⁻³)	2.128	1.855	1.935	1.842	1.765
μ (mm ⁻¹)	7.946	5.330	5.492	5.331	4.796
Total refls	3773	4030	8226	5692	13213
Abs corr	multi-scan	multi-scan	multi-scan	multi-scan	multi-scan
<i>T</i> _{min} , <i>T</i> _{max}	0.106, 0.356	0.209, 0.619	0.429, 0.547	0.116, 0.726	0.587, 0.746
θ _{max} (°)	25.03	27.41	27.52	27.58	27.473
Uniq refls	1799	1929	3382	3446	3881
<i>R</i> _{int}	0.0308	0.0417	0.0378	0.0368	0.0503
Uniq refls [<i>I</i> > 2σ(<i>I</i>)]	1539	1609	2684	2684	3351
<i>R</i> ₁	0.0282	0.0536	0.0339	0.0559	0.0313
<i>wR</i> ₂ (all data)	0.0775	0.1428	0.1177	0.1774	0.0574
Flack param.	–	–	–	–	0.011(8)
GOF	1.108	1.058	0.819	1.035	1.048
Res. dens. (e Å ⁻³)	0.482, -0.746	1.603, -1.841	0.650, -0.801	1.422, -1.173	0.405, -0.420

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