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Article

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# Switchable Synthesis of Pyrroles and Pyrazines via Rh(II)-Catalyzed Reaction of 1,2,3-Triazoles with Isoxazoles: Experimental and DFT Evidence for the 1,4-Diazahexatriene Intermediate

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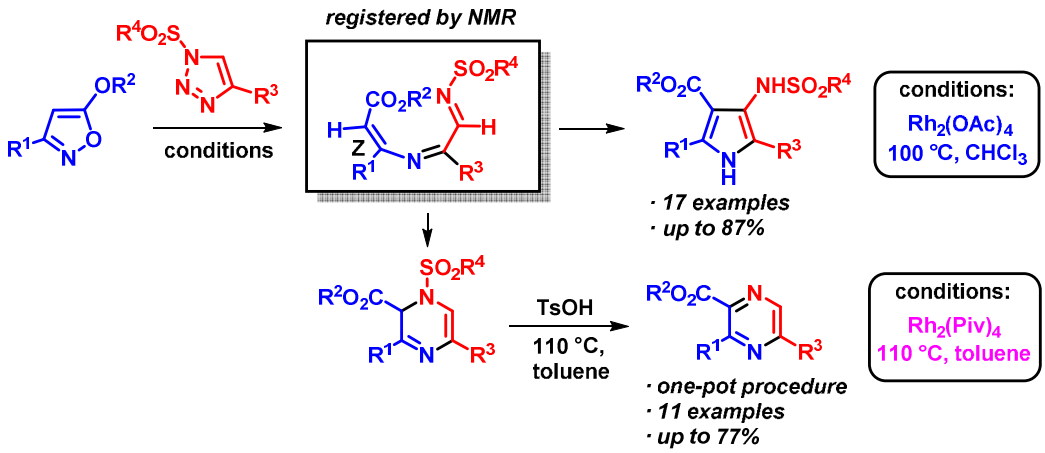
*Graphical abstract*

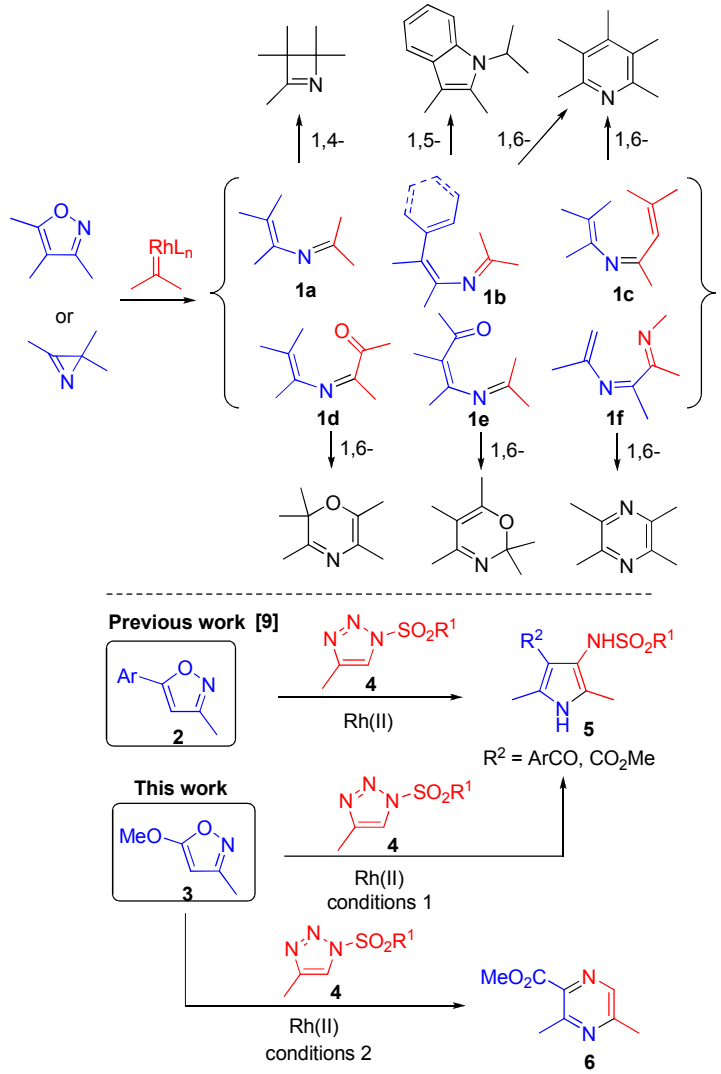



ABSTRACT: 4-Aminopyrrole-3-carboxylates and pyrazine-2-carboxylates were synthesized from 5-alkoxyisoxazoles and 1-sulfonyl-1,2,3-triazoles by tuning the Rh(II) catalyst and the reaction conditions. The reaction in chloroform at 100 °C under $Rh_2(OAc)_4$ catalysis provides 4-aminopyrrole-3-carboxylates in good yields. The use of $Rh_2(Piv)_4$ in refluxing toluene results in the formation of 1,2-dihydropyrazine-2-carboxylates as the main products which can be converted by a one-pot procedure to pyrazine-2-carboxylates by heating with catalytic amounts of TsOH. According to the NMR and DFT investigations of the reaction mechanism pyrroles and dihydropyrazines are formed respectively via 1,5- and 1,6-cyclization of common (5*Z*)-1,4-diazahexa-1,3,5-triene intermediates. The influence of the nature of the catalyst on the product distribution is rationalized in terms of the Rh-catalyzed isomerization of a pyrroliniosulfonylamide zwitterion, the primary product of 1,4-diazahexatriene 1,5-cyclization.

## Introduction

Conjugated azapolyenes have found wide application in the synthesis of various nitrogen heterocycles, most of which belong to six-membered systems.[1] In recent years electron-poor azapolyenes have attracted increasing attention due to the discovery of a wide range of new effective and selective reactions leading to the formation of not only six- and five-, but even four-membered systems. Furthermore, the synthetic sequence "azapolyene formation – cyclization" can provide a convenient tool for transferring of synthetically important functional groups from readily available low-molecular starting compounds to the target heterocycle.

**Scheme 1. N- and N,O-heteropolyenes in the synthesis of 4–6-membered heterocycles**



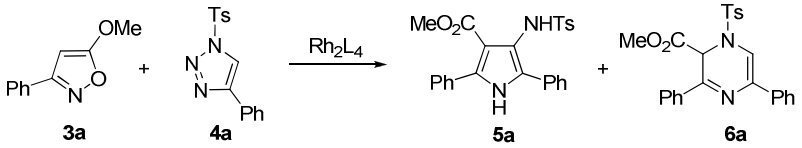
Depending on the substituents, azapolyenes at ambient temperature can be both stable compounds and reactive intermediates which rapidly and selectively undergo 1,4-, 1,5- or 1,6-cyclizations to form four-[2], five-[2a,c,3] and six-membered N-[4] and N,O-heterocycles.[5] The most convenient method for the preparation of the starting azapolyenes is the reaction of rhodium carbenoids with isoxazoles or 2*H*-azirines (Scheme 1). 2-Azabuta-1,3-dienes **1a**, 2-azahexa-1,3,5-trienes **1b**, 3-azahexa-1,3,5-trienes **1c**, 1-oxa-4-azahexa-1,3,5-trienes **1d**, and 1-oxa-5-azahexa-1,3,5-trienes **1e**, which are convenient precursors of 2,3-dihydroazetes, indoles, pyridines, 2*H*-1,4-oxazines, and 2*H*-1,3-oxazines were synthesized by the reaction of azirines with carbenoids generated from α-diazo carbonyl compounds (Scheme 1).[2,4b,5a–d] The synthesis of pyrazine derivatives from α-diazo oxime ethers and 2*H*-azirines, involving transient formation of 1,4-diaza-1,3,5-hexatriene **1f**, was also recently reported.[6] According to recent researches isoxazoles proved to be a much more convenient starting material than azirines for the generation of 2-azabuta-1,3-dienes[2b,c,5b] and 3-azahexa-1,3,5-trienes.[4f] A lot of simple and effective methods for the introduction of various substituents in all positions of the isoxazole ring are known.[7] This, together with the usability and simplicity in storage, makes isoxazoles one of the most attractive building blocks for the incorporation of the C=C–N moiety into an azapolyene system. Within our ongoing project on the application of alkoxyisoxazoles for the synthesis of highly functionalized heterocycles, we have set the goal to employ the azapolyene methodology for the preparation of N,N-heterocyclic compounds, specifically, pyrazine derivatives **6**, by 5-alkoxyisoxazole–α-imino carbenoid coupling. Rhodium α-imino carbenoids (or rhodium azavinyl carbenes) were generated from the corresponding 1-sulfonyl-1,2,3-triazoles **4** under Rh(II)-catalysis.[8] While our research was underway, Lei, Li et al. reported the formation of 3-aminopyrroles **5** from alkyl-/aryl-substituted isoxazoles and *N*-sulfonyl-1,2,3-triazoles under Rh(II) catalysis.[9] Meanwhile we found that the use of readily available alkoxyisoxazoles in these reactions provides the capability of the application of α-imino carbenoids in the synthesis of not only five-, but also six-membered heterocycles. Virtually at the same time it has been established that the Rh(II)-catalyzed reaction of 2*H*-azirines with *N*-sulfonyl-1,2,3-triazoles also leads to pyrrole and pyrazine derivatives.[10–13] However, the factors controlling the formation of these products are still not clear. Thus, Ryu et al. reported the Rh(II)-catalyzed reaction of azirine-2-carboxylates with *N*-sulfonyl-1,2,3-triazoles, leading to pyrazines through the intermediate formation of 1,2-dihydropyrazines,[10] while Wang et al. reported the Rh(II)-catalyzed reaction of azirine-2-carboxylates with *N*-sulfonyl-1,2,3-triazoles leading exclusively to 3-aminopyrroles.[11] Furthermore, Zhao et al. observed the formation of both 3-aminopyrroles and 1,2-dihydropyrazines.[12] These experimental findings require explanation which can be found with the help of a detailed study of the reaction mechanism.

Herein we report the switchable synthesis of 4-aminopyrrole-3-carboxylates and pyrazine-2-carboxylates from 5-alkoxyisoxazoles and *N*-sulfonyl-1,2,3-triazoles, achieved simply by changing the Rh(II) catalyst and the reaction conditions. The synthesis is supplemented by a theoretical and an experimental study of the reaction mechanism, which allowed effective reaction control. The obtained results were also employed to rationalize the mechanistic features of the published reactions of azirines with 1,2,3-triazoles.

## Results and Discussion

**Reactions of *N*-Sulfonyl-1,2,3-triazoles with 5-Alkoxyisoxazoles.** In contrast to the above-mentioned reaction[9] of alkyl-/aryl-substituted isoxazoles, treatment of 5-methoxy-3-phenylisoxazole **3a** (1.0 equiv) with 4-phenyl-1-tosyl-1*H*-1,2,3-triazole **4a** (2.5 equiv) under $Rh_2(Piv)_4$ catalysis gave two products, 3-aminopyrrole **5a** and 1,2-dihydropyrazine **6a**, in nearly equal amounts and a good overall yield (Table 1, entry 1). This result induced us to carry out additional optimization experiments in order to improve the reaction selectivity. It was found that such a bulky catalyst as $Rh_2(esp)_2$ provides the same selectivity as $Rh_2(Piv)_4$, but the use of Rh(II) catalysts with less bulky ligands, such as $Rh_2(OAc)_4$ or $Rh_2(Oct)_4$, increases both the reaction time and the yield of pyrrole **5a** (entries 2, 3). With another rhodium carboxylate, $Rh_2(tfa)_4$, only traces of the products were obtained (entry 4). We also found that carrying out the reaction in dilute solutions promotes formation of 1,2-dihydropyrazine **6a** (entries 5, 6), clearly indicating that the formation of pyrrole **5a** involves intermolecular processes. The $Rh_2(Piv)_4$ catalyst in refluxing toluene proved to be the conditions of choice for the synthesis of **6a** (entry 7), whereas the reaction in chloroform led mostly to pyrrole **5a** (entry 11). It was found that the decomposition of the triazole occurs much more rapidly in toluene or TFT than in chloroform. Next, it was observed that addition of the triazole in smaller portions also affects the **5a**/**6a** ratio, providing 1,2-dihydropyrazine **6a** in 67% yield (entry 8). The decrease of the reaction temperature disfavors dihydropyrazine formation (entry 9) but promotes pyrrole formation (entry 12). A decrease in catalyst loading (2.5 mol %) slightly affects the reaction course in toluene (entry 10) but rises the pyrrole share in chloroform (entry 13). Thus, the maximal yields of pyrroles **5** can be achieved by use of 2.5 mol % $Rh_2(OAc)_4$ in chloroform at 100 °C (sealed tube) (Method A). The best conditions for the synthesis of dihydropyrazines **6** are the addition of a 2–3 fold excess of the triazole in 0.5 equiv portions in each 0.5–1-min steps to a refluxing solution of isoxazole and $Rh_2(Piv)_4$ (Method B).

**Table 1. Optimization of Reaction Conditions for Synthesis of 5a and 6a**[a]

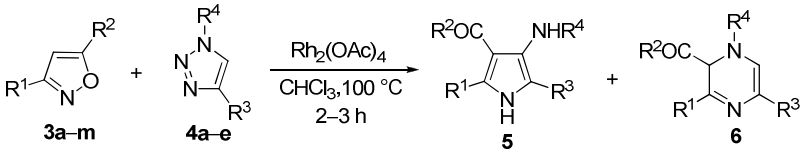



| entry | catalyst, mol % | conditions | ratio **5a** : **6a**[b] | yield of **5a** (%)[c] | yield of **6a** (%)[c] |
|---|---|---|---|---|---|
| 1 | $Rh_2(Piv)_4$, 5.0 | TFT (0.5 mL), 102 °C | 1.1: 1 | 49 | 44 |
| 2 | $Rh_2(OAc)_4$, 5.0 | TFT (0.5 mL), 102 °C | 2.9 : 1 | 64 | 22 |
| 3 | $Rh_2(Oct)_4$, 5.0 | TFT (0.5 mL), 102 °C | 2.3 : 1 | 56 | 24 |
| 4 | $Rh_2(tfa)_4$, 5.0 | TFT (0.5 mL), 102 °C | - | - | - |
| 5 | $Rh_2(Piv)_4$, 5.0 | TFT (1 mL), 102 °C | 1 : 1.3 | 39 | 51 |
| 6 | $Rh_2(Piv)_4$, 5.0 | TFT (3 mL), 102 °C | 1 : 1.8 | 33 | 59 |
| 7 | $Rh_2(Piv)_4$, 5.0 | toluene (3 mL), 110 °C | 1 : 2.3 | 27 | 62 |
| 8[d] | $Rh_2(Piv)_4$, 5.0 | toluene (3 mL), 110 °C | 1 : 2.9 | 23 | 67 |
| 9[d] | $Rh_2(Piv)_4$, 5.0 | toluene (3 mL), 90 °C | 1 : 1.7 | 33 | 57 |
| 10[d] | $Rh_2(Piv)_4$, 2.5 | toluene (3 mL), 110 °C | 1 : 3.0 | 23 | 69 |
| 11 | $Rh_2(OAc)_4$, 5.0 | $CHCl_3$ (0.5 mL), 100 °C | 3.5 : 1 | 70 | 20 |
| 12 | $Rh_2(OAc)_4$, 5.0 | $CHCl_3$ (0.5 mL), 85 °C | 4.0 : 1 | 76 | 19 |
| 13 | $Rh_2(OAc)_4$, 2.5 | $CHCl_3$ (0.5 mL), 100 °C | 5.5 : 1 | 82 | 15 |

[a]Reaction conditions: **3a** (0.29 mmol), **4a** (2.5 equiv for entries 1–10, 1.5 equiv for entries 11–13); TFT = α,α,α-trifluorotoluene, Oct = octanoate, Piv = pivalate, tfa = trifluoroacetate, esp = α,α,α',α'-tetramethyl-1,3-benzenedipropanoate. [b]Ratios were determined by $^1$H NMR spectroscopy. [c]$^1$H NMR yields using 1-methylnaphthalene as an internal standard. [d]0.72 mmol of **4a** was added in 5 equal portions.

With the optimized reaction conditions in hand, we next turned attention to the scope of the reaction for the synthesis of both 3-aminopyrroles and 1,2-dihydropyrazines (Table 2). Generally, 3-aminopyrroles **5** can be obtained in good yields from differently substituted alkoxyisoxazoles and 1-sulfonyl-1,2,3-triazoles by the method A. Only in the case of strong electron-withdrawing substituents in the phenyl ring, such as *p*-$NO_2$, *p*-CN, or *o*-F (entries 8, 9, 15), the yields of pyrroles **5** are noticeably lower due to the formation of significant amounts of corresponding dihydropyrazines **6**. In contrast, electron-donating substituents strongly facilitate the formation of 3-aminopyrroles, and no dihydropyrazines were detected in the reaction mixtures obtained under the conditions of the method A (entries 4, 5). The reaction also could be applied to the synthesis of pyrroles with carboxamide (entry 16) and benzoyl substituents (entry 17), although the yields of the products in these cases are lower. Unfortunately, we could not obtain the desired products from 4-butyl-1-tosyl-1,2,3-triazole **1f** because of the enhanced tendency of the intermediate carbenoid to undergo 1,2-H-shift.[12]

**Table 2. Synthesis of Pyrroles and Dihydropyrazines from Isoxazoles 3 and 1-sulfonyl-1,2,3-triazoles 4** [a,b]



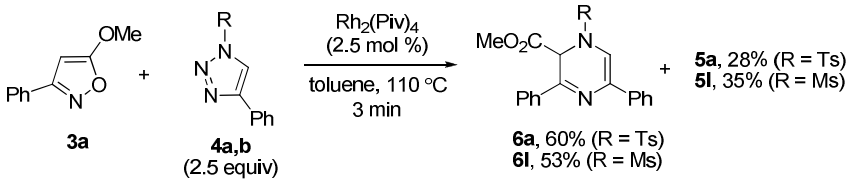

| entry | $R^1/R^2$ | $R^3/R^4$ | yield of **5** and **6** (%) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| 1 | Ph/MeO (**3a**) | Ph/Ts (**4a**) | 76 (**5a**), 15 (**6a**) |
| 2 | 4-$MeC_6H_4$/MeO (**3b**) | Ph/Ts (**4a**) | 81 (**5b**), 6 [c] (**6b**) |
| 3 | 2,4-$(Me)_2C_6H_3$/MeO (**3c**) | Ph/Ts (**4a**) | 77 (**5c**), 7 [c] (**6c**) |
| 4 | 4-$MeOC_6H_4$/MeO (**3d**) | Ph/Ts (**4a**) | 87 (**5d**), 0 [c] (**6d**) |
| 5 | 3,4-$(O(CH_2)_2O)C_6H_3$/MeO (**3e**) | Ph/Ts (**4a**) | 75 (**5e**), 0 (**6e**) |
| 6 | 4-$BrC_6H_4$/MeO (**3f**) | Ph/Ts (**4a**) | 66 (**5f**), 26 (**6f**) |
| 7 | 4-$ClC_6H_4$/MeO (**3g**) | Ph/Ts (**4a**) | 61 (**5g**), 25 (**6g**) |
| 8 | 4-$NCC_6H_4$/MeO (**3h**) | Ph/Ts (**4a**) | 17 (**5h**), 30 (**6h**) |
| 9 | 4-$O_2NC_6H_4$/MeO (**3i**) | Ph/Ts (**4a**) | 29 (**5i**), 62 (**6i**) |
| 10 | Ph/*t*BuO (**3j**) | Ph/Ts (**4a**) | 65 (**5j**), 23 (**6j**) |
| 11 | Me/MeO (**3k**) | Ph/Ts (**4a**) | 55 (**5k**), 5 [c] (**6k**) |
| 12 | Ph/MeO (**3a**) | Ph/Ms (**4b**) | 78 (**5l**), 8 [c] (**6l**) |
| 13 | Ph/MeO (**3a**) | 4-$MeOC_6H_4$/Ts (**4c**) | 55 (**5m**), 0 (**6m**) |
| 14 | Ph/MeO (**3a**) | 4-$ClC_6H_4$/Ts (**4d**) | 60 (**5n**), 18 [c] (**6n**) |
| 15 | Ph/MeO (**3a**) | 2-$FC_6H_4$/Ts (**4e**) | 43 (**5o**), 33 (**6o**) |
| 16 | Ph/pyrrolidin-1-yl (**3l**) | Ph/Ts (**4a**) | 28 (**5p**), 0 [c] (**6p**) |
| 17 | Ph/Ph (**3m**) | Ph/Ts (**4a**) | 45 (**5q**), 7 (**6q**) |

[a]Reaction conditions: **3** (0.29 mmol), **4** (1.5 equiv), $Rh_2(OAc)_4$ (0.025 equiv), $CHCl_3$ (0.5 mL) in sealed tube. [b]Isolated yield. [c]$^1H$ NMR yields using 1-methylnaphthalene as an internal standard.

Optimization experiments showed that the method B results in preferred formation of dihydropyrazines (Table 1, entry 10). Even though these compounds proved to be rather unstable, they can be prepared in an analytically pure form. Thus, dihydropyrazines **6a,l** were obtained in toluene under reflux in the presence of 2.5 mol % $Rh_2(Piv)_4$ in reasonable yields (Scheme 2).

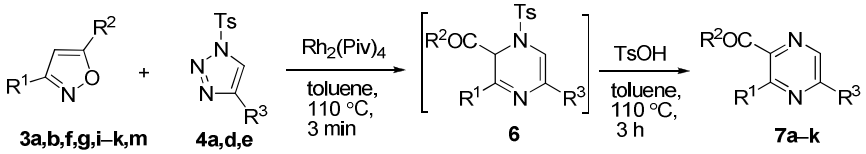
**Scheme 2. Synthesis of 1,2-dihydropyrazines**




The compounds **6a,l** decompose on storage to form the corresponding pyrazines **7**, along with several unidentified products. Assuming that this reaction could be used for preparing the target pyrazine-2-carboxylates we took effort to optimize the reaction conditions. For transformation of dihydropyrazines **6** to pyrazines **7**, several conditions were examined: reflux in toluene in the presence of (a) $Et_3N$, (b) *p*-toluenesulfonic acid (TsOH), or (c) azobisisobutyronitrile and (d) reflux in *o*-xylene without any additive. All these conditions were found to be suitable for the transformation (20% $Et_3N$, 130 °C, 10 h; *o*-xylene, 144 °C, 5 h), but we chose TsOH in refluxing toluene, which allows smooth conversion of dihydropyrazines **6** to pyrazines **7** within 3 h. We assume that the acid may facilitate elimination of toluenesulfinic acid through protonation of the carbonyl oxygen. One-pot protocol for the preparation of pyrazines

from isoxazoles and triazoles without isolation of dihydropyrazines was found to be more effective. Thus, isoxazole **3a** (1 equiv) was reacted with triazole **4a** (2.5 equiv) in the presence of $Rh_2(Piv)_4$ (2.5 mol %) in toluene under reflux (method B). The resulting mixture, without isolation of dihydropyrazine **6a**, was further treated with TsOH (0.2 equiv) and refluxed for an additional 3 h to give pyrazine **7a** in 63% yield (Table 3, entry 1). To test the generality of the protocol, other isoxazoles (except for isoxazoles bearing strong electron-donating groups) and triazoles were examined under the one-pot conditions. Expectedly, pyrazines having electron-withdrawing substituents were obtained in good yields (entries 3–5, 8–10). It was encouraging that under the given conditions pyrazines can be prepared in acceptable yields from isoxazoles which produce only traces of dihydropyrazines under the conditions of the method A (entries 2, 7, 11). The reaction also proceeds smoothly also with isoxazole **3j** containing the bulky *tert*-butoxy group to form the corresponding pyrazine in 72% yield (entry 6).

**Table 3. One-Pot Synthesis of Pyrazines from Isoxazoles and 1-Sulfonyl-1,2,3-triazoles**[a,b]



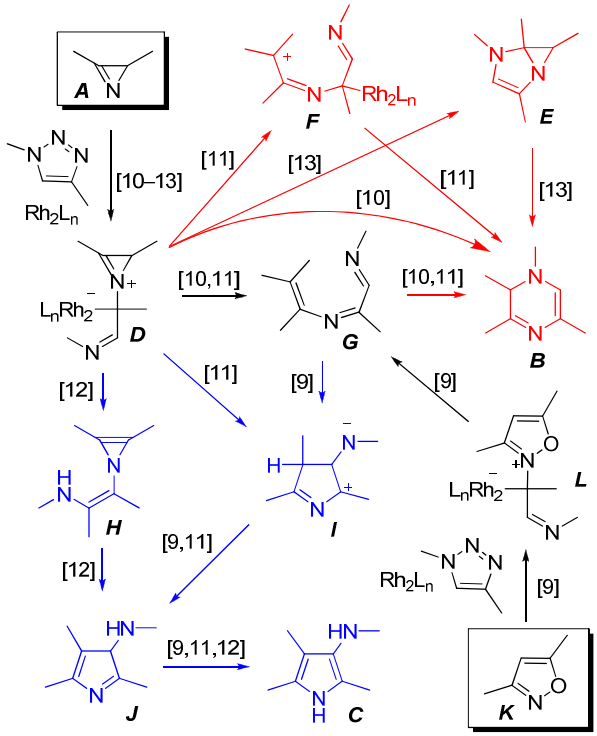

| entry | **3** | $R^1/R^2$ | **4** | $R^3$ | yield of **7** (%) |
|---|---|---|---|---|---|
| 1 | **3a** | Ph/MeO | **4a** | Ph | 63 (**7a**) |
| 2 | **3b** | 4-$MeC_6H_4$/MeO | **4a** | Ph | 44 (**7b**) |
| 3 | **3f** | 4-$BrC_6H_4$/MeO | **4a** | Ph | 70 (**7c**) |
| 4 | **3g** | 4-$ClC_6H_4$/MeO | **4a** | Ph | 72 (**7d**) |
| 5 | **3i** | 4-$O_2NC_6H_4$/MeO | **4a** | Ph | 77 (**7e**) |
| 6 | **3j** | Ph/*t*BuO | **4a** | Ph | 72[c] (**7f**)[d] |
| 7 | **3k** | Me/MeO | **4a** | Ph | 32[c] (**7g**) |
| 8 | **3a** | Ph/MeO | **4d** | 4-$ClC_6H_4$ | 61 (**7h**) |
| 9 | **3a** | Ph/MeO | **4e** | 2-$FC_6H_4$ | 75 (**7i**) |
| 10 | **3g** | 4-$ClC_6H_4$/MeO | **4d** | 4-$ClC_6H_4$ | 71 (**7j**) |
| 11 | **3m** | Ph/Ph | **4a** | Ph | 25 (**7k**) |

[a] Reaction conditions: **3** (0.29 mmol), **4** (2.5 equiv), $Rh_2(Piv)_4$ (0.025 equiv), TsOH (0.2 equiv), toluene (3 mL). [b] Isolated yield. [c] $Et_3N$ (2 equiv) was used instead of TsOH. [d] 2,6-Diphenylpyrazine (**7l**) in 53% yield was obtained under reflux in *o*-xylene without any additive on the 2nd stage.

**Experimental exploration of the reaction mechanism.** One can find in the literature three different mechanisms for the formation of dihydropyrazines ***B*** from 1-sulfonyl-1,2,3-triazoles and azirines ***A*** under Rh(II) catalysis (Scheme 3).[10–13] In all cases the reaction is supposed to occur via metal-bounded ylide ***D***. Zhang and coauthors suggested that dihydropyrazine ***B*** is formed from ylide ***D*** via 1,5-cyclization followed by aziridine ring opening.[13] However, this hypothesis contradicts the experimental data for 3-aryl-2*H*-azirine-2-carboxylates obtained by Lee and coauthors who, in turn, suggested two other possibilities for

the transformation of ***D*** into ***B***: a) one-step transformation or b) ring opening to 1,4-diazahexatriene ***G*** followed by 1,6-cyclization.[10] The formation of intermediate ***G*** was not excluded by Wang, Lei and Tang as well.[11] However, relying on the effect of $C^2$-substituents in the azirine on the ***B***/***C*** ratio, they preferred intermediate ***F*** as a precursor of dihydropyrazine ***B***. All authors concur on the intermediate formation of metal-bounded ylide ***D*** on the route both to dihydropyrazine ***B*** and pyrrole ***C***. One of the two suggested mechanisms for the formation of pyrrole ***C*** involves the generation of a 1*H*-azirine intermediate, its recyclization to 3*H*-pyrrole ***J*** followed by isomerization to pyrrole ***C***.[12] The alternative version inclines to the formation of a 3*H*-pyrrole intermediate ***J*** via the transformation of ylide ***D*** to zwitter-ion ***I***.[11] Diazatriene ***G*** was not considered as an intermediate on the route to pyrrole ***C*** from ylide ***D***, but the formation of ***G*** was postulated for rationale of the formation of pyrrole ***C*** from isoxazolium ylide ***L***, generated from isoxazole ***K*** and 1-sulfonyl-1,2,3-triazole.[9]

**Scheme 3. Published mechanistic schemes**

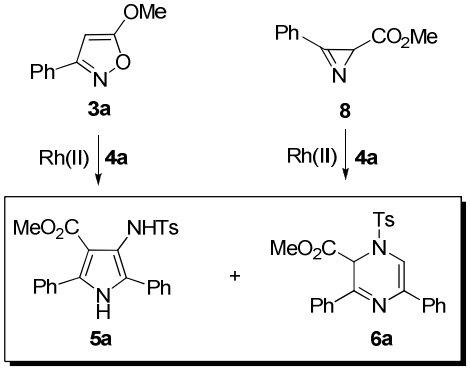



None of the above-mentioned mechanisms can explain why the reaction outcome depends on temperature and on the change of the starting material from azirine to isoxazole. The structure of the common precursor (if any) of pyrrole and dihydropyrazine and mechanistic differences in the transformations of azirinium and isoxazolium ylides to final products are the key issues remaining unclear.

To gain insight into the mechanism of the formation of 3-aminopyrroles and 1,2-dihydropyrazines, several additional experiments were performed (Table 4). Firstly, isoxazole **3a** and azirine **8** were reacted with triazole **4a** under the conditions of methods A and B. Under conditions A ($Rh_2(OAc)_4$/$CHCl_3$/100 °C) isoxazole **3a** and azirine **8** did not display considerable difference in products yields (Table 4, entries 1, 2). In contrast, under conditions B ($Rh_2(Piv)_4$/toluene/110 °C) azirine **8** gave 3-aminopyrrole **5a** substantially while from isoxazole **3a** dihydropyrazine **6a** was obtained as a major product (Table 4, entries 3, 4). Thus, a key point for successful synthesis of dihydropyrazines/pyrazines is the use of 5-alkoxyisoxazoles but not corresponding azirine-2-carboxylates.

An additive of TsOH in the reaction of isoxazole **3a** with triazole **4a** led to a significant increase of pyrrole/dihydropyrazine ratio and somewhat decreased overall yield of products (Table 4, entry 5). It is interesting that water did not have any effect on the ratio and yields of aminopyrrole **5a** and 1,2-dihydropyrazine **6a** (Table 4, entry 6).

**Table 4. Reactions of Triazole 4a with Isoxazole 3a and Azirine 8 under Rh(II) catalysis**




| entry | starting compounds | conditions[a] (additive) | **5a** : **6a** ratio[b] | overall yield[c], % |
|---|---|---|---|---|
| 1 | **3a** + **4a** | A | 3.6 : 1 | 93 |
| 2 | **8** + **4a** | A | 4.1 : 1 | 90 |
| 3 | **3a** + **4a** | B | 1 : 3 | 91 |
| 4 | **8** + **4a** | B | 1.4 : 1 | 90 |
| 5 | **3a** + **4a** | B (0.05 equiv TsOH) | 1.1 : 1 | 72 |
| 6 | **3a** + **4a** | B (1 equiv $H_2O$) | 1 : 3 | 94 |

[a] Conditions A: **4a** (1.5 equiv), $Rh_2(OAc)_4$ (0.025 equiv), $CHCl_3$, 100 °C, 2 h; conditions B: **4a** (2.5 equiv), $Rh_2(Piv)_4$ (0.025 equiv), toluene, 110 °C, 3 min;
[b] The ratios were determined by $^1$H NMR spectroscopy.
[c] The yields were determined by $^1$H NMR spectroscopy using 1-methylnaphthalene as an internal standard.

To find out what is the possible intermediate on the way to isomeric products **5** and **6**, we have analyzed the reaction mixture obtained by the method B at the early stage of the reaction (addition of 1 equiv of triazole **4a** to isoxazole **3a**, heating for 30 s followed by fast cooling). To our delight, according to $^1$H NMR, along with aminopyrrole **5a** and dihydropyrazine **6a**, a

significant amount of another compound was present in the reaction mixture (Figure 1, record 1). The positions of signals of this intermediate in the $^1$H NMR spectrum (8.89, 5.48 and 3.59 ppm) and cross peaks in the 2D $^1$H-$^{13}$C HSQC spectrum ($^1$H 8.89 ppm – $^{13}$C 165.2 ppm, $^1$H 5.48 ppm – $^{13}$C 96.3 ppm) (Fig. S-1, Supporting Information) allowed unequivocal identification of (5*Z*)-1,4-diaza-1,3,5-triene *Z*-**9a** (Scheme 4). The chemical shift of the $C^6$ atom less than 100 ppm in the $^{13}$C NMR spectrum is characteristic of the 3-aminocinnamate moiety with *Z* configuration of the C=C bond.[2b,5b] The diazatriene *Z*-**9a**/pyrrole **5a**/dihydropyrazine **6a** ratio in the reaction mixture after 30 s was 3.7 : 1 : 2.4 (Figure 1, record 1). Unfortunately, all attempts to isolate this compound by chromatography failed due to its instability. Meanwhile, $^1$H NMR monitoring of the reaction mixture has proved to be helpful for study of the transformations of intermediate *Z*-**9a**. When kept in toluene for 24 h at room temperature, intermediate *Z*-**9a** gradually transformed mainly into pyrrole **5a** ($CH_3O$ shift is 3.42 ppm) with partial decomposition (Figure 1, record 2). While under reflux in toluene for 5 min about three quarters of diazatriene *Z*-**9a** converted into dihydropyrazine **6a** ($CH_3O$ shift is 3.66 ppm) and only one quarter, into pyrrole **5a** (Figure 1, record 3). These results provide unequivocal evidence showing that both 3-aminopyrrole **5a** and 1,2-dihydropyrazine **6a** are formed from the same precursor, (5*Z*)-1,4-diaza-1,3,5-triene *Z*-**9a** (Scheme 4).

**Scheme 4. Formation of 1,4-Diazatriene Intermediates 9a in the Reactions of Triazole 4a with Isoxazole 3a and Azirine 8**

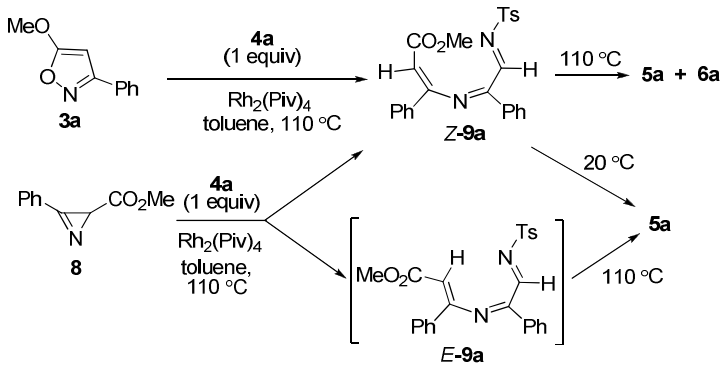
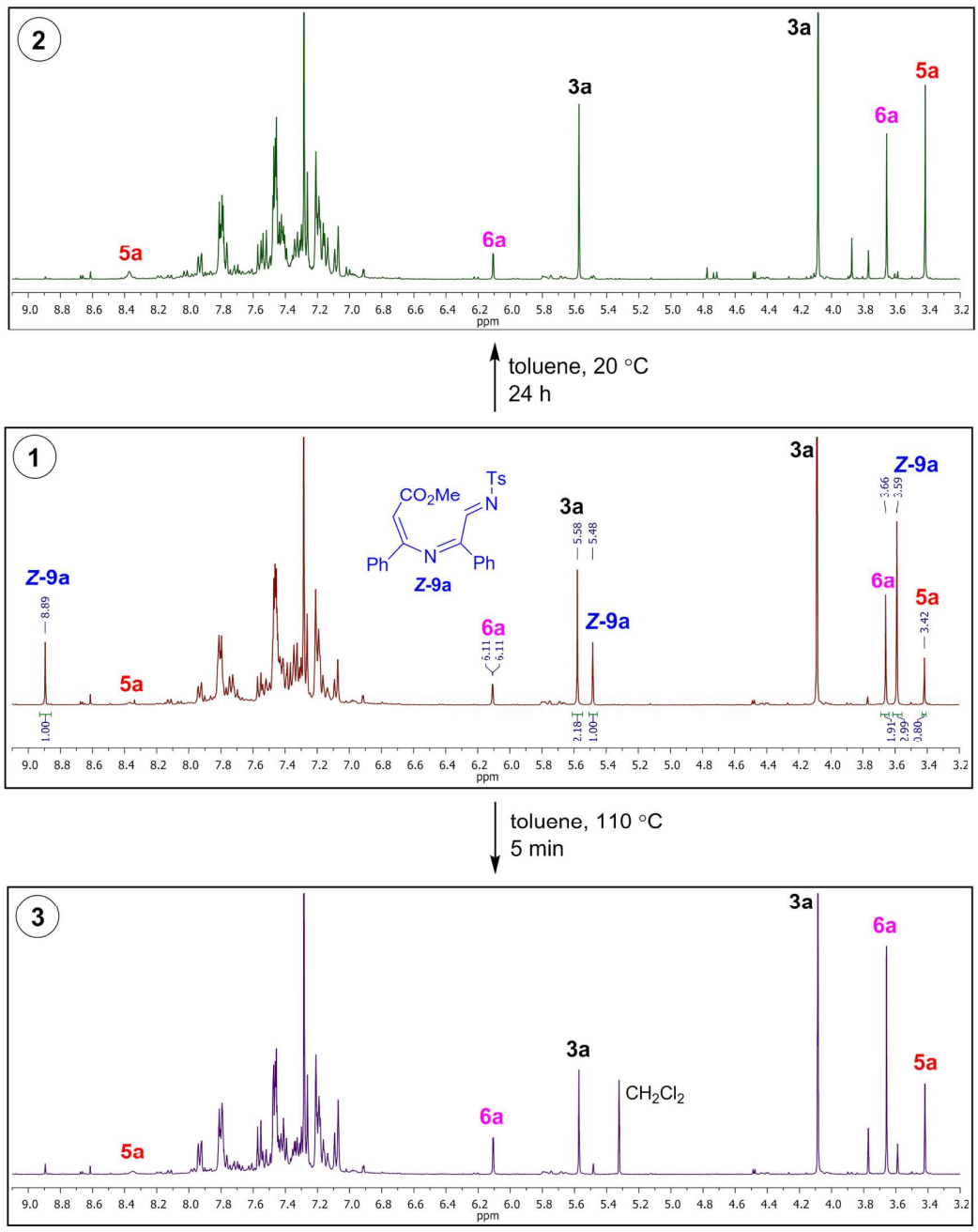



**Figure 1. $^1$H NMR Monitoring ($CDCl_3$) of the Transformation of Intermediate *Z*-9a in the reaction of Triazole 4a and Isoxazole 3a**




The reaction of triazole **4a** with azirine **8** (Scheme 4) under the same conditions and stopped by cooling after 30 s gave the same three products, *Z*-**9a**,**5a**, and **6a** (Fig. S-2, Supporting Information), but, according to $^{1}$H NMR, their ratio (1 : 6 : 2) differed markedly from that observed in the reaction of isoxazole **3a** (Figure 1, record 1). The dramatic effect of substrate nature on the reaction progress and product distribution can be rationalized in terms of a change in the key intermediate: from diazatriene *Z*-**9a** in isoxazole reaction to diazatriene *E*-**9a** in azirine reaction (Scheme 4). Isoxazole **3a** reacts with α-imino carbenoid to form diazatriene *Z*-**9a** exclusively, while the reaction of azirine **8** can yield both isomers: *E*-**9a** and *Z*-**9a**. The

stereoselectivity of the latter reaction is defined by the selectivity of ring opening in the metal-bounded azirinium ylide ***D*** (Scheme 3) or the metal-free azirinium ylide formed after elimination of the catalyst. It is known that related azirinium ylides with the same substitution pattern of the ring, generated from azirines and diazo carbonyl compounds, provide a mixture of isomeric azadienes across C=C bond with the *E/Z* ratio *ca*. 2 : 1.[2b,5c] Thereby, there is every reason to believe that an isoxazolium ylide undergoes ring-opening into diazatriene *Z*-**9a** exclusively, while an azirinium ylide provides both the *E*-**9a** and *Z*-**9a** diazatrienes with a significant prevalence of the former isomer (Scheme 4). The absence of isomer *E*-**9a** in the reaction mixture, resulted from azirine **8**, can be explained by its higher reactivity in comparison with *Z*-**9a** toward isomerization to pyrrole **5a**. To validate these hypotheses, we performed quantum-chemical calculations of the transformation pathways of diazatriene species to compounds **5** and **6**.

**Theoretical calculations**. DFT calculations were used to compare the two competitive routes of cyclization of isomeric diazatrienes and to clarify the reasons for the high sensitivity of the reaction outcome to temperature and reagent concentrations. The pathways for the transformations of model diazatrienes *Z*-**9b** (*Z* configuration of the C=C bond) and *E*-**9b** (*E* configuration of the C=C bond) generated from 1-mesyl-4-phenyl-1,2,3-triazole (**4b**) and isoxazole **3a** or azirine **8** were studied using Gaussian 09 programs package at B3LYP 6-31+G(d,p) theory level. To take into account the influence of the solvent, the PCM solvation model for toluene was employed (Scheme 5, Figure 2). In the Fig. 2 for clarity only the transformations with the lowest barriers are presented.

The calculations reveal that dihydropyrazine **6l** is formed directly via 1,6-cyclization of diazatriene *Z*-**9b** (TS1) (Fig. 2, blue line). The alternative two-step pathway involving the formation of 2*H*-1,3-oxazine **17** and Cope-rearrangement does not occur due to the absence of pericyclic transition state on the second stage: the rearrangement of oxazine **17** to dihydropyrazine **6l** occurs via TS1 as well. Nevertheless, 1,3-oxazine **17** is really generated in this reaction and exists in equilibrium with diazatriene *Z*-**9b**. The transition state energies for 1,5-cyclization of *Z*-**9b** and *E*-**9b** (TS2 and TS4) are significantly lower than those for 1,6-cyclizations (TS1 and TS3). The barriers for alternative 1,5-cyclizations of these intermediates through transition states TS6 and TS7 are significantly higher (Fig. S-3, Supporting Information). It is important, that unlike 1,6-cyclizations, the formation of a 5-membered ring is a reversible process in all cases under the used reaction conditions. Diazatriene *Z*-**9b** cyclizes to zwitterion *cis*-**10b** that exists in rapid equilibrium with aziridine *cis*-**11b**. With isomeric diazatriene *E*-**9b**, 1,5-cyclization and aziridine ring closure occur in one step to give aziridine *trans*-**11b** which is 4.3 kcal·mol$^{-1}$ less stable than initial *E*-**9b**. The search for the unimolecular isomerization pathways of zwitterion *cis*-**10b** to final pyrrole **5l** did not reveal any with the

energy profile lying below than that for the competitive 1,6-cyclization of *Z*-**9b** to dihydropyrazine **6l** (TS1). The following unimolecular transformations as initial steps were calculated (Scheme 5): C→C [1,2]-H-shift to 3-iminopyrroline **14** (TS9, route *a*), C→O 1,4-prototropic shift to 3*H*-pyrrole **15** (TS10, route *b*), and C→N 1,2-prototropic shift to 3*H*-pyrrole **16** (TS11, route *c*) (Fig. S-3, Supporting Information). Pyrrole **5l** most probably results from low-barrier intramolecular 1,5-*H*-shifts in 3*H*-pyrrole **13b** which, in turn, could be formed in an unimolecular fashion only from aziridine *trans*-**11b** (TS12), the 1,5-cyclization product of diazatriene *E*-**9b** (Fig. 2, red line). According to the calculations, the transformation of *trans*-**11b** to 3*H*-pyrrole **12b** occurs via C→O 1,5-prototropic shift coupled with aziridine ring opening (TS12). The alternative isomerization pathways of aziridine *trans*-**11b** via C→O 1,4-prototropic shift (TS13) and C→N 1,3-prototropic shift (TS14) have much higher barriers (Figure S-3, Supporting Information). The unimolecular isomerization of isoxazole-derived diazatriene *Z*-**9b** into pyrrole **5l** via *cis*-**11b** or zwitterion *cis*-**10b** (similar to isomerization *trans*-**11b**→**12b**) is not feasible due to the *trans* arrangement of $H^3$ and sulfonylamide moiety in these species. At the same time, the experiments showed that the isomerization of diazatriene *Z*-**9a** to pyrrole **5a** occurs in the reaction mixture even at room temperature (Figure 1, records 1, 2), while the increasing temperature favors 1,6-cyclization. These facts, as well as the pronounced effect of the nature of the rhodium catalyst and dilution of the reaction mixture on the **5**/**6** ratio (Table 1) are the arguments for a) intermolecular character of isomerization of zwitterion *cis*-**10b** to pyrrole **13b** and b) participation of the rhodium catalyst in this process. We assumed that dirhodium tetracarboxylate catalyzes the prototropic shift in zwitterion *cis*-**10b** via the intermediate formation of *cis*-**10b**·$RhL_n$ complex. The latter further undergoes intermolecular prototropic shift to pyrrole **13b**, most likely under the promotion of the basic diazatriene *Z*-**9b**. The sulfonylamide moiety in zwitterion *cis*-**10b** is shielded by the *cis*-methoxycarbonyl group, which should result in a significant depression of the N-complexation ability. On the other hand, the less sterically hindered zwitterion *trans*-**10b** (not shown in Scheme 5), which does not exist in a free state (Fig. 2), could be trapped by dirhodium tetracarboxylate as a complexation agent. Moreover, $Rh_2(OAc)_4$ with less bulky carboxylate ligands must be much more active complexation agent than $Rh_2(Piv)_4$ and $Rh_2(esp)_2$. According to the quantum-chemical calculations (DFT B3LYP/6-31G(d)/Stuttgart RSC 1997 ECP), zwitterion *trans*-**10b** which has no local minimum on the PPE gave N–Rh-complexes *trans*-**10b**·$Rh_2(RCO_2)_4$ (Fig. S-4, Supporting Information). The significant lengthening of the N–Rh bond in *cis*-**10b**·$Rh_2(Piv)_4$ in comparison with *cis*-**10b**·$Rh_2(OAc)_4$ reflects the lower stability of the former, and therefore, its lower concentration in the solution. Evidence for the above-mentioned destabilizing effect of the *cis*-oriented $CO_2Me$ group in complexes *cis*-**10b**·$Rh_2(Piv)_4$ and *cis*-**10b**·$Rh_2(OAc)_4$ comes from

the fact that they have higher energies than *trans*-**10b**·$Rh_2(Piv)_4$ and *trans*-**10b**·$Rh_2(OAc)_4$: 16.9 and 8.9 kcal/mol, respectively. Thus, the highest concentration of a zwitterion complex active toward intermolecular isomerization into pyrrole **5** has to be expected in a $Rh_2(OAc)_4$-catalyzed reaction of azirine-2-carboxylates, while the lowest, in a $Rh_2(Piv)_4$-catalyzed reaction of 5-alkoxyisoxazoles. Besides, these facts provide a good rationale for observed low stability of diazatriene *E*-**9a** in the "azirine reaction" in comparison with diazatriene *Z*-**9a** stability in the "isoxazole reaction".

**Scheme 5. Possible Pathways for the Formation of Pyrrole 5l and Dihydropyrazine 6l from Diazatrienes *Z*-9b and *E*-9b**

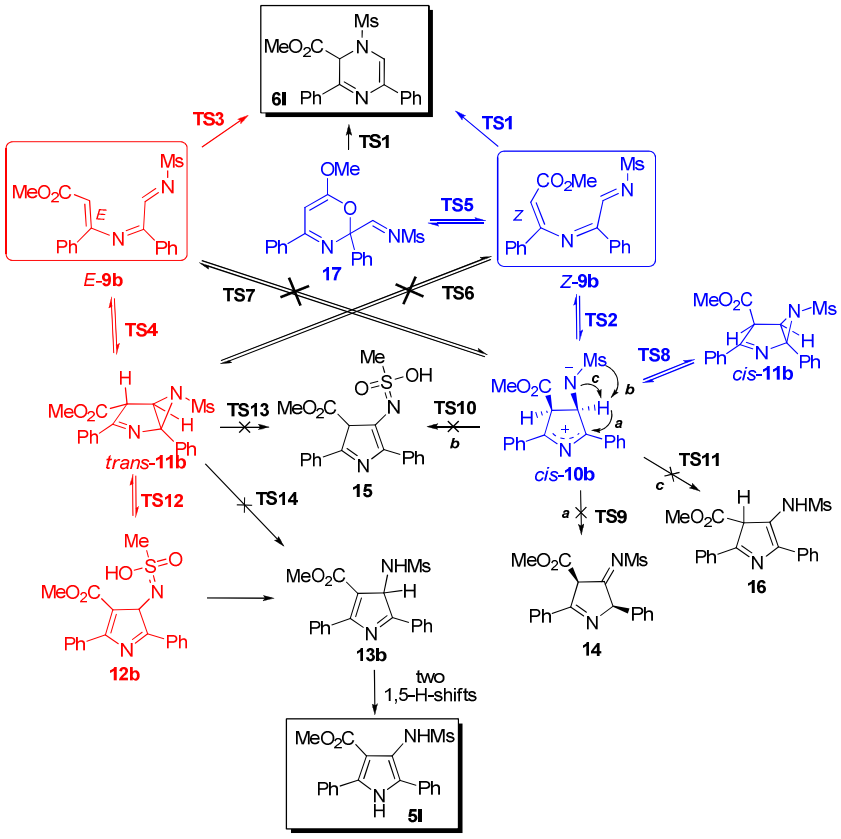
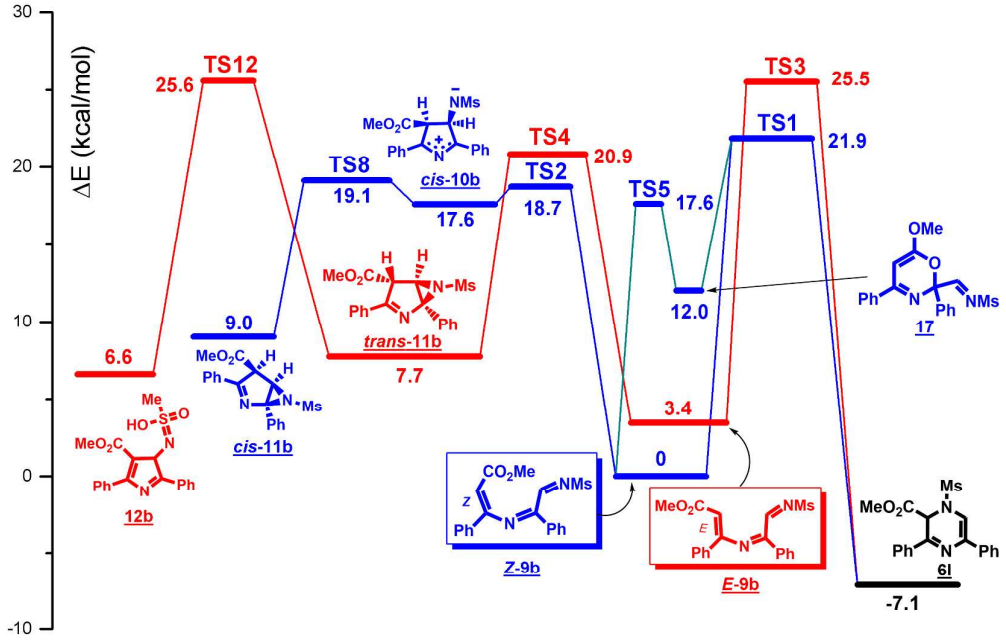



**Figure 2. Energy Profiles (Zero-point Exclusive Energies, B3LYP/6-31+G(d,p), kcal·mol$^{-1}$, 373K, toluene) for Unimolecular Transformations of Diazatrienes *Z*-9b and *E*-9b**



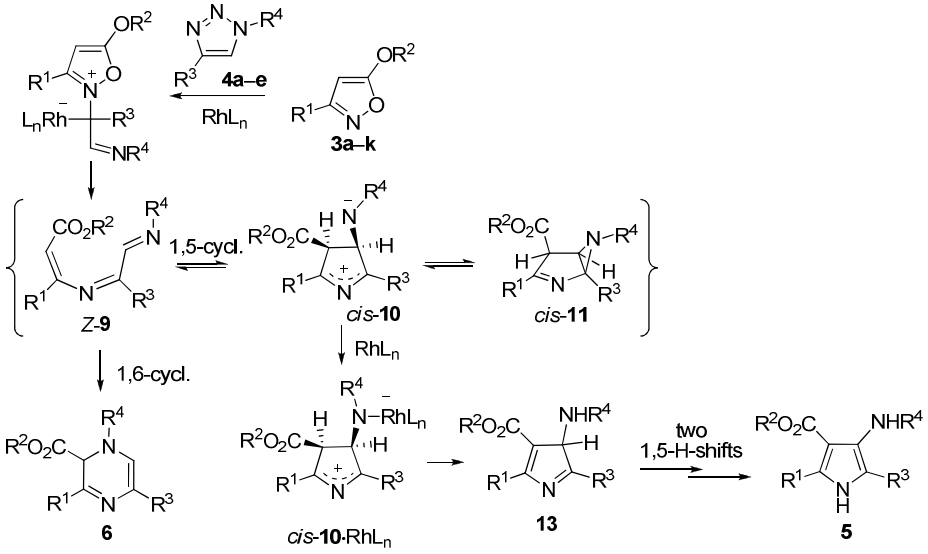

The significant effect of aryl substituents on the **5**/**6** ratio (Table 2) can be explained in the context of their cation-stabilizing ability in complexes *cis*-**10**·RhL$_n$. Electron-withdrawing aryl substituents adjacent to the cationic center destabilize the zwitterion, and the dihydropyrazine percentage increases (Table 2). In contrast, electron-donating aryl substituents at the same positions stabilize the zwitterion, which reveals itself in the observed full absence of dihydropyrazine.

Addition of an acid in the reaction mixture can facilitate the isomerization of intermediate *cis*-**10b**·RhL$_n$ complex to 3*H*-pyrroles **13b**, a precursor of 1*H*-pyrrole **5l**, via N-protonation/C-deprotonation, resulting in increase of the **5**/**6** ratio. Such effect was indeed observed in the reaction of isoxazole **3a** with triazole **4a** when catalytic amounts of TsOH were added (Table 4, entry 5).

Thus, the following features become apparent upon analysis of the calculation results and experimental data: a) both stereoisomeric diazatrienes undergo relatively slow but irreversible 1,6-cyclization to the dihydropyrazine, while 1,5-cyclization occurs rapidly and reversibly; b) azirine-derived *E*-diazatriene undergoes 1,5-cyclization with a lower barrier than isoxazole-derived *Z*-diazatriene; c) there is no one single unimolecular step competitive with 1,6-cyclization on the way from the primary 1,5-cyclization products of *Z*-diazatrienes to pyrroles **5**; and d) the formation of pyrrole **5** in both azirine and isoxazole reactions is controlled by the ability of the azirinopyrrole intermediate to produce via aziridine ring opening the zwitterion

intermediate or/and its rhodium complex. Taking into account these data the mechanistic scheme for the catalytic reaction of isoxazoles **3a–k** with triazoles **4a–e** (Scheme 6) involves the formation of diazatriene *Z*-**9** that exists in equilibrium with zwitterion *cis*-**10** and azirinopyrrole *cis*-**11**. At elevated temperatures and in more dilute solutions, the diazatriene preferably undergoes irreversible 1,6-cyclization to dihydropyrazine **6**. And, conversely, a decrease in temperature and an increase in concentration of reactants accelerates the competitive reaction of zwitterion *cis*-**10** with the catalyst to form a rhodium complex. The latter irreversibly isomerizes to 3*H*-pyrrole **13** which further undergoes two 1,5-H-shifts to give pyrrole **5**.

**Scheme 6. Reaction mechanism**




## Conclusion

In conclusion, 4-aminopyrrole-3-carboxylates and pyrazine-2-carboxylates were synthesized by a Rh(II)-catalyzed reaction of 1-sulfonyl-1,2,3-triazoles with stable and readily available 5-alkoxyisoxazoles. The reasonable yields of each product were achieved by tuning the Rh(II) catalyst and the reaction conditions. The reaction in chloroform at 100 °C in the presence of $Rh_2(OAc)_4$ as a catalyst is most suitable for the synthesis of 4-aminopyrrole-3-carboxylates. The use of $Rh_2(Piv)_4$ in refluxing toluene results in the formation of 1,2-dihydropyrazine-2-carboxylates as the main products which were transformed to pyrazine-2-carboxylates in a one-pot procedure by heating with catalytic amounts of TsOH. The NMR data and DFT calculations revealed that both products, pyrrole and dihydropyrazine, are formed via 1,4-diazahexa-1,3,5-triene intermediate having C=C bond with *Z* configuration. The *E*-diazatriene isomer generated from the azirine-2-carboxylate isomeric to the 5-alkoxyisoxazole produces predominantly the

corresponding 4-aminopyrrole-3-carboxylate, which makes the azirine-type substrates poorer candidates for the preparation of pyrazine-2-carboxylate derivatives. The influence of the nature of the rhodium catalyst on the product distribution is rationalized in terms of the Rh-catalyzed isomerization of the pyrroliniosulfonamide zwitterion, the primary product of 1,4-diazahexatriene 1,5-cyclization.

## EXPERIMENTAL SECTION

**General methods.** Melting points were determined on a melting point apparatus and are uncorrected. The $^{1}$H NMR spectra were recorded at 400 MHz. The $^{13}$C NMR spectra were recorded at 100 MHz. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane in solvents indicated below. High-resolution mass spectra were recorded on an HRMS-ESI-QTOF instrument, electrospray ionization, positive mode. Thin-layer chromatography (TLC) was conducted on aluminum sheets precoated with $SiO_2$ ALUGRAM SIL G/UV254. Column chromatography was performed on silica gel 60 M (0.04–0.063 mm). All solvents were distilled and dried prior to use. Toluene was distilled and stored over sodium metal. Chloroform was washed with concentrated $H_2SO_4$, water, then distilled from $P_2O_5$ and stored refrigerated in the dark over anhydrous $K_2CO_3$. The catalysts $Rh_2(Oct)_4$,[14] $Rh_2(Piv)_4$[15] and $Rh_2(esp)_2$[16] were prepared by the reported procedures and gave satisfactory elemental analyses. Isoxazoles **3a**–**h**,[2b] **3l**,[17] **3m,**[18] 1,2,3-triazoles **4a–c,f,**[19] and azirine **8**[20] were prepared by the reported procedures.

**General procedure for the preparation of 5-methoxyisoxazoles 3i,k.**[2b] To a stirred suspension/solution of isoxazolone (1 equiv) in dry $Et_2O$ (50 mL) a solution of diazomethane (2 equiv) in $Et_2O$, prepared from *N*-nitroso-*N*-methylurea and KOH, was added dropwise at 0 °C. The resulting mixture was stirred at rt for 2 h and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent petroleum ether–EtOAc 3:1).

*5-Methoxy-3-(4-nitrophenyl)isoxazole (**3i**)*. Compound **3i** was obtained from 3-(4-nitrophenyl)isoxazol-5(4*H*)-one **19** and a solution of diazomethane as a colorless solid (1.71 g, yield 74%); mp 122–124 °C ($Et_2O$/hexane); $R_f$ = 0.42 (hexane/EtOAc 2:1); $^{1}$H NMR ($CDCl_3$) δ 8.35–8.29 (m, 2H), 7.98–7.92 (m, 2H), 5.63 (s, 1H), 4.11 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 175.0, 162.3, 148.7, 135.6, 127.3, 124.1, 75.8, 59.0; HRMS−ESI $[M + Na]^+$ calcd for $C_{10}H_8N_2O_4Na^+$ 243.0376; found 243.0381.

*5-Methoxy-3-methylisoxazole (**3k**).*[21] Compound **3k** was obtained from 3-methylisoxazol-5(4*H*)-one[21] and a solution of diazomethane as a colorless smelly oil (350 mg, yield 56%); $R_f$ = 0.41 (hexane/EtOAc 2:1); $^{1}$H NMR ($CDCl_3$) δ 5.07 (s, 1H), 3.96 (s, 3H), 2.21 (s, 3H) $^{13}$C NMR

($CDCl_3$) δ 174.1, 162.2, 77.7, 58.5, 12.3; HRMS-ESI $[M + H]^+$ calcd for $C_5H_8NO_2^+$ 114.0550; found 114.0550.

*5-(tert-Butoxy)-3-phenylisoxazole (**3j**).*[22] A mixture of 5-chloro-3-phenylisoxazole[22] (500 mg, 2.8 mmol), potassium *tert*-butoxide (374 mg, 3.34 mmol) in dry tetrahydrofuran (7 mL) was refluxed for 1 h. The precipitate of potassium chloride was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent petroleum ether–$Et_2O$ 3:1) to give compound **3j** as a colorless oil (549 mg, yield 91%). $R_f$ = 0.61 (hexane/EtOAc 2:1); $^1H$ NMR ($CDCl_3$) δ 7.81–7.76 (m, 2H), 7.50–7.42 (m, 3H), 5.68 (s, 1H), 1.56 (s, 9H); $^{13}C$ NMR ($CDCl_3$) δ 172.0, 163.9, 129.85, 129.84, 128.8, 126.4, 84.9, 82.4, 28.3; HRMS−ESI $[M + Na]^+$ calcd for $C_{13}H_{15}O_2NNa^+$ 240.0995; found 240.0999.

**General procedure for the preparation of 1-sulfonyl-1,2,3-triazoles 4d,e.**[19] To a stirred solution of terminal alkyne (1.1 equiv), sulfonyl azide (1 equiv), and 2-aminophenol (0.05 equiv) in MeCN was added $Cu(OAc)_2·H_2O$ (0.1 equiv) at room temperature. After sulfonyl azide was consumed (0.5–3 h, monitored by TLC) the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (eluent petroleum ether–EtOAc 3:1).

*4-(4-Chlorophenyl)-1-(4-methylphenylsulfonyl)-1H-1,2,3-triazole (**4d**).*[23] White solid (1.26 g, yield 59%); $R_f$ = 0.56 (hexane/EtOAc 2:1); $^1H$ NMR ($CDCl_3$) δ 8.33 (s, 1H), 8.05 (d, $J$ = 8.5 Hz, 2H), 7.79 (d, $J$ = 8.5 Hz, 2H), 7.45–7.40 (m, 4H), 2.48 (s, 3H).

*4-(2-Fluorophenyl)-1-(4-methylphenylsulfonyl)-1H-1,2,3-triazole (**4e**).* White solid (550 mg, yield 70%); mp 132–134 °C; $R_f$ = 0.56 (hexane/EtOAc 2:1); $^1H$ NMR ($CDCl_3$) δ 8.50 (d, $J$ = 3.4 Hz, 1H), 8.28 (td, $J$ = 7.6, 1.8 Hz, 1H), 8.06 (d, $J$ = 8.4 Hz, 2H), 7.41 (d, $J$ = 8.4 Hz, 2H), 7.40–7.33 (m, 1H), 7.27 (td, $J$ = 7.6, 1.2 Hz, 1H), 7.18 (ddd, $J$ = 11.0, 8.3, 1.1 Hz, 1H), 2.47 (s, 3H) ; $^{13}C$ NMR ($CDCl_3$) δ 159.4 (d, $J$ = 249 Hz), 147.3, 140.86 (d, $J$ = 2.2 Hz), 133.1, 130.5, 130.3 (d, $J$ = 8.7 Hz), 128.7, 128.07 (d, $J$ = 3.0 Hz), 124.68 (d, $J$ = 3.5 Hz), 121.93 (d, $J$ = 13.7 Hz), 117.06 (d, $J$ = 12.6 Hz), 115.8 (d, $J$ = 21.4 Hz), 21.8; HRMS−ESI $[M + H]^+$ calcd for $C_{15}H_{13}FN_3O_2S^+$ 318.0707; found 318.0706.

**Rh-catalyzed reactions of isoxazoles 3a–m with 1-sulfonyl-1,2,3-triazoles 4a–e.**

**Method A.** Isoxazole **3** (0.29 mmol, 1 equiv), triazole **4** (0.32 mmol, 1.1 equiv), $Rh_2(OAc)_4$ (3.2 mg, 0.025 equiv), and $CHCl_3$ (0.5 mL) were placed to a screw cap glass tube and heated at 100 °C (oil bath temperature) under stirring for 1–6 h until full consumption of isoxazole was detected (control by TLC, hexane–$Et_2O$ 3:1), if necessary, an additional amount of triazole was added (total amount see below). The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (eluent petroleum ether–EtOAc 3:1 unless otherwise stated) to give the desired products.

**Method B.** Isoxazole **3** (0.29 mmol, 1 equiv), $Rh_2(Piv)_4$ (4.4 mg, 0.025 equiv), and toluene (3.0 mL) were placed to a round-bottom flask under an ambient atmosphere and rapidly heated to reflux (oil bath temperature 130 °C) under stirring. Then triazole **4** as a solid was added in 0.5 equiv portions (total amount see below) until full consumption of isoxazole was detected (control by TLC, hexane–$Et_2O$ 3:1). Each subsequent portion of triazole was added after the nitrogen evolution has stopped (about 0.5–1 min). The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (eluent petroleum ether–$Et_2O$ 3:1 unless otherwise stated) to give the desired products. For the synthesis of pyrazines **7** the above reaction mixture before chromatographic purification was treated with *p*-toluenesulfonic acid (10 mg, 0.2 equiv) and refluxed for 3 h.

*Methyl 4-(4-methylbenzenesulfonamido)-2,5-diphenyl-1H-pyrrole-3-carboxylate (**5a**).* Obtained from isoxazole **3a** and triazole **4a** (1.5 equiv, 128 mg, 0.43 mmol) according to the method A as a white solid (98 mg, yield 76%); mp 166−168 °C; $R_f$ = 0.53 (hexane/EtOAc 1:1); $^1$H NMR (acetone-$d_6$) $\delta$ 10.77 (br s, 1H), 7.87 (d, $J$ = 7.3 Hz, 2H), 7.76 (s, 1H), 7.56−7.51 (m, 2H), 7.45 (d, $J$ = 8.1 Hz, 2H), 7.42−7.31 (m, 5H), 7.25 (t, $J$ = 7.3 Hz, 1H), 7.19 (d, $J$ = 8.1 Hz, 2H), 3.37 (s, 3H), 2.34 (s, 3H); $^{13}$C NMR (acetone-$d_6$) $\delta$ 165.1, 143.9, 137.9, 136.3, 132.7, 132.2, 130.3, 130.1, 129.8, 128.93, 128.90, 128.6, 128.4, 127.9, 127.8, 118.7, 110.8, 50.8, 21.4; HRMS−ESI $[M + H]^+$ calcd for $C_{25}H_{23}O_4N_2S^+$ 447.1373; found 447.1390.

*Methyl 2-(4-methylphenyl)-4-(4-methylbenzenesulfonamido)-5-phenyl-1H-pyrrole-3-carboxylate (**5b**).* Obtained from isoxazole **3b** and triazole **4a** (1.2 equiv, 102 mg, 0.34 mmol) according to the method A as a white solid (108 mg, yield 81%); mp 174−176 °C; $R_f$ = 0.55 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.62 (s, 1H), 9.03 (s, 1H), 7.66−7.61 (m, 2H), 7.38 (d, $J$ = 8.2 Hz, 2H), 7.32 (d, $J$ = 8.2 Hz, 2H), 7.27 (t, $J$ = 7.4 Hz, 2H), 7.24−7.18 (m, 3H), 7.10 (d, $J$ = 8.2 Hz, 2H), 3.32 (s, 3H), 2.34 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 164.0, 142.0, 137.9, 137.2, 134.5, 130.7, 129.8, 128.84, 128.79, 128.6, 128.4, 127.8, 127.0, 126.6, 126.5, 115.9, 111.0, 50.3, 20.85, 20.81; HRMS−ESI $[M + Na]^+$ calcd for $C_{26}H_{24}N_2NaO_4S^+$ 483.1349; found 483.1342.

*Methyl 2-(2,4-dimethylphenyl)-4-(4-methylbenzenesulfonamido)-5-phenyl-1H-pyrrole-3-carboxylate (**5c**).* Obtained from isoxazole **3c** and triazole **4a** (1.4 equiv, 119 mg, 0.40 mmol) according to the method A as a white solid (104 mg, yield 76%); mp 186−188 °C; $R_f$ = 0.59 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.67 (s, 1H), 8.80 (s, 1H), 7.76−7.71 (m, 2H), 7.33 (d, $J$ = 8.2 Hz, 2H), 7.30 (t, $J$ = 7.5 Hz, 2H), 7.20 (t, $J$ = 7.3 Hz, 1H), 7.14 (d, $J$ = 8.2 Hz, 2H), 7.08 (d, $J$ = 7.5 Hz, 2H), 7.02 (d, $J$ = 7.9 Hz, 1H), 3.16 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 2.09 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163.3, 142.2, 137.5, 137.3, 137.1, 135.0, 130.9, 130.4, 130.1,

129.3, 128.83, 128.78, 127.9, 126.8, 126.56, 126.49, 125.6, 115.3, 111.1, 50.0, 20.86, 20.76, 19.5; HRMS−ESI $[M + Na]^+$ calcd for $C_{27}H_{26}O_4N_2NaS^+$ 497.1505; found 497.1510.

*Methyl 2-(4-methoxyphenyl)-4-(4-methylbenzenesulfonamido)-5-phenyl-1H-pyrrole-3-carboxylate (**5d**).* Obtained from isoxazole **3d** and triazole **4a** (1.3 equiv, 111 mg, 0.37 mmol) according to the method A as a white solid (118 mg, yield 86%); mp 163−165 °C; $R_f$ = 0.44 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.58 (s, 1H), 8.98 (s, 1H), 7.65 (d, $J$ = 7.5 Hz, 2H), 7.44 (d, $J$ = 8.6 Hz, 2H), 7.33 (d, $J$ = 8.1 Hz, 2H), 7.27 (t, $J$ = 8.4 Hz, 2H), 7.21 (t, $J$ = 7.2 Hz, 1H), 7.11 (d, $J$ = 8.1 Hz, 2H), 6.97 (d, $J$ = 8.6 Hz, 2H), 3.79 (s, 3H), 3.32 (s, 3H), 2.28 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 164.0, 159.0, 142.0, 137.9, 134.6, 130.7, 130.3, 129.6, 128.8, 127.8, 127.0, 126.5 (2C), 123.8, 115.8, 113.2, 110.6, 55.2, 50.2, 20.9; HRMS−ESI $[M + H]^+$ calcd for $C_{26}H_{25}O_5N_2S^+$ 477.1479; found 477.1492.

*Methyl 2-(2,3-dihydrobenzo[b][1,4]-dioxin-6-yl)-4-(4-methylbenzenesulfonamido)-5-phenyl-1H-pyrrole-3-carboxylate (**5e**).* Obtained from isoxazole **3e** and triazole **4a** (1.2 equiv, 102 mg, 0.34 mmol) according to the method A (filtration and washing with $CHCl_3$ instead of column chromatography) as a white solid (108 mg, yield 74%); mp 232−234 °C; $R_f$ = 0.36 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.55 (s, 1H), 8.98 (s, 1H), 7.66−7.61 (m, 2H), 7.31 (d, $J$ = 8.2 Hz, 2H), 7.27 (t, $J$ = 7.3 Hz, 2H), 7.20 (t, $J$ = 7.3 Hz, 1H), 7.10 (d, $J$ = 8.0 Hz, 2H), 7.03 (d, $J$ = 2.1 Hz, 1H), 6.96 (dd, $J$ = 8.4, 2.1 Hz, 1H), 6.87 (d, $J$ = 8.4 Hz, 1H), 4.27 (s, 4H), 3.32 (s, 3H), 2.28 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 164.0, 143.3, 142.6, 142.0, 137.9, 134.1, 130.6, 129.6, 128.9, 127.8, 127.0, 126.6, 126.5, 124.5, 122.2, 117.6, 116.4, 115.8, 110.8, 64.2, 64.1, 50.3, 20.9; HRMS−ESI $[M + Na]^+$ calcd for $C_{27}H_{24}N_2NaO_6S^+$ 527.1247; found 527.1248.

*Methyl 2-(4-bromophenyl)-4-(4-methylbenzenesulfonamido)-5-phenyl-1H-pyrrole-3-carboxylate (**5f**) and methyl 3-(4-bromophenyl)-1-(4-methylphenylsulfonyl)-5-phenyl-1,2-dihydropyrazine-2-carboxylate (**6f**).* Obtained from isoxazole **3f** and triazole **4a** (1.2 equiv, 102 mg, 0.34 mmol) according to the method A. *Compound **5f**.* White solid (99 mg, yield 65%); mp 115−118 °C; $R_f$ = 0.58 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.76 (s, 1H), 9.07 (s, 1H), 7.63 (d, $J$ = 7.3 Hz, 2H), 7.61 (d, $J$ = 8.5 Hz, 2H), 7.46 (d, $J$ = 8.5 Hz, 2H), 7.32 (d, $J$ = 8.1 Hz, 2H), 7.28 (d, $J$ = 7.3 Hz, 2H), 7.23 (t, $J$ = 7.3 Hz, 1H), 7.10 (d, $J$ = 8.1 Hz, 2H), 3.34 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163.8, 142.0, 137.8, 133.0, 130.9, 130.7, 130.52, 130.48, 130.46, 128.8, 127.9, 127.1, 126.8, 126.5, 121.1, 116.1, 111.6, 50.4, 20.8; HRMS−ESI $[M + H]^+$ calcd for $C_{25}H_{22}O_4N_2{}^{79}BrS^+$ 525.0478; found 525.0496. *Compound **6f**.* Unstable yellow oil (39 mg, yield 26%); $^1$H NMR ($CDCl_3$) $\delta$ 7.83−7.75 (m, 4H), 7.62−7.55 (m, 4H), 7.41 (t, $J$ = 7.2 Hz, 2H), 7.34 (t, $J$ = 7.2 Hz, 1H), 7.12 (d, $J$ = 8.1 Hz, 2H), 7.08 (d, $J$ = 1.3 Hz, 1H), 6.03 (d, $J$ = 1.3 Hz, 1H), 3.65 (s, 3H), 2.34 (s, 3H).

*Methyl 2-(4-chlorophenyl)-4-(4-methylbenzenesulfonamido)-5-phenyl-1H-pyrrole-3-carboxylate (**5g**) and methyl 3-(4-chlorophenyl)-1-(4-methylphenylsulfonyl)-5-phenyl-1,2-dihydropyrazine-2-carboxylate (**6g**).* Obtained from isoxazole **3g** and triazole **4a** (1.1 equiv, 94 mg, 0.31 mmol) according to the method A. *Compound **5g***. White solid (85 mg, yield 61%); mp 189−191 °C; $R_f$ = 0.61 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-d$_6$) $\delta$ 11.76 (s, 1H), 9.07 (s, 1H), 7.67−7.62 (m, 2H), 7.52 and 7.47 (AB-q, $J$ = 8.7 Hz, 4H), 7.32 (d, $J$ = 8.2 Hz, 2H), 7.29 (t, $J$ = 7.6 Hz, 2H), 7.22 (t, $J$ = 7.2 Hz, 1H), 7.10 (d, $J$ = 8.2 Hz, 2H), 3.33 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (DMSO-d$_6$) $\delta$ 163.8, 142.0, 137.9, 133.0, 132.5, 130.7, 130.47, 130.45, 130.2, 128.9, 127.9, 127.8, 127.1, 126.8, 126.5, 116.1, 111.6, 50.4, 20.8; HRMS−ESI [M + H]$^+$ calcd for $C_{25}H_{22}O_4N_2{}^{35}ClS^+$ 481.0983; found 481.0995. *Compound **6g***. Unstable yellow oil (35 mg, yield 25%); $^1$H NMR ($CDCl_3$) $\delta$ 7.88 (d, $J$ = 8.6 Hz, 2H), 7.81−7.76 (m, 2H), 7.57 (d, $J$ = 8.2 Hz, 2H), 7.46−7.38 (m, 4H), 7.34 (t, $J$ = 7.2 Hz, 1H), 7.12 (d, $J$ = 8.2 Hz, 2H), 7.08 (d, $J$ = 1.0 Hz, 1H), 6.05 (s, 1H), 3.65 (s, 3H), 2.33 (s, 3H).

*Methyl 2-(4-cyanophenyl)-4-(4-methylbenzenesulfonamido)-5-phenyl-1H-pyrrole-3-carboxylate (**5h**) and methyl 3-(4-cyanophenyl)-1-(4-methylphenylsulfonyl)-5-phenyl-1,2-dihydropyrazine-2-carboxylate (**6h**).* Obtained from isoxazole **3h** and triazole **4a** (1.6 equiv, 138 mg, 0.46 mmol) according to the method A. Column chromatography (petroleum ether−EtOAc 6:1−3:1). *Compound **5h***. White solid (23 mg, yield 17%); mp 157−159 °C; $R_f$ = 0.55 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-d$_6$) $\delta$ 11.96 (s, 1H), 9.16 (s, 1H), 7.87 (d, $J$ = 8.4 Hz, 2H), 7.70 (d, $J$ = 8.4 Hz, 2H), 7.66−7.61 (m, 2H), 7.34−7.22 (m, 5H), 7.09 (d, $J$ = 8.1 Hz, 2H), 3.37 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (DMSO-d$_6$) $\delta$ 163.8, 142.1, 137.8, 135.7, 132.0, 131.7, 131.5, 130.2, 129.5, 128.9, 127.9, 127.2, 127.1, 126.5, 118.8, 116.5, 112.8, 109.9, 50.6, 20.8; HRMS−ESI [M + Na]$^+$ calcd for $C_{26}H_{21}O_4N_3NaS^+$ 494.1145; found 494.1168. *Compound **6h***. Yellow solid (41 mg, yield 30%); mp 121−123 °C; $R_f$ = 0.40 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 8.06 (d, $J$ = 8.3 Hz, 2H), 7.80−7.73 (m, 4H), 7.61 (d, $J$ = 8.2 Hz, 2H), 7.43 (t, $J$ = 7.3 Hz, 2H), 7.36 (t, $J$ = 7.3 Hz, 1H), 7.15 (d, $J$ = 8.2 Hz, 2H), 7.12 (d, $J$ = 1.2 Hz, 1H), 6.08 (d, $J$ = 1.2 Hz, 1H), 3.65 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.6, 145.2, 145.0, 139.4, 135.4, 135.1, 135.0, 132.3, 129.8, 128.6, 128.2, 128.0, 126.5, 124.8, 118.3, 113.9, 111.0, 53.3, 52.5, 21.5; HRMS−ESI [M + Na]$^+$ calcd for $C_{26}H_{21}O_4N_3NaS^+$ 494.1145; found 494.1166.

*Methyl 4-(4-methylbenzenesulfonamido)-2-(4-nitrophenyl)-5-phenyl-1H-pyrrole-3-carboxylate (**5i**) and methyl 1-(4-methylphenylsulfonyl)-3-(4-nitrophenyl)-5-phenyl-1,2-dihydropyrazine-2-carboxylate (**6i**).* Obtained from isoxazole **3i** and triazole **4a** (1.5 equiv, 128 mg, 0.43 mmol) according to the method A. *Compound **5i***. Yellow solid (40 mg, yield 28%); mp 186−188 °C; $R_f$ = 0.50 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-d$_6$) $\delta$ 12.00 (s, 1H), 9.21 (s, 1H), 8.25 (d, $J$ = 8.8 Hz, 2H), 7.78 (d, $J$ = 8.8 Hz, 2H), 7.65−7.60 (m, 2H), 7.34−7.22 (m, 5H), 7.09

(d, $J$ = 8.1 Hz, 2H), 3.39 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163.7, 146.3, 142.1, 137.8, 137.6, 131.9, 131.4, 130.1, 129.6, 128.9, 127.9, 127.3, 127.1, 126.5, 123.0, 116.7, 113.4, 50.7, 20.8; HRMS−ESI $[M + Na]^+$ calcd for $C_{25}H_{21}N_3NaO_6S^+$ 514.1043; found 514.1050. *Compound* ***6i***. Orange solid (88 mg, yield 62%); mp 136−138 °C; $R_f$ = 0.45 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 8.31 (d, $J$ = 8.7 Hz, 2H), 8.13 (d, $J$ = 8.7 Hz, 2H), 7.79 (d, $J$ = 7.4 Hz, 2H), 7.63 (d, $J$ = 8.1 Hz, 2H), 7.44 (t, $J$ = 7.4 Hz, 2H), 7.37 (t, $J$ = 7.2 Hz, 1H), 7.20−7.12 (m, 3H), 6.13 (s, 1H), 3.66 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.6, 148.8, 145.1, 144.8, 141.0, 135.4, 135.1, 134.9, 129.9, 128.6, 128.4, 128.2, 126.5, 124.8, 123.7, 111.2, 53.3, 52.6, 21.5; HRMS−ESI $[M + Na]^+$ calcd for $C_{25}H_{21}N_3NaO_6S^+$ 514.1043; found 514.1046.

*tert-Butyl 4-(4-methylbenzenesulfonamido)-2,5-diphenyl-1H-pyrrole-3-carboxylate* ***(5j)*** *and tert-butyl 1-(4-methylphenylsulfonyl)-3,5-diphenyl-1,2-dihydropyrazine-2-carboxylate* ***(6j)***. Obtained from isoxazole **3j** and triazole **4a** (1.5 equiv, 128 mg, 0.43 mmol) according to the method A. *Compound* ***5j***. White solid (92 mg, yield 65%); mp 200−201 °C (dec.); $R_f$ = 0.65 (hexane/EtOAc 1:1); $^1$H NMR ($CDCl_3$) $\delta$ 8.30 (br s, 1H), 7.71 (d, $J$ = 7.5 Hz, 2H), 7.57 (s, 1H), 7.51 (d, $J$ = 8.1 Hz, 2H), 7.44−7.34 (m, 7H), 7.28 (t, $J$ = 7.2 Hz, 1H), 7.11 (d, $J$ = 7.5 Hz, 2H), 2.36 (s, 3H), 1.22 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 163.8, 143.0, 136.0, 135.2, 132.0, 131.0, 129.3, 128.9, 128.5, 128.4, 128.0, 127.7, 127.5, 127.4, 126.4, 118.8, 109.8, 80.8, 27.9, 21.4; HRMS−ESI $[M + Na]^+$ calcd for $C_{28}H_{28}N_2NaO_4S^+$ 511.1662; found 511.1670. *Compound* ***6j***. Unstable yellow oil (32 mg, yield 23%); $^1$H NMR ($CDCl_3$) $\delta$ 7.97−7.92 (m, 2H), 7.78 (d, $J$ = 7.4 Hz, 2H), 7.58 (d, $J$ = 8.1 Hz, 2H), 7.49−7.37 (m, 5H), 7.33 (t, $J$ = 7.4 Hz, 1H), 7.10 (d, $J$ = 8.1 Hz, 2H), 7.04 (s, 1H), 5.97 (s, 1H), 2.32 (s, 3H), 1.30 (s, 9H); HRMS−ESI $[M + Na]^+$ calcd for $C_{28}H_{28}N_2NaO_4S^+$ 511.1662; found 511.1669.

*Methyl 2-methyl-4-(4-methylbenzenesulfonamido)-5-phenyl-1H-pyrrole-3-carboxylate* ***(5k)***. Obtained from isoxazole **1k** and triazole **4a** (1.2 equiv, 102 mg, 0.34 mmol) according to the method A as a white solid (61 mg, yield 55%); mp 194−196 °C; $R_f$ = 0.41 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-$d_6$) δ 11.47 (s, 1H), 8.77 (s, 1H), 7.65−7.59 (m, 2H), 7.31 (d, $J$ = 8.2 Hz, 2H), 7.27 (t, $J$ = 7.4 Hz, 2H), 7.18 (t, $J$ = 7.4 Hz, 1H), 7.13 (d, $J$ = 8.1 Hz, 2H), 3.31 (s, 3H), 2.36 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) δ 164.1, 141.9, 138.0, 134.1, 131.1, 128.7, 127.9, 127.5, 126.6, 126.24, 126.15, 114.9, 109.5, 49.9, 20.8, 12.9; HRMS−ESI $[M + Na]^+$ calcd for $C_{20}H_{20}O_4N_2NaS^+$ 407.1036; found 407.1046.

*Methyl 4-(methanesulfonamido)-2,5-diphenyl-1H-pyrrole-3-carboxylate* ***(5l)***. Obtained from isoxazole **3a** and triazole **4b** (1.2 equiv, 76 mg, 0.34 mmol) according to the method A as a white solid (83 mg, yield 77%); mp 179−181 °C; $R_f$ = 0.44 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.83 (s, 1H), 8.81 (s, 1H), 7.87−7.82 (m, 2H), 7.58−7.53 (m, 2H), 7.47−7.36 (m, 5H), 7.30 (t, $J$ = 7.3 Hz, 1H), 3.64 (s, 3H), 2.61 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 164.4, 135.0,

131.6, 130.7, 129.9, 129.1, 128.2, 127.9, 127.8, 127.2, 127.1, 116.4, 111.0, 50.7, 40.4; HRMS−ESI $[M + H]^+$ calcd for $C_{19}H_{19}O_4N_2S^+$ 371.1060; found 371.1071.

*Methyl 5-(4-methoxyphenyl)-4-(4-methylbenzenesulfonamido)-2-phenyl-1H-pyrrole-3-carboxylate (**5m**).* Obtained from isoxazole **3a** and triazole **4c** (1.3 equiv, 125 mg, 0.38 mmol) according to the method A as a white solid (76 mg, yield 55%); mp 187−190 °C; $R_f$ = 0.48 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.58 (s, 1H), 8.98 (s, 1H), 7.56 (d, $J$ = 8.8 Hz, 2H), 7.51−7.46 (m, 2H), 7.40 (t, $J$ = 7.3 Hz, 2H), 7.37−7.30 (m, 3H), 7.10 (d, $J$ = 8.1 Hz, 2H), 6.84 (d, $J$ = 8.8 Hz, 2H), 3.78 (s, 3H), 3.32 (s, 3H), 2.28 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 164.0, 158.3, 141.9, 138.1, 133.9, 131.5, 130.2, 128.9, 128.8, 128.4, 127.8, 127.6, 126.5, 123.2, 115.1, 113.3, 111.1, 55.0, 50.3, 20.8; HRMS−ESI $[M + Na]^+$ calcd for $C_{26}H_{24}N_2NaO_5S^+$ 499.1298; found 499.1299.

*Methyl 5-(4-chlorophenyl)-4-(4-methylbenzenesulfonamido)-2-phenyl-1H-pyrrole-3-carboxylate (**5n**).* Obtained from isoxazole **3a** and triazole **4d** (1.2 equiv, 114 mg, 0.34 mmol) according to the method A as a white solid (84 mg, yield 60%); mp 156−157 °C; $R_f$ = 0.57 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.78 (s, 1H), 9.10 (s, 1H), 7.63 (d, $J$ = 8.6 Hz, 2H), 7.53−7.48 (m, 2H), 7.42 (t, $J$ = 7.3 Hz, 2H), 7.36 (t, $J$ = 7.3 Hz, 1H), 7.34−7.29 (m, 4H), 7.10 (d, $J$ = 8.1 Hz, 2H), 3.37 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163.9, 142.2, 137.9, 134.8, 131.4, 131.3, 129.4, 128.9, 128.8, 128.7, 128.6, 127.9, 127.8 (2C+2C), 126.5, 116.5, 111.5, 50.4, 20.9; HRMS−ESI $[M + Na]^+$ calcd for $C_{25}H_{21}{}^{35}ClN_2NaO_4S^+$ 503.0803; found 503.0802.

*Methyl 5-(2-fluorophenyl)-4-(4-methylbenzenesulfonamido)-2-phenyl-1H-pyrrole-3-carboxylate (**5o**) and methyl 5-(2-fluorophenyl)-1-(4-methylphenylsulfonyl)-3-phenyl-1,2-dihydropyrazine-2-carboxylate (**6o**).* Obtained from isoxazole **3a** and triazole **4e** (1.3 equiv, 118 mg, 0.37 mmol) according to the method A. *Compound **5o**.* White solid (58 mg, yield 43%); mp 89−92 °C; $R_f$ = 0.60 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.80 (s, 1H), 8.99 (s, 1H), 7.51−7.45 (m, 3H), 7.41 (t, $J$ = 7.4 Hz, 2H), 7.38−7.31 (m, 2H), 7.27 (d, $J$ = 8.0 Hz, 2H), 7.17−7.10 (m, 2H), 7.08 (d, $J$ = 8.0 Hz, 2H), 3.41 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 164.0, 159.1 (d, $J$ = 248 Hz), 142.0, 137.5, 134.5, 131.34 (d, $J$ = 2.5 Hz), 131.30, 129.41 (d, $J$ = 5.1 Hz), 128.8, 128.6, 127.9, 127.8, 126.3, 124.6, 123.78 (d, $J$ = 2.8 Hz), 118.60 (d, $J$ = 14.6 Hz), 117.5, 115.38 (d, $J$ = 21.8 Hz), 110.5, 50.4, 20.9; HRMS−ESI $[M + Na]^+$ calcd for $C_{25}H_{21}FN_2NaO_4S^+$ 487.1098; found 487.1093. *Compound **6o*** (mixture with pyrazine **7i**). Unstable yellow oil (44 mg, yield 33%); $^1$H NMR ($CDCl_3$) $\delta$ 8.02−7.92 (m, 3H), 7.63 (d, $J$ = 8.3 Hz, 2H), 7.40 (s, 1H), 7.22−7.08 (m, 4H), 6.15 (s, 1H), 3.65 (s, 3H), 2.32 (s, 3H).

*N-[2,5-Diphenyl-4-(pyrrolydine-1-carbonyl)-1H-pyrrol-3-yl]-4-methylbenzenesulfonamide (**5p**).* Obtained from isoxazole **3l** and triazole **4a** (2.2 equiv, 188 mg, 0.63 mmol) according

to the method A. Column chromatography (petroleum ether−EtOAc 2:1). White solid (39 mg, yield 28%); mp 127−128 °C; $R_f$ = 0.45 (EtOAc); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.35 (s, 1H), 9.25 (s, 1H), 7.61−7.54 (m, 2H), 7.46 (d, $J$ = 7.4 Hz, 2H), 7.42−7.32 (m, 2H), 7.30−7.16 (m, 4H), 7.05 (d, $J$ = 7.4 Hz, 2H), 3.17 (br s, 2H), 2.76 (br s, 2H), 2.25 (s, 3H), 1.57 (br s, 2H), 1.41 (br s, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 164.1, 141.8, 138.2, 131.8, 130.7, 130.1, 128.7, 128.5, 127.7, 127.3, 126.9 (2C), 126.4, 126.3, 125.7, 118.8, 114.4, 46.6, 44.9, 25.0, 23.8, 20.8; HRMS−ESI [M + Na]$^+$ calcd for $C_{28}H_{27}O_3N_3NaS^+$ 508.1665; found 508.1677.

*N-(4-Benzoyl-2,5-diphenyl-1H-pyrrol-3-yl)-4-methylbenzenesulfonamide (**5q**)*[9] *and (3,5-diphenyl-1-tosyl-1,2-dihydropyrazin-2-yl) (phenyl)methanone (**6q**).* Obtained from isoxazole **3m** and triazole **4a** (2.2 equiv, 188 mg, 0.63 mmol) according to the method A. *Compound **5q***. White solid (64 mg, yield 45%); mp 118−120 °C; $R_f$ = 0.57 (hexane/EtOAc 1:1); $^1$H NMR (DMSO-$d_6$) $\delta$ 11.71 (s, 1H), 9.17 (s, 1H), 7.69−7.63 (m, 2H), 7.46−7.40 (m, 2H), 7.36 (t, $J$ = 7.4 Hz, 1H), 7.28 (t, $J$ = 7.4 Hz, 2H), 7.25−7.10 (m, 10H), 6.79 (d, $J$ = 8.0 Hz, 2H), 2.03 (s, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 191.3, 141.8, 137.8, 136.8, 133.3, 131.7, 131.2, 130.5, 130.3, 129.5, 128.7, 128.3, 127.9, 127.8, 127.4, 127.2, 127.1, 126.7, 126.5, 120.3, 116.1, 20.7; HRMS−ESI [M + H]$^+$ calcd for $C_{30}H_{25}O_3N_2S^+$ 493.1580; found 493.1594. *Compound **6q***. White solid (10 mg, yield 7%); mp 124−126 °C; $R_f$ = 0.50 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 8.23 (d, $J$ = 7.2 Hz, 2H), 7.72−7.63 (m, 5H), 7.55 (t, $J$ = 7.7 Hz, 2H), 7.48−7.33 (m, 8H), 6.95 (d, $J$ = 8.1 Hz, 2H), 6.75 (d, $J$ = 0.9 Hz, 1H), 6.62 (d, $J$ = 0.9 Hz, 1H), 2.29 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 193.7, 151.3, 144.7, 140.3, 136.2, 135.2, 134.5, 134.2, 133.7, 130.9, 129.4, 129.2, 128.7, 128.44 (2C), 128.39, 127.4, 126.4, 125.4, 107.9, 56.6, 21.5; HRMS−ESI [M + H]$^+$ calcd for $C_{30}H_{25}O_3N_2S^+$ 493.1580; found 493.1595.

*Methyl 1-(4-methylbenzenesulfonyl)-3,5-diphenyl-1,2-dihydropyrazine-2-carboxylate (**6a**).* Obtained from isoxazole **3a** and triazole **4a** (2.0 equiv, 174 mg, 0.58 mmol) according to the method B. Column chromatography (petroleum ether−$Et_2O$ 10:1). Yellow oil (82 mg, yield 63%); $R_f$ = 0.45 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 7.97−7.92 (m, 2H), 7.83−7.79 (m, 2H), 7.57 (d, $J$ = 8.3 Hz, 2H), 7.51−7.38 (m, 5H), 7.34 (t, $J$ = 7.4 Hz, 1H), 7.11−7.05 (m, 3H), 6.12 (s, 1H), 3.66 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.0, 147.4, 144.6, 135.6, 135.5 (3C), 130.8, 129.7, 128.49, 128.47, 128.0, 127.7, 126.4, 124.9, 109.8, 53.1, 52.8, 21.5; HRMS−ESI [M + H]$^+$ calcd for $C_{25}H_{23}O_4N_2S^+$ 447.1373; found 447.1373.

*Methyl 1-(methanesulfonyl)-3,5-diphenyl-1,2-dihydropyrazine-2*-carboxylate (**6l**). Obtained from isoxazole **3a** and triazole **4b** (2.5 equiv, 162 mg, 0.73 mmol) according to the method B as a yellow oil (57 mg, yield 53%); $R_f$ = 0.44 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 8.18−8.11 (m, 2H), 7.86 (d, $J$ = 7.5 Hz, 2H), 7.56−7.51 (m, 3H), 7.44 (t, $J$ = 7.5 Hz, 2H), 7.36 (t, $J$ = 7.2 Hz, 1H), 6.98 (s, 1H), 6.16 (s, 1H), 3.69 (s, 3H), 3.16 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.8, 147.6,

135.6, 135.5, 134.2, 131.1, 128.8, 128.6, 128.0, 127.8, 124.9, 110.1, 53.3, 52.5, 41.4; HRMS−ESI $[M + Na]^+$ calcd for $C_{19}H_{18}N_2NaO_4S^+$ 393.0879; found 393.0870.

*Methyl 3,5-diphenylpyrazine-2-carboxylate (**7a**).* Obtained from isoxazole **3a** and triazole **4a** (2.0 equiv, 174 mg, 0.58 mmol) according to the method B as a white solid (53 mg, yield 63%); mp 98−100 °C; $R_f$ = 0.44 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 9.04 (s, 1H), 8.21−8.16 (m, 2H), 7.77−7.73 (m, 2H), 7.59−7.50 (m, 6H), 3.89 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.8, 153.0, 152.7, 141.7, 138.4, 137.4, 135.4, 130.7, 129.6, 129.1, 128.7, 128.4, 127.4, 52.8; HRMS−ESI $[M + Na]^+$ calcd for $C_{18}H_{14}N_2NaO_2^+$ 313.0947; found 313.0952.

*Methyl 3-(4-methylphenyl)-5-phenylpyrazine-2-carboxylate (**7b**).* Obtained from isoxazole **3b** and triazole **4a** (2.5 equiv, 218 mg, 0.73 mmol) according to the method B as a white solid (39 mg, yield 44%); mp 85−87 °C; $R_f$ = 0.45 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 9.01 (s, 1H), 8.21−8.15 (m, 2H), 7.66 (d, $J$ = 7.9 Hz, 2H), 7.59−7.51 (m, 3H), 7.33 (d, $J$ = 7.9 Hz, 2H), 3.91 (s, 3H), 2.46 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.0, 152.9, 152.6, 141.5, 139.8, 138.1, 135.5, 134.5, 130.6, 129.2, 129.1, 128.7, 127.4, 52.8, 21.4; HRMS−ESI $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_2^+$ 305.1285; found 305.1287.

*Methyl 3-(4-bromophenyl)-5-phenylpyrazine-2-carboxylate (**7c**).* Obtained from isoxazole **3f** and triazole **4a** (2.5 equiv, 218 mg, 0.73 mmol) according to the method B as a white solid (75 mg, yield 70%); mp 168−169 °C; $R_f$ = 0.43 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 9.05 (s, 1H), 8.20−8.13 (m, 2H), 7.66 and 7.61 (AB-q, $J$ = 8.6 Hz, 4H), 7.59−7.53 (m, 3H), 3.91 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.5, 152.8, 152.1, 141.2, 138.8, 136.4, 135.1, 131.6, 130.9, 130.4, 129.2, 127.4, 124.3, 53.0; HRMS−ESI $[M + Na]^+$ calcd for $C_{18}H_{13}{}^{79}BrN_2NaO_2^+$ 391.0053; found 391.0054.

*Methyl 3-(4-chlorophenyl)-5-phenylpyrazine-2-carboxylate (**7d**).* Obtained from isoxazole **3g** and triazole **4a** (2.5 equiv, 218 mg, 0.73 mmol) according to the method B as a white solid (68 mg, yield 72%); mp 154−155 °C; $R_f$ = 0.42 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 9.05 (s, 1H), 8.19−8.14 (m, 2H), 7.68 (d, $J$ = 8.6 Hz, 2H), 7.60−7.53 (m, 3H), 7.50 (d, $J$ = 8.6 Hz, 2H), 3.91 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.5, 152.8, 152.0, 141.3, 138.7, 136.0, 135.9, 135.1, 130.8, 130.1, 129.1, 128.7, 127.4, 53.0; HRMS−ESI $[M + Na]^+$ calcd for $C_{18}H_{13}{}^{35}ClN_2NaO_2^+$ 347.0558; found 347.0573.

*Methyl 3-(4-nitrophenyl)-5-phenylpyrazine-2-carboxylate (**7e**).* Obtained from isoxazole **3i** and triazole **4a** (2.5 equiv, 218 mg, 0.73 mmol) according to the method B. Column chromatography ($CHCl_3$). White solid (75 mg, yield 77%); mp 211−212 °C; $R_f$ = 0.30 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 9.14 (s, 1H), 8.39 (d, $J$ = 8.8 Hz, 2H), 8.21−8.15 (m, 2H), 7.89 (d, $J$ = 8.8 Hz, 2H), 7.62−7.56 (m, 3H), 3.93 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 165.9,

153.2, 151.6, 148.4, 143.8, 141.2, 139.7, 134.8, 131.2, 129.9, 129.3, 127.5, 123.6, 53.2; HRMS−ESI $[M + Na]^+$ calcd for $C_{18}H_{13}N_3NaO_4^+$ 358.0798; found 358.0808.

*tert-Butyl 3,5-diphenylpyrazine-2-carboxylate (**7f**).* Obtained from isoxazole **3j** and triazole **4a** (3 equiv, 260 mg, 0.87 mmol) according to the method B. After the decomposition of the last triazole portion, the reaction mixture was transferred to a screw cap glass tube and heated at 90 °C (oil bath temperature) with $Et_3N$ (50 mg, 0.5 mmol) as additive for 5 h. Further workup according to the method **B** gave compound **7f** as a white solid (69 mg, yield 72%); mp 109−111 °C; $R_f$ = 0.57 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 9.03 (s, 1H), 8.19−8.13 (m, 2H), 7.78−7.73 (m, 2H), 7.58−7.49 (m, 6H), 1.43 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 165.6, 152.4, 152.1, 143.7, 138.5, 137.9, 135.6, 130.4, 129.3, 129.0, 128.9, 128.3, 127.3, 83.2, 27.6; HRMS−ESI $[M + Na]^+$ calcd for $C_{21}H_{20}N_2NaO_2^+$ 355.1417; found 355.1421.

*Methyl 3-methyl-5-phenylpyrazine-2-carboxylate (**7g**).* Obtained from isoxazole **3k** and triazole **4a** (2.5 equiv, 218 mg, 0.73 mmol) according to the method B**.** After the decomposition of the last triazole portion, the reaction mixture was transferred to a screw cap glass tube and heated at 90 °C (oil bath temperature) with $Et_3N$ (50 mg, 0.5 mmol) as additive for 5 h. Further workup according to the method **B** gave compound **7g** as a white solid (21 mg, yield 32%); mp 64−66 °C; $R_f$ = 0.36 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.15−8.09 (m, 2H), 7.60−7.51 (m, 3H), 4.05 (s, 3H), 2.96 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 165.7, 155.1, 153.5, 140.0, 138.3, 135.5, 130.7, 129.1, 127.4, 52.9, 23.6; HRMS−ESI $[M + Na]^+$ calcd for $C_{13}H_{12}N_2NaO_2^+$ 251.0791; found 251.0791.

*Methyl 5-(4-chlorophenyl)-3-phenylpyrazine-2-carboxylate (**7h**).* Obtained from isoxazole **3a** and triazole **4d** (2 equiv, 194 mg, 0.58 mmol) according to the method B as a white solid (58 mg, yield 61%); mp 111−113 °C; $R_f$ = 0.43 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 9.01 (s, 1H), 8.13 (d, $J$ = 8.6 Hz, 2H), 7.76−7.70 (m, 2H), 7.56−7.50 (m, 5H), 3.88 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.7, 153.0, 151.5, 141.9, 138.1, 137.2, 137.1, 133.8, 129.7, 129.4, 128.7, 128.6, 128.5, 52.9; HRMS−ESI $[M + Na]^+$ calcd for $C_{18}H_{13}{}^{35}ClN_2NaO_2^+$ 347.0558; found 347.0564.

*Methyl 5-(2-fluorophenyl)-3-phenylpyrazine-2-carboxylate (**7i**).* Obtained from isoxazole **3a** and triazole **4e** (2.5 equiv, 228 mg, 0.72 mmol) according to the method **B** as a white solid (67 mg, yield 75%); mp 101−103 °C; $R_f$ = 0.52 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 9.14 (d, $J$ = 2.5 Hz, 1H), 8.21 (td, $J$ = 7.8, 1.8 Hz, 1H), 7.77−7.71 (m, 2H), 7.57−7.47 (m, 4H), 7.34 (td, $J$ = 7.8, 1.0 Hz, 1H), 7.25 (ddd, $J$ = 11.3, 8.4, 0.8 Hz, 1H), 3.90 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.7, 160.9 (d, $J$ = 252 Hz), 153.0, 149.36 (d, $J$ = 3.4 Hz), 142.0, 141.9, 137.2, 132.24 (d, $J$ = 8.7 Hz), 131.26 (d, $J$ = 2.5 Hz), 129.7, 128.7, 128.5, 124.91 (d, $J$ = 3.5 Hz), 123.51 (d, $J$ = 12.0 Hz), 116.47 (d, $J$ = 22.7 Hz), 52.9; HRMS−ESI $[M + Na]^+$ calcd for $C_{18}H_{13}FN_2NaO_2^+$ 331.0853; found 331.0863.

*Methyl 3,5-di(4-chlorophenyl)pyrazine-2-carboxylate (**7j**).* Obtained from isoxazole **3g** and triazole **4d** (2.5 equiv, 243 mg, 0.73 mmol) according to the method B as a white solid (74 mg, yield 71%); mp 158−160 °C; $R_f$ = 0.44 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 9.01 (s, 1H), 8.11 (d, $J$ = 8.6 Hz, 2H), 7.66 (d, $J$ = 8.5 Hz, 2H), 7.53 (d, $J$ = 8.6 Hz, 3H), 7.49 (d, $J$ = 8.5 Hz, 2H), 3.91 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.4, 152.0, 151.6, 141.6, 138.4, 137.2, 136.1, 135.6, 133.5, 130.1, 129.4, 128.7, 128.6, 53.0; HRMS−ESI $[M + Na]^+$ calcd for $C_{18}H_{12}{}^{35}Cl_2N_2NaO_2^+$ 381.0168; found 381.0176.

*(3,5-Diphenylpyrazin-2-yl)(phenyl)methanone (**7k**).* Obtained from isoxazole **3m** and triazole **4a** (3 equiv, 260 mg, 0.87 mmol) according to the method **B** as a white solid (24 mg, yield 25%); mp 137−139 °C; $R_f$ = 0.57 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 9.07 (s, 1H), 8.26−8.20 (m, 2H), 7.95 (d, $J$ = 7.2 Hz, 2H), 7.78−7.71 (m, 2H), 7.65−7.53 (m, 4H), 7.49 (t, $J$ = 7.7 Hz, 2H), 7.44−7.36 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 194.3, 152.6, 152.1, 148.4, 138.0, 136.9, 135.9, 135.7, 133.8, 130.5, 130.4, 129.6, 129.16, 129.14, 128.63, 128.60, 127.3; HRMS−ESI $[M + H]^+$ calcd for $C_{23}H_{17}N_2O^+$ 337.1346; found 337.1335.

*2,6-Diphenylpyrazine (**7l**).*[24] Obtained from isoxazole **3j** and triazole **4a** (3 equiv, 260 mg, 0.87 mmol) according to the method B. After the decomposition of the last portion of triazole the solvent was removed *in vacuo* and the residue was dissolved in *o*-xylene (3.0 mL) and refluxed for 2 h. Further workup according to the method **B** gave compound **7l** as a white solid (35 mg, yield 53 %); mp 84–86 °C (lit.[24] 84–86 °C); $R_f$ = 0.47 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) $\delta$ 9.00 (s, 2H), 8.22–8.16 (m, 4H), 7.61–7.49 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 151.6, 139.9, 136.5, 129.9, 129.0, 127.0; HRMS−ESI $[M + H]^+$ calcd for $C_{16}H_{13}N_2^+$ 233.1073; found 233.1073.

*Methyl 3-(4-nitrophenyl)-3-oxopropanoate (**18**).*[25] The procedure of Clark et al.[26] was modified. To a rapidly stirred solution of diisopropylamine (16.3 mL, 116 mmol) in dry tetrahydrofuran (60 ml) under argon at –80 °C was added *n*-butyllithium (2.5 M in hexane, 47 mL), followed after 10 min by methyl acetate (9.3 mL, 116 mmol). The mixture was maintained below –80 °C for 5 min, after which time a solution of methyl 4-nitrobenzoate (10.2 g, 56.3 mmol) in dry tetrahydrofuran (50 mL) was introduced *via* syringe. The mixture was stirred at –80 °C until no starting 4-nitrobenzoate was observed by TLC (about 10–15 min), then quenched with 20% hydrochloric acid (60 mL) and extracted with ether (600 mL). The organic layer was washed intensively with 5% $NaHCO_3$ (300 mL), water (300 mL) and brine (300 mL), dried and concentrated *in vacuo*, affording the product as a pale yellow solid (11.4 g, yield 91%); mp 103–105 °C (lit.[25] 110 °C). $R_f$ = 0.51 (hexane/EtOAc 2:1); $^1$H NMR ($CDCl_3$) δ [keto form] 8.39–8.34 (m, 2H), 8.17–8.11 (m, 2H), 4.08 (s, 2H), 3.79 (s, 3H); [enol form] 12.51 (s, 1H), 8.33–8.27 (m, 2H), 8.00–7.93 (m, 2H), 5.80 (s, 1H), 3.86 (s, 3H).

*3-(4-Nitrophenyl)isoxazol-5(4H)-one (**19**).*[26] Methyl 3-(4-nitrophenyl)-3-oxopropanoate **18** (3.0 g, 13.5 mmol) and $H_2NOH \cdot HCl$ (2.8 g, 40.3 mmol) were refluxed in water (15 mL) for 5 min. Then ethanol (18 mL) was added to the reaction mixture and refluxing continued for 30 min. The mixture was cooled and filtered off to give isoxazolone **19** as a yellow solid (2.5 g, 89%); mp 143–146 °C (lit.[26] 145–148 °C).

## ASSOCIATED CONTENT

Supporting Information

Figures S-1, S-2 with NMR spectra of reaction mixtures, S-3 with energy profiles for the transformations of diazatrienes **9b**, $^1H$ and $^{13}C$ NMR spectra for all new compounds, computation details with energies of the reactants, transition states, their Cartesian coordinates, and tube representation of the calculated molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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