5,5'-Bistriazoles as axially chiral, multidentate ligands: Synthesis, configurational stability and catalytic application of their scandium(III) complexes

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The design and development of 5,5'-bistriazoles featuring aminomethyl substituents is discussed. An efficient synthetic procedure for the selective preparation of 4,4'-bis(aminomethyl)-5,5'-bistriazoles from commercially available propargylamine derivatives and benzyl azide has been optimized. The first experimental determination of the configurational stability of 5,5'-bistriazoles is disclosed on the basis of rotational energy barriers and half-life times. Fast racemization was observed for a bistriazole possessing solely axial chirality whereas a more heavily substituted bistriazole involving axial and central chirality proved to be configurationally stable. A successful catalytic application has been implemented by using a *N*,*N*-dimethylpropargylamine-derived 5,5'-bistriazole as a multidentate ligand controlling the product selectivity (single *vs*. double addition) in scandium(III)-catalyzed nucleophilic additions of indoles to isatin electrophiles.

1. Introduction

Since the pioneering and independent discoveries by the groups of Meldal,[1] and Fokin and Sharpless[2] on the copper-catalyzed azide–alkyne cycloaddition (CuAAC), this reaction has become a commonly employed ligation tool enabling the synthesis of 1,4-disubstituted 1,2,3-triazoles in a highly efficient, reliable and regioselective manner.[3] As a consequence, countless applications for triazole chemistry in diverse disciplines, such as medicinal chemistry,[4] bioconjugation,[5] polymer science[6] or supramolecular systems,[7] amongst others, have been developed.

On the other hand, the coordination organometallic chemistry of 1,2,3-triazoles is receiving increasing attention, and this topic has been widely reviewed.[8] The presence of two sp^2 nitrogen atoms bearing accessible lone electron pairs within the triazole ring offers two possible N donor sites (N2 and N3) for binding to metal centers (nitrogen ligands). Additionally, the highly polarized C–H bond of this heterocycle enables coordination to metals through the C5 carbon atom (N-heterocyclic carbene ligands).[8d] Consequently, 1,4-functionalized 1,2,3-triazoles constitute valuable and versatile ligand systems for transition metals. When acting as N ligands, triazoles generally coordinate to metals through the more electron-rich N3 nitrogen atom, this leading to the formation of stable transition metal complexes.[8c]

Metal-catalyzed transformations mediated by triazole ligands benefit from the easy fine-tuning of these nitrogen ligands thanks to the wide structural diversity achievable with the CuAAC reaction.3 Moreover, the chemical inertness of triazoles is an additional advantage in view of their use as metal-supporting platforms in catalysis. In this context, our laboratory has introduced C_3-symmetric, modular tris(triazolyl)methanol (TTM) ligands and derivatives[9] (**I**, Fig. 1), which have proved to be highly efficient oligotriazole ligands in CuAAC reactions as well as in Cu-catalyzed carbene transfer reactions. Another highlighted multidentate ligand family comprises the bistriazole-based tetradentate ligand architecture **II**, depicted in Fig. 1 and successfully applied in Mn-catalyzed epoxidation of terminal olefins.[10] Regarding examples of oligotriazole-based chiral ligands, our group developed the preparation of the C_2-symmetric bis(triazolecarboxamido) derivative **III** (Fig. 1), which was used as a tetradentate ligand in Mo-catalyzed asymmetric allylic alkylation reactions.[11] Both triazole units proved to be key elements for catalytic activity and enantioselectivity, participating in the chelation of the metal. More recently, a new multidentate chiral ligand design appeared in the literature, featured by the dimeric *Cinchona* alkaloid-derived 4,4'-linked bistriazole **IV** (Fig. 1).[12] This chiral system mediated Cu-catalyzed enantioselective Michael additions, evidencing

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† Electronic Supplementary Information (ESI) available: XRD analyses, mechanistic insights, full experimental details, rotational energy barriers and half-life times, compound characterization and NMR spectra. Supplementary crystallographic data for this paper include the following CCDC deposition numbers: 1523647 (**4a**), 1523648 (**4b**·2HCl), 1523649 (**4a**·2HOTf), 1523650 (**9eb**), 1523651 (**9cc**), 1523652 (**10dc**), 1523653 (**9fa**), 1523654 (**9aa**), 1523655 (**9ib**) and 1525528 (**9dh**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

the key role of bistriazole linker for effective chirality transfer. Interestingly, the bistriazole core was deemed to be a coordinating site rather than a spacer, and its replacement by a single triazole implied significant decrease in enantioselectivity.

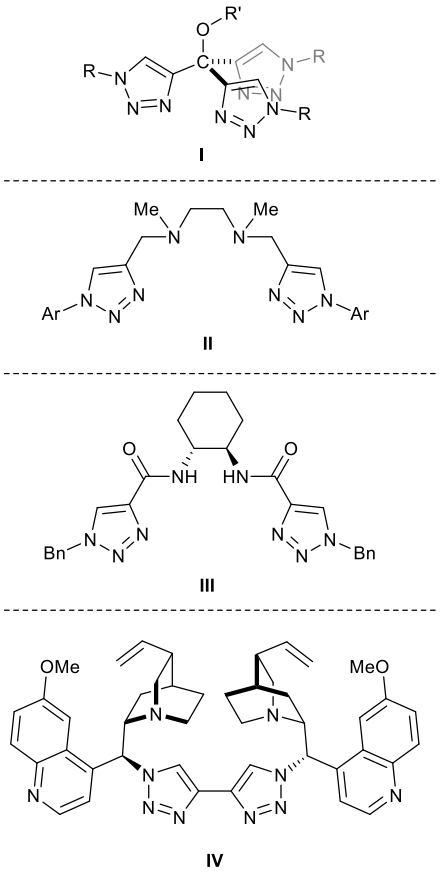


Fig. 1 Selected oligotriazole-based multidentate ligands applied in transition metal-catalyzed (asymmetric) transformations.

Considering the aforementioned key role of oligotriazole-based systems as multidentate ligands controlling the outcome of metal-mediated processes, we devised a novel 5,5'-bistriazole-based ligand skeleton with a tailored 4,4'-disubstitution pattern which confers axial chirality and further coordination capacities to the atropisomeric ligand core (Fig. 2). Our ligand design involves the presence of metal-coordinating aminomethyl groups on both triazole units. The resulting multidentate ligand depicts dual functionality:[13] the amino and triazole functionalities are expected to operate in concert, with the more basic tertiary amine likely facilitating the catalytic function by providing additional electron density on the metal center.[14] In this manner, the envisioned ligand system would involve an intrinsically axially chiral and doubly chelating 4,4'-difunctionalized 5,5'-bistriazole. This new class of C_2-symmetric oligotriazole ligands presumably could form two distal, rigid five-membered chelates between the N3 nitrogen of each triazole ring and its proximal amino group leading to cooperative effects (Fig. 2).

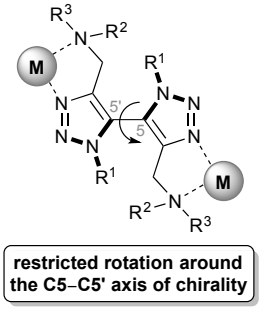
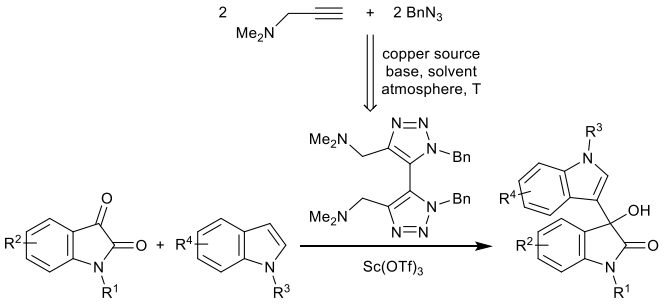


Fig. 2 Rational ligand design and proposed working hypothesis.

Many different CuAAC-based synthetic procedures for the preparation of diverse 4,4'-disubstituted 5,5'-bistriazoles have been reported in the literature during the last decade.[15] However, at a difference with a wide array of functional groups (alcohol, ether, amide, ester, cyano) the presence of aminomethyl substituents on the 5,5'-bistriazole framework is not documented. On the other hand, the opportunities offered by the 5,5'-bistriazole scaffold in catalysis, although pointed out by different authors,[15a,c,g,j,l,m] remain essentially unexplored.[15i,l] Also to be noted, the configurational stability of these heterobiaryl atropisomers has never been studied in spite of its relevance in view of potential application in asymmetric catalysis.

We wish to report in the present paper the preparation of novel 4,4'-bis(aminomethyl)-substituted 5,5'-bistriazoles and the experimental study of their configurational stability (rotational energy barriers and half-life times). Additionally, the atropoisomeric dimer resulting from the reaction of *N*,*N*-dimethylpropargylamine with benzyl azide has been successfully applied as a multidentate ligand in scandium-catalyzed nucleophilic additions of indoles to isatin electrophiles (Scheme 1).



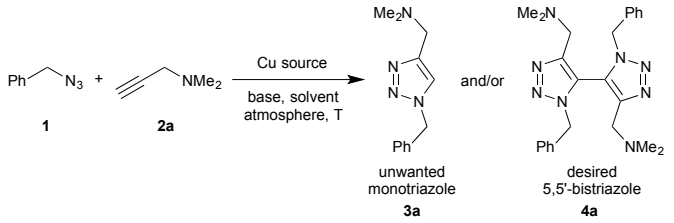
Scheme 1 Ligand-controlled scandium-catalyzed addition of indoles to isatins by using a 4,4'-bis(aminomethyl)-5,5'-bistriazole as a multidentate ligand.

2. Results and Discussion

2.1 Preparation of axially chiral 4,4'-bis(aminomethyl)-substituted 5,5'-bistriazoles

Our approach to 4,4'-bis(aminomethyl)-5,5'-bistriazole **4a** involved a tandem CuAAC–oxidative homocoupling process by starting from benzyl azide (**1**) and *N*,*N*-dimethylpropargylamine (**2a**) as reactive partners (Scheme 2).

The Cu-catalyzed [3+2] cycloaddition reaction between **1** and **2a** has been widely studied in the literature.[16] Surprisingly, despite many different copper-based catalytic systems and reaction conditions have been applied to perform this transformation, no formation of 5,5′-bistriazole **4a** has ever been observed, with monotriazole **3a** as the single reaction product reported so far. In fact, it has already been mentioned before (*vide supra*) that amines have never been incorporated into the 5,5′-bistriazole framework.



1 **2a** **3a** **4a**

Scheme 2 Competing formation of monotriazole **3a** and 5,5′-bistriazole **4a** in the Cu-catalyzed cycloaddition of azide **1** with alkyne **2a**.

The formation of 5,5′-bistriazoles, originally considered as minor undesired reaction products, has been observed since the early days of the CuAAC reaction.[2,17] These products were found to be formed under oxidative conditions, presumably by oxidative coupling of copper triazolide species,[18] and their formation could be suppressed under strict exclusion of oxygen and oxidative impurities.[19] Alternatively, it has been demonstrated how the formation of 5,5′-linked bistriazoles as the major reaction products can be facilitated by using appropriate reaction conditions, although this process is substrate-dependent.[15n] With these precedents, we set out to explore the selective synthesis of bistriazole **4a** by screening first some reported conditions for efficient 5,5′-bistriazole formation (Table 1). In this particular case, however, most of these procedures were completely inefficient, bistriazole **4a** being only detected in trace amount (entries 1–3). The ratio of desired bistriazole **4a** could be enhanced by following the synthetic protocol described by Li and Zhang *et al*.[15h] Thus, the use of catalytic CuBr in a buffered NaOEt/EtOH medium yielded 80% conversion and 80:20 **3a**/**4a** selectivity, respectively (entry 4). After column chromatography, the target 5,5′-bistriazole **4a** could be isolated in 19% yield. The 5-alkynyltriazole **5a**, a common side product in 5,5′-bistriazole formation,[15a,c,g,h,j,l,m] could also be isolated in trace amount (1% yield). Gratifyingly, the structure of **4a** could be unambiguously established by single-crystal X-ray diffraction (SCXRD) analysis.§

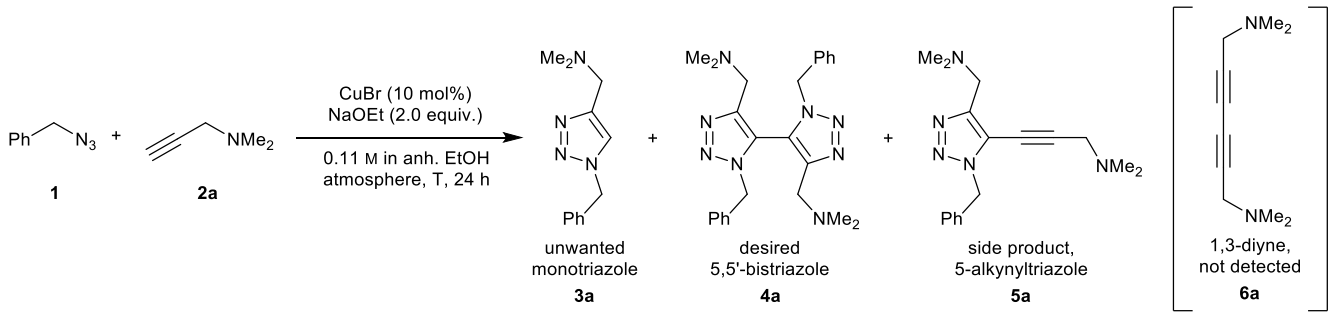
Table 1 Assessment of literature procedures[a]

Entry	Reaction conditions[b]	Conv. (%)[c]	**3a**/**4a**[c]
1	Cu powder (1.0 equiv.), 1.0 M aq. $CuSO_4$ (10 mol%), 2.0 M aq. Na_2CO_3 (3.0 equiv.), MeCN[15a]	2	100:0
2	CuBr (1.0 equiv.), 2.0 M aq. Cs_2CO_3 (2.0 equiv.), MeCN/H_2O (1:1)[15l]	100	100:0
3	CuI (10 mol%), 2.0 M aq. Na_2CO_3 (3.0 equiv.), MeCN[15e]	70	94:6
4	CuBr (10 mol%), NaOEt (2.0 equiv.), EtOH[15h]	80	80:20

[a] Reaction shown in Scheme 2. [b] All reactions were conducted by using 1.0 equiv. of azide **1** and 1.1 equiv. of alkyne **2a** under open-air atmosphere and at rt for 24 h. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture.

The latter results (see Table 2, entry 1) were then taken as the starting point for the optimization of the selective preparation of **4a**. An exhaustive and systematic screening of different reaction conditions was performed with the goal of improving the yield of **4a** and minimizing or suppressing the formation of unwanted products **3a** and **5a**. 1,3-Diyne **6a**,[20] which could arise from a Glaser-type coupling of the terminal alkyne **2a**, was never detected.

Table 2 Optimization of the preparation of **4a**[a]



1 **2a** **3a** **4a** **5a** **6a**

Entry	**1**/**2a** (equiv.)	Modifications[a]	Atmosphere	T (°C)	Conv. (%)[b]	**3a**/**4a**/**5a**[b]	**3a**/**4a**[b]	Isolated yields (%)[c]
1	1.0/1.1	none	open-air[d]	25	80	76:18:6	80:20	**3a**: 55; **4a**: 19; **5a**: 1
2	1.0/1.1	none	dry air[e]	25	91	60:35:5	63:37	not isolated
3	1.0/1.1	CuI as catalyst	dry air[e]	25	100	83:13:4	87:13	not isolated
4	1.0/1.1	$Cu(OEt)_2$ as catalyst	dry air[e]	25	0	–	–	–
5	1.0/1.1	NaOEt (0.30 equiv.)	dry air[e]	25	82	63:37:0	63:37	not isolated
6	1.0/1.1	TFE as solvent	dry air[e]	25	100	100:0:0	100:0	**3a**: 87
7	1.0/1.1	none	dry air[e]	0	86	31:64:5	33:67	**4a**: 22
8	2.0/1.0	none	dry air[e]	0	84	14:84:2	14:86	**4a**: 39
9	2.5/1.0	none	dry air[e]	0	100	25:73:2	25:75	**4a**: 54
10	2.5/1.0	none	oxygen[f]	0	85	29:63:8	31:69	not isolated
11	2.5/1.0	1,4-NTQ[g] (1.0 equiv.)	dry air[e]	0	29	82:15:3	84:16	not isolated
12	2.5/1.0	0.22 M in anh. EtOH	dry air[e]	0	100	16:83:1	16:84	**3a**: 11; **4a**: 59
13	2.5/1.0	0.22 M & NaOMe/MeOH[h]	dry air[e]	0	100	37:53:10	41:59	**3a**: 20; **4a**: 54
14	2.5/1.0	0.22 M & NaO^{i}Pr/^{i}PrOH[i]	dry air[e]	0	100	10:38:52	20:80	**4a**: 18; **5a**: 26
15	2.5/1.0	0.50 M & NaOBn/BnOH[j]	dry air[e]	0	90	69:27:4	72:29	not isolated
16	2.5/1.0	0.22 M & CuBr (30 mol%)	dry air[e]	0	100	32:64:4	33:67	**4a**: 53

[a] All reactions were conducted by using 10 mol% of CuBr and 2.0 equiv. of solid NaOEt in anhydrous EtOH (0.11 M) for 24 h, unless otherwise indicated. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yields of isolated pure products after column chromatography. [d] Open flask exposed to ambient air atmosphere. [e] Flask sealed with a glass tube refilled with anhydrous $CaCl_2$. [f] Flask connected to an oxygen balloon under atmospheric O_2 pressure. [g] 1,4-Naththoquinone added as an external oxidant. [h] 2.0 equiv. of solid NaOMe in anhydrous MeOH. [i] 2.0 equiv. of solid NaO^{i}Pr in anhydrous ^{i}PrOH. [j] 2.0 equiv. of NaOBn solution, 1.0 M in BnOH.

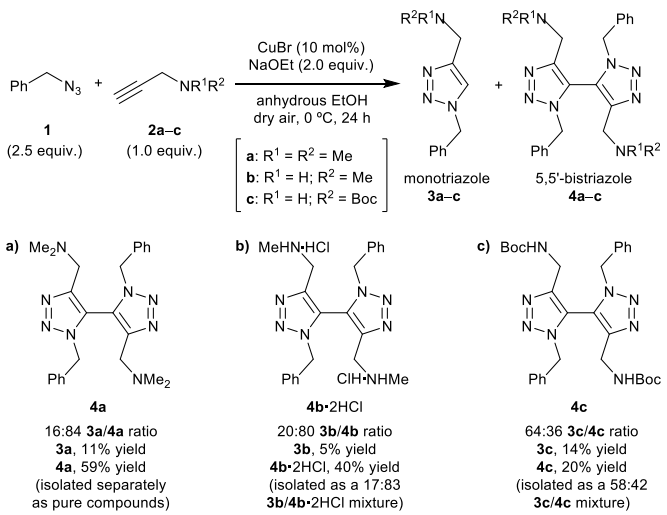
As shown in Table 2, the replacement of open-air atmosphere by dry air atmosphere led to an enhancement of both conversion and product selectivity, with the ratio of bistriazole **4a** increasing from 80:20 to 63:37 **3a**/**4a**, respectively (*cf.* entries 1 and 2). The use of CuI[21] (entry 3) or $Cu(OEt)_2$ (entry 4) as the catalyst, or the use of a substoichiometric amount of base (entry 5) did not lead to any improvement, while the use of TFE, a solvent much more acidic than EtOH,‡ completely blocked the formation of **4a** (entry 6). Temperature was found to be a crucial factor for the reaction outcome. Thus, lowering the reaction temperature from 25 to 0 °C led to a selectivity switch in favor of **4a**, with only a slight decrease in conversion (entry 7). Further screening revealed the beneficial effect of adding excess of azide **1** with respect to alkyne **2a**, while working at 0 °C. The use of 2.0 equiv. of **1** led to the highest product selectivity (14:84:2 **3a**/**4a**/**5a** ratio; entry 8) while the use of slightly higher excess of **1** (2.5 equiv.) further increased the isolated yield of **4a** (from 39% to 54%; entry 9). No improvement on the results was observed by conducting the reaction under oxygen atmosphere (entry 10), whereas the use of an external oxidant (1,4-naphthoquinone) was found to be detrimental for both conversion and selectivity (entry 11).

The best conditions were found when the reaction was conducted at higher concentration (from 0.11 to 0.22 M in EtOH), with the 5,5'-bistriazole **4a** isolated in an optimal 59% yield (entry 12). From these optimized conditions, a more extensive screening aimed to investigate the influence of the base, defined as a buffered alcoholic solution of the corresponding sodium alkoxide, was performed. Reduced selectivity and lower yield were achieved with the slightly more acidic NaOMe/MeOH system, in comparison to NaOEt/EtOH‡ (*cf.* entries 12 and 13). Complete conversion and unexpected selectivity were obtained with the more basic NaO^{i}Pr/^{i}PrOH‡ buffer, a medium delivering the 5-alkynyltriazole **5a** as the major reaction product (entry 14). On the contrary, the use of a solution of NaOBn in benzyl alcohol‡ afforded unwanted monotriazole **3a** as the major product (entry 15). Finally, we tested an increased catalyst loading of CuBr (30 mol%) without finding any improvement on the results (*cf.* entries 12 and 16).

The reaction conditions optimized for the selective synthesis of 5,5'-bistriazole **4a** (Scheme 3a) from *N*,*N*-dimethylpropargylamine (**2a**) were used to study the influence of the nature of the amino group on the terminal alkyne on product selectivity (Scheme 3). To this end, commercially available propargylamine derivatives **2b** and **2c** were reacted with benzyl azide (**1**).

With *N*-methylpropargylamine (**2b**), product selectivity was very similar to that obtained with **2a** (Scheme 3b). Interestingly, bistriazole **4b** could be isolated as its diammonium salt **4b**·2HCl, as confirmed by means of SCXRD analysis.§

In comparison to *N*-alkyl-substituted propargylamines **2a** and **2b**, the use of *N*-Boc-protected propargylamine **2c** under the same reaction conditions favored the monotriazole product (**3c**/**4c** = 64/36) (Scheme 3c). These results tend to indicate that the preferential formation of bistriazoles **4** correlates with electron density at the nitrogen substituent. The better the electron-donating ability of the amine, the higher the ratio of 5,5'-bistriazole, with the most electron-rich *N*,*N*-dimethylamino group of **2a** affording the best results. On the basis of control experiments and literature precedents, a dinuclear stepwise mechanism for the formation of 5,5'-bistriazoles **4** has been tentatively proposed.§



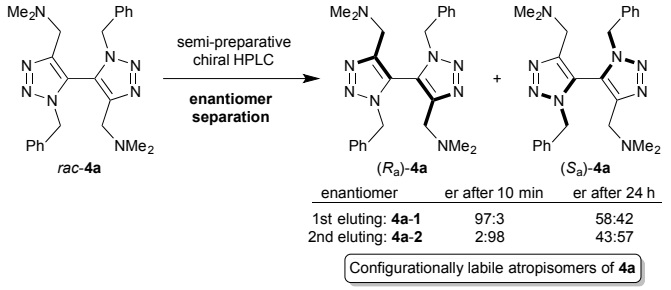
Scheme 3 Formation of 5,5′-bistriazoles **4a**–**c** from benzyl azide (**1**) and propargylamine derivatives **2a**–**c**.

2.2 Determination of configurational stability of 5,5'-bistriazoles 4

The determination of configurational stability of axially chiral 5,5′-bistriazoles has never been accomplished to date, although it has been often stated that quantitative information on this issue would open new avenues for the application of these heterobiaryl atropisomers as chiral ligands in transition metal-mediated asymmetric catalysis,[15l,m] as it is the case for biaryl atropisomers.[22]

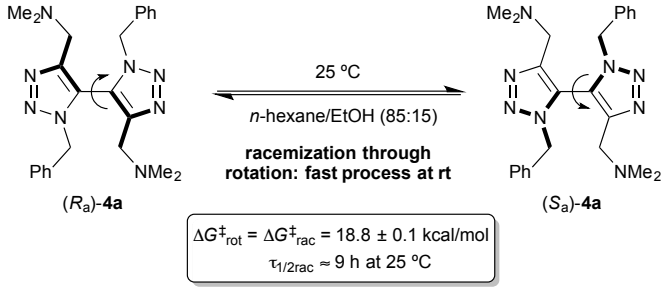
The study of dynamic axial chirality in atropisomeric 5,5′-bistriazoles for the determinination of the configurational stability requires to perform kinetic studies allowing the determination of key physical parameters such as rate constants (k), half-life times (τ), and free Gibbs activation energies ($\Delta G^{\ddagger}$) for the racemization processes.

As the starting point in this study, we selected bistriazole **4a**, where only axial chirality is present. Conditions for semi-preparative chiral HPLC separation of the enantiomeric atropisomers were optimized (Scheme 4), and samples of (R_a)-**4a** and (S_a)-**4a** became readily available (the 1st eluting enantiomer encoded as **4a**-**1**, and the 2nd eluting one as **4a**-**2**).§ The enantiomeric purity (ee measurement) of each atropisomer was evaluated immediately after collecting the perfectly separated fractions. Chiral HPLC analyses, however, revealed slight erosion in the enantiopurity of both atropisomers **4a**-**1** and **4a**-**2**. After 24 h in solution, the enantiomeric excesses drastically droped to 16% ee and −14% ee for **4a**-**1** and **4a**-**2**, respectively, according to chiral HPLC (Scheme 4). The conformational lability of **4a** in solution at room temperature being clear from these results.



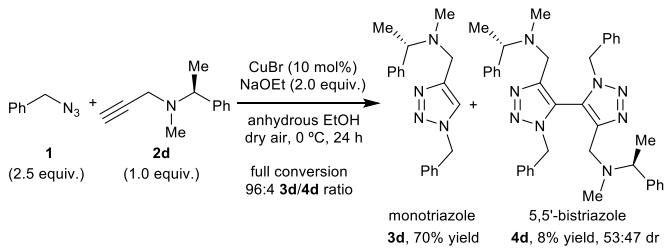
Scheme 4 Resolution of racemic bistriazole **4a** (*rac*-**4a**) by semi-preparative chiral HPLC.

The monitoring of enantiomeric ratios of **4a**-**1** and **4a**-**2** as a function of time by HPLC analyses on a chiral stationary phase allowed the determination of the rotational/racemization energy barrier ($\Delta G^{\ddagger}_{rot} = \Delta G^{\ddagger}_{rac}$) of **4a**. By following the well-established Curran's method,[23] a kind of Eyring plot was built up from the former data. The slope of the resultant graph was directly correlated to the racemization rate constant (k_{rac}) and the thermodynamic parameters for the racemization process were calculated by using the Eyring equation.[24] In addition, the half-life time of racemization ($\tau_{1/2rac}$) was determined from the rate constant (Scheme 5).§ The process was studied at ambient temperature (25 °C) in 85:15 *n*-hexane/EtOH solution (HPLC conditions). The free Gibbs activation energy barrier to racemization ($\Delta G^{\ddagger}_{rac}$) of atropisomeric bistriazole **4a** was determined to be *ca.* 18.8 kcal/mol and the corresponding half-life time ($\tau_{1/2rac}$) was *ca*. 9 h at 25 °C.



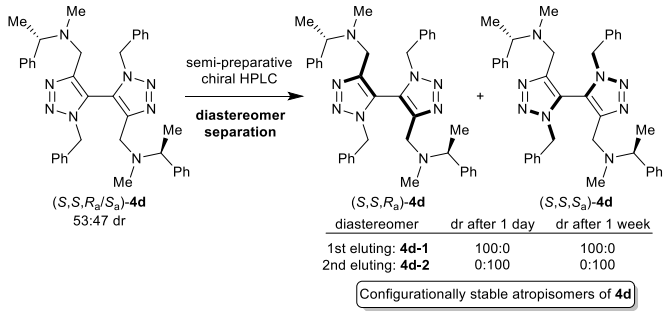
Scheme 5 Rotational energy barrier and half-life time for axially chiral bistriazole **4a** (same results obtained from **4a**-**1** and **4a**-**2**).

Since we were particularly interested in configurationally stable 5,5′-bistriazoles for application in asymmetric catalysis, we next decided to study the influence of bulkier substituents at the bistriazole core on the rotation barrier of **4**. To this end, enantiopure (*S*)-*N*-methyl-*N*-propargyl-1-phenylethylamine (**2d**) was reacted with benzyl azide (**1**).§ In this case, the conditions previously optimized for bistriazole **4a** afforded a 96:4 mixture of monotriazole **3d** and bistriazole **4d**, respectively. After column chromatography purification, the minor 5,5′-bistriazole **4d** was obtained in 8% yield as a 53:47 mixture of diastereomers (Scheme 6).



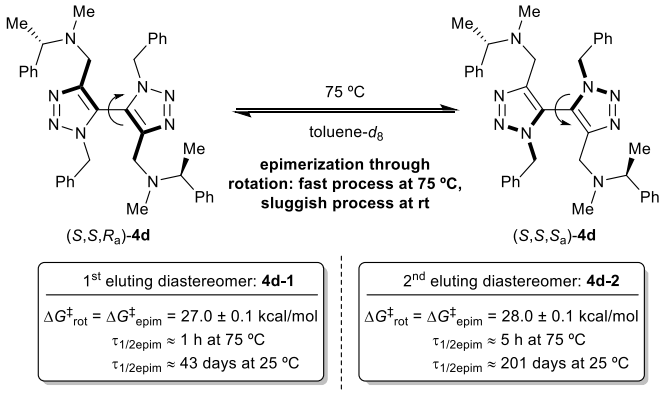
Scheme 6 Preparation of **4d** from chiral, enantiopure alkyne **2d**.

The two diastereomers of bistriazole **4d** [(*S*,*S*,*R*$_a$)-**4d** and (*S*,*S*,*S*$_a$)-**4d**] could be easily separated by means of semi-preparative HPLC on a chiral stationary phase (the 1st eluting diastereomer encoded as **4d**-**1**, and the 2nd eluting one as **4d**-**2**).§ To our delight, no epimerization at all was observed in this case, even after one week in solution (Scheme 7).



Scheme 7 Resolution of a diastereomeric mixture of bistriazole **4e** [(*S*,*S*,*R*$_a$/*S*$_a$)-**4e**] by semi-preparative chiral HPLC.

To cover a broader range of temperature, the variable-temperature (VT) ^{1}H NMR study of **4d**-**1** and **4d**-**2** was performed in toluene-d_8. For both diastereomers, the epimerization process became detectable at 338 K (65 ºC). The results from VT-NMR experiments aided us to fix the temperature at 348 K (75 ºC) for further studying the epimerization kinetics of **4d**-**1** and **4d**-**2** in toluene-d_8 by means of dynamic ^{1}H NMR spectroscopy. In this manner, we could determine the rotational energy barriers ($\Delta G^{\ddagger}_{rot}$) of **4d**-**1** and **4d**-**2**, respectively, which for these bistriazoles possessing axial and central chirality correspond to the energy barrier to epimerization ($\Delta G^{\ddagger}_{epim}$).§ We have summarized in Scheme 8 all the relevant information arising from this study. As the most remarkable conclusion, the simple introduction of an α-branched group on the amino substituents at C-4 (*i.e.*; from methyl to α-methylbenzyl) is enough to extend the half-life time of atropisomers up to >200 days, thus converting enantio- and diastereomerically pure 5,5´-bistriazoles **4d**-**1** and **4d**-**2** into suitable ligand candidates for enantioselective catalysis applications.

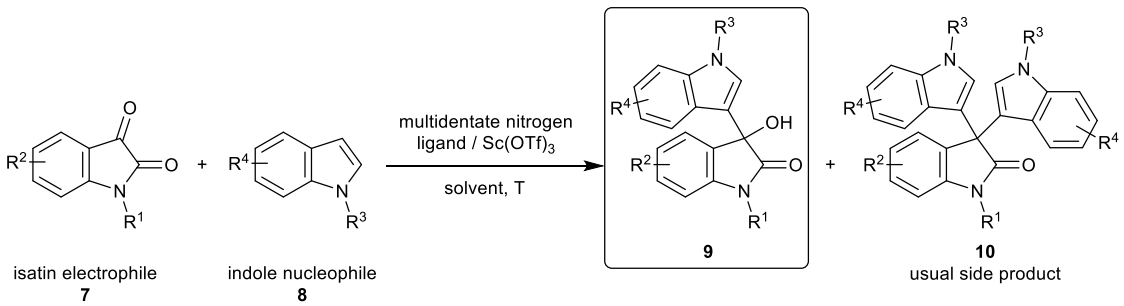


Scheme 8 Rotational energy barriers and half-life times for axially and centrally chiral diastereomeric bistriazoles **4d**-**1** and **4d**-**2**.

2.3 Application of 5,5'-bistriazoles 4 in the scandium-catalyzed addition of indoles to isatins

Taking into account the coordinating characteristics of bistriazoles **4**, we decided to explore the use of the corresponding scandium complexes in catalysis. We selected $Sc(OTf)_3$ as the metal source for the unique characteristics of this rare earth metal triflate; *i.e.*, its water-compatibility, recoverability, and strong Lewis acidity. Furthermore, this environmentally benign Lewis acid shows extremely high catalytic activity in many transformations, facilitated by the small ionic radius of scandium.[25]

In particular, the scandium-catalyzed Friedel–Crafts (FC) alkylation of indoles (**8**) with isatins (**7**) emerged as the application of choice[26] for ligands **4**. This reaction usually requires the use of multidentate nitrogen ligands at low temperatures to achieve selectivity in favor of the desired chiral monoaddition products (**9**) (Scheme 9), and we speculated on the suitability of **4**·$Sc(OTf)_3$ to achieve chemocontrol of this reaction under convenient conditions.



Scheme 9 Product divergence in Sc-catalyzed nucleophilic addition of indoles to isatins.

The target 3-substituted 3-hydroxy-2-oxindole derivatives **9**[27] are prominent core scaffolds commonly encountered in drug candidates as well as in natural products exhibiting a broad spectrum of biological and pharmacological activities. For instance, this privileged pharmacophore constitutes the core structure of the oncology drug candidate depicted in Fig. 3, which was reported to display cytotoxic activity against human cancer cell lines.[28] Other noteworthy examples (Fig. 3) include the elongation cycle inhibitor ECi8[29] (a potent antimicrobial lead drug), the natural alkaloid schewanelline A[30] (an antitumor agent), the narrow-spectrum inhibitor of *Campylobacter jejuni* (a major cause of food-borne illness) CCG-198215,[31] and the inhibitor of preadipocyte differentiation B528,[32] potentially useful for prevention and treatment of obesity, dyslipidemia, fatty liver or diabetes.

In addition, 3-hydroxy-3-indolyl-2-oxindoles containing a hydroxy-substituted quaternary carbon stereocenter, are key chiral building blocks used in enantioselective total syntheses of complex natural products with a wide range of biological activities, such as the fungal-derived alkaloid (+)-gliocladine C[33] or the cyclotryptamine alkaloids (–)- and (+)-folicanthine.[34]

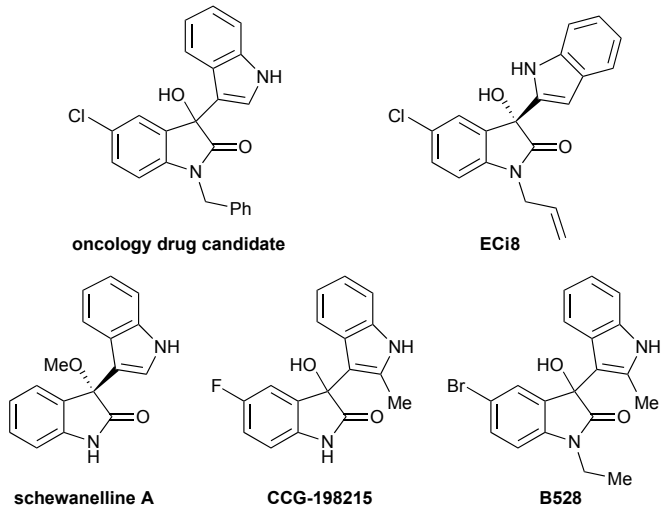
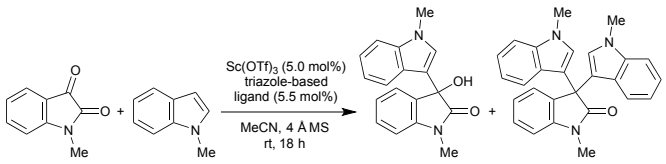


Fig. 3 Selected examples of bioactive 3-hydroxy-3-indolyl-2-oxindole derivatives.

The Sc-catalyzed alkylation of *N*-methylindole (**8a**) with *N*-methylisatin (**7a**) was chosen as our benchmark reaction, and both bistriazoles **4** and the corresponding monotriazoles **3** were evaluated in the reaction (Table 3). Reactions were all conducted in MeCN in the presence of 4 Å molecular sieves, and a 3:1 ratio of **8a** and **7a**, respectively, was used. The catalyst systems were generated *in situ* from $Sc(OTf)_3$ (5.0 mol%) and the corresponding ligand by using a 1:1.1 metal-to-ligand ratio. Under these conditions, triazole ligands **3a** and **3d** led to equimolar mixtures or exclusive formation of undesired double addition product **10aa**, respectively (entries 1 and 2). On the other hand, when 5,5'-bistriazole **4a** was used as the ligand, the desired single addition product **9aa** could be isolated in 93% yield and excellent chemoselectivity (96:4 **9aa**/**10aa** ratio) (entry 3). The same trend was also observed for other isatin electrophiles as well as indole nucleophiles when comparing the catalytic performances and reaction outcomes imposed by monotriazole **3a** *versus* bistriazole **4a** as scandium-supporting ligands for this transformation.§

Table 3 Ligand effect in the Sc-catalyzed addition of *N*-methylindole (**8a**) to *N*-methylisatin (**7a**)[a]



Entry	Ligand	**9aa**/**10aa**[b]	**9aa** yield (%)[c]	**10aa** yield (%)[c]
1	**3a**	56:44	57	36
2	**3d**	0:100	0	99
3	**4a**	96:4	93	6
4	**4d**-**1**	100:0[d]	62[e]	0
5	**4d**-**2**	80:20	80[e]	19
6	none	0:100	0	n.d.[f]
7	**4a**[g]	n.r.[h]	0	0
8	**4a**[i]	98:2[j]	87	1

[a] All reactions were conducted under argon atmosphere on a 0.2 mmol scale by using 1.0 equiv. of isatin **7a** and 3.0 equiv. of indole **8a**, and proceeded with full conversion after 18 h at rt, unless otherwise indicated. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of isolated pure product after column chromatography. [d] 70% conversion. [e] Racemic product. [f] Not determined. [g] Without $Sc(OTf)_3$. [h] No reaction. [i] 1:2.2 metal/ligand ratio tested by adding 11 mol% of **4a**. [j] 90% conversion.

The enantiopure chiral bistriazoles **4d-1** and **4d-2** were next tested in the reaction. While the relative configuration of the stereogenic centers and axes in these ligands had some influence on its relative performance (*cf.* entries 4 and 5, Table 3), in both cases **9aa** was isolated as a racemic product. According to these disappointing results, no further attention was paid to the possibility of achieving

enantiocontrol in the scandium-catalyzed FC reaction mediated by axially chiral, enantiopure 5,5'-bistriazoles **4**. It is to be mentioned axially chiral urazoles26[c] and C_2-symmetric chiral bisoxazolines26[a,b] are, indeed, able to exert enantiocontrol in this reaction. In any case, the current design of axially chiral 5,5'-bistriazoles **4** leads to an excellent chemocontrol, delivering the target single addition products **9** with optimal product selectivity.26[a] In this regard, a plausible working model for the rationalization of the observed chemoselectivity through the operation of a coordination polymer, with scandium atoms connecting **4a** units, has been proposed.§

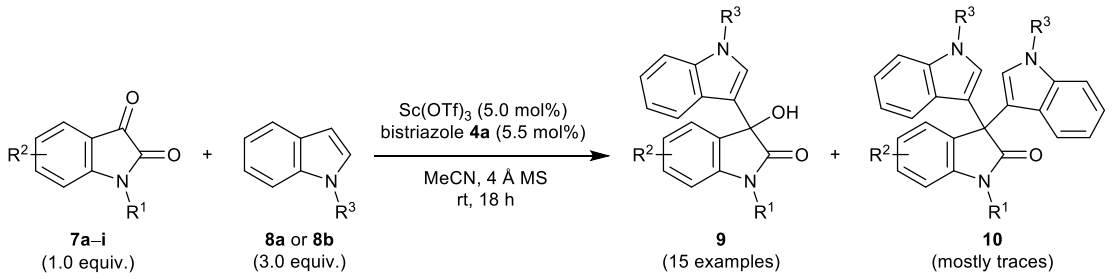
The crucial role of **4a** as a multidentate ligand dictating the product selectivity (9aa/10aa ratio) was further confirmed after performing some control experiments (Table 3, entries 6–8). Full conversion was achieved by running the reaction with only $Sc(OTf)_3$ and no ligand added (entry 7). Under these conditions, the 3,3-di(indolyl)-2-oxindole 10aa was found to be the exclusive reaction product, consistently with previous literature results.26[a] On the other hand, no reaction at all was observed with 4a in the absence of $Sc(OTf)_3$ (entry 8). Finally, the influence of the metal-to-ligand ratio was also investigated. When a double amount of 4a (11 mol%) with respect to $Sc(OTf)_3$ (5.0 mol%) was used, conversion slightly decreased (*cf.* entries 3 and 8). The scandium/ligand ratio was accordingly fixed to *ca.* 1:1, as previously found for other multidentate ligand systems.26

With the optimized conditions in hand (see Table 3, entry 3), we then explored the substrate scope of the Sc-catalyzed, Friedel-Crafts-type (FC) hydroxyalkylation of indole nucleophiles (**8**) with isatins (**7**) in the presence of **4a**.§

Initially, we studied the scope of isatin electrophiles in front of *N*-methylindole (**8a**) as the nucleophile (Scheme 10A). Under the conditions previously optimized with *N*-methylisatin **7a**, the scope was successfully extended to a broad range of N-substituted isatins (**7c**–**g**) tolerating aryl, benzyl, allyl and propargyl N-substituents as well as to the parent isatin **7b** bearing a free NH group. In all cases, the use of bistriazole **4a** led to very high chemoselectivities (**9**/**10** ratios), products **9** being isolated with generally very high yields (87–100%). The structures of products **9aa** and **9fa**, derived from *N*-methylisatin (**7a**) and *N*-allylisatin (**7f**), respectively, were unambiguously confirmed by SCXRD analysis.§

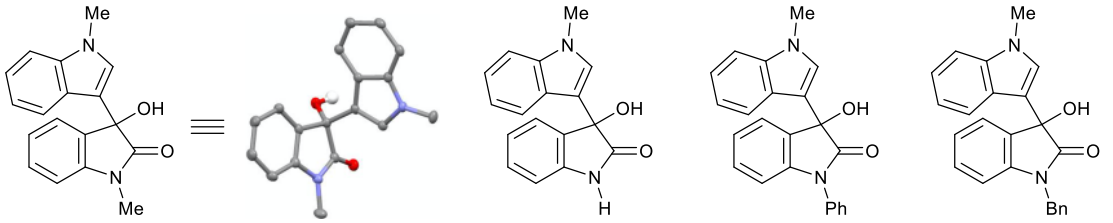
We were pleased to find that the FC reaction was also working notoriously well with the parent indole **8b**, bearing a free NH group, in front of differently substituted isatins (Scheme 10B). The reactions of **8b** with isatins **7a** and **7c**–**i** proceeded with very high selectivities in almost all cases, affording the corresponding products **9** with 78–100% isolated yields. Structural characterization of 3-hydroxy-3-indolyl-2-oxindole products **9eb** and **9ib**, derived from *N*-benzyl-7-trifluoromethylisatin (**7e**) and *N*-allyl-5-chloroisatin (**7i**), respectively, was unambiguously established by means of SCXRD analysis.§ Interestingly, this ligand-controlled methodology provided an atom-economical and straightforward access to some biologically relevant compounds. In particular, **9hb** is an important oncology drug candidate[28] (see Fig. 3) while **9ib** is a novel C3 regioisomer of the potent antimicrobial ECi8[29] (see Fig. 3).

The use of the more challenging *N*-benzylindole (**8c**) was also investigated (Scheme 11). In general, electron-rich indoles (like **8c**) tend to undergo double FC reaction so that single FC products need to be prepared through indirect procedures.[34c,35] Gratifyingly, we succeeded to prepare monoaddition products **9cc** (Scheme 11Aa) and **9dc** (Scheme 11Ba) from *N*-phenylisatin (**7c**) and *N*-benzylisatin (**7d**), respectively, in one-step and with complete chemoselectivity by using **4a**·$Sc(OTf)_3$, although the reactions could not be driven to completion. All attempts to improve the yields of **9cc** or **9dc** by increasing reaction time or temperature were unsuccessful, and a complete selectivity switch in favor of the doubly alkylated product **10cc** (Scheme 11Ab) or **10dc** (Scheme 11Bb) was observed when the loading of catalyst was increased to 10 mol%. Interestingly, the structures of products **9cc** and **10dc** could be unambiguously established by means of SCXRD analysis.§

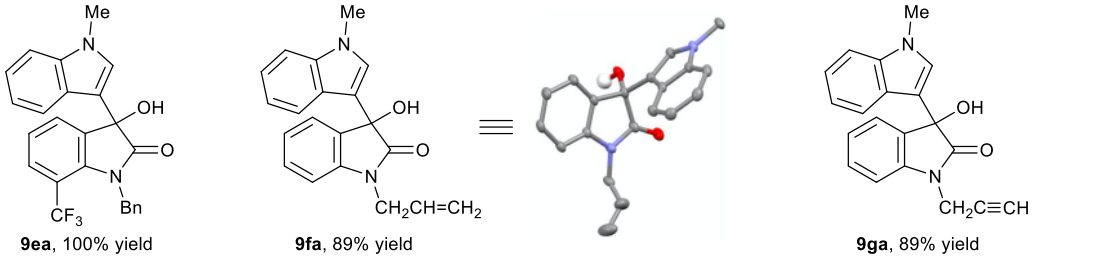


7a–i (1.0 equiv.) + **8a** or **8b** (3.0 equiv.) → **9** (15 examples) + **10** (mostly traces)

A) *N*-Methylindole (**8a**) with isatins

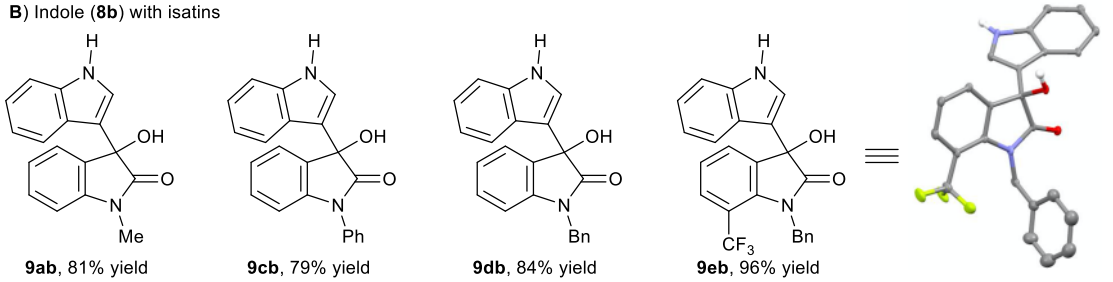


9aa, 93% yield (96:4 **9aa**/**10aa**) ≡ [**9aa**, X-ray]; **9ba**, 49% yield (62% conv.) (96:4 **9ba**/**10ba**); **9ca**, 87% yield (99:1 **9ca**/**10ca**); **9da**, 88% yield (90:10 **9da**/**10da**)

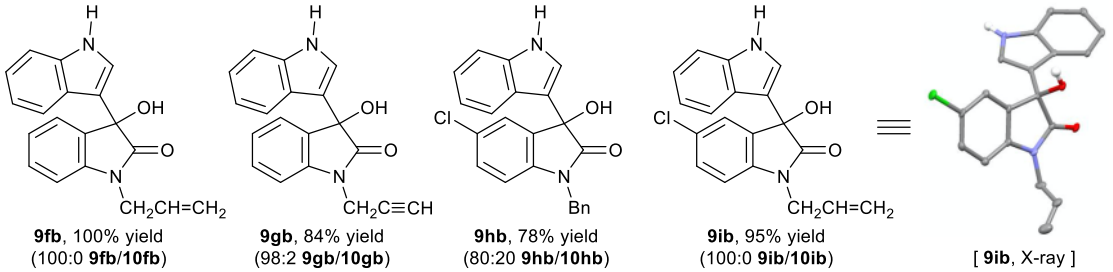


9ea, 100% yield (100:0 **9ea**/**10ea**); **9fa**, 89% yield (89:11 **9fa**/**10fa**) ≡ [**9fa**, X-ray]; **9ga**, 89% yield (100:0 **9ga**/**10ga**)

B) Indole (**8b**) with isatins

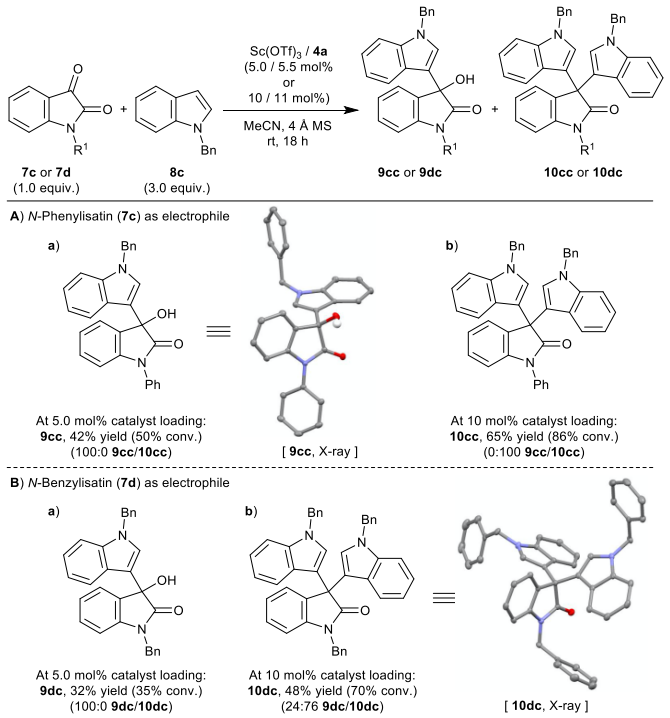


9ab, 81% yield (100:0 **9ab**/**10ab**); **9cb**, 79% yield (100:0 **9cb**/**10cb**); **9db**, 84% yield (98:2 **9db**/**10db**); **9eb**, 96% yield (100:0 **9eb**/**10eb**) ≡ [**9eb**, X-ray]



9fb, 100% yield (100:0 **9fb**/**10fb**); **9gb**, 84% yield (98:2 **9gb**/**10gb**); **9hb**, 78% yield (80:20 **9hb**/**10hb**); **9ib**, 95% yield (100:0 **9ib**/**10ib**) ≡ [**9ib**, X-ray]

Scheme 10 Scope of the FC reaction of indoles **8a** and **8b** with isatins **7a**–**i** catalyzed by **4a**·$Sc(OTf)_3$.



Scheme 11 Outcome of the FC reaction of isatin **7c** or **7d** with the challenging nucleophile *N*-benzylindole (**8c**).

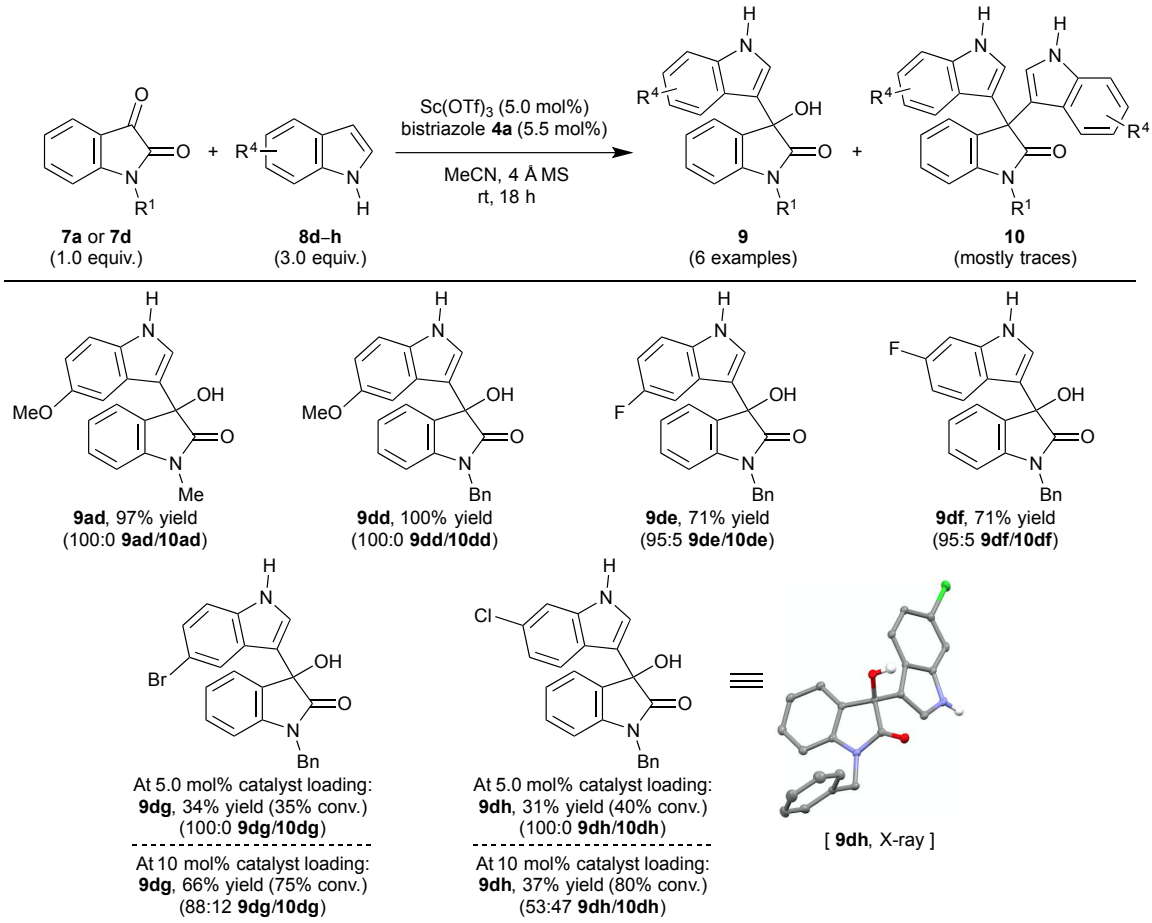
The scope of indole substrates in the selective hydroxyalkylation was completed by exploring the use of indoles **8d**–**h** bearing substituents at the aromatic ring (Scheme 12). The FC reaction of 5-methoxyindole (**8d**) catalyzed by **4a**·Sc(OTf)$_3$ proceeded with total selectivity and quantitative yield with both *N*-methylisatin (**7a**) and *N*-benzylisatin (**7d**). The drug-like, fluorinated 3-hydroxy-3-indolyl-2-oxindoles **9de** and **9df** were also efficiently prepared. Finally, the reaction outcome found for the more challenging 5-bromoindole (**8g**) and 6-chloroindole (**8h**) in the reaction with **7d** revealed perfect selectivity but moderate conversion under standard conditions (5.0 mol% catalyst loading). Also in these cases, attempts to increase conversion with the use of a higher catalyst loading led to decreased chemoselectivity. The solid-state structure of **9dh** was unequivocally elucidated by SCXRD analysis.§

3. Conclusions

A new family of 5,5'-bistriazole ligands featuring appropriately tethered aminomethyl substituents (**4**) has been developed. Compounds **4** display axial chirality both in solution and in the solid state, as confirmed by SCXRD characterization.§

The configurational stability of atropisomeric 5,5'-bistriazoles **4** has been determined for the first time making use of dynamic chiral HPLC or ^{1}H NMR measurements. While the solely axially chiral **4a** suffers from a relatively fast racemization process (half-life time of *ca*. 9 h at room temperature), axially and centrally chiral bistriazole **4d**, derived from a bulky, enantiopure propargylamine, proved to be configurationally stable under ambient conditions (half-life time of up to *ca*. 201 days).

The potential of compounds **4** as catalytic ligands has been demonstrated through the implementation of a highly chemoselective Friedel–Crafts-type hydroxyalkylation of indoles with isatins. This transformation tolerated a very broad substrate scope (23 examples) while delivering a wide variety of biologically relevant 3-hydroxy-3-indolyl-2-oxindole derivatives (including two drug candidates) with good to excellent yields (79% average yield).



Scheme 12 Scope of the FC reaction of isatin **7a** or **7d** with indoles **8d**–**h** catalyzed by **4a**·Sc(OTf)$_3$.

Acknowledgements

This work was funded by MINECO (Grant CTQ2015-69136-R), the Generalitat de Catalunya (Grant 2014SGR827) and the CERCA Programme (Generalitat de Catalunya). We also thank MINECO for support through the Severo Ochoa Excellence Accreditation 2014–2018 (SEV-2013-0319).

Notes and references

‡ pK_a values in water (ordered according to acidity scale): $NaOCH_2CF_3$/TFE = 12.5; NaOBn/BnOH = 15.4; NaOMe/MeOH = 15.5; NaOEt/EtOH = 16.0; NaO^{i}Pr/^{i}PrOH = 16.5.
§ See the ESI† for details.

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