RESEARCH ARTICLE doi.org/10.1002/adsc.202400103

Advanced Synthesis & Catalysis

N-Tosylhydrazones as *[N,N]* Synthons in Heterocyclic Chemistry: Synthesis of 3,5-Disubstituted *N*-Alkenyl-1*H*-pyrazoles

Antonio Velázquez-Stavínov,[a] Helena F. Piedra,[a] Aarón Gutiérrez-Collar,[a, d] Manuel Álvarez-Márquez,[a] M. Isabel Menéndez,[b] Isabel Merino,[c] María-Paz Cabal,[a,*] and Enrique Aguilar[a,*]

[a] Centro de Innovación en Química Avanzada (ORFEO-CINQA). Instituto Universitario de Química Organometálica "Enrique Moles". Departamento de Química Orgánica e Inorgánica. Universidad de Oviedo. C/Julián Clavería, 8. 33006, Oviedo, Spain
Phone: +34-985102990
Fax: +34-985103446
Phone: +34-985104951
Fax: +34-985103446
E-mail: pcabal@uniovi.es; eah@uniovi.es
[b] Departamento de Química Física y Analítica. Universidad de Oviedo. C/Julián Clavería, 8. 33006, Oviedo, Spain
[c] Servicios Científico-Técnicos. Unidad de RMN. Universidad de Oviedo. C/Fernando Bongera, s/n, 33006, Oviedo, Spain
[d] Present address: Sygnature Discovery Ltd, Bio City, Pennyfoot St, Nottingham NG1 1GR, UK

Manuscript received: January 27, 2024; Revised manuscript received: March 19, 2024;
Version of record online: April 24, 2024

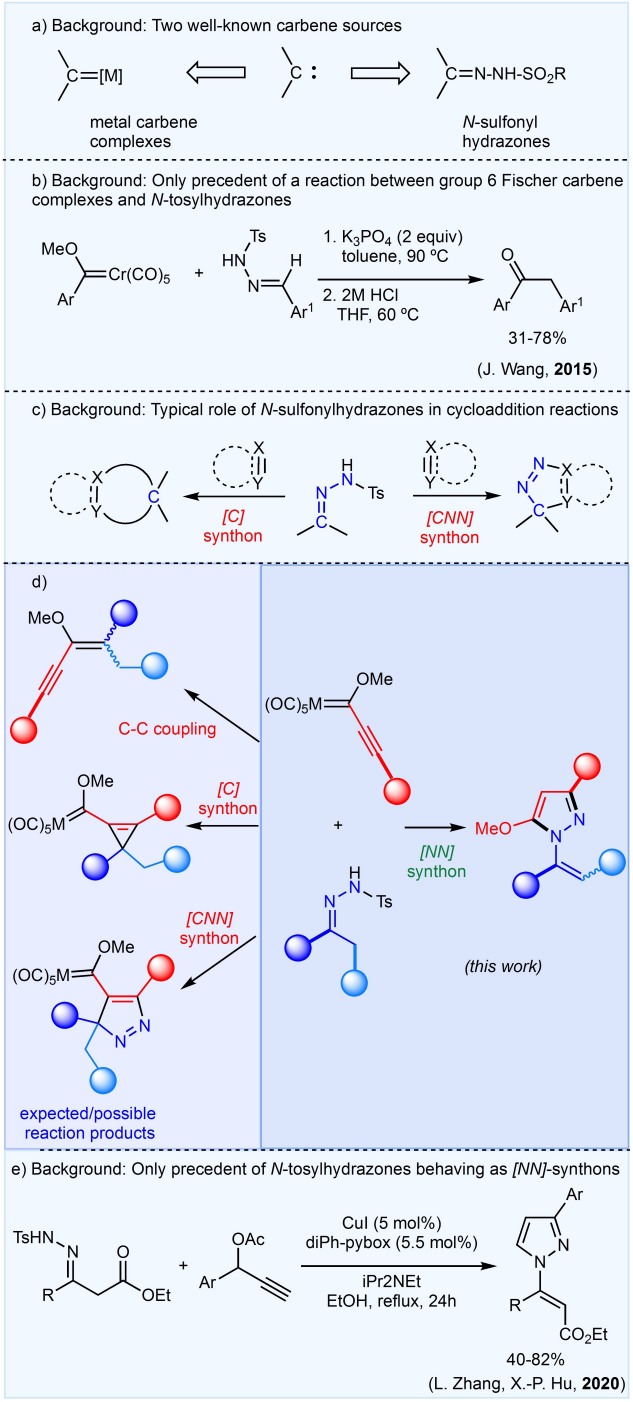
Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202400103

Abstract: A new mode of reactivity of *N*-sulfonylhydrazones towards alkynes is described: ketone-derived *N*-tosylhydrazones (NTHs) bearing α-H atoms *behave as [NN] synthons* in their reactions with alkoxy alkynyl Fischer carbene complexes (FCCs) and only the two N atoms are incorporated into the newly formed pyrazole ring. The scope of the reaction, leading to 5-methoxy-*N*-alkenyl pyrazoles, proved to be wide regarding both partners; thus, a variety of aryl and primary, secondary, and tertiary alkyl substituents are tolerated within the FCC, while aryl alkyl NTHs, symmetric and asymmetric dialkyl NTHs and NTHs derived of cyclic ketones can be also employed. In addition, the reaction can be performed at large scale and applied for late-stage diversification of natural products. A reasonable reaction mechanism is also proposed, which is supported by deuteration experiments and DFT calculations.

Keywords: Carbenes; Cycloaddition; Heterocycles; Hydrazones; Pyrazoles

Introduction

Carbenes, highly useful neutral divalent reaction intermediates, rarely exist as free stable species and they usually need to be prepared from appropriate precursors, of which metal carbene complexes and *N*-sulfonyl hydrazones are two prime sources (Scheme 1a). Interestingly, both types of compounds have found paramount application in synthetic organic chemistry. Particularly, group 6 metal Fischer carbene complexes (FCCs) have shown to be highly valuable reagents,[1] not only as carbene precursors but also by displaying a wide-range of reactivity patterns (*chemical multitalents*).[2] Specifically, they have found remarkable application in heterocyclic synthesis, becoming appropriate starting materials for the preparation of three- to eight-membered ring heterocycles.[3] Noting the popularity of the classic Bamford-Stevens and Shapiro reactions, the great synthetic versatility of *N*-tosylhydrazones (NTHs) has been demonstrated in organic chemistry[4] both as precursors of diazo compounds[5] and in cross-coupling reactions, either catalyzed by a metal[6] or without metal catalysis.[7] In addition, the only example to date of a reaction



Scheme 1. Background and purpose of this research.

involving both tosylhydrazones and Fischer carbene complexes, reported by J. Wang, describes the coupling between aromatic aldehyde derived tosylhydrazones and methoxy aryl chromium carbene complexes for the synthesis of 1,2-diarylethanones (Scheme 1b).[8] NTHs have shown indeed a chameleonic behavior in their reactions with alkynes, operating either as synthons of three atom units (*[CNN]* synthons, which is the most usual manner) to form pyrazoles in [3+2] cycloaddition reactions[9,10] or as synthons of a carbon atom (*[C]* synthons) in cyclopropenation reactions,[11] depending mainly on the nature of the tosylhydrazone (Scheme 1c). They also can act as *[C]* synthons with alkenes[12] and fullerenes[13] to form cyclopropanes.

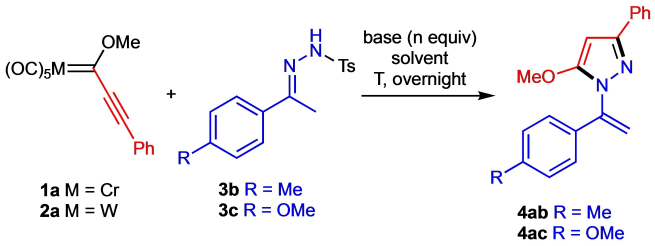
With this state of the art, we have planned to analyze the behavior of these two carbene sources under the same reaction conditions by extending the reactivity of NTHs to a very special class of alkynes: alkoxy alkynyl group 6 metal FCCs. By considering the functional groups present in the FCC individually, three main patterns were foreseen for the reaction between these two species (Scheme 1d): (i) a C–C coupling, not really expected because of the low propensity to C–C coupling of alkoxy alkynyl FCCs; (ii) a [2+1] or (iii) a [3+2] cycloaddition reactions with the NTH acting respectively as a *[C]*- or a *[CNN]*-synthon. However, the product obtained under the tested reaction conditions turned out to be an alkenyl pyrazole derived from a behavior of the NTH as a *[NN]* synthon. When those initial results were reached, they represented an unprecedent finding as, for the first time, only the two N atoms partake in the cycloaddition reaction.[14] However, more recently, such behavior has also been observed in the copper(I)-catalyzed reaction of NTHs derived of β-ketoesters and aromatic propargyl acetates (Scheme 1e).[15]

Although the *[NN]* synthon behavior of NTHs is, indeed, a major finding reported in this current research, it is also worth mentioning that pyrazoles show a wide range of biological and pharmaceutical activities,[16] so a variety of synthetic approaches to them have been developed;[17] however, the number of methods to prepare *N*-alkenyl pyrazoles is rather limited,[10] and they are mainly based in the direct addition of *N*-unsubstituted pyrazoles to alkynes.[18] Therefore, the development of new protocols to access *N*-alkenyl pyrazoles involving the *de novo* construction of the pyrazole ring is highly valued.

Results and Discussion

With all these considerations, our initial hypothesis was tested by employing the same conditions previously used for the reactions between *N*-tosyl hydrazones and alkynes and leaving the reaction to proceed overnight.[9e] However, only a complex mixture was obtained (Table 1, entry 1). In addition, no reaction was observed at room temperature (entry 2), while compound **4ab** could be isolated at 60 °C although in 14% yield. Solvent (entries 3–5) and base (entries 3, 6–8) screening indicated that 1,4-dioxane and K_2CO_3 could be a good combination, although THF and NaH showed promising results too. Nevertheless, several other experiments with NaH as base (not included in table) did not improve yields. A slight improvement

Table 1. Optimization of the reaction conditions.



Entry[a]	FCC	Solvent/Conc (M)[b]	T (°C)	Base (n equiv.)	Reaction Product	Yield[c]
1	**1a**	1,4-dioxane/0.03	reflux	K_2CO_3 (2.0)	Complex mixture	–
2[d]	**1a**	1,4-dioxane/0.03	rt	K_2CO_3 (2.2)	n.r.	–
3	**1a**	Toluene/0.1	60	K_2CO_3 (1.0)	**4ab**	14
4	**1a**	1,4-dioxane/0.1	60	K_2CO_3 (2.0)	**4ab**	27
5	**1a**	THF/0.1	60	K_2CO_3 (2.0)	**4ab**	31
6	**1a**	THF/0.1	rt	NaH (1.1)	**4ab**	31
7	**1a**	1,4-dioxane/0.1	60	NaOH (2.0)	**4ab**	17
8	**1a**	1,4-dioxane/0.1	60	KO^{t}Bu (1.1)	**4ab**	17
9[e]	**1a**	1,4-dioxane/0.1	60	K_2CO_3 (2.0)	**4ab**	35
10	**2a**	1,4-dioxane/0.1	reflux	K_2CO_3 (2.0)	**4ab**	38
11	**2a**	1,4-dioxane/0.1	reflux	K_2CO_3 (2.0)	**4ac**	40
12	**2a**	1,4-dioxane/0.1	60	K_2CO_3 (8.5)	**4ac**	46
13[f]	**2a**	1,4-dioxane/0.2	60	K_2CO_3 (10.0)	**4ac**	62
14[g]	**2a**	1,4-dioxane/0.15	60	K_2CO_3 (5.0)	**4ac**	60
15[g]	**2a**	DMF/0.1	60	K_2CO_3(5.0)	**4ac**	86

[a] Reaction scale: limiting reagent (0.1 mmol), except for entries 2 (0.09 mmol) and 13 (0.3 mmol). Stoichiometry: FCC/hydrazone = 1/1, unless otherwise indicated.
[b] Molar concentration of hydrazone.
[c] Isolated yield.
[d] **3b** (1.1 equiv.).
[e] **1a** (2.0 equiv.).
[f] **3c** (2.0 equiv.).
[g] **3c** (1.5 equiv.); optimized reaction conditions (reaction time: 2 h).

was reached when the amount of FCC was increased (entry 9). Performing the reaction under reflux showed that the concentration played an important role in the reaction outcome (see entry 1 vs entries 10,11). Tuning the amount of NTH (entries 13–14) and increasing that of K_2CO_3 (entries 12–14) allowed an important rising of the reaction yield. Part of the optimization screening was performed with tungsten FCC **2a** instead of chromium FCC **1a**; in general, higher reaction yields were reached when **2a** was employed (entries 10–14 vs entries 1–9), probably because of the higher stability of tungsten FCCs. Altogether, with the employment of DMF as solvent, we established the optimized reaction conditions to be those reported in entry 15: tungsten FCC (1 equiv.), NTH (1.5 equiv.), K_2CO_3 (5 equiv.) at 60 °C for 2 h.

The reaction was completely regioselective. The structure of the product was established by 1D (^{1}H, ^{13}C) and 2D (COSY, HSQC, HMBC, and NOESY) NMR experiments for compound **4ab**. The regiochemistry was established through a long range optimized ^{1}H^{15}N HMBC experiment (J_{HN} = 3 Hz) which allowed the detection of $^4J_{HN}$ coupling constants of the N atoms with their surrounding hydrogen atoms.[19] The observation of a cross peak between the ortho H atoms of the phenyl group and the imine-type N atom (δ ^{15}N = 279 ppm), together with an additional cross peak between the ortho H atoms of the tolyl group with the amine-type N atom (δ ^{15}N = 195 ppm) ascertained the proposed structure **4ab** and discarded an alternative regioisomer as **5ab**, whose spectrum should only display cross peaks at the same N chemical shift for the two types of ortho H atoms (Figure 1).

The analysis of the reaction scope was initiated with Ph-substituted FCC **2a** and shown to display wide tolerance for *para*-substitution at the aryl ring of acetophenone derived NTHs, either with electron-donating or electron-withdrawing groups, leading to pyrazoles **4aa-af** in good to high yields (Scheme 2A). As expected, placement of a methyl group on the vinyl moiety leads to the formation of both E and Z diastereomers (**4ag**) in which the *E*-isomer predominates. On the other hand, pyrazoles bearing different substitution patterns on the aromatic ring (*meta*,

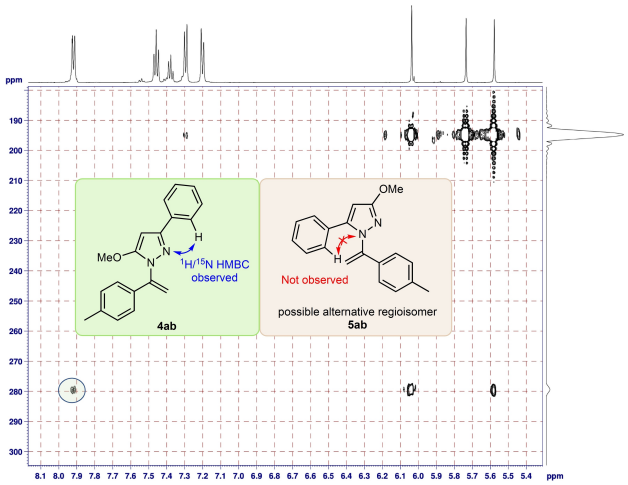


Figure 1. ^{1}H^{15}N HMBC experiment for the determination of the regiochemistry of the reaction.

4ah,**ai**; *ortho*, **4aj**) are also formed in similar or slightly lower yields to that for *p*-substitution. 2-Benzothiophene-derived pyrazole **4ak** was also synthesized although in lower yield.

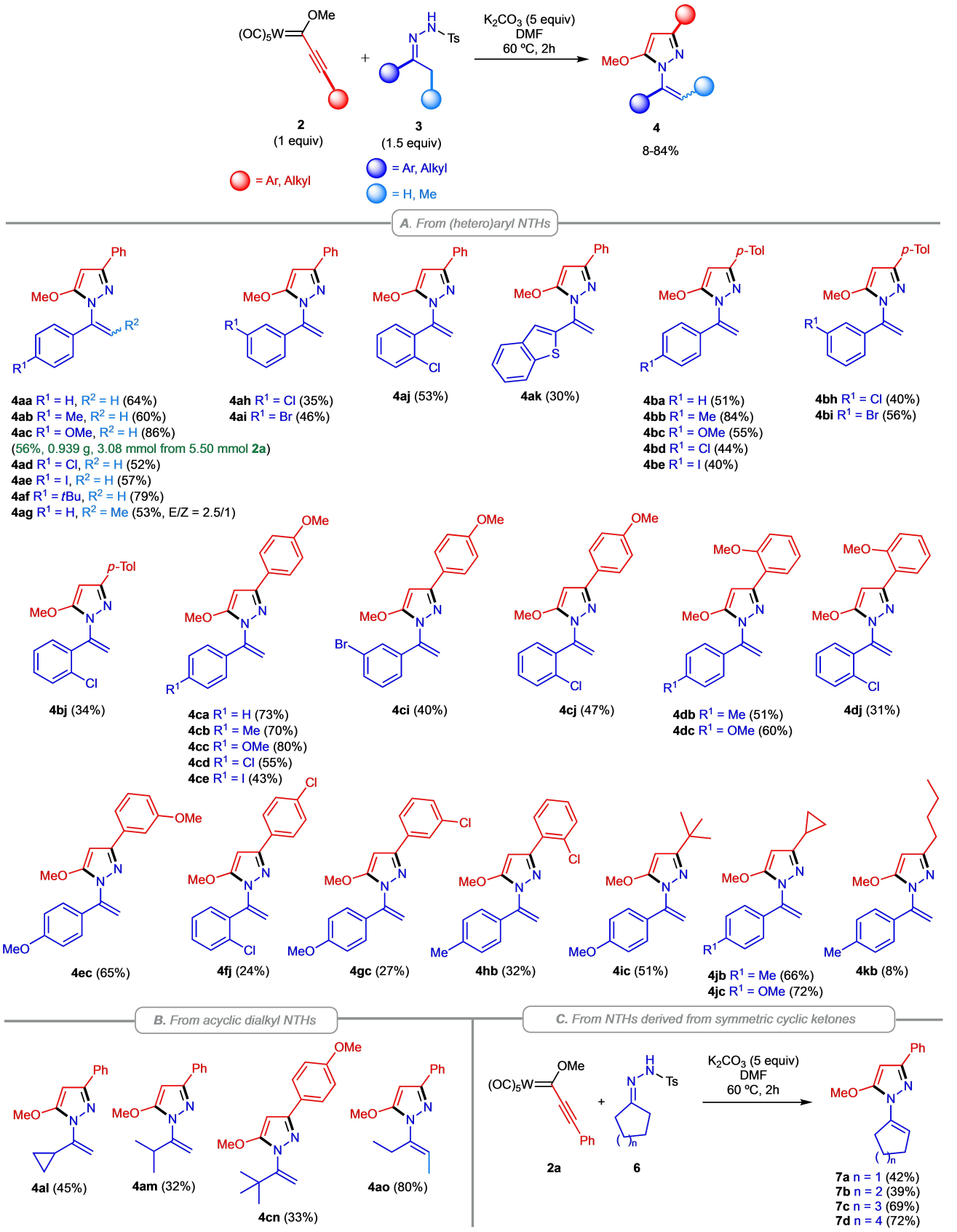
A similar trend was observed when the substitution of the carbene moiety was explored. Thus, 1-alkenylpyrazoles **4ba-be**, **4bh-bj**, **4ca-ce**, **4ci**,**cj** were prepared from methoxy *p*-tolylethynyl and *p*-methoxyphenylethynyl carbene complexes **2b** and **2c**, bearing electron-donating substituents at the *para* position, in similar yields to the ones previously described. Electron-donating substitution at the *ortho*- and *meta*-positions of the aryl substituent of the FCC was also tolerated as evidenced by the formation of alkenylpyrazoles **4db-dc**, **4dj**, and **4ec**, displaying a variety of electronic effects in the NTH component. The reaction also takes place when electron-withdrawing substituents were placed on the aryl group of the carbene complex, and tolerates *para*-, *ortho*- and *meta*-substitution; however, in general, lower reaction yields of alkenylpyrazoles **4fj**, **4gc**, and **4hb**, displaying different substitution patterns and electronic effects within the NTH moiety, were observed. In addition, alkyl substituents added to the terminus of the triple bond of the FCC are also compatible: alkenylpyrazoles **4ic**, **4jb** and **4jc**, bearing secondary and tertiary alkyl groups, were isolated in synthetically useful yields. On the other hand, a limitation of our protocol was found when the FCC carries a primary alkyl group, since a lower yield of alkenylpyrazole **4kb** was obtained; this result can be attributed to the higher acidity of the hydrogen atoms in alpha position to the triple bond for FCC **2k** bearing a primary alkyl group in comparison to those bearing secondary or tertiary alkyl groups. A second limitation is inherently linked to the currently existing methodology for the preparation of alkoxy alkynyl FCCs, which relays exclusively on the successive addition of alkynyl lithium species and a strong alkylating agent to hexacarbonyl metal(0) complexes; the lack of tolerance of many functional groups to the employment of organolithium reagents imposes a restriction in the scope of the FCC component. Regarding the NTH component, this transformation does not tolerate the presence of cyano, ester or nitro groups, or some heterocyclic moieties such as 2-indolyl or 2-pyridyl.[20a]

The reaction has been extended to dialkyl NTHs. Thus, firstly, the reaction turned out to be completely regioselective when cyclopropyl methyl ketone-derived NTH (bearing secondary and methyl groups) was chosen as starting material as alkenylpyrazole **4al** was obtained as the only product (Scheme 2B). This last result raised the question of whether the complete regioselectivity achieved was due to the rigidity of the cyclopropyl ring or simply to the fact that is a secondary group; this question was fully clarified when alkenylpyrazole **4am** was obtained as the only regioisomer. Secondly, *tert*-butyl methyl ketone derived NTH could also be transformed into alkenylpyrazole **4cn** with complete regioselectivity, although in only moderate yield, probably because of sterics. Thirdly, 3-pentanone-derived symmetric NTH led to pyrazole **4ao** in high yield and in a completely diastereoselective manner (*E*-isomer). Finally, and not surprisingly, the reaction with a non-symmetrical dialkyl NTH bearing alpha-H atoms in both a primary alkyl group and a methyl group led to an almost 1:1 mixture of regioisomers; their separation by column chromatography proved to be difficult and only fractions enriched in one or the other regioisomer could be obtained.[20b]

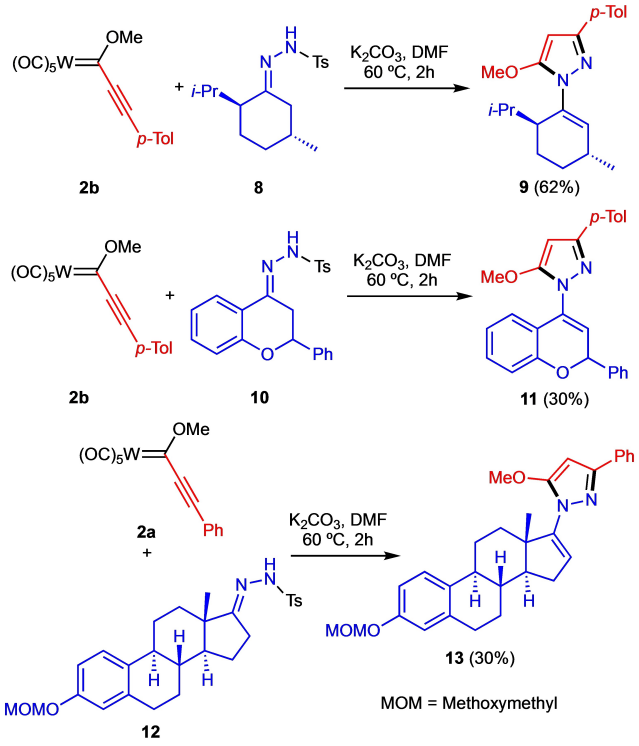
In the same manner, NTHs **6**, derived from symmetric cyclic ketones, proved to be appropriate reaction partners. Thus, cyclopentanone- to cyclooctanone-derived *N*-tosylhydrazones **6** provided the expected 1-(cycloalken-1-yl)-5-methoxy-1H pyrazoles **7** in moderate to good yields (39–72%, Scheme 2C).

To prove the synthetic usefulness of the methodology, a reaction was performed at large scale. Thus, pyrazole **4ac** was obtained in 56% yield at 5.5 mmol scale, much lower than the yield for the reaction at the usual scale but still synthetically useful (see yield of **4ac** in Scheme 2A).

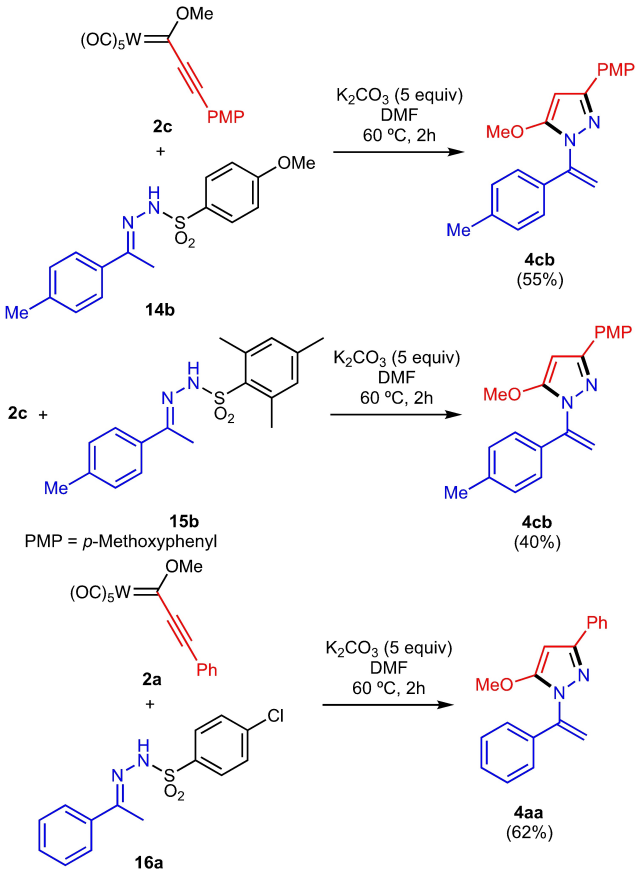
In addition, it is worthy to point out that this methodology can be applied for late-stage diversification of natural products,[21] as shown in Scheme 3. Thus, menthone-derived NTH **8**, chromanone-derived NTH **10** and estrone-derived NTH **12** were easily transformed into the corresponding 1-alkenyl-5-methoxy-1*H*-pyrazole derivatives **9**, **11** and **13** under the optimized reaction conditions. The obtention of pyrazole **9** is particularly remarkable as it was obtained as a single enantiomer, given that both menthone and



Scheme 2. Scope of the reaction. In brackets, isolated yields.



Scheme 3. Late-stage diversification: synthesis of 1-alkenyl-5-methoxy-1*H*-pyrazoles from natural product derived NTHs. In brackets, isolated yields.



Scheme 4. Role of the leaving group: reaction with *N*-sulfonyl hydrazones bearing a group other than tosyl. In brackets, isolated yields.

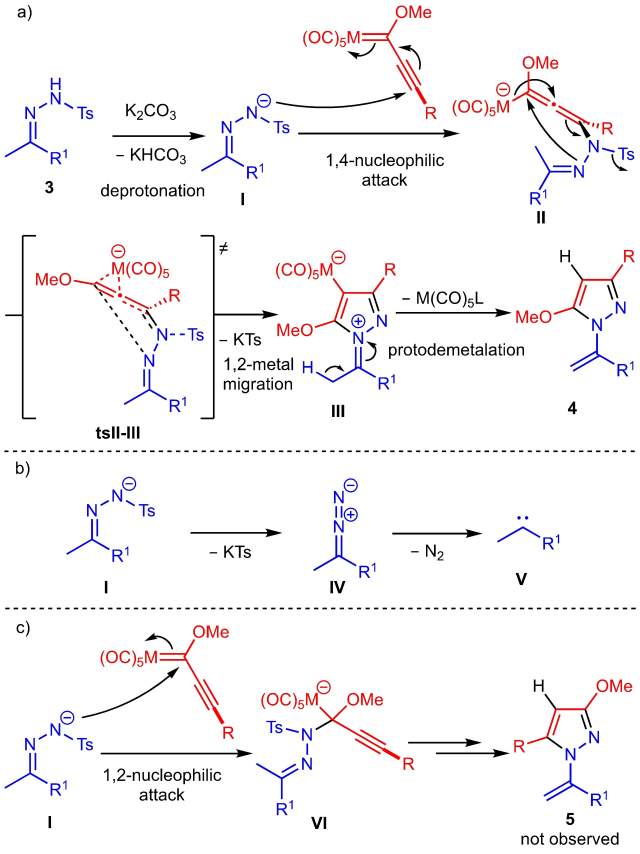
its derived NTH **8** have been reported to undergo partial epimerization of the α-carbon.[22,23]

Sulfonyl hydrazones containing a group other than tosyl were also tested under the optimized conditions, to verify the role of the leaving group in the outcome (Scheme 4). In this regard, both electronics and sterics at the sulfonyl moiety appear to influence the yield of the final product as a notable decrease was found when *N*-sulfonyl hydrazones **14b** (bearing a more electron-donating *p*-methoxy group) or **15b** (sterically hindered) were employed (compare Scheme 4 results vs yield of compound **4cb** −70%- in Scheme 2A). On the contrary, the employment of a *N*-sulfonyl hydrazone bearing a mild electron-withdrawing group led to very similar yields to the tosyl group. As expected, no cycloaddition occurred when a *N*-sulfonyl hydrazone bearing a *p*-nitro group was tested.[20a]

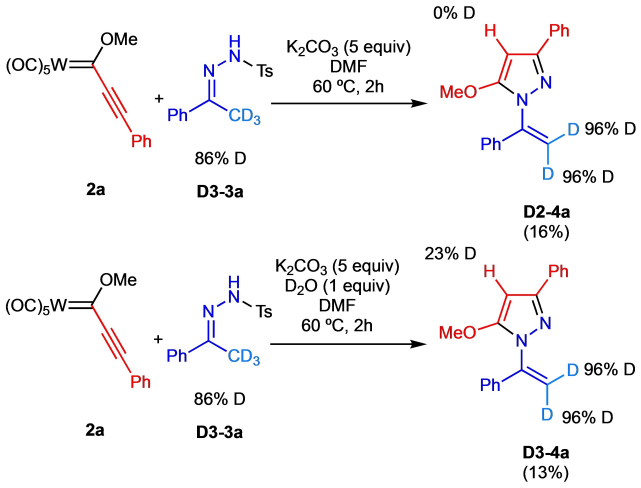
The proposed mechanism to account for the observed results is outlined in Scheme 5. Thus, an initial deprotonation of the tosylhydrazone in the presence of K_2CO_3 to form anion **I** is proposed (Scheme 5, a). Typically, deprotonated NTHs evolve upon warming by sequentially losing the tosyl group to form diazocompound **IV** and extruding N_2 to generate carbene **V** (Scheme 5, b). However, in this reaction, (i) N_2 extrusion definitively does not take place as the two N atoms are incorporated into the final product, and (ii) the formation of diazocompound **IV** seems unlikely as it usually requires higher temperatures while this reaction also takes place at room temperature (table 1, entry 6).[20c,d] Therefore, the direct nucleophilic attack of NTH-derived anion **I** at the electrophilic position 4 of the Fischer carbene complex seems the most realistic option to form intermediate **II**.

At this stage is worth to mention that alkoxy alkynyl FCCs display two electrophilic reactive positions: the beta carbon of the triple bond (position 4) and the carbene carbon (position 2). The attack to one or to the other position depends on the nature of nucleophile and the reaction conditions and determines the regioselectivity of the reaction.[1]

For NTH-derived anion **I**, the alternative nucleophilic attack at the other electrophilic position of the FCC (the carbene carbon) is discarded as it should lead, through metalated intermediate **VI**, to the opposite regioisomer **5** which has not been observed (Scheme 5, c). Then, allenyl metalate **II** should evolve by a 1,2-metal migration with either concomitant or stepwise departure of the Ts group to zwitterionic intermediate **III**, through transition state **tsII-III**,



Scheme 5. Proposed reaction mechanism.



Scheme 6. Deuteration experiments. In brackets, isolated yields.

which resembles a butterfly with asymmetric wings.[20e] The 1,2-metal migration is a well-established step in the chemistry of group 6 metal carbene complexes and characterized by NMR measurements[24] and DFT calculations.[25] Finally, a protodemetalation step with formation of the double bond should generate reaction product **4**.

At this point we questioned whether the protodemetalation should take place intra or intermolecularly, so deuteration experiments were performed to gain insight into this step of the reaction mechanism. Thus, deuterated tosyl hydrazone **D3–3 a** was readily prepared bearing 86% D incorporation.[26,27] Then, the reaction with FCC **2 a** under the optimized conditions led to pyrazole **D2–4 a** with 96% of D at the olefin but no deuteration in the pyrazole ring (Scheme 6, top). This result indicates that: (1) there is no intramolecular D migration in the mechanism, but (2) a kinetic effect causes a preference for the breaking of a C–H bond over a C–D bond and leads to deuterium enrichment from 86% to 96% at the olefin carbon atom. A second experiment was performed in the presence of D_2O (one equiv.) and, in addition to the deuterium enrichment at the olefin carbon atom, the pyrazole obtained showed 23% deuterium incorporation (Scheme 6, bottom). This observation suggests the presence of a negative charge at that position at some stage during the reaction mechanism. All these results are in agreement with the proposed mechanism.

DFT calculations (M06/6-31+G(d)+LANL2DZ for W), performed for the reaction of FCC **2 a** and NTH **3 a**, confirm the proposed mechanism. In DMF solvent, tosyl hydrazone **3 a** can be deprotonated by carbonate ions to yield the negatively charged intermediate **I** (Scheme 5). **I** approaches the Fischer carbene complex, forming a pre-reactive species, **R** (Figure 2), that is considered the starting point for the next steps in the reaction process. Deprotonated N atom at **I** performs a nucleophilic attack to beta-position of the FCC through **TS-R-II** with a barrier of 7.5 kcal/mol relative to **R**. This step leads to intermediate **II**, −10.3 kcal/mol more stable than the reference state, where a new N–C bond is already formed. From **II** the $W(CO)_5$ moiety undergoes a 1,2 transposition to reach intermediate **IIb** (10.9 kcal/mol). No TS could be found for the metal fragment rearrangement, which may mean that the migration happens progressively, or the assumed transition state is very similar both in geometry and energy to intermediate **IIb**. **TS-II–III** (23.1 kcal/mol) is the rate limiting step and corresponds to the simultaneous cyclization and tosyl elimination leading to **III**. Intermediate **III** is very stable (−44.2 kcal/mol) and is ready for the protodemetalation step to form the experimentally observed product.

Conclusion

In conclusion, we have developed a novel protocol for the synthesis of *N*-alkenylpyrazoles by reaction between alkoxy alkynyl tungsten FCCs and NTHs derived from ketones bearing α-H under basic conditions. Remarkably, this route represents a *de novo* approach to *N*-alkenylpyrazoles where *the NTH acts as*

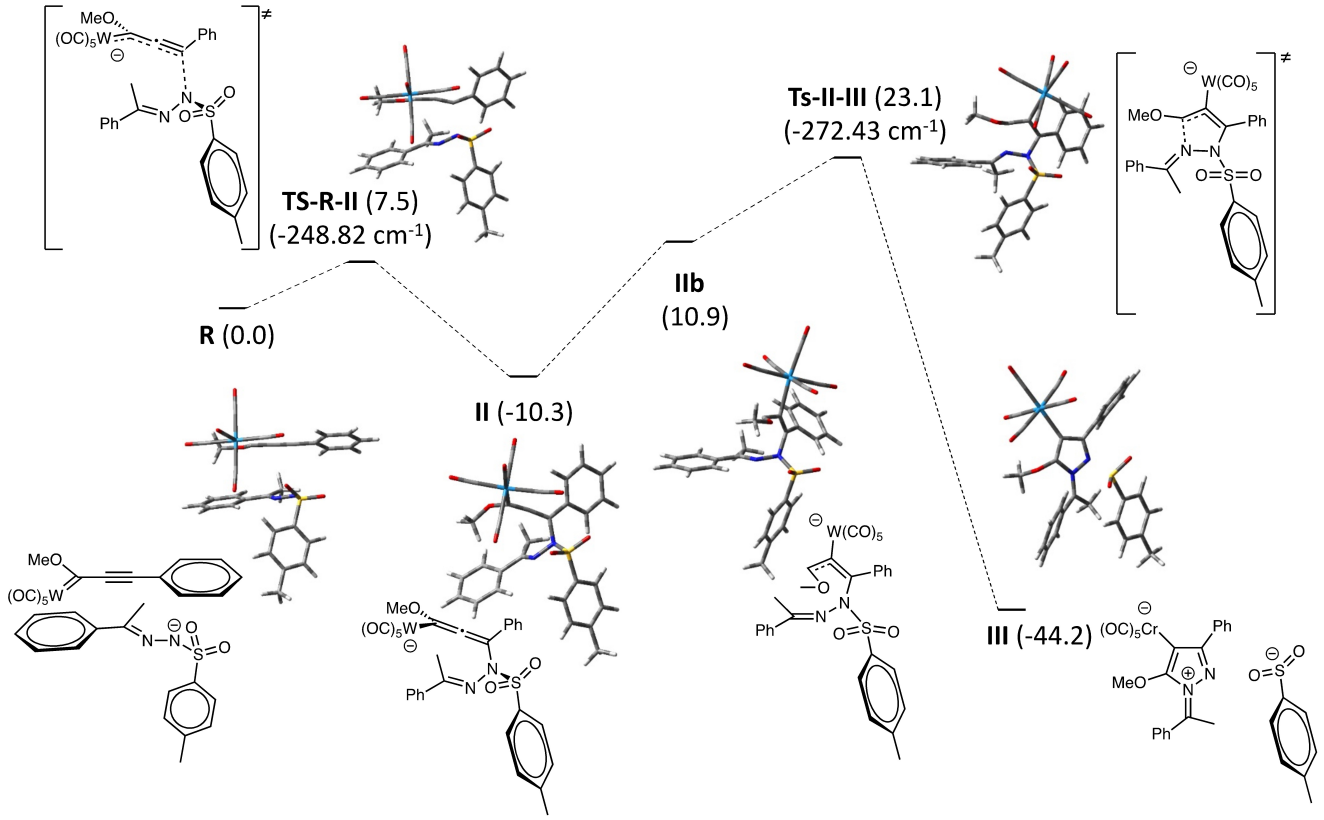


Figure 2. M06/6-31+G(d) (LANL2DZ for W) Gibbs energy profile (in kcal/mol) confirming the reaction mechanism proposed in Scheme 5a. Imaginary frequencies of the transition states are also given in cm^{-1}.

a [NN] synthon transferring only the two N atoms to form the pyrazole ring. The optimized conditions (K_2CO_3, DMF, 60 °C, 2 h) allow a wide reaction scope, which include a variety of substituents both in the FCC (aryl groups with different substitution patterns and electronic effects, as well as primary, secondary and tertiary alkyl substituents), and the NTH (aryl alkyl, symmetric and asymmetric dialkyl, cyclic) partners. In addition, the reaction proved to be synthetically useful at large scale and amenable for late-stage diversification of natural products, as illustrated for terpene, chromanone and steroid derivatives. Finally, deuteration experiments shed light into and helped to support the proposed reaction mechanism, which was confirmed by DFT calculations.

Experimental Section

General procedure for the synthesis of 1,3-disubstituted-5-methoxy-1*H*-pyrazoles 4, 7, 9, 11 and 13. The tungsten Fischer methoxyalkynylcarbene complex (1.0 equiv.), the *N*-sulfonylhydrazone (1.5 equiv.) and K_2CO_3 (5.0 equiv.) were placed under inert atmosphere in an oven-dried reaction vessel. Anhydrous DMF (0.1 M) was added, and the reaction was heated to 60 °C for 2 h. Toluene was added and the azeotropic mixture of solvents was subsequently removed under reduced pressure. The residue was extracted with AcOEt, and the combined organic phase was washed with brine (x 2) and water and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product, which was purified by deactivated silica gel column chromatography, eluting with hexane/AcOEt mixtures.

Acknowledgements

Authors would like to acknowledge the technical support provided by Servicios Científico-Técnicos de la Universidad de Oviedo. Additionally, we are grateful for the financial support of this work by Ministerio de Ciencia, Innovación y Universidades of Spain (Agencia Estatal de Investigación: PID2022-140635NB-I00 funded by MICIU/AEI/10.13039/501100011033/ERDF/EU and PID2019-107580GB-I00 funded by MICINN/AEI/10.13039/501100011033) and Gobierno del Principado de Asturias [FICYT-FEDER: IDI/2018/000231, and FICYT "Severo Ochoa" predoctoral fellowship to H. F. P. (BP21/050)].

References

[1] For general reviews about the chemistry of group 6 metal Fischer carbene complexes, see: a) J. Barluenga, E. Aguilar, *Adv. Organomet. Chem.* **2017**, *67*, 1–150; b) E. Aguilar, L. A. López, in *Science of Synthesis, Knowledge*

Updates, *Vol. 2*, **2014**, Georg Thieme Verlag KG, Stuttgart, pp. 1–137; c) K. H. Dötz, J. Stendel, *Chem. Rev.* **2009**, *109*, 3227–3274. For most recent although more specific reviews, see: d) A. Feliciano, J. L. Vázquez, L. J. Benítez-Puebla, I. Velazco-Cabral, D. C. Cruz, F. Delgado, M. A. Vázquez, *Chem. Eur. J.* **2021**, *32*, 8233–8251; e) R. A. Fernandes, A. Kumari, R. S. Pathare, *Synlett* **2020**, *31*, 403–420; f) T. Bera, K. Pandey, R. Ali, *ChemistrySelect* **2020**, *5*, 5239–5267; g) K. Wang, J. Wang, *Synlett* **2019**, *30*, 542–551; h) I. Hoskovcová, J. Ludvík, *Curr. Opin. Electrochem.* **2019**, *15*, 65–174.

[2] a) Y. T. Wu, A. de Meijere, *Top. Organomet. Chem.* **2004**, *13*, 21–57; b) A. de Meijere, H. Schirmer, M. Duetsch, *Angew. Chem. Int. Ed.* **2000**, *39*, 3964–4002.

[3] a) H. Kagoshima, K. Fuchibe, T. Akiyama, *Chem. Rec.* **2007**, *7*, 104–114; b) J. Barluenga, S. Martínez, *ARKIVOK* **2006**, *vii*, 129–147; c) J. Barluenga, J. Santamaría, M. Tomás, *Chem. Rev.* **2004**, *104*, 2259–2284.

[4] Y. Xia, J. Wang, *Chem. Soc. Rev.* **2017**, *46*, 2306–2362.

[5] J. Wang, *Pure Appl. Chem.* **2018**, *90*, 617–623.

[6] a) R. Barroso, M. P. Cabal, C. Valdés, *Synthesis* **2017**, *49*, 4434–4447; b) H. Wang, Y.-H. Deng, Z. Shao, *Synthesis* **2018**, *50*, 2281–2306.

[7] a) M. Paraja, M. Plaza, C. Valdés, *Synlett* **2017**, *28*, 2373–2389; b) D. Arunprasath, B. D. Bala, G. Sekar, *Adv. Synth. Catal.* **2019**, *361*, 1172–1207.

[8] F. Hu, J. Yang, Y. Xia, C. Ma, H. Xia, Y. Zhang, J. Wang, *Org. Chem. Front.* **2015**, *2*, 1450–1456.

[9] a) V. K. Aggarwal, J. de Vicente, R. V. Bonnert, *J. Org. Chem.* **2003**, *68*, 5381–5383; b) P. Liu, Q. Xu, C. Dong, X. Lei, G. Lin, *Synlett* **2012**, *23*, 2087–2092; c) L. Wu, Y. Ge, T. He, L. Zhang, X. Fu, H. Fu, H. Chen, R. Li, *Synthesis* **2012**, *44*, 1577–1583; d) G. Khalili, *Synth. Commun.* **2013**, *43*, 3170–3174; e) M. C. Pérez-Aguilar, C. Valdés, *Angew. Chem. Int. Ed.* **2013**, *52*, 7219–7223; f) N. Shao, T. Chen, T. Zhang, H. Zhu, Q. Zheng, H. Zou, *Tetrahedron* **2014**, *70*, 795–799; g) M. C. Pérez-Aguilar, C. Valdés, *Angew. Chem. Int. Ed.* **2015**, *54*, 13729–13733; h) C. Zhu, H. Zeng, C. Liu, Y. Cai, X. Fang, H. Jiang, *Org. Lett.* **2020**, *22*, 809–813.

[10] S. H. Kurma, B. Sridhar, C. R. Bhimapaka, *J. Org. Chem.* **2021**, *86*, 2271–2282.

[11] R. Barroso, A. Jiménez, M. C. Pérez-Aguilar, M.-P. Cabal, C. Valdés, *Chem. Commun.* **2016**, *52*, 3677–3680.

[12] a) J. Barluenga, N. Quiñones, M. Tomás-Gamasa, M.-P. Cabal, *Eur. J. Org. Chem.* **2012**, 2312–2317; b) J.-L. Zhang, P. W. H. Chan, C.-M. Che, *Tetrahedron Lett.* **2003**, *44*, 8733–8737; c) V. K. Aggarwal, J. de Vicente, R. V. Bonnert, *Org. Lett.* **2001**, *3*, 2785–2788.

[13] O. Fernandez-Delgado, E. Castro, C. R. Ganivet, K. Fosnacht, F. Liu, T. Mates, Y. Liu, X. Wu, L. Echegoyen, *ACS Appl. Mater. Interfaces* **2019**, *11*, 34408–34415.

[14] A. Velázquez-Stavínov, *Master Thesis*, Univ. Oviedo, **2020**.

[15] J. Han, Y.-W. Xu, X.-M. Wang, L. Zhang, X.-P. Hu, *Tetrahedron Lett.* **2020**, *61*, 151409.

[16] For selected recent reviews about the pharmaceutical properties of pyrazoles see: a) G. Li, Y. Cheng, C. Han, C. Song, N. Huang, Y. Du, *RSC Med. Chem.* **2022**, *13*, 1300–1321; b) R. F. Costa, L. C. Turones, K. V. N. Cavalcante, I. A. Rosa Júnior, C. H. Xavier, L. P. Rosseto, H. B. Napolitano, P. F. D. S. Castro, M. L. F. Neto, G. M. Galvão, R. Menegatti, G. R. Pedrino, E. A. Costa, J. L. R. Martins, J. O. Fajemiroye, *Front. Pharmacol.* **2021**, *12*, 666725.

[17] For general reviews about the chemistry of pyrazoles, see: a) J. Elguero, A. M. S. Silva, A. C. Tomé, in *Modern Heterocyclic Chemistry*, 1st Edition; (J. Álvarez-Builla, J. J. Vaquero, J. Barluenga, Eds.), Wiley-VCH Verlag GmbH & Co, 2011; pp 635–725; b) A. Schmidt, A. Dreger, A. Curr Org, *Chem.* **2011**, *15*, 1423–1463; c) S. Fustero, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev.* **2011**, *111*, 6984–7034. For more recent reviews about specific types of pyrazoles, see: d) P. K. Mykhailiuk, *Chem. Rev.* **2021**, *121*, 1670–1715, for fluorinated pyrazoles; e) D. D. Priya, M. Nandhakumar, S. M. Roopan, *Synth. Commun.* **2020**, *50*, 3535–3562 for pyrazolo[1,5-*a*]pyridines; f) M. A. Abd ul-Malik, R. M. Zaki, A. M. Kamal El-Dean, S. M. Radwan, *J. Heterocycl. Chem.* **2018**, *55*, 1828–1853, for pyrazolopyrazines.

[18] a) V. Garg, P. Kumar, A. K. Verma, *J. Org. Chem.* **2017**, *82*, 10247–10262; b) U. K. Das, S. Mandal, A. Anoop, M. Bhattacharjee, *J. Org. Chem.* **2014**, *79*, 9979–9991; c) T. Tsuchimoto, K. Aoki, T. Wagatsuma, Y. Suzuki, *Eur. J. Org. Chem.* **2008**, 4035–4040; d) U. K. Das, M. Bhattacharjee, *Chem. Eur. J.* **2012**, *18*, 5180–5183.

[19] a) P. D. Ortiz, M. Ortiz, R. Suardíaz, A. Fragoso, P. J. Ortiz, *Magn. Reson. Chem.* **2015**, *53*, 539–543; b) P. A. McDonnell, A. D. Gauthier, M. P. Ferro, *Magn. Reson. Chem.* **1998**, *36*, 35–38.

[20] See SI for: a) unsuccessfully tested *N*-sulfonyl hydrazones; b) result of the reaction with 2-butanone-derived NTH; c) a discarded related mechanism involving diazo-compound nucleophilic attack to position 4 of the FCC; d) an alternative and discarded mechanism involving intramolecular H^+ transfer; e) a stepwise mechanism for the transformation of intermediate **II** into **III**, suggested by a reviewer.

[21] B. Hong, T. Luo, X. Lei, *ACS Cent. Sci.* **2020**, *6*, 622–635.

[22] M. C. Garner, B. C. Mossman, M. E. Prince, *Tetrahedron Lett.* **1993**, *34*, 4273–4276.

[23] Nevertheless, enantiomerically pure menthone-derived NTH **8** has been successfully employed in: Shapiro reactions, a) S. Álvarez, Y. Pazos-Randulfe, H. Khanwalkar, P. Germain, R. Álvarez, H. Gronemeyer, A. R. de Lera, *Bioorg. Med. Chem.* **2008**, *16*, 9719–9728; transition metal-free reductive coupling with boronic acids, b) M. Plaza, M. C. Pérez-Aguilar, C. Valdés, *Chem. Eur. J.* **2016**, *22*, 6253–6257.

[24] J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaría, R. J. Carbajo, F. López-Ortiz, S. García-Granda, P. Pertierra, *Chem. Eur. J.* **1996**, *2*, 88–97.

[25] For recent examples, see: a) A. Gómez, I. Funes-Ardoiz, D. Sampedro, J. Santamaría, *Org. Lett.* **2018**, *20*, 4099–4102; b) J. González, A. Gómez, I. Funes-Ardoiz, J. Santamaría, D. Sampedro, *Chem. Eur. J.* **2014**, *20*, 7061–7068.

[26] H. Jiang, W. Fu, H. Chen, *Chem. Eur. J.* **2012**, *18*, 11884–11888.

[27] In all cases, percentaje of deuterium labeling was accurately determined by ^{1}H-NMR measurements. See SI for details.