CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Stereoselective and Enantiospecific Mono and Bis C-H azidation of Tröger Bases. Insight on Bridgehead Iminium Intermediates and Application to Anion-Binding Catalysis

Authors: Alessandro Bosmani, Sandip Pujari, Laure Guenee, Céline Besnard, Amalia Isabel Poblador Bahamonde, and Jerome Lacour

To be cited as: *Chem. Eur. J.* 10.1002/chem.201700845

Link to VoR: http://dx.doi.org/10.1002/chem.201700845

Supported by
ACES

WILEY-VCH

10.1002/chem.201700845

WILEY-VCH

FULL PAPER

Stereoselective and Enantiospecific Mono and Bis C-H azidation of Tröger Bases. Insight on Bridgehead Iminium Intermediates and Application to Anion-Binding Catalysis

Alessandro Bosmani,[a] Sandip A. Pujari,[a] Céline Besnard,[b] Laure Guénée,[b] Amalia I. Poblador-Bahamonde,[a] Jérôme Lacour*[a]

Abstract: In the context to Tröger base chemistry, regio and stereoselective C_{sp3}-H azidation reactions are reported. Azide functional groups are introduced at either one or the two benzylic positions selectively. Mild conditions and good yields are afforded by the combination of $TMSN_3$ and iodosobenzene PhIO. The process occurs with high enantiospecificity (*es* 96-99%) and, interestingly and importantly, *via* bridgehead iminium intermediates as shown by mechanistic and *in-silico* studies. Finally, mono and bis triazole derivatives were prepared in high yields and enantiospecificity using CuAAC reactions; some of the products being used as anion-binding organocatalysts for the tritylation of amines and alcohols.

Introduction

In today's organic chemistry, the azide functional group (-N_3) is commonly used for the introduction and manipulation of nitrogen atoms.[1] Azides are typically incorporated by nucleophilic substitutions on substrates pre-functionalized with leaving groups.[2] Direct azide introduction by C-H functionalization is also possible.[3] In most cases, the reactions are coupled to selective oxidation processes.[4] In this framework, hypervalent iodine(III) reagents are particularly useful.[5] For instance, C-H azidation of tertiary carbon centers and carbonyl compounds can be achieved using azidobenziodoxole and other iodine (III) reagents.[6] β-Functionalization of enol ethers and α-azidation of *N*,*N*-dialkyl anilines can be achieved using combinations of iodosobenzene (PhIO) and $TMSN_3$ (Figure 1, top).[7],[8] In this latter study, only simple anilines were used and a two-electron oxidation mechanism iminium intermediates was postulated (Figure 1, middle). It was therefore debatable whether this reaction could be extended to more complex frameworks, and bicyclic derivatives with bridgehead nitrogen atoms in particular, such as Tröger bases **1a** (Figure 1, bottom). In fact, Tröger bases (TB),[9] classical

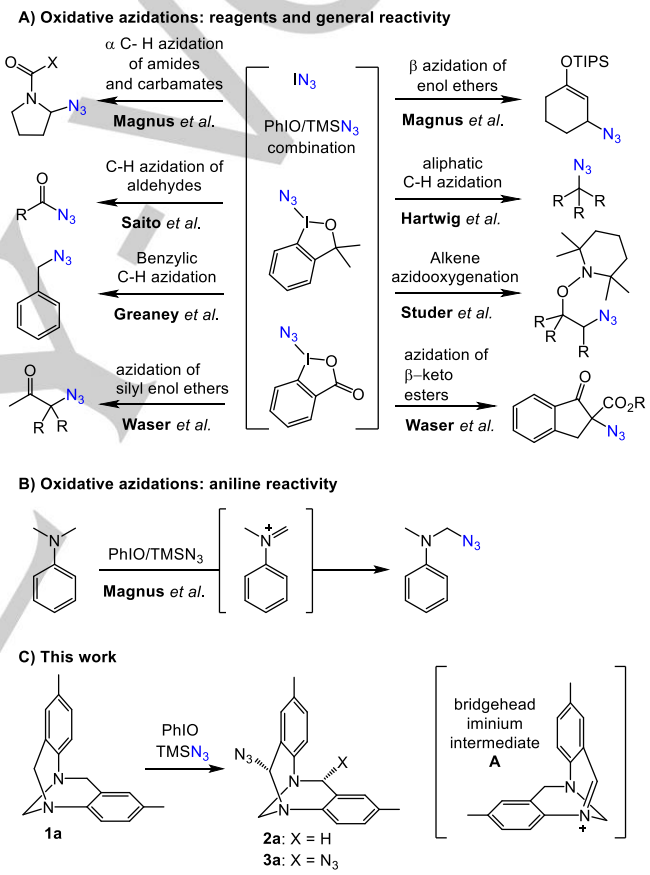


Figure 1. Oxidative azidations using hypervalent iodine reagents

chiral molecules due to the presence of stereogenic nitrogen atoms, are amenable to selective oxidation processes. On one hand, in the presence of permanganate ions, original and interesting twisted bisamide derivatives are synthesized in one step.[10] On the other hand, treatments of **1a** with catalytic amounts of palladium(II)acetate, NBS and either KOAc or NaN_3 afford α-C-H acetylation and azidation processes.[11] In both cases, oxidations occurred at benzylic positions exclusively.[12] A mechanistic rationale was proposed in the latter study suggesting, as one possible pathway but without evidence, the formation of a carbocation (iminium) intermediate. While half of the substrates

[a] A. Bosmani, Dr. S. A. Pujari, Dr. A. I. Poblador-Bahamonde, Prof. J. Lacour
Department of Organic Chemistry, University of Geneva
Quai Ernest Ansermet 30, 1211 Geneva 4 (Switzerland)
E-mail: jerome.lacour@unige.ch
[b] Dr. C. Besnard, Dr. L. Guénée
Laboratory of Crystallography, University of Geneva
Quai Ernest Ansermet 24, 1211 Geneva 4 (Switzerland)

Supporting information for this article is given via a link at the end of the document.

10.1002/chem.201700845

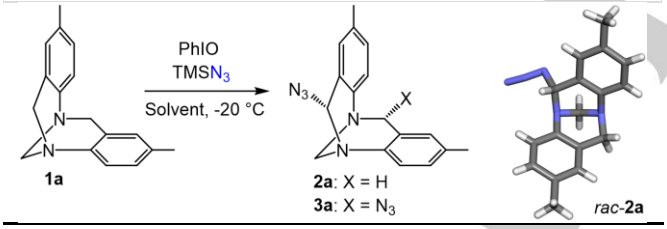
gave cleanly mono adducts **2**, bis-azido derivatives **3** were obtained in the other cases, sometimes as major product. Herein, it is shown that mono or bis-azidation Tröger bases can be achieved selectively using the combination of PhIO and $TMSN_3$ as reagents. In products **2** or **3**, azides are introduced α to the N-atoms. In addition, the reactions proceed with full diastereoselectivity (diastereomeric ratio *d.r.* > 49:1) and enantiospecificity (*es* 96-99%). Interestingly, evidence was found for bridgehead iminium species. In fact, substitution of azide groups by indoles under *Lewis* acid activation and DFT calculations validate the existence of such strained intermediates. Care was finally taken to develop an application of compounds **2** in anion-binding catalysis using products derived by double copper-catalyzed alkyne azide cycloadditions (CuAAC, Huisgen-Click).[13]

Results and Discussion

Initial observation, optimization and scope

As mentioned, PhIO and $TMSN_3$ react in the presence of (planar) *N*,*N*-dialkyl anilines to generate α-azido derivatives.[7b] With this reactive combination, bis azido adducts can be obtained selectively by essentially doubling the quantity of reagents. This methodology was thus deemed interesting for the targeted purpose. Tröger base **1a** (R = Me, Table 1) was treated with PhIO (2.4 equiv) and $TMSN_3$ (2.4 equiv) in $CHCl_3$ (0.1 M) at –20 °C. To our satisfaction, C-H azidation proceeded smoothly with complete regiocontrol in favor of a functionalization of the benzylic positions over the aminal bridge.

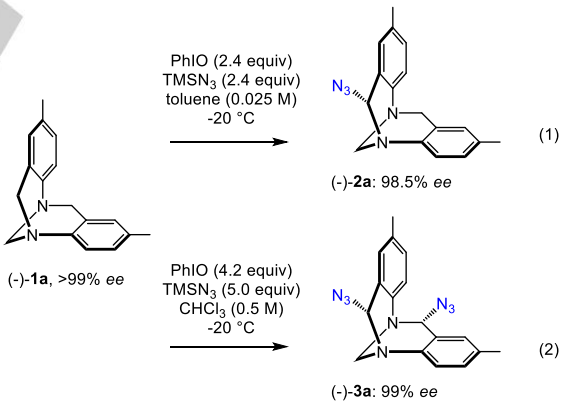
Table 1. Optimization of the mono and bis azidation of Tröger Base **1a** [a]



Entry	Solvent	Conc. (M)	PhIO (equiv)	$TMSN_3$ (equiv)	**2a**:**3a**
1	$CHCl_3$	0.1	2.4	2.4	1.2:1
2	$CHCl_3$	0.1	4.2	5.0	1:1.8
3	$CHCl_3$	0.2	4.2	5.0	1:4.1
4	CH_2Cl_2	0.2	4.2	5.0	1:2.6
5	$CHCl_3$	0.5	4.2	5.0	**1:>20** (71) [b]
6	$CHCl_3$	0.025	2.4	2.4	3.5:1
7	CH_3CN	0.025	2.4	2.4	6.6:1
8	CH_3CN	0.0125	2.4	1.8	7.4:1
9	Toluene	0.025	2.4	2.4	**>10:1** (57) [b]

[a] Reaction conditions: **1a** (1.0 equiv), PhIO, $TMSN_3$, solvent –20 °C. [b] Isolated yields in parenthesis. Stick view of the crystal structure of *rac*-**2a**.

A mixture of **2a** and **3a** (1.2:1 ratio) was however isolated. As expected, increasing the amount of PhIO and $TMSN_3$ (4.2 and 5 equiv respectively), and performing the reactions at higher concentration favored the bis azidation (**2a**:**3a** up to 1:4.1, entries 2 and 3). Changing solvent from $CHCl_3$ to CH_2Cl_2 was detrimental (entry 4) but increasing the concentration further to 0.5 M afforded **3a** exclusively (entry 5, 71% isolated yield). With these optimized conditions for **3a** in hand, the focus was shifted towards a selective preparation of mono azidation product **2a**. Dilution of the reaction medium to 0.025 M and decreasing the amount of PhIO/$TMSN_3$ (2.4 equiv each) improved the **2a**:**3a** ratio (3.5:1, entry 6). Changing the solvent from $CHCl_3$ to CH_3CN and diluting further the reaction medium increased the selectivity up to 7.4:1 (entries 7 and 8). Finally, for the isolation of the mono azide adduct, toluene was found to be optimal affording **2a** in 57% isolated yield (**2a**:**3a** >10:1, entry 9).[14] Interestingly, compounds **2a** and **3a** are produced as single diastereomers. The relative configuration was determined by NMR spectroscopy and confirmed by X-ray crystallography (Table 1). Not surprisingly, the azide functional groups in **2**a and **3a** are introduced on the convex side (*exo*) of the cyclic heterocycles. Such a result is consistent with previous observations in TB chemistry.[9h,11,15],[16] With these optimized conditions, care was also taken to perform the two azidation processes on enantiopure (–)-**1a**.[17] To our satisfaction, chiral stationary phase (CSP) HPLC analysis (Chiralpak IC, Hexane/Isopropyl alcohol 90/10) indicated a very high enantiospecificity as products (–)-**2a** and (–)-**3a** were obtained as single enantiomers (*ee* 98.5% and > 99% respectively). For these two reactions (eq. 1 & 2), a retention of configuration of the Tröger base core is assumed.



Then, Tröger bases **1b**-**1f** were subjected to mono azidation conditions (Figure 2). Not surprisingly, the oxidative process was more effective with TB carrying electron donating groups (**2b**, **2c**: 54, 51%) than with electron withdrawing substituents (**2d**, **2e**: 19, 10%).[18] Interestingly, **2f** was formed in quite higher yield (83%) using PhIO and $TMSN_3$ in only 1.5 equivalents each. This result is in line with a previously-detailed reactivity of **1f** with nitrenes, in which substantial amounts of C-H amination at benzylic positions were noticed over the "classical" aminimide formation.[19] It can be rationalized by the presence of the *ortho* substituents that shield sterically the nitrogen atoms. Bis azidation reactions to products

10.1002/chem.201700845

3b, **3d**, **3f**-**3h** gave similar results with sometimes better yields (in particular with **1d**). In all cases and as expected, high levels of diastereoselectivity and enantiospecificity were obtained (**2b**-**2f**: *d.r.* > 49:1, *es* 96-99%).

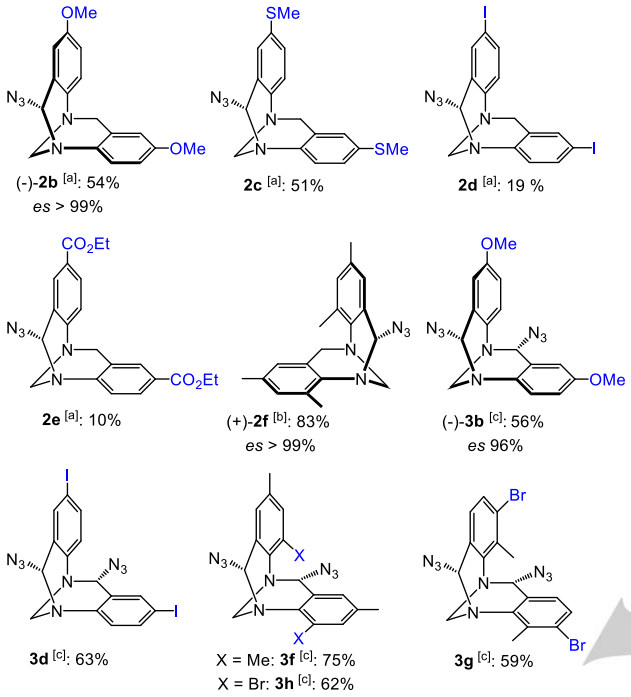


Figure 2. Conditions: **1b**-**1h** (1.0 equiv) and [a]: PhIO and $TMSN_3$ (2.4 equiv), toluene (0.025 M), –20 °C; [b]: PhIO and $TMSN_3$ (1.5 equiv), toluene (0.025 M), –20 °C; [c]: PhIO (4.2 equiv), $TMSN_3$ (5.0 equiv), $CHCl_3$ (0.5 M), –20 °C.

Mechanistic studies, theoretical and experimental

At that stage, in view of the generality of the process, a study of the reaction mechanism was undertaken. First, it was demonstrated that only the combination of iodosobenzene and $TMSN_3$ afforded azido products **2** and **3** reliably. Substrate **1a** was treated with various combinations of PIDA or PIFA (2.4-4.2 equiv) and $TMSN_3$, or with isolated reagent 1-azido-1,2-benziodoxol-3(1*H*)-one,[6f] to afford unreacted starting material in most cases or minor trace amounts of acetoxy derivatives.[11] Knowing that the PhIO/$TMSN_3$ combination favors two-electron processes over radical ones,[7] the previous proposition of cationic (iminium) ions as intermediates for this type of reactions (**A**, Figure 1) was considered favorably.[11] However, species of type **A** are bridgehead iminium ions.[20],[21] Care was thus taken to evaluate the formation and the stability of such species as the [3.3.1] bicyclic skeleton of TB could be large enough to accommodate the strain, and this using both theoretical and experimental approaches.

In fact, DFT calculations on TB **1a** and proposed intermediate **A** were carried out at the B3LYP level of theory. The geometry of the substrate, which is in good agreement with crystallographic data, presents longer N-CH_2 and CH_2-C_{ring} distances that those computed on the proposed cation. The comparison of the ϕ angle formed by the planes of the aromatic rings in the characteristic V-shaped structure increases by 22° from the TB substrate to the proposed iminium intermediate (ϕ = 102° *vs.* 124°) allowing the accommodation of the positive charge (see key angles and distances on Figure 3). In order to discard the possibility of a non-classical structure for cation **A**, the distance between the charged carbon and the plane formed by the neighboring N-H-C_{ring} atoms was calculated. The minimal disturbance (0.09 Å) invalidates such a proposition. In addition, no pyramidalization of the positively-charged carbon is observed.

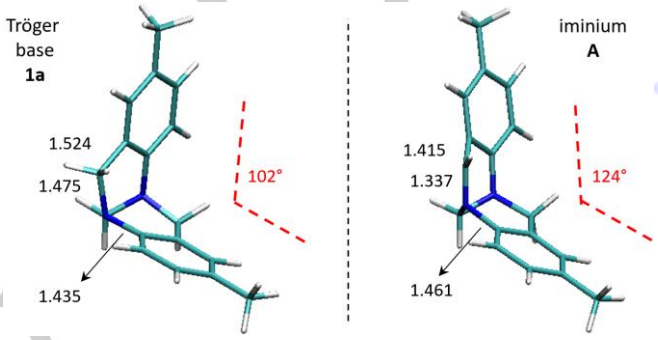


Figure 3. Computed DFT (B3LYP) geometrical parameters (Å and °) for TB **1a** and iminium intermediate **A**.

The calculation of the LUMO orbitals of TB **1a** and iminium ion **A**, represented in Figure 4, assesses the charge distribution for each system and underlines the differences. The LUMO of **1a** depicts empty π* orbitals of both benzene moieties while intermediate **A** mainly distributes its cationic character on the π* orbital of C=N bond, which is in agreement with the subsequent functionalization observed experimentally.

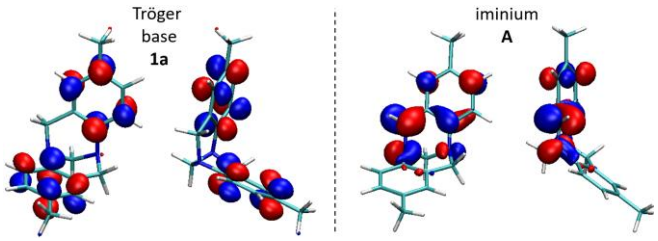


Figure 4. DFT (B3LYP) computed LUMO orbitals of TB **1a** (left) and iminium intermediate **A** (right). The value of the isodensity surface is 0.04 au.

With these calculations indicating a viability for bridgehead iminium species **A**, experimental evidences were looked for. In one set of studies, the “reversibility” of the azide addition was utilized to demonstrate the presence of intermediates **A**. In fact, it is established that azides can behave as leaving groups in the presence of Lewis acids and (stabilized) carbenium ions result from the elimination.[1a,22][23] In presence of nucleophiles, the electrophilic species can be trapped in-situ. The formation of

10.1002/chem.201700845

products of elimination-then-addition is then considered as a proof of occurrence of the cationic intermediates. Experimentally, the two-step process was realized by treating mixtures of indoles (2.0 equiv) and Tröger base **2a** at -65 °C with trimethyl aluminum (2.0 equiv). As expected, heterocycles **4aA** to **4fA** were afforded – in good to excellent yields (77-93%, Figure 5). The formal substitution of the azido group by indole moieties was ascertained by NMR spectroscopy and X-ray analysis (**4bA**). Importantly, a retention of configuration is observed at the benzylic position. This indicates that a S_N1-type mechanism is at play and that the indole nucleophiles approach intermediates of type **A** from the convex side selectively, as azides do under the regular reaction conditions.[24]

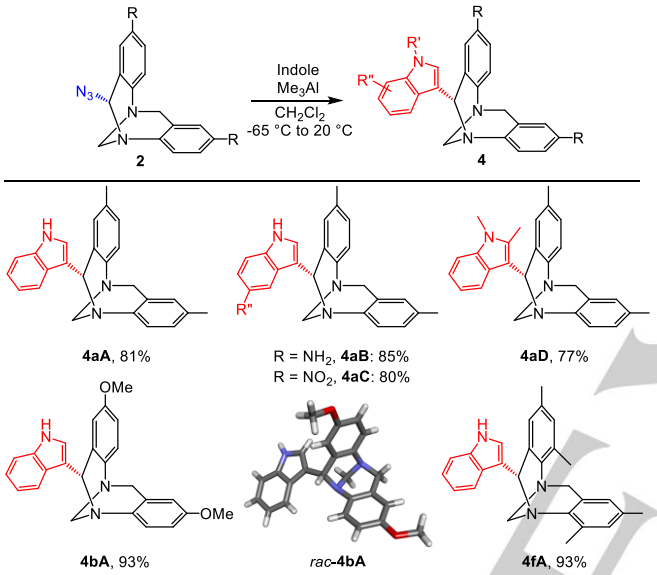
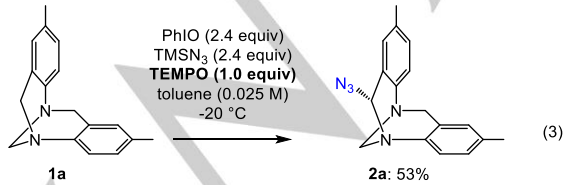


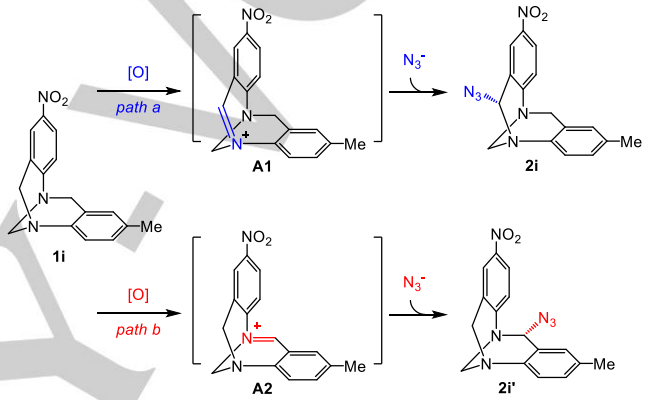
Figure 5. Conditions: **2a-2f** (1.0 equiv), indole (2.0 equiv), Me_3Al (2.0 equiv), -65 °C to 20 °C. Stick view of the crystal structure of *rac*-**4bA**.

Finally, to fine-tune the mechanistic rationale, two experiments were performed. First, classical TB **1a** was treated with PhIO/$TMSN_3$ in the presence of a stoichiometric amount of TEMPO (eq. 3). The reaction proceeded to form **2a** in 53% yield, *ie* in virtually the same yield as under optimized conditions (57%). This and the lack of products containing TEMPO fragments suggest that the two-electron pathway occurs through hydride abstraction and not by consecutive single electron transfer steps.



(3)

Then, the reaction was performed with unsymmetrically-substituted Tröger base **1i** carrying electron-donating and electron-withdrawing substituents on the two aromatic rings respectively (Me and NO_2, Scheme 1).[25] To our surprise, a 1:2 mixture of regioisomers **2i** and **2i'** was isolated. The reaction was unusually slow and a moderate conversion and combined yield (22%) was achieved. Structure determination of **2i** and **2i'** was realized by 2D NMR analysis, and HMBC experiments in particular (see Figures S2-S8). Initially, model compound **1i** was built expecting that the oxidation of the electron-rich nitrogen atom (*para* to Me) would be highly favored over the electron-poor N-atom (*para* to NO_2),[26],[27] and this would lead to the predominant formation of **2i** (Scheme 1, path a, *via* iminium ion **A1**). It is clearly not the case with the preferred formation of **2i'** (path b *via* iminium **A2**).



Scheme 1. Regioselective azidation of TB **1i.** Conditions: **1i** (1.0 equiv), PhIO and $TMSN_3$ (2.4 equiv), 0.025 M ($CHCl_3$), -20 °C.

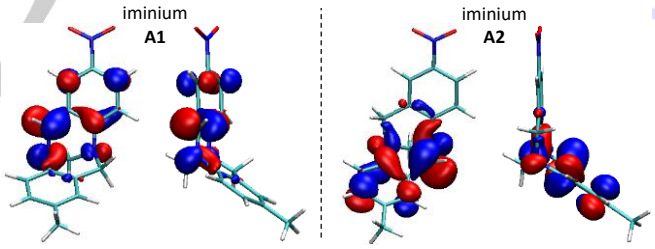


Figure 6. DFT (B3LYP) computed LUMO orbitals of iminium intermediates **A1** (left) and **A2** (right). The value of the isodensity surface is 0.04 au.

Geometry optimizations of iminium intermediates **A1** and **A2** were modelled. The calculation of the LUMO orbitals shown in Figure 6 confirms that both cationic species continues to favor the build-up of charge on the $\pi^*_{C=N}$ orbitals over the aromatic moiety. Interestingly, the comparison of the relative energies indicates that **A2** is more stable than **A1** by 2.4 kcal mol^{-1}. This preferred stability of **A2** is in agreement with the favored formation of product **2i'**. Yet, the moderate ratio (2:1) in favor of **2i'** indicates that kinetic factors, and not just thermodynamic, should be considered to explain the selectivity.

10.1002/chem.201700845

Application to catalysis

Recently, Garcia Mancheño and her group have reported poly triazoles moieties that behave as anion receptors and anion-binding organo-catalysts.[28] In fact, molecules **5a** and **5b** complex negative ions thanks to the acidic C-H bonds carried by the triazole units (Figure 7). Then, using these compounds as catalysts, dearomatization of *N*-heteroarenes and tritylations of primary amines were developed.[28] This original reactivity of compounds **5** led us to consider an application of azido derivatives **2** in this domain.

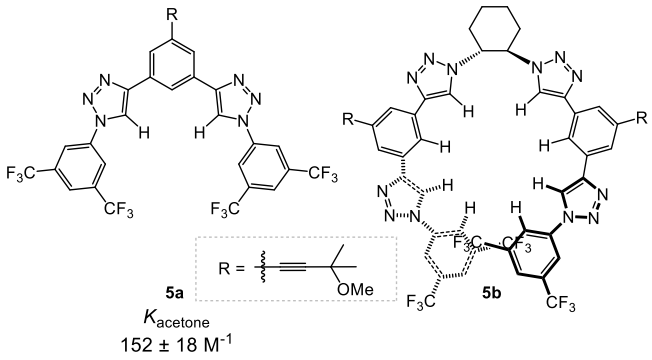


Figure 7. Polytriazole-based ligands **5** for anion binding catalysis.

However, prior to consider the formation of TB analogues of **5**, care was taken to study the CuAAC reactivity of mono **2** and bis-triazole **3** derivatives. The results are summarized in Figure 8. Under standard CuAAC conditions, good to excellent yields of **6aA**-**6fA** and **7aA**-**7bA** were obtained (64-91%).[29]. Using enantioenriched (–)-**2a** (*ee* 98.5%) and (–)-**3a** (*ee* 99%) triazoles **6aA** and **7aA** were obtained in very high enantiospecificity (*es* > 99%) demonstrating an excellent stereochemical fidelity.

With these results in hand, bis alkynyl pyridine **8a** and benzene **8b** were prepared (Figure 9).[30] Treatment of these substrates with (–)-**2a** under standard conditions yielded then (–)-**9a** and (–)-**9b** in good yields, 71% and 75% respectively, and very high enantiospecificity (*es* > 99%). In fact, the CuAAC coupling was realized with enantiopure (–)-**2a** to ensure the homochirality of **9a** and **9b**, and avoid hence *meso* stereoisomers.

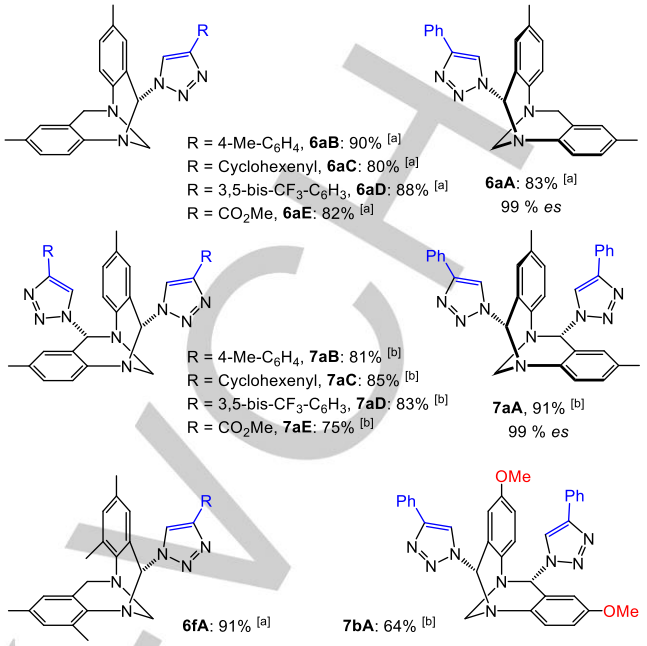


Figure 8. Conditions: **2a**, **2b** or **2f** (1.0 equiv) and [a]: alkyne (1.2 equiv), $CuSO_4.5H_2O$ (0.10 equiv), ascorbic acid (0.17 equiv), $NaHCO_3$ (0.17 equiv) THF:H_2O (1:1, 0.56 M), 20 °C; [b]: alkyne (2.5 equiv), $CuSO_4.5H_2O$ (0.20 equiv), ascorbic acid (0.34 equiv), $NaHCO_3$ (0.34 equiv) THF:H_2O (1:1, 0.56 M), 20 °C;.

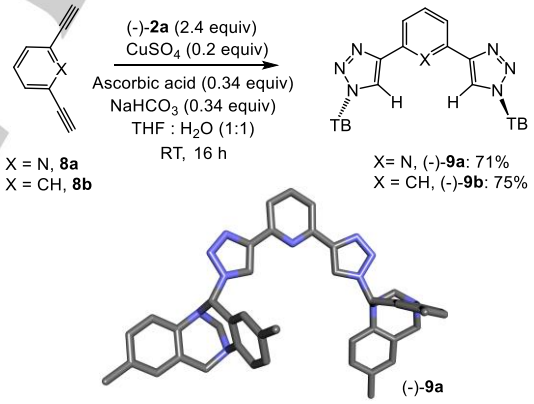


Figure 9. Synthesis of bistriazole (–)-**9a** and (–)-**9b** starting from (–)-**2a**. Stick view of the crystal structure of (–)-**9a,** hydrogen atoms omitted.

The ability of **9a** and **9b** to bind chloride anions was studied by ^{1}H NMR titration using TBACl (tetrabutylammonium chloride) as analyte. Care was taken to follow conditions reported by Garcia Mancheño *et al*.[28] Part of the experiment with **9a** is reported in Figure 10; the most shifted NMR signal being the triazole C-H protons as expected.[31] The data was treated with HypNMR 2008.[32] Not too surprisingly, in view of the electron-rich nature of the TB framework, the values for the binding constants of **9a** and **9b** are quite low using acetone as solvent ($K_{acetone}$ 11.5 ± 1.1 M^{-1} and 47.9 ± 1.1 M^{-1} respectively).[33]

10.1002/chem.201700845

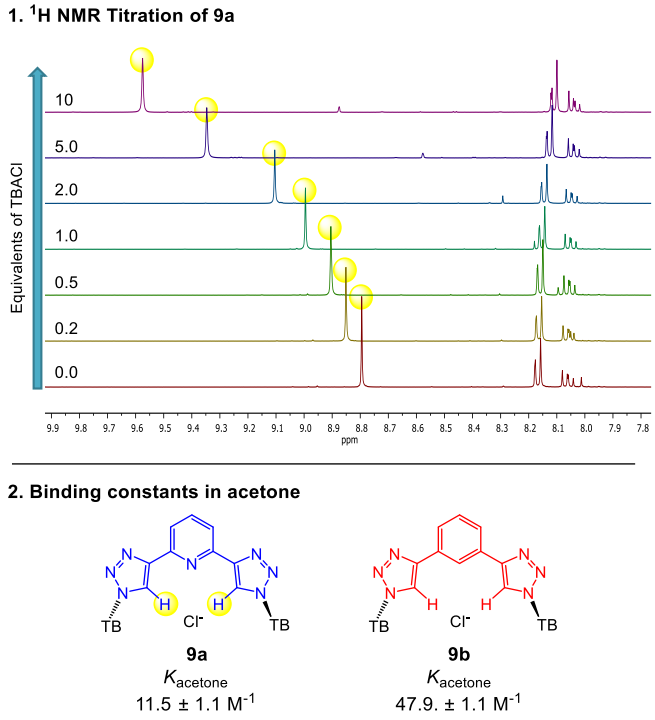


Figure 10. Titration of **9a** and **9b**. Top: ^{1}H NMR spectra of **9a** with various amounts of TBACl. Bottom: Binding constants determined using the variation of chemical shift of the triazole proton highlighted in yellow.

The phenyl derivative possesses a stronger binding than the pyridine-based receptor; the lone-pair on nitrogen inducing probably a repulsion with the anion. Nevertheless, the ability of compounds **9** to behave as anion-binding catalysts was tested. In fact, tritylations of primary amines and alcohols were investigated using the adduct (salt) of DMAP and tritylchloride as reagent.[28b] In the absence of compounds **9**, no reactivity was observed with amine substrates while, with benzyl alcohol, a moderate formation of **10** was noticed (28%). On the other hand, reactions proceeded smoothly under mild conditions (45 °C) in the presence of **9a** and **9b** to afford products **11a**-**11c** in good yields (55-89%, Figure 11). Long reaction times were however necessary in line with previously-reported results.[28b]

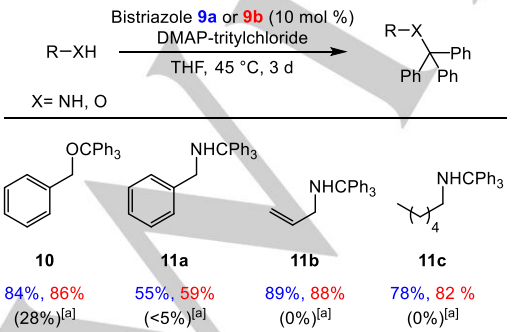


Figure 11. Tritylation of alcohol and primary amines with DMAP-trityl chloride salt. Yields for reactions with **9a** and **9b** reported in blue and red colors respectively. [a] In the absence of catalyst.

Conclusions

Regio and diastereoselective mono and bis C-H azidations of Tröger bases were accomplished under mild reaction conditions and high enantiospecificity (*es* 96-99%). Mechanistic studies have further revealed the importance of bridgehead iminium cations as reactive intermediates. Finally, mono and bis triazole derivatives were prepared in high yields and enantiospecificity using CuAAC reactions; some of the products being used as anion-binding organocatalysts for the tritylation of amines and alcohols.

Experimental section

Synthetic procedures and spectral characterization of new compounds are reported in the electronic supporting information. CCDC 1533697 to 1533700, products **2a**, **4bA**, **7aE**, **9a**, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We thank the University of Geneva and the Swiss NSF for financial support. We also acknowledge the contributions of the Sciences Mass Spectrometry (SMS) platform at the Faculty of Sciences, University of Geneva. We would also like to thank Carmine Chiancone for technical support.

Keywords: Anion-binding catalysis • Azide • Bridgehead • C-H functionalization • Enantiospecificity • Iminium intermediate • Tröger base

[1] a) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240; b) J. Haase, in *Organic Azides*, John Wiley & Sons, Ltd, **2009**, pp. 29-51.

[2] a) E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, *88*, 297-368; b) Y. Sawama, S. Nagata, Y. Yabe, K. Morita, Y. Monguchi, H. Sajiki, *Chem. Eur. J.* **2012**, *18*, 16608-16611; c) Y. Sawama, K. Shibata, Y. Sawama, M. Takubo, Y. Monguchi, N. Krause, H. Sajiki, *Org. Lett.* **2013**, *15*, 5282-5285.

[3] a) F. Xie, Z. Qi, X. Li, *Angew. Chem. Int. Ed.* **2013**, *52*, 11862-11866; b) X. Huang, T. M. Bergsten, J. T. Groves, *J. Am. Chem. Soc.* **2015**, *137*, 5300-5303; c) A. Sharma, J. F. Hartwig, *Nature* **2015**, *517*, 600-604; d) X. Huang, J. T. Groves, *ACS Catal.* **2016**, *6*, 751-759.

[4] a) S. De Sarkar, A. Studer, *Org. Lett.* **2010**, *12*, 1992-1995; b) X. Zhang, H. Yang, P. Tang, *Org. Lett.* **2015**, *17*, 5828-5831; c) R. Ren, H. Zhao, L. Huan, C. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 12692-12696; d) X. Sun, X. Li, S. Song, Y. Zhu, Y.-F. Liang, N. Jiao, *J. Am. Chem. Soc.* **2015**, *137*, 6059-6066.

[5] V. V. Zhdankin, *ARKIVOC* **2009**, 1-62.

[6] a) V. V. Zhdankin, A. P. Krasutsky, C. J. Kuehl, A. J. Simonsen, J. K. Woodward, B. Mismash, J. T. Bolz, *J. Am. Chem. Soc.* **1996**, *118*, 5192-5197; b) H. Tohma, *Chem. Commun.* **1998**, 173-174; c) H. Tohma, H. Morioka, S. Takizawa, M. Arisawa, Y. Kita, *Tetrahedron* **2001**, *57*, 345-352; d) C. M. Pedersen, L. G. Marinescu, M. Bols, *Org. Biomol. Chem.* **2005**, *3*, 816-822; e) M. V. Vita, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 5290-5292; f) M. V. Vita, P. Caramenti, J. Waser, *Org. Lett.* **2015**, *17*, 5832-5835; g) M. V. Vita, J. Waser, *Org. Lett.* **2013**, *15*, 3246-3249; h) Y. Shinomoto, A. Yoshimura, H. Shimizu, M. Yamazaki, V. V. Zhdankin, A. Saito, *Org. Lett.* **2015**, *17*, 5212-5215; i) P. T. G. Rabet, G. Fumagalli, S. Boyd, M. F. Greaney, *Org. Lett.* **2016**, *18*, 1646-1649.

[7] a) P. Magnus, J. Lacour, *J. Am. Chem. Soc.* **1992**, *114*, 767-769; b) P. Magnus, J. Lacour, W. Weber, *J. Am. Chem. Soc.* **1993**, *115*, 9347-9348; c) P. Magnus, J. Lacour, P. A. Evans, M. B. Roe, C. Hulme, *J. Am. Chem. Soc.* **1996**, *118*, 3406-3418; d) P. Magnus, J. Lacour, P. A. Evans, P. Rigollier, H. Tobler, *J. Am. Chem. Soc.* **1998**, *120*, 12486-12499.

[8] For references detailing direct C-H functionalization adjacent to nitrogen atoms, see a) K. Tani, B. M. Stoltz, *Nature* **2006**, *441*, 731-734; b) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069-1084; b) X. Ye, C. Xie, Y. Pan, L. Han, T. Xie, *Org. Lett.* **2010**, *12*, 4240-4243; c) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092-10142.

[9] a) J. Tröger, *J. Prakt. Chem.* **1887**, *36*, 225-245; b) V. Prelog, P. Wieland, *Helv. Chim. Acta* **1944**, *27*, 1127-1134; c) M. Demeunynck, C. Fontaine, J. Lhomme, *Magn. Reson. Chem.* **1999**, *37*, 73-76; d) M. Demeunynck, A. Tatibouet, *Prog. Heterocycl. Chem.* **1999**, *11*, 1-20; e) M. Valik, R. M. Strongin, V. Kral, *Supramol. Chem.* **2005**, *17*, 347-367; f) D. Didier, S. Sergeyev, *Targets Heterocycl. Syst.* **2007**, *11*, 258-283; g) S. Sergeyev, *Helv. Chim. Acta* **2009**, *92*, 415-444; h) Ö. V. Rúnarsson, J. Artacho, K. Wärnmark, *Eur. J. Org. Chem.* **2012**, *2012*, 7015-7041; i) B. Dolensky, M. Havlik, V. Kral, *Chem. Soc. Rev.* **2012**, *41*, 3839-3858.

[10] a) J. Artacho, E. Ascic, T. Rantanen, J. Karlsson, C. J. Wallentin, R. Wang, O. F. Wendt, M. Harmata, V. Snieckus, K. Wärnmark, *Chem. Eur. J.* **2012**, *18*, 1038-1042; b) J. Artacho, E. Ascic, T. Rantanen, C. J. Wallentin, S. Dawaigher, K. E. Bergquist, M. Harmata, V. Snieckus, K. Wärnmark, *Org. Lett.* **2012**, *14*, 4706-4709; c) R. Pereira, L. Pfeifer, J. Fournier, V. Gouverneur, J. Cvengroš, *Org. Biomol. Chem.* **2017**, *15*, 628-633.

[11] R. Pereira, P. Ondrisek, A. Kubincová, E. Otth, J. Cvengroš, *Adv. Synth. Catal.* **2016**, *358*, 2739 –2744.

[12] These methods of benzylic functionalizations are complementary to that involving base-induced deprotonations followed by alkylations. See, M. Harmata, M. Kahraman, *Tetrahedron: Asymmetry* **2000**, *11*, 2875-2879.

[13] a) R. Huisgen, G. Szeimies, L. Mobius, *Chem. Ber.* **1967**, *100*, 2494; b) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; c) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128-1137.

[14] A complete lack of reaction is noticed if iodosobenzene PhIO is replaced by PIDA (iodosobenzenediacetate) or PIFA (iodosobenzeneditrifluoroacetate).

[15] S. Dawaigher, K. Månsson, E. Ascic, J. Artacho, R. Mårtensson, N. Loganathan, O. F. Wendt, M. Harmata, V. Snieckus, K. Wärnmark, *J. Org. Chem.* **2015**, *80*, 12006-12014.

[16] The inner concave (endo) sides of TB **1a** are considerably more hindered.There are only rare examples of such functionalization: J. Artacho, E. Ascic, T. Rantanen, C. J. Wallentin, S. Dawaigher, K. E. Bergquist, M. Harmata, V. Snieckus, K. Wärnmark, *Org. Lett.* **2012**, *14*, 4706.

[17] a) S. Satishkumar, M. Periasamy, *Tetrahedron: Asymmetry* **2006**, *17*, 1116-1119; b) S. Satishkumar, M. Periasamy, *Tetrahedron: Asymmetry* **2009**, *20*, 2257-2262; c) S. Suresh, M. Periasamy, *Tetrahedron: Asymmetry* **2015**, *26*, 203-208

[18] With *p*-nitro substituents, only traces of conversion are observed under standard conditions.

[19] S. A. Pujari, L. Guenee, J. Lacour, *Org. Lett.* **2013**, *15*, 3930-3933.

[20] B. R. Bear, S. M. Sparks, K. J. Shea, *Angew. Chem. Int. Ed.* **2001**, *40*, 820-849.

[21] J. Y. W. Mak, R. H. Pouwer, C. M. Williams, *Angew. Chem. Int. Ed.* **2014**, *53*, 13664-13688.

[22] a) C. Doebelin, M. Schmitt, C. Antheaume, J. J. Bourguignon, F. Bihel, *J. Org. Chem.* **2013**, *78*, 11335-11341; b) L. Chabaud, Y. Landais, *Tetrahedron Lett.* **2003**, *44*, 6995-6998; c) A. Banerjee, P. S. Kumar, S. Baskaran, *Chem. Commun.* **2011**, *47*, 12218-12220; d) D. S. Reddy, W. R. Judd, J. Aubé, *Org. Lett.* **2003**, *5*, 3899-3902.

[23] Lewis acids enhance the nucleofugal character of the azide group and facilitate the elimination steps. See reference 7d.

[24] Using enantiopure (**–**)-**2a**, racemic product **4a** is however obtained. Such a result is not clearly rationalized at this stage.

[25] C. Pardo, M. Ramos, A. Fruchier, J. Elguero, *Magn. Reson. Chem.* **1996**, *34*, 708-710.

[26] S. A. Pujari, C. Besnard, T. Buergi, J. Lacour, *Angew. Chem. Int. Ed.* **2015**, *54*, 7520-7523.

[27] The symmetrical dinitro-substituted Tröger base is unreactive under the reactions conditions – even with a large excess of $PhIO/TMSN_3$.

[28] a) S. Beckendorf, S. Asmus, C. Muck-Lichtenfeld, O. García Mancheño, *Chem. Eur. J.* **2013**, *19*, 1581-1585; b) S. Asmus, S. Beckendorf, M. Zurro, C. Muck-Lichtenfeld, R. Frohlich, O. García Mancheño, *Chem. Asian. J.* **2014**, *9*, 2178-2186; c) M. Zurro, S. Asmus, S. Beckendorf, C. Mück-Lichtenfeld, O. García Mancheño, *J. Am. Chem. Soc.* **2014**, *136*, 13999-14002; d) O. García Mancheño, S. Asmus, M. Zurro, T. Fischer, *Angew. Chem. Int. Ed.* **2015**, *54*, 8823-8827; e) T. Fischer, J. Bamberger, O. García Mancheño, *Org. Biomol. Chem.* **2016**, *14*, 5794-5802; f) M. Zurro, S. Asmus, J. Bamberger, S. Beckendorf, O. García Mancheño, *Chem. Eur. J.* **2016**, *22*, 3785-3793; g) M. Zurro, O. García Mancheño, *Chem. Rec.* **2016**, *17*, 1-15; h) T. Fischer, Q.-N. Duong, O. García Mancheño, *Chem. Eur. J.* **2017**, *23*, DOI: 10.1002/chem.201605660.

[29] For structural information on bis-triazolo TB **7aE**, check the crystallographic data contain in CCDC 1533699

[30] A. Orita, T. Nakano, D. L. An, K. Tanikawa, K. Wakamatsu, J. Otera, *J. Am. Chem. Soc.* **2004**, *126*, 10389-10396.

[31] For the analogous titration experiment with phenyl **9b**, see Figure S11.

[32] C. Frassineti, S. Ghelli, P. Gans, A. Sabatini, M. S. Moruzzi, A. Vacca, *Anal. Biochem.* **1995**, *231*, 374-382.

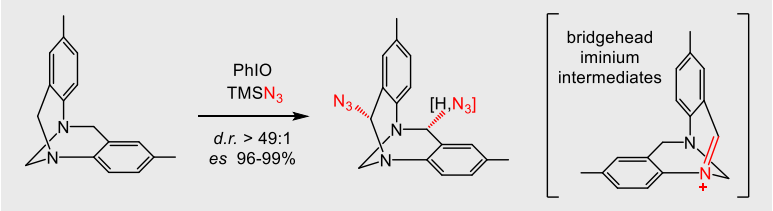
[33] For **9a** and **9b**, log (β) = 1.06 ± 0.06 and 1.68 ± 0.06 respectively

10.1002/chem.201700845

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

FULL PAPER



Regio and stereoselective C_{sp3}-H azidations of Tröger bases are reported. Both mono and bis azide functionalizations are available using $TMSN_3$ and PhIO as reagent. High enantiospecificity is achieved (*es* 96-99%). Interestingly, bridgehead iminium intermediates are evidenced by mechanistic and *in-silico* studies. With the azido products in hand, tailored bis triazole derivatives were prepared for application in anion-binding catalysis.

*Alessandro Bosmani, Dr. Sandip A. Pujari, Dr. Céline Besnard, Dr. Laure Guénée, Dr. Amalia I. Poblador-Bahamonde, Prof. Jérôme Lacour**

Page No. – Page No.

Stereoselective and Enantiospecific Mono and Bis C-H azidation of Tröger Bases. Insight on Bridgehead Iminium Intermediates and Application to Anion-Binding Catalysis