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Letter

## Asymmetric Neber Reaction in the Synthesis of Chiral 2-(Tetrazol-5-yl)-2H-Azirines

Α

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**Abstract** A successful one-pot methodology for the synthesis of chiral 2-tetrazolyl-2*H*-azirines has been established, resorting to organocatalysis. The protocol involves the *in situ* tosylation of  $\beta$ -ketoxime-1*H*-tetrazoles followed by the Neber reaction, in the presence of chiral organocatalysts. Among the organocatalysts studied a novel thiourea catalyst derived from 6 $\beta$ -aminopenicillanic acid afforded excellent enantioselectivities.

**Key words** 2*H*-azirines, asymmetric Neber reaction, organocatalysis, tetrazoles, thiourea, 6β-aminopenicillanic acid

Due to their unique structural features, 2*H*-azirines have been widely used as valuable synthetic intermediates in the synthesis of a plethora of nitrogen-containing compounds.<sup>1-7</sup> In fact, the high ring strain along with the activated iminic bond and the *N*-lone pair on the azirine make these heterocycles highly reactive and enable them to participate in organic reactions not only as nucleophiles and electrophiles, but also as dienophiles and dipolarophiles. Moreover, under the appropriate reaction conditions, highly reactive intermediates such as vinylnitrenes, nitrile ylides, and iminocarbenes can be generated from selective bond cleavage, broadening the reactivity of these small molecules.

The isolation of chiral naturally occurring 2*H*-azirines, such as azirinomycin (1), dysidazirine (2), and antazirine (3), with promising biological properties, has raised the interest in the development of efficient asymmetric synthetic methodologies towards chiral 2*H*-azirine-2-carboxylates and their analogues (Figure 1).<sup>8,9</sup> In fact, the synthesis of



chiral 2H-azirine-2-carboxylates using alkaloid-promoted Neber reactions<sup>10</sup> as well as asymmetric Neber reaction using bifunctional chiral thioureas as catalysts have been described.<sup>11</sup> These methodologies have been applied to the synthesis of (-)-(Z)-dysidazirine<sup>10d,e,11</sup> and both isomers (*E*) and (*Z*) of antazirine.<sup>10f</sup> More recently, an organocatalytic asymmetric Neber approach towards chiral spirooxindole-2H-azirine and spiropyrazolone-2H-azirine derivatives promoted by hydroquinidine 1,4-phthalazinediyl diether [DHQD]<sub>2</sub>PHAL] has been reported.<sup>12</sup>



The chemistry of these interesting molecules has been one of our topics of research. We have previously developed a highly efficient method for the preparation of 2-halo-2*H*azirines starting from  $\alpha$ -oxophosphorus ylides, based on a nonclassical Wittig reaction.<sup>13</sup> These compounds have proven to be versatile building blocks for several transformations giving rise to an array of cyclic and acyclic nitrogencontaining compounds.<sup>14</sup>

On the other hand, we reported the synthesis of (1*H*-tetrazol-5-yl)-allenes,<sup>15</sup> tetrazolyl-tryptamines, and 2-halo-2-(tetrazol-5-yl)-2*H*-azirines and the use of these compounds for the construction of tetrazolyl-heterocycles, namely 3-tetrazolyl- $\beta$ -carbolines with anticancer activity.<sup>15-18</sup>

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Building blocks bearing a tetrazolyl substituent are a particularly interesting synthetic tool to explore carboxylic acid/tetrazole bioisosterism as a way to find new molecules with enhanced biological activity. In this context, we have selected 2-(tetrazol-5-yl)-2H-azirines as our target molecules due not only to their interesting chemical features but also considering that these heterocycles are bioisosters of relevant 2H-azirine-2-carboxylates.<sup>19,20</sup> The established synthetic methodology involves the preparation of β-ketoximes-1H-tetrazoles which undergo in situ tosylation and the subsequent Neber reaction to give 2-(tetrazol-5-yl)-2Hazirines, bearing phenyl, furan-2-yl, thiophen-2-yl, or pyrrol-2-vl substituents at C-3. Furthermore, it was demonstrated that the alkaloid-mediated Neber reaction allows the asymmetric synthesis of 2-(tetrazol-5-vl)-2H-azirines. Using a stoichiometric amount of quinidine (6), a smooth conversion of tosylate ketoxime 4 into the desired enriched 2H-azirine was observed affording predominantly the R enantiomer (54% ee) whereas in the presence of quinine (8) the S enantiomer was selectively formed (44% ee). Thus, the pseudoenantiomers of the alkaloids gave opposite antipodes of the 2H-azirine (Scheme 1).



Herein, we report a one-pot synthetic approach towards chiral 2-(tetrazol-5-yl)-2H-azirine derivatives by carrying out the *in situ* tosylation of  $\beta$ -ketoxime tetrazoles followed by the Neber reaction in the presence of chiral organocatalysts. We selected the conversion of  $\beta$ -ketoxime **5** into the corresponding 2H-azirine 7 as our model reaction and started our investigations using quinidine (6) as organocatalyst. Optimization studies were carried out, and different parameters such as solvent, temperature, reaction time, and co-base were evaluated in order to improve the selectivity of this transformation (Table 1).

 Table 1
 Optimization of the Model Reaction



<sup>a</sup> Determined by HPLC analysis on a chiral stationary column.

It was found that the solvent plays an important role in the reaction, with the desired product (R)-7 being obtained when the reactions were performed in dichloromethane, diethyl ether, or toluene (Table 1, entries 2–4, respectively) whereas no reaction occurred when using acetonitrile (Table 1, entry 1). Among the former, the reaction carried out in toluene, in the presence of only 20 mol% of guinidine, allowed the synthesis of the target compound in the highest yield (67%) along with 60% ee (Table 1, entry 4). In addition, the use of K<sub>2</sub>CO<sub>3</sub> led to the product in higher yield than carrying out the reaction in the presence of Na<sub>2</sub>CO<sub>3</sub> (Table 1, entries 4 and 5, 67% vs. 19% yield). Based on these preliminary results, toluene and K<sub>2</sub>CO<sub>3</sub> were selected for further studies. To our delight, by increasing the reaction time to 48 h it was possible to isolate 2H-azirine (R)-7 in excellent yield (87%) albeit with moderate enantiomeric excess (66% ee, Table 1, entry 6).

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Unfortunately, decreasing the reaction temperature to 0 °C resulted in poorer efficiency and lower enantioselectivity (24% yield and 55% ee, Table 1, entry 7). In addition, the increase of the reaction time to 72 h led to a drastic drop in the yield (7%, Table 1, entry 8). This outcome is presumably due to the lack of stability of these heterocycles when subjected to long reaction times. Lastly, the amount of quinidine was decreased to 10 mol% affording the 2*H*-azirine (*R*)-**7** in moderate yield (66%) and 63% ee (Table 1, entry 9). Thus, the best results were obtained carrying out the synthesis of 2-(tetrazol-5-yl)-2*H*-azirine (*R*)-**7** in toluene in the presence of 10 equivalents of K<sub>2</sub>CO<sub>3</sub> and 20 mol% of quinidine at room temperature for 48 h (Table 1, entry 6).<sup>21</sup>

Aiming at the formation of the 2H-azirine (S)-7, guinine, the pseudoenantiomer of quinidine, was also evaluated as organocatalyst (Table 1). Carrying out the reaction in toluene in the presence of 60 mol% of guinidine at room temperature for 48 h, the target heterocycle (S)-7 was obtained in moderate yield (52%) and 51% ee (Table 1, entry 10). Using 20 mol% of quinine, 2H-azirine was obtained in slightly lower yield and lower enantiomeric excess after carrying out the reaction of ketoxime 5 for 24 h (48% yield and 41% ee, Table 1, entry 11). However, increasing the reaction time to 48 h raised the conversion to 61% yield and improved slightly the enantiomeric excess to 44% (Table 1, entry 12). Carrying out the reaction for 72 h led to a dramatic decrease in the efficiency of the reaction (15% yield and 7% ee, Table 1, entry 13), as previously observed when quinidine was used as organocatalyst.

Next, under the previously optimized reaction conditions using quinidine, we explored a series of epi-cinchonidine derivatives bearing different amino acids and heterocycle moieties at the C-9 carbon as catalysts (Figure 2).<sup>22</sup> In some cases, the synthesis of 2-(tetrazol-5-yl)-2H-azirine was performed in dichloromethane due to the poor solubility of these catalysts in toluene. As expected, reactions carried out with these organocatalysts afforded the R enantiomer as the major product. In general, organocatalysts bearing triazolyl moieties afforded the lowest yields (4-20% yield) and ee (14-27%) whereas organocatalysts bearing amino acid moieties led to better results (for details, see Supporting Information). Among the latter, compound 9a bearing a N-benzoyl substituent was the most promising organocatalyst affording (R)-7 in 55% yield and 56% ee (Scheme 2).

The asymmetric Neber reaction of  $\beta$ -ketoxime tosylate, generated *in situ* from  $\beta$ -ketoxime **5** and TsCl, promoted by  $6\beta$ -aminopenicilanic acid (**10a**, 6-APA) was also investigated. 6-APA is a very cheap, easily available, enantiopure chiral compound and it is the active nucleus common to all penicillins.<sup>23</sup> As far as we know, 6-APA has only been used as organocatalyst for a direct cross-aldol reaction.<sup>24</sup> After 24 h of reaction, 2*H*-azirine (*R*)-**7** was isolated in only 15% yield and 52% ee, with this catalyst inducing selectivity for the *R* isomer. Increasing the reaction time to 48 h did not



Figure 2 Organocatalysts derived from *epi*-cinchonidine



**Scheme 2** Asymmetric Neber reaction using an *epi*-cinchonidine derivative and 6-APA as catalysts (Bzh = benzhydryl group)

improve the efficiency, on the contrary, (R)-7 was obtained in less than 5% yield. We thought that this outcome could result from the low solubility of 6-APA in toluene, so we decided to synthesize its benzhydryl ester analogue and evaluate its catalytic activity. Thus, the 6-APA benzhydryl ester **10b** was prepared following a previously developed twostep procedure starting from 6-APA.<sup>25</sup> The reaction of **10a** with diphenyldiazomethane in dichloromethane for 2 days at room temperature, followed by treatment with HCl, afforded the corresponding hydrochloride of 6-APA benzhydryl ester in quantitative yield. This, upon treatment with base, originates **10b** which was then used as catalyst in our Synlett C. Alves et al.

transformation. Unfortunately, the reaction outcome was not very different from the one observed in the 6-APA-promoted reaction, furnishing 2*H*-azirine (*R*)-**7** in slightly higher yield (19%) but with very poor enantioselectivity (13% ee, Scheme 2). These disappointing results observed with 6-APA and its ester may be attributed to the presence of the unprotected amino group, since the presence of TsCl in the reaction medium may lead to the catalyst amino group tosylation.

Based on the aforementioned considerations we decided to attempt the synthesis of a new 6-APA derivative, a bifunctional thiourea (Scheme 3). In the past decade bifunctional thioureas have been successfully used as organocatalysts in several asymmetric reactions, namely the Neber reaction.<sup>11</sup> Inspired by these reports, we envisaged that a 6-APA-derived thiourea could be an effective catalyst for our transformations. Thus, 6-APA benzhydryl ester (**10b**) reacted smoothly with 3,5-bis(trifluoro)phenyl isothiocyanate (**11**) in THF at room temperature for 3 h, affording the corresponding 6-APA-derived thiourea **12** in 48% yield (Scheme 3).



After successfully synthesizing the 6-APA-derived thiourea, we set out to investigate its application as organocatalyst in the conversion of  $\beta$ -ketoxime **5** into the corresponding 2*H*-azirine (*R*)-7 (Table 2). Initially, the reaction was performed under the previously optimized reaction conditions for quinidine in toluene at room temperature for 48 h using K<sub>2</sub>CO<sub>3</sub> as co-base, in the presence of 20 mol% of thiourea 12 (Table 2, entry 1). Unfortunately, the reaction outcome was not as expected, leading to the isolation of the product in 34% yield along with 5% ee. No reaction occurred when  $\beta$ -ketoxime **5** was left to react at 0 °C for 24 h (Table 2, entry 2). However, to our delight, after 48 h at 0 °C our target azirine was isolated in 51% yield with 92% ee (Table 2, entry 3). Increasing the reaction time to 72 h did not improve the efficiency of the reaction, and 2H-azirine was isolated in lower yield with slightly lower ee (12% yield, 84% ee, Table 2, entry 4).

Furthermore, the Neber reactions promoted by thiourea **12** led to the preferential formation of the *R* isomer of 2*H*-azirine (*R*)-**7**, indicating that the new thiourea induces the same selectivity as quinidine. It is noteworthy that this synthetic methodology involves two consecutive reactions, the *in situ* tosylation followed by the Neber reaction, and therefore, the efficiency and selectivity obtained with this catalyst is quite remarkable. This selectivity can be rationalized

 Table 2
 Asymmetric Neber Reaction Using 6-APA-Derived Thiourea 12

 as Catalyst
 Image: Catalyst



<sup>a</sup> Determined by HPLC analysis on a chiral stationary column.

as resulting from the double hydrogen-bonding interaction between the thiourea NH groups and the S=O moieties of the *in situ* generated ketoxime tosylate, as previously observed in asymmetric Neber reactions promoted by other chiral thioureas.<sup>11</sup>

This study was extended to the asymmetric synthesis of tetrazolyl-2H-azirine derivatives bearing heterocyclic substituents at C-3 (e.g., furan-2-yl and thiophen-2-yl, Table 3). Thus, the enantioselective Neber reaction of β-ketoxime tosylates, generated *in situ* from  $\beta$ -ketoximes **13** and TsCl, was carried out in toluene for 48 h using thiourea 12, quinidine, and quinine as catalysts. In the synthesis of 2-(tetrazol-5yl)-3-(thiophen-2yl)-2H-azirine (14a), higher selectivity for the *R* isomer was achieved under thiourea 12 catalysis with an enantiomeric excess of up to 74% (Table 3, entry 1) whereas the quinidine-mediated reaction afforded 14a in the highest yield (86%) albeit with slightly lower enantioselectivity (55% ee, Table 3, entry 3). On the other hand, the quinine-catalyzed reaction led to the preferential formation of the S isomer of azirine **14a** in good yield (52%) although with low enantiomeric excess (29%, Table 3, entry 5).

In general, reactions with ketoxime **13b** bearing a furanyl substituent afforded lower conversions and selectivity than those with ketoximes **5** and **13a** (Table 3, entries 2, 4, and 6). In fact, 2-(tetrazol-5-yl)-3-(furan-2-yl)-2*H*-azirine (**14b**) was isolated under thiourea **12** catalysis in moderate yield (57%) with 8% ee (Table 3, entry 2). Nevertheless, better results were achieved using quinidine as catalyst, providing 3-(furan-2-yl)-2-(tetrazol-5-yl)-2*H*-azirine (**14b**) in good yield (71%), albeit with 24% ee (Table 3, entry 4). Furthermore, the quinine-mediated Neber reaction led to the preferential formation of the *S*-isomer of **14b** in 41% yield and 8% ee (Table 3, entry 6). These rather disappointing results could be derived from the lower stability of these furanyl-substituted 2*H*-azirine derivatives.

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Table 3 Asymmetric Neber Reaction of  $\beta$ -Ketoximes 13 with Several Organocatalysts

R = thiophen-2-yl 13b R = furan-2-yl		organocatalyst (20 mol%) TsCl (1.1 equiv) K <sub>2</sub> CO <sub>3</sub> (10 equiv) toluene, 48 h		$\frac{N}{PNB}$ $\frac{N}{N-N}$ $\frac{4a}{b}R = furan-2-yl$	
Entry	Catalyst	Temp	Product 14	Yield (%)	ee (%)ª
1	12	0 °C	14a	44	74 ( <i>R</i> ) <sup>b</sup>
2	12	0 °C	14b	57	8 (R) <sup>b</sup>
3	6	rt	14a	86	55 (R)
4	6	rt	14b	71	24 (R)
5	8	rt	14a	52	29 (S)
6	8	rt	14b	41	8 (S)

<sup>&</sup>lt;sup>a</sup> Determined by HPLC analysis on a chiral stationary column.

<sup>b</sup> Using 18 mol% of **12**.

Structure of 2*H*-azirine **7** was confirmed by single-crystal X-ray diffraction. Details of the data collection and crystallographic structure refinement are given in the supplementary data. The compound crystallizes in the centrosymmetric monoclinic space group  $P2_1/c$  with unit cell parameters a = 15.228(4), b = 7.231(2), c = 13.866(4) Å,  $\beta = 97.008(11)^\circ$ . An ORTEP plot of the molecule with the atom numbering scheme is depicted in Figure 3.



**Figure 3** ORTEP diagram of 2*H*-azirine **7** with anisotropic displacement ellipsoids drawn at the 50% probability level.

Bond lengths and angles in this molecule are within the expected average ranges reported in the CCSD database, the exceptions being bond lengths C2–C4 (1.455(3) Å) and C19–C3 (1.440(3) Å) which are shorter than average values. The azirine N1=C3 double bond length is 1.256(3) Å whereas the N1–C2 single bond length is 1.549(3) Å. The C2–N1=C3 angle is  $61.41(16)^{\circ}$ ). The phenyl and nitrobenzyl rings are in a *syn,syn* conformation and almost parallel, the

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angle between the least-squares planes of the two rings being 9.76(9)°. The tetrazole ring is almost perpendicular to each of the aromatic rings (dihedral angles of 85.11(8)° and 75.35(9)° for rings C10.C15 and C19.C24, respectively). The observed molecular conformation in the crystal maximizes the  $\pi$ - $\pi$  interaction between the electron clouds of the phenyl rings and minimizes steric repulsion effects. As the molecules lacks any strong H-bonding donor, the only significant intermolecular interactions spotted in the crystal structure involve C-H groups acting as donors (D) and N or O atoms as acceptors (A), namely C(15)-H(15). $N(5)^{i}$ , i = 1-x, 1-v, 1-z (D...A = 3.435(4) Å) and C(22)-H(22).O(17)<sup>ii</sup>, ii = 2-x, -1/2+y, 3/2-z (D-A = 3.466(3) Å). In addition, the two short intramolecular contacts C(9)-H(9A).N(1) (D...A = 3.102(3) Å) and C(15)–H(15).N(8) (2.861(3) Å) deserve to be remarked.

In conclusion, a one-pot synthetic methodology towards chiral 2-(tetrazol-5-yl)-2*H*-azirines starting from  $\beta$ -ketox-ime-1*H*-tetrazoles has been developed by exploring organocatalysis.<sup>26</sup> The target 2*H*-azirines were obtained in moderate to high yields (up to 87% yield) and moderate to excellent enantioselectivities (up to 92% ee). Within the catalysts tested, the novel 6-APA-derived thiourea presented a remarkable catalytic activity, yielding 3-phenyl-2-(tetrazol-5-yl)-2*H*-azirine **7** in 92% ee.

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## **Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691533.

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- (21) General Procedure for the Optimized Asymmetric Synthesis of 2*H*-azirines 7, 14a, and 14b To a solution of the appropriate  $\beta$ -ketoxime 5 or 13a,b (0.15 mmol), K<sub>2</sub>CO<sub>3</sub> (1.50 mmol, 10 equiv), and tosyl chloride (0.17 mmol, 1.1 equiv) in toluene (4 mL) under a nitrogen atmosphere was added the organocatalyst (18 or 20 mol%) in toluene (1 mL). The mixture was stirred for 48 h at the appropriate temperature. The solvent was evaporated under reduced pressure, and the crude reaction was dissolved in ethyl acetate (20 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered, and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography (ethyl acetate/hexane, 1:1). The characterization data for 7, 14a, and 14b agreed with those previously reported.<sup>19</sup>
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- (26) Procedure for the Synthesis of (2S,6R)-Benzhydryl 6β-{3-[3,5-bis(trifluoromethyl)phenyl] thioureido}-aminopenicillanate (12)

To a solution of benzhydryl 6β-aminopenicillanate **10b** (1.94 mmol, 0.74 g) under inert atmosphere in dry THF (3.5 mL) was added dropwise 3,5-bis(trifluoromethyl)phenyl isothiocyanate (11, 1.94 mmol, 0.35 mL). After stirring for 3 h at room temperature, the solvent was evaporated, and the crude product was purified by flash chromatography (eluting with ethyl acetate/hexane, 1:2) and recrystallized with diethyl ether/hexane; yield 48%; white solid; mp 77.0–78.0 °C. IR (KBr): v = 682, 697, 1128, 1251, 1175, 1276, 1491, 1735, 2968, 2933, 3032, 3066, 3271. 3291 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>2</sub>):  $\delta$  = 7.93 (s. 1 H). 7.84 (s, 2 H), 7.50 (s, 1 H), 7.35-7.31 (m, 11 H), 6.96 (s, 1 H), 5.19 (d, J = 2 Hz, 1 H), 4.25 (dd, J = 3.2 Hz and J = 1.2 Hz, 1 H), 3.92 (s, J = 2 Hz, 1 H), 3.92 (1 H), 1.64 (s, 3 H), 1.00 (s, 3 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 182.8, 170.6, 167.3, 139.1, 138.9, 133.9, 132.4 (q, J = 34.0 Hz, 2 C), 128.8, 128.9, 128.6, 128.5, 128.2, 127.9, 127.7, 126.9, 126.8, 126.6, 124.1, 122.9 (m, 1 C), 121.4, 78.7, 73.3, 66.5, 65.5, 65.1, 60.6, 26.3, 26.1 ppm. <sup>19</sup>F NMR (376 MHz CDCl<sub>3</sub>):  $\delta$  = 62.8 (s, 6 F). HRMS (ESI): *m*/*z* calcd for C<sub>30</sub>H<sub>26</sub>F<sub>6</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub> [MH<sup>+</sup>]: 654.1314; found: 654.1301.