Synthesis M. Kaasik et al. Paper

Synthesis of Chiral Triazole-Based Halogen Bond Donors

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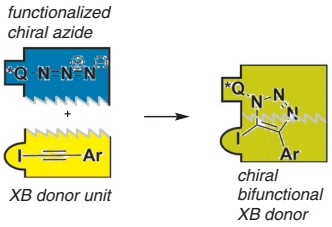

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Abstract The number of applications that use halogen bonding in the fields of self-assembly, supramolecular aggregation, and catalysis is growing. However, the accessibility of chiral halotriazoles shows that there is still a lot more to explore. The simple click-chemistry is applied for the straightforward synthesis of enantiomerically pure mono- and bidentate as well as multifunctional iodotriazole-based XB donors. The methodology is characterized by a wide variability due to easy access of chiral azides.

Key words click chemistry, nitrogen heterocycles, halogen bonds, hydrogen bonds, chiral compounds

Non-covalent interactions are of importance in biology and chemistry.[1] In chemistry, self-assembly, supramolecular aggregation, and often catalysis are based on these interactions. The past ten years have seen remarkable advances in the use of halogen bonding in these fields.[2] A halogen bond (XB) is similarly to a hydrogen bond (HB) a non-covalent interaction of an electrophilic atom with some Lewis base.[3] The strength of the XB depends on the structures of both the acceptor and the donor. The donor ability is connected with the polarizability of the halogen atom and changes in the order I > Br > Cl > F.[4] Electron-withdrawing groups connected with the halogen can further polarize the halogen atom and therefore increase its donor ability.[5]

Over the years the choice of XB donor scaffolds has considerably expanded. The first XB donors to be described were dihalogens and interhalogens (Figure 1).[6] However, organic scaffolds offer wider opportunities to modify the XB donor ability of the halogen atom. For example, the XB donor ability increases with an increase in the s-character on the carbon atom when comparing haloalkanes, haloarenes, and haloalkynes.[4,7] *N*-Haloimides have also been used as strong XB donors, due to the strongly polarizing effect of the carbonyl groups.[8] Nitrogen-containing cycles (pyridines, imidazoles, and triazoles)[9] are especially valuable as the quaternization of the nitrogen atom makes it possible to increase the electronegativity of the core.[5a,10]

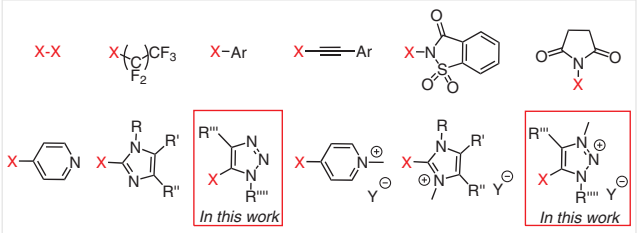


Figure 1 Typical examples of halogen bond donor scaffolds. Most commonly the donor atom X in the XB donor is either iodine or bromine

Triazole-based XB donors are readily accessible via a copper-catalyzed click reaction between haloalkyne and organic azide.[11] Alternatively, terminal alkynes can also be used, in which case halogenation is carried out in situ.[12] The halotriazoles have been used in ion-pair recognition,[13] as anion receptors,[10b,14] in organocatalysis,[15] and in polymer chemistry.[16] Iodotriazoles as XB donors were first introduced by Beer.[17] In spite of a wide variety of available chiral azides, the application of chiral triazole-based XB donors is quite limited. The pioneering work in this field was published by Huber et al. in 2012.[15a] We have recently shown enantiodiscrimination via XBs using chiral iodotriazoles.[18] Beer et al. have used chiral triazole-based rotaxanes.[19] BINOL-based receptors have been designed for the enantioselective recognition of anions.[14b,20] Interestingly, a stereogenic unit was also used as a bridge between two XB donor units. In addition, a macrocyclic pseudopeptide containing

three triazole cores was used as a halide receptor by Kubik et al.[14c] Selected examples of chiral XB donors are depicted in Figure 2.

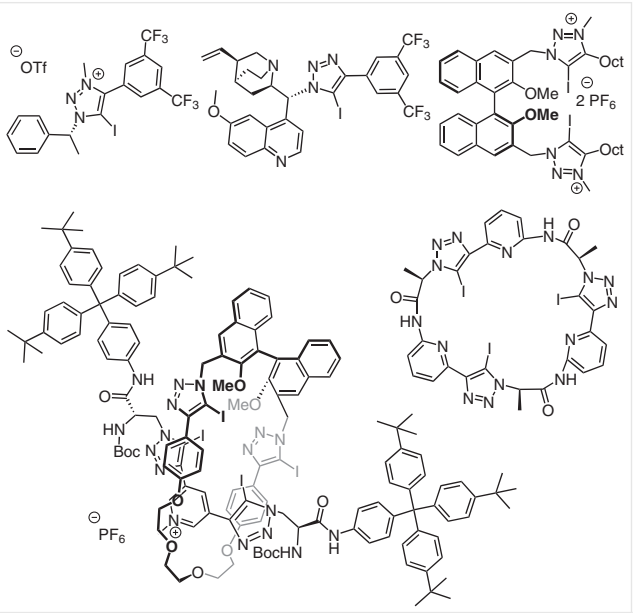


Figure 2 Examples of chiral iodotriazole-based XB donors

To broaden the scope of available chiral XB donors, we describe herein the synthesis of enantiomerically pure triazole derivatives. The synthesis of mono- and bidentate as well as multifunctional donors containing both XB and hydrogen bond donor moieties will be discussed.

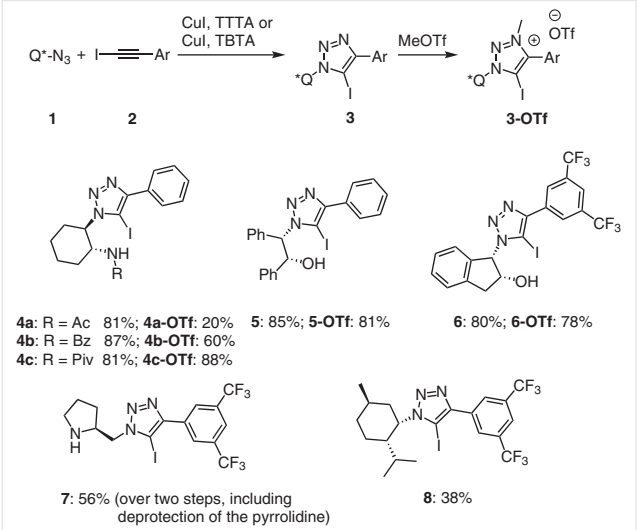
To start with, enantiomerically pure monodentate XB donors were synthesized from monoalkynes (iodoethynyl)benzene or 1-(iodoethynyl)-3,5-bis(trifluoromethyl)benzene (Scheme 1). Chiral amines or alcohols were used to obtain azides for a click reaction. Amines were directly converted into azides by reaction with imidazole-1-sulfonyl azide hydrochloride with the retention of the stereocenter. Alcohols were converted into corresponding mesylates and nucleophilic substitution resulted in azides with the inversion of the stereocenter (for details, see Supporting Information).

First, (1*R*,2*R*)-1,2-diaminocyclohexane was used as a chiral starting compound. Monoprotection of the diamine using phthalic anhydride, followed by acylation, then deprotection and azidation using imidazole-1-sulfonyl azide hydrochloride afforded azides with acyl-, benzoyl- or pivaloyl-protected amino groups.[21,22] A click reaction in the presence of CuI and tris[(1-*tert*-butyl-1*H*-1,2,3-triazolyl)methyl]amine (TTTA)[11b] led to triazoles **4a–c** in good yields (81–87%). The following quaternization with methyl trifluoromethanesulfonate (MeOTf) afforded XB donors **4a**-OTf to **4c**-OTf with an amide-based HB donor group.

The second group of XB donors contained a hydroxyl group as the HB donor unit (compounds **5** and **6**). *cis*-(1*S*,2*R*)-1-Amino-2-indanol and (1*S*,2*R*)-2-amino-1,2-diphenylethan-1-ol were transformed into the corresponding azides, which were then used to get XB donors **5** and **6** (85% and 80%, respectively) and corresponding triazolium salts (**5**-OTf, **6**-OTf).

For the synthesis of donors **7** and **8**, the second approach, converting the hydroxyl group into an azido group, was used. The synthesis of compound **7** started from Boc-protected (*S*)-prolinol. It was mesylated and treated with sodium azide to give the azide. After the formation of the triazole, the Boc-protecting group was removed affording the target containing a basic amino group in 56% yield (yield for two steps). A similar strategy was used to convert (–)-menthol into XB donor **8** with a bulky substituent. Unfortunately the click reaction worked reasonably well only with tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) and gave the product in a lower yield (38%; for details, see Supporting Information).

The iodotriazoles **8** and **4b**-OTf were analyzed and characterized by single-crystal X-ray crystallography (Figure 3). In the case of triazole **8**, an XB formed between the iodine atom of one donor and the nitrogen atom in the triazole core of another molecule of **8**. The distance of 2.947 Å corresponds to a reduction of the sum of the van der Waals radii by 16%. In the case of **4b**-OTf the carbonyl oxygen acted as an XB acceptor and the distance of 2.724 Å corresponds to a reduction of the sum of the van der Waals radii by 22%. Notably, in contrast to the triazolium salts previously studied,[18] which formed XBs to the counter anions, the carbonyl group of **4b**-OTf outcompeted the trifluoromethanesulfonate anion as an XB acceptor.



Scheme 1 Synthesis of monodentate XB donors

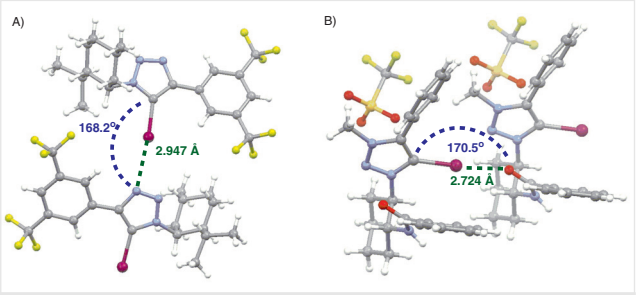
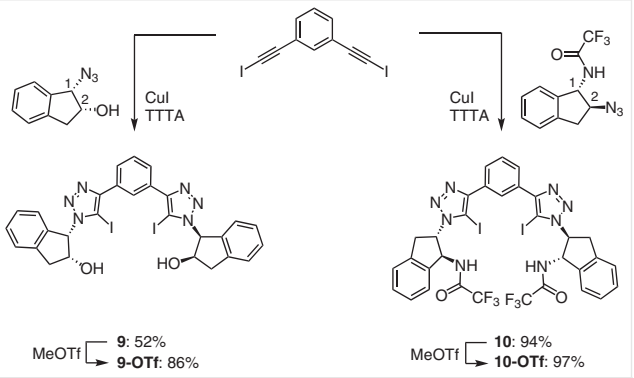


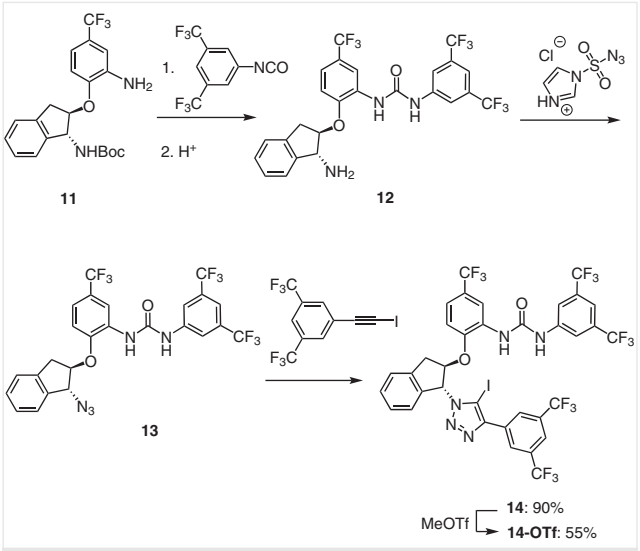
Figure 3 Ball and stick representations of **8** (**A**) and **4b**-OTf (**B**) showing the angle and distances of the XB between the molecules (see Supporting Information for details)

Next, bidentate C_2-symmetric XB donors **9** and **10** were synthesized starting from *cis*-(1*S*,2*R*)-1-amino-2-indanol and *meta*-bis(iodoethynyl)benzene (Scheme 2). Compound **9** was obtained by azidating the free amino group, followed by a click reaction. On the other hand, the selective *N*-trifluoroacetylation of *cis*-aminoindanol allowed the transformation of the unprotected hydroxyl group into azide by the previously described mesylation/substitution method with inversion of the configuration. This synthon for the click reaction differed from the synthon obtained by direct azidation in the relative configuration of the substituents on the indane ring. Also, the azido group and the respective bond with the triazole ring changed from the first to the second position on the indane ring. The click reaction proceeded smoothly affording triazole **10** in an excellent yield. Compounds **9** and **10** were again converted into corresponding triazolium salts in high yields. The obtained XB donors possessed different HB moieties and formed chiral pockets for acceptors with different geometries.



Scheme 2 Synthesis of bidentate XB donors

The synthetic potential of chiral azides and a click reaction was further harnessed to access triazole and urea-containing polyfunctional donor **14** (Scheme 3).



Scheme 3 Synthesis of urea-containing XB donor **14**-OTf

Aminoindanol derivative **11** was used as a chiral linker to connect urea and triazole moieties.[23] The reaction of 3,5-bis(trifluoromethylphenyl) isocyanate with the aromatic amine **11** afforded after acidic deprotection urea **12** in 92% yield. The following azidation with imidazole-1-sulfonyl azide hydrochloride and a click reaction resulted in the formation of triazole **14**.

In conclusion, we have shown a straightforward approach to enantiomerically pure XB donors. A click reaction provides a direct entry to the target compounds. Monodentate, bidentate, and polyfunctional XB donors can be obtained in high yields. Further studies on the applications of these compounds are ongoing.

NMR spectra were measured on a Bruker Avance III 400 MHz instrument. The spectra are reported in parts per million (δ) referenced to the residual solvent signal [$CDCl_3$ δ = 7.26, CD_3OD δ = 3.31, DMSO-d_6 δ = 2.50, acetone-d_6 δ = 2.05 (for ^{1}H NMR); $CDCl_3$ δ = 77.16, CD_3OD δ = 49.00, DMSO-d_6 δ = 39.52, acetone-d_6 δ = 29.84 (for ^{13}C NMR)]). High-resolution mass spectra were recorded on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. Single crystal X-ray diffraction data was collected at 123K on Rigaku Compact HomeLab diffractometer, equipped with a Saturn 944 HG CCD detector and Oxford Cryostream cooling system using monochromatic Cu-Kα radiation (1.54178Å) from a MicroMax™-003 sealed tube microfocus X-ray source. Optical rotations were obtained using an Anton Paar GWB Polarimeter MCP 500. IR absorption frequencies in wavenumbers are listed, with the relative strength in parentheses (w = weak, m = medium, s = strong, br = broad). Precoated silica gel 60 F_{254} plates from Merck were used for TLC, whereas for column chromatography, silica gel Kieselgel 40–63 μm was used. The measured melting points are uncorrected. Purchased chemicals and solvents were used as received. CH_2Cl_2 was distilled over P_2O_5 and

MeOH was dried by distillation over Na metal. Petroleum ether (PE) has a boiling point of 40–60 °C. The reactions were performed without additional moisture elimination, unless stated otherwise.

Click Reaction; General Procedure

CuI (0.004 g, 0.021 mmol) and TTTA (0.010 mg, 0.023 mmol) were dissolved in freshly distilled THF (2.3 mL, 0.2 M) under argon atmosphere and stirred at r.t. for 30 min. The (iodoethynyl)benzene or 1-(iodoethynyl)-3,5-bis(trifluoromethyl)benzene (0.45 mmol) and azide (0.45 mmol) were added and the reaction mixture was stirred at r.t. overnight. The mixture was concentrated, NH_4OH (10 mL, 10% w/w) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (anhyd Na_2SO_4), concentrated, and purified by column chromatography on silica gel (starting from 10% EtOAc in PE) to provide the triazole.

Conversion of Triazoles into Triazolium Salts; General Procedure

The respective triazole (0.19 mmol) was dissolved in CH_2Cl_2 (4 mL, 0.05 M) under argon atmosphere. MeOTf (0.033 mL, 0.29 mmol) was added dropwise and the reaction mixture was stirred at r.t. for 3 days. Et_2O was added to the mixture and the precipitate formed was filtered to provide the trifluoromethanesulfonic salt.

N-[(1*R*,2*R*)-2-(5-Iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)cyclohexyl]acetamide (4a)

Colorless solid; yield: 0.145 g (0.353 mmol, 81%); mp >187 °C (dec.); $[\alpha]_D^{20}$ –11.9 (*c* 0.43, $CHCl_3$).

IR (KBr): 3278 (s), 3073 (w), 2928 (s), 2857 (m), 1655 (s), 1552 (s), 1447 (m), 1375 (w), 1318 (w), 1228 (w), 1173 (w), 1065 (w), 985 (m), 807 (w), 768 (m), 697 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.89 (m, 2 H), 7.48–7.43 (m, 2 H), 7.43–7.36 (m, 1 H), 5.57 (d, *J* = 8.2 Hz, 1 H), 4.77 (td, *J* = 10.8, 4.9 Hz, 1 H), 4.47–4.20 (m, 1 H), 2.30–2.08 (m, 3 H), 2.02–1.79 (m, 3 H), 1.76 (s, 3 H), 1.62–1.40 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.6, 149.0 (based on HMBC), 130.4, 128.7, 128.6, 127.9, 63.5 (based on HSQC), 53.8 (based on HSQC), 32.7, 31.9, 25.0, 24.9, 23.7. The iodine bonded C-atom was not detected because of low intensity of the signal.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{20}IN_4O$: 411.0676; found: 411.0674.

1-[(1*R*,2*R*)-2-Acetamidocyclohexyl]-5-iodo-3-methyl-4-phenyl-1*H*-1,2,3-triazol-3-ium Trifluoromethanesulfonate (4a-OTf)

The product was crystallized twice; colorless solid; yield: 0.040 g (0.070 mmol, 20%); mp 192–194 °C; $[\alpha]_D^{20}$ +40.7 (*c* 0.18, MeOH).

IR (KBr): 3311 (m), 2933 (m), 2862 (w), 1651 (s), 1554 (m), 1449 (w), 1372 (w), 1285 (s), 1253 (s), 1224 (w), 1163 (m), 1030 (s), 768 (w), 707 (w), 637 cm^{-1} (s).

^1H NMR (400 MHz, CD_3OD): δ = 7.81–7.48 (m, 5 H), 4.75–4.60 (m, 1 H), 4.23 (s, 3 H), 4.16 (s, 1 H), 2.44–2.27 (m, 2 H), 2.12–1.89 (m, 3 H), 1.84 (s, 3 H), 1.77–1.47 (m, 3 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 172.8, 147.8, 133.2, 131.3, 130.8, 124.3, 121.8 (q, *J* = 318.6 Hz), 92.3, 70.2, 55.2, 39.7, 32.2, 31.7, 25.4, 25.3, 22.8.

HRMS (ESI): *m*/*z* [M – CF_3O_3S]$^+$ calcd for $C_{17}H_{23}IN_4O$: 425.0833; found: 425.0829; *m*/*z* [OTf]$^-$ calcd for CF_3O_3S: 148.9526; found: 148.9529.

N-[(1*R*,2*R*)-2-(5-Iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)cyclohexyl]benzamide (4b)

Eluent for chromatography: starting from 5% of EtOAc in CH_2Cl_2; colorless solid; yield: 0.335 g (0.709 mmol, 87%); mp 193–196 °C; $[\alpha]_D^{20}$ –28.6 (*c* 0.30, $CHCl_3$).

IR (KBr): 3318 (m), 3063 (w), 2940 (m), 2856 (m), 1638 (s), 1579 (w), 1543 (s), 1493 (m), 1447 (w), 1322 (s), 1286 (w), 1236 (w), 1170 (w), 983 (m), 803 (w), 769 (m), 695 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.79 (m, 2 H), 7.57–7.50 (m, 2 H), 7.47–7.27 (m, 6 H), 6.13 (d, *J* = 8.0 Hz, 1 H), 4.97 (td, *J* = 10.8, 4.8 Hz, 1 H), 4.66–4.43 (m, 1 H), 2.37–2.16 (m, 3 H), 2.10–1.87 (m, 3 H), 1.62–1.47 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.3, 149.1 (based on HMBC), 134.6, 131.6, 130.4, 128.6, 128.6, 128.6, 127.9, 126.9, 63.2 (based on HSQC), 54.3 (based on HSQC), 32.8, 31.9, 25.1, 25.0. The iodine bonded C-atom was not detected because of low intensity of the signal.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}IN_4O$: 473.0833; found: 473.0828.

1-[(1*R*,2*R*)-2-Benzamidocyclohexyl]-5-iodo-3-methyl-4-phenyl-1*H*-1,2,3-triazol-3-ium Trifluoromethanesulfonate (4b-OTf)

The product precipitated from the reaction mixture and was recrystallized from hot CH_2Cl_2; colorless solid; yield: 0.187 g (0.294 mmol, 60%); mp >230 °C (dec.); $[\alpha]_D^{20}$ –5.0 (*c* 0.21, MeOH).

IR (KBr): 3304 (m), 2938 (w), 2860 (w), 1641 (s), 1580 (w), 1535 (m), 1488 (w), 1455 (w), 1323 (m), 1283 (s), 1257 (s), 1225 (w), 1155 (m), 1031 (s), 771 (w), 697 (m), 638 cm^{-1} (s).

^1H NMR (400 MHz, CD_3OD): δ = 7.81–7.75 (m, 2 H), 7.70–7.53 (m, 4 H), 7.50–7.37 (m, 4 H), 4.84–4.78 (m, 1 H), 4.46 (ddd, *J* = 11.8, 10.1, 4.4 Hz, 1 H), 4.27 (s, 3 H), 3.35 (s, 1 H), 2.53–2.36 (m, 2 H), 2.21–1.85 (m, 4 H), 1.75–1.54 (m, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 169.6, 147.8, 134.6, 133.2, 133.2, 131.2, 130.7, 129.6, 128.5, 124.2, 92.6, 70.3, 55.7, 39.8, 32.1, 31.9, 25.6, 25.4.

HRMS (ESI): *m*/*z* [M – CF_3O_3S]$^+$ calcd for $C_{22}H_{25}IN_4O$: 487.0989; found: 487.0985; *m*/*z* [OTf]$^-$ calcd for CF_3O_3S: 148.9526; found: 148.9529.

N-[(1*R*,2*R*)-2-(5-Iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)cyclohexyl]pivalamide (4c)

Reaction conducted in 0.3 M solution of THF; colorless solid; yield: 0.108 g (0.239 mmol, 81%); mp 206–210 °C; $[\alpha]_D^{20}$ +3.8 (*c* 0.87, $CHCl_3$).

IR (KBr): 3406 (m), 2932 (s), 2865 (w), 1650 (s), 1513 (s), 1477 (m), 1448 (m), 1317 (w), 1230 (m), 1193 (m), 1169 (w), 985 (m), 957 (w), 769 (m), 696 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.79 (m, 2 H), 7.49–7.42 (m, 2 H), 7.42–7.36 (m, 1 H), 5.53 (d, *J* = 7.9 Hz, 1 H), 4.89 (dd, *J* = 16.2, 10.7 Hz, 1 H), 4.46–4.18 (m, 1 H), 2.30–2.04 (m, 3 H), 2.02–1.79 (m, 3 H), 1.59–1.42 (m, 2 H), 0.94 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.1, 149.1 (based on HMBC), 130.5, 128.6 (*o*- and *m*-C overlapped, based on HSQC), 127.9, 62.8 (based on HSQC), 53.9 (based on HSQC), 38.8, 32.8, 32.0, 27.5, 25.2, 25.1. The iodine bonded C-atom was not detected because of low intensity of the signal.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{26}IN_4O$: 453.1146; found: 453.1138.

5-Iodo-3-methyl-4-phenyl-1-[(1*R*,2*R*)-2-pivalamidocyclohexyl]-1*H*-1,2,3-triazol-3-ium Trifluoromethanesulfonate (4c-OTf)

Colorless solid; yield: 0.143 g (0.232 mmol, 88%); mp 218–219 °C; $[\alpha]_D^{20}$ +54.3 (*c* 0.20, MeOH).

IR (KBr): 3354 (m), 2937 (m), 2865 (w), 1623 (s), 1529 (s), 1485 (m), 1455 (m), 1367 (w), 1319 (w), 1284 (s), 1223 (m), 1149 (s), 1093 (w), 1032 (s), 826 (w), 766 (w), 697 (m), 637 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.41 (m, 5 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 5.08–4.87 (m, 1 H), 4.23 (s, 3 H), 4.15–4.03 (m, 1 H), 2.53–2.39 (m, 1 H), 2.25 (q, *J* = 12.5 Hz, 1 H), 2.11–1.75 (m, 4 H), 1.65–1.36 (m, 2 H), 1.07 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.3, 146.1, 132.2, 130.1, 129.9, 122.6, 89.1, 68.7, 54.7, 39.5, 38.8, 31.3, 31.1, 27.7, 24.7, 24.3.

HRMS (ESI): *m*/*z* [M – CF_3O_3S]$^+$ calcd for $C_{20}H_{29}IN_4O$: 467.1302; found: 467.1302; *m*/*z* [OTf]$^-$ calcd for CF_3O_3S: 148.9526; found: 148.9529.

(1*R*,2*S*)-2-(5-Iodo-4-phenyl-1*H*-1,2,3-triazol-1-yl)-1,2-diphenylethan-1-ol (5)

Reaction conducted in 0.3 M solution of THF; colorless solid; yield: 0.183 g (0.392 mmol, 85%); mp >164 °C (dec.); $[\alpha]_D^{20}$ +63.1 (*c* 0.25, $CHCl_3$).

IR (KBr): 3227 (br m), 2924 (m), 1604 (w), 1494 (w), 1474 (w), 1454 (m), 1322 (w), 1239 (w), 1158 (w), 1048 (s), 985 (w), 828 (m), 761 (m), 748 (s), 718 (w), 697 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.82 (m, 2 H), 7.47–7.22 (m, 13 H), 5.90 (dd, *J* = 5.5, 2.5 Hz, 1 H), 5.68 (d, *J* = 5.5 Hz, 1 H), 3.70 (d, *J* = 2.5 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.4, 139.2, 133.9, 130.0, 129.2, 129.0, 128.8, 128.7, 128.5, 128.4, 128.4, 127.7, 126.9, 78.4, 75.6, 71.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}IN_3O$: 468.0567; found: 468.0562.

1-[(1*S*,2*R*)-2-Hydroxy-1,2-diphenylethyl]-5-iodo-3-methyl-4-phenyl-1*H*-1,2,3-triazol-3-ium Trifluoromethanesulfonate (5-OTf)

Colorless solid; yield: 0.099 g (0.157 mmol, 81%); mp 188–189 °C; $[\alpha]_D^{20}$ –54.8 (*c* 0.16, MeOH).

IR (KBr): 3386 (br w), 1487 (w), 1456 (w), 1251 (s), 1165 (m), 1030 (s), 756 (w), 703 (m), 639 cm^{-1} (m).

^1H NMR (400 MHz, CD_3OD): δ = 7.81–7.74 (m, 2 H), 7.70–7.58 (m, 3 H), 7.55–7.45 (m, 3 H), 7.45–7.31 (m, 7 H), 6.09 (d, *J* = 8.6 Hz, 1 H), 5.73 (d, *J* = 8.5 Hz, 1 H), 4.24 (s, 3 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 148.0, 141.1, 134.5, 133.3, 131.1, 131.0, 130.7, 130.7, 130.1, 130.0, 129.8, 128.0, 123.8, 93.1, 76.2, 75.5, 39.8.

HRMS (ESI): *m*/*z* [M – CF_3O_3S]$^+$ calcd for $C_{23}H_{21}IN_3O$: 482.0724; found: 482.0723; *m*/*z* [OTf]$^-$ calcd for CF_3O_3S: 148.9526; found: 148.9533.

(1*S*,2*R*)-1-{4-[3,5-Bis(trifluoromethyl)phenyl]-5-iodo-1*H*-1,2,3-triazol-1-yl}-2,3-dihydro-1*H*-inden-2-ol (6)

Et_3N (2 equiv) was used instead of TTTA; eluent for chromatography: starting from 20% of EtOAc in PE; off-white solid; yield: 0.188 g (0.349 mmol, 80%); mp 114–116 °C; $[\alpha]_D^{20}$ +109.3 (*c* 1.45, $CHCl_3$).

IR (KBr): 3396 (br m), 1621 (w), 1374 (w), 1307 (m), 1279 (s), 1127 (s), 897 (m), 847 (w), 809 (w), 746 (m), 699 (m), 683 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.42 (br s, 2 H), 7.89 (br s, 1 H), 7.46–7.21 (m, 4 H), 6.10 (d, *J* = 6.4 Hz, 1 H), 4.99 (dq, *J* = 10.0, 6.7 Hz, 1 H), 3.40 (d, *J* = 6.8 Hz, 2 H), 2.93 (d, *J* = 10.1 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.5, 141.3, 136.9, 132.1, 132.0 (q, *J* = 33.6 Hz), 130.1, 127.6, 127.4–127.2 (m), 125.7, 124.5, 123.1 (q, *J* = 272.9 Hz), 122.4–122.0 (m), 79.1, 73.8, 67.3, 40.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{13}F_6IN_3O$: 540.0002; found: 540.0002.

4-[3,5-Bis(trifluoroomethyl)phenyl]-1-[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]-5-iodo-3-methyl-1*H*-1,2,3-triazol-3-ium Trifluoromethanesulfonate (6-OTf)

White solid; yield: 0.091 g (0.129 mmol, 78%); mp 176–179 °C; $[\alpha]_D^{25}$ –22.0 (*c* 1.10, $CHCl_3$).

IR (KBr): 3421 (m), 1623 (w), 1371 (m), 1283 (s), 1139 (s), 1030 (s), 911 (m), 848 (w), 757 (m), 704 (m), 680 (m), 640 cm^{-1} (s).

^1H NMR (400 MHz, CD_3OD): δ = 8.40 (br s, 1 H), 8.36 (br s, 2 H), 7.53–7.32 (m, 4 H), 6.51 (d, *J* = 6.3 Hz, 1 H), 5.09 (q, *J* = 6.7 Hz, 1 H), 4.19 (s, 3 H), 3.41 (dd, *J* = 16.1, 7.0 Hz, 1 H), 3.14 (dd, *J* = 16.2, 6.9 Hz, 1 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 145.5, 144.0, 136.0, 134.3 (q, *J* = 33.6 Hz), 132.8–132.5 (m), 132.0, 128.9, 127.8, 127.2, 127.1–126.9 (m), 126.6, 124.2 (q, *J* = 272.5 Hz), 94.4 (based on HMBC), 73.7, 73.2, 40.0, 39.9.

HRMS (ESI): *m*/*z* [M – CF_3O_3S]$^+$ calcd for $C_{20}H_{15}F_6IN_3O$: 554.0159; found: 554.0159.

(*S*)-4-[3,5-Bis(trifluoromethyl)phenyl]-5-iodo-1-(pyrrolidin-2-ylmethyl)-1*H*-1,2,3-triazole (7)

Triazole **7** was synthesized by the general procedure for the click reaction [yield of Boc-protected **7**: 0.149 g (0.252 mmol, 88%)] followed by removal of the Boc-protecting group.

To a solution of *tert*-butyl (*S*)-2-[4-(3,5-bis(trifluoromethyl)phenyl]-5-iodo-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidine-1-carboxylate (0.126 g, 0.213 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.400 mL, 5.22 mmol) at 0 °C and the reaction mixture was stirred at r.t. for 3 h. The mixture was concentrated, triturated with Et_2O, and filtered to provide the salt of **7**, which was treated with sat. aq $NaHCO_3$ (2 mL). After stirring for 15 min, the aqueous phase was extracted with CH_2Cl_2 (7 × 3 mL), dried (Na_2SO_4), and concentrated. Removal of solvent under reduced pressure afforded triazole **7** as an off-white solid; yield: 0.068 g (0.139 mmol, 65%); mp 103–104 °C; $[\alpha]_D^{20}$ +11.1 (*c* 0.68, MeOH).

IR (KBr): 2926 (m), 1620 (w), 1373 (w), 1316 (m), 1285 (s), 1183 (m), 1128 (s), 896 (m), 821 (w), 698 (w), 683 cm^{-1} (w).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (br s, 2 H), 7.90 (br s, 1 H), 4.41 (qd, *J* = 13.7, 6.7 Hz, 2 H), 3.82 (ddd, *J* = 13.5, 7.4, 5.9 Hz, 1 H), 3.10–2.93 (m, 2 H), 2.03–1.74 (m, 4 H), 1.67–1.57 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.7, 132.5, 132.0 (q, *J* = 33.5 Hz), 127.4–127.2 (m), 123.2 (q, *J* = 272.7 Hz), 122.2–121.8 (m), 78.6, 57.7, 55.6, 46.5, 29.3, 25.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}F_6IN_4$: 491.0162; found: 491.0157.

4-[3,5-Bis(trifluoromethyl)phenyl]-5-iodo-1-[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]-1*H*-1,2,3-triazole (8)

TBTA was used instead of TTTA; eluent for chromatography: starting from 5% CH_2Cl_2 in PE; colorless solid; yield: 0.048 g (0.088 mmol, 38%); mp 132–134 °C; $[\alpha]_D^{20}$ +5.9 (*c* 0.04, $CHCl_3$).

IR (KBr): 2964 (m), 2845 (w), 1622 (w), 1462 (w), 1371 (m), 1309 (m), 1280 (s), 1243 (w), 1183 (s), 1139 (s), 898 (m), 846 (w), 809 (w), 711 (w), 700 (m), 682 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (br s, 2 H), 7.89 (br s, 1 H), 5.07–4.93 (m, 1 H), 2.38 (qd, *J* = 13.2, 4.0 Hz, 1 H), 2.02–1.93 (m, 1 H), 1.93–1.76 (m, 3 H), 1.55–1.45 (m, 2 H), 1.44–1.35 (m, 1 H), 1.05 (qd, *J* = 13.2, 4.2 Hz, 1 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 0.85 (d, *J* = 6.4 Hz, 3 H), 0.78 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.8, 132.8, 132.0 (q, *J* = 33.5 Hz), 127.7–127.4 (m), 123.4 (d, *J* = 274.7 Hz), 122.2–121.9 (m), 79.0, 59.6, 47.2, 40.6, 35.0, 29.0, 25.32, 25.28, 22.1, 21.5, 21.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}F_6IN_3$: 546.0835; found: 546.0841.

(1*S*,1′*S*,2*R*,2′*R*)-1,1′-[1,3-Phenylenebis(5-iodo-1*H*-1,2,3-triazole-4,1-diyl)]bis(2,3-dihydro-1*H*-inden-2-ol) (9)

CuI (0.10 equiv) and TTTA (0.10 equiv) were used; eluent for chromatography: starting from 20% of EtOAc in PE; off-white solid; yield: 0.240 g (0.33 mmol, 52%); mp 198–203 °C; $[\alpha]_D^{20}$ +23.4 (*c* 0.36, MeOH).

IR (KBr): 3406 (br s), 2918 (w), 1610 (w), 1461 (m), 1344 (m), 1241 (m), 1215 (w), 1169 (w), 1100 (s), 985 (m), 887 (w), 796 (m), 744 (s), 718 (w), 685 cm^{-1} (m).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.61–8.56 (m, 1 H), 7.98 (dt, *J* = 7.8, 1.9 Hz, 2 H), 7.66 (t, *J* = 7.8 Hz, 1 H), 7.45–7.20 (m, 8 H), 6.09 (d, *J* = 6.5 Hz, 2 H), 5.42 (d, *J* = 5.9 Hz, 2 H), 4.83 (tt, *J* = 6.5, 6.7 Hz, 2 H), 3.23 (dd, *J* = 15.6, 6.9 Hz, 2 H), 3.10 (dd, *J* = 15.7, 6.9 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 147.1, 142.2, 138.1, 131.1, 129.1, 129.0, 126.9, 126.6, 125.9, 125.3, 125.0, 83.0, 71.9, 66.8, 66.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{23}I_2N_6O_2$: 728.9966; found: 728.9974.

4,4′-(1,3-Phenylene)bis{1-[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]-5-iodo-3-methyl-1*H*-1,2,3-triazol-3-ium} Trifluoromethanesulfonate (9-OTf)

White solid; yield: 0.164 g (0.155 mmol, 86%); mp 147–150 °C; $[\alpha]_D^{25}$ –8.7 (*c* 0.70, MeOH).

IR (KBr): 3423 (br s), 1624 (w), 1556 (w), 1479 (w), 1254 (s), 1166 (s), 1100 (m), 1029 (s), 891 (w), 815 (w), 756 (m), 696 (w), 639 cm^{-1} (s).

^{1}H NMR (400 MHz, CD_3OD): δ = 8.09–7.98 (m, 4 H), 7.53–7.40 (m, 6 H), 7.40–7.31 (m, 2 H), 6.51 (d, *J* = 6.5 Hz, 2 H), 5.09 (q, *J* = 6.8 Hz, 2 H), 4.24 (s, 6 H), 3.40 (dd, *J* = 16.1, 7.0 Hz, 2 H), 3.14 (dd, *J* = 16.1, 6.9 Hz, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 146.6, 144.0, 136.1, 135.1, 133.5, 132.3, 131.9, 128.8, 127.8, 126.5, 126.1, 93.9 (based on HMBC), 73.7, 73.0, 40.1, 39.9.

HRMS (ESI): *m*/*z* [M – 2 CF_3O_3S – CH_3]$^+$ calcd for $C_{29}H_{25}I_2N_6O_2$: 743.0123; found: 743.0124.

***N*,*N*′-{(1*S*,1′*S*,2*S*,2′*S*)-[1,3-Phenylenebis(5-iodo-1*H*-1,2,3-triazole-4,1-diyl)]bis(2,3-dihydro-1*H*-indene-2,1-diyl)}bis(2,2,2-trifluoroacetamide) (10)**

CuI (0.10 equiv) and TTTA (0.10 equiv) were used, 0.1 M solution. The product was purified mostly by crystallization. The crude product was dissolved in EtOAc (0.2 mL), then CH_2Cl_2 (2 mL) was added and the fine precipitate formed was filtered to provide bistriazole **10** as off-white crystals [yield: 0.141 g (0.154 mmol, 67%)]. The mother liquid was concentrated and purified by column chromatography on silica gel (starting from 20% of acetone in PE) to provide an additional amount of **10** as a white solid; yield: 0.057 g (0.062 mmol, 27%); total yield: 94%; mp 172–174 °C; $[\alpha]_D^{25}$ +31.9 (*c* 0.60, acetone).

IR (KBr): 3428 (br m), 3073 (w), 1713 (s), 1548 (m), 1462 (w), 1208 (s), 1166 (s), 983 (w), 929 (w), 791 (w), 750 (m), 717 cm^{-1} (w).

^{1}H NMR (400 MHz, acetone-d_6): δ = 9.20 (d, *J* = 8.5 Hz, 2 H), 8.71 (t, *J* = 1.8 Hz, 1 H), 8.08 (dd, *J* = 7.8, 1.8 Hz, 2 H), 7.68 (t, *J* = 7.8 Hz, 1 H), 7.46–7.26 (m, 8 H), 6.19 (t, *J* = 7.9 Hz, 2 H), 5.76 (td, *J* = 8.5, 7.3 Hz, 2 H), 3.81 (dd, *J* = 16.1, 8.6 Hz, 2 H), 3.70 (dd, *J* = 16.0, 8.3 Hz, 2 H).

^{13}C NMR (101 MHz, acetone-d_6): δ = 157.91 (q, *J* = 37.0 Hz), 149.8, 139.8, 139.3, 132.1, 129.9, 129.8, 128.7, 128.2, 126.9, 125.8, 124.6, 116.9 (q, *J* = 287.9 Hz), 80.2, 67.0, 61.7, 37.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{23}F_6I_2N_8O_2$: 918.9932; found: 918.9925.

4,4′-(1,3-Phenylene)bis{5-iodo-3-methyl-1-[(1*S*,2*S*)-1-(2,2,2-trifluoroacetamido)-2,3-dihydro-1*H*-inden-2-yl]-1*H*-1,2,3-triazol-3-ium} Trifluoromethanesulfonate (10-OTf)

Colorless solid; yield: 0.135 g (0.108 mmol, 97%); mp >213 °C (dec.); $[\alpha]_D^{20}$ +21.0 (*c* 0.70, acetone).

IR (KBr): 3456 (br m), 1720 (s), 1555 (m), 1482 (w), 1251 (s), 1166 (s), 1031 (s), 757 (w), 639 (m), 518 cm^{-1} (w).

^{1}H NMR (400 MHz, acetone-d_6): δ = 9.40 (d, *J* = 7.8 Hz, 2 H), 8.36–8.00 (m, 4 H), 7.56–7.22 (m, 8 H), 6.09 (dt, *J* = 8.8, 6.6 Hz, 2 H), 6.1–5.9 (m, 2 H), 4.44 (s, 6 H), 4.04 (dd, *J* = 16.7, 8.5 Hz, 2 H), 3.78 (dd, *J* = 16.7, 6.8 Hz, 2 H).

^{13}C NMR (101 MHz, acetone-d_6): δ = 158.46 (q, *J* = 37.3 Hz), 147.0, 139.4, 138.2, 134.9, 133.3, 132.0, 130.4, 129.0, 125.9, 125.6, 124.8, 116.78 (q, *J* = 287.7 Hz), 92.8, 70.4, 62.6, 40.5, 38.0.

HRMS (ESI): *m*/*z* [M – 2 $CF_3O_3S/2$]$^+$ calcd for $C_{34}H_{28}F_6I_2N_8O_2/2$: 474.0159; found: 474.0165; *m*/*z* [OTf]$^-$ calcd for CF_3O_3S: 148.9526; found: 148.9542.

1-(2-{[(1*R*,2*R*)-1-Azido-2,3-dihydro-1*H*-inden-2-yl]oxy}-5-(trifluoromethyl)phenyl)-3-[3,5-bis(trifluoromethyl)phenyl]urea (13)

The urea **12** was prepared following the literature procedure.[22] Aminourea **12** (0.408 g, 0.725 mmol) was dissolved in a suspension of K_2CO_3 (0.151 g, 1.088 mmol) and $CuSO_4{\cdot}5H_2O$ (0.002 mg, 0.007 mmol) in MeOH (10 mL). Imidazole-1-sulfonyl azide hydrochloride (0.182 g, 0.868 mmol) was added and the mixture stirred overnight at r.t. The solvent was removed under reduced pressure, then the solid was dissolved in H_2O (5 mL), acidified with aq HCl (10 mL, 1 M), and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (starting from 5% of EtOAc in PE) to provide the azide **13**, after removal of solvent under reduced pressure, as an off-white solid; yield: 0.297 g (0.504 mmol, 70%); mp >205 °C (dec.); $[\alpha]_D^{20}$ –87.0 (*c* 0.98, MeOH).

IR (KBr): 3346 (m), 2103 (m), 1659 (m), 1556 (m), 1490 (m), 1447 (m), 1386 (m), 1339 (m), 1279 (s), 1181 (s), 1135 (s), 920 (w), 885 (w), 682 cm^{-1} (w).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.05 (s, 1 H), 8.52 (s, 1 H), 8.41 (s, 1 H), 8.06 (s, 2 H), 7.66 (s, 1 H), 7.49 (d, *J* = 7.1 Hz, 1 H), 7.46–7.32 (m, 5 H), 5.34 (s, 1 H), 5.31 (dd, *J* = 7.1, 3.8 Hz, 1 H), 3.69 (dd, *J* = 17.0, 7.0 Hz, 1 H), 3.11 (dd, *J* = 16.9, 3.7 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.1, 148.3, 141.2, 140.0, 137.1, 130.8 (q, *J* = 32.8 Hz), 129.6, 129.0, 127.5, 125.4, 124.8, 124.3 (q, *J* = 271.2 Hz), 123.2 (q, *J* = 272.8 Hz), 121.8 (q, *J* = 31.9 Hz), 119.8–119.7 (m), 117.9–117.7 (m), 115.4–115.2 (m), 114.8–114.7 (m), 113.0, 83.9, 69.2, 36.6.

HRMS (ESI): *m*/*z* [M – N_2 + H]$^+$ calcd for $C_{25}H_{17}F_9N_3O_2$: 562.1172; found: 562.1185.

1-[3,5-Bis(trifluoromethyl)phenyl]-3-{[2-((1*R*,2*R*)-1-{4-[3,5-bis(trifluoromethyl)phenyl]-5-iodo-1*H*-1,2,3-triazol-1-yl}-2,3-dihydro-1*H*-inden-2-yl)oxy]-5-(trifluoromethyl)phenyl}urea (14)

Triazole **14** was synthesized by the general procedure for the click reaction; eluent for chromatography: starting from 15% EtOAc in PE; off-white solid; yield: 0.171 g (0.179 mmol, 90%); mp 197–199 °C; $[\alpha]_D^{20}$ –69.0 (*c* 0.43, $CHCl_3$).

IR (KBr): 3369 (w), 1671 (w), 1617 (w), 1547 (m), 1477 (w), 1445 (w), 1386 (m), 1338 (m), 1280 (s), 1133 (s), 899 (w), 702 (w), 683 cm^{-1} (w).

^1H NMR (400 MHz, DMSO-d_6): δ = 9.98 (s, 1 H), 8.65–8.59 (m, 1 H), 8.54–8.50 (m, 1 H), 8.45 (s, 2 H), 8.25–8.15 (m, 1 H), 8.08 (s, 2 H), 7.71–7.62 (m, 1 H), 7.52–7.48 (m, 1 H), 7.45 (dd, *J* = 7.5 Hz, 1 H), 7.37–7.27 (m, 1 H), 7.26–7.17 (m, 1 H), 7.17–7.08 (m, 2 H), 6.55 (d, *J* = 5.0 Hz, 1 H), 6.09–5.98 (m, 1 H), 3.95 (dd, *J* = 16.1, 7.3 Hz, 1 H), 3.43 (dd, *J* = 16.4, 5.3 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 151.5, 147.5, 145.5, 140.7, 139.3, 136.7, 132.3, 130.3 (q, *J* = 32.8 Hz), 130.2 (q, *J* = 33.0 Hz), 129.3, 129.1, 127.3, 126.8–126.5 (m), 124.9, 123.7, 122.7 (q, *J* = 272.7 Hz), 122.6 (q, *J* = 273.3 Hz), 121.7, 121.5–121.4 (m), 121.8 (q, *J* = 31.9 Hz), 120.2 (q, *J* = 270.0 Hz), 118.9, 117.5–117.2 (m), 115.0–114.6 (m), 114.3–114.1 (m), 113.8–113.7 (m), 84.0, 70.0, 36.3. The iodine bonded C-atom was not detected because of low intensity of the signal.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{20}F_{15}IN_5O_2$: 954.0417; found: 954.0406.

4-[3,5-Bis(trifluoromethyl)phenyl]-1-[(1*R*,2*R*)-2-(2-{3-[3,5-bis(trifluoromethyl)phenyl]ureido}-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl]-5-iodo-3-methyl-1*H*-1,2,3-triazol-3-ium Trifluoromethanesulfonate (14-OTf)

Colorless solid; yield: 0.068 g (0.061 mmol, 55%); mp 144–146 °C; $[\alpha]_D^{20}$ –88.1 (*c* 0.82, MeOH).

IR (KBr): 3372 (w), 1550 (m), 1445 (w), 1387 (m), 1282 (s), 1135 (s), 1030 (m), 704 (w), 682 (w), 639 cm^{-1} (w).

^1H NMR (400 MHz, CD_3OD): δ = 8.60 (d, *J* = 1.8 Hz, 1 H), 8.41 (s, 1 H), 8.37 (s, 2 H), 8.08 (s, 2 H), 7.61–7.50 (m, 4 H), 7.48–7.36 (m, 2 H), 7.30 (d, *J* = 8.6 Hz, 1 H), 6.90 (d, *J* = 2.7 Hz, 1 H), 5.92 (dt, *J* = 6.3, 2.9 Hz, 1 H), 4.24 (s, 3 H), 4.03 (dd, *J* = 17.3, 6.7 Hz, 1 H), 3.44 (dd, *J* = 17.3, 3.1 Hz, 1 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.0, 149.2, 146.4, 143.8, 142.7, 135.9, 134.3 (q, *J* = 34.4 Hz), 133.3 (q, *J* = 33.1 Hz), 132.7–132.5 (m), 132.2, 130.8, 129.3, 127.3, 127.2–126.9 (m), 126.89, 126.9, 125.7 (q, *J* = 273.6 Hz), 124.7 (q, *J* = 271.8 Hz), 124.2 (q, *J* = 272.5 Hz), 121.8 (q, *J* = 318.5 Hz), 121.4–121.1 (m), 119.4–119.0 (m), 118.0–117.8 (m), 116.4–116.1 (m), 114.1, 94.0, 84.7, 76.5, 40.1, 38.7.

HRMS (ESI): *m*/*z* [M – CF_3O_3S]$^+$ calcd for $C_{36}H_{22}F_{15}IN_5O_2$: 968.0573; found: 968.0575.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610864.

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