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Search for Ideal Sulfinyl Dienophile and Dipolarophile

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ABSTRACT: *By analysis, the advantages and drawbacks of the differently substituted vinyl sulfoxides so far reported, (Z)-3-p-tolylsulfinyl acrylonitriles are proposed as the best sulfinyl dienophiles. The stereoselective synthesis of these compounds was optimized by hydrocyanation of sulfinyl alkynes with Et_2AlCN. Their behavior as chiral dienophiles and dipolarophiles is responsible for the high stereocontrol of Diels–Alder and 1,3-dipolar reactions, respectively.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:453–462, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10066

INTRODUCTION

The sulfinyl group has proved to be one of the best chiral inductors in asymmetric Diels–Alder reactions because of its high ability to differentiate diastereotopic faces at dienophilic double bonds [1]. Nevertheless, this ability is manifested only in the presence of an additional activating group at the double bond, which restricts the conformational mobility around the C—S bond, because in its absence the influence of the sulfinyl group on both reactivity and stereoselectivity is rather small. It can easily be deduced from the results obtained in the reaction of cyclopentadiene with the simplest sulfinyl dienophile, vinyl *p*-tolyl sulfoxide [2], which required a temperature of 110°C in a sealed tube to yield significant amounts of the four possible adducts. The obtained 64:36 endo/exo ratio indicates a low endo-orientating character of the sulfinyl group. Additionally, the observed π-facial diastereoselectivity was also low (70:30), which indicated that such a group does not exert an efficient control on it. The latter results can be rationalized by assuming a significant participation of the *s-cis* and *s-trans* conformations of the sulfinyl oxygen around the C—S bond, both of them with similar reactivities, where the bulky tolyl group is arranged towards a different face of the double bond (Fig. 1).

The first condition that any additional group must fulfil so as to improve the dienophilic features of vinyl sulfoxides, i.e. increasing the reactivity, can be performed by any electron withdrawing group. Moreover, the substituent must be able to enhance both the endo/exo and the π-facial diastereoselectivities. In this sense, the relative position of the substituent is quite important (see Fig. 2).

When the substituent is located in a trans arrangement relative to the sulfinyl group, its influence on the facial selectivity must be scarce or null, as it should have no influence on the composition of the conformational equilibrium around the C—S bond. On the othe hand, its endo-orientating character should compete with that of the sulfinyl group, and therefore a good endo–exo selectivity is not to be expected. The results obtained from the studied trans-substituted vinyl sulfoxides [3] confirm these predictions.

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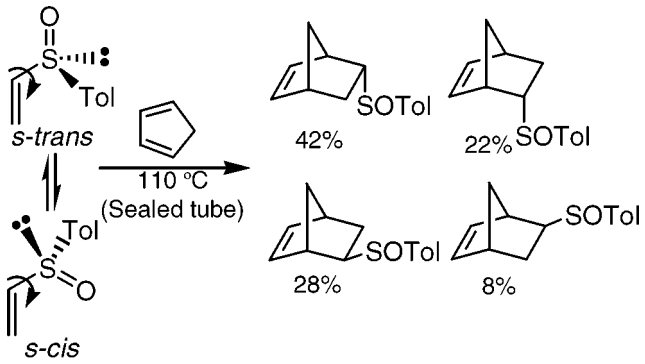

FIGURE 1 Dienophilic features of vinyl *p*-tolyl sulfoxide.

When the substituent is located at the geminal position, it will be able to shift the conformational equilibrium towards the *s-cis* rotamer provided that it can exhibit strong electrostatic repulsions towards the sulfinyl oxygen. In these cases, a significant improvement in the π-facial selectivity must be expected. Additionally, the formation of a chelated species in the presence of some Lewis acids used as catalysts, allows the inversion of this selectivity, thus increasing the interest of these groups, which have been widely studied [4]. Nevertheless, the relative position of the functional groups determines the competition of their endo-orientating effects, thus affording mixtures of the two possible endo adducts.

In order to improve the endo–exo selectivity, the incorporation of an additional functional group, which would enhance the endo-orientating character of the first one, has been considered. This is the case of sulfinyl maleates [5] and maleimides [6], and sulfinyl quinones [7], which mainly evolve into one endo adduct with higher reactivities than those of monosubstituted vinyl sulfoxides.

However, one of the main problems associated with the behavior of the gem- and *trans*-substituted vinyl sulfoxides derives from the absence of a substituent in a cis arrangement with respect to the sulfinyl group, which accounts for the easy desulfinylation of the adducts—it yields conjugated double bonds—with the loss of some of the newly formed chiral centers and even their aromatization in some cases (Fig. 3). This evolution is out of control when started from acyclic dienes, which strongly restricts the usefulness of the dienophiles.

As it can be seen in Fig. 2, (*Z*)-substituted vinyl sulfoxides are considered to be the most efficient dienophiles as they are able to restrict the rotamers formed by rotation around the C—S bond and, simultaneously, reinforce the endo-orientating character of the sulfinyl group. Additionally, the spatial arrangement of the substituent precludes the desulfinylation yielding a conjugated double bond, thus minimizing the problems derived from this

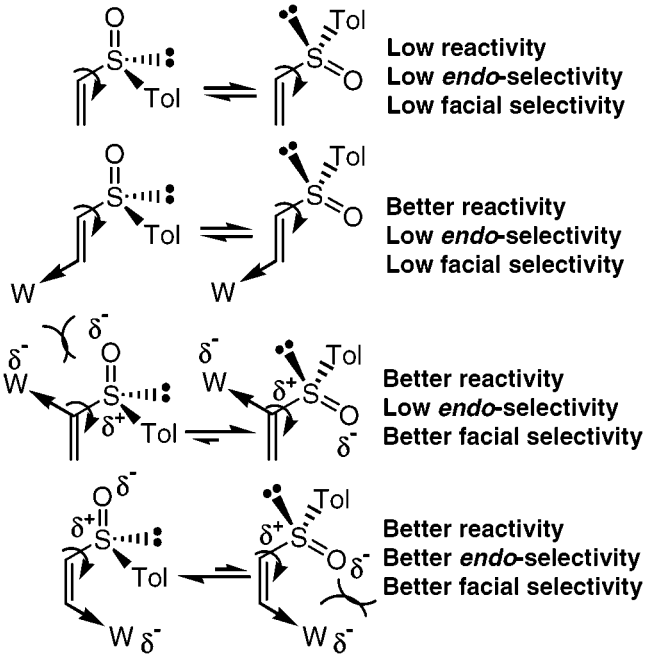

FIGURE 2 Influence of the relative position of an electron withdrawing group on the dienophilic features of vinyl sulfoxides.

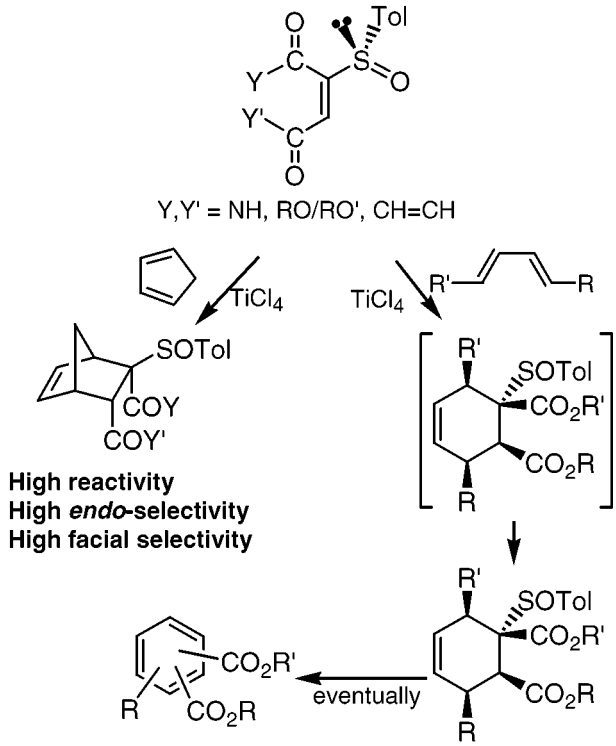

FIGURE 3 Dienophilic features of sulfinyl maleates.

reaction. In this sense, the best results so far reported have been obtained with the alkoxycarbonyl group. The results obtained by reaction of *n*-butyl (*Z*)-3-*p*-tolylsulfinyl acrylate with cyclopentadiene are depicted in Fig. 4. As seen, a significant improvement of the π-facial selectivity is observed in refluxing benzene [8] (it becomes almost complete at lower temperatures [9]) but the endo selectivity remains rather moderate, which is also the case of the reactivity of the dienophile, unable to react with furan and acyclic dienes, that are less reactive than cyclopentadiene.

In order to increase the dienophilic reactivity, it was necessary to synthesize sulfoxides bearing deactivated aromatic rings instead of the *p*-tolyl group. Thus, pyridylsulfinyl derivatives were able to react slowly with furan at room temperature yielding a mixture of adducts with a quite high facial selectivity (88%) but very low endo selectivity (36%) [10]. Moreover, the synthesis of these menthyl pyridylsulfinyl acrylates is rather complex because of the many steps required, some of them evolving with moderate yields and modest de's. Despite these drawbacks, the interest of the obtained adducts as key intermediates in the asymmetric synthesis of many natural products has determined the use of these reactions to obtain the precursors of methyl epishikimate [11], *C*-nucleosides [12], glyoxalase I inhibitors [13], and other compounds (see Fig. 5).

The efficient control of the π-facial selectivity observed in Diels–Alder reactions of (*Z*)-3-sulfinyl acrylates can be explained by assuming that the conformational equilibrium around the C—S bond must be completely shifted towards the rotamer with the sulfinyl oxygen adopting an s-trans arrangement so as to minimize its electrostatic interactions with the alkoxycarbonyl oxygens. This conformation displays one of its diastereotopic faces strongly hindered by the aromatic ring, precluding the approach of the diene to such a face. In order to rationalize the moderate reactivity and endo selectivity of these sulfoxides, the distortion of the planarity of the ester group as a consequence of its steric interactions with

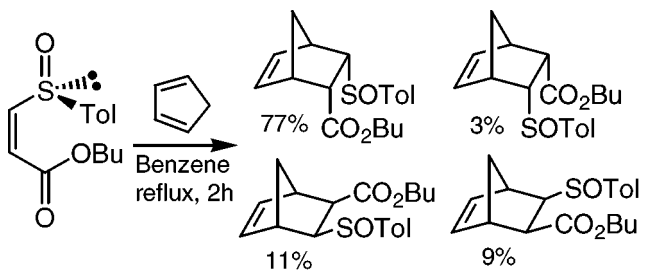

FIGURE 4 Diels–Alder reaction of *n*-butyl (*Z*)-*p*-tolylsulfinyl acrylate with cyclopentadiene in benzene.

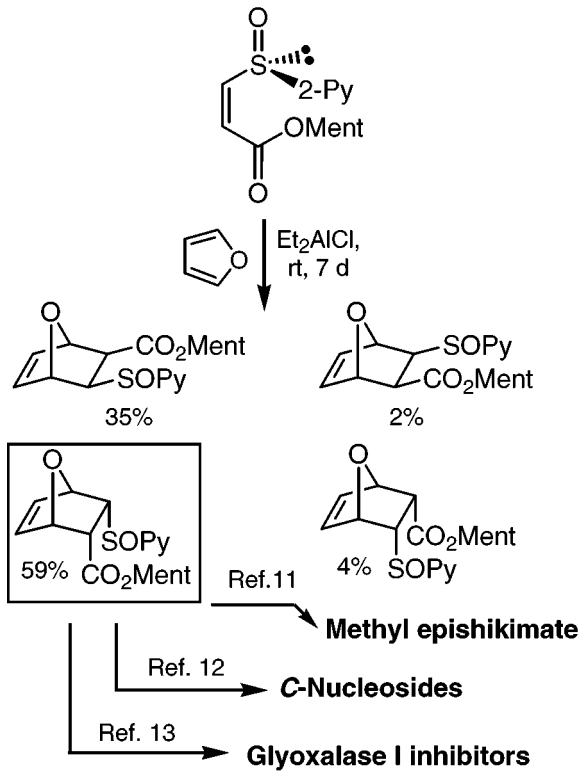

FIGURE 5 Diels–Alder reaction of 2-pyridylsulfinyl acrylate with furan.

the *cis*-sulfinyl group can be invoked. Such a distortion would justify the decrease in both dienophilic reactivity of the acrylate and endo-orientating character of the ester group because of its steric interactions with the approaching diene. In support of this assumption, the incorporation of a larger number of alkoxycarbonyl groups at the dienophilic double bond did not improve significantly either the reactivity or the stereoselectivity of their Diels–Alder reactions [14], which was explained as a consequence of the strong planarity distortions of the ester groups (shown in Fig. 6).

RESULTS AND DISCUSSION

On the basis of the above considerations, we reasoned that the change of the alkoxycarbonyl group by the cyano one would allow us to solve the problems inherent in the lost of planarity because of the linear structure of the latter group. Taking into account the similar electron withdrawing features of the CN and CO_2R groups, we should expect that sulfinyl nitriles would exhibit higher reactivity and endo selectivity than their ester counterparts. Additionally, the dipolar repulsion of the CN and SO bonds suggests that the s-trans conformation would be clearly favored, thus controlling the π-facial

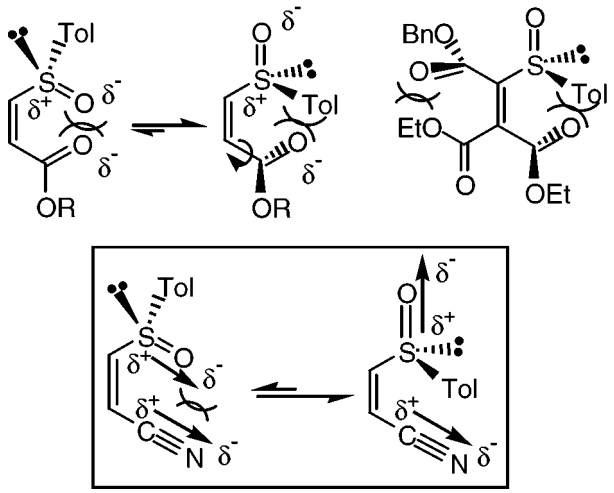

FIGURE 6 Conformational behavior of sulfinyl acrylates and sulfinyl acrylonitriles.

diastereoselectivity (Fig. 6). In other words, sulfinyl acrylonitriles could be the ideal sulfinyl dienophiles.

Because the synthesis of the (*Z*)-2-*p*-tolylsulfinyl acrylonitriles had never been reported and we needed these compounds to be used as general starting dienophiles, it was necessary to design a short, simple, and versatile method to prepare them. On account of the high stereoselectivity observed in reactions of β-ketosulfoxides with Et_2AlCN [15], which was attributed to the association of the aluminum with the sulfinyl oxygen as a previous step to the intramolecular cyanide transfer, we reasoned that similar hydrocyanation processes could also take place with sulfinyl alkynes.

The reaction of Et_2AlCN with alkynyl sulfoxides took place smoothly in short reaction times yielding (*Z*)-2-*p*-tolylsulfinyl acrylonitriles with an almost complete control of the stereoselectivity [16]. The formation of these vinyl sulfoxides was rationalized by assuming the association of the reagent to the sulfinyl oxygen followed by the intramolecular cyanide transfer to yield the *Z* isomers (Fig. 7).

As the starting alkynyl sulfoxides can easily be prepared in optically pure form by the Andersen reaction of the terminal alkynes with menthyl sulfinate in the presence of a base [16,17], the sequence herein indicated is a simple and efficient general method to prepare (*Z*)-sulfinyl acrylonitriles in two steps from commercially available alkynes.

Once the problem of the synthesis of the nitriles was solved, we studied their behavior as dienophiles. The reactions with cyclopentadiene [16] afforded easily separable mixtures of endo and exo adducts (Fig. 8). The dienophilic reactivity and the endo selectivity were strongly dependent on the substituent at the dienophile, and as expected both were highest

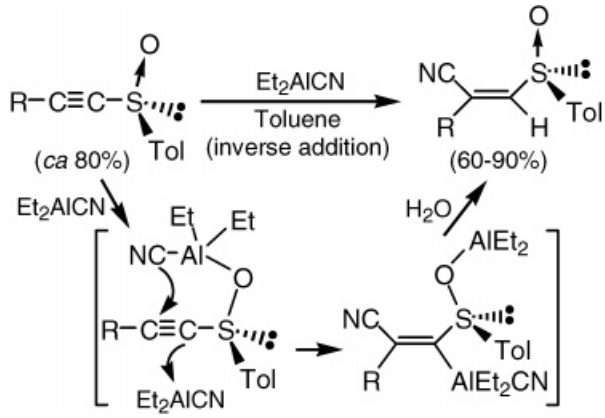

FIGURE 7 Stereoselective hydrocyanation of sulfinyl alkynes with Et_2AlCN.

when R = H. With this substrate the reaction was complete in 1 h at room temperature in the presence of $ZnBr_2$ as the catalyst, yielding a mixture of endo and exo adducts. From this mixture, it was possible to isolate the major one, in its diastereomerically pure form, in 80% yield by simple crystallization. Reactivity and endo selectivity sharply decreased when R = benzyl or *n*-Bu, 1 and 3 days being necessary, respectively, to obtain almost identical amounts of endo and exo adducts (Fig. 8).

When the reactions of (*Z*)-sulfinyl acrylonitriles with cyclopentadiene were conducted under BF_3 catalysis only one endo adduct could be detected regardless of the nature of the R group. This product had a carboxamide group instead of the cyano one and showed the opposite configuration at sulfur to that in the starting dienophile and this was established by X-ray diffraction studies and chemical correlation. Therefore, these reactions evolved with complete endo selectivity and π-facial selectivity,

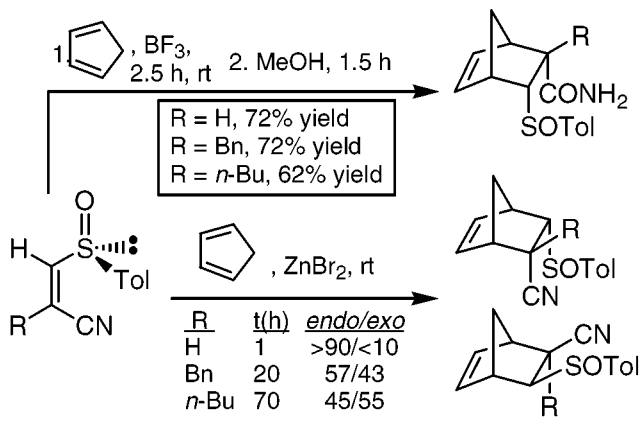

FIGURE 8 Diels–Alder reactions of sulfinyl acrylonitriles with cyclopentadiene.

which was the opposite to that exhibited under the previously described conditions. The posibility of inverting the sense of the facial selectivity by simply modifying the reaction conditions had not been reported for their acrylate counterparts, which increases the interest of these sulfinyl nitriles as dienophiles.

The most outstanding feature of these reactions was their complete π-facial selectivity, which determined the obtention of one (endo) or two (endo and exo) adducts resulting from the approach of the diene to only one of the faces of the dienophile. After unequivocal configurational assignment of the adducts by X-ray diffraction studies, we proposed the evolution depicted in Fig. 9 to explain the stereochemical results. In the absence of any catalyst, the strong dipolar repulsions destabilize the *s-cis* rotamer of the starting nitrile and shift its conformational equilibrium around the C—S bond towards the *s-trans* conformation (see Fig. 9). As the *p*-tolyl group hinders the diene approach to the lower face of this conformation, it takes place exclusively at the less hindered upper face of the dienophile, which bears the lone electron pair.

In order to explain the complete inversion of the π-facial selectivity observed in reactions catalized by BF_3, we assumed the formation of the cyclic intermediate resulting from the nucleophilic attack of the sulfinyl oxygen at the cyano group activated by the catalyst. It displays the *p*-tolyl group hindering the upper face, whereas in the starting sulfoxide it is oriented towards the lower face (Fig. 9). As a consequence, the approach of the diene takes place at a different face under both conditions. The obtention of carboxamides instead of nitriles and the inversion of the configuration at sulfur were the consequence of the opening of the resulting tricyclic adduct by methanol.

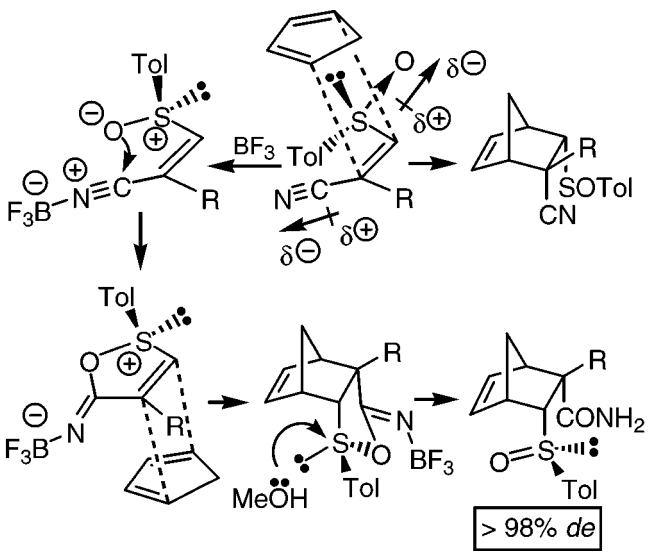

FIGURE 9 Stereochemical pathways of Diels–Alder reactions of sulfinyl acrylonitriles with cyclopentadiene.

We also studied the reactions of our dienophile with furan since the resulting adducts would be synthetically equivalent to those derived from sulfinylacrylates, which had been used as key intermediates in the asymmetric synthesis of many natural products (see Fig. 5). The reactions with furan required longer times but the stereochemical results were similar to those obtained with cyclopentadiene. Thus, a 86:14 ratio of the two adducts, resulting from the endo and exo approaches of diene to the same face of the dienophile, was obtained in 1 day by using furan as the solvent and $ZnBr_2$ as the catalyst [18]. Comparison of these results with those obtained from pyridylsulfinyl acrylate (see above) shows that the reaction time was clearly shorter in the case of the nitrile, which gives evidence of a higher reactivity, despite the fact that the acrylate is a pyridyl derivative. Moreover, the π-facial selectivity and to a greater extent the endo selectivity are both higher for sulfinyl nitriles, which confirms their better dienophilic features.

We also performed the reactions of (*Z*)-*p*-tolylsulfinyl acrylonitrile with acyclic dienes [18]. They had never been studied with sulfinyl acrylates because of their low reactivity. The use of 1-methoxybutadiene as the solvent allowed complete evolution of the nitrile in 4 days to afford an 85:15 ratio of the adducts easily separable by chromatography. The major one could be isolated in 70% yield. Under high pressure reactions with piperylene also afforded the corresponding two adducts after 10 days with an even higher endo selectivity. The major endo adduct could also be isolated in 70% yield.

The last studied Diels–Alder reaction was performed with Dane's diene, one of the most useful dienes to prepare the steroidal skeleton [4e,19]. The reaction required high pressure and Lewis acids as catalysts, yielding exclusively one adduct which could be isolated under the optimal conditions in 84% yield (Fig. 10). This result demonstrated that the evolution of our *cis*-sulfinyl acrylonitrile with Dane's diene is completely stereoselective and both π-facial and endo selectivities were totally controlled by the sulfinyl group.

The low reactivity of the acyclic dienes and furan determined that their reactions were successful only with sulfinyl acrylonitrile lacking in substituents. In order to overcome this problem and simultaneously to invert the π-facial selectivity we studied these reactions under BF_3 catalysis, but

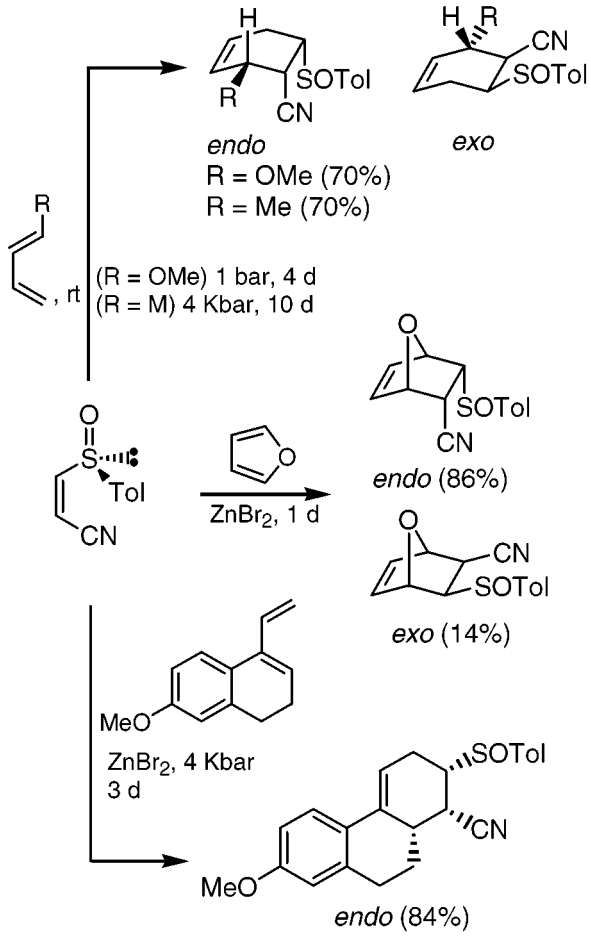

FIGURE 10 Diels–Alder reactions of sulfinyl acrylonitriles with furan and acyclic dienes.

unfortunately they were unsuccessful because of the immediate polymerization of the dienes in the presence of this catalyst. Nevertheless, a fortuitous finding allowed us to sort out this problem. In one of the experiments involving the reaction of the unsubstituted sulfinyl acrylonitrile with cyclopentadiene and catalyzed by BF_3, we could detect and characterize a small amount of a byproduct whose spectroscopic data suggested a sulfilimine structure with an endocyclic sulfur–nitrogen double bond, which in turn could be confirmed by X-ray diffraction studies (Fig. 11) [20]. The unusual structure of this compound (so far only suggested as a reaction intermediate) as well as its high configurational stability, infrequent in sulfilimines, drew our attention to its potential interest as a dienophile since its rigid cyclic structure suggested a complete control of the π-facial selectivity. Moreover, it should be the opposite to that observed from its precursor sulfinylnitrile because the relative positions of the most bulky *p*-tolyl group were different in both substrates, which

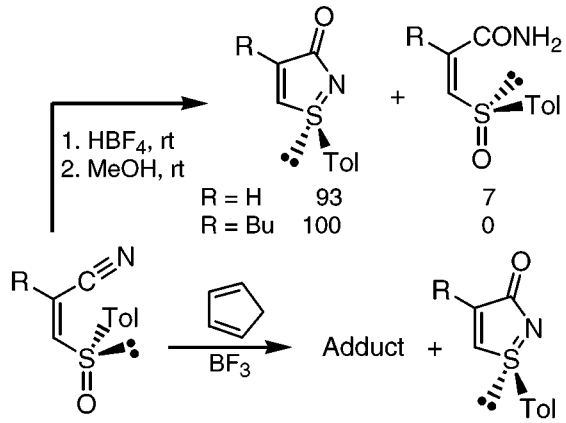

FIGURE 11 Formation of cyclic sulfilimines starting from sulfinyl acrylonitriles.

would allow the adducts to be formed with the characteristic stereochemistry of the reactions conducted under BF_3 catalysis.

Therefore, our next goal was the search for the most efficient conditions to obtain these compounds. The treatment of the nitriles with HBF_4 in CH_2Cl_2 followed by addition of methanol gave the desired sulfilimine as the major product along with a little amount of the sulfinyl acrylamide, which was furtherly revealed as a reaction intermediate.

The reaction of the sulfilimine with cyclopentadiene quantitatively afforded the endo adduct under mild conditions [20]. The reactivity of this new dienophile is lower than that of the precursor sulfinyl nitrile, but the π-facial selectivity and mainly the endo selectivity are almost complete, yielding exclusively one endo adduct. Its configurational assignment could be established from its spectroscopic data and chemical correlation with the adduct resulting from the reaction of cyclopentadiene with the (*Z*)-*p*-tolylsulfinyl acrylonitrile catalyzed by $ZnBr_2$. As can be seen in Fig. 12, the sulfenyl carboxamides resulting from the respective reduction and hydrolysis of both adducts are enantiomers, thus demonstrating that the π-facial diastereoselectivities of the cycloadditions of sulfinylnitrile and sulfilimine were opposite as a consequence of the change in the relative spatial arrangement of the *p*-tolyl group in both substrates. Therefore, both dienophiles could be considered as complementary.

These results prompted us to study the reactions of sulfilimines with acyclic dienes and furan, a reaction which had been unsuccessful starting from sulfinyl nitriles and BF_3. The reaction of the sulfilimine with furan required 4–5 days at $-20^{\circ}C$ under BF_3 catalysis to afford the exo adduct in 85% isolated yield of diastereomerically pure product, the *de* of the process being 92% [21]. The reasons determining the

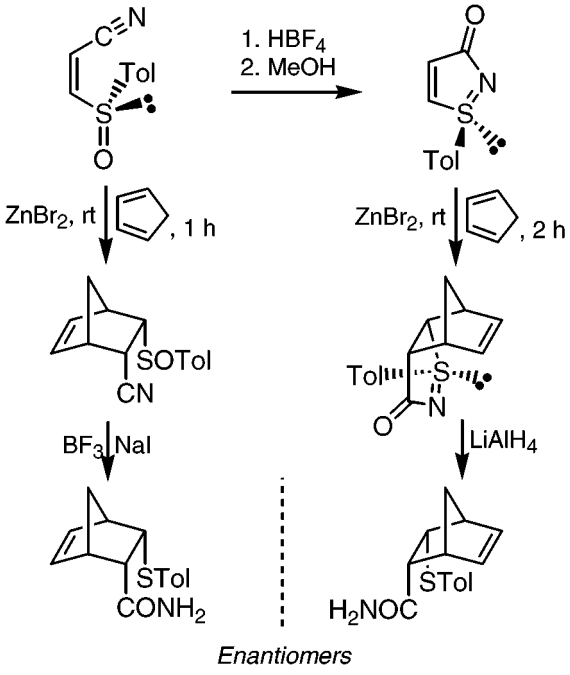

FIGURE 12 Complementary π-facial diastereoselectivities in the Diels–Alder reactions of sulfinyl acrylonitriles and cyclic sulfilimines.

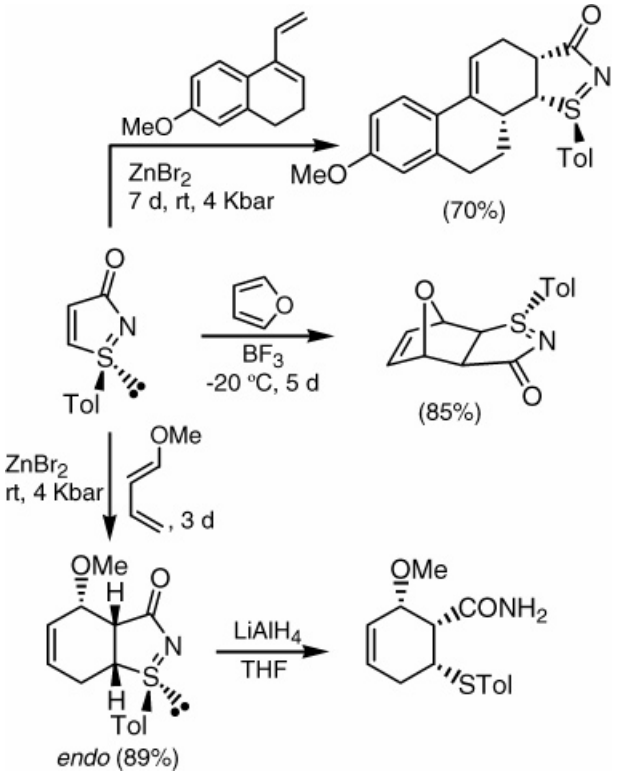

FIGURE 13 Diels–Alder reactions of cyclic vinyl sulfilimines with furan and acyclic dienes.

strong exo selectivity of the sulfilimines are not so clear, specially after demonstration that the equilibration between the endo and exo adducts does not take place under the reaction conditions, which excludes the obtention of the exo adducts as a result of a thermodinamically controlled Diels–Alder reaction.

Under high pressure the reactions with less reactive acyclic dienes required 3 days and acid catalysis to be complete. Thus, 1-methoxybutadiene evolved into just one endo adduct, which could be isolated in 89% yield, at 4 Kbar under $ZnBr_2$ catalysis [21]. As can be seen in Fig. 13, the endo and π-facial selectivities, as well as the regioselectivity were complete. Piperylene evolved in a similar stereochemical way, although the regioselectivity was not complete, yielding an 8:1 mixture of regioisomers [21].

Finally we studied the reactions with Dane's diene. To our surprise, they afforded a mixture of two endo and exo adducts, resulting from the attack of the diene at the same face of the sulfilimine. As it was expected, the π-facial selectivity was opposite to that observed in reactions of Dane's diene with sulfinyl acrylonitriles, but unexpectedly the regioselectivity of the reactions also changed [21]. As these facts are not actually well understood, these reactions are currently under study.

In conclusion, cyclic vinylsulfilimines show a behavior that can be considered as complementary to that of their precursor sulfinyl nitriles because they always evolve with the opposite π-facial selectivity. Additionally, both dienophiles evolve with the opposite endo/exo selectivity or regioselectivity in their reactions with furan and Dane's diene, respectively.

The good results obtained in the asymmetric Diels–Alder reactions of sulfinyl nitriles prompted us to study their behavior as dipolarophiles. The first studied 1,3-dipole was diazomethane [22]. The reactions took place under very mild conditions (see Fig. 14). Thus, about 1 h was required to obtain cycloadducts in quantitative yields at temperatures under 0°C, even in the case of the highly hindered *t*-butyl derivative, unable to react with cyclopentadiene under more severe conditions. When R = H, cycloaddition as well as desulfinylation were instantaneous affording the corresponding cyanopyrazolin. Only one pyrazoline was obtained in all cases, which indicates that the reactions evolved in a complete regio and stereoselective manner. The reactions with diazoethane were even more interesting. They were even faster since less than 10 min were required to reach completion and both regio and stereoselectivity remained complete, yielding only the adduct bearing the methyl group in the trans arrangement with respect to the sulfinyl one, as it was unequivocally established by the X-ray diffraction studies.

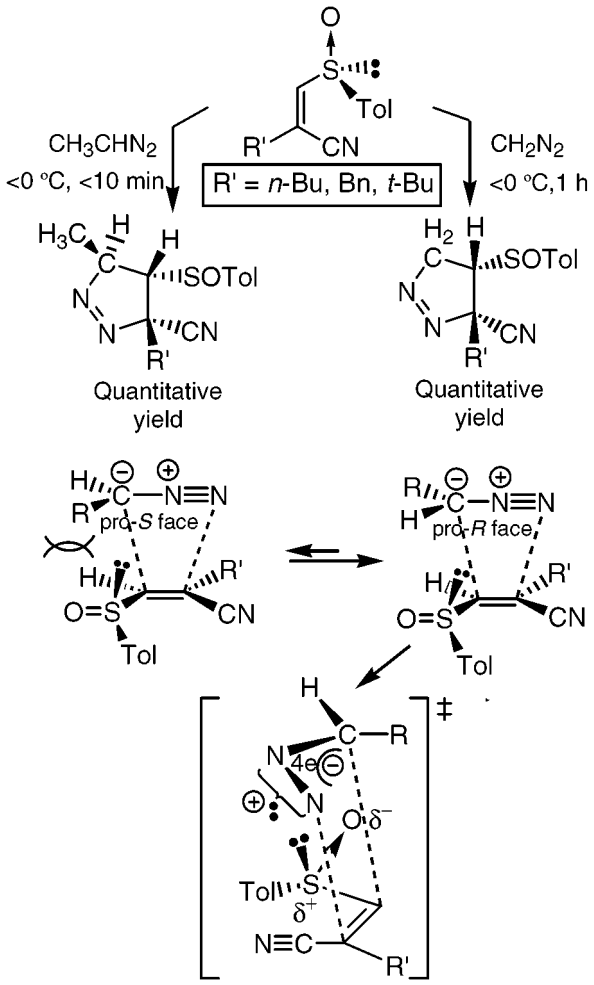

FIGURE 14 1,3-Dipolar cycloadditions of sulfinyl acrylonitriles with diazoalkanes.

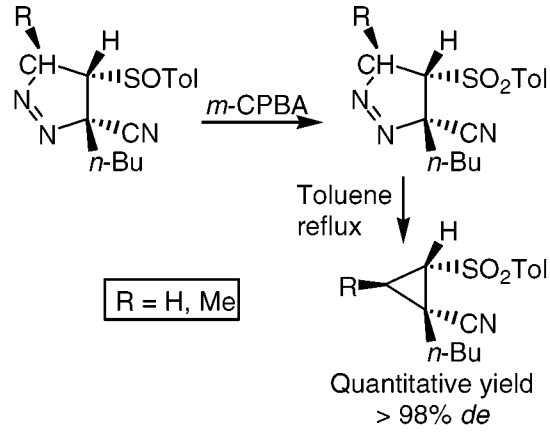

FIGURE 15 Highly stereoselective preparation of polisubstituted cyclopropanes from cyanosulfinyl pyrazolines.

These results point out that dipolarophiles are able to control the configuration at all chiral centers created during the reaction, even those formed at the dipole fragment. This can be explained by assuming the approach of the dipole to the less hindered upper face of the dipolarophiles in their most stable *s-trans* conformation. As shown in Fig. 14, the approach to the pro-*R* face of the diazoethane would lead to the most stable endo-like TS because the approach to the pro-*S* face would be destabilized by the interaction between the Me and SOTol groups.

These pyrazolines were very useful as starting materials for the syntheses of cyclopropanes (García Ruano et al., unpublished results). Accordingly, their oxidation with *m*-PBCA yielded the corresponding sulfones, which easily evolved into cyclopropanes in refluxing toluene (Fig. 15). The yields of these transformations were almost quantitative and the stereoselectivity was complete, even in the case of the pyrazolines derived from diazoethane. The configuration at the methylated carbon does not change during the reaction. Taking into account that the so far postulated mechanisms for these nitrogen extrusions involve the formation of dirradicals or even zwitterionic species as intermediates, both of them configurationally unstable, the exclusive formation of these cyclopropanes is unexpected and suggests that other more stereoselective pathways could be involved in these transformations. We are now working in this field so as to clarify both the mechanism and the scope of these reactions.

The reactions of the sulfinyl acrylonitriles with other dipoles have also been studied. Thus, they react with the azomethine ylides (see Fig. 16) in a few minutes at room temperature with complete control of the regioselectivity and stereoselectivity to yield just one adduct bearing the aromatic rings and the CO_2Et group in a trans arrangement (García Ruano et al., unpublished results).

The stereochemical model used to explain these results is based on the assumption that the approach of the dipole takes place exclusively at the less hindered face of the dienophile adopting the most stable *s-trans* conformation. The TS resulting from the endo approach of the dipole, with the CO_2Et group adopting the syn conformation, must be favored with respect to the similar approach of the dipole adopting the anti conformation because of the interactions between the sulfinyl and ester groups in the latter.

Finally, we also studied the reactions of some cyclic nitrones with sulfinyl acrylonitriles (Fig. 17). All the reactions were completely stereoselective, each yielding only one endo adduct, bearing the ring in a *cis* arrangement with respect to the cyano and sulfinyl groups, which resulted from the approach to the less hindered face of the dipolarophile (García Ruano et al., unpublished results). Despite

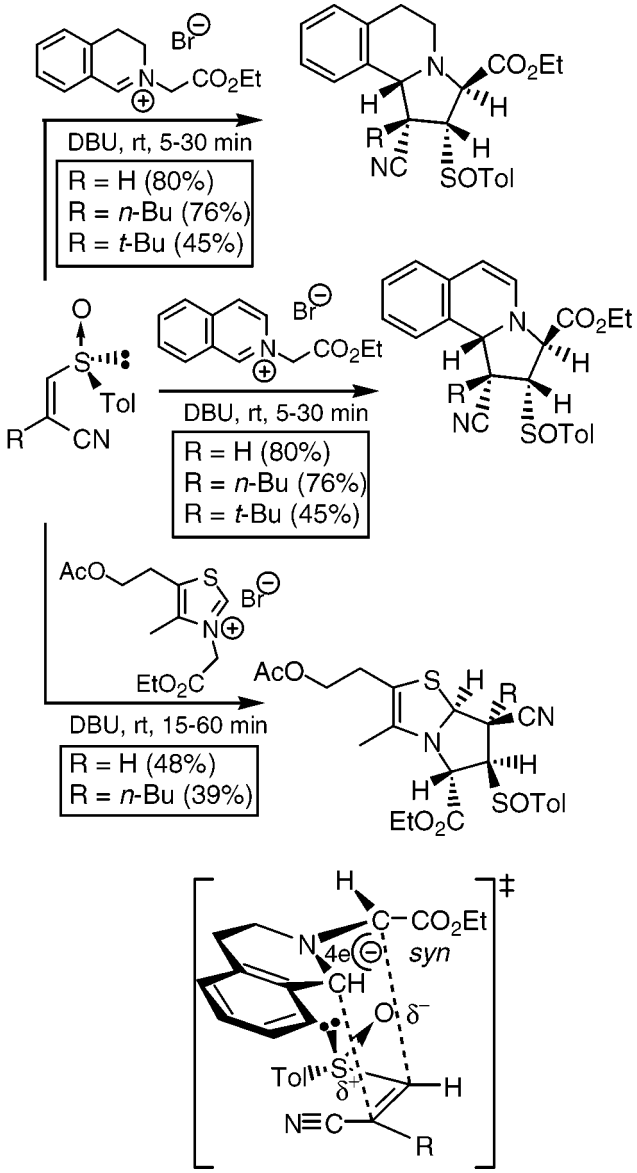

FIGURE 16 1,3-Dipolar cycloadditions of sulfinyl acrylonitriles with azomethine ylides.

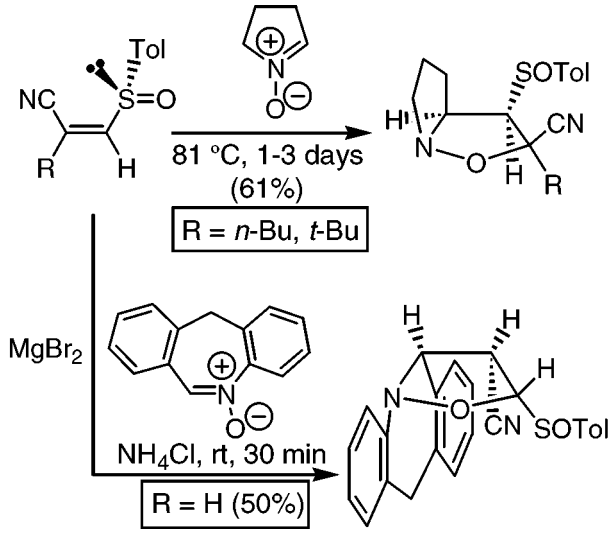

FIGURE 17 1,3-Dipolar cycloadditions of sulfinyl acrylonitriles with cyclic nitrones.

these excellent synthetic results, there are many issues with regard to these reactions requiring clarification. Thus, the large differences in reactivity and mainly the completely opposite regioselectivity observed in reactions of these two nitrones are not understood so far.

CONCLUSIONS

In conclusion, we can state that (*Z*)-3-*p*-tolylsulfinyl acrylonitriles were the best monoactivated vinyl sulfoxides so far reported in asymmetric Diels–Alder reactions. They were able to react with cyclic and acyclic dienes as well as with furan with a complete control of the regioselectivity and facial diastereoselectivity. The endo selectivity was very high and in some cases almost complete. Moreover, the behavior of these substrates as dipolarophiles was even more satisfactory because their reactivity was much higher and the endo selectivity was complete in all cases. Taking into account that the synthesis of these compounds can easily be performed in just two steps from commercially available alkynes, *cis*-*p*-tolylsulfinyl acrylonitriles seem to be the ideal sulfinyl dienophiles and dipolarophiles.

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