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Chemodivergent and Stereoselective Access to Fused Isoxazoline Azetidines and Thietanes through [3 + 2]-Cycloadditions

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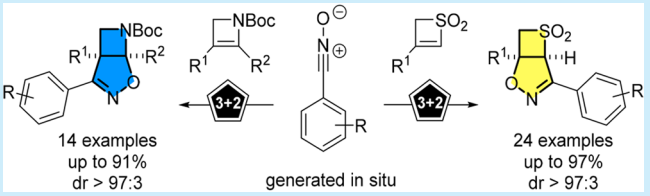
Supporting Information

ABSTRACT: By combining efficient methodologies for the preparation of substituted azetines and thietes with a highly regio- and diastereoselective [3 + 2]-cycloaddition, a straightforward pathway for the synthesis of fused isoxazoline azetidines and thietanes has been designed. With minimal steps and starting from commercial sources, a new library of elaborated architectures was synthesized opening up a new class of molecules with large potential in pharmacology. Finally, a retro [2 + 2]-cycloaddition leading to substituted isoxazoles is described.



Driven by the ever-increasing pace of drug discovery, small rings, particularly strained cyclobutenes and their heterocyclic analogs azetines and thietes, have gained increased attention due to their great range of reactivity. The unique possibilities afforded by strained bonds in organic synthesis have been dignified for decades. Recent advances by the group of Baran and Carreira demonstrated the tremendous significance of strained bioisosteres such as propellanes,[1] azetidines,[2] and oxetanes[3] in synthesis. Above all, there is an urgent need to bring such groups directly and economically onto core scaffolds. Driven by the need to push the boundaries of unexplored structural libraries, we recently reported the synthesis of new building blocks containing cyclobutenes,[4] azetines,[5] and thietes.[6] These allowed us to develop new methodologies toward the stereocontrolled formation of alkylidenecyclobutanes,[7] alkylideneazetidines,[8] and cyclopropylketones[9] formed by oxidative ring contraction of cyclobutenes.

Outlined herein is the stereoselective formation of fused isoxazoline derivatives containing azetidine- and thietane-cores by [3 + 2] dipolar cycloadditions with nitrile oxides.[10] Notably, besides the well-known β-lactams penicillin and cephalosporin, isoxazoles, isoxazolines, and the fully saturated isoxazolidine variants can be found in numerous bioactive substances[11] (Figure 1). Among these very important classes of compounds, several fused azetidine-containing substances have shown interesting tumor activities.[12] In addition, thietane cores present attractive pharmacological properties and have been used as pesticides,[13] sweetener,[14] and anticancer[15] drugs. Moreover, the oxidized thietanes were described as powerful enzyme inhibitors,[16] antidepressants,[17] antitumor agents,[18] and herbicides.[19]

Only a few reports describe the formation of the isoxazoline core fused with an azetidine/thietane[20] moiety, and with restrained variety and efficiency. To fill this gap, our general sequence for generating complexity in a modular fashion starts with the formation of substituted unsaturated azetines and thietes. In our previous work we used organometallic species such as

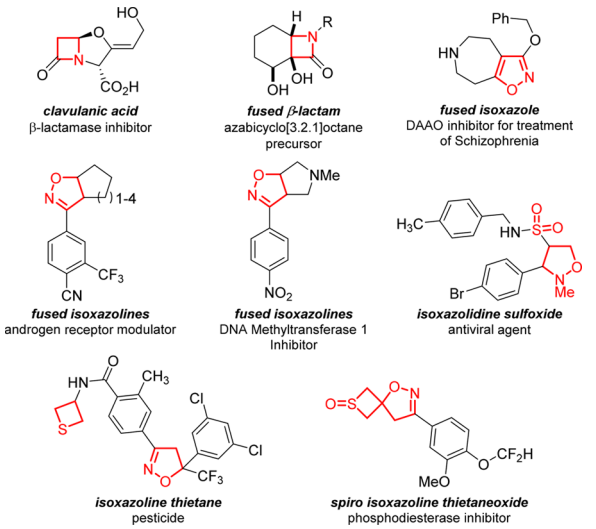


Figure 1. Few examples of biologically active fused four-and five-membered heterocycles.

Grignard or lithium reagents for 1,2-nucleophilic additions on commercially available 3-thietanone[6] **1** and 1-Boc-3-azetidinone[5] **4** (Scheme 1) to obtain the corresponding tertiary alcohols.

Following a sequence that we recently reported,[6] thiete derivatives **3** were accessed in good yields (51 to 78%) through intermediate formation of tertiary alcohols **2**. Similarly, azetines **6** were synthesized in good to excellent yields (66 to 98%), in a sequence based on a key α-lithiation of methylated alcohols **5**.[21] 3-Azetinyllithium intermediates can then be used in electrophilic trapping reactions with H_2O or with boron isopropoxide. Room temperature stable organoboronates were also used in Suzuki−

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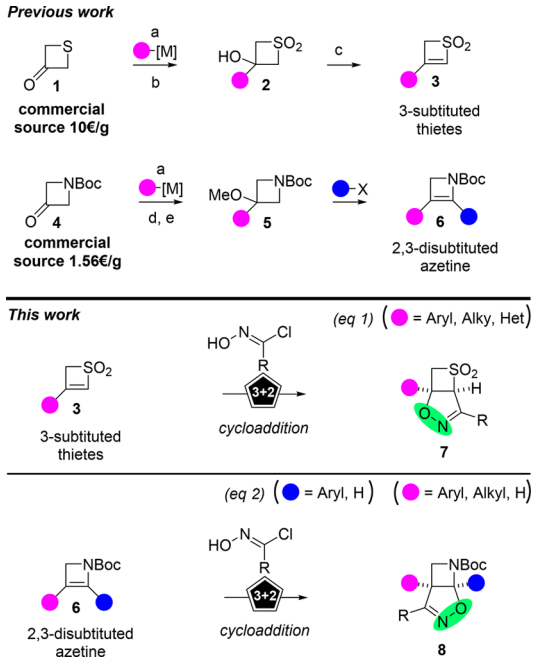
Scheme 1. Previous Work on Functionalization of Azetines and Thietes and Their Transformation in [3 + 2]-Cycloadditions[a]

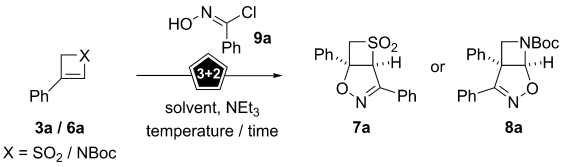


[a]For **3**/**6**: (a) Organolithium (M = Li) or organomagnesium (M = MgBr) (1.2 equiv); reactions were performed in THF at −30 °C. For **3**: (b) *m*CPBA (2 equiv), CH_2Cl_2, 0 °C to rt. (c) MsCl (3 equiv), NEt_3 (3 equiv), CH_2Cl_2, rt. For **6**: (d) NaH, MeI, THF, 0 °C to rt. (e) *s*-BuLi (2 equiv), TMEDA (1 equiv), THF, −78 °C.

Miyaura cross-coupling, affording 2,3-bis-arylated azetines.[5] With efficient access to diversely substituted azetines **6** and thietes **3**, dipolar [3 + 2]-cycloadditions were undertaken.

To tackle the ambitious formation of complex fused ring systems, we first performed optimizations to find adequate conditions for the [3 + 2]-cycloaddition. Therefore, different solvents, temperatures, techniques, and equivalents of the unexpansive or easily prepared[22] *N*-hydroxybenzimidoyl chloride **9a** were tested (Table 1). While lower temperature did not afford full conversions over prolonged periods of time (entries 4 and 5), reactions performed at 80 to 100 °C proved to give the expected products at higher rates. Running the transformations in pressure tubes greatly improved the overall conversions, but optimal yields were obtained under microwave irradiations (entries 1−4/6 and 7−9). Finally, the introduction of an excess of **9a** (3 equiv) proved to be inevitable, mostly due to its dimerization. It became apparent that the amount of triethylamine plays an important role, being essential to the formation of the 1,3-dipole during the reaction. Reaction times to completion were further improved by switching the solvent to dichloromethane (entry 8), while similar rates were observed when employing ethyl acetate instead of diethyl ether.

Table 1. Optimization in [3 + 2]-Cycloadditions



entry	solvent	NEt_3 (equiv)	temp (°C)	**9** (equiv)	time (h)	conv (%)[a] **7a**/**8a**
1	Et_2O	1	80[b]	1	16	30/25
2	Et_2O	2	80[b]	2	16	89/85
3	Et_2O	4	80[b]	2	16	94/90
4	Et_2O	4	40[b]	2	16	78/77
5	Et_2O	4	rt	2	16	68/55
6	Et_2O	6	80[b]	2	16	92/93
7	Et_2O	6	100[c]	2	2	90/89
8	**CH_2Cl_2**	**6**	**100[c]**	**3**	**1.5**	**97/95**
9	EtOAc	6	100[c]	3	1.5	80/81

[a]Determined by GC. [b]Pressure tube. [c]Microwave irradiations (6 bar).

With an optimized cycloaddition sequence in hand, 3-phenylthiete **3a** was first used to establish the scope of 1,3 dipoles **9a−g** (for details, see Supporting Information, SI) and to investigate the regioselectivity and diastereoselectivity of the fused thietanes (Scheme 2). Electron-donating groups on the hydroxyl-imidoylchloride increased the yield (**7b**, 97%), whereas the presence of electron-withdrawing substituents tended to decrease the conversion into the desired compounds (**7c**, 90%). Halo-substituted hydroxyl-imidoylchloride furnished **7d−e** in good yields (up to 90%). Due to the monosubstitution of the dipolarophiles **3**, only one regioisomer (see below) together with diastereoselectivity higher than 97% was obtained. With 3-naphtylthiete **3b**, good to excellent yields were isolated (**7h−j**, up to 92%).

The scope of the transformation was established by employing a range of different substituted 3-thietes such as 4-methoxy-phenyl **3c**, 4-fluoro-phenyl **3d**, 3-bromo-phenyl **3e**, and 4- or 2-biphenyl **3f/g**, leading to a small library of unprecedented fused thietanes in good to excellent yields (**7k−v**). It is worth noting that, using **3i** led to **7w** in moderate yields (57%), X-ray crystallography supported the proposed stereochemical outcome of this transformation. Taking advantage of a simple access to substituted thietes that we developed previously, we pushed the method further by engaging 3-heteroarylated thiete **3j** with *N*-hydroxybenzimidoyl chloride **9a** and *N*-hydroxy-4-methoxybenzimidoyl chloride **9b** to isolate **7y−z** in good to excellent yields (84 to 94%). Switching the group on position 3 for a butyl chain (**3l**) furnished the corresponding thietanes **7ab−ac** in 84% and 94% yields, respectively. Unfortunately, [3 + 2] strategies on 2,3-disubstituted-thietes did not afford the desired fused ring systems.

According to this simple transformation, we started to explore [3 + 2]-cycloadditions with 3-substituted azetines.

Therefore, we used azetidines **5a−e** to form mono-substituted azetines, employing a deprotonation/elimination/deprotonation/electrophilic-trapping sequence (Scheme 3). Those azetines were directly engaged without prior purification in [3 + 2]-cycloadditions with hydroxyl-imidoyl chlorides **9a−b**. Due to the rearrangement and ring opening under slightly acidic conditions, no further purification of the 3-substituted azetines were implemented. However, for compound **8g** an isolation of the 3-azetine was possible, thus showing the efficiency of the [3 + 2]-cycloaddition by a very good yield of 91%. Without any purification at intermediate steps, arylated building blocks **5a−d** afforded sophisticated architectures **8a−f/h** in moderate to good yields as a single regioisomer and with high stereochemical ratios. It is also worth noting that the regiochemistry appears to be inverse compared to the thietes. Looking at the different regiochemical outcomes of thietes and azetines after successful [3 + 2]-cycloaddition with nitrile oxides **9a−g**, a side-inversed attack of the 1,3-dipole was observed (Figure 2). First, due to different electronic effects on the carbon atoms 2 and 3, we propose a favored approach with the congruent charge (±) of the

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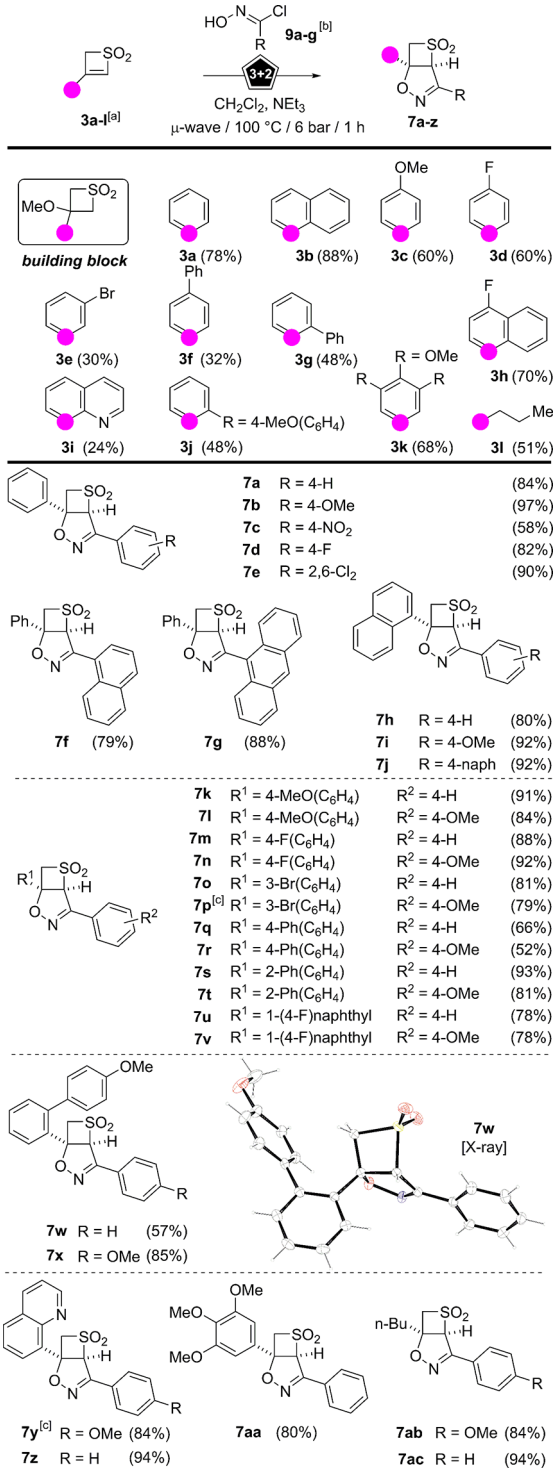
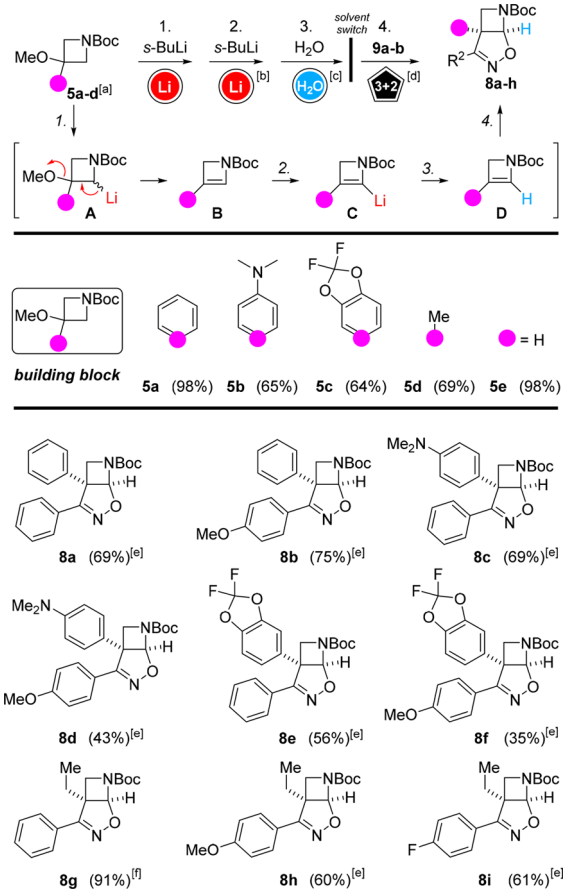
Scheme 2. [3 + 2]-Cycloaddition Towards Fused Isoxazoline Thietanes



[a]0.1 mmol scale. [b]1,3-dipole (3 equiv), CH_2Cl_2, 100 °C, 6 bar, 1 h, microwave irradiations. [c]X-ray structures are reported in the SI.

1,3-dipole to the dipolarophile, thus forming a six-electron Hückel aromatic transition state.[23] Second, the Boc-group in azetine structures presumably reinforces the regiocontrol through favorable steric repulsion, the transition state of which being potentially stabilized by electrostatic interactions between the two aromatic moieties and leading to one regioisomer.

Scheme 3. Lithiation/Electrophilic-Trapping/[3 + 2]-Cycloaddition Sequence Towards Fused Isoxazoline Azetidines



[a]0.5 mmol scale. [b]*s*-BuLi (2.0 equiv), TMEDA (2.0 equiv) THF, −78 °C, 1 h. [c]Excess, −78 °C to rt. [d]1,3-Dipole (2.5 equiv), CH_2Cl_2, 100 °C, 6 bar, 1 h, microwave irradiations. [e]Isolated yield over all steps. [f]Isolated yield for step 4.

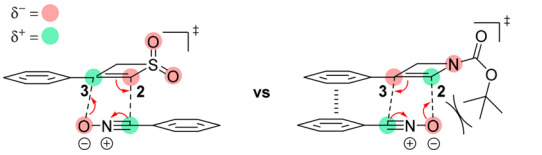


Figure 2. Proposed transition states for the [3 + 2]-cycloaddition with nitrile oxide **9a**.

Next, 2,3-disubstituted azetines were examined. In a similar sequence, azetidines **5** were employed in the formation of the lithiated intermediate **C**, and the corresponding boronate species were generated by addition of boron isopropoxide (Scheme 4). A subsequent Suzuki cross-coupling was performed in the presence of $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (4 mol %) and the appropriate coupling partner (aryl iodides). Without additional purification, the corresponding 2,3-disubstituted azetines were subjected to [3 + 2]-cycloadditions under optimized conditions. With aryl groups on both sides, poor control of the regioselectivity was witnessed, as a mixture of two regioisomers **10a/b** (1:4.5) and **11a/b** (1:3) was isolated, showing, however, excellent diastereoisomeric ratios. This observation suggests that electron densities of carbon atoms 2 and 3 are not as distinct as in monosubstituted azetines, hence decreasing regioisomeric ratios of the transformation

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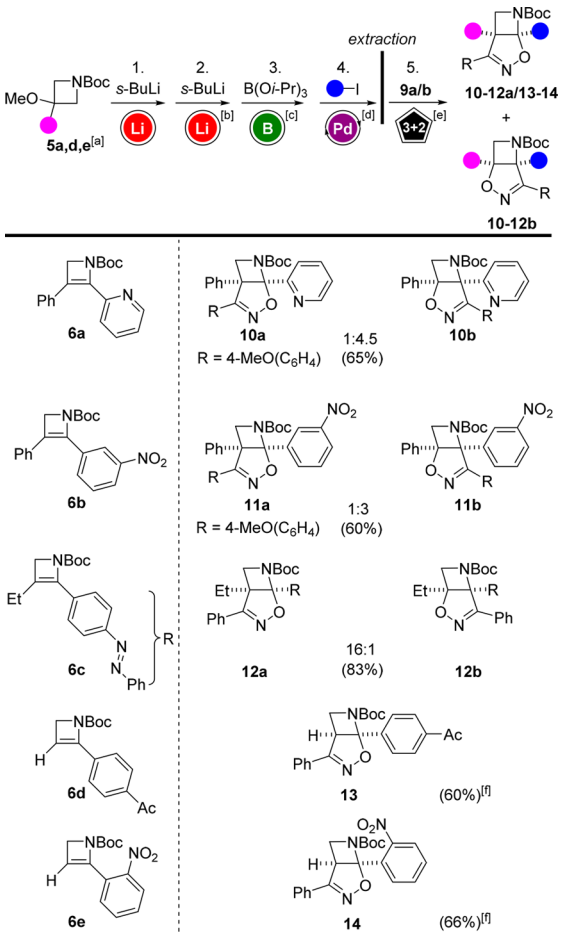
Scheme 4. [3 + 2]-Cycloaddition of 2-Substituted Azetines



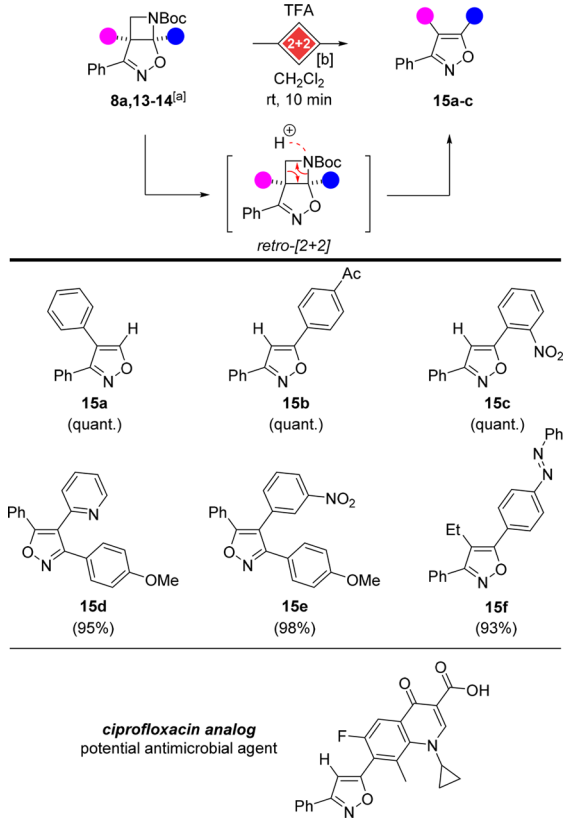
[a]0.5 mmol scale. [b]*s*-BuLi (2.0 equiv), TMEDA (2.0 equiv) THF, −78 °C, 1 h. [c]$B(OiPr)_3$ (1.5 equiv), −78 °C, 1 h then 0 °C, 1 h. [d]$Pd(dppf)Cl_2.CH_2Cl_2$ (4 mol %), Ar−I (1 equiv), NaOH (3 equiv), rt, 48 h. [e]1,3-Dipole (3 equiv), CH_2Cl_2, 100 °C, 6 bar, 1 h, μ-wave. [f]1,3-Dipole (2.5 equiv), CH_2Cl_2, rt, 1 h.

(Figure 2). Bearing an alkyl chain at position 3 and an aryl chain at position 2, the regioselectivity of the reaction raises to 16:1 (**12a** and **12b**), pointing out the significant role of electronic interactions in the transition state. Consequently, the disubstituted azetine **6c** furnished **12** in good yield (83%) and excellent regioisomeric ratio (16:1). In contrast, monosubstituted azetines at position 2 (**6d** and **6e**) gave exclusively one regioisomer, and **13** and **14** were isolated in 60 to 66% yields over 5 steps.

It is worth noting that the reaction already proceeded in satisfying rate at room temperature without microwave irradiation, pointing out the higher reactivity of these last systems compared to previously mentioned examples.

Considering the broad versatility of this synthetic method, we finally set out to access disubstituted isoxazoles through retro-[2 + 2]-cycloadditions (Scheme 5). Brønsted acid-catalyzed conditions were applied, and the transformation proceeded in quantitative yields within a few minutes at room temperature, driven by the favorable formation of an aromatic ring (**15a−c**). Additional support of the regiochemical outcome of the [3 + 2] cycloaddition was provided by unambiguous assignments of NMR signals on isoxazoles. Noteworthy, engaging previously synthesized thietanes under same conditions, no transformation to isoxazoles took place, concluding that these compounds are

Scheme 5. Retro-[2 + 2]-Cycloadditions Towards Functionalized Isoxazoles



much more stable than the azetidine derivatives. Fully substituted isoxazoles **15d−f** were also obtained in excellent yields (93 to 95%). It is important to note that isoxazole motifs are present in a number of biologically active compounds such as the analog of ciprofloxacin (Scheme 5).[24]

In summary, we have unlocked a new library of unique isoxazolines fused with azetidine or thietane moieties with great diastereoselectivity and regioselectivity. Moreover, using fused isoxazoline azetidines, a new pathway to unprecedented disubstituted isoxazoles is provided. This surely represents a valuable tool for drug discovery and opens up an entire platform for high throughput screenings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02848.

Experimental procedures and characterization (IR, HRMS, and ^1H and ^{13}C NMR data) for all new compounds (PDF)

Accession Codes

CCDC 1863063−1863064 and 1872242 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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