**Diazo Compounds**

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# Synthesis of Chiral Pyrazoles: A 1,3-Dipolar Cycloaddition/[1,5] Sigmatropic Rearrangement with Stereoretentive Migration of a Stereogenic Group

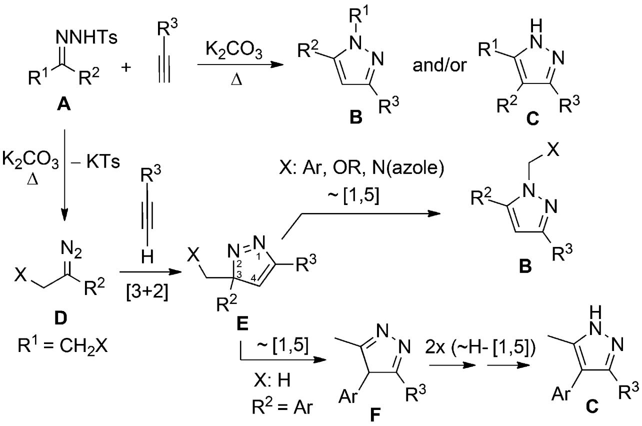
*M. Carmen Pérez-Aguilar and Carlos Valdés**

**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. The cascade reaction includes 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 has been successfully applied to the synthesis of structurally diverse chiral pyrazoles through α-chiral tosylhydrazones, obtained from α-phenylpropionic acid, α-amino acids, and 2-methoxycyclohexanone. Notably, the stereoretention of the [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 use as antimicrobials, analgesics, and anti-inflamatory agents, as well as 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 pyrazole is a chiral pyrazole having a stereogenic carbon center attached at the N-position. Limited examples of this type of chiral pyrazole with biological activity have been reported,[13] but their usefulness has been hampered by the lack of general methods for their preparation. Chiral pyrazoles with a sterogenic center attached at the nitrogen atom 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 pyrazoles.

We have recently reported the regioselective synthesis of the 1,3,5-trisubstituted pyrazoles **B** and 3,4,5-trisubstituted pyrazoles **C** from the reaction of tosylhydrazones **A** 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 **D**, 2) 1,3-dipolar cycloaddition of the diazo compound with the terminal alkyne to form a 3*H*-pyrazole **E**,[19,20] 3) [1,5] sigmatropic rearrangement which may lead to either the 1,3,5-substituted 1*H*-pyrazole **B** or the new 4*H*-pyrazole **F**. The latter will undergo additional [1,5] sigmatropic shifts to provide **C** (Scheme 1). The step that determines the regioselectivity of the reaction is the [1,5] sigmatropic rearrangement. For tosylhydrazones derived from acetophenones (X = H, $R^2$ = Ar), the only product obtained is the result of the migration of the aryl group to C4 **C**. In contrast, for 2-substituted acetophenones, in many cases the major or exclusive product obtained is the pyrazole **B**, derived from the migration of the $CH_2X$ group to the nitrogen position. This reaction is indeed an intriguing case of double selectivity: a) chemoselectivity on the migrating group, b) regioselectivity on the sense of the migration.



***Scheme 1.*** Regioselective synthesis of trisubstituted pyrazoles and mechanism proposed. Ts = 4-toluenesulfonyl.

According to our experimental results and DFT computational studies, these [1,5] migrations on the 3*H*-pyrazoles **I** (Scheme 2) proceed through [1*s*,5*s*] concerted mechanisms.[21,22] Thus, the migration of stereogenic groups should

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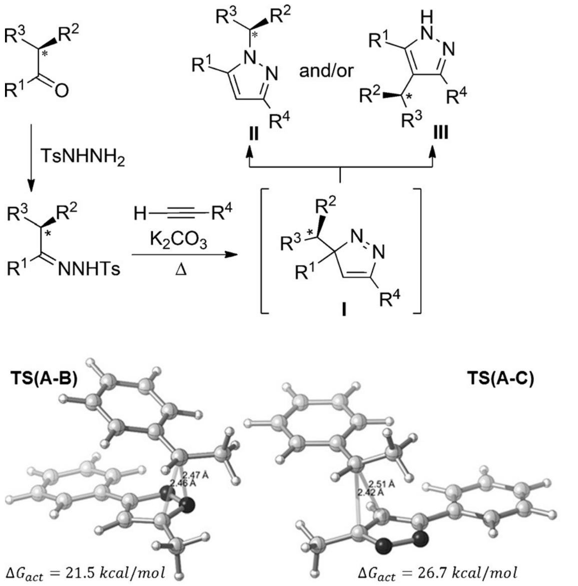
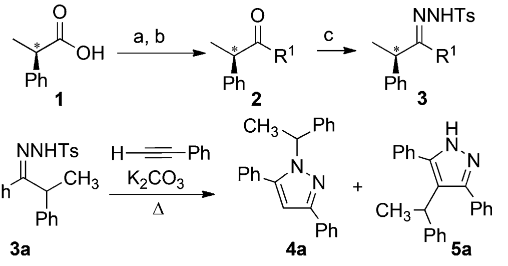


***Scheme 2.*** Proposed synthesis of chiral pyrazoles through a cascade process involving a [1,5] sigmatropic rearrangement with retention of configuration within the migrating group. **TS(A-B)** and **TS(A-C)**: transition states predicted for the [1,5] sigmatropic rearrangement of **I** leading to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



***Scheme 3.*** Synthesis of the chiral tosylhydrazones **3**, and preliminary studies on the reaction sequence for the synthesis of the chiral pyrazole **4a**. a) NH(OMe)Me·HCl, Et($i$Pr)$_2$NH, CH$_2$Cl$_2$, −5 °C; b) R$^1$MgBr, Et$_2$O, 0 °C, 1 h; c) TsNHNH$_2$, MeOH, RT, 6 h. **3a**: R = Ph; **3b**: R = Et; **3c**: R = Me. Complete description of the synthesis of tosylhydrazones **3** from **1** are provided in the Supporting Information.

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 which proceeds with retention of configuration of the migrating group.[23–25] Additionally, no synthetic application oriented towards the preparation of enantiomerically enriched materials has been developed based on this principle.

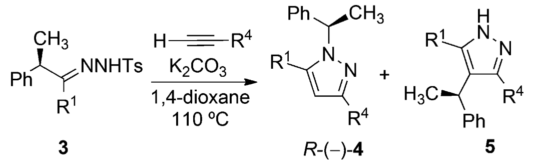
We have previously shown that tosylhydrazones can be employed to achieve transformations of α-chiral ketones with preservation of the configuration of the α-carbon atom, in both palladium-catalyzed processes and intramolecular [3+2] cycloadditions.[26] Taken together, we decided to investigate the employment 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 (Scheme 2). Additionally, we also anticipated that it might represent a novel way to prepare enantiomerically enriched chiral pyrazoles with appealing structures for medicinal chemistry.

We initiated our study with α-chiral ketones (**2**), which can be obtained in enantiomerically pure form from commercially available carboxylic acids (**1**, Scheme 3; see the Supporting Information for details and experimental procedures). Preliminary experiments with the racemic ketone **2a** (R$^1$ = Ph) showed that the cascade sequence proceeded with good yield and moderate regioselectivity. Several 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$_2$CO$_3$, 1,4-dioxane, 110 °C) turned out to be appropriate. As expected, the 1,3,5-trisubstitued pyrazole **4a** was the major isomer (6:1 **4a**/**5a** as determined by $^1$H NMR spectroscopy on the crude reaction mixture and GC/MS),[18] which could be easily obtained in pure form after chromatography.

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. Remarkably, the complete process from the chiral ketone ($R$)-(−)-**2a**, which involves a) formation of the tosylhydrazone **3**, b) decomposition of **3** to give a diazo compound, c) 1,3-dipolar cycloaddition, and d) [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** ($[\alpha]_D^{24} = -149.3°$), the same compound was synthesized by Mitsunobu reaction of the corresponding NH-pyrazole with ($R$)-1-phenylethanol,[15,27] 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, 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, heteroarenes, a benzyl substituent, and even a trialkylsilyl group. Regarding the non-migrating substituent on the hydrazine, R$^1$, aryl and primary alkyl groups were tolerated. Importantly, chiral pyrazoles with a stereogenic center attached to the nitrogen atom and different substituents (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 ($S$)-

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

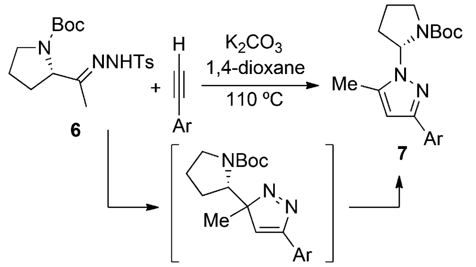


| Entry | R¹ | R⁴ | 4/5[a] | *ee* [%][b] | 4, Yield [%][c] |
|---|---|---|---|---|---|
| 1 | Ph | Ph | 86:14 | 99 | **4a** 51 |
| 2 | Ph | 4-Tol | 85:15 | 99 | **4b** 54 |
| 3 | Ph | 4-MeOC$_6$H$_4$ | 93:7 | 93 | **4c** 65 |
| 4 | Ph | 4-NCC$_6$H$_4$ | 82:18 | 98 | **4d** 71 |
| 5 | Ph | Si(*i*Pr)$_3$ | 73:27 | 99 | **4e** 57 |
| 6 | Ph | 3-thienyl | 88:12 | 98 | **4f** 57 |
| 7 | Ph | Bn | 85:15 | 97 | **4g** 33 |
| 8 | Et | Ph | 68:32 | 92 | **4h** 45 |
| 9 | Et | 4-FC$_6$H$_4$ | 64:36 | 99 | **4i** 58 |
| 10 | Me | 4-NCC$_6$H$_4$ | 70:30 | 97 | **4j** 43 |
| 11 | Me | 4-MeOC$_6$H$_4$ | 100:0 | –[d] | **4k** 40 |

[a] Determined by $^1$H NMR analysis of the reaction crude reaction mixture. [b] Determined by chiral-phase HPLC and comparison with a sample prepared from the racemic tosylhydrazone. [c] Yield of the major isolated isomer **4** after column chromatography. [d] The *ee* value was not determined because of the decomposition of the material under the HPLC conditions.

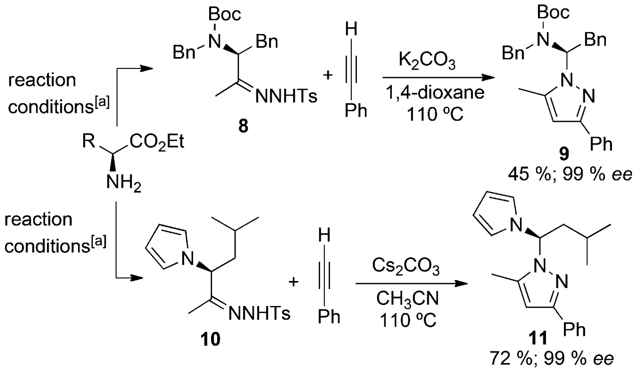
(+)-**4a**, would give a mixture of the two possible regioisomers derived from the alkylation of each nitrogen atom.

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 the L-proline-derived 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, thus furnishing **7** with very high enantiomeric ratios.[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 a unique regioisomer, and importantly with 99% *ee* (Scheme 5).



**7a**, Ar = Ph; 71 %; 97 % *ee*; **7b**, Ar = 4-MeO-C$_6$H$_4$; 41 %; 80 % *ee*
**7c**, Ar = 4-ClC$_6$H$_4$; 45 %; 99 % *ee*; **7d**, Ar = 4-CNC$_6$H$_4$; 61 %[a]

***Scheme 4.*** Synthesis of the chiral pyrazoles **7** from proline derivatives. [a] The *ee* value was not determined because of the decomposition of the material under the HPLC conditions. Boc = *tert*-butoxycarbonyl.

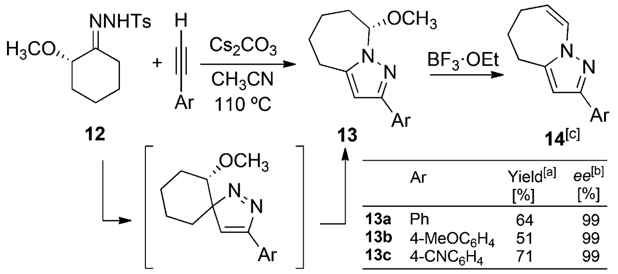


***Scheme 5.*** Synthesis of the chiral pyrazoles **9** and **11**. [a] Synthetic details for the tosylhydrazones **8** and **10** are provided in the Supporting Information.

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 end, the 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, thus 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 to tosylhydrazones derived from cyclic ketones and the hydrazone of the 2-methoxycyclohexanone **12** was chosen for this study (Scheme 6). After some experimentation, it was found that the cycloaddition/rearrangement sequence proceeded successfully by performing the reaction in CH$_3$CN and employing Cs$_2$CO$_3$ as a base, thus leading to the pyrazole **13**. Interestingly, treatment of the reaction mixture with BF$_3$·OEt$_2$ led quantitatively to the new pyrazole **14** by loss of methanol.

Notably, previous examples of the cycloaddition/rearrangement cascade on cyclic tosylhydrazones furnished 3,4,5,-trisubstitued 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



| | Ar | Yield[a] [%] | ee[b] [%] |
|---|---|---|---|
| **13a** | Ph | 64 | 99 |
| **13b** | 4-MeOC$_6$H$_4$ | 51 | 99 |
| **13c** | 4-CNC$_6$H$_4$ | 71 | 99 |

***Scheme 6.*** Synthesis of chiral fused pyrazoles **13**. [a] Yield of the major isolated isomer **13** after column chromatography. [b] The *ee* value was determined by chiral-phase HPLC and comparison with a sample prepared from the racemic tosylhydrazone. [c] Formed upon addition of BF$_3$·OEt$_2$ to the reaction mixture.

formation of the pyrazoles **13**. Importantly, determination of the enantiomeric purity on the products derived from the enantiomerically pure tosylhydrazone revealed an enantiomeric ratio of greater than 99:1, thus indicating that the whole process had proceeded again with complete preservation of the chiral information.

In summary, we have presented herein a straightforward synthesis of unprecedented chiral pyrazoles from terminal alkynes and α-chiral-N-tosylhydrazones, through a cascade process which involves a 1,3-dipolar cycloaddition followed by a [1,5] sigmatropic rearrangement. It is important to note that the appropriate selection of substituents in the starting tosylhydrazones leads to reactions that are highly selective on three different levels: 1) chemoselectivity: one of the two possible groups undergoes migration; 2) regioselectivity: the migration takes place preferentially to one of the two possible positions; 3) 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 within the migrating group which does not involve spirocyclic systems. The reaction also employs 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.

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[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 outmost importance to obtain the pyrazole with high and reproducible enantiomeric ratio. The tosylhydrazones **3**, which had been stored for some time, provided pyrazoles with lower enantiomeric purity.

[29] Partial epimerization over the time has been observed for some pyrazoles (**4** and **7**). To obtain reliable values of the enantiomeric ratio it is important to conduct the HPLC analysis directly after the isolation.

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