Noncovalent Interactions

Neutral Chiral Tetrakis-Iodo-Triazole Halogen-Bond Donor for Chiral Recognition and Enantioselective Catalysis

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Abstract: Halogen bonding represents a powerful tool in the field of noncovalent interactions. However, applications in enantioselective recognition and catalysis remain almost nonexistent, due in part to the distinct features of halogen bonds, including long covalent and noncovalent bond distances and high directionality. Herein, this work presents a novel chiral tetrakis-iodo-triazole structure as a neutral halogen bond donor for both chiral anion-recognition and enantioinduction in ion-pair organocatalysis. NMR-titration studies revealed significant differences in anion affinity between the halogen bonding receptor and its hydrogen bonding parent. Selective recognition of chiral dicarboxylates and asymmetric induction in a benchmark organocatalytic reaction were demonstrated using the halogen bond donor. Inversions in the absolute sense of chiral recognition, enantioselectivity, and chiroptical properties relative to the related hydrogen donor were observed. Computational modeling suggested that these effects were the result of distinct anion-binding modes for the halogen- versus hydrogen-bond donors.

Noncovalent halogen bonding (XB)[1] has recently emerged as a powerful tool in medicinal[2] and supramolecular chemistry,[3] complementing the more prominent and well explored hydrogen bonding (HB) interactions.[4] Differences between XB and HB have been noted, including distinct selectivity patterns towards Lewis bases and solvent effects.[4d,5k–m] In the last few years, further applications of XBs have created great interest, providing new possibilities in selective recognition[5,6–9] and organocatalysis.[10] However, XB-donors present several challenges that need to be overcome to effectively implement them for enantioselective applications: 1) the non-covalent XB-interaction is highly directional (R-X—LB, $\approx 180^{\circ}$); 2) in terms of chiral induction or recognition, the larger size of the halogen atom versus a hydrogen results in higher distances between the chiral backbone of the XB-donor and the bound substrate (LB); 3) although the more widely used charged XB-donors (such as iodo-imidazolium or triazolium salts) usually show significantly higher binding compared to their neutral derivatives, possible solubility issues and additional interactions between their counter anions and the bound substrate can interfere with the XB process itself.[11] Consequently, only scarce applications of chiral XB-donors in enantioselective recognition and catalysis have been reported so far. These can be categorized as follows: i) XB in dual catalysis as a secondary interaction;[12] ii) the use of a positively charged XB-donor in combination with a chiral phosphate counteranion;[13] and iii) the more challenging application of XB as the primary determinant of selectivity. In the latter case, Kanger and co-workers achieved the moderately selective recognition of (*S*,*S*)-Takemoto's thiourea catalyst with a chiral monodentate iodo-triazolium salt.[14,15] The groups of Kubik[6] and Beer[7,9,15–17] have significantly contributed to the field with bi- and multidentate iodo-triazole,[6,16] triazolium[17] BINOL-based and interlocked rotaxane systems[7,9] as chiral XB-donors, achieving moderate to good chiral recognition of mono- and dicarboxylates as well as phosphoric acids. More recently, the group of Huber presented a chiral bis(imidazolium) based XB-donor that was able to discriminate between enantiomers of a chiral 1,2-diamine and induce enantioselectivity in a Mukaiyama aldol reaction.[18] However, the design and synthesis of XB donor motifs for enantioselective recognition or catalysis remains a significant challenge. Chiral, neutral donors could be of particular value in this regard, since their halogen bonding interactions do not benefit from charge assistance and are not subject to interference by counteranions.

Inspired by our previous results in enantioselective anion-binding catalysis with chiral helical tetrakistriazole HB-donors, we envisioned the transfer of our design[19] into a novel, neutral, chiral multidentate XB-donor **1** to achieve anion binding

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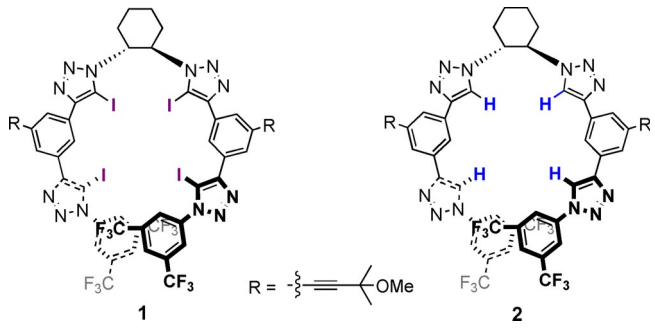
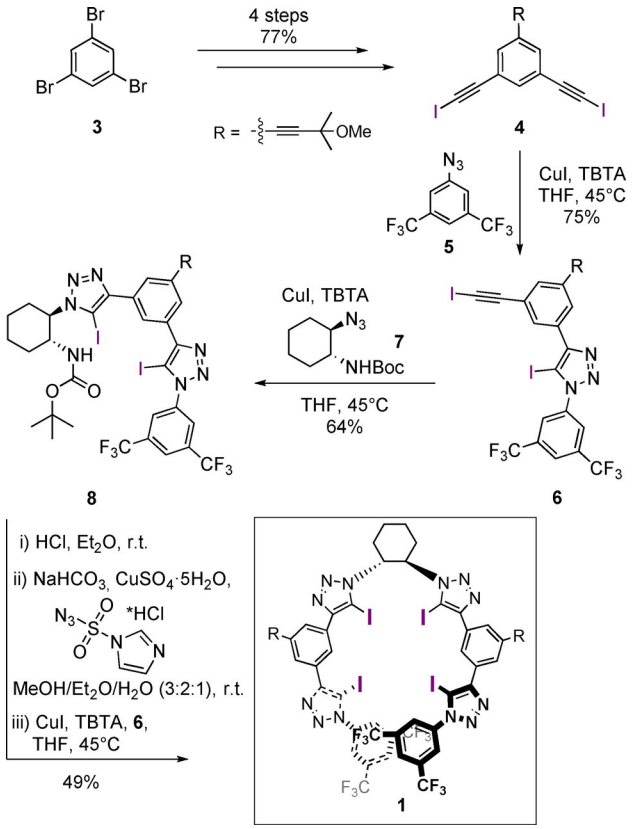


Figure 1. Novel neutral chiral XB-donor **1** based on the pseudo-helical HB-donor tetrakistriazole backbone **2**.

and effective chiral recognition (Figure 1). This chiral covalent motif should provide a defined spatial orientation, while allowing flexibility to properly orient the substrates for efficient recognition and chirality transfer in a given reaction.

We began our study with the synthesis of the XB-donor **1**, embracing robust cross-coupling reactions and challenging copper-catalyzed azide-iodoalkyne cyclizations (CuAXAC) with azides derived from chiral *trans*-1,2-diamines (Scheme 1).[20] Hence, tribromobenzene **3** was used as a readily available starting material for two consecutive Sonogashira-couplings and CuAXAC click reactions. First, the alkyne residue R, which was found to be important for highly enantioselective organocatalysis by tetrakistriazole HB-donor **2**,[19] was introduced, followed by two TMS protected acetylene groups. After TMS-deprotection and iodination of the terminal acetylenes, the bis-iodoalkyne **4** was obtained in 77% yield over 4 steps. The triazole units were then incorporated by sequential CuAXAC reactions in the presence of a tridentate ligand (tris((1-benzyl-4-triazolyl)methyl)amine, TBTA), in THF solvent to avoid or minimized the undesired dehalo-protonation side reaction.[20] After desymmetrization of **4** with azide **5**, a further click reaction with azide **7** was carried out to introduce the (*R*,*R*)-diaminocyclohexane-derived chiral scaffold. Deprotection of the Boc group of **8**, conversion of the amine to the corresponding azide and a final click-reaction with **6** furnished the XB-donor **1**.



Scheme 1. Synthesis of chiral Tetrakis-I-Triazole XB-donor **1**.

The anion binding properties of XB-donor **1** towards commercially available tetrabutylammonium salts (TBAX) were analyzed by NMR-titration experiments in a solvent mixture of [D_6]acetone and $CDCl_3$ in a ratio of 1:1 and compared with the HB-donor **2** (Table 1; see the Supporting Information for complete analysis). As anticipated, the binding constants towards halides and acetate for the XB-donor **1** were significantly higher compared to the HB-donor **2** (entries 1–4; for example, $1.1\times10^3\ M^{-1}$ vs. $99\ M^{-1}$ for Cl^-).[3e,5e–h,j] In accordance with previous reports of multidentate XB-donors, receptor **1** displayed selectivity towards I^-, with an affinity of $3.6\times10^3\ M^{-1}$, more than 40-fold higher than that of the HB-donor **2** (entry 3).[21] Interestingly, for bisulfate-, hydrogen phosphate- and nitrate, **1** showed low to no binding (entries 5–7), while the HB-donor **2** bound to these anions in preference to the halides. Kubik and co-workers also noted a preference for binding of halides over oxoanions for a macrocyclic, peptide-based tris(iodotriazole) receptor (2.5% D_2O-[D_6]DMSO).[6]

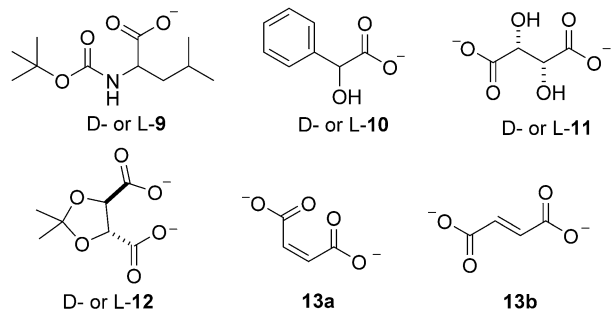
Table 1. Comparative anion-binding studies of XB-donor **1** and HB-donor **2**.

Entry	Anion[a]	XB-donor **1** K_1[M^{-1}][b]	HB-donor **2** K_1 [M^{-1}][b]
1	Cl^-	1125 (11)	99 (5)
2	Br^-	1109 (7)	92 (2)
3	I^-	3642 (29)	88 (6)
4	AcO^-	455 (11)	179 (8)
5	$H_2PO_4^-$	152 (17)	544 (14)
6	HSO_4^-	64 (29)	338 (7)
7	NO_3^-	–	102 (4)

[a] Anions added as TBA-salts between 0–10 equiv. [b] Host concentration 2.5 mM, binding constants K_1 of 1:1 complexes in $CDCl_3$:[D_6]acetone (1:1%vol) fitted and calculated with Bindfit (fitting errors in % in parentheses).[22] K_1 are the average of two measurements.

Encouraged by its appreciable affinity for acetate ($K_1 = 455\ M^{-1}$: Table 1, entry 4), we evaluated the ability of the XB-donor **1** to differentiate between isomeric mono- or bis- carboxylates. With this in mind, TBA-carboxylate salts **9**–**13** were synthesized and tested with both chiral XB- and HB-donors (Table 2). The NMR-titration with Boc-protected D- and L-leucine TBA-salts **9** did not lead to any observable discrimination by either the XB- or the HB-donor (entries 1 and 2). However, for the mandelic acid salt **10** a low selectivity for the D-enan-

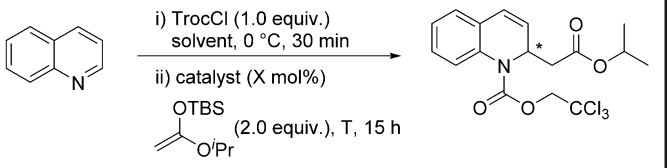
Table 2. Discrimination of enantiomeric or isomeric TBA-carboxylates by XB-donor **1** and HB-donor **2**.



Entry	Anion[a]	XB-donor **1** K [M^{-1}][b]	K_D/K_L **1**	HB-donor **2** K [M^{-1}][b]	K_D/K_L **2**
1	D-**9**	309 (9)	1.04	69 (3)	1.03
2	L-**9**	296 (6)		67 (2)	
3	D-**10**	492 (22)	1.41	90 (3)	0.78
4	L-**10**	349 (24)		116 (3)	
5	D-**11**	2679 (27)	2.10	104 (3)	2.23
6	L-**11**	1278 (17)		47 (3)	
7	D-**12**	–	–	46 (7)	0.94
8	L-**12**	–		49 (8)	
9	**13a**	1725 (38)	2.09[c]	93 (2)	0.08[c]
10	**13b**	827 (32)		1177 (22)	

[a] Anions added as TBA-salts. [b] Binding constants K_1 of 1:1 complexes in $CDCl_3$:[D_6]acetone (1:1 %vol) fitted and calculated with Bindfit (fitting errors in % in parentheses). [c] K_Z/K_E.

Table 3. Asymmetric Reissert-type reaction.[a]



Entry	Catalyst (mol%)	Solvent	T [°C]	Yield[b] [%]	*e.r.*[c]	Conf.
1	**1** (10)	Et_2O	−78	99	39:61	(*S*)
2	**1** (10)	toluene	−78	99	47:53	(*S*)
3	**1** (10)	$CHCl_3$	−60	99	35:65	(*S*)
4	**1** (10)[d]	$CHCl_3$	−60	94	35:65	(*S*)
5	**1** (1)	$CHCl_3$	−60	77	37:63	(*S*)
6	**2** (10)	$CHCl_3$	−60	80	78:22	(*R*)
7	**2** (1)	$CHCl_3$	−60	61	59:41	(*R*)
8	–	$CHCl_3$	−60	41	50:50	–

[a] 0.1 mmol scale, $c = 0.05$ M with dry solvents and under argon atmosphere. [b] Isolated yields. [c] Determined by chiral SFC analysis. [d] Recycled catalyst.

tiomer was observed for donor **1** ($K_D/K_L = 1.41$), while **2** showed a slight preference for the L-enantiomer ($K_D/K_L = 0.78$). Next, the selective binding of dicarboxylates was examined. Titration of XB-donor **1** with the tartrate TBA-salts **11** revealed a good selectivity of 2.10 for the D-enantiomer (entries 6 and 7). For **2**, a similar selectivity of 2.23 could be observed, albeit at significantly lower binding constants. Titrations were also conducted on the tartrate-derived acetonides D- and L-**12**, which are less conformationally flexible than **11** and lack the free diol group. While the selectivity of HB-donor **2** completely vanished, surprisingly, the addition of more than 2 equivalents of D- or L-**12** led to a quantitative iodo-deuterium exchange of the lower triazoles of the XB-donor **1** and, thus, the binding constants could not be determined (entries 9 and 10, see SI). Interestingly, this dehalogenation was only observed with **12**.[23] The abilities of the receptors to discriminate between the isomeric TBA-salts of maleate **13a** and fumarate **13b** were also tested. XB-donor **1** displayed a preference for maleate over fumarate by a factor 2.09 (entries 7 and 8). However, for the HB-donor **2**, the selectivity was inverted, with a significant (>12-fold) preference for the binding of fumarate **13b** over maleate **13a** ($K_Z/K_E = 0.08$).

Additionally, we wanted to explore the catalytic potential of the XB-donor **1**. To that purpose, a Reissert-type dearomatization of quinoline with a silylketeneacetal as nucleophile was chosen as a benchmark reaction (Table 3).[19a] First, the active *N*-acylquinolinium chloride salt was formed by addition of Troc-Cl to the quinoline substrate. Next, the mixture was cooled to the desired temperature, and the catalyst and the nucleophile were added. A solvent screen (entries 1–3; see SI for additional data) revealed that $CHCl_3$ affords the best results with the XB-donor, reaching a 35:65 e.r. and close to quantitative yield at −60 °C (entry 3). Moreover, the XB-donor **1** proved stable under the catalytic conditions, allowing its quantitative reisolation and recycling (entry 4). Under the same conditions, the HB-donor **2** provided a lower conversion (80 % yield) but a higher chiral induction (78:22 e.r., entry 6).[24] Strikingly, the two catalysts displayed opposite senses of asymmetric induction, with XB-donor **1** favoring the (*S*) product versus the (*R*)-enantiomer for HB-donor **2**. Reducing the loading of the XB-donor catalyst **1** to 1 mol % did not result in a significant change in the enantioselectivity (entry 5), whereas the HB-donor **2** gave a significantly lower yield and a dramatic drop in enantioselectivity at this loading (59:41 e.r., entry 7). It should be noted that the catalysts have to overcome a strong background reaction, which leads to a 41 % yield of the (racemic) product under the same conditions (entry 8). Presumably, the superior results obtained for the XB- versus HB-donor at low loadings reflect the ability of the latter to more reliably outcompete the uncatalyzed background reaction. Although the enantioselectivity of the acyl-Mannich reaction catalyzed by **1** was moderate, it is on par with the best results obtained using catalysts that rely solely on XB to achieve asymmetric induction,[18] and the first such example that employs an uncharged halogen bond donor.

To gain further insights on the behavior of the receptor **1** upon binding to anions such as chloride, circular dichroism (CD) titrations were carried out and compared with the parent HB-donor **2** (Figure 2). In line with the opposite senses of asymmetric induction observed for the two catalysts in the test reaction, XB-donor **1** and HB-donor **2** displayed contrasting chiroptical properties in the presence of exogenous chloride (added as TBACl) in THF (Figures 2a and 2b). Whereas the chloride complex of **2** displayed a positive Cotton effect, the opposite was observed for **1**,[19a] along with a slight shift to-

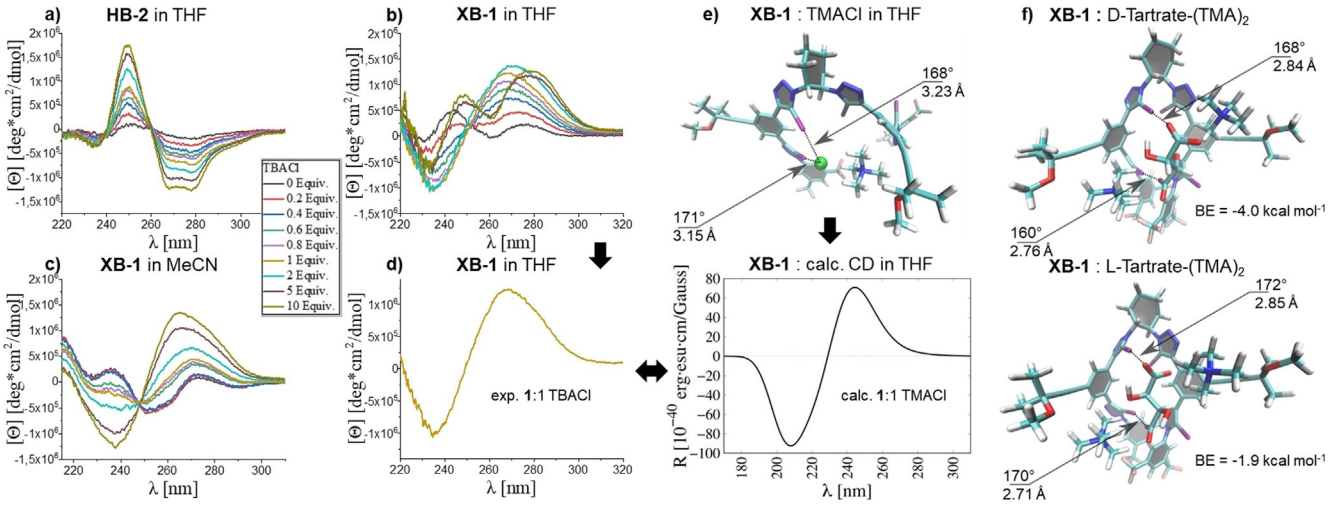


Figure 2. CD-spectra of the XB-donor **1** [62.5 μM] and HB-donor **2** [62.5 μM] in THF (**a** and **b**) and of **1** in MeCN (**c**). (**d**) isolated CD-spectrum of **1** in THF upon addition of 1 equiv of TBACl. (**e**) Optimized structure including solvent effects (SMD model) and CD-spectrum for a model XB-**1**:TMACl complex in THF. (**f**) XB-**1**:D and L-tartrate-$(TMA)_2$ complexes and calculated binding energies (BE = E[XB-**1**:D- or L-Tartrate-$(TMA)_2$]–E[XB-**1**]–E[D-Tartrate-$(TMA)_2$]) in kcal mol^{-1}, I–O distances and C-I-O angles. See Supporting Information for more details.

wards shorter wavelengths in the presence of the anion (minima ≈235 nm and maxima ≈270 nm). Further evolution of the CD spectrum of **1** was evident at higher chloride concentrations (≥5 equiv), indicating a different complexation (i.e. different XB-dentate complexes, also see theoretical CDs in Supporting Information). Considering that the concentration of 'free' chloride in solution under the conditions of catalysis is quite low, it seems unlikely that this spectral feature arises from a species that is relevant to the enantioselective reaction. Furthermore, we examined the solvent effect by conducting the CD-experiment in more polar solvents such as MeCN (Figure 2c). Remarkably, the shape of the CD spectrum for the XB-donor **1**:TBACl complex was maintained in this medium, whereas it was not observed for HB-donor **2** (see the Supporting Information for details and additional titrations).

To complement our experimental findings, quantum chemistry calculations based on density functional theory (DFT) were carried out using the Gaussian16 program.[25] The structures of the 1:1 complexes of the XB-donor **1** and tetramethylammonium salts (TMAX) were optimized in the gas-phase using the M062X functional[26] with 6-31G(d,p)[27] basis set for all atoms but iodine and LAND2Z[28] basis set for iodine atoms.[29] Additionally, for the CD spectra of the complex with TMACl in THF, an optimization was carried out using the SMD implicit solvent model (see details in Supporting Information).[30] Simulated CD spectra were generated for five optimized geometries of the **1**·TMACl complex having calculated energies differing by less than 2.2 kcal mol^{-1} (see Supporting Information). Although a complex with a tridentate halogen bonding could be envisioned, the closest correspondence to the experimental CD spectrum (Figure 2d, with 1 equiv of TBACl) was found for bidentate complexes involving the two triazole units of a single arm of the catalyst (Figure 2e, see Supporting Information for complete details). In this case, two halogen bonds (C-I-Cl angles of ≈170° and I–Cl distances of ≈3.2 Å) participate in the binding to the chloride anion. A similar bidentate binding mode was observed for the complexes of **1** with other halides (see Supporting Information), as well as with the chiral dicarboxylates D- and L-tartrate (Figure 2f). It appears that the introduction of the large iodo substituents to this scaffold causes a distortion of the helical cavity that prevents a higher coordination number. Interestingly, in the bidentate complexes with tartrate, a single-point halogen bonding interaction between each iodotriazole and a carboxylate unit was observed. Moreover, in qualitative agreement with the observed binding affinities, the calculated energy of the XB-bidentate complex of **1** with D-tartrate was lower than that of L-tartrate by 2.1 kcal mol^{-1} (see Supporting Information for more details).

In conclusion, we have presented a chiral tetrakis-iodo-triazole as a novel XB-donor. Its anion binding properties were examined by NMR-titration experiments and compared to its parent HB-donor **2**. Both receptors were applied for the recognition of chiral or *E*/*Z*-diastereomeric carboxylates. Moderate to good selectivities, especially for dicarboxylates such as the D/L-tartrate or fumarate/maleate series, were observed. Moreover, the capability for asymmetric induction was tested in a benchmark reaction, showing the potential of XB-donors in enantioselective organocatalysis. The remarkable inversion of stereoselectivity versus the corresponding hydrogen bond donor was examined by CD-experiments and further reinforced by DFT calculations. XB-donor **1** displays markedly different anion-binding properties relative to HB-donor **2** and provides superior performance as a chiral receptor in moderately polar media such as chloroform or MeCN. Further efforts and studies towards improved anion receptor structures and the application of chiral XB-donors in asymmetric organocatalysis are currently ongoing in our labs.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chiral anion recognition · DFT · halogen bonding · NMR titration · organocatalysis

[1] G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo, *Chem. Rev.* **2016**, *116*, 2478.
[2] a) R. Wilcken, M. O. Zimmermann, A. Lange, A. C. Joerger, F. M. Boeckler, *J. Med. Chem.* **2013**, *56*, 1363; b) N. K. Shinada, A. G. de Brevern, P. Schmidtke, *J. Med. Chem.* **2019**, *62*, 9341.
[3] a) P. Metrangolo, G. Resnati, *Chem. Eur. J.* **2001**, *7*, 2511; b) P. Metrangolo, F. Meyer, T. Pilati, G. Resnati, G. Terraneo, *Angew. Chem. Int. Ed.* **2008**, *47*, 6114; *Angew. Chem.* **2008**, *120*, 6206; c) A. Priimagi, G. Cavallo, P. Metrangolo, G. Resnati, *Acc. Chem. Res.* **2013**, *46*, 2686; d) P. M. J. Szell, S. Zablotny, D. L. Bryce, *Nat. Commun.* **2019**, *10*, 916; e) M. S. Taylor, *Coord. Chem. Rev.* **2020**, *413*, 213270; f) E. A. John, C. J. Massena, O. B. Berryman, *Chem. Rev.* **2020**, *120*, 2759.
[4] a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; *Angew. Chem.* **2006**, *118*, 1550; c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; d) S. Beckendorf, S. Asmus, O. García Mancheño, *ChemCatChem* **2012**, *4*, 926.
[5] a) M. G. Sarwar, B. Dragisic, S. Sagoo, M. S. Taylor, *Angew. Chem. Int. Ed.* **2010**, *49*, 1674; *Angew. Chem.* **2010**, *122*, 1718; b) A. Caballero, N. G. White, P. D. Beer, *Angew. Chem. Int. Ed.* **2011**, *50*, 1845; *Angew. Chem.* **2011**, *123*, 1885; c) M. G. Chudzinski, C. A. McClary, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 10559; d) M. Cametti, K. Raatikainen, P. Metrangolo, T. Pilati, G. Terraneo, G. Resnati, *Org. Biomol. Chem.* **2012**, *10*, 1329; e) T. M. Beale, M. G. Chudzinski, M. G. Sarwar, M. S. Taylor, *Chem. Soc. Rev.* **2013**, *42*, 1667; f) N. H. Evans, P. D. Beer, *Angew. Chem. Int. Ed.* **2014**, *53*, 11716; *Angew. Chem.* **2014**, *126*, 11908; g) L. C. Gilday, S. W. Robinson, T. A. Barendt, M. J. Langton, B. R. Mullaney, P. D. Beer, *Chem. Rev.* **2015**, *115*, 7118; h) A. Brown, P. D. Beer, *Chem. Commun.* **2016**, *52*, 8645; i) R. Tepper, U. S. Schubert, *Angew. Chem. Int. Ed.* **2018**, *57*, 6004; *Angew. Chem.* **2018**, *130*, 6110; j) M. Kaasik, S. Kaabel, K. Kriis, I. Järving, T. Kanger, *Synthesis* **2019**, *51*, 2128; k) C. C. Robertson, J. S. Wright, E. J. Carrington, R. N. Perutz, C. A. Hunter, L. Brammer, *Chem. Sci.* **2017**, *8*, 5392; l) M. G. Sarwar, B. Dragisic, L. J. Salsberg, C. Gouliaras, M. S. Taylor, *J. Am. Chem. Soc.* **2010**, *132*, 1646; m) M. G. Sarwar, B. Dragisic, L. J. Salsberg, C. Gouliaras, M. S. Taylor, *Chem. Eur. J.* **2013**, *19*, 2050.
[6] D. Mungalpara, S. Stegmüller, S. Kubik, *Chem. Commun.* **2017**, *53*, 5095.
[7] J. Y. C. Lim, I. Marques, L. Ferreira, V. Félix, P. D. Beer, *Chem. Commun.* **2016**, *52*, 5527.
[8] J. Y. C. Lim, I. Marques, V. Félix, P. D. Beer, *J. Am. Chem. Soc.* **2017**, *139*, 12228.
[9] J. Y. C. Lim, I. Marques, V. Félix, P. D. Beer, *Angew. Chem. Int. Ed.* **2018**, *57*, 584; *Angew. Chem.* **2018**, *130*, 593.
[10] a) S. M. Walter, F. Kniep, E. Herdtweck, S. M. Huber, *Angew. Chem. Int. Ed.* **2011**, *50*, 7187; *Angew. Chem.* **2011**, *123*, 7325; b) A. Dreger, E. Engelage, B. Mallick, P. D. Beer, S. M. Huber, *Chem. Commun.* **2018**, *54*, 4013; c) J. Bamberger, F. Ostler, O. García Mancheño, *ChemCatChem* **2019**, *11*, 5198; d) R. L. Sutar, S. M. Huber, *ACS Catal.* **2019**, *9*, 9622; e) X. Liu, S. Ma, P. H. Toy, *Org. Lett.* **2019**, *21*, 9212; f) M. Breugst, J. J. Koenig, *Eur. J. Org. Chem.* **2020**, 5473; g) J. Wolf, F. Huber, N. Erochok, F. Heinen, V. Guérin, C. Y. Legault, S. F. Kirsch, S. M. Huber, *Angew. Chem. Int. Ed.* **2020**, *59*, 5510; *Angew. Chem.* **2020**, *132*, 5552.
[11] S. H. Jungbauer, S. M. Walter, S. Schindler, L. Rout, F. Kniep, S. M. Huber, *Chem. Commun.* **2014**, *50*, 6281.
[12] a) L. Zong, X. Ban, C. W. Kee, C.-H. Tan, *Angew. Chem. Int. Ed.* **2014**, *53*, 11849; *Angew. Chem.* **2014**, *126*, 12043; b) T. Arai, T. Suzuki, T. Inoue, S. Kuwano, *Synlett* **2017**, *28*, 122; c) S. Kuwano, T. Suzuki, Y. Hosaka, T. Arai, *Chem. Commun.* **2018**, *54*, 3847; d) S. Kuwano, Y. Nishida, T. Suzuki, T. Arai, *Adv. Synth. Catal.* **2020**, *362*, 1674.
[13] a) Y.-C. Chan, Y.-Y. Yeung, *Org. Lett.* **2019**, *21*, 5665; b) R. A. Squitieri, K. P. Fitzpatrick, A. A. Jaworski, K. A. Scheidt, *Chem. Eur. J.* **2019**, *25*, 10069.
[14] M. Kaasik, S. Kaabel, K. Kriis, I. Järving, R. Aav, K. Rissanen, T. Kanger, *Chem. Eur. J.* **2017**, *23*, 7337.
[15] For the first example of iodo-triazole derivatives as XB-donors, see: N. L. Kilah, M. D. Wise, C. J. Serpell, A. L. Thompson, N. G. White, K. E. Christensen, P. D. Beer, *J. Am. Chem. Soc.* **2010**, *132*, 11893.
[16] A. Borissov, J. Y. C. Lim, A. Brown, K. E. Christensen, A. L. Thompson, M. D. Smith, P. D. Beer, *Chem. Commun.* **2017**, *53*, 2483.
[17] J. Y. C. Lim, I. Marques, V. Félix, P. D. Beer, *Chem. Commun.* **2018**, *54*, 10851.
[18] R. L. Sutar, E. Engelage, R. Stoll, S. M. Huber, *Angew. Chem. Int. Ed.* **2020**, *59*, 6806; *Angew. Chem.* **2020**, *132*, 6872.
[19] a) M. Zurro, S. Asmus, S. Beckendorf, C. Mück-Lichtenfeld, O. García Mancheño, *J. Am. Chem. Soc.* **2014**, *136*, 13999; b) O. García Mancheño, S. Asmus, M. Zurro, T. Fischer, *Angew. Chem. Int. Ed.* **2015**, *54*, 8823; *Angew. Chem.* **2015**, *127*, 8947; c) Q.-N. Duong, L. Schifferer, O. García Mancheño, *Eur. J. Org. Chem.* **2019**, 5452; d) T. Fischer, J. Bamberger, M. Gómez-Martínez, D. G. Piekarski, O. García Mancheño, *Angew. Chem. Int. Ed.* **2019**, *58*, 3217; *Angew. Chem.* **2019**, *131*, 3250; e) D. G. Piekerski, P. Steinforth, M. Gómez-Martínez, J. Bamberger, F. Ostler, M. Schönhoff, O. García Mancheño, *Chem. Eur. J.* **2020**, https://doi.org/10.1002/chem.202003994.
[20] J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless, V. V. Fokin, *Angew. Chem. Int. Ed.* **2009**, *48*, 8018; *Angew. Chem.* **2009**, *121*, 8162.
[21] H. A. Klein, P. D. Beer, *Chem. Eur. J.* **2019**, *25*, 3125.
[22] a) P. Thordarson, *Chem. Soc. Rev.* **2011**, *40*, 1305; b) D. Brynn Hibbert, P. Thordarson, *Chem. Commun.* **2016**, *52*, 12792; c) Bindfit v0.5 available at http://app.supramolecular.org/bindfit/.
[23] The XB-donor **1** (except for titration with **12**, see Supporting Information) and HB-donor **2** proved stable during throughout the titration experiments and could be fully recovered from the NMR samples and reused.
[24] The HB-donor **2** shows a remarkable enantioselectivity in this reaction of up to 96% *ee* in Et_2O at −78 °C. See ref. [19a].
[25] Gaussian 16, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Gaussian Inc., Wallingford CT, **2016**.
[26] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.
[27] W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257.
[28] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299.
[29] Single point energy corrections were performed at B3LYP-GD3BJ/def2tzvp: a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; b) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297; c) S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, *32*, 1456. BP86/def2tzvp: d) J. P. Perdew, *Phys. Rev. B* **1986**, *33*, 8822; e) A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098. Quasi-rigid-rotor-harmonic oscillator correction for wavenumbers below 100 cm^{-1}: f) I. Funes-Ardoiz, R. S. Paton, GoodVibes: Good-

Vibes 2.0.2, **2016**, http://doi.org/10.5281/zenodo.595246; g) S. Grimme, *Chem. Eur. J.* **2012**, *18*, 9955. Basis set superposition correction error: h) S. F. Boys, F. Bernardi, *Mol. Phys.* **1970**, *19*, 553.

[30] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378.

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