

Synthesis of chiral pyrazoles through a 1,3-dipolar cycloaddition/[1,5]-sigmatropic rearrangement with stereoretentive migration of a stereogenic group

M. Carmen Pérez-Aguilar,^[a] and Carlos Valdés^{*[a]}

"This is the peer reviewed version of the following article: Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem. Int. Ed.* 2015, 54, 13729, which has been published in final form <http://dx.doi.org/10.1002/anie.201506881>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving."

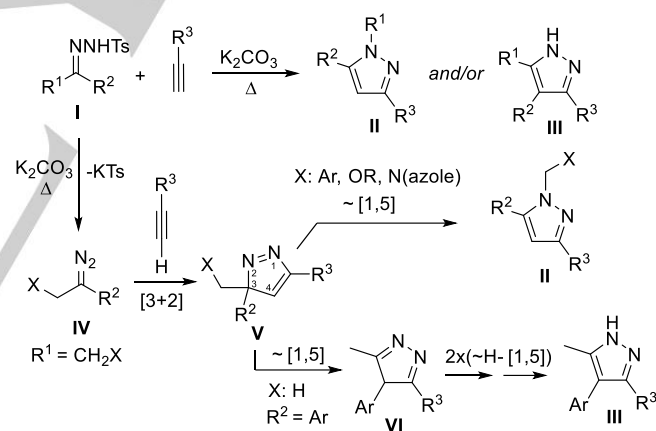
Abstract: The reactions between terminal alkynes and α -chiral tosylhydrazones lead to the obtention of chiral pyrazoles with a stereogenic group directly attached at a nitrogen atom, through cascade reactions that include decomposition of the hydrazone into a diazocompound, 1,3-dipolar cycloaddition of the diazo compound with the alkyne and 1,5-sigmatropic rearrangement with migration of the stereogenic group. This strategy have been succesfully applied to the synthesis of structurally diverse chiral pyrazoles from α -chiral tosylhydrazones obtained from α -phenylpropionic acid, α -aminoacids and 2-methoxycyclohexanone. Noteworthy, the stereoretentive 1,5-sigmatropic rearrangements represent very rare examples of this stereospecific transformation.

The pyrazole ring is a five-membered heterocycle present in a large number of molecules with biological activity.^[1] Compounds containing substituted pyrazoles find widespread as antimicrobials, analgesics, anti-inflammatory agents, CNS and oncology drugs.^[2-5] Indeed, pyrazoles are constantly employed as building blocks in drug discovery programs.^[6,7] Moreover, structures built around the pyrazole scaffold are also found as key constituents of ligands for transition metals with biological or catalytic activity,^[8] receptors in supramolecular chemistry,^[9] and functional organic materials.^[10] For these reasons, and in spite of the variety of existing methods, the development of new methodologies for the efficient regioselective synthesis of polysubstituted pyrazoles is still an area of very active research.^[11,12]

A particularly challenging type of pyrazoles are chiral pyrazoles with a stereogenic carbon attached at N-position. Limited examples of this type of chiral pyrazoles with biological activity have been reported,^[13] but their usefulness have been hampered by the lack of general methods for their preparation. Chiral pyrazoles with a stereogenic center attached at the nitrogen

have been synthesized from chiral amines,^[14] and also by alkylation of the corresponding N-H pyrazole through Mitsunobu reactions of chiral alcohols,^[13,15] ring opening of chiral or *meso* epoxides,^[16] and organocatalytic aza-Michael reactions.^[17] Nevertheless, these methods are far from general and have been mostly employed on unsubstituted pyrazole.

We have recently reported the regioselective synthesis of 1,3,5-trisubstituted pyrazoles **II** and 3,4,5-pyrazoles **III** from the reaction of tosylhydrazones **I** and terminal alkynes by a 1,3-dipolar cycloaddition/1,5-sigmatropic rearrangement sequence (Scheme 1).^[18] The mechanism proposed for these cascade processes involves the following steps: 1) decomposition of the tosylhydrazone to produce a diazo compound **IV**, 2) 1,3-dipolar cycloaddition of the diazo compound with the terminal alkyne to form a 3*H*-pyrazole **V**,^[19,20] 3) 1,5-sigmatropic rearrangement which may lead to 1,3,5-substituted 1*H*-pyrazole **II** or to a new 4*H*-pyrazole **VI**. The latter will undergo additional [1,5]-sigmatropic shifts to provide the aromatic 3,4,5-pyrazole **III** (Scheme 1).



Scheme 1. Regioselective synthesis of trisubstituted pyrazoles and mechanism proposed.

The step that determines the regioselectivity of the reaction is the [1,5]-sigmatropic rearrangement. For tosylhydrazones derived from acetophenones (X = H, R² = Ar), the only product obtained is the resultant of the migration of the aryl group to C4 **III**. In contrast, for 2-substituted acetophenones, in many cases the major or exclusive product obtained is the pyrazole **II**, derived from the migration of the CH₂X group to the nitrogen position. This is indeed a quite intriguing case of double selectivity, i) chemoselectivity on the migrating group, ii) regioselectivity on the sense of the migration.

According to our experimental results and DFT-computational modeling studies, these 1,5-migrations on 3*H*-pyrazoles **A** (Scheme 2) proceed through [1s, 5s] concerted mechanisms.^[21,22]

[a] M. C. Pérez-Aguilar, Dr. C. Valdés
Departamento de Química Orgánica e Inorgánica and Instituto
Universitario de Química Organometálica "Enrique Moles".
Universidad de Oviedo
c/ Julián Clavería 8, Oviedo. 33006. Spain
E-mail: acvg@uniovi.es

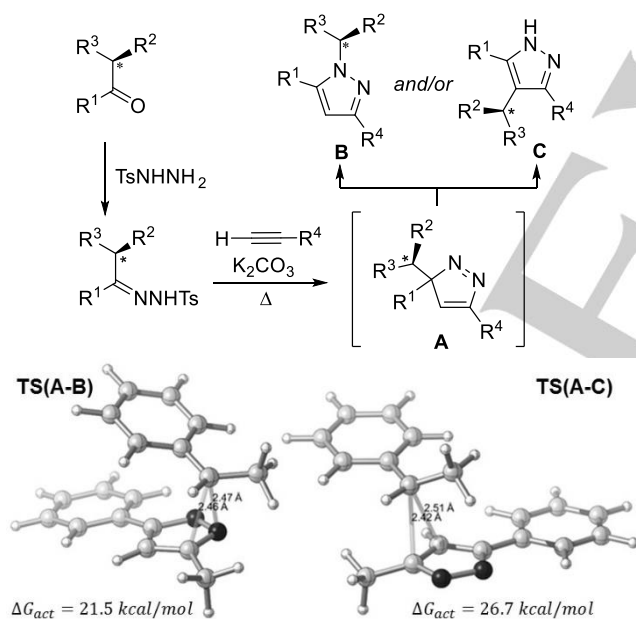
Supporting information for this article is given via a link at the end of the document. (Please delete this text if not appropriate)

COMMUNICATION

Thus, the migration of stereogenic groups should take place with retention of configuration in the migrating group.

Noteworthy, 1,5-sigmatropic rearrangements with retention of configuration in the migrating group, although theoretically predicted by the Woodward-Hoffmann rules, are very rare. To the best of our knowledge, the classic example of the stereospecific rearrangement of a methyl-substituted spiro[4.4]nona-1,3-diene stands as the unique example of a 1,5-rearrangement stereoretentive on the migrating group.^[23-25] Additionally, no synthetic application oriented to the preparation of enantiomerically enriched materials has been developed based on this principle.

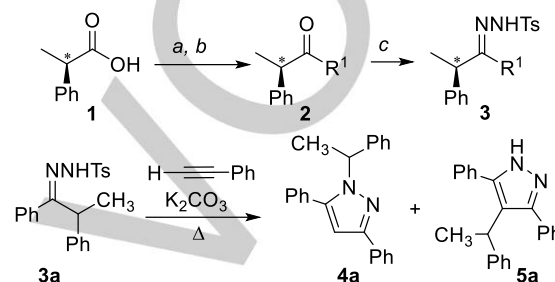
We have previously shown that tosylhydrazones can be employed to achieve transformations of α -chiral ketones with preservation of the configuration of the α -carbon, in both Pd-catalyzed processes and intramolecular [3+2]-cycloadditions.^[26] Taking all this expertise together, we decided to investigate the employment of tosylhydrazones derived from α -chiral ketones in the cycloaddition/rearrangement cascade as a model to study the [1,5]-sigmatropic shift with migration of a stereogenic center. Additionally, we also anticipated that it might represent a novel way to prepare enantiomerically enriched chiral pyrazoles with appealing structures for medicinal chemistry (Scheme 2).



Scheme 2. Proposed synthesis of chiral pyrazoles through a cascade process involving a [1,5]-sigmatropic rearrangement with retention of configuration on the migrating group. **TS(A-B)** and **TS(A-C)**: transition states predicted for the [1,5]-sigmatropic rearrangements on **A** leading to the chiral *N*-substituted and *NH*-pyrazoles **B** and **C** respectively (b3lyp/6-311++G** (PCM, 1,4-dioxane).^[20]

We initiated our study with α -chiral ketones **2**, which can be obtained in enantiomerically pure form from commercially available carboxylic acid **1** (see supplementary material for details and experimental procedures). Preliminary experiments from the racemic ketone **2a** ($R^1 = \text{Ph}$) showed that the cascade sequence proceeded with good yield and moderate regioselectivity

(Scheme 3). An array of reactions were carried out on the model system to establish proper experimental conditions, by modifying solvent, temperature and base. Nevertheless, the conditions developed in our previous work (K_2CO_3 , 1,4-dioxane, 110 °C) turned out to be appropriate again. As expected, the 1,3,5-trisubstituted pyrazole **4a** turned out to be the major isomer (6: 1, **4a**: **5a** ratio as determined by ^1H NMR on the reaction crude and GC/MS),^[18] which could be very easily obtained in pure form after chromatography, due to the very different eluting properties of both regioisomers.



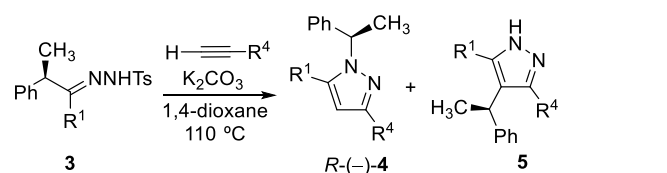
Scheme 3. Synthesis of chiral tosylhydrazones **3**, and preliminary studies on the [3+2]/[1,5] sequence for the synthesis of chiral pyrazole **4a**. a) $\text{NH}(\text{OMe})\text{Me}\cdot\text{HCl}$, $\text{Et}(\text{iPr})_2\text{NH}$, CH_2Cl_2 , -5 °C; b) R^1MgBr , Et_2O , 0 °C, 1h; c) TsNHNH_2 , MeOH , r.t., 6 h. **3a**, $\text{R} = \text{Ph}$; **3b**, $\text{R} = \text{Et}$; **3c**, $\text{R} = \text{Me}$. Complete description of the synthesis of tosylhydrazones **3** from **1** are provided as supporting information.

The same reaction was then conducted with the tosylhydrazone obtained from the enantiomerically pure carboxylic acid (*R*)-(-)-2-phenylpropionic acid. Delightfully, a 99 % ee was obtained, as determined by chiral phase HPLC analysis of the enantiomeric purity. Remarkably, the complete process from the chiral ketone (*R*)-(-)-**2a**, which involves i) formation of the tosylhydrazone **3**, ii) decomposition of **3** to give a diazo compound, iii) 1,3-dipolar cycloaddition, iv) 1,5-sigmatropic rearrangement, had taken place with preservation of the enantiomeric purity (Table 1, entry 1). To determine the absolute configuration of the chiral pyrazole (-)-**4a** ($[\alpha]_{\text{D}}^{24} = -149.3^\circ$), the same compound was synthesized by Mitsunobu reaction of the corresponding *NH*-pyrazole with (*R*)-1-phenylethanol.^[15,27] The opposite enantiomer (*S*)-(+)-**4a** was obtained ($[\alpha]_{\text{D}}^{26} = +151.3^\circ$) as determined by the opposite sign of the optical rotation. This observation establishes the *R* configuration for the stereogenic center of (-)-**4a** and confirms that the cascade reaction has indeed taken place with retention of configuration.

The cascade sequence was then extended to various systems featuring different substituents at R^1 and R^4 (Table 1). In all cases, moderate to high regioselectivities and very high enantiomeric excesses for the major isomer were obtained.^[28,29] The reaction was compatible with an array of substituents on the terminal position of the alkyne, including aromatics with different electronic properties, heteroaromatics, a benzyl substituent, and even a trialkylsilyl group. Regarding the non migrating substituent on the hydrazone R^1 , aryl and primary alkyl groups were tolerated. Importantly, chiral pyrazoles with a stereogenic center attached at the nitrogen and with different substituents at R^1 and R^4 , such as compounds **4b-k**, would be difficult to prepare in a regioselective

manner through alternative methodologies. Approaches involving the alkylation of the N-H pyrazole, such as the Mitsunobu reaction used in the synthesis of (S)-(+)-**4a**, would give a mixture of the two possible regioisomers derived from the alkylation of each nitrogen.

Table 1: Synthesis of chiral pyrazoles *R*-(-)-**4** from α -chiral tosylhydrazones **3** and terminal alkynes.

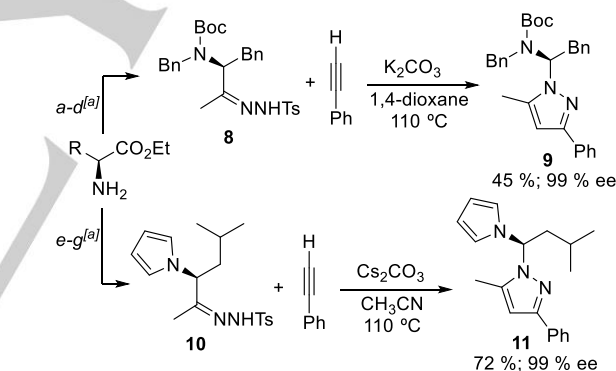
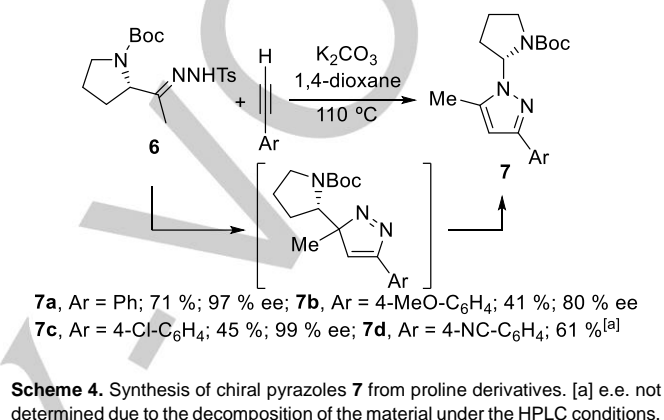


Entry	R ¹	R ⁴	4 : 5 ^[a]	e.e. (%) ^[b]	Yield 4 (%) ^[c]
1	Ph	Ph	86: 14	99	4a 51
2	Ph	4-Tol	85: 15	99	4b 54
3	Ph	4-MeO-C ₆ H ₄	93: 7	93	4c 65
4	Ph	4-NC-C ₆ H ₄	82: 18	98	4d 71
5	Ph	Si(<i>i</i> Pr) ₃	73: 27	99	4e 57
6	Ph	3-Thiophen	88: 12	98	4f 57
7	Ph	Bn	85: 15	97	4g 33
8	Et	Ph	68: 32	92	4h 45
9	Et	4-F-C ₆ H ₄	64: 36	99	4i 58
10	Me	4-NC-C ₆ H ₄	70: 30	97	4j 43
11	Me	4-MeO-C ₆ H ₄	100: 0	- ^[d]	4k 40

[a] Determined by ¹H NMR on the reaction crude. [b] Determined by chiral phase HPLC by comparison with a sample prepared from the racemic tosylhydrazone. [c] Isolated yield of the major isomer **4** after column chromatography. [d] e.e. not determined due to the decomposition of the material under the HPLC conditions.

To expand the scope of the synthesis of *N*-chiral pyrazoles to different classes of chiral ketones, we decided to explore the reaction with the tosylhydrazones of α -aminoketones derived from α -amino acids. Indeed, the reactions of *L*-proline derived chiral tosylhydrazone **6**^[26a] with terminal alkynes gave rise to the *N*-substituted pyrazoles **7** with complete regioselectivity (Scheme 4), as the NH-pyrazole derived from the migration to C4 was not even detected. Again, the cascade process proceeded with nearly perfect retention of configuration in most cases, furnishing the pyrazoles **7** with very high enantiomeric ratio.^[29] Similarly, starting from *N*-Bn-*N*-Boc-(*L*)-phenylalanine, the tosylhydrazone **8** was prepared. The cycloaddition/rearrangement sequence led to the *N*-chiral pyrazole **9** as unique regioisomer, and importantly with 99 % ee (Scheme 5).

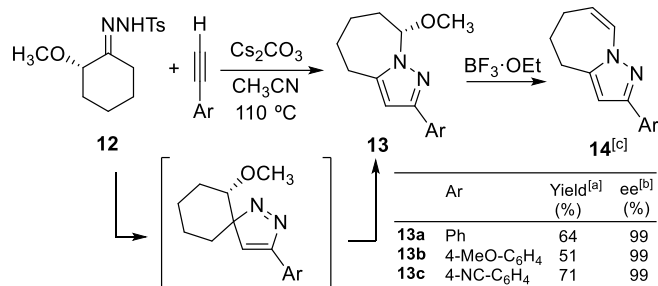
In our previous communication,^[18] we had reported that tosylhydrazones derived from α -*N*-azole substituted ketones, led to the 1,3,5-trisubstituted pyrazoles with high yields and total regioselectivity. Therefore, we decided to explore the same reaction with the analogous chiral derivatives. To this aim, chiral tosylhydrazone **10** was prepared from *L*-Leucine in enantiomerically pure form (Scheme 5). As expected, the 1,3-dipolar cycloaddition/1,5-rearrangement occurred with total regioselectivity, leading to the chiral 1-(1*H*-1-pyrrolyl)ethyl-1*H*-pyrazole **11** with complete retention of configuration (99 % ee).



Finally, we turned our attention into tosylhydrazones derived from cyclic ketones. The hydrazone of 2-methoxycyclohexanone **12** was chosen for this study. After some experimentation, it was found that the cycloaddition/rearrangement sequence proceeded successfully by performing the reaction in CH₃CN and employing Cs₂CO₃ as base, leading to the pyrazole **13**. Interestingly, treatment of the reaction mixture with BF₃·OEt₂ led quantitatively to the new pyrazole **14** with loss of methanol (Scheme 6).

Noteworthy, previous examples of the cycloaddition/rearrangement cascade on cyclic tosylhydrazones furnished 3,4,5-trisubstituted pyrazoles with counterclockwise migration to C4.^[18,19] Thus, in the examples above, the presence of the methoxy group is essential to drive the reaction towards the formation of the pyrazoles **13**. Importantly, determination of the

enantiomeric purity on the products derived from the enantiomerically pure tosylhydrazone revealed an enantiomeric ratio > 99:1, indicating that the whole process had proceeded again with complete preservation of the chiral information.



Scheme 6. Synthesis of chiral fused pyrazoles **13**. [a] Isolated yield of the major isomer **13** after column chromatography. [b] ee determined by chiral phase HPLC by comparison with a sample prepared from the racemic tosylhydrazone. [c] Formed upon addition of BF₃·OEt₂ to the reaction mixture.

As summary, we have presented herein a straightforward synthesis of unprecedented chiral pyrazoles from terminal alkynes and α -chiral-*N*-tosylhydrazones, through a cascade process that involves a 1,3-dipolar cycloaddition followed by a 1,5-sigmatropic rearrangement. It is important to note that the adequate selection of substituents in the starting tosylhydrazones leads to reactions that are highly selective in three different levels: i) chemoselectivity: one of the two possible groups undergoes migration; ii) regioselectivity: the migration takes place preferentially to one of the two possible positions; iii) stereospecificity: the migration of stereogenic groups occurs with retention of configuration. From a mechanistic point of view, to the best of our knowledge, we have provided here the first 1,5-sigmatropic rearrangements with retention of configuration on the migration group that do not involve spirocyclic systems, and also that employ enantiomerically pure materials. Therefore, these are unique examples of a largely anticipated stereospecific transformation. Finally, and taking into account the ready availability of the starting materials required for these reactions, these results open the possibility of developing applications of these new classes of pyrazoles in medicinal chemistry and as chiral ligands for transition metals.

Acknowledgements

Financial support of this work by Ministerio de Economía y Competitividad of Spain (Grant: MINECO-CTQ2013-41336-P). A FPI predoctoral fellowship to M. C. P.-A. is gratefully acknowledged.

Keywords: pyrazole • tosylhydrazone • [1,5]-sigmatropic rearrangement • diazo compound • stereospecific

[1] J. Elguero, A. M. S. Silva, A. C. Tomé in *Modern Heterocyclic Chemistry*, Vol. 2 (Eds. J. Alvarez-Builla, J. J. Vaquero, J. Barluenga) Wiley-VCH, Weinheim, **2011**, pp. 635-725.

- [2] A. Schmidt, A. Dreger, *Curr. Org. Chem.* **2011**, *15*, 1423
- [3] T. D. Penning et al. *J. Med. Chem.* **1997**, *40*, 1347.
- [4] R. Riedel, *Arzneim.-Forsch.* **1981**, *31*, 655.
- [5] M. L. Isidro, F. Cordido, *Mini-Rev. Med. Chem.* **2009**, *9*, 664.
- [6] For a selection some recent examples: a) R. B. Pathak, P. T. Chovatia, H. H. Parekh, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5129; b) T. B. Abu, M. Arnsmann, F. Totzke, J. E. Ehler, M. H. G. Kubbutat, C. Schachtele, M. O. Zimmermann, P. Koch, F. M. Boeckler, S. A. Laufer, *J. Med. Chem.* **2012**, *55*, 961; c) S. R. Donohue, R. F. Dannals, C. Halldin, V. W. Pike, *J. Med. Chem.* **2012**, *54*, 2961; d) F. A. Ragab, N. M. Abdel Gawad, H. H. Georgey, M. F. Said, *Eur. J. Med. Chem.* **2013**, *63*, 645; B. S. Park, M. M. Al-Sanea, A. Z. Abdelazem, H. M. Park, E. J. Roh, H.-M. Park, K. H. Yoo, T. Sim, J. S. Tae, S. H. Lee, *Bioorg. Med. Chem.* **2014**, *22*, 3871.
- [7] For some recent reviews: a) H. Kumar, D. Saini, S. Jain, N. Jain, *Eur. J. Med. Chem.* **2013**, *70*, 248; b) S. G. Kucukguzel, S. Senkardes, *Eur. J. Med. Chem.* **2015**, *5*, 786.
- [8] See for instance a) F. Keter, J. Darkwa, *Biometals* **2012**, *25*, 9; b) L. Bellarosa, J. Diez, J. Gimeno, A. Lledos, F. J. Suarez, G. Ujaque, C. Vicent, *Chem. Eur. J.* **2012**, *18*, 7749.
- [9] J. Pérez, L. Riera, *Eur. J. Inorg. Chem.* **2009**, 4913.
- [10] For some examples see: a) E. Cavero, S. Uriel, P. Romero, J. L. Serrano, R. Giménez, *J. Am. Chem. Soc.* **2007**, *129*, 11608; b) E. Beltrán, E. Cavero, J. Barberá, J. L. Serrano, A. Elduque, R. Giménez, *Chem. Eur. J.* **2009**, *15*, 9017. c) S. Moyano, J. L. Serrano, A. Elduque, R. Giménez, *Soft Matter* **2012**, *8*, 6799
- [11] For a recent review see: S. Fustero, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev.* **2011**, *111*, 6984.
- [12] For some relevant recent examples: a) Y. Kong, M. Tang, Y. Wang, *Org. Lett.* **2014**, *16*, 576; b) L. Hao, J.-J. Hong, J. Zhu, Z.-P. Zhan, *Chem. Eur. J.* **2013**, *19*, 5715; c) J. Zhang, Y. Shao, H. Wang, Q. Luo, J. Chen, D. Xu, X. Wan, *Org. Lett.* **2014**, *16*, 3312; d) E. Decuyper, S. Specklin, S. Gabillet, D. Audisio, H. Liu, L. Plougastel, S. Kolodych, F. Taran, *Org. Lett.* **2015**, *17*, 362; e) W. Yang, S. Ye, D. Fanning, T. Coon, Y. Schmidt, P. Krenitsky, D. Stamos, J.-Q. Yu, *Angew. Chem.* **2015**, *127*, 2531; *Angew. Chem. Int. Ed.* **2015**, *54*, 2501; f) J. Comas-Barceló, R. S. Foster, B. Fiser, E. Gomez-Bengoa, J. P. A. Harrity, *Chem. Eur. J.* **2015**, *21*, 3257; g) S. Mantenuto, F. Mantellini, G. Favi, O. A. Attanasi, *Org. Lett.* **2015**, *17*, 2014
- [13] a) F. Brookfield, J. Burch, R. A. Goldsmith, B. Hu, K. H. L. Lau, C. H. Mackinnon, D. F. Ortwine, Z. Pei, G. Wu, P.-W. Yuen, Y. Zhang, WO2014023258, Hoffmann-La Roche AG, Switz.; 2014. b) S. Stokes, N. Foloppe, A. Fiumana, M. Drysdale, S. Bedford, P. Webb, WO2009093012, Vernalis R & D Ltd, 2009.
- [14] C. M. Park, D. J. Jeon, *Org. Biomol. Chem.* **2012**, *10*, 2613.
- [15] H. Mastalerz, M. Chang, P. Chen, P. Dextraze, B. E. Fink, A. Gavai, B. Goyal, W.-C. Han, W. Johnson, D. Langley, F. Y. Lee, P. Marathe, A. Mathur, S. Oppenheimer, E. Ruediger, J. Tarrant, J. S. Tokarski, G. D. Vite, D. M. Vyas, H. Wong, T. W. Wong, H. Zhang, G. Zhang, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2036.
- [16] X. Hu, B. Gao, Y. Chu, W. Li, X. Liu, L. Lin, X. Feng, *Chem. Eur. J.* **2012**, *18*, 3473.
- [17] Q. Lin, D. Meloni, Y. Pan, M. Xia, J. Rodgers, S. Shepard, M. Li, L. Galya, B. Metcalf, T.-Y. Yue, P. Liu, J. Zhou, *Org. Lett.* **2009**, *11*, 1999.
- [18] M. C. Pérez-Aguilar, C. Valdés, *Angew. Chem.* **2013**, *125*, 7360; *Angew. Chem. Int. Ed.* **2013**, *52*, 7219.
- [19] In a very recent publication employing terminal alkynes and cycloalkyltosylhydrazones, under very similar reaction conditions, the 3*H*-pyrazoles could be isolated in some cases: R. R. Merchant, D. M. Allwood, D. C. Blakemore, S. V. Ley, *J. Org. Chem.* **2014**, *79*, 8800.
- [20] a) Y.-P. Yen, S.-F. Chen, Z.-C. Heng, J.-C. Huang, L.-C. Kao, C.-C. Lai, R. S. H. Liu, *Heterocycles* **2001**, *55*, 1859; b) K. Banert, O. Plefka, *Angew. Chem.* **2011**, *123*, 6295; *Angew. Chem. Int. Ed.* **2011**, *50*, 6171; c) D. Gladow, S. Doniz-Kettenmann, H.-U. Reissig, *Helv. Chim. Acta* **2014**, *97*, 808.
- [21] See supporting information for details on computational studies.

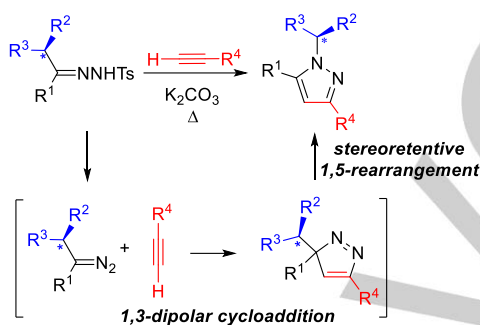
- [22] For the [1,5]-sigmatropic rearrangements on 3*H*-pyrazole-5-carboxylates and 3*H*-pyrazoles-4,5-dicarboxylates, depending on the nature of the migrating substituent, mechanisms that span from concerted 1,5-sigmatropic rearrangements to ionic stepwise processes involving the presence of ion pairs have been proposed: a) E. A. Jefferson, J. Warkentin, *J. Am. Chem. Soc.* **1992**, *114*, 6318; b) E. A. Jefferson, J. Warkentin, *J. Org. Chem.* **1994**, *59*, 455.
- [23] a) M. A. M. Boersma, J. W. De Haan, H. Kloosterziel, L. J. M. Van de Ven, *J. Chem. Soc. Chem. Commun.* **1970**, 1168; b) K. B. Carpenter, *J. Am. Chem. Soc.* **1995**, *117*, 6336.
- [24] [1,5]-Rearrangements on bicyclo[2.1.0]heptadienyl derivatives, so called "walk rearrangements" take place with inversion at the migrating center: a) F.-G. Klärner, B. Brassel, *J. Am. Chem. Soc.* **1980**, *102*, 2469. c) W. T. Borden, J. G. Lee, S. D. Young, *J. Am. Chem. Soc.* **1980**, *102*, 4841.
- [25] Alkyl shifts with retention of configuration on the migrating group are known for 1,2-shifts such as pinacol and Wagner-Meerwein rearrangements: a) J. J. Beggs, M. B. Meyers, *J. Chem. Soc. B* **1970**, 930; b) W. Kirmse, W. Gruber, J. Knist, *Chem. Ber.* **1973**, *106*, 1376; c) T. Shono, K. Fujita, S. Kumai, *Tetrahedron Lett.* **1973**, *14*, 3123. d) G. I. Borodkin, Y. B. Panova, M. M. Shakirov, V. G. Shubin, *J. Org. Chem. USSR* **1983**, *19*, 103; d) J. D. Trzuppek, D. Lee, B. M. Crowley, V. M. Marathias, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 8506; e) C. Zheng, Q.-F. Wu, S.-L. You, *J. Org. Chem.* **2013**, *78*, 4357.
- [26] a) J. Barluenga, M. Escribano, F. Aznar, C. Valdés, *Angew. Chem.* **2010**, *122*, 7008; *Angew. Chem. Int. Ed.* **2010**, *49*, 6856; b) J. Barluenga, N. Quiñones, M.-P. Cabal, F. Aznar, C. Valdés, *Angew. Chem.* **2011**, *123*, 2398; *Angew. Chem. Int. Ed.* **2011**, *50*, 2350; c) R. Barroso, M. Escribano, M.-P. Cabal, C. Valdes, *Eur. J. Org. Chem.* **2014**, *2014*, 1672.
- [27] The description of the synthesis of (+)-**4a** through the Mitsunobu reaction is included in the supporting information.
- [28] The employment of a freshly prepared tosylhydrazone is of utmost importance to obtain the pyrazole with high and reproducible enantiomeric ratio. Tosylhydrazones **3** that had been stored for some time provided pyrazoles with lower enantiomeric purity.
- [29] Partial epimerization over the time have been observed for some pyrazoles **4** and **7**. To obtain reliable values of the enantiomeric ratio it is important to conduct the HPLC analysis readily after the isolation.

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

Layout 1:

COMMUNICATION

Retention of configuration in [1,5]-sigmatropic shifts, predicted by the Woodward-Hoffmann rules but very poorly documented experimentally, is observed in the reactions of α -chiral tosylhydrazones with terminal alkynes. The chiral pyrazoles obtained are formed through a cascade involving a 1,3-dipolar cycloaddition followed by a site-regio- and stereospecific [1s,5s]-sigmatropic rearrangement.



M. Carmen Pérez-Aguilar, Carlos Valdés*

Page No. – Page No.

Synthesis of chiral pyrazoles through a 1,3-dipolar cycloaddition/[1,5]-sigmatropic rearrangement with stereoretentive migration of a stereogenic group