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# Proximity-assisted cycloaddition reactions of ω-azido cyanohydrin ethers: Synthesis of diversely functionalized bicyclic tetrazoles*

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*Abstract*: Aliphatic azidonitriles separated by three or four carbon atoms undergo facile cycloadditions in the presence of $BF_3{\cdot}OEt_2$ at room temperature or lower, to give bicyclic tetrazoles. 1-Azido-[2-aryl-1,3-dioxolanyl]-glycerols afford oxabicyclic tetrazoles with trimethylsilyl cyanide (TMSCN). Aspects of these facile proximity-induced 1,3-dipolar cycloadditions are discussed with mechanistic interpretations.

*Keywords*: acetals; azides; cycloadditions; nitriles; tetrazoles.

## INTRODUCTION

Compounds containing the tetrazole nucleus have been known for over a century since Bladin [1] reported the intermolecular cycloaddition reaction between a nitrile and sodium azide under thermal conditions. Mono- and disubstituted tetrazoles have gained considerable importance in recent years, with useful applications in medicinal chemistry, agrochemistry, polymers, and explosives, to mention a few [2].

The more common tetrazole derivatives are 1,5-disubstituted. As such, they have been incorporated in peptidic motifs as conformational mimics of *cis*-amide bonds [3]. A number of therapeutically important compounds contain a 1,5-disubstituted tetrazole unit (Fig. 1) [3].

Monosubstituted 1*H*-tetrazoles have similar acidities as some carboxylic acids, hence their use as isosteres in existing drugs and clinical candidates [2,3] (Fig. 2). Many examples of the intermolecular synthesis of 5-substituted 1*H*-tetrazoles have been reported in recent years involving mostly the condensation of a nitrile with different sources of azide [4,5]. Other methods starting with oximes [6], amides [4], and acyl cyanides [7] are also known. Seminal contributions by Sharpless and co-workers featuring "click" chemistry rely on the formation of triazoles and tetrazoles, even in biological media [8].

Early examples of intramolecular cycloadditions of nitriles and azides present in the same molecule led to 5,5- and 6,5-bicyclic 1,5-disubstituted tetrazoles [9]. Fleet [10], Hotha [11], and their respective co-workers have reported the synthesis of fused bi- and tricyclic tetrazoles from carbohydrates containing appropriately spaced nitrile and azide groups. Only in rare cases has it been possible to effect intramolecular cyclocondensation reactions to form tetrazole derivatives at temperatures below 100 °C [12,13].

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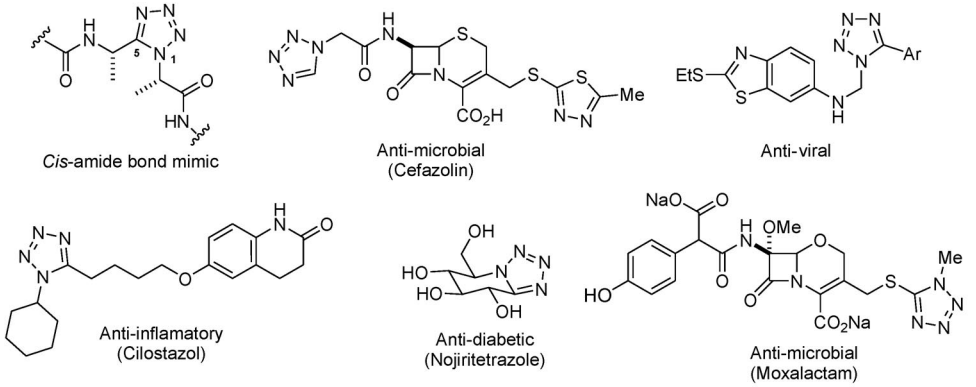



**Fig. 1** 1,5-Disubstituted and related tetrazoles as conformational mimics of *cis*-amide bonds, and as medicinally important compounds.

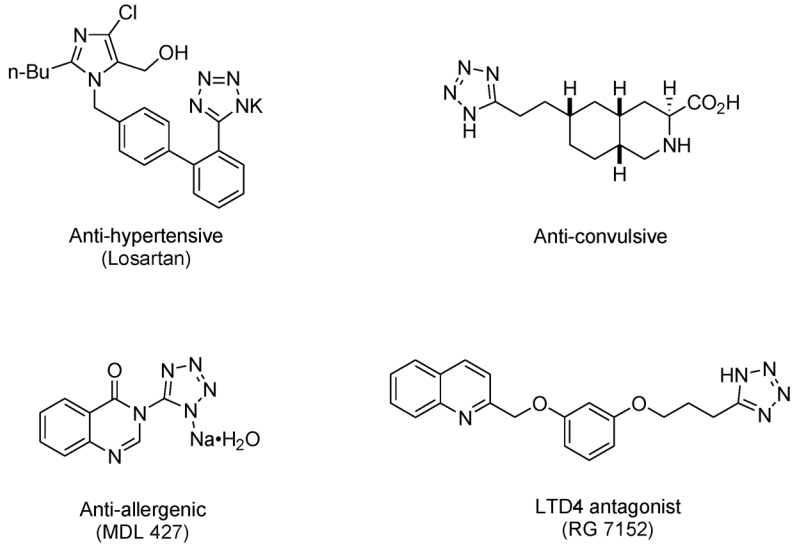



**Fig. 2** 1*H*-tetrazoles as medicinally important 5-substituted compounds.

## BACKGROUND

During our studies directed toward the total synthesis of malayamycin A [14], we explored an approach that necessitated the synthesis of an anomeric nitrile from a 3-azido-3-deoxy-D-ribopyranosyl triacetate **1** (Fig. 3). Treatment of **1** with trimethylsilyl cyanide (TMSCN) in the presence of $BF_3{\cdot}OEt_2$ in nitromethane did not afford the desired anomeric nitrile **2**. Instead, an excellent yield of a tetracyclic tetrazole was obtained under mild conditions. A single-crystal X-ray structure provided definitive proof of the stereochemical and constitutional identity of this novel compound [15]. Presumably, initial formation of a 1,2-acetoxonium ion was followed by an *endo*-addition of cyanide as in **3** to afford an intermediate cyanoacetal **4**, which would undergo a 1,3-dipolar cycloaddition leading to the observed tetracyclic tetrazole **5** (Scheme 1). The facile cycloaddition under very mild conditions as compared with precedents in the literature led us to further explore the scope of this reaction with simpler substrates (Scheme 2).

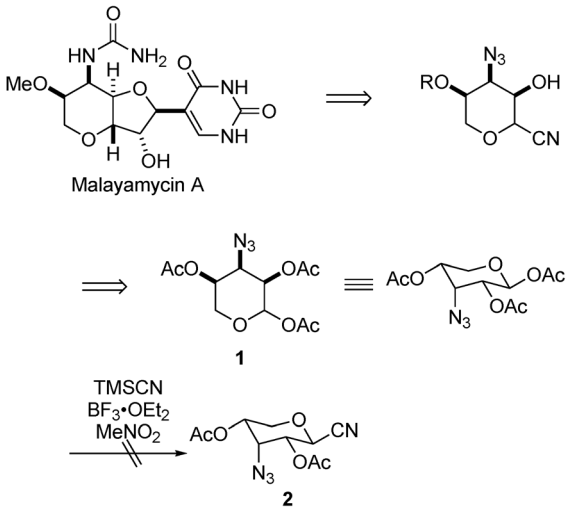
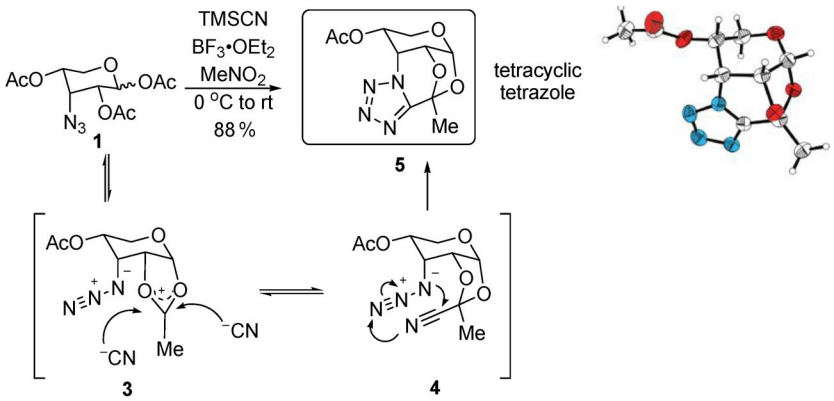
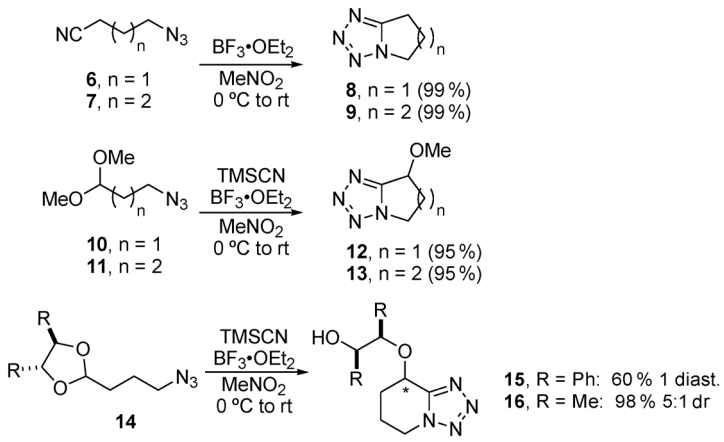



**Fig. 3** The structure of malayamycin A and a glycosyl cyanide approach.




**Scheme 1** Synthesis of a tetracyclic tetrazole.



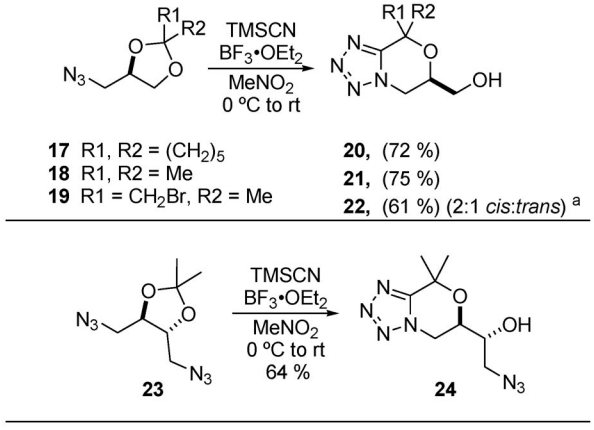

**Scheme 2** Intramolecular cycloaddition reactions leading to bicyclic tetrazoles.

Simple 1,3- and 1,4-substituted azido nitriles **6** and **7** underwent cycloaddition under the same $BF_3{\cdot}OEt_2$-mediated conditions to give the corresponding bicyclic tetrazoles **8** and **9** in essentially quantitative yields (Scheme 2). Smaller and larger rings were not possible, as observed by others under strongly acidic conditions [9].

With an external source of cyanide provided by TMSCN, terminally substituted azido dimethyl acetals **10** and **11**, separated by three and four carbon atoms, could be cleanly converted to methoxy bicyclic tetrazoles **12** and **13**, respectively, in excellent yields (Scheme 2). Under the same conditions, the cyclic acetal **14**, originally derived from (*R*,*R)*-stilbene diol and (*R*,*R*)-2,3-butane diol gave the corresponding bicyclic tetrazoles as a single diastereomer (**15**), and 5:1 mixture of diastereomers (**16**), respectively [14].

## OXABICYCLIC TETRAZOLES

Extension of the cycloaddition reaction to racemic 2-substituted 1,3-dioxolanes of glycerol containing a terminal azide group led to a wide diversity of oxabicyclic tetrazoles with a hydroxymethyl appendage [15]. These reactions could be extended to enantiopure acetals, easily prepared from D-mannitol, or from enantioenriched (*R*)- or (*S*)-glycidols after conversion to the corresponding 1-azides. Thus, the 2,2'-cyclopentylidene, the 2,2'-dimethyl and 2-methyl-2'-bromomethyl acetals **17–19** afforded the corresponding *gem*-disubstituted tetrazoles **20–22** in 61–75 % yields (Scheme 3). The acetal from bromoacetone **19** gave a 2:1 diastereomeric mixture. The $C_2$ symmetrical 2,2'-dimethyl acetal **23** led to the enantiopure oxabicyclic tetrazole **24** in 64 % yield.




**Scheme 3** Oxabicyclic tetrazoles. [a]NMR ratio.

The scope of the TMSCN-mediated formation of oxabicyclic tetrazoles was widened by a study of 1-azido-(2-aryl-1,3-dioxolanyl)-glycerols exemplified by **25a–n** (Table 1). Depending on the nature of the substituent on the phenyl ring, excellent to modest yields of the cycloaddition products **26a–n** and **27a–n** were obtained. In all cases, the *cis*-isomers **27a–n** predominated. A single-crystal X-ray structure of the *cis*-2-phenyl analog **27a** provided definitive proof of its stereochemical and constitutional identity [15].

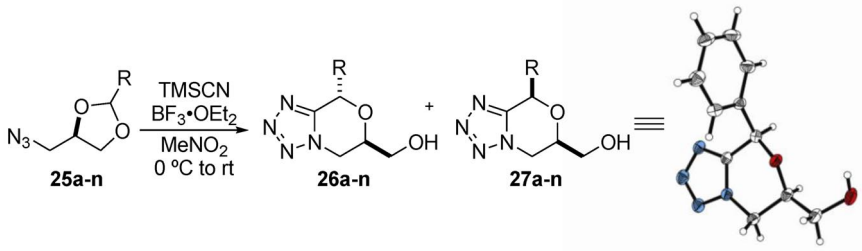


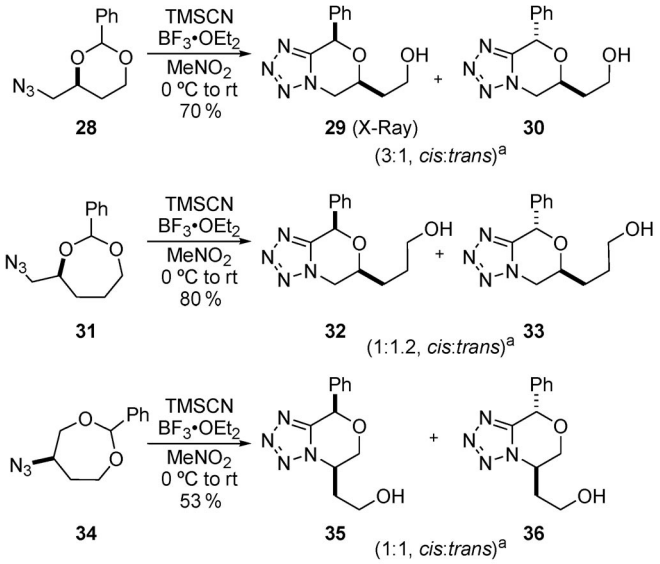

**Table 1** Formation of oxabicyclic tetrazoles from 1-azido-(2-aryl-1,3-dioxolanyl)-glycerols.

| Entry | R[a] | Yield (%)[b] | *cis*(27):*trans*(26)[c] |
|---|---|---|---|
| **a** | Ph[d] | 94 | >19:1 |
| **b** | *o*-Cl-Ph | 74 | 10:1 |
| **c** | *m*-Cl-Ph | 74 | >19:1 |
| **d** | *p*-Cl-Ph | 78 | >19:1 |
| **e** | *m*-$NO_2$-Ph | 48 | 10:1 |
| **f** | *p*-$NO_2$-Ph | 29 | 10:1 |
| **g** | *m*-MeO-Ph | 97 | >19:1 |
| **h** | *m*-Br-Ph | 73 | 10:1 |
| **i** | *m*-$CF_3$-Ph | 43 | >19:1 |
| **j** | *m*-CN-Ph | 46 | >19:1 |
| **k** | 3-MeO-4-Cl-Ph | 76 | Only *cis* |
| **l** | 3,5-di-*t*-Bu-Ph | 69 | 10:1 |
| **m** | 3,5-di-MeO-Ph | 85 | >19:1 |
| **n** | 1-naphthyl | 67 | >19:1 |

[a]Racemic series.
[b]Isolated yield.
[c]NMR ratio.
[d]From enantiopure **25a**, 81 %, >19:1.

Diastereomeric ratios were eroded as the size of the acetal ring was increased (Scheme 4). Thus, the 2-phenyl-1,3-dioxane analog **28** afforded a 3:1 mixture of *cis*- and *trans*-oxabicyclic tetrazoles **29** and **30**, respectively, which could be separated by column chromatography. The 1,3-dioxepane analogs **31** and **34** led to the respective oxabicyclic tetrazoles as 1:1 mixtures of *cis*- and *trans*-isomers, differing in the position of the appended hydroxylalkyl groups as in **32**, **33** and **35**, **36**, respectively.

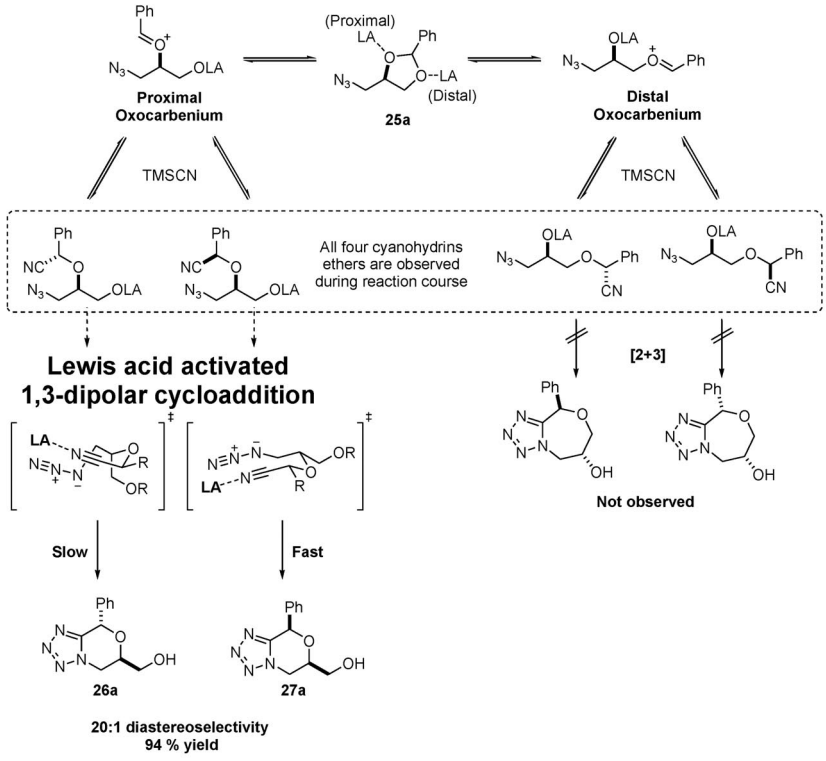



**Scheme 4** Reaction of 2-phenyl-1,3-dioxane and 1,3-dioxepane analogs. [a]NMR ratios.

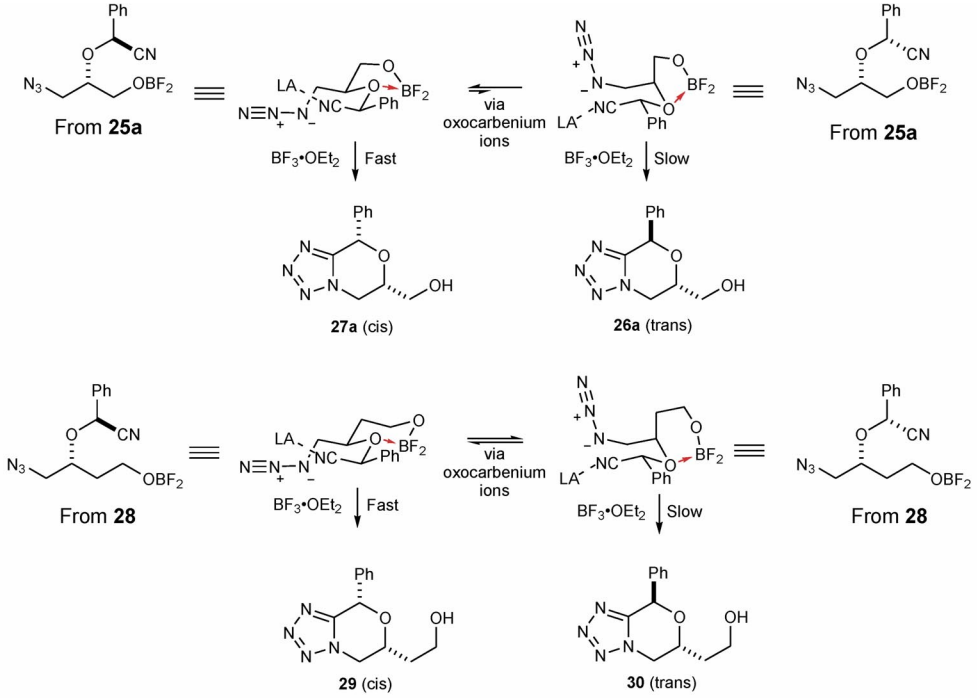
## MECHANISTIC STUDIES

A plausible mechanism for the formation of the oxabicyclic tetrazoles is shown for the 2-phenyl-1,3-dioxolane analog **25a** in Scheme 5 [16]. Coordination of the Lewis acid can take place at either of the acetal oxygen atoms, resulting in the formation of all four possible diastereomeric cyanohydrin ethers [17]. In fact, all four adducts could be seen on thin-layer chromatography (TLC) plates and could be isolated individually by careful silica gel column chromatography. Two of these resulting from coordination to the proximal acetal oxygen led to the observed oxabicyclic tetrazole in high yield and in over 20:1 diastereoselectivity favoring the *cis*-isomer **27a**. Not unexpectedly, the other pair of cyanohydrin ethers did not give 7,5-oxabicyclic tetrazoles. Rather, they were involved in a reversible equilibrium, eventually leading to the observed 6,5-oxabicyclic tetrazoles. In fact, treatment of each cyanohydrin ether with $BF_3{\cdot}OEt_2$ and TMSCN in $MeNO_2$ simulating the original reaction conditions, also led to the same ratio of oxabicyclic tetrazoles (**25a** → **26a/27a**, Table 1) (Scheme 5).

The preponderance of the *cis*-isomer **27a** over the *trans*-isomer **26a**, with diequatorial and equatorial/axial substituents, respectively, is most likely due to a faster cycloaddition in a *B*-coordinated intermediate. Presumably, the energy difference between the *B*-coordinated intermediates in the 2-phenyl-1,3-dioxane case (**28** → **29** and **30**) is not as pronounced as in the case of **26a** and **27a** (Scheme 6). The presence of *B*-coordinated species was inferred from the mass spectra of samples taken during the reaction, corresponding to incorporation of a $BF_2OH$ unit ($C_{11}H_{12}BF_2N_4O_3$ m/e 297.0971) and a $BF_3$ unit ($C_{11}H_{12}BF_3N_4O_2$ m/e 299.0927, negative ion peak) at the hydroxymethyl carbon atom in **27a** [18]. The progress of the cycloaddition reaction could be monitored and followed by React IR spectroscopy for the 2-phenyl-1,3-dioxane analog **34** (Fig. 4).




**Scheme 5** Proposed mechanism for the formation of oxabicyclic tetrazoles.




**Scheme 6** Transition-state models for *cis*-/*trans*-selectivity.

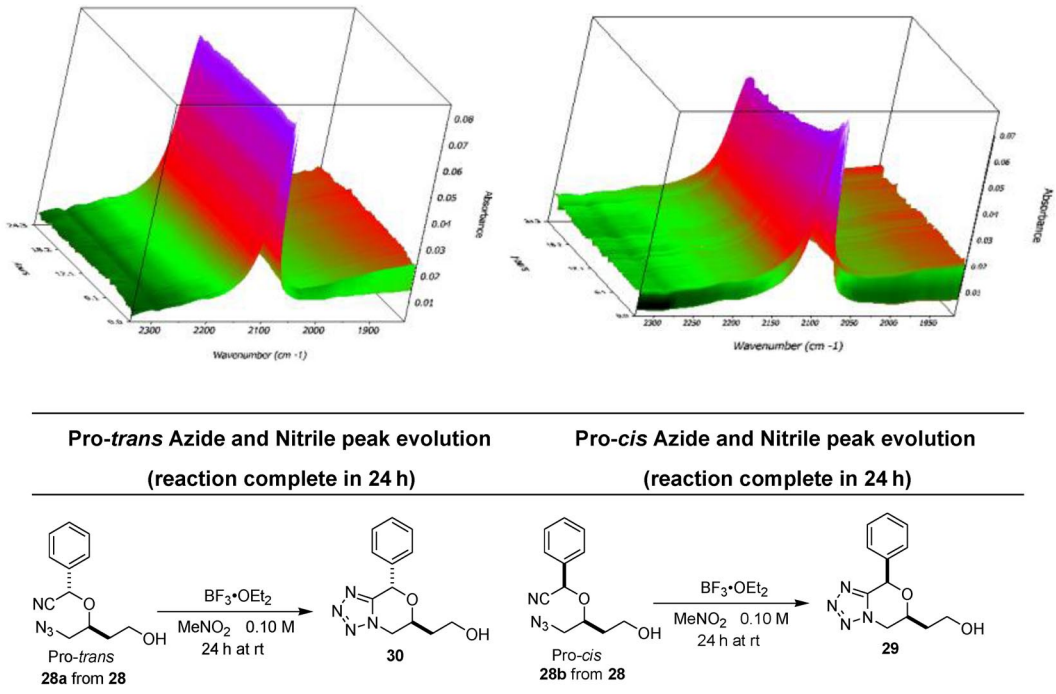



**Fig. 4** Progress of the cycloaddition reaction by React IR spectroscopy.

A study of Lewis acids and solvents indicated that $BF_3{\cdot}OEt_2$ (2.1 equiv) in $MeNO_2$ provided the highest yields and selectivities (Table 2) [19]. It appears that coordinating solvents such as diethyl ether and tetrahydrofuran (THF) are detrimental to the success of the reaction. Neutral solvents such as $CHCl_3$, toluene, and dichloromethane afforded excellent selectivities, albeit only in modest yields. Reactions in neat $BF_3{\cdot}OEt_2$ or in hexanes led to good diastereoselectivity results but were not experimentally practical. The results were in agreement with the complexing ability of $BF_3{\cdot}OEt_2$ to different solvents [20]. The activation of the transition state for cycloaddition was decreased with increased solvent complexation to the Lewis acid (Table 2).

Acetals containing an aryl moiety with a strong electron-donating group in the *ortho*- or *para*-positions failed to give any corresponding oxabicyclic tetrazole. Instead, the equivalent of a Schmidt–Aubé rearrangement [21] took place, leading to a dihydro-oxazine as shown for the 2-*p*-methoxyphenyl-1,3-dioxolane analog **38** (Scheme 7). Thus, the resonance-stabilized oxocarbenium ions **37a** and **37b** are not attacked by cyanide ion to give the expected cyanohydrin ethers. Rather, an intramolecular attack by the proximal azide nitrogen takes place, favoring a 6-*endo* trajectory [22] in **37a**, followed by a loss of $N_2$ to give the (5*R*)-hydroxy-2-*p*-methoxyphenyl-1,3-dihydro-oxazinium tetrafluoroborate **38**, whose structure and stereochemistry were ascertained by single-crystal X-ray analysis (Scheme 7). The same product was obtained in the case of **25a** in the presence of traces of water.

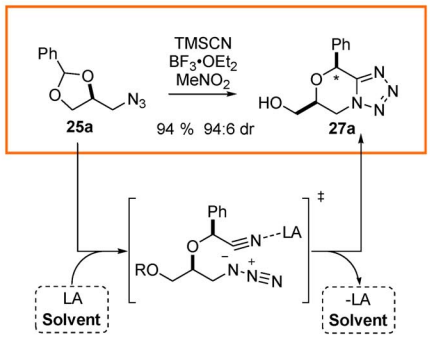
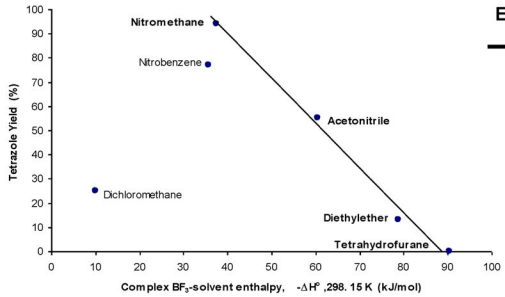
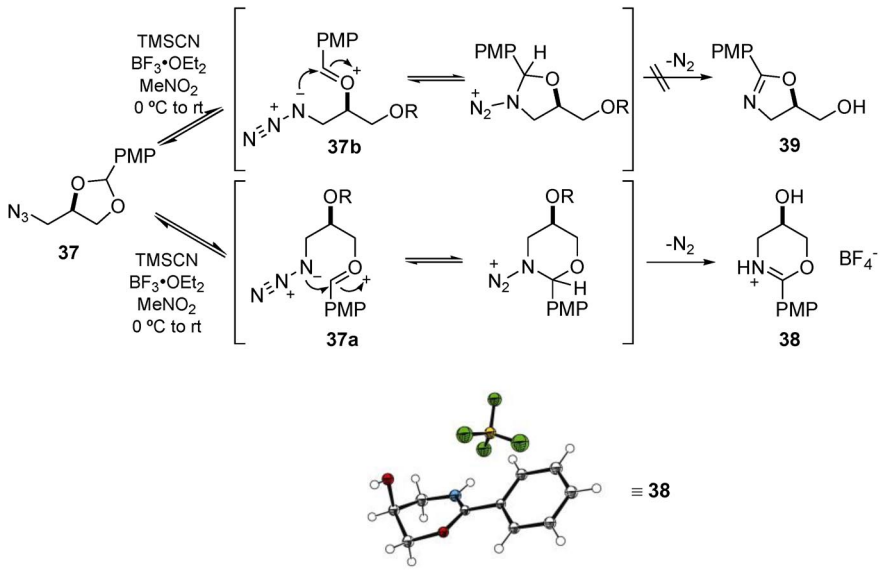



**Table 2** Solvent and Lewis acid Scan.

| Entry | Solvent | Lewis acid | Yield (%) | Diastereoselectivity (*syn*:*anti*) |
|---|---|---|---|---|
| 1 | $MeNO_2$ | $BF_3OEt_2$ | 94 | 94:6 |
| 2 | $MeNO_2$ | $Me_2AlCl$ (Hexanes) | 81 | 85:15 |
| 3 | $MeNO_2$ | $ZnBr_2$ | 77 | 81:19 |
| 4 | $MeNO_2$ | $AlCl_3$ | 75 | 72:18 |
| 5 | $MeNO_2$ | $Me_3Al$ (hexanes) | 52 | 91:9 |
| 6 | $MeNO_2$ | $ZnCl_2$ | 0 | - |
| 7 | $MeNO_2$ | TMSOTf | 0 | - |
| 8 | $MeNO_2$ | $TiCl_4$ | 0 | - |
| 9 | $MeNO_2$ | $Ti(OiPr)_4$ | 0 | - |
| 10 | $MeNO_2$ | $TiCl_4$ / $Ti(OiPr)_4$ | 0 | - |




| Entry | Solvent | Lewis acid | Yield (%) | Diastereoselectivity (*syn*:*anti*) |
|---|---|---|---|---|
| 1 | $MeNO_2$ | $BF_3OEt_2$ | 94 | 94:6 |
| 2 | Hexanes | $BF_3OEt_2$ | 90 | 90:10 |
| 3 | Neat | $BF_3OEt_2$ | 90 | 91:9 |
| 4 | $PhNO_2$ | $BF_3OEt_2$ | 77 | 86:14 |
| 5 | $CH_3CN$ | $BF_3OEt_2$ | 55 | 92:8 |
| 6 | $CHCl_3$ | $BF_3OEt_2$ | 49 | 95:5 |
| 7 | Toluene | $BF_3OEt_2$ | 46 | 94:6 |
| 8 | DCM | $BF_3OEt_2$ | 25 | 95:5 |
| 9 | $Et_2O$ | $BF_3OEt_2$ | 13 | 91:9 |




**Scheme 7** Formation of (5*R*)-hydroxy-2-*p*-methoxyphenyl-1,3-dihydro-oxazinium tetrafluoroborate and its X-ray structure.

## CONCLUSION

Proximity effects play a decisive role in lowering the energetic barrier for Lewis acid-mediated intramolecular 1,3-dipolar cycloaddition reactions of suitably spaced nitrile and azide groups in acyclic molecules. 1-Azido-(2-substituted-1,3-dioxolanyl)-glycerols and 1-azido-(2-phenyl-1,3-dioxolanyl)-butanediol prepared from D- or DL-glycerol and 1,2,4-butanetriol, respectively, undergo facile intramolecular cycloaddition in the presence of TMSCN and $BF_3{\cdot}OEt_2$. The reaction proceeds by the initial formation of diastereomeric cyanohydrin ethers as a result of the opening of the acetals via oxocarbenium ion intermediates. The major products in the case of 2-substituted-1,3-dioxolanes are the *cis*-isomers with a diequatorial disposition of a hydroxymethyl and aryl(alkyl) group in the oxabicyclic tetrazoles. Larger ring acetals such as 2-substituted dioxanes or dioxepans lead to significantly lower ratios of diastereomeric oxabicyclic tetrazoles.

The 1,3-dipolar cycloaddition is facilitated in non-basic solvents such as nitromethane and in the presence of $BF_3{\cdot}OEt_2$ as the preferred Lewis acid.

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