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The Neber Approach to 2-(Tetrazol-5-yl)-2*H*-Azirines

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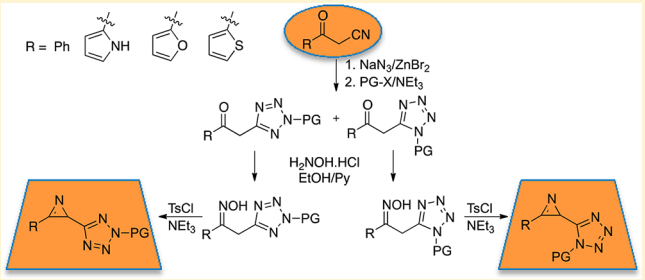
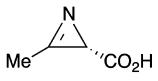
Supporting Information

ABSTRACT: The synthesis of 2-(tetrazol-5-yl)-2*H*-azirines is reported for the first time. Using the Neber approach, *β*-ketoxime-1*H*-tetrazoles were converted into the target 2*H*-azirines bearing phenyl, furan-2-yl, thiophen-2-yl, or pyrrol-2-yl substituents at C-3. It was demonstrated that the alkaloid-mediated Neber reaction allows the asymmetric synthesis of 2-(tetrazol-5-yl)-2*H*-azirines.

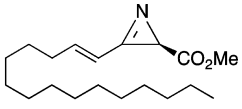


INTRODUCTION

2*H*-Azirines are the smallest unsaturated nitrogen heterocyclic systems with two carbon atoms and an imine bond. The rich and quite high chemical reactivity of these strained heterocycles makes them versatile building blocks for organic synthesis.[1] Chiral derivatives bearing a carboxylic acid or an ester group at C-2 are of particular interest due to their biological behavior. In fact, naturally occurring azirinomycin (1), isolated from *Streptomyces aureus*, and its methyl ester exhibit antibiotic activity.[2] Moreover, (-)-dysidazirine (2), isolated from *Dysidea fragilis*, shows potent antifungal activity against *Candida albicans and Saccharomyces cerevisiae*.[3] Therefore, the development of new asymmetric syntheses of 2*H*-azirine-2-carboxylates has attracted significant attention.



Azirinomycin (**1**)



(-)-(*E*)-Dysidazirine (**2**)

Chiral 2*H*-azirines have been prepared by the elimination reaction of N-substituted aziridines, namely, dehydrochlorination of *N*-chloroaziridines,[4a] Swern oxidation of aziridines[4b] and elimination from *N*-sulphynilaziridines.[4c] It has been reported that the dehydrochlorination of methyl 2-chloroaziridine-2-carboxylates generates enantiopure 2-substituted 2*H*-azirine-3-carboxylate, which was not isolated but could be trapped by Diels–Alder reaction with cyclopentadiene.[4d] These interesting methods involve, nevertheless, the use of high enantiopure aziridine esters as starting materials.

A different approach to chiral 2*H*-azirines consisting of an alkaloid-mediated Neber reaction has also been described.[5] In fact, the Neber rearrangement of *β*-ketoxime tosylates, derived from 3-oxocarboxylic acids, mediated by *Cinchona* alkaloids of *β*-ketoxime tosylates, afforded optically enriched 2*H*-azirines.[5c−e] The same strategy was applied to the synthesis of chiral 2-phosphinyl-2*H*-azirines[5f] and alkyl- and arylazirines carrying phosphonate groups,[5g] being the asymmetry attributed to a strong hydrogen bond formed between the base hydroxyl group and one of the S=O functionalities of the ketoxime. The enantioselective Neber reaction of *β*-ketoxime sulfonates catalyzed by a bifunctional chiral thiourea has also been reported.[5h]

It is well-established that 5-substituted 1*H*-tetrazoles are effective bioisosteres of carboxylic acids, with similar acidities, but higher lipophilicities and metabolic stability.[6] In fact, several literature works report the enhanced biological activity and metabolical stability of compounds in which the carboxylic group has been substituted by tetrazole. Thus, the tetrazole ring has been successfully incorporated into pharmacological drug formulations, namely, cardiovascular or hypertension drugs. Furthermore 1,5-disubstituted tetrazoles are conformational mimics of *cis* blocked peptide bonds, like those found in a wide variety of biologically important peptides.[7] Thus, in drug design, a strategy to find new lead compounds is to explore the carboxylic acid/tetrazole bioisosterism.[8]

We developed a general route to 2-halo-2*H*-azirines starting from haloazidoalkenes[9] and became, recently, interested in the development of synthetic routes to functionalized 5-(substituted)-1*H*-tetrazoles.[10] The hetero-Diels–Alder reaction of 3-(1*H*-tetrazol-5-yl)-1,2-diaza-1,3-butadienes and 3-(1*H*-tetrazol-5-yl)nitrosoalkenes was explored, giving access to a diversity

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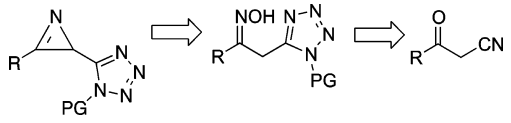
of tetrahydro-1,2-oxazines, tetrahydro-pyridazines, open-chain oximes, and hydrazones bearing the tetrazole moiety.

Herein, bringing together our interest in the chemistry of small ring heterocycles and tetrazoles, we report the synthesis of novel 2-(tetrazol-5-yl)-2*H*-azirines, isosteres of 2*H*-azirine-2-carboxylates. The target three-membered heterocyclic compounds can be particularly interesting as building blocks for the synthesis of new 5-substituted tetrazoles. The strategy outlined was to explore the Neber reaction of *β*-ketoxime tetrazole derivatives (Scheme 1).

Scheme 1. Synthetic Strategy for the Synthesis of 2-(1*H*-Tetrazol-5-yl)-2*H*-azirines



RESULTS AND DISCUSSION

Nitrile **3a** was prepared in high yield (90%) following a known synthetic procedure based on the acylation of nitrile anions with ethyl esters.[11] We were pleased to observe that the same approach could be applied to the synthesis of 3-oxo-3-(thiophen-2-yl)propanenitrile (**3c**), although, in this case, a longer reaction time was required (24 h), leading to the target compound in 70% yield. Cyanoacetylation of 1*H*-indole and 1*H*-pyrrole was also carried out by reacting these heterocycles with cyanoacetic acid and acetic anhydride, affording the corresponding *β*-ketonitriles **3d** and **3e** in 82% and 75% yield, respectively (Scheme 2).[12]

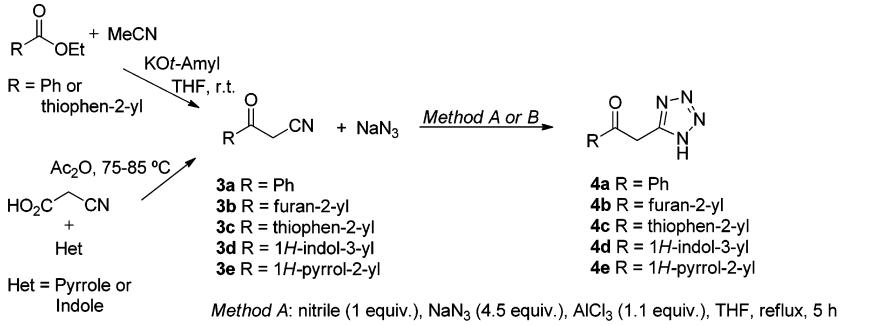
The conversion of nitriles **3** into the corresponding 1*H*-tetrazole derivatives was carried out by reaction with an azide source under Lewis acid catalysis[6,13,14] (Scheme 2 and Table 1). Nitrile **3a** reacted with aluminum azide, generated in situ by treatment of aluminum chloride with sodium azide in refluxing THF, to give 1*H*-tetrazole **4a** in 73% yield as previously described[13c] (Table 1, entry 1). However, when we tried to extend this method to other nitriles, the results were very disappointing. In fact, under these reaction conditions, *β*-keto-1*H*-tetrazole **4b** could only be isolated in very low yield from the commercially available *β*-ketonitrile **3b** (Table 1, entry 2). Thus, the approach to 5-substituted 1*H*-tetrazoles reported by Sharpless et al.[14] involving the reaction of nitriles with sodium azide and zinc bromide in water was explored. Initially, the reactivity of nitrile **3a** was studied under different reaction conditions. Carrying out the reaction under reflux for 24 h, the corresponding 1*H*-tetrazole **4a** was isolated in only 20% yield (entry 3). This result is in agreement with the reactivity previously observed for alkyl nitriles, which require very high temperatures, achieved by using sealed glass pressure reactors.[14] In consonance with this observation, the thermolysis of nitrile **3a** at 140 °C for 24 h in a sealed tube led to an improvement, allowing the isolation of 1*H*-tetrazole **4a** in 48% yield (entry 4). Furthermore, the increase of the reaction time to 36 h resulted in the synthesis of *β*-keto-1*H*-tetrazole **4a** in 77% yield (entry 5). Similar efficiency was observed when *β*-ketonitrile **3a** was subjected to sealed tube thermolysis at 170 °C for 24 h (entry 6). The same synthetic methodology was applied in the synthesis of 1*H*-tetrazoles **4b**−**4d** (entries 7−12). Carrying out the reaction for 24 h yields between 54% and 85% were obtained. However, these yields were significantly improved increasing the reaction time to 36 h. Under these conditions, 1*H*-tetrazoles **4b**, **4c**, and **4d** were obtained in 72, 66, and 94% yield, respectively (entries 8, 10, and 12). Because of the low pK_a of 1*H*-tetrazoles (ca. 3−5) and their highly crystalline nature, it is possible, by the simple acidification of alkaline aqueous solutions of *β*-keto-1*H*-tetrazoles **4a**−**4d**, to precipitate these compounds in pure form.

In the case of *β*-ketonitrile **3e**, the conversion into the corresponding 1*H*-tetrazole **4e** was not so efficient (entry 13). After heating in a sealed tube at 140 °C for 3 h, the reaction was stopped, since a dark precipitate was formed. Nevertheless, 1*H*-tetrazole **4e** could be isolated in 44% yield, obtained in pure form by crystallization of the crude product.

As an initial approach, we decided to explore the possibility of using ketoxime tosylates of unprotected *β*-keto-1*H*-tetrazoles in the synthesis of 2*H*-azirines. Ketoximes **5a** and **5c** were obtained in good yield by the reaction of the corresponding *β*-keto-1*H*-tetrazoles with hydroxylamine hydrochloride in EtOH/Py (Scheme 3). However, attempts to form the azirine from these tetrazoles via in situ tosylation in the presence of NEt_3 failed, leading only to degradation products. Therefore, we could conclude that the N-protection of the 5-substituted-tetrazoles **4** was necessary so that they could be used as 2*H*-azirine precursors.

The triphenylmethyl group (Tr) was initially selected as the protecting group since it is known that the tritylation of 5-substituted tetrazoles usually proceeds selectively at the 2-position of the tetrazole ring and deprotection can be achieved under mild reaction conditions.[6,15−17] Following a reported procedure,[15] we carried out the reaction of 1*H*-tetrazole **4a** with triphenylmethyl chloride in a mixture of toluene and aqueous sodium hydroxide solution, at room temperature for 4 h. However, no evidence for the N-protected derivative was observed. Since phase-transfer catalysis is often used,[16] the tritylation was also attempted under these conditions, but the

Scheme 2. Synthesis of *β*-Keto-1*H*-tetrazoles



Method A: nitrile (1 equiv.), NaN_3 (4.5 equiv.), $AlCl_3$ (1.1 equiv.), THF, reflux, 5 h
Method B: nitrile (1 equiv.), NaN_3 (1.1 equiv.), $ZnBr_2$ (1 equiv.), H_2O/*i*PrOH (10% v:v)

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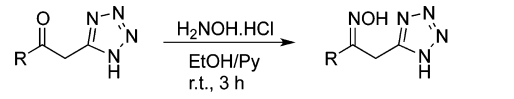
Table 1. Synthesis of 5-Substituted 1*H*-Tetrazoles from *β*-Ketonitriles[a]

entry	*β*-ketonitrile	reaction conditions	isolated yield of **4** (%)
1	**3a**	*Method A*	73
2	**3b**	*Method A*	12
3	**3a**	*Method B*, reflux, 24 h	20
4	**3a**	*Method B*, sealed tube, 140 °C, 24 h	48
5	**3a**	*Method B*, sealed tube, 140 °C, 36 h	77
6	**3a**	*Method B*, sealed tube, 170 °C, 24 h	76
7	**3b**	*Method B*, sealed tube, 140 °C, 24 h	54
8	**3b**	*Method B*, sealed tube, 140 °C, 36 h	72
9	**3c**	*Method B*, sealed tube, 140 °C, 24 h	58
10	**3c**	*Method B*, sealed tube, 140 °C, 36 h	66
11	**3d**	*Method B*, sealed tube, 140 °C, 24 h	85
12	**3d**	*Method B*, sealed tube, 140 °C, 36 h	94
13	**3e**	*Method B*, sealed tube, 140 °C, 3 h	44

[a]*Method A*: nitrile (1 equiv), NaN_3 (4.5 equiv), $AlCl_3$ (1.1 equiv), THF, reflux, 5 h. *Method B*: nitrile (1 equiv), NaN_3 (1.1 equiv), $ZnBr_2$ (1 equiv), H_2O/*i*PrOH (10% v:v).

Scheme 3. Synthesis of *β*-Ketoxime-1*H*-tetrazoles 5



4a R = Ph
4c R = thiophen-2-yl

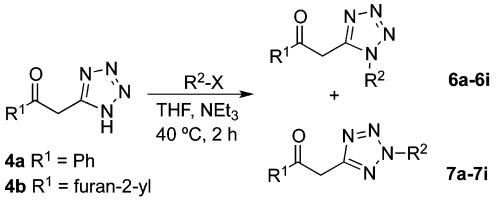
5a R = Ph 83%
5c R = thiophen-2-yl 77%

outcome was the same. We were pleased to observed that, when performing the reaction of 1*H*-tetrazole **4a** with triphenylmethyl chloride in the presence of triethylamine, in THF at 40 °C for 2 h,[17] the expected *N*-trityl-tetrazoles **6a**/**7a** were obtained in 81% overall yield. As expected, the N-protection was regioselective, giving the 2-trityl-2*H*-tetrazole **7a** as the major product (Table 2, entry 1). Using the same reaction conditions, tritylation of tetrazoles **4c** and **4e** was accomplished, leading to the desired products in high yields and good selectivities (entries 2 and 3).

Because the Neber rearrangement of *β*-ketoxime tosylates derived from *N*-trityl-tetrazole could be hampered due to the presence of the bulky trityl group, we decided to carry out the protection with less bulkier groups that could also be easily removed later on. Reaction of *β*-keto-1*H*-tetrazole **4a** with benzyl chloride in the presence of triethylamine, in THF at 40 °C for 1 h, gave the corresponding benzyl derivatives **6d** and **7d** as a 1:1 mixture in low yield (28%). However, using benzyl bromide as the N-protecting reagent, the target compounds could be obtained in good yield (71%), although in a 1:1 ratio of 1,5- and 2,5-disubstituted isomers (Table 1, entry 4). Aiming to achieve a better regioselectivity, the protection of **4a**−**4e** with *p*-nitrobenzyl bromide (PNBBr) was carried out under the optimized tritylation reaction conditions, resulting in the formation of the corresponding *p*-nitrobenzyl-tetrazole derivatives **6** and **7** in good overall yield (entries 5−9). The regioselectivity was dependent on the substituent at the 5-position. Nevertheless, moderate selectivity for the formation of 1,2-disubstituted-2*H*-tetrazoles was observed, starting from *β*-keto-1*H*-tetrazoles **4a**, **4b**, **4c**, and **4e**. In contrast with this observation, tetrazole **4d** bearing a 1*H*-indolyl group, afforded 1,5-disubstituted-1*H*-tetrazole **6i** as the major product (entry 8). The structural assignment of the *N*-protected tetrazoles was based on the analysis of the NOESY spectra of 2*H*-azirines derived from tetrazoles **6e** and **7e** (see below). Moreover, the regioisomeric *N*-benzyl and *N*-(*p*-nitrobenzyl)tetrazole derivatives can be easily distinguished by ^{1}H NMR. Isomers **6** always show the methylenic protons of the tetrazole 5-substituent at higher chemical shifts than isomers **7**, whereas the chemical shift of the methylenic protons of the protecting group are observed at lower chemical shifts (see Table S1, Supporting Information). The structural assignment of the *N*-protected tetrazoles was also confirmed by the analysis of the NOESY spectra of 2*H*-azirines derived from tetrazoles **6e** and **7e** (see below). Isomers **6** and **7** were easily separated by flash chromatography and were used separately in the following reactions.

β-Keto-1*H*-tetrazoles **6d**−**6i** and *β*-keto-2*H*-tetrazoles **7d**−**7i** were readily converted into the corresponding ketoximes **8a**−**8f** and **9a**−**9f**, respectively, by treatment with hydroxylamine hydrochloride in refluxing EtOH/pyridine for 3 h (Scheme 4). The target compounds **8** and **9** were obtained in high yields (81−98%) as a mixture of *syn* and *anti* isomers.

Table 2. Alkylation of *β*-Keto-1*H*-tetrazoles 4



4a R^1 = Ph
4b R^1 = furan-2-yl
4c R^1 = thiophen-2-yl
4d R^1 = 1*H*-indol-3-yl
4e R^1 = 1*H*-pyrrol-2-yl

6a-6i
7a-7i

a R^1 = Ph, R^2 = Tr
b R^1 = thiopen-2-yl, R^2 = Tr
c R^1 = 1*H*-pyrrol-2-yl, R^2 = Tr
d R^1 = Ph, R^2 = Bn
e R^1 = Ph, R^2 = PNB
f R^1 = furan-2-yl, R^2 = PNB
g R^1 = thiophen-2-yl, R^2 = PNB
h R^1 = 1*H*-indol-3-yl, R^2 = PNB
i R^1 = 1*H*-pyrrol-2-yl, R^2 = PNB

entry	*β*-keto-1*H*-tetrazole	R^2	overall yield (%)	(**6**:**7**)[a]
1	**4a**	Tr	81	(18:82)
2	**4c**	Tr	79	(10:90)
3	**4e**	Tr	90	(18:82)
4	**4a**	Bn	71	(50:50)[b]
5	**4a**	PNB	78	(40:60)
6	**4b**	PNB	77	(37:63)
7	**4c**	PNB	66	(43:57)
8	**4d**	PNB	69	(60:40)
9	**4e**	PNB	74	(46:54)

[a]Ratio determined by ^{1}H NMR. [b]Reaction time = 18 h.

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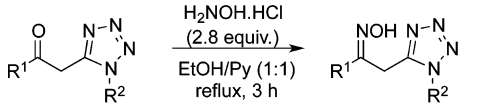
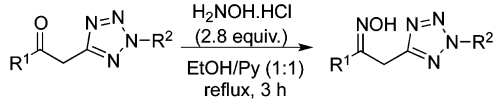
Scheme 4. Synthesis of β-Ketoxime-tetrazoles 8 and 9



6d-i

8a	R^1 = Ph, R^2 = Bn	87%
8b	R^1 = Ph, R^2 = PNB	84%
8c	R^1 = furan-2-yl, R^2 = PNB	81%
8d	R^1 = thiophen-2-yl, R^2 = PNB	96%
8e	R^1 = 1*H*-indol-3-yl, R^2 = PNB	98%
8f	R^1 = 1*H*-pyrrol-2-yl, R^2 = PNB	90%

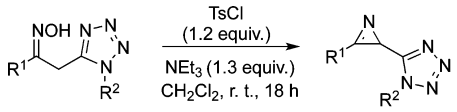


7d-i

9a	R^1 = Ph, R^2 = Bn	89%
9b	R^1 = Ph, R^2 = PNB	83%
9c	R^1 = furan-2-yl, R^2 = PNB	93%
9d	R^1 = thiophen-2-yl, R^2 = PNB	94%
9e	R^1 = 1*H*-indol-3-yl, R^2 = PNB	94%
9f	R^1 = 1*H*-pyrrol-2-yl, R^2 = PNB	92%

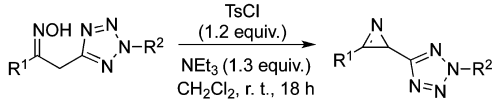
The synthesis of 2-(tetrazol-5-yl)-2*H*-azirines from β-ketoxime-tetrazoles via in situ tosylation in the presence of a base was then explored (Scheme 5). The reaction of β-ketoxime of *N*-

Scheme 5. Synthesis of 2*H*-Azirines 10 and 11



8a-d

10a	R^1 = Ph, R^2 = Bn	63%
10b	R^1 = Ph, R^2 = PNB	86%
10c	R^1 = furan-2-yl, R^2 = PNB	59%
10d	R^1 = thiophen-2-yl, R^2 = PNB	70%



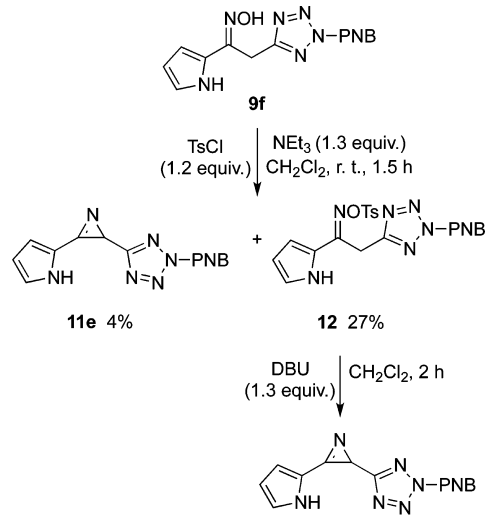
9a-d

11a	R^1 = Ph, R^2 = Bn	77%
11b	R^1 = Ph, R^2 = PNB	73%
11c	R^1 = furan-2-yl, R^2 = PNB	61%
11d	R^1 = thiophen-2-yl, R^2 = PNB	66%

trityltetrazoles **7a–7c** with tosyl chloride in the presence of triethylamine did not lead to the formation of the corresponding 2*H*-azirines. These results, although disappointing, were somehow expected due to the presence of the bulky trityl group. However, a different outcome was observed when the reaction of β-ketoxime-tetrazoles **8** and **9** was carried out. To our delight, treatment of β-ketoxime-1*H*-tetrazoles **8a–8d** with tosyl chloride and triethylamine in dichloromethane at room temperature for 18 h gave a smooth conversion into the desired 2*H*-azirines **10a–10d** in yields ranging from 59% to 86%. In a similar way, β-ketoxime-2*H*-tetrazoles **9a–9d** afforded the corresponding 2*H*-azirines **11a–11d** in good yield (61–77%). From the reaction of β-ketoximes **9c** and **9d**, the β-ketoxime tosylate intermediates were also isolated in low yield (6–7%). The structural assignment of compounds **10b**, **10d**, **11b**, and **11d** was established based on two-dimensional NOESY experiments. In the spectra of **10b** and **10d**, connectivity was observed between the proton of the 2*H*-azirine ring and the methylenic protons of the *p*-nitrobenzyl group, whereas, for azirines **11b** and **11d**, no connectivity was observed between the same protons.

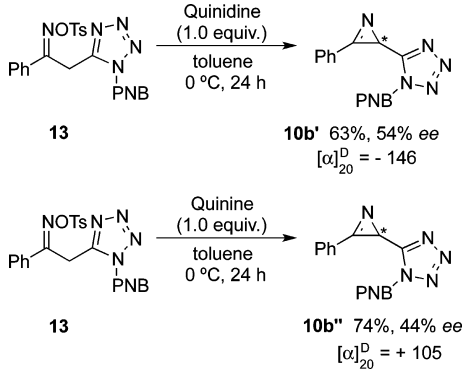
In the case of β-ketoximes **9e** and **9f**, the conversion into the corresponding 2*H*-azirines was not so straightforward. Reaction of **9e** with tosyl chloride in the presence of triethylamine for 18 h did not lead to the desired product, affording only degradation products. As for of β-ketoxime **9f**, after 1.5 h, the TLC control indicated that there was no more starting material, and due to the darkening of the reaction mixture, it was stopped. Nevertheless, after purification by flash chromatography, 2-(2*H*-tetrazol-5-yl)-2*H*-azirine **11e** and ketoxime tosylate **12** could be isolated in 4% and 27% yield, respectively. No reaction was observed when ketoxime tosylate **12** was treated with triethylamine in dichloromethane for 24 h. However, the DBU-mediated Neber reaction of ketoxime tosylate **12** gave the desired product in 23% yield (Scheme 6).

Scheme 6. Synthesis of 2*H*-Azirine 11e



We then investigated wether the two alkaloids, quinidine and quinine, first reported by Zwannenburg and co-workers,[5c] might be used effectively in the Neber reaction to achieve an asymmetric synthesis of 2*H*-azirine **10b**. To our delight, treatment of ketoxime tosylate **13** with a stoichiometric amount of quinidine in toluene at 0 °C for 24 h gave a smooth conversion to the desired enriched 2*H*-azirine **10b′** with 54% *ee* ($[\alpha]_D^{20}$ = −146, CH_2Cl_2, *c* = 1.3) (Scheme 7). On the other hand, carrying

Scheme 7. Asymmetric Synthesis of 2*H*-Azirine 10b



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out the reaction of **13** under the same reaction conditions, but in the presence of quinine, led to the synthesis of 2*H*-azirine **10b″** in good yield, albeit with 44% *ee* ($[\alpha]_D^{20}$ = +105, CH_2Cl_2, *c* = 1.0). The enantiomeric purity of 2*H*-azirines **10b′** and **10b″** was determined by NMR using $Yb(tfc)_3$ as a chiral shift reagent (20 mg shift reagent vs 20 mg substrate). The determination of enantiomeric excess was calculated by the ratio of the signals (two doublets) corresponding to the two aromatic *p*-nitrobenzylic protons observed at higher chemical shift. As previously observed in Zwannenburg's work, the pseudoenantiomers of the alkaloid bases gave opposite antipodes of the 2*H*-azirine **10b**.

Correlation with the optical rotation previously reported for (*S*)- and (*R*)-3-phenyl-2*H*-azirine-2-carboxylates[4b] allows us to propose the absolute configuration of 2*H*-azirines **10b**. Thus, 2*H*-azirine **10b′** is characterized by an optical rotation with a negative sign, indicating that the use of quinidine leads predominantly to the *R* enantiomer. On the other hand, the quinine-mediated Neber reaction led to 2*H*-azirine **10b″** having an optical rotation with a positive sign corresponding to the selective formation of the *S* enantiomer.

CONCLUSIONS

Synthesis of novel 2-(tetrazol-5-yl)-2*H*-azirines bearing phenyl, furan-2-yl, thiophen-2-yl, and pyrrol-2-yl substituents at C-3 via the Neber reaction of *β*-ketoxime tetrazole derivatives is reported. These three-membered heterocyclic compounds can be particularly interesting as building blocks for the synthesis of new 5-substituted tetrazoles. Preliminary studies on the asymmetric synthesis of 2-(tetrazol-5-yl)-2*H*-azirines showed that quinidine- and quinine-mediated Neber reactions lead to enantioselectivity, being the major enantiomer dependent on the alkaloid used.

EXPERIMENTAL SECTION

NMR spectra were run in $CDCl_3$ or DMSO-d_6 on a 400 MHz instrument and recorded at the following frequencies: proton (^{1}H, 400 MHz), carbon (^{13}C, 100 MHz). Chemical shifts are expressed in parts per million related to internal TMS and coupling constants (*J*) are in hertz. Infrared spectra (IR) were recorded on a Fourier transform spectrometer. Mass spectra were recorded under electrospray ionization (ESI). Melting points were determined in open glass capillaries and are uncorrected. Thin-layer chromatography (TLC) analyses were performed using precoated silica gel plates. Flash column chromatography was performed with silica gel 60 as the stationary phase. Optical rotations were recorded with a path length of 1 dm, and concentrations, *c*, are in g/100 mL. The preparation of 5-substituted-tetrazoles was carried out in an Ace pressure tube, Bushing type, B (volume ∼ 35 mL). Nitriles were prepared using general procedures described in the literature (**3a**,[11] **3c**,[11] **3d**,[12] and **3e**[12]).

3-Oxo-3-(thiophen-2-yl)propanenitrile (3c). Nitrile **3c** was prepared following the reported procedure[11] with a slight modification. To a solution of acetonitrile (1.0 equiv, 3.5 mmol) in THF (12 mL) stirred at room temperature was added dropwise a solution of KO*t*-Amyl (3.0 equiv, 1.7 M in PhMe), followed by dropwise addition of ethyl thiophenecarboxylate (3 equiv). After 24 h at room temperature, the reaction mixture was diluted with 0.25 M HCl (120 mL) and ethyl acetate (120 mL). The layers were separated, and the organic layer was washed sequentially with H_2O (2 × 50 mL) and brine (2 × 50 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated off, affording the corresponding nitrile **3c** ,which was recrystallized in ethyl acetate/hexane. Yield: 70%, 0.37 g, light yellow solid, mp 131−133 °C; IR (KBr) 735, 857, 1232, 1394, 1416, 1516, 1666, 2256, 2951, 3091, 3115 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 4.00 (s, 2H), 7.20 (t, *J* = 4.4 Hz, 1H), 7.78−7.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 29.6, 113.5, 128.7, 133.7, 136.3, 140.9, 179.6; HRMS (ESI, TOF) calcd for C_7H_6NOS 152.01646 [MH^+], found 152.01679.

General Procedure for the Preparation of 5-Substituted-1*H*-Tetrazoles. Tetrazoles were prepared following the reported procedure[14] with a slight modification. To a pressure tube was added the nitrile (5.17 mmol), sodium azide (0.37 g, 5.69 mmol), zinc bromide (1.16 g, 5.17 mmol), water (12 mL), and ^{i}PrOH (1.5 mL). The sealed tube was submerged in an oil bath at 140 °C and stirred vigorously for the appropriate time. After cooling the tube to room temperature, the tube was opened, HCl (3 N, 8 mL) and ethyl acetate (25 mL) were added, and vigorous stirring was continued until no solid was present. The organic layer was isolated, and the aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were evaporated, 50 mL of 0.25 N NaOH was added, and the mixture was stirred for 30 min, until the original precipitate was dissolved and a suspension of zinc hydroxide was formed. The suspension was filtered through Celite, and the Celite pad was washed with 5 mL of 1 N NaOH. To the filtrate was added 10 mL of 3 N HCl with vigorous stirring, causing the tetrazole to precipitate. The tetrazole was filtered and dried.

*1-Phenyl-2-(1H-tetrazol-5-yl)ethanone) (**4a**):*[13c] Yield: 76%, 0.74 g, light yellow solid, mp 178−180 °C (187−188 °C from literature);[13c] IR (KBr) 1385, 1450, 1568, 1597, 1684, 2895, 2951, 3028 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 4.96 (s, 2H), 7.60 (pseudo t, *J* = 7.6 Hz, 2H), 7.71−7.73 (m, 1H), 8.10 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 34.0, 128.4, 128.9, 134.0, 135.4, 150.8, 193.9; HRMS (ESI, TOF) calcd for $C_9H_9N_4O$ 189.07709 [MH^+], found 189.07693.

*1-(Furan-2-yl)-2-(1H-tetrazol-5-yl)ethanone (**4b**):* Yield: 72%, 0.66 g, brown solid, mp 181−183 °C; IR (KBr) 1396, 1464, 1574, 1672, 2854, 2966, 3142 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6,) *δ* 4.71 (s, 2H), 6.80−6.81 (m, 1H), 7.69 (d, *J* = 3.2 Hz, 1H), 8.11 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 33.3, 112.9, 120.4, 148.8, 150.7, 181.6; HRMS (ESI, TOF) calcd for $C_7H_6N_4NaO_2$ 201.03830 [MNa^+], found 201.03759.

*2-(1H-Tetrazol-5-yl)-1-(thiophen-2-yl)ethanone (**4c**):* Yield: 73%, 0.73 g, light brown solid, mp 166−168 °C; IR (KBr) 1328, 1417, 1524, 1560, 1655, 2891, 3007, 3099 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 4.89 (s, 2H), 7.33 (pseudo t, *J* = 4.4 Hz, 1H), 8.12 (d, *J* = 4.8 Hz, 1H), 8.19 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 34.1, 129.0, 135.0, 136.2, 142.2, 150.5, 186.7; HRMS (ESI,TOF) calcd for $C_7H_6N_4NaOS$ 217.01545 [MNa^+], found 217.01535.

*1-(1H-Indol-3-yl)-2-(1H-tetrazol-5-yl)ethanone (**4d**):* Yield: 94%, 1.10 g, light pink solid, mp 223−225 °C; IR (film) 1437, 1520, 1549, 1631, 3055, 3288 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 4.72 (s, 2H), 7.19−7.26 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 8.60 (d, *J* = 2.8 Hz, 1H), 12.36 (br s, N-H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 34.1, 112.4, 115.2, 121.0, 122.1, 123.1, 125.3, 135.4, 136.7, 187.6; HRMS (ESI, TOF) calcd for $C_{11}H_9N_5NaO$ 250.06993 [MNa^+], found 250.06985.

*1-(1H-Pyrrol-2-yl)-2-(1H-tetrazol-5-yl)ethanone (**4e**):* Yield: 44%, 0.40 g, brown solid, mp 235−237 °C; IR (KBr) 1402, 1443, 1545, 1651, 2713, 2870, 3307 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 4.59 (s, 2H), 6.27 (pseudo t, *J* = 1.6 Hz, 1H), 7.19−7.22 (m, 2H), 12.02 (br s, N-H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 32.8, 110.3, 118.3, 126.8, 130.4, 182.2; HRMS (ESI, TOF) calcd for $C_7H_8N_5O$ 178.07234 [MH^+], found 178.07223.

General Procedure for the Preparation of 2-Trityl-5-Substituted-2*H*-tetrazoles. 5-Substituted-1*H*-tetrazole (10 mmol) was slurried in THF (12 mL), and Et_3N (1.48 mL, 10.5 mmol) was added. The temperature of the solution was increased to 40 °C, and triphenylmethyl chloride (10.5 mmol) in THF (6 mL) was added slowly. The solution was stirred at 40 °C for 5 h, whereupon the mixture was allowed to cool and the precipitated triethylammonium chloride was filtered, and washed with cold THF. The solvent was evaporated under vacuum, giving the crude product as a mixture of the 1,5- and 2,5-disubstituted isomers. The 2,5-disubstituted isomer **7** was the major isomer and was isolated by recrystallization in diethyl ether.

*2-(1-Trityl-1H-tetrazol-5-yl)-1-phenylethanone (**6a**) and 2-(2-Trityl-2H-tetrazol-5-yl)-1-phenylethanone (**7a**):* Yield: 81%, 3.49 g. **6a** and **7a** were obtained in a (18:82) ratio, and compound **7a** was separated by recrystallization in diethyl ether. *2-(2-Trityl)-2H-tetrazol-5-yl)-1-phenylethanone* (**7a**): Light yellow solid, mp 142−144 °C; IR (KBr) 698, 756, 1001, 1448, 1493, 1597, 1695, 3061 cm^{-1}; ^{1}H NMR

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(400 MHz, $CDCl_3$) δ 4.64 (s, 2H), 7.10−7.11 (m, 6H), 7.29−7.35 (m, 9H), 7.44−7.48 (m, 2H), 7.57−7.60 (m, 1H), 7.98 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.6, 83.1, 127.8, 127.9, 128.3, 128.5, 128.8, 130.2, 133.5, 136.0, 141.3, 159.8, 193.7; HRMS (ESI, TOF) calcd for $C_{28}H_{22}N_4NaO$ 453.16858 [MNa^+], found 453.16766.

*2-(1-Trityl-1H-tetrazol-5-yl)-1-(thiophen-2-yl)ethanone (**6b**) and 2-(2-Trityl-2H-tetrazol-5-yl)-1-(thiophen-2-yl)ethanone (**7b**):* Yield: 79%, 3.45 g. **6b** and **7b** were obtained in a (10:90) ratio, and compound **7b** was separated by recrystallization in diethyl ether. *2-(2-Trityl)-2H-tetrazol-5-yl)-1-(thiophen-2-yl)ethanone* (**7b**): Light yellow solid, mp 136−138 °C; IR (KBr) 638, 698, 748, 1225, 1416, 1446, 1493, 1668, 3064 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (s, 2H), 7.11−7.14 (m, 7H), 7.30−7.35 (m, 9H), 7.67 (d, J = 4.8 Hz, 1H), 7.78 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.1, 83.2, 127.8, 128.2, 128.4, 130.2, 133.0, 134.4, 141.2, 142.9, 159.4, 186.3; HRMS (ESI, TOF) calcd for $C_{26}H_{20}N_4NaOS$ 459.12500 [MNa^+], found 459.12585.

*1-(1H-Pyrrol-2-yl)-2-(1-Trityl-1H-tetrazol-5-yl)ethanone (**6c**) and 1-(1H-Pyrrol-2-yl)-2-(2-trityl-2H-tetrazol-5-yl)ethanone (**7c**):* Yield: 90%, 3.77 g. **6c** and **7c** were obtained in a (18:82) ratio, and compound **7c** was separated by recrystallization in diethyl ether. *1-(1H-Pyrrol-2-yl)-2-(2-trityl-2H-tetrazol-5-yl)ethanone* (**7c**): Light yellow solid, mp 122−124 °C; IR (KBr) 640, 700, 754, 883, 1109, 1275, 1398, 1444, 1639, 1778, 3290 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.53 (s, 2H), 6.23−6.25 (m, 1H), 7.01−7.05 (m, 6H), 7.11−7.13 (m, 1H), 7.15−7.16 (m, 1H), 7.37−7.41 (m, 9H), 11.96 (br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 35.0, 82.2, 110.1, 118.0, 126.4, 127.9, 128.4, 129.6, 130.6, 140.9, 160.5, 183.2; HRMS (ESI, TOF) calcd for $C_{26}H_{21}N_5NaO$ 442.16383 [MNa^+], found 442.16368.

General Procedure for the Alkylation of 5-Substituted-1H-Tetrazoles with Benzyl Bromides. 5-Substituted-1*H*-tetrazole (10 mmol) was slurried in THF (12 mL), and Et_3N (1.48 mL, 10.5 mmol) was added. The temperature of the solution was increased to 40 °C, and benzyl bromide or *p*-nitrobenzyl bromide (10.5 mmol) in THF (6 mL) was added slowly. The solution was stirred at 40 °C for 2−3 h, whereupon the mixture was allowed to cool and the precipitate triethylammonium bromide was filtered and washed with cold THF. The solvent was evaporated under vacuum, giving the crude product as a variable mixture of the 1,5- and 2,5-disubstituted isomers, which were separated by flash chromatography (ethyl acetate/hexane).

*2-(1-Benzyl-1H-tetrazol-5-yl)-1-phenylethanone (**6d**) and 2-(2-Benzyl-2H-tetrazol-5-yl)-1-phenylethanone (**7d**):* Yield: 71%, 1.98 g. **6d** and **7d** were obtained in a (50:50) ratio and separated by flash chromatography [ethyl acetate/hexane (1:1)], giving by order of elution: *2-(2-Benzyl-2H-tetrazol-5-yl)-1-phenylethanone* (**7d**): Yellow solid, mp 63−65 °C; IR (KBr) 995, 1219, 1396, 1448, 1597, 1705, 2968, 3062 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.81 (s, 2H), 5.94 (s, 2H), 7.34−7.42 (m, 5H), 7.55−7.58 (m, 2H), 7.67−7.71 (m, 1H), 8.05 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 35.7, 55.8, 128.2, 128.4, 128.5, 128.8, 133.7, 134.2, 135.7, 161.0, 194.7; HRMS (ESI, TOF) calcd for $C_{16}H_{15}N_4O$ 279.12404 [MH^+], found 279.12332. *2-(1-Benzyl-1H-tetrazol-5-yl)-1-phenylethanone* (**6d**): Yellow solid, mp 119−121 °C; IR (KBr) 993, 1217, 1333, 1467, 1599, 1687, 2962, 3070 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.07 (s, 2H), 5.64 (s, 2H), 7.31−7.34 (m, 5H), 7.57−7.61 (m, 2H), 7.71−7.74 (m, 1H), 8.05 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.7, 50.0, 128.2, 128.5, 128.7, 128.8, 134.0, 134.5, 135.3, 150.7, 193.4; HRMS (ESI, TOF) calcd for $C_{16}H_{15}N_4O$ 279.12404 [MH^+], found 279.12334.

*2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-1-phenylethanone (**6e**) and 2-(2-(4-Nitrobenzyl)-2H-tetrazol-5-yl)-1-phenylethanone (**7e**):* Yield: 78%, 2.52 g. **6e** and **7e** were obtained in a (40:60) ratio and separated by flash chromatography [ethyl acetate/hexane (1:1)], giving by order of elution: *2-(2-(4-Nitrobenzyl)-2H-tetrazol-5-yl)-1-phenylethanone* (**7e**): Light yellow solid, mp 112−114 °C; IR (KBr) 1352, 1518, 1597, 1691, 2958 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.83 (s, 2H), 6.15 (s, 2H), 7.55−7.61 (m, 4H), 7.68−7.71 (m, 1H), 8.05 (d, J = 7.6 Hz, 2H), 8.27 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 36.6, 54.9, 124.0, 128.8, 129.5, 133.8, 135.6, 147.5, 161.3, 194.6; HRMS (ESI, TOF) calcd for $C_{16}H_{14}N_5O_3$ 324.10912 [MH^+], found 324.10920. *2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-1-phenylethanone* (**6e**): Light yellow solid, mp 192−194 °C; IR (KBr) 1350, 1518, 1597, 1676, 1691, 2968; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.11 (s, 2H), 5.82 (s, 2H), 7.54−7.61 (m, 4H), 7.70−7.72 (m, 1H), 8.03 (d, J = 7.6 Hz, 2H), 8.22 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.7, 49.1, 123.7, 128.5, 128.8, 129.4, 134.1, 135.3, 141.9, 147.3, 151.2, 193.5; HRMS (ESI, TOF) calcd for $C_{16}H_{14}N_5O_3$ 324.10912 [MH^+], found 324.10912.

*1-(Furan-2-yl)-2-(1-(4-nitrobenzyl)-1H-tetrazol-5-yl)ethanone (**6f**) and 1-(Furan-2-yl)-2-(2-(4-nitrobenzyl)-2H-tetrazol-5-yl)ethanone (**7f**):* Yield: 77%, 2.41 g. **6f** and **7f** were obtained in a (37:63) ratio and separated by flash chromatography [ethyl acetate/hexane (1:1)], giving by order of elution: *1-(Furan-2-yl)-2-(2-(4-nitrobenzyl)-2H-tetrazol-5-yl)ethanone* (**7f**): Brown solid, mp 106−108 °C; IR 1344, 1460, 1525, 1566, 1668, 3003 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.64 (s, 2H), 6.19 (s, 2H), 6.82−6.83 (m, 1H), 7.65−7.69 (m, 3H), 8.11 (br s, 1H), 8.32 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 35.0, 54.8, 112.8, 120.2, 124.0, 129.6, 141.2, 147.5, 148.6, 150.9, 160.8, 182.3; HRMS (ESI, TOF) calcd for $C_{14}H_{12}N_5O_4$ 314.08838 [MH^+], found 314.08911. *1-(Furan-2-yl)-2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-ethanone* (**6f**): Brown solid, mp 154−156 °C; IR 1345, 1460, 1524, 1661, 3005 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.89 (s, 2H), 5.84 (s, 2H), 6.80−6.81 (m, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 3.6 Hz, 1H), 8.09 (br s, 1H), 8.23 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.0, 49.2, 112.9, 120.3, 123.7, 129.4, 141.9, 147.3, 148.7, 150.5, 150.6, 181.1; HRMS (ESI, TOF) calcd for $C_{14}H_{12}N_5O_4$ 314.08838 [MH^+], found 314.08828.

*2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-1-(thiophen-2-yl)ethanone (**6g**) and 2-(2-(4-Nitrobenzyl)-2H-tetrazol-5-yl)-1-(thiophen-2-yl)-ethanone (**7g**):* Yield: 66%, 2.17 g. **6g** and **7g** were obtained in a (43:57) ratio and separated by flash chromatography [ethyl acetate/hexane (1:1)], giving by order of elution: *2-(2-(4-Nitrobenzyl)-2H-tetrazol-5-yl)-1-(thiophen-2-yl)ethanone* (**7g**): Brown solid, mp 120−122 °C; IR 1346, 1416, 1527, 1657, 2980 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.75 (s, 2H), 6.14 (s, 2H), 7.30 (pseudo t, J = 4.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 4.8 Hz, 1H), 8.13 (d, J = 3.6 Hz, 1H), 8.26 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 35.7, 54.8, 124.0, 128.9, 129.6, 134.8, 136.0, 141.3, 142.5, 147.5, 161.0, 187.4; HRMS (ESI, TOF) calcd for $C_{14}H_{11}N_5NaO_3S$ 352.04748 [MNa^+], found 352.04754. *2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-1-(thiophen-2-yl)ethanone* (**6g**): Brown solid, mp 174−176 °C; IR 1346, 1414, 1518, 1655, 2968 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.06 (s, 2H), 5.84 (s, 2H), 7.33 (pseudo t, J = 4.4 and 4.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 8.12 (d, J = 4.8 Hz, 1H), 8.17 (d, J = 3.6 Hz, 1H), 8.22 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 33.6, 49.2, 123.7, 129.0, 129.4, 135.2, 136.3, 141.9, 147.3, 150.8, 186.1; HRMS (ESI, TOF) calcd for $C_{14}H_{12}N_5O_3S$ 330.06554 [MH^+], found 330.06573.

*1-(1H-Indol-3-yl)-2-(1-(4-nitrobenzyl)-1H-tetrazol-5-yl)ethanone (**6h**) and 1-(1H-Indol-3-yl)-2-(2-(4-nitrobenzyl)-2H-tetrazol-5-yl)-ethanone (**7h**):* Yield: 69%, 2.50 g. **6h** and **7h** were obtained in a (60:40) ratio and separated by flash chromatography [ethyl acetate/hexane (2:1)], giving by order of elution: *1-(1H-Indol-3-yl)-2-(2-(4-nitrobenzyl)-2H-tetrazol-5-yl)ethanone* (**7h**): Light yellow solid, mp 181−183 °C; IR 1346, 1428, 1522, 1633, 2950, 3222 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.59 (s, 2H), 6.14 (s, 2H), 7.19−7.26 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 8.12 (d, J = 7.6 Hz, 1H), 8.27 (d, J = 8.4 Hz, 2H), 8.51 (d, J = 3.2 Hz, 1H), 12.09 (br s, N-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 36.0, 54.8, 112.2, 115.5, 121.1, 122.0, 123.0, 124.0, 125.3, 129.6, 135.2, 136.6, 141.4, 147.5, 162.0, 188.6; HRMS (ESI, TOF) calcd for $C_{18}H_{15}N_6O_3$ 363.12001 [MH^+], found 363.11888. *1-(1H-Indol-3-yl)-2-(1-(4-nitrobenzyl)-1H-tetrazol-5-yl)-ethanone* (**6h**): Light yellow solid, mp 189−191 °C; IR 1346, 1429, 1524, 1633, 2968, 3111, 3419 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.94 (s, 2H), 5.91 (s, 2H), 7.24−7.30 (m, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 7.6 Hz, 1H), 8.26 (d, J = 8.4 Hz, 2H), 8.61 (s, 1H), 12.23 (br s, N-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.6, 49.3, 112.3, 115.2, 121.1, 122.1, 123.2, 123.7, 125.2, 129.4, 135.5, 136.6, 142.0, 147.2, 151.6, 187.1; HRMS (ESI, TOF) calcd for $C_{18}H_{15}N_6O_3$ 363.12001 [MH^+], found 363.11887.

*2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-1-(1H-pyrrol-2-yl)ethanone (**6i**) and 2-(2-(4-Nitrobenzyl)-2H-tetrazol-5-yl)-1-(1H-pyrrol-2-yl)-ethanone (**7i**):* Yield: 74%, 2.31 g. **6i** and **7i** were obtained in a (46:54) ratio and separated by flash chromatography [ethyl acetate/

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hexane (2:1)], giving by order of elution: *2-(2-(4-Nitrobenzyl)-2H-tetrazol-5-yl)-1-(1H-pyrrol-2-yl)ethanone* (**7i**): Brown solid, mp 141−143 °C; IR 1344, 1394, 1518, 1643, 3372 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.46 (s, 2H), 6.13 (s, 2H), 6.24 (br s, 1H), 7.15 (br s, 2H), 7.61 (d, J = 8.4 Hz, 2H), 8.26 (d, J = 8.4 Hz, 2H), 11.94 (br s, N-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.7, 54.8, 110.1, 118.1, 123.9, 126.5, 129.5, 130.7, 141.3, 147.5, 161.7, 183.1; HRMS (ESI, TOF) calcd for $C_{14}H_{12}N_6NaO_3$ 335.08631 [MNa^+], found 335.08675. *2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-1-(1H-pyrrol-2-yl)ethanone* (**6i**): Brown solid, mp 221−222 °C; IR 1348, 1396, 1514, 1641, 3411 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.79 (s, 2H), 5.84 (s, 2H), 6.28 (br s, 1H), 7.18 (br s, 1H), 7.24 (br s, 1H), 7.55 (d, J = 8.4 Hz, 2H), 8.22 (d, J = 8.4 Hz, 2H), 12.00 (br s, N-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 32.4, 49.2, 110.3, 118.6, 123.7, 126.9, 129.3, 130.2, 142.0, 147.2, 151.3, 181.7; HRMS (ESI, TOF) calcd for $C_{14}H_{13}N_6O_3$ 313.10436 [MNa^+], found 313.10347.

General Procedure for the Preparation of Oximes 8 and 9. Tetrazoles **6** or **7** (3.5 mmol) were dissolved in a mixture of ethanol/pyridine (1:1) (10 mL), and hydroxylamine hydrochloride (3 equiv, 10.5 mmol, 0.73 g) was added. The reaction mixture was heated under reflux for 3 h. The solvent was evaporated under reduced pressure, and the crude substrate was dissolved in cold water (20 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated off, affording the corresponding oximes, which were recrystallized in diethyl ether.

2-(1-Benzyl-1H-tetrazol-5-yl)-1-phenylethanone oxime (***8a***): Yield: 87%, 0.89 g, white solid, mp 142−144 °C; IR (KBr) 1066, 1109, 1288, 1493, 1514, 3037, 3207 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.42 (s, 2H), 5.72 (s, 2H), 7.28−7.30 (m, 2H), 7.38−7.40 (m, 6H), 7.61−7.63 (m, 2H), 11.83 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.8, 49.8, 126.0, 127.9, 128.3, 128.4, 128.8, 129.1, 134.4, 134.9, 150.4, 152.1; HRMS (ESI) calcd for $C_{16}H_{16}N_5O$ 294.13494 [MH^+], found 294.13415.

2-(2-Benzyl-2H-tetrazol-5-yl)-1-phenylethanone oxime (***9a***): Yield: 89%, 0.91 g, white solid, mp 99−101 °C; IR (KBr) 970, 1273, 1444, 1489, 2931, 3068 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.37 (s, 2H), 5.85 (s, 2H), 7.22−7.24 (m, 2H), 7.33−7.37 (m, 6H), 7.66−7.67 (m, 2H), 11.57 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.9, 55.6, 126.0, 128.0, 128.3, 128.4, 128.7, 128.9, 134.2, 135.4, 151.4, 162.7; HRMS (ESI) calcd for $C_{16}H_{16}N_5O$ 294.13494 [MH^+], found 294.13413.

2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-1-phenylethanone oxime (***8b***): Yield: 84%, 1.00 g, white solid, mp 172−174 °C; IR (KBr) 1348, 1417, 1510, 1525, 1608, 3217 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.34 (s, 2H), 5.91 (s, 2H), 7.37−7.39 (m, 3H), 7.50 (d, J = 8.8 Hz, 2H), 7.64−7.66 (m, 2H), 8.24 (d, J = 8.4 Hz, 2H), 11.76 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.9, 49.0, 123.8, 126.0, 128.4, 129.0, 129.1, 134.9, 141.8, 147.3, 150.4, 152.6; HRMS (ESI, TOF) calcd for $C_{16}H_{15}N_6O_3$ 339.12001 [MH^+], found 339.12065.

2-(2-(4-Nitrobenzyl)-2H-tetrazol-5-yl)-1-phenylethanone oxime (***9b***): Yield: 83%, 0.98 g, white solid, mp 138−140 °C; IR (KBr) 1348, 1489, 1525, 1612, 2857, 3242 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.38 (s, 2H), 6.06 (s, 2H), 7.36−7.37 (m, 3H), 7.47 (d, J = 8.4 Hz, 2H), 7.66−7.67 (m, 2H), 8.21 (d, J = 8.4 Hz, 2H), 11.58 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.9, 54.6, 123.8, 126.0, 128.3, 128.8, 129.2, 134.4, 141.4, 147.4, 151.4, 163.0; HRMS (ESI, TOF) calcd for $C_{16}H_{15}N_6O_3$ 339.12001 [MH^+], found 339.12082.

1-(Furan-2-yl)-2-(1-(4-nitrobenzyl)-1H-tetrazol-5-yl)ethanone oxime (***8c***): Yield: 81%, 0.93 g, light brown solid, mp 136−138 °C; IR (KBr) 951, 1111, 1352, 1460, 1525, 1610, 2858, 3161 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.32 and 4.38 (s, 2H), 5.87 and 5.91 (s, 2H), 6.58 and 6.64 (br s, 1H), 6.84 (d, J = 2.8 Hz) and 7.33 (d, J = 3.2 Hz), 7.49−7.56 (m, 2H), 7.70 and 7.72 (br s, 1H), 8.24 (d, J = 8.4 Hz, 2H), 11.68 and 11.77 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.8 and 25.4, 49.0, 110.4, 111.7, 112.3, 117.2, 123.8, 129.0, 129.3, 140.2, 141.8, 143.0 and 143.1, 144.2 and 144.6, 147.3, 149.0, 152.4 and 152.8; HRMS (ESI, TOF) calcd for $C_{14}H_{13}N_6O_4$ 329.09928 [MH^+], found 329.09876.

1-(Furan-2-yl)-2-(2-(4-nitrobenzyl)-2H-tetrazol-5-yl)ethanone oxime (***9c***): Yield: 93%, 1.07 g, light brown solid, mp 124−126 °C; IR (KBr) 986, 1198, 1348, 1514, 1606, 3149, 3440 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.19 and 4.23 (s, 2H), 6.09 (s, 2H), 6.55 (pseudo t, J = 1.2 Hz, 1H) and 6.62 (pseudo t, J = 1.6 Hz, 1H), 6.79 (d, J = 3.2 Hz) and 7.34 (d, J = 3.2 Hz), 7.50−7.54 (m, 2H), 7.70 and 7.71 (br s, 1H), 8.24 (d, J = 8.4 Hz, 2H), 11.51 and 11.72 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.0, 54.7, 110.0, 111.6, 112.1, 117.0, 123.9, 129.2 and 129.3, 141.2 and 141.5, 142.9, 143.9, 145.0, 147.4, 163.8; HRMS (ESI, TOF) calcd for $C_{14}H_{13}N_6O_4$ 329.09928 [MH^+], found 329.09955.

2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-1-(thiophen-2-yl)ethanone oxime (***8d***): Yield: 96%, 1.16 g, white solid, mp 164−167 °C; IR (KBr) 951, 1350, 1425, 1470, 1527, 1601, 2845, 2989, 3147 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.45 (s, 2H), 5.91 (s, 2H), 7.07 (pseudo t, J = 4.4 Hz and J = 4.0 Hz, 1H), 7.41 (d, J = 3.2 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 5.2 Hz, 1H), 8.23 (d, J = 8.4 Hz, 2H), 11.70 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.4, 49.0, 123.8, 127.3, 127.4, 127.5, 128.9, 138.8, 141.8, 146.7, 147.3, 152.3; HRMS (ESI, TOF) calcd for $C_{14}H_{13}N_6O_3S$ 345.07644 [MH^+], found 345.07683.

2-(2-(4-Nitrobenzyl)-2H-tetrazol-5-yl)-1-(thiophen-2-yl)ethanone oxime (***9d***): Yield: 94%, 1.13 g, white solid, mp 133−138 °C; IR (KBr) 964, 1340, 1435, 1493, 1527, 1612, 2951, 3111, 3236 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.33 and 4.37 (s, 2H), 6.09 (s, 2H), 7.05 (pseudo t, J = 4.4 Hz and J = 4.0 Hz, 1H) and 7.11 (pseudo t, J = 4.4 Hz), 7.36 (d, J = 3.2 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 4.8 Hz, 1H), 8.23 (d, J = 8.4 Hz, 2H), 11.50 and 12.01 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.4 and 29.8, 54.7, 123.9, 125.6, 127.0, 127.3, 129.1, 129.3, 129.4, 130.6, 130.9, 139.4, 141.4, 144.7, 147.4 and 147.8, 162.7 and 162.8; HRMS (ESI, TOF) calcd for $C_{14}H_{13}N_6O_3S$ 345.07644 [MH^+], found 345.07687.

1-(1H-Indol-3-yl)-2-(1-(4-nitrobenzyl)-1H-tetrazol-5-yl)ethanone oxime (***8e***): Yield: 98%, 1.29 g, light yellow solid, mp 197−200 °C; IR (KBr) 1103, 1348, 1406, 1437, 1524, 1595, 1608, 3128, 3263 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 446 (s, 2H), 5.91 (s, 2H), 7.03 (pseudo t, J = 7.2 Hz and J = 7.6 Hz, 1H), 7.15 (pseudo t, J = 7.6 Hz and J = 7.2 Hz, 1H), 7.38−7.43 (m, 3H), 7.77 (s,1H), 7.99 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.4 Hz, 2H), 11.12 (br s, N-H), 11.40 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.7, 48.9, 111.4, 111.6, 119.9, 122.2, 123.7, 123.9, 124.2, 127.2, 128.7, 136.1, 136.8, 141.9, 147.1, 148.1, 149.6, 153.2; HRMS (ESI, TOF) calcd for $C_{18}H_{16}N_7O_3$ 378.13091 [MH^+], found 378.13240.

1-(1H-Indol-3-yl)-2-(2-(4-nitrobenzyl)-2H-tetrazol-5-yl)ethanone oxime (***9e***): Yield: 94%, 1.24 g, light yellow solid, mp 193−195 °C; IR (KBr) 906, 1340, 1439, 1495, 1518, 1612, 3076, 3246 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.35 (s, 2H), 6.05 (s, 2H), 7.06 (pseudo t, J = 7.2 Hz and J = 7.6 Hz, 1H), 7.15 (pseudo t, J = 7.6 Hz and J = 7.2 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.72 (s,1H), 8.11 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.4 Hz, 2H), 10.82 (br s, N-H), 11.34 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.8, 54.6, 111.5, 112.0, 119.8, 122.1, 122.4, 123.9, 124.4, 126.9, 129.2, 136.8, 141.5, 147.4, 149.3, 163.8; HRMS (ESI, TOF) calcd for $C_{18}H_{16}N_7O_3$ 378.13091 [MH^+], found 378.13216.

2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-1-(1H-pyrrol-2-yl)ethanone oxime (***8f***): Yield: 90%, 1.03 g, light yellow oil; IR (film) 987, 1111, 1348, 1419, 1522, 1608, 3215, 3427 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.28 and 4.32 (s, 2H), 5.80 and 5.87 (s, 2H), 6.06 and 6.13 (br s, 1H), 6.41 and 6.59 (br s, 1H), 6.79 and 6.92 (br s, 1H), 7.44−7.50 (m, 2H), 8.19−8.22 (m, 2H), 11.01 and 11.30 (br s, N-H), 11.07 and 11.34 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.2 and 26.2, 49.2, 107.9, 108.3, 110.3, 112.8, 121.1, 121.8, 123.4, 123.7, 123.8, 128.9, 129.3, 141.4, 141.8, 141.9, 144.4, 147.2, 152.9; HRMS (ESI, TOF) calcd for $C_{14}H_{14}N_7O_3$ 328.11526 [MH^+], found 328.11521.

2-(2-(4-Nitrobenzyl)-2H-tetrazol-5-yl)-1-(1H-pyrrol-2-yl)ethanone oxime (***9f***): Yield: 92%, 1.05 g, light yellow solid, mp 160−162 °C; IR (KBr) 985, 1111, 1348, 1433, 1525, 1610, 3124, 3419 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.09 and 4.19 (s, 2H), 6.03−6.09 (m, 3H), 6.35 and 6.48 (br s, 1H), 6.77 and 6.89 (br s, 1H), 7.55 (d, J = 8.4 Hz, 2H), 8.24 (d, J = 8.4 Hz, 2H), 10.85 and 11.01 (br s, N-H), 11.29 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.2 and 28.9, 54.7, 107.7, 108.2, 109.7, 112.5, 120.6, 121.3, 123.8, 123.9, 127.2, 129.3, 129.4, 141.4, 141.5,

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142.6, 145.5, 147.5, 163.4 and 164.1; HRMS (ESI, TOF) calcd for $C_{14}H_{14}N_7O_3$ 328.11526 [MH^+], found 328.11469.

General Procedure for the Synthesis of 2*H*-Azirines 10a−10d and 11a−11d. To a solution of oxime **8** or **9** (1.0 mmol) in dichloromethane (20 mL), at 0 °C under a nitrogen atmosphere, was added triethylamine (1.3 equiv) and tosyl chloride (1.2 equiv). The mixture was allowed to warm at room temperature, and the reaction mixture was stirred for 12 h. The solvent was evaporated under vacuum, 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 $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography (ethyl acetate/hexane).

*2-(1-Benzyl-1H-tetrazol-5-yl)-3-phenyl-2H-azirine (**10a**):* Yield: 63%, 0.17 g, yellowish oil; IR (film) 1319, 1452, 1520, 1605, 1755, 2854, 2927 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.27 (s, 1H), 5.62 (d, J = 15.6 Hz, 1H), 5.74 (d, J = 15.6 Hz, 1H), 7.22−7.26 (m, 2H), 7.31−7.33 (m, 3H), 7.51−7.54 (m, 2H), 7.61−7.65 (m, 1H), 7.77 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 51.2, 122.2, 127.5, 128.9, 129.2, 129.4, 130.5, 133.7, 134.3, 154.2, 161.4; HRMS (ESI) calcd for $C_{16}H_{14}N_5$ 276.12437 [MH^+], found 276.12364.

*2-(2-Benzyl-2H-tetrazol-5-yl)-3-phenyl-2H-azirine (**11a**):* Yield: 77%, 0.21 g, yellow solid, mp 83−85 °C; IR (KBr) 1277, 1450, 1504, 1597, 1749, 3028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.53 (s, 1H), 5.69 (s, 2H), 7.34−7.36 (m, 5H), 7.55−7.58 (m, 2H), 7.62−7.65 (m, 1H), 7.92−7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 56.8, 123.0, 128.5, 129.0, 129.3, 130.3, 133.1, 133.7, 160.9, 167.0; HRMS (ESI) calcd for $C_{16}H_{14}N_5$ 276.12437 [MH^+], found 276.12360.

*3-Phenyl-2-(1-(4-nitrobenzyl)-1H-tetrazol-5-yl)-2H-azirine (**10b**):* Yield: 86%, 0.28 g, white solid, mp 130−132 °C; IR (KBr) 1348, 1450, 1522, 1605, 1757, 2938, 3066 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.84 (s, 1H), 6.16 (s, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.70−7.71 (m, 2H), 7.72−7.74 (m, 1H), 7.96 (d, J = 7.2 Hz, 2H), 8.34 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.3, 49.2, 121.7, 124.1, 129.0, 129.7, 130.3, 134.4, 142.0, 147.4, 155.5, 159.5; HRMS (ESI, TOF) calcd for $C_{16}H_{13}N_6O_2$ 321.10945 [MH^+], found 321.10991.

*3-Phenyl-2-(2-(4-nitrobenzyl)-2H-tetrazol-5-yl)-2H-azirine (**11b**):* Yield: 73%, 0.23 g, white solid, mp 124−126 °C; IR (KBr) 1348, 1521, 1605, 1757, 3068, 3199 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.68 (s, 1H), 6.13 (s, 2H), 7.63−7.65 (m, 2H), 7.71−7.74 (m, 2H), 7.79−7.81 (m, 1H), 8.01 (d, J = 7.2 Hz, 2H), 8.30 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.0, 54.9, 122.3, 124.0, 129.6, 129.7, 130.0, 134.1, 141.1, 147.5, 160.3, 166.6; HRMS (ESI, TOF) calcd for $C_{16}H_{13}N_6O_2$ 321.10945 [MH^+], found 321.10895.

*3-(Furan-2-yl)-2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-2H-azirine (**10c**):* Yield: 59%, 0.18 g, brown solid, mp 146−148 °C; IR (KBr) 1417, 1524, 1560, 1661, 2891, 3007, 3111 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.84 (s, 1H), 6.09 (s, 2H), 6.92 (d, J = 1.6 Hz, 1H), 7.57−7.60 (m, 3H), 8.29 (d, J = 8.4 Hz, 2H), 8.34 (br s,1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.2, 49.2, 113.6, 123.4, 124.1, 129.0, 138.4, 141.9, 147.4, 149.1, 151.2, 155.0; HRMS (ESI, TOF) calcd for $C_{14}H_{11}N_6O_3$ 311.08871 [MH^+], found 311.08852.

*3-(Furan-2-yl)-2-(2-(4-Nitrobenzyl)-2H-tetrazol-5-yl)-2H-azirine (**11c**):* Yield: 61%, 0.19 g, light brown solid, mp 112−114 °C; IR (KBr) 1348, 1466, 1522, 1608, 1759, 3008, 3134 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.70 (s, 1H), 6.15 (s, 2H), 6.96 (d, J = 1.6 Hz, 1H), 7.64−7.68 (m, 3H), 8.31 (d, J = 8.4 Hz, 2H), 8.37 (br s,1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.8, 55.0, 113.5, 122.6, 124.0, 129.6, 139.0, 141.1, 147.5, 150.0, 150.8, 166.1; HRMS (ESI, TOF) calcd for $C_{14}H_{11}N_6O_3$ 311.08871 [MH^+], found 311.08840.

*2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-3-(thiophen-2-yl)-2H-azirine (**10d**):* Yield: 70%, 0.23 g, light brown solid, mp 144−146 °C; IR (KBr) 1344, 1412, 1522, 1610, 1751, 3076, 3126 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.90 (s, 1H), 6.15 (s, 2H), 7.48 (pseudo t, J = 4.4 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 2.8 Hz, 1H), 8.35 (d, J = 8.8 Hz, 2H), 8.41 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.3, 49.2, 123.5, 124.1, 129.0, 129.4, 136.8, 137.6, 142.0, 147.4, 152.9, 155.2; HRMS (ESI, TOF) calcd for $C_{14}H_{11}N_6O_2S$ 327.06587 [MH^+], found 327.06562.

*2-(2-(4-Nitrobenzyl)-2H-tetrazol-5-yl)-3-(thiophen-2-yl)-2H-azirine (**11d**):* Yield: 66%, 0.22 g, light brown solid, mp 119−121 °C; IR (KBr) 1332, 1457, 1563, 1607, 1742, 3074, 3111 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.68 (s, 1H), 6.10 (s, 2H), 7.42 (pseudo t, J = 4.4 Hz and J = 4.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 2.8 Hz, 1H), 8.26 (d, J = 8.4 Hz, 2H), 8.33 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.9, 54.9, 124.0, 124.4, 129.3, 129.6, 136.3, 136.9, 141.1, 147.5, 153.7, 166.3; HRMS (ESI, TOF) calcd for $C_{14}H_{11}N_6O_2S$ 327.06587 [MH^+], found 327.06525.

*Synthesis of 5-(3-(1H-pyrrol-2-yl)-2H-azirin-2-yl)-2-(4-nitrobenzyl)-2H-tetrazole (**11e**). 2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-1-(1H-pyrrol-2-yl)ethanone O-Tosyl Oxime (**12**).* To a solution of oxime **9f** (1.0 mmol, 0.33 g) in dichloromethane (20 mL), at 0 °C under a nitrogen atmosphere, was added triethylamine (1.3 equiv) and tosyl chloride (1.2 equiv, 1.2 mmol, 0.23 g). The mixture was allowed to warm at room temperature, and the reaction mixture was monitored by TLC. After 1.5 h, there was no evidence of oxime and the reaction mixture was isolated. The solvent was evaporated under vacuum, 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 $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography [ethyl acetate/hexane (1:1)], giving by order of elution: *O-tosyl oxime* (**12**, 27%, 0.13 g) and 2*H*-azirine **11e** (4%, 12 mg). Data for compound **12**: light brown oil; ^1H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H), 4.27 (s, 2H), 6.10 (s, 2H), 6.26 (pseudo d, J = 1.2 Hz, 1H), 6.92 (br s, 1H), 7.15 (br s, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 8.23 (d, J = 8.4 Hz, 2H), 11.5 (br s, N-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1, 28.5, 54.7, 110.0, 118.9, 120.1, 123.9, 125.3, 128.3, 129.2, 129.7, 131.8, 141.4, 145.2, 147.4, 151.3, 162.3; HRMS (ESI, TOF) calcd for $C_{21}H_{19}N_6O_5S_2$ 499.08529 [MH^+], found 499.08502.

*3-(1H-Pyrrol-2-yl)-2-(2-(4-nitrobenzyl)-2H-tetrazol-5-yl)-2H-azirine (**11e**).* To a solution of oxime **12** (0.25 mmol, 0.12 g) in dichloromethane (5 mL), at room temperature under a nitrogen atmosphere, was added DBU (1.3 equiv). The mixture was monitored by TLC, and after 2 h, there was no evidence of oxime. The solvent was evaporated under vacuum, 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 $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography [ethyl acetate/hexane (1:1)]. Yield: 23%, 18 mg, light brown oil; ^1H NMR (400 MHz, DMSO-d_6) δ 3.65 (s, 1H), 6.09 (s, 2H), 6.45 (br s, 1H), 6.97 (br s, 1H), 7.49 (br s, 1H), 7.62 (d, J = 7.2 Hz, 2H), 8.34 (d, J = 6.8 Hz, 2H), 12.59 (br s, N-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.2, 49.1, 111.4, 114.3, 119.1, 124.0, 128.0, 128.9, 142.1, 147.4, 148.5, 155.9; HRMS (ESI, TOF) calcd for $C_{14}H_{12}N_7O_2$ 310.10470 [MH^+], found 310.10448.

General Procedure for the Preparation of oximes 5. Tetrazoles **4a** or **4c** (3.5 mmol) were dissolved in a mixture of ethanol/pyridine (1:1) (10 mL), and hydroxylamine hydrochloride (3 equiv, 10.5 mmol) was added. The reaction mixture was heated under reflux for 3 h. The solvent was evaporated under reduced pressure, and cold water (20 mL) and ice (10 g) were added, causing the oximes to precipitate. The oximes were filtered and recrystallized in diethyl ether.

*1-Phenyl-2-(1H-tetrazol-5-yl)ethanone oxime (**5a**):* Yield: 83%, 0.59 g, white solid, mp 176−178 °C; IR (KBr) 690, 748, 972, 1065, 1286, 1412, 1441, 1495, 1570, 1896, 2598, 2885, 3230 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.37 (s, 2H), 7.40−7.41 (m, 3H), 7.72−7.74 (m, 2H), 11.73 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.4, 126.0, 128.4, 129.0, 135.2, 150.8; HRMS (ESI, TOF) calcd for $C_9H_{10}N_5O$ 204.08799 [MH^+], found 204.08759.

*2-(1H-Tetrazol-5-yl)-1-(thiophen-2-yl)ethanone oxime (**5c**):* Yield: 77%, 0.56 g. **5c** was obtained as a mixture of isomers (15:85). White solid, mp 173−175 °C; IR (KBr) 692, 851, 960, 1016, 1072, 1263, 1321, 1410, 1433, 1558, 1606, 2889, 3007, 3213 cm^{-1}; *Major isomer*: ^1H NMR (400 MHz, DMSO-d_6) δ 4.37 (s, 2H), 7.09 (pseudo t, J = 4.4 Hz, 1H), 7.44 (d, J = 2.8 Hz, 1H), 7.53 (d, J = 4.4 Hz, 1H), 11.63 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.8, 127.3, 127.4, 131.2, 139.1, 147.2; *Minor isomer*: ^1H NMR (400 MHz, DMSO-d_6) δ 4.42 (s, 2H), 7.16 (pseudo t, J = 4.4 Hz, 1H), 7.59 (d, J = 2.8 Hz, 1H), 7.79 (d, J = 4.4 Hz,

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1H), 12.12 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.8, 125.7, 129.1, 130.5, 144.0, 152.4; HRMS (ESI, TOF) calcd for $C_7H_8N_5OS$ 210.04441 [MH^+], found 210.04452.

2-(1-(4-Nitrobenzyl)-1H-tetrazol-5-yl)-1-phenylethanone O-Tosyl Oxime (13). To a solution of oxime **8b** (0.34 g, 1.0 mmol, 1 equiv) in THF (5 mL) at 0 °C were added *p*-toluenesulfonic chloride (1 equiv) and K_2CO_3 (2 equiv). The reaction mixture was stirred at room temperature for 24 h. The resulting mixture was then filtered, and the solvent was evaporated off and purified by flash chromatography [ethyl acetate/hexane (1:2)]. Yield: 39%, 0.19 g, white solid, mp 141−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 4.35 (s, 2H), 5.74 (s, 2H), 7.28−7.30 (m, 6H), 7.31−7.35 (m, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 8.15 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.3, 50.1, 124.4, 128.3, 128.9, 129.0, 130.0, 130.8 131.4, 139.7, 146.2, 148.2, 150.1, 158.9; HRMS (ESI, TOF) calcd for $C_{23}H_{21}N_6O_5S$ 493.12886 [MH^+], found 493.12886.

General Procedure for the Asymmetric Synthesis of 2*H*-Azirines 10b′ and 10b″.[5c] To a stirred solution of alkaloid base (1 equiv) in toluene (45 mL), a solution of ketoxime tosylate **13** (100 mg, 0.2 mmol) in toluene (5 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 24 h, whereupon aqueous HCl (0.05M, 25 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 25 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was evaporated under vacuum. The crude product was purified by flash chromatography [ethyl acetate/hexane (1:1)].

(-)-3-Phenyl-2-(1-(4-nitrobenzyl)-1H-tetrazol-5-yl)-2H-azirine (10b′). Following the general procedure, using quinidine, **13** gave, after workup and purification, **10b′** as a white solid (40.4 mg, 0.126 mmol). Yield: 63% (54% *ee*); $[\alpha]_D^{20}$ = −146 ($CHCl_3$, c = 1.3).

(+)-3-Phenyl-2-(1-(4-nitrobenzyl)-1H-tetrazol-5-yl)-2H-azirine (10b″). Following the general procedure, using quinine, **13** gave, after workup and purification, **10b″** as a white solid (47.4 mg, 0.148 mmol). Yield: 74% (44% *ee*); $[\alpha]_D^{20}$ = +105 ($CHCl_3$, c = 1.0).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds and NOESY spectra of compounds **10b**, **10d**, **11b**, and **11d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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