JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Stereo-, Regio-, and Chemoselective [3 + 2]-Cycloaddition of (2*E*,4*E*)-Ethyl 5-(Phenylsulfonyl)penta-2,4-dienoate with Various Azomethine Ylides, Nitrones, and Nitrile Oxides: Synthesis of Pyrrolidine, Isoxazolidine, and Isoxazoline Derivatives and a Computational Study

Ulaganathan Sankar,[†] Ch. Venkata Surya Kumar,[‡] V. Subramanian,*[,‡] K. K. Balasubramanian,*[,§] and S. Mahalakshimi[†]

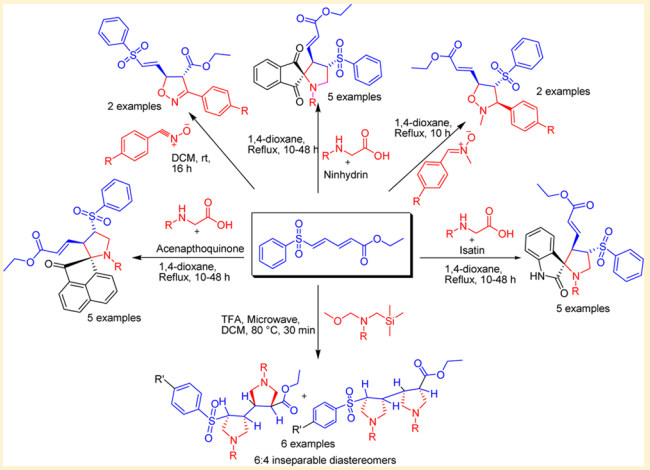
[†]Department of Chemistry, Pachaiyappa's College, University of Madras, Chennai 600030, India

[‡]Chemical Laboratory, CSIR-Central Leather Research Institute, Adyar, Chennai 600020, India

[§]INSA Senior Scientist, Department of Chemistry, Indian Institute of Technology Madras, Chennai 600020, India

Supporting Information

ABSTRACT: One-pot chemo-, regio-, and stereoselective synthesis of series of heterocyclic and spiroheterocyclic compounds was accomplished through mono- and bis[3 + 2]-cycloaddition reactions of (2*E*,4*E*)-ethyl 5-(phenylsulfonyl)penta-2,4-dienoate as a dipolarophile with azomethine ylides, nitrones, and nitrile oxides in good yields. The structures of the products were established by spectroscopic techniques as well as by single-crystal XRD study, and DFT calculations were performed to further understand the mechanism of this [3 + 2]-cycloaddition reaction.



INTRODUCTION

The [3 + 2]-cycloaddition, also known as the Huisgen cycloaddition,[1a] is a classical and fundamental reaction in organic chemistry involving the reaction of 1,3-dipoles with olefinic or acetylenic dipolarophiles leading to production of various heterocyclic scaffolds, which are particularly useful for the creation of diverse chemical libraries of druglike molecules for biological screening.[1−5] There has been tremendous activity in this area since the discovery of the click reaction.[5f] Functionalized pyrrolidines, isoxazolidines, and pyrrolizidines with spirooxindole ring systems are the central skeletons for numerous alkaloids and pharmacologically important compounds.[6] The isoxazolidine unit constitutes an easily accessible nucleus that is present in a number of natural and pharmacological compounds and displays a wide range of biological activity. Isoxazolidines are masked γ-amino alcohols. The N−O bond in isoxazolidines can be reductively cleaved to γ-amino alcohols, which are present in a wide range of biologically active compounds.[7] Spiroheterocyclic compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties. Gelesmine, pseudotabersonine, isoformosanine, and mitraphylline are some of the alkaloids containing spirooxindole ring systems.[8] Of particular interest, spiropyrrolidinyloxindole ring systems are also found in a number of alkaloids such as horsifiline, spirotryprostatine A and B, and elacomine, etc.[9]Derivatives of spirooxindoles find very wide biological applications as antimicrobial and anti-inflammatory agents, antitumorals, antibiotic agents, and inhibitors of human NK-1 receptors.[10] Hence, there has been renewed interest in the synthesis of spirooxindoles.[11]

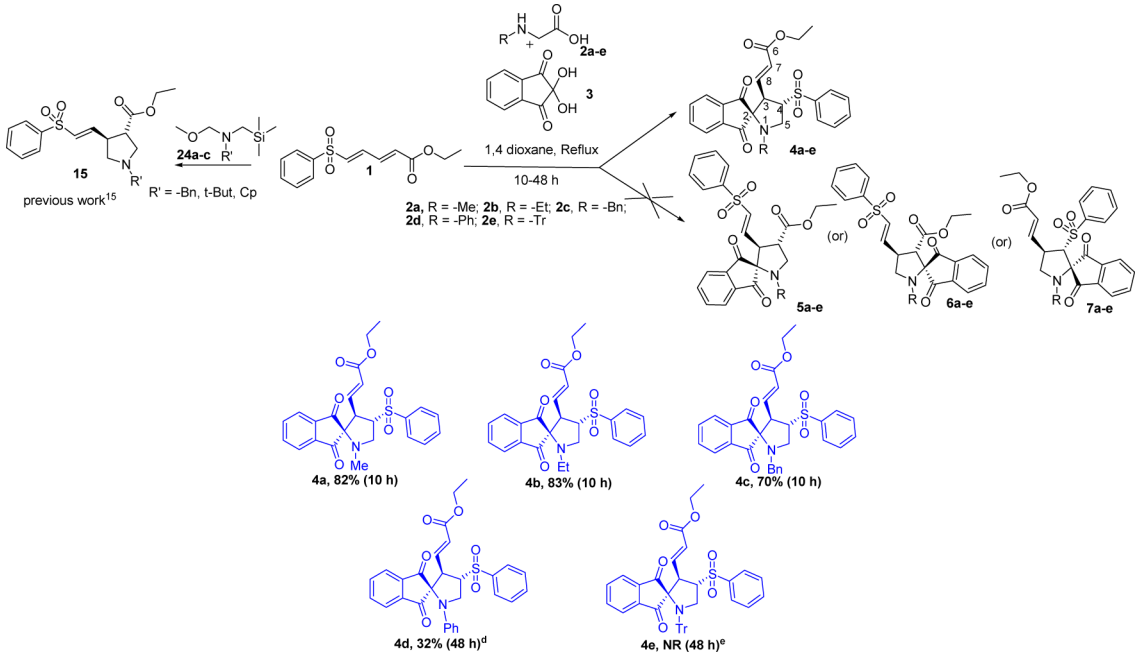
RESULTS AND DISCUSSION

Sulfonyl dienes like 1-arylsulfonyl 4-substituted (*E*,*E*)-1,3-dienes have attracted considerable attention as dipolarophiles, and in many cases, they have been transformed into synthetically useful cycloadducts via chemoselective [3 + 2]-cycloaddition.[12a−c] Raj et al.[13a] and Rusil et al.[13b] have reported the [3 + 2]-cycloaddition of various azomethine ylides to

Received: December 16, 2015
Published: February 17, 2016

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354

Scheme 1. Synthesis of Spiropyrrolidines 4a−e[a−c] via [3 + 2]-Cycloaddition of Diene 1 and Ninhydrin 3 with Various *N*-Substituted Glycines 2a−e



[a]All reactions were carried out with **1** (1 mmol), **3** (1 mmol), and **2a−e** (1 mmol) in 1,4-dioxane (10 mL) at reflux for 10−48 h. [b]Isolated yield of the pure product. [c]All of the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS). [d]Crude LC−MS yield. [e]No reaction.

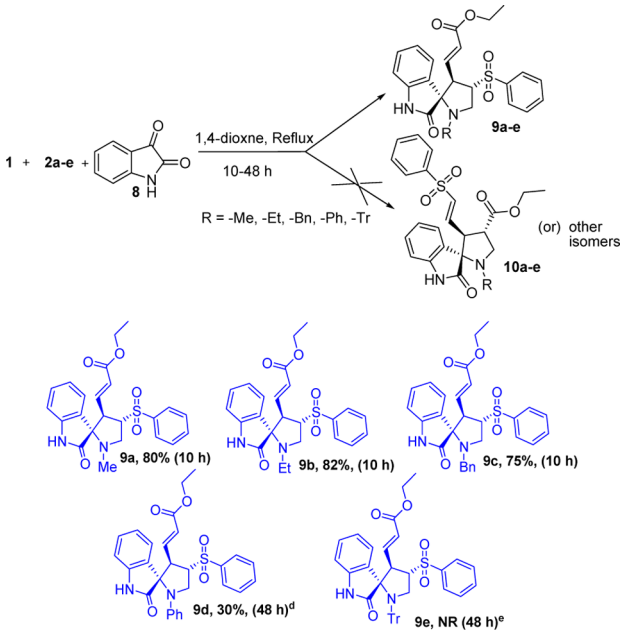
dipolarophiles containing exocyclic double bonds. Recently, patahak et al.[13c] reported the DFT calculations of regioselective [3 + 2]-cycloaddition of vinyl sulfones with sugar azides. Houk et al.[14] have reported the HOMO−LUMO calculations for a number of electronegative alkenes. According to their FMO theory of calculation, the orbital coefficient of LUMO for ethyl acrylate is larger than that of phenyl vinyl sulfone, and carboxylate is a more powerful electron-withdrawing group compared to that of the phenylsulfonyl group. On this basis, one can expect that the mono-cycloaddition reaction of 1-arylsulfonyl 4-substituted (*E*,*E*)-1,3-dienes to azomethine ylides might exhibit high chemoselectivity and that the reaction would occur at the acrylate double bond rather than at the vinyl sulfone double bond. In fact, we had observed this chemoselectivity in the case of [3 + 2]-cycloaddition of simple acyclic azomethine ylides[15] to 1-arylsulfonyl 4-substituted (*E*,*E*)-1,3-dienes. We have recently observed that the chemoselectivity is dictated by the nature as well as by the steric bulk of the ylide (Scheme 1). In the case of azomethine ylides, the chemoselectivity could be tuned in favor of the vinyl sulfonyl double bond by changing its size, which is also predicted by our DFT calculations.

In this publication, we describe a stereo- and regioselective route for the synthesis of highly functionalized pyrrolidines based on chemoselective [3 + 2]-cycloaddition of azomethine ylides generated from *N*-alkyl-*α*-amino acids and cyclic ketones to (2*E*,4*E*)-ethyl 5-(phenylsulfonyl)penta-2,4-dienoate and present the conclusions derived from the DFT calculations of this cycloaddition reaction. Azomethine ylides can be generated via a number of methods,[16] among which the decarboxylation route offers a convenient method for the synthesis of pyrrolidines. We first investigated the one-pot [3 + 2]-cycloaddition reaction of (2*E*,4*E*)-ethyl 5-(phenylsulfonyl)-penta-2,4-dienoate **1**[15] with dipoles generated in situ from sarcosine **2** and ninhydrin **3** as outlined in Scheme 1. A clean reaction was observed when **1** was refluxed in 1,4-dioxane for 10 h with sarcosine and ninhydrin without any catalyst, affording **4a** as the only cycloaddition product in very good yield (Scheme 1). LC−MS analysis of the crude product did not indicate the presence of any isomeric products like **5a**, **6a**, and **7a** (Scheme 1). The cycloadduct **4a** was characterized by ^{1}H and ^{13}C NMR spectra, HRMS, and X-ray single-crystal analysis.[17] The reaction of **1** with in situ generated azomethine ylides from ninhydrin and ethylglycine, benzylglycine, phenylglycine, or tritylglycine (**2b−e**) in refluxing 1,4-dioxane (10−48 h) afforded the corresponding cycloadduct, viz., of (*E*)-ethyl 3-(1′-alkyl-1,3-dioxo-4′-(phenylsulfonyl)-1,3-dihydrospiro-[indene-2,2′-pyrrolidin]-3′-yl)acrylate **4b−e** (Scheme 1) in good yield. We could not detect the presence of the other regioisomers **5a−e**, **6a−e**, and **7a−e** in any of the cases when the crude products were analyzed by LC−MS. While it was easy to rule out the alternative structures from ^{1}H, ^{13}C, DEPT, COSY, and HMBC spectral data, the relative stereochemistry at the spirocenter **C2** in the cases of **4a−e** could not be deduced from the NMR data. However, it could be fixed from the single-crystal X-ray data of **4a** (see the Supporting Information).

Similarly, the reaction of **1** with in situ generated azomethine ylides from isatin **8** and sarcosine, ethylglycine, benzylglycine, phenylglycine, or tritylglycine (**2a−e**) in refluxing 1,4-dioxane furnished, respectively, the cycloadducts **9a−e**[17] in good yield (Scheme 2). The reaction was highly chemo-, stereo-, and regioselective in all cases, occurring only at the vinylsulfone double bond. Similarly, azomethine ylides generated from acenaphthenequinone reacted smoothly and yielded the spiropyrrolidines **12a−e** in good yields (Scheme 3). The chemoselectivity observed in the present case is in contrast to that observed in the case of acyclic azomethine ylide generated through the desilylative method.[15]

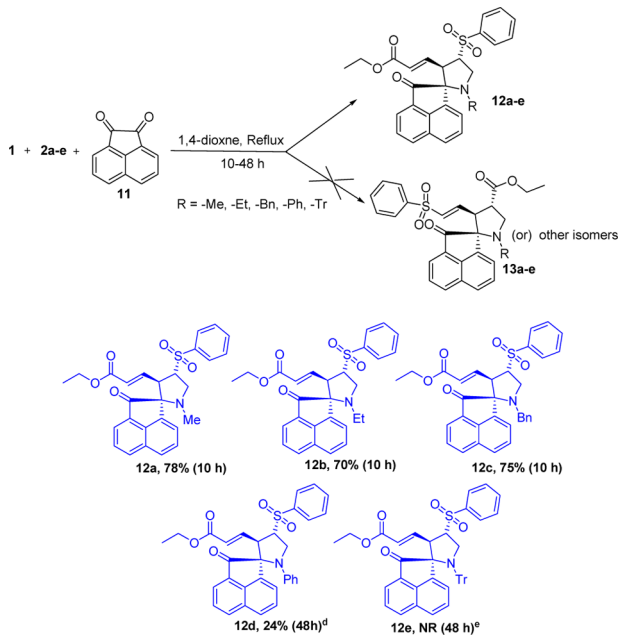
DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354

Scheme 2. Substrate Scope for Synthesis of Spirooxindoles 9a–e[a–c]



[a]All reactions were carried out with**1** (1 mmol), **8** (1 mmol), and **2a–e** (1 mmol) in 1,4-dioxane (10 mL) at reflux for 10–48 h. [b]Isolated yield of the pure product. [c]All of the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS). [d]Crude LC–MS yield. [e]No reaction.

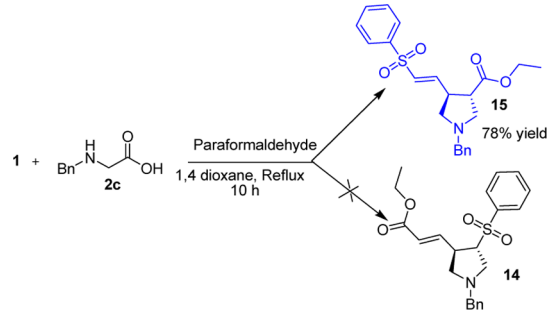
Scheme 3. Substrate Scope for Synthesis of Spiropyrrolidines 12a–e[a–c]



[a]All of the reactions were carried out with**1** (1 mmol), **11** (1 mmol), and **2a–e** (1 mmol) in 1,4-dioxane (10 mL) at reflux for 10–48 h. [b]Isolated yield of the pure product. [c]All of the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS). [d]Crude LC–MS yield. [e]No reaction.

The chemoselectivity in the case of acyclic azomethine ylides generated by the desilylative method[15] was not altered when the same ylide was generated by the decarboxylative method (Scheme 4), indicating that the chemoselectivity is not influenced by the mode of generation of the ylide but is purely governed by the steric factors associated with the azomethine ylides. This inference has been supported by DFT calculations, which also clearly reveal that chemoselectivity of cycloaddition is determined by the steric bulk of azomethine ylide.

Scheme 4. Synthesis of Pyrrolidine 15[a] via [3 + 2]-Cycloaddition of Diene 1 and *N*-Benzylglycine 2c with Paraformaldehyde



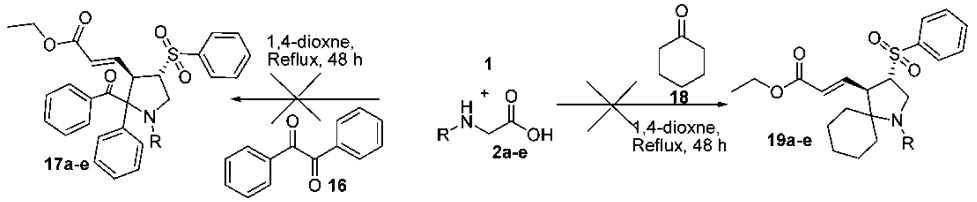
[a]A reaction was carried out on **1** (1 mmol), paraformaldehyde (2 mmol), and **2c** (1 mmol) in 1,4-dioxane (10 mL) at reflux for 10 h. [b]The product was fully characterized by its spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS).

We studied the reaction of **1** with in situ generated azomethine ylides from ninhydrin **3** and sarcosine **2a** in various solvents, viz., toluene, methanol, 1,4-dioxane, and acetonitrile. 1,4-Dioxane was found to be the best in terms of yield and chemo-, regio-, and stereoselectivity. Strangely, there was no reaction in the case of tritylglycine even after 48 h, and in the case of phenylglycine, the yields of the cycloadduct **4d**, **9d**, and **12d** were rather low (20–24%). While isatin, ninhydrin, and acenaphthenequinone showed good reactivity, cyclohexanone and benzil did not react under these conditions (Scheme 5). An attempt to react the mono-cycloadduct **4a** with an additional 1 equiv or more of the azomethine ylide to obtian the bisadduct was in vain, even after prolonged heating (48 h).With a view to explore the scope of this [3 + 2]-cycloaddition and also to find out whether the same chemoselectivity will be encountered in the case of other kinds of 1,3-dipoles, we investigated the reaction of **1** with nitrones **20a–b** and nitrile oxides precursor **22a,b**.[18a] In the event, we were surprised to note that while the cycloaddition in the case of nitrones occurred at the vinyl sulfonyl double bond, in the case of nitrile oxides it was the acrylate double bond that participated in the cycloaddition as outlined in Scheme 6.

Nitrones (**20a,b**) were prepared according to literature procedure.[18b] A smooth reaction was observed when **1** was refluxed with nitrones **20a** in 1,4-dioxane for 10 h without any catalyst, affording isoxazolidine derivative **21a** in 56% yield (Scheme 6). LC–MS analysis of the crude product did not indicate the presence of any isomeric products. Similarly, treatment of **1** with nitrone **20b** afforded the isoxazolidine **21b**. Structural elucidation of the isoxazolidine **21b** was accomplished using 1D, 2D NMR spectroscopy and HRMS. We have observed in our previous work[15] that the olefinic protons of the vinyl sulfonyl moiety in the mono-[3 + 2]-cycloadducts resonate in the region of δ 6.6 and 6.9 as doublet and doublet of doublet, respectively. In the case of the adduct **21b**, the

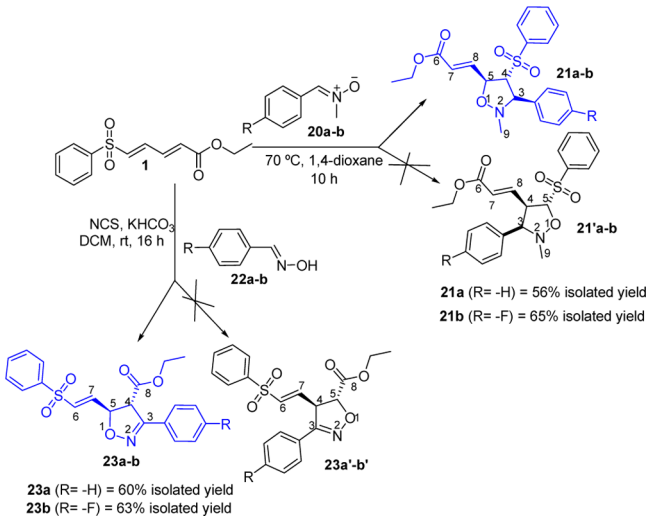
DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340–2354

Scheme 5. Attempted Synthesis of Spiropyrrolidines 17a−e and 19a−e[a] via [3 + 2]-Cycloaddition of Diene 1 and *N*-Alkylglycines 2a−e with Benzil 16 or Cyclohexanone 18



[a]All of the reactions were carried out with diene **1** (1 mmol), benzil **16**, or cyclohexanone **18** (1 mmol) and **2a−e** (1 mmol) in 1,4-dioxane (10 mL) at reflux for 10−48 h.

Scheme 6. Substrate Scope for Synthesis of Isoxazolidines 21a,b[a,b] and Isoxazolines 23a,b[c,d]



[a]Reaction conditions for nitrone cycloaddition: All of the the reactions were carried out on diene **1** (1 mmol) with nitrone **20a,b** (1 mmol) in 1,4-dioxane (10 mL) at 70 °C for 10 h. [b]All of the the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS). [c]Reaction conditions for nitrile oxide cycloaddition: All the reactions were carried out on diene **1** (1 mmol) with Oxime **22a,b**(1 mmol), NCS (1.1 mmol), and $KHCO_3$ (1.5 mmol) in DCM (10 mL) at rt for 16 h. [d]All of the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS).

signals of olefinic protons appeared at δ 5.9 and 6.8, indicating that the cycloaddition has occurred on the vinylsulfonyl double bond. This was further evident from the HMBC spectrum which showed a correlation between the olefinic proton H7 at δ 5.93 (1H, d, J = 15.5 Hz) and the ester carbonyl at 165.91 (see the SI). In the ^{1}H NMR spectrum of **21b**, the H4 and H3 proton of the isoxazolidine moiety resonated as doublet of doublet at δ 3.85 (J = 7.6, 4.4 Hz) and doublet at δ 3.95 (J = 7.2 Hz), respectively. The H5 proton of the ring appeared as triplet at δ 5.19 (J = 5.5 Hz). The H7 alkene proton appeared as doublet at δ 5.93 (J = 15.50 Hz) and the H8 alkene proton resonated at δ 6.86 as a multiplet. The H,H-COSY spectrum revealed a correlation between the H4 proton at δ 3.85 ppm with the H3 proton at δ 3.95 ppm, while there was no correlation between the H5 proton at δ 5.19 ppm with the H3 proton at δ 3.95 ppm, which is consistent with the observed regioselectivity of cycloaddition. The NOESY NMR spectrum was also informative. It showed a correlation between the H3 and H5 protons, indicating a cis relationship. A correlation between the H4 with H8 protons was also noticed in the NOESY spectrum. Thus, the relative stereochemistry between the three centers, viz. 3, 4, and 5, have been fixed. The chemoselectivity observed in the case of nitrones was also predicted by DFT calculations. The regiochemistry observed in the present study was similar to what has been reported in literature for nitrone [3 + 2]-cycloaddition to electron-deficient olefins.[18c−f]

The reaction of **1** with nitrile oxides[18g] generated in situ from benzaldoxime (**22a,b**) furnished, respectively, the 2-isoxazolines derivatives **23a,b** in good yield (Scheme 6). Interestingly, the chemoselectivity observed in the case of nitrile oxide cycloaddition was opposite to that of the nitrone cycloaddition reaction.This was evident from a glance of the ^{1}H NMR spectrum, particularly that of the olefinic region (see the SI). One of the alkene protons, viz. H6, appeared as a doublet at δ 6.76 (J = 14.9 Hz) and the other proton H7 as a doublet of doublet at δ 6.96 (J = 14.9 Hz, J = 4.4 Hz). The ^{1}H NMR spectrum of **23a** exhibited a doublet at δ 4.36 (J = 5.6 Hz) for the H4 proton of the 2-isoxazoline moiety. While the H5 proton resonated as triplet at δ 5.62 (J = 5.8 Hz). The H,H COSY spectrum of **23a** showed correlation between the olefinic proton H7 at δ 6.96 ppm with the proton at H5 δ 5.62 ppm, which in turn showed correlation with the proton H4 at δ 4.36 ppm, establishing the regioselectivity as well chemoselectivity. The correlation observed in the HMBC spectrum was in accordance with the assigned structure.

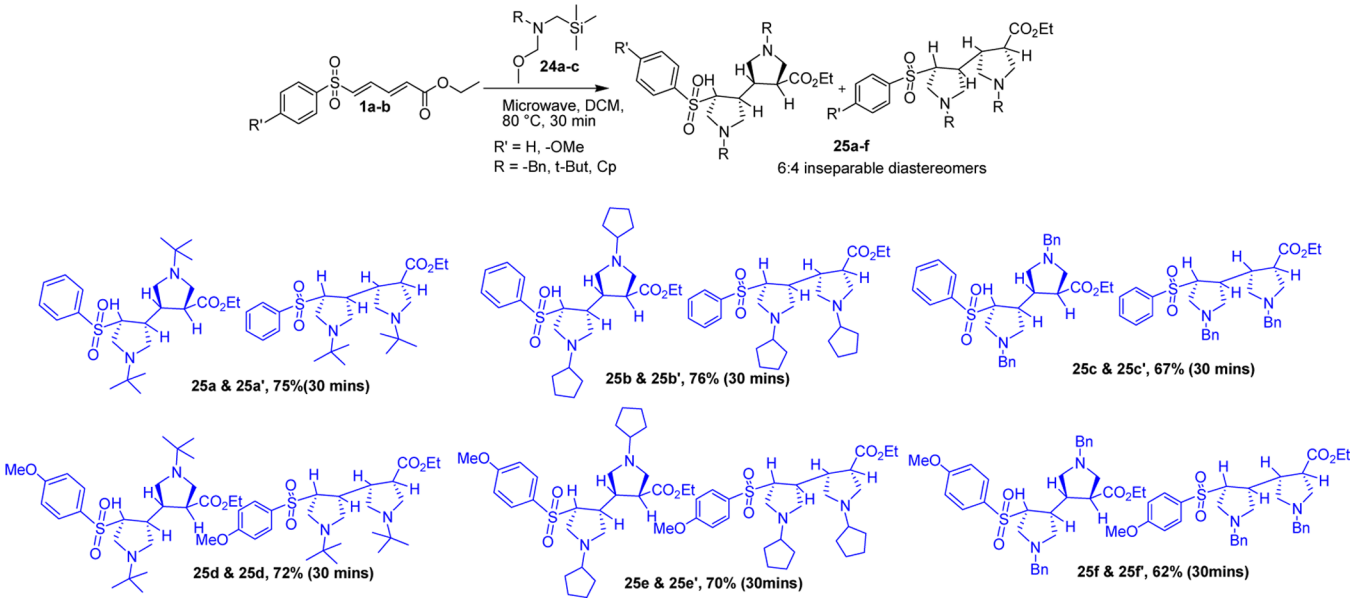
BIS-[3 + 2]-CYCLOADDITION

Next, we explored the feasibility of synthesis of bis-pyrrolidine by bis-[3 + 2]-cycloaddition of azomethine ylides **24a−c** to the dienes **1a,b**.

Literature survey[19,20] shows that [3 + 2]-cycloaddition of azomethine ylides with conjugated dienes leads to a mixture of mono- and bis-pyrrolidines. In the present work, bis[3 + 2]-cycloaddition reaction of azomethine ylides generated in situ by desilylation of synthons **24a−c** with 1-(arylsulfonyl)-4-ethoxycarbonyl 1,3-dienes **1a,b** under microwave condition was investigated. Initially, *N*-(methoxymethyl)-*N*-((trimethylsilyl)-methyl)benzylamine (**24c**) was selected as the dipole for the bis[3 + 2]-cycloaddition of diene**1a** as outlined in Scheme 7. All of the azomethine precursors **24a−c** were prepared by the known literature procedure[21] and were characterized thoroughly by spectral means. When **1a** reacted with **24a−c** in the absence of microwave irradiation, it led to a mixture of mono- and bisadduct only even under prolonged heating conditions (24 h) in various solvents. However, under microwave conditions, the bisadducts were obtained in good yield as a mixture of two inseparable diastereomers in all of the examples studied. In a typical experiment, microwave irradiation of a

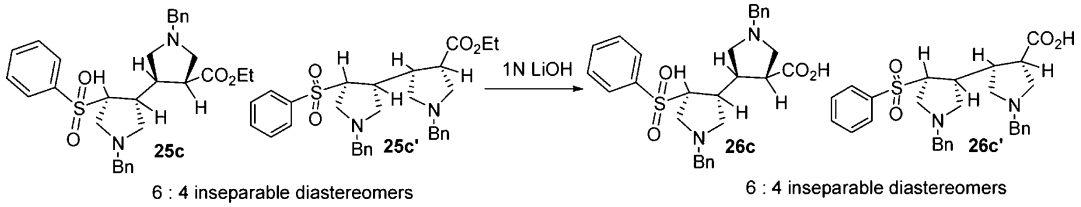
DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354

Scheme 7. Substrate Scope for Synthesis of Bis-pyrrolidines 25a–f[a–c] via [3 + 2]-Cycloaddition of Dienes 1 with *N*-(Methoxymethyl)-*N*-((trimethylsilyl)methyl)alkylamines 24a–c



[a]All reactions were carried out on **1a,b** (1 mmol), **24a–c** (3 mmol), and TFA (0.2 mmol) in DCM (5 mL), microwave at 80 °C for 30 min. [b]Isolated yield after flash column chromatography. [c]All of the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS).

Scheme 8



solution of TFA azomethine ylide precursor **24c** and the dipolarophile **1a** in dry dichloromethane in the presence of TFA at 80 °C in a microwave for 30 min led to clean reaction, affording the bis cycloadduct as an inseparable mixture of diastereomers **25c** and **25c′** in 67% yield. Under these conditions, the monoadduct was not observed. By adopting this method, a number of bis-pyrrolidine derivatives **25a–f** (Scheme 7) were synthesized in good yields. In all cases, the products appeared to be homogeneous on TLC, and the complexity could not be deciphered from ^{1}H and ^{13}C NMR spectra. HPLC analysis of the bisadducts from reaction of **24a,b** showed only a single peak in several solvent systems studied. However, in the case of the bis-adduct from the reaction of **24c**, HPLC showed two peaks with retention times of 21.927 and 22.069 min in the ratio of 6:4 (SI) and revealed it to be a mixture of two products. LC–MS revealed them to be isomeric, suggesting that they are diastereomers. When the monopyrrolidine adduct **15**, independently synthesized,[15] was reacted with another equivalent of the same azomethine ylide **24c** under microwave irradiation conditions, it afforded the same bisadduct **25c** as was obtained from the direct reaction. It was hoped that hydrolysis of the ester functionality in **25c** would furnish the diastereomeric acids which would show different TLC mobility and thus facilitate their separation by column chromatography. With this intention, hydrolysis of the bisadduct **25c** was carried out under mild basic conditions to ensure that in this process the stereocenters at the sulfonyl end and ester end would not undergo epimerization. Exposure of the mixture of diastereomeric esters **25c** and **25c′** to a 1 N solution of LiOH at rt for 16 h led to a smooth saponification and furnished a mixture of the diastereomeric acids **26c** and **26c′** as depicted in Scheme 8.

The diastereomeric ratio of the carboxylic acids **26c** and **26c′** was determined by reversed-phase HPLC analysis and found to be nearly the same (6:4) (SI) as that of the starting esters **25c** and **25c′**. Esterification of these diastereomeric mixtures of carboxylic acids **26c** and **26c′** with ethanol and oxalyl chloride furnished a product that exhibited the same diastereomeric ratio and retention time in HPLC as that of the original ester **25c** and **25c′** obtained in the direct bis-cycloaddition reaction, thus confirming that in the course of the basic hydrolysis the chiral centers were not epimerized and were intact. Since the [3 + 2]-cycloaddition is a concerted syn process, the stereochemistry at centers **2** and **5** as well as at **6** and **9** can be fixed as *trans*. Both cycloadditions can occur on the same phase of the 1,3-diene π framework or they can occur on the opposite phases of the 1,3-diene π framework. Thus, the two diastereomers should differ only in the configuration at the 3,4 carbons of one of the pyrrolidines rings as visualized in Figure 1.

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340–2354

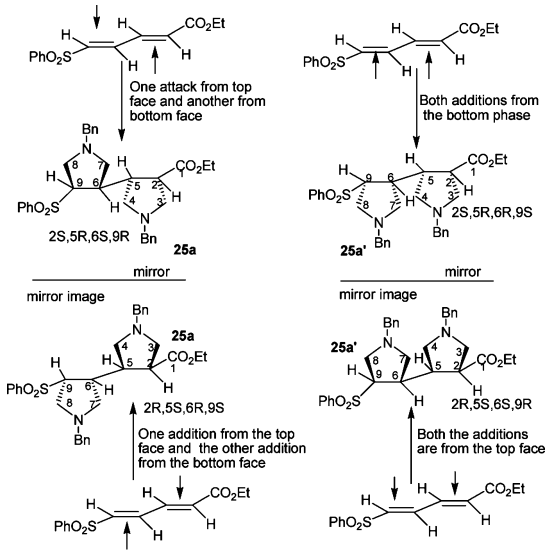


Figure 1. Mode of bis dipolar cycloaddition of dipole **24c** with diene **1**.

COMPUTATIONAL DETAILS

The geometries of reactants, products, and all transition states (TSs) were optimized using density functional theory (DFT) based Becke's three-parameter hybrid functional and Lee–Yang–Parr's[22] correlation functional (B3LYP) method employing the 6-31G(d)[23] basis set. All of these calculations were performed using the Gaussian 09 suite of programs.[24] All gas-phase-optimized geometries were verified as minima or first-order saddle points by the frequency calculations. As in the standard practice, the presence of one imaginary frequency criteria was used for the characterization of TSs. Further, the transition states were also verified by the intrinsic reaction coordinate (IRC) calculations.[25,26] The fragment distortion and interaction energies were computed at the M06-2X/6-311G-(d,p) level of theory by single-point energy calculations on B3LYP/6-31G(d)-optimized geometries.

The global reactivity indices were estimated using the standard working equations proposed by Parr and Yang.[27] The global hardness (η) and electronic chemical potentials (μ) were evaluated using the energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). The Hirschfeld charges were calculated using the B3LYP/dnd method implemented in the DMOL^3 program. These charges were used to calculate the local reactivity descriptors such as condensed Fukui functions of reactants.

The aim of the computational calculation performed is to understand the mechanism of cycloaddition reaction. The nature of the reactants and their feasibility to undergo reaction upon substitution on ylides with different groups was also investigated.

First of all, we examined the regioselectivity between **1** and the ylides. Overall reactivity and site selectivity of reactants and their individual atoms can be explained using global and local reactivity indices. The global nucleophilicity (N)[28] was calculated by using eq 1

$$N = E_{\mathrm{HOMO(nucleophile)}} - E_{\mathrm{HOMO(TCE)}} \quad (1)$$

where tetracyanoethelene (TCE) is taken as a reference as it has lowest HOMO energy and large electrophilicity value (ω = 5.90 eV).

The local reactivity indices, such as local electrophilicity (ω^+_k)[29] and the local nucleophilicity (N_k)[30] condensed to a particular atom k were calculated from nucleophilic and electrophilic Fukui functions[31] using eqs 2 and 3

$$\omega^+_k = \omega f^+_k \quad (2)$$

and

$$N_k = N f^-_k \quad (3)$$

where f^+_k and f^-_k are Fukui functions.

Reactants. The reactant (2*E*,4*E*)-ethyl 5-(phenylsulfonyl)-penta-2, 4-dienoate (**1**) is an acyclic conjugated diene. The double bond that is next to the ester group is denoted as C1–C2, and the double bond adjacent to phenyl sulfonyl group is referred to as C3–C4. Compound **1** prefers to exist in the *s-trans* conformation for steric reasons, but during the [2 + 3] cycloaddtion reaction it reacts with its counterparts in the *s-cis* conformation. The *s-cis* conformation is less stable than the *s-trans* conformation only by 3.31 kcal/mol due to the steric interaction between hydrogens of C1 and C4 atoms. We have carried out the calculations for the reaction of *s-trans* diene with all of the dipoles. However, we could locate the transition states only for the reaction outline in Scheme 1. For the [2 + 3] cycloaddition reaction outlined in Scheme 1, the calculated energy of activation in the case of reaction involving the diene **1** in *s-trans* confirmation is quite appreciably high when compared to that of *s-cis* diene ($\Delta G^{\ddagger}_{s\text{-}trans} - \Delta G^{\ddagger}_{s\text{-}cis} \sim 6.0$ kcal/mol). Under the reaction conditions (reflux in dioxane), **1** is easily converted from *s-trans* into the more reactive *s-cis* conformation and tries to achieve a flat planar structure before it reacts with the dienophile. The energy profile for *s-trans* to *s-cis* transformation is shown in Figure 2.

Global and Local Properties. In order to rationalize the chemoselectivity and regioselectivity, we calculated conceptual density functional theory based global and local reactive

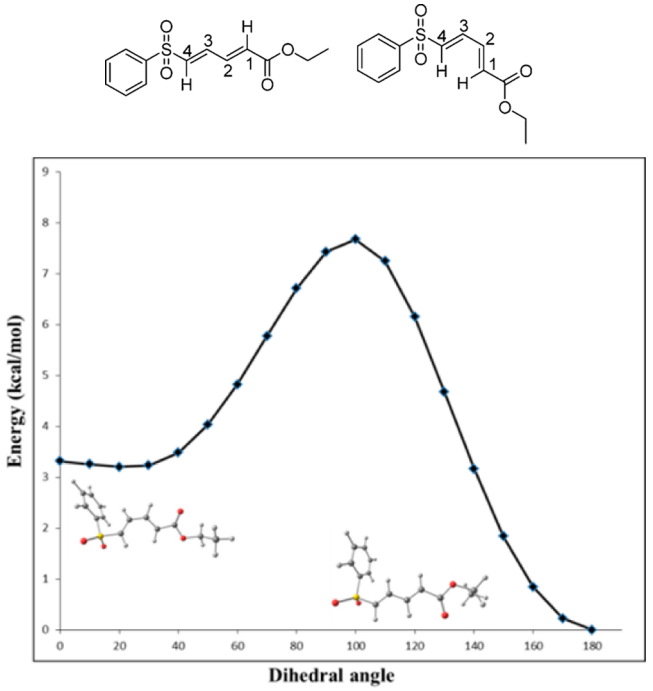


Figure 2. Structures of *s-cis*, *s-trans* conformations and *s-trans*, *s-cis* transformation of **1**.

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340–2354

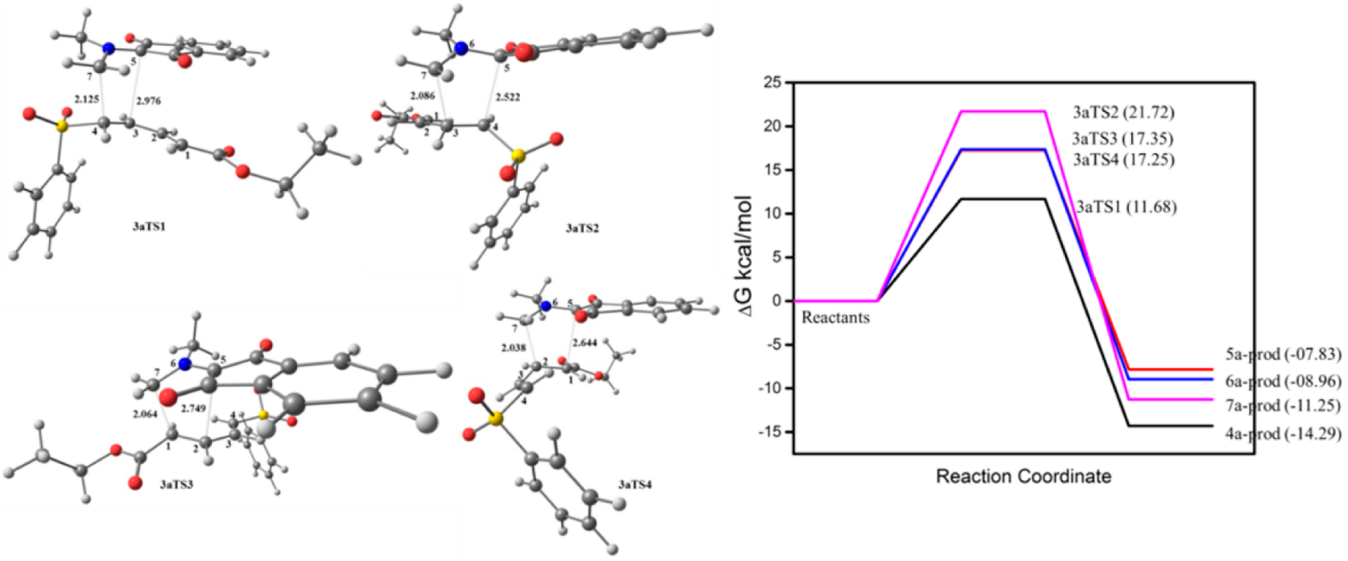


Figure 3. Optimized geometries of TSs and energy profile for the reaction of **1** with the ylide of **3a** (Scheme 1), computed using the B3LYP/6-31g(d) level (gray, carbon; white, hydrogen; yellow, sulfur; red, oxygen; and blue, nitrogen).

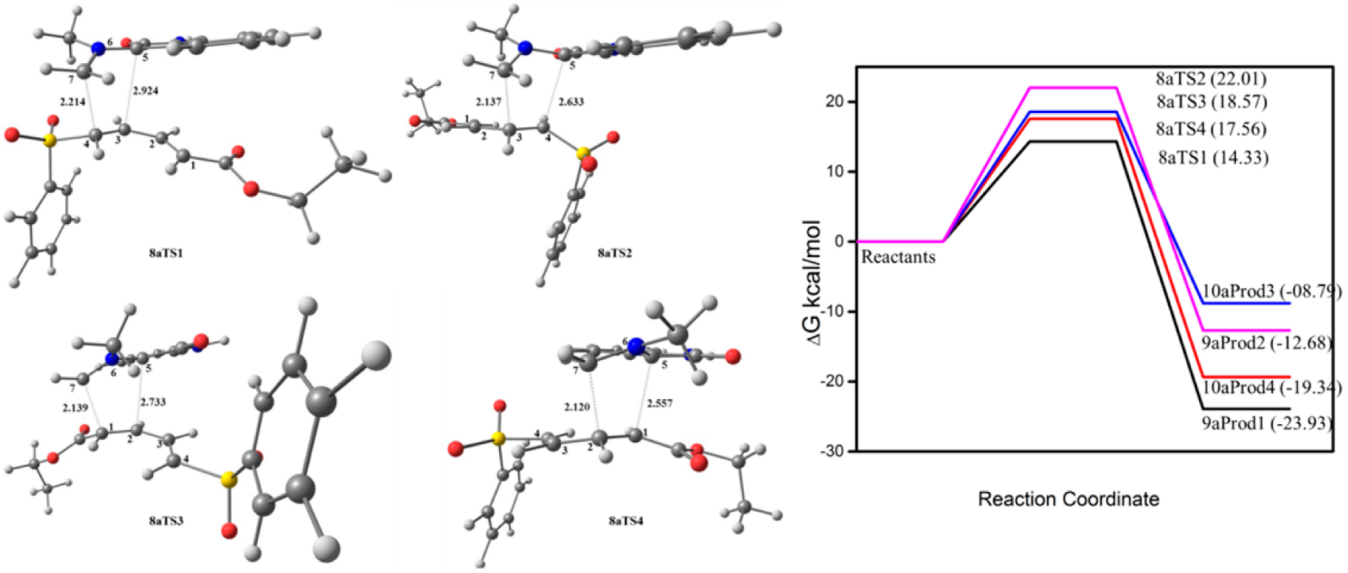


Figure 4. Optimized geometries of TSs and energy profile for the reaction of **1** with the ylide of **8a** (Scheme 2), computed using the B3LYP/6-31g(d) level (gray, carbon; white, hydrogen; yellow, sulfur; red, oxygen; and blue, nitrogen).

descriptors. The calculated reactivity descriptors are listed in the Supporting Information (Tables S1 and S2, respectively). The analysis of global reactive indices suggests that electronic chemical potential of dipoles (azomethine ylides, nitrones, and nitrile oxides) (−0.110 to −0.135 au) is higher than that of dipolarophile (**1**) (−0.173 au), indicating that the charge transfer will take place from the dipole toward dipolarophile. Compound **1** has strong electrophilic character with large global electrophilicity (ω) value of 2.35 eV. The chosen dipoles are nucleophilic in nature due to their low ω values (0.4−2.1 eV) and high global nucleophilicity values (N). The dipoles of **18** (**18a**−**e**) have large ω values compared to other dipoles. Thus, the dipoles of **18** may react slowly with **1**. It can be seen from the results for Schemes 1−5 that the nucleophilic nature of ylides increases gradually with substitution of alkyl groups on nitrogen, which is due to the electron-releasing nature of the alkyl group. On the other hand, for Scheme 6, the nucleophilic nature of dipole decreases due to the substitution of electronegative fluorine atom. On the whole, diene **1** will act as an electrophile and dipoles will act as nucleophiles.

The diene **1** has highest electrophilic activation (ω_k^+ = 0.25 eV) at C4 in contrast to the other three active carbons C1, C2, and C3. C1 has more nucleophilic character (N_k = 0.26 eV) when compared to C4 (N_k = 0.21 eV). In other words, even though the electrophilic nature of C1 is nearly as same as C4, nucleophilic character of C1 atom dominates its electrophilic character, making C4 atom, a preferable electrophilic site in diene **1** for nucleophilic attack. The electrophilicity at C4 can be attributed due to the presence of a strong electron-withdrawing phenylsulfonyl group. On the other hand at C1, the ester group which is also an electron-withdrawing but not as strong as phenylsulfonyl. It is clear from the results that C3−C4 is a more favorable double bond for 1,3-dipolar cycloaddition reaction than the C1−C2 double bond, and C4 becomes the

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354

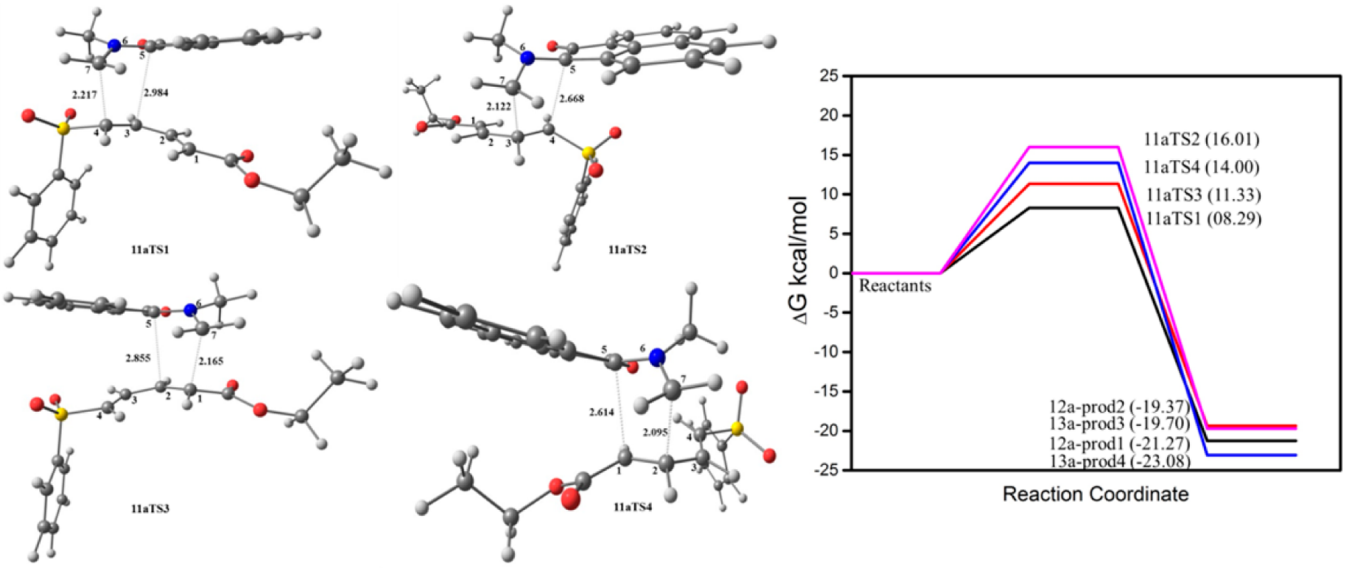


Figure 5. Optimized geometries of TSs and energy profile for the reaction of **1** with the ylide of **11a** (Scheme 3), computed using the B3LYP/6-31g(d) level (gray, carbon; white, hydrogen; yellow, sulfur; red, oxygen; and blue, nitrogen).

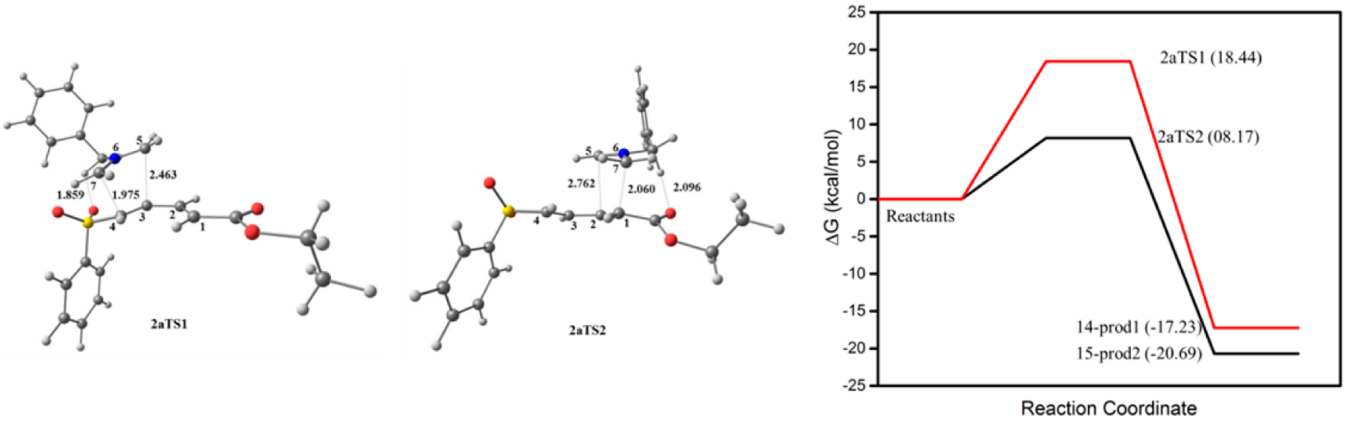


Figure 6. Optimized geometries of TSs and energy profile for the reaction of **1** with the ylide of **2a** (Scheme 4), computed using the B3LYP/6-31g(d) level (gray, carbon; white, hydrogen; yellow, sulfur; red, oxygen; and blue, nitrogen).

preferable electrophilic site for nucleophilic attack. The dipoles have the largest nucleophilic activation at C7 (O7 for nitrone and nitrile oxide). Thus, C7 and O7 are the nucleophilic sites in dipoles. These findings reveal that C4 of **1** is a preferred electrophilic site for nucleophilic attack (C7/O7) of dipoles, which confirms the regioselectivity of 1,3-dipolar cycloaddition reactions.

Geometries of TSs. The geometries of TSs and the respective energy profile for Schemes 1−6 are depicted in Figures 3−10, respectively. The TS structures are named according to their corresponding ylide/nitrone labeling (numbering). The careful examination of geometrical parameters of various TSs reveals that, for Scheme 1, the newly forming C−C bonds for TS1 are longer than the forming C−C bonds of TS2, TS3, and TS4. The longer forming C−C bonds of TS1 implying lesser steric repulsion between reacting groups. The geometrical parameters of this transition state (TS1) resemble reactants indicating an early-transition-state nature. On the other hand, the shorter forming C−C bonds of TS2, TS3, and TS4 reveal that there is a considerable increase in the steric repulsion between the reacting groups, which leads to the destabilization of the corresponding transition states. The reactivity trend similar to that of Scheme 1 is also observed in the case of Schemes 2 and 3. It is interesting to note different trends in the reactivity for Scheme 4. The newly forming C−C bonds in TS1 are shorter than that of the corresponding C−C bonds in TS2. In all of the transition states of all the schemes, the incoming bonds (C−C bonds in Schemes 1−5 and C−O and C−C bonds in Scheme 6) form with unequal bond lengths showing the asynchronous nature of transition states. The degree of synchronicity can be measured by the difference between the ratios of the forming bond lengths in the TS and the corresponding bond lengths in the product ($\Delta d_{TS/P}$).[32] The bond lengths of newly forming bonds and $\Delta d_{TS/P}$ values are listed in the SI (Table S3). For Schemes 1−6, $\Delta d_{TS/P}$ values indicate TSs are asynchronous in nature. However, $\Delta d_{TS/P}$ for TSs in Scheme 5 is higher (>0.70), which indicates that the reactions are strongly asynchronous.

Distortion/Interaction Analysis. The distortion/interaction transition-state model developed by Ess and Houk is a highly insightful method for understanding reactivity and activation barriers in cycloadditions.[33] The energy of activation ($\Delta E^{\ddagger}$) is divided into two major components called distortion energy ($\Delta E^{\ddagger}_{dist}$) and interaction energy ($\Delta E^{\ddagger}_{int}$). Distortion

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354

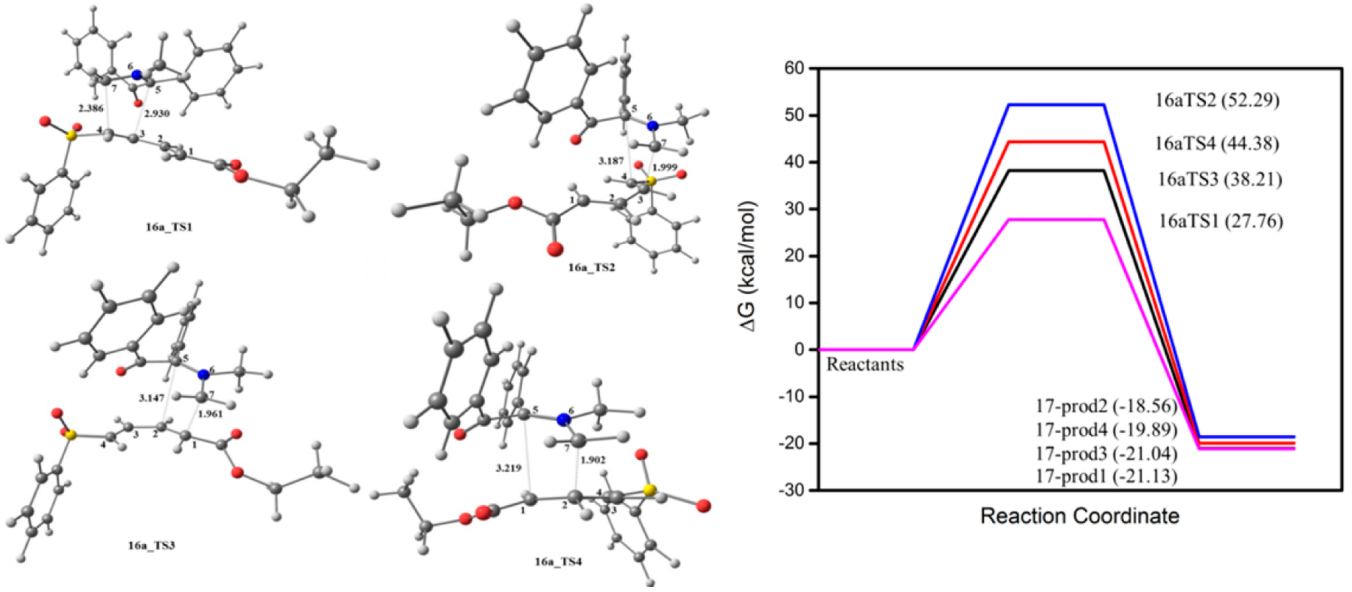


Figure 7. Optimized geometries of TSs and energy profile for the reaction of **1** with the ylide of **16a** (Scheme 5), computed using the B3LYP/6-31g(d) level (gray, carbon; white, hydrogen; yellow, sulfur; red, oxygen; and blue, nitrogen).

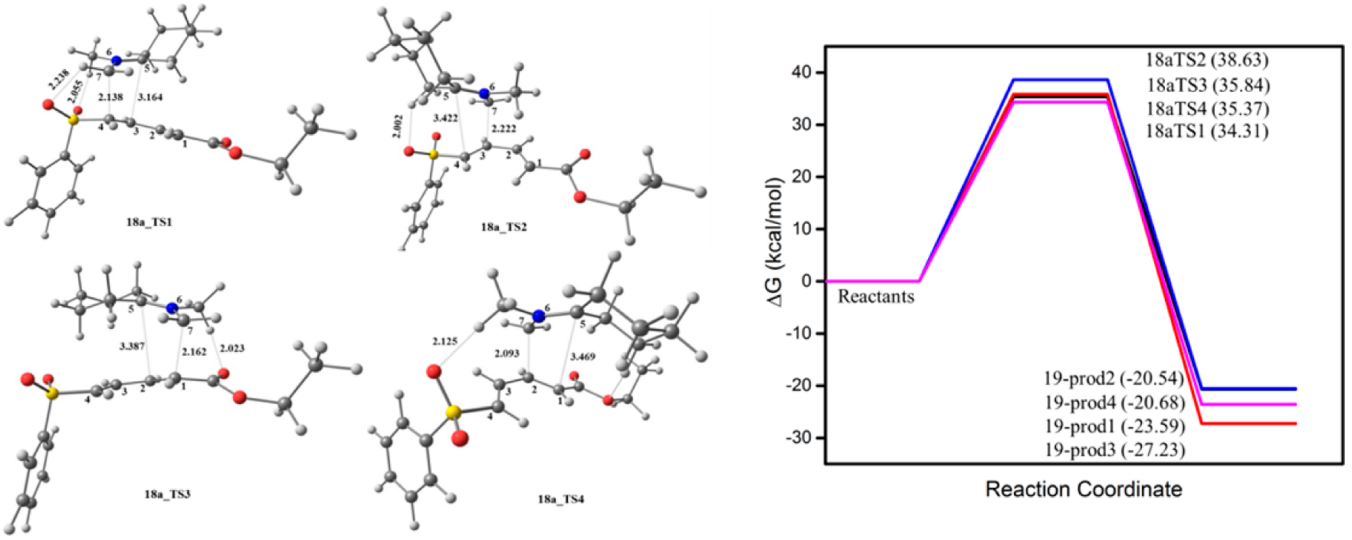


Figure 8. Optimized geometries of TSs and energy profile for the reaction of **1** with the ylide of **18a** (Scheme 5), computed using the B3LYP/6-31g(d) level (gray, carbon; white, hydrogen; yellow, sulfur; red, oxygen; and blue, nitrogen).

energy is calculated as the difference in energy of the reactants between distorted geometry and the fully optimized ground-state geometry. The interaction energy is the difference between the energy of the geometry on the reaction coordinate and the energy of the corresponding distorted diene and dienophile parts. The $\Delta E^{\ddagger}_{dist}$ is the energy utilized for distorting reactant geometry to form product. A higher value of $\Delta E^{\ddagger}_{dist}$ signifies requirement of considerable activation barrier.

The calculated distortion and interaction energies are tabulated in the SI (Tables S4 and S5). It is evident from the results that the TS which has low distortion energy and high interaction energy has low activation barrier. In the case of Schemes 1−3, TS1 and TS3 have low and comparable distortion energies. Thus, the reactivity is governed by interaction energy. $\Delta E^{\ddagger}_{int}$ is highest for TS1, which confirms the requirement of low activation barrier. For Scheme 4, TS2 has less distortion and more interaction energies and hence lowest activation barrier.

In the case of Scheme 5, the reaction is completely controlled by the distortion energy of reactants. It can be seen that there is no appreciable contribution from the $\Delta E^{\ddagger}_{int}$. Since $\Delta E^{\ddagger}_{dist}$ is high, the activation barriers are also high. On the other hand, for Scheme 6, in the case of nitrones, TS2 exhibits less activation energy, which is controlled by $\Delta E^{\ddagger}_{int}$ as the distortion energy is similar for all the TSs. As compared with nitrones in Scheme 6, nitrile oxide dipoles have high $\Delta E^{\ddagger}_{dist}$. This is may be due to the presence of triple bond in nitrile oxide which requires more energy for distortion. As a consequence, the activation barriers are high.

The distortion/interaction analysis also suggest the stereoselectivity of 1,3-dipolar cycloaddition reaction. For all of the schemes, exo TSs exhibit low $\Delta E^{\ddagger}_{dist}$, which is responsible for

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354

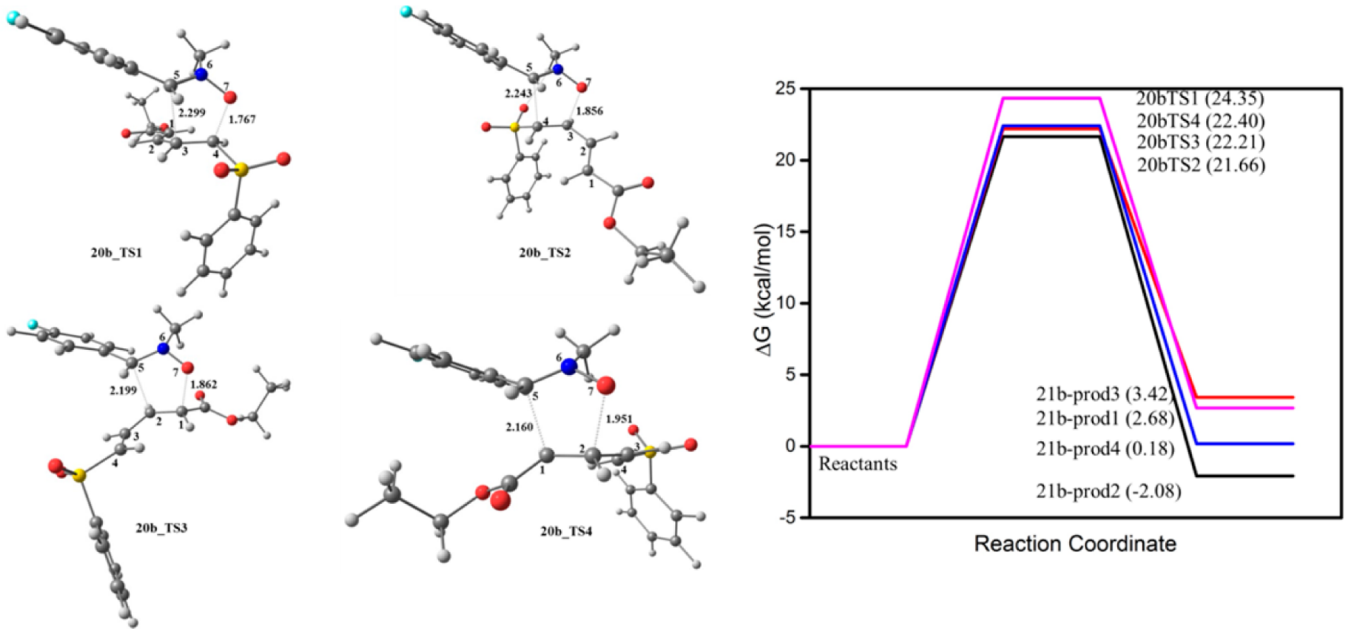


Figure 9. Optimized geometries of TSs and energy profile for the reaction of **1** with the ylide of **20a** (Scheme 6), computed using the B3LYP/6-31g(d) level (gray, carbon; white, hydrogen; yellow, sulfur; red, oxygen; and blue, nitrogen).

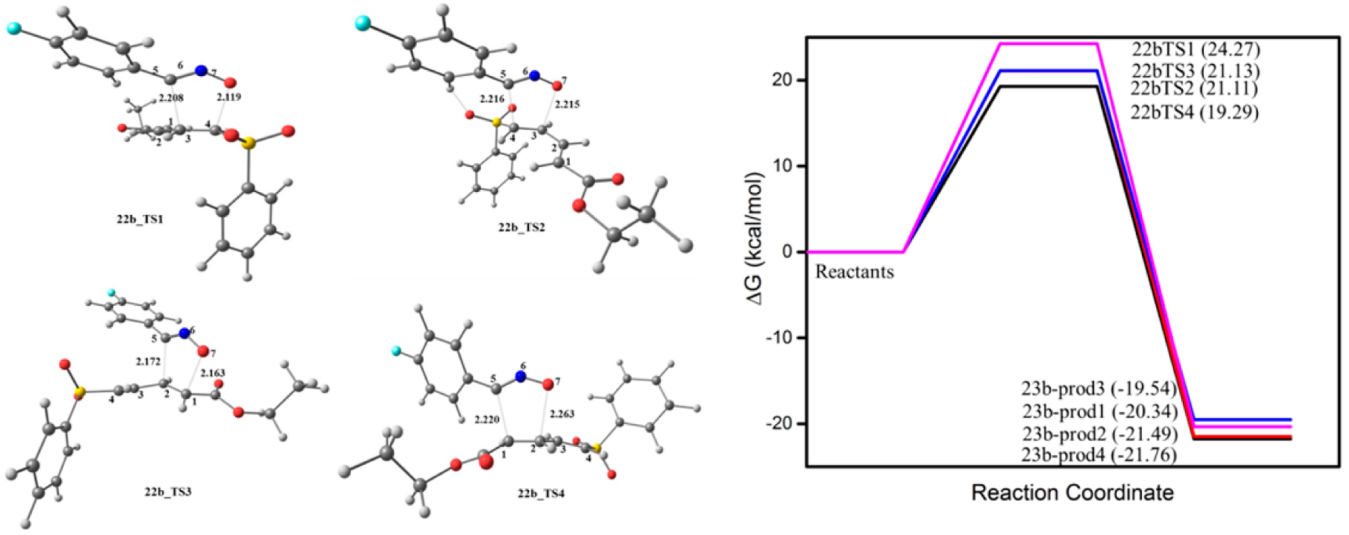


Figure 10. Optimized geometries of TSs and energy profile for the reaction of **1** with the ylide of **22a** (Scheme 6), computed using the B3LYP/6-31g(d) level (gray, carbon; white, hydrogen; yellow, sulfur; red, oxygen; and blue, nitrogen).

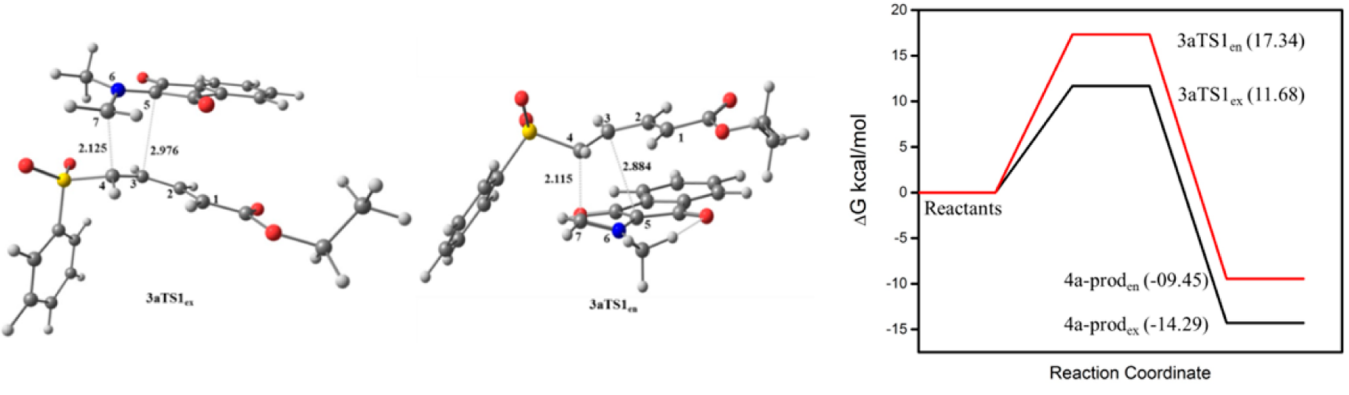


Figure 11. Optimized geometries and energy profile of exo and endo TSs for the reaction of **1** with the ylide of **3a** (Scheme 1).

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354

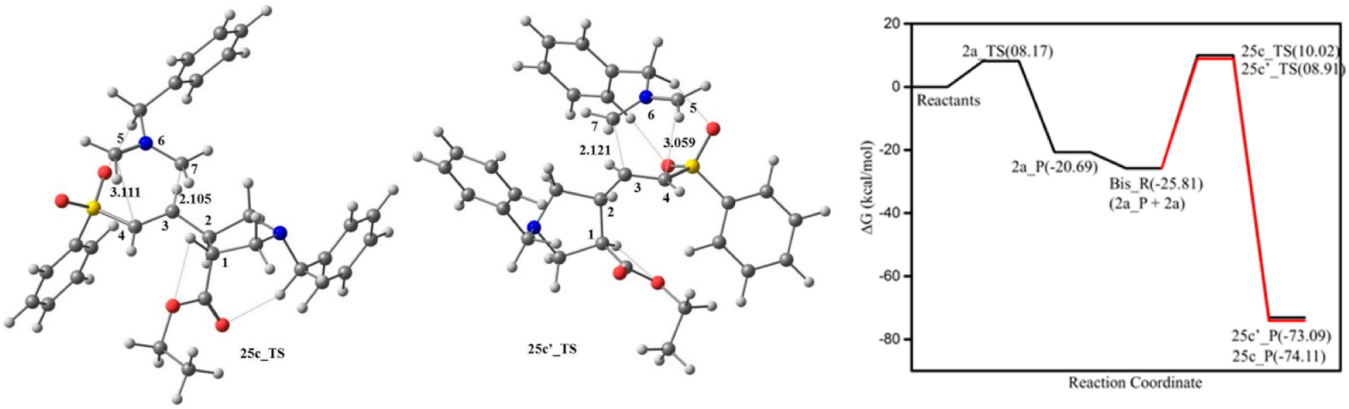


Figure 12. Optimized geometries and energy profile for TSs of the bis reaction (Scheme 7).

low activation barrier than endo TS. The $\Delta E^{\ddagger}_{int}$ values also suggest that the reaction pathway involving TS_{ex} is feasible.

Energies of TSs. The reaction energies and activation barriers associated with TSs of all schemes are compiled in the SI (Table S6). In the case of Schemes 1−3, the reaction pathway associated with TS1 is more favorable as the activation barriers are low. Accordingly, it can be predicted that the product associated with TS1 of these schemes will be dominating, in agreement with the experimental observations. In the case of Scheme 4, TS2 has the lowest activation barrier compared to TS1. Hence, the reaction at C1−C2 is favorable for Scheme 4. In the case of Scheme 5, the activation barriers are very high (30−50 kcal/mol). This may be due to the steric repulsions exerted by bulky groups. It requires more energy to cross the activation barrier. Thus, the reaction may not proceed further under normal reaction conditions. In the case of Scheme 6, for dipoles of nitrone **20b**, the activation barrier for TS2 is low, which means nitrone (**20b**) reacts with the C3−C4 double bond by bonding the most nucleophilic O7 with C3, whereas for nitrile oxide the reaction happens at C1−C2 double bond through TS4. In this case, most nucleophilic O7 bonded with C1.

The stereoselectivity of [3 + 2]-cycloaddition reactions can be explained by reaction energies of exo,endo isomers. The reaction involved TS_{ex} is the most favorable reaction pathway due to its low activation barrier and formation of stable product. The TSs of exo and endo pathways for [3 + 2]-cycloaddition reaction of **1** with dipole **3a** (Scheme 1), and their corresponding energy profiles are shown in Figure 11 (geometries and energy profiles of all other schemes are given in the SI as Figures S3−S12). The activation energies of endo and exo attacks for all the schemes are tabulated in the SI (Table S7).

Scheme 7 illustrates the addition of dipole at the free double bond to form a bisproduct. The two possible reaction path ways for bisaddition of dipole were investigated. The TSs and corresponding energy profiles for bis addition are shown in Figure 12. The reaction energies are given in the SI (Table S8). The TSs associated with the two pathways have high activation barriers (34−35 kcal/mol), which elucidate that the reaction may be possible on heating. The TSs and products of both pathways are separated by 1.0 kcal/mol each. Thus, the reaction is possible via both pathways, which may lead to the formation of racemic mixture of products (**25c** and **25c′**).

CONCLUSIONS

In conclusion, we have demonstrated that the chemoselectivity of the cycloaddition of azomethine ylides to (2*E*,4*E*)-ethyl 5-(phenylsulfonyl)penta-2,4-dienoate is dependent upon the nature of the dipole as well as by its steric bulk. While simple azomethine ylides underwent the [3 + 2]-cycloaddition preferentially at the acrylate double bond, sterically bulky azomethine ylides exhibited opposite chemoselectivity, reacting at the vinylsulfonyl double bond. In the case of nitrones, the cycloaddition occurred at the vinyl sulfonyl double bond, whereas in the case of nitrile oxides it took place at the acrylate double bond. The analysis of activation barriers, global and local reactive indices has been studied in order to rationalize the regioselectivity. The nucleophilic and electrophilic sites involved in the reaction, and the effect of substitution on ylides is explained using global and local reactive descriptors. The regioselectivity is also revealed by the reaction energies. Geometrical parameters and bond lengths of newly forming bonds indicate that the cycloaddition reactions follow a concerted mechanism with asynchronous transition states. The failure of the diene **1** to undergo the [2 + 3]-cycloaddtion with the 1,3-dipoles generated from benzil **16**/cyclohexanone **18** and *N*-alkylglycines **2a−e**, outlined in Scheme 5, is also explained by the high activation barriers of the transition states.

EXPERIMENTAL SECTION

General Considerations. All reactions were carried out under an atmosphere of dry nitrogen. All reagents were purchased from commercial sources and used without further purification. Solvents were distilled prior to use. Column chromatography was performed on flash silica gel (230−400 mesh).^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) were recorded using $CDCl_3$ or DMSO as solvent and TMS as an internal standard (chemical shifts in δ, ppm). High-resolution mass spectrometry (HRMS) data were obtained using electron ionization (EI), and a quadruple double focusing mass analyzer was used. Melting points were determined on a melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using commercially available silica gel coated aluminum plates and visualized using iodine vapor and a shortwave UV lamp. All microwave reactions were performed on a Biotage Initiator+ microwave reactor operating at high-frequency microwave 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 300 W maximum power.

General Procedure for Synthesis of Spiropyrrolidines 4a−e, 9a−e, and 12a−e. A mixture of (2*E*,4*E*)-ethyl 5-(phenylsulfonyl)-penta-2,4-dienoate **1** (1 mmol), ninhydrin **3**, or isatin **8**, or acenaphthenequinone **11** (1 mmol) and sarcosine, ethylglycine, benzylglycine, phenylglycine, or tritylglycine **2a−e** (1 mmol) was

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354

refluxed in 1,4-dioxane (10 mL) for 10−48 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure. Purification of the residue on a silica gel (230−400 mesh) column chromatograph using 30−40% of ethyl acetate in petroleum ether as eluent furnished analytically pure (*E*)-ethyl 3-(1′-alkyl-1,3-dioxo-4′-(phenylsulfonyl)-1,3-dihydrospiro[indene-2,2′-pyrrolidin]-3′-yl)acrylate (**4a**−**e**), (*E*)-ethyl 3-(1′-alkyl-2-oxo-4′-(phenylsulfonyl)spiro[indoline-3,2′-pyrrolidin]-3′-yl)acrylate (**9a**−**e**), and (*E*)-ethyl 3-(1′-alkyl-2-oxo-4′-(phenylsulfonyl)-2*H*-spiro[acenaphthylene-1,2′-pyrrolidin]-3′-yl)acrylate (**12a**−**e**).

*(E)-Ethyl 3-(1′-methyl-1,3-dioxo-4′-(phenylsulfonyl)-1,3-dihydrospiro[indene-2,2′-pyrrolidin]-3′-yl)acrylate (**4a**):* colorless solid (377 mg, 82%); mp 158.1−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.86 (m, 6H), 7.60−7.53 (m, 3H), 6.20 (dd, *J* = 15.5,5.7 Hz, 1H), 5.50 (d, *J* = 15.5 Hz, 1H), 4.18 (m, 1H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.80 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.70 (t, *J* = 9.5 Hz, 1H), 3.51 (t, *J* = 10.0 Hz 1H), 2.20 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 198.3, 164.4, 141.6, 140.5, 139.4, 137.9, 136.9, 136.8, 134.1, 129.4, 128.7, 126.1, 123.5, 122.9, 76.7, 65.6, 60.3, 54.0, 49.8, 35.9, 14.0 ppm; HRMS(EI) *m*/*z* calcd for $C_{24}H_{23}NO_6S$ (M)$^+$ 453.1246, found 453.1245.

*(E)-Ethyl 3-(1′-ethyl-1,3-dioxo-4′-(phenylsulfonyl)-1,3-dihydrospiro[indene-2,2′-pyrrolidin]-3′-yl)acrylate (**4b**):* pale yellow solid (393 mg, 83%); mp 148.8−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.79 (m, 6H), 7.53−7.45 (m, 3H) 6.07 (dd, *J* = 15.5, 5.7 Hz, 1H), 5.41 (d, *J* = 15.5 Hz, 1H), δ 4.16 (m, 1H), 3.86 (q, *J* = 7.0 Hz, 2H), 3.80 (dd, *J* = 5.0, 5.3 Hz, 1H), 3.59 (t, *J* = 9.6 Hz, 1H), 3.41 (t, *J* = 10.0 Hz, 1H), 2.32 (m, 2H), 1.04 (t, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 198.7, 164.3, 141.6, 140.3, 139.2, 137.8, 136.8, 136.7, 134.0, 129.3, 128.7, 126.2, 123.3, 122.8, 65.3, 60.2, 51.2, 50.0, 44.4, 14.4, 13.9; HRMS(EI) *m*/*z* calcd for $C_{25}H_{25}NO_6S$ (M)$^+$ 467.1402, found 467.1401.

*(E)-Ethyl 3-(1′-benzyl-1,3-dioxo-4′-(phenylsulfonyl)-1,3-dihydrospiro[indene-2,2′-pyrrolidin]-3′-yl)acrylate (**4c**):* pale yellow solid (419 mg, 78%); mp 179.5−179.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.79 (m, 6H), 7.60 (m, 1H), 7.53 (m, 2H), 7.14 (m, 3H), 7.06 (m, 2H), 6.21 (dd, *J* = 15.5, 5.8 Hz, 1H), 5.54 (d, *J* = 15.5 Hz, 1H), 4.23 (m, 1H), 3.94 (q, *J* = 7.1 Hz, 2H), 3.67 (m, 2H), 3.49 (m, 3H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 196.6, 162.8, 140.1, 138.6, 137.7, 135.9, 135.1, 135.06, 134.8, 132.5, 127.7, 127.3, 127.1, 126.6, 126.0, 124.7, 121.6, 121.3, 63.9, 58.7, 52.7, 50.4, 48.4, 12.4; HRMS(EI) *m*/*z* calcd for $C_{30}H_{27}NO_6S$(M)$^+$ 529.1559, found 529.1558.

*(E)-Ethyl 3-(1′-methyl-2-oxo-4′-(phenylsulfonyl)spiro[indoline-3,2′-pyrrolidin]-3′-yl)acrylate (**9a**):* colorless solid (357 mg, 80%); mp 177.4−178.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.76 (m, 1H), 7.64−7.52 (m, 3H), 7.29 (m, 2H), 7.09 (m, 1H), 6.78 (d,*J* = 7.5 Hz, 1H), 6.41 (dd, *J* = 15.6, 6.9 Hz, 1H), 5.38 (d, *J* = 15.6 Hz, 1H), 4.25 (m, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 3.73 (m, 1H), 3.58 (m, 2H), 2.1 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 165.0, 141.2, 140.5, 138.2, 133.9, 130.0, 129.3, 128.6, 125.8, 125.6, 124.4, 123.4, 109.9, 64.7, 60.3, 52.5, 51.6, 34.9, 14.0; HRMS(EI) *m*/*z* calcd for $C_{23}H_{24}N_2O_5S$ (M)$^+$ 440.1405, found 440.1404.

*(E)-Ethyl 3-(1′-ethyl-2-oxo-4′-(phenylsulfonyl)spiro[indoline-3,2′-pyrrolidin]-3′-yl)acrylate (**9b**):* colorless solid (378 mg, 82%); mp 141.7−142.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 2.8 Hz, 2H), 7.60−7.52 (m, 3H), 7.52 (b, 1H), 7.20−7.26 (m, 2H), 7.07 (m, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.33 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.32 (d, *J* = 15.6 Hz, 1H), 4.22 (m, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.85 (m, 1H), 3.51 (m, 2H), 2.29 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H), δ 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 164.9, 141.1, 140.2, 138.1, 133.9, 129.8, 129.3, 128.7, 126.4, 125.6, 124.3, 123.4, 109.8, 64.4, 60.3, 51.8, 49.7, 43.2, 14.0, 13.7; HRMS(EI) *m*/*z* calcd for $C_{24}H_{26}N_2O_5S$ (M)$^+$ 454.1562, found 454.1560.

*(E)-Ethyl 3-(1′-benzyl-2-oxo-4′-(phenylsulfonyl)spiro[indoline-3,2′-pyrrolidin]-3′-yl)acrylate (**9c**):* colorless solid (393 mg, 75%); mp 206.6−207.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H, −NH), 7.85 (d, *J* = 7.9 Hz, 2H), 7.62 (m, 1H), 7.52 (m, 2H), 7.30−7.07 (m, 8H), 6.80 (d, 1H, *J* = 7.7 Hz), 6.47 (dd, *J* = 15.6, 6.7 Hz, 1H), 5.45 (d, *J* = 15.6 Hz, 1H), 4.31 (m, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.57 (m, 3H), 3.47 (d, *J* = 13.2 Hz, 1H), 3.31 (d, *J* = 13.1 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 165.0, 141.5, 140.4, 137.6, 137.5, 133.9, 130.1, 129.3, 128.9, 128.3, 128.0, 127.2, 126.1, 125.7, 124.2, 123.6, 110.2, 64.7, 60.4, 52.8, 51.8, 50.0, 14.1; HRMS(EI) *m*/*z* calcd for $C_{29}H_{28}N_2O_5S$ (M)$^+$ 516.1718, found 516.1715.

*((E)-Ethyl 3-(1′-methyl-2-oxo-4′-(phenylsulfonyl)-2H-spiro-[acenaphthylene-1,2′-pyrrolidin]-3′-yl)acrylate (**12a**):* yellow solid (376 mg, 78%); mp 133.1−134.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d,*J* = 8.0 Hz, 1H), 7.96 (d, *J* = 6.8 Hz, 2H),7.90 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 6.8 Hz, 1H), 7.73−7.2 (m, 6H), 6.19 (dd, *J* = 15.6,6.4 Hz, 1H), 5.24 (d, *J* = 15.6 Hz, 1H), 4.37 (m, 1H), 3.89−3.67 (m, 5H), 2.00 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 164.8, 143.1, 140.7, 138.4, 136.2, 134.1, 132.4, 131.6, 130.6, 129.5, 129.0, 128.8, 128.4, 125.9, 125.3, 120.9, 120.9, 80.1, 65.3, 60.2, 53.3, 52.2, 35.1, 14.1; HRMS(EI) *m*/*z* calcd for $C_{27}H_{25}NO_5S$ (M)$^+$ 475.1453, found 475.1450.

*((E)-Ethyl 3-(1′-ethyl-2-oxo-4′-(phenylsulfonyl)-2H-spiro-[acenaphthylene-1,2′-pyrrolidin]-3′-yl)acrylate (**12b**):* yellow solid (347 mg, 70%); mp 155.9−156.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 5.6 Hz, 2H),7.88 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 6.4 Hz, 1H), 7.71−7.26 (m, 6H), 6.16 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.16 (d, *J* = 15.6 Hz, 1H), 4.41 (m, 1H), 3.95 (d, *J* = 10.6 Hz, 1H), 3.84 (q, *J* = 7.2 Hz, 2H), 3.72 (m, 1H), 3.63 (t, *J* = 10.4 Hz, 1H), 2.21 (m, 1H), 2.10 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 164.6, 142.8, 140.3, 138.1, 136.5, 133.9, 132.2, 131.3, 130.3, 129.3, 129.2, 128.9, 128.8, 128.3, 125.6, 125.7, 120.8, 120.6, 80.0, 64.9, 60.1, 52.2, 50.3, 43.0, 14.0, 13.9; HRMS(EI) *m*/*z* calcd for $C_{28}H_{27}NO_5S$ (M)$^+$ 489.1609, found 489.1605.

*((E)-Ethyl 3-(1′-benzyl-2-oxo-4′-(phenylsulfonyl)-2H-spiro-[acenaphthylene-1,2′-pyrrolidin]-3′-yl)acrylate (**12c**):* yellow solid (420 mg, 75%); mp 207.3−207.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 1H), 7.88 (m, 4H), 7.74−7.52 (m, 6H), 7.23 (m, 3H), 7.13 (d, *J* = 6.6 Hz, 2H), 6.27 (dd, *J* = 15.6, 6.5 Hz, 1H), 5.28 (d, *J* = 15.6 Hz, 1H), 4.23 (m, 1H), 3.90 (q, *J* = 7.1 Hz, 2H), 3.82 (m, 1H), 3.68 (m, 2H), 3.29 (d, 1H), 3.23 (d, 1H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 164.7, 143.04, 140.3, 137.7, 136.3, 133.9, 132.3, 131.3, 130.4, 129.3, 129.0, 128.9, 128.4, 128.3, 128.2, 127.8, 127.8, 127.2, 125.8, 125.3, 121.1, 120.6, 79.8, 65.2, 60.2, 52.7, 52.2, 50.7, 14.0; HRMS(EI) *m*/*z* calcd for$C_{33}H_{29}NO_5S$ (M)$^+$ 551.1766, found 551.1765.

Synthesis of 1,3,4-Trisubstituted Pyrrolidine 15. A mixture of (2*E*,4*E*)-ethyl 5-(phenylsulfonyl)penta-2,4-dienoate **1** (1 mmol), paraformaldehyde (2 mmol), and benzylglycine **2c** (1 mmol) was refluxed in 1,4-dioxane (10 mL) for 10 h. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was evaporated under reduced pressure. Purification of the residue on a silica gel (230−400 mesh) column chromatograph using 30−40% of ethyl acetate in petroleum ether as eluent furnished analytically pure (*E*)-ethyl 1-benzyl-4-(2-(phenylsulfonyl)vinyl)pyrrolidine-3-carboxylate **15**.

*(E)-Ethyl 1-benzyl-4-(2-(phenylsulfonyl)vinyl)pyrrolidine-3-carboxylate (**15**):* colorless syrup (271 mg, 67%); ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.86 (m, 2H), 7.62−7.51 (m, 3H), 7.31−7.24 (m, 5H), 7.01 (dd,*J* = 15.2, 8.2 Hz,1H), 6.39 (d, *J* = 15.2 Hz, 1H), 4.11 (q,*J* = 7.2 Hz, 2H), 3.61 (s, 2H), 3.27 (m, 1H), 2.84 (m, 4H), 2.50 (m, 1H), 1.18 (t, *J* = 7.2 Hz,3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 147.0, 140.3, 138.1, 133.2, 130.7, 129.3, 128.7, 128.4, 127.1, 126.9, 60.9, 59.3, 58.2, 56.1, 48.3, 42.9, 14.1; HRMS(EI) *m*/*z* calcd for $C_{22}H_{25}NO_4S$ (M)$^+$ 399.1504, found 399.1503.

General Procedure for Isoxazolidines 21a,b. A mixture of (2*E*,4*E*)-ethyl 5-(phenylsulfonyl)penta-2,4-dienoate **1** (1 mmol) and nitrones **20a,b** (1 mmol) was heated at 70 °C in 1,4-dioxane (10 mL) for 10 h. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was evaporated under reduced pressure. Purification of the residue on a silica gel (230−400 mesh) column chromatograph using 40−50% of ethyl acetate in petroleum

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354

ether as eluent furnished analytically pure (*E*)-ethyl 3-(2-methyl-3-phenyl-5-(phenylsulfonyl)isoxazolidin-4-yl)acrylate **21a** and (*E*)-ethyl 3-(3-(4-fluorophenyl)-2-methyl-5-(phenylsulfonyl)isoxazolidin-4-yl)-acrylate **21b**.

*(E)-Ethyl 3-(2-methyl-3-phenyl-5-(phenylsulfonyl)isoxazolidin-4-yl)acrylate (**21a**):* pale yellow solid (228 mg, 56%); mp 132.5−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.56 (m,1H), 7.43 (m, 2H), 7.21 (m, 3H), 7.08 (m, 2H), 6.93 (dd, J = 15.6, 5.6 Hz, 1H), 5.99 (d, J = 15.6 Hz, 1H), 5.18 (t, J = 4.0 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.91 (m,2H), 2.56 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 145.0, 137.8, 135.8, 134.3, 129.5, 128.8, 128.6,128.5, 128.0, 122.5, 80.0, 75.9, 74.3, 60.8, 42.6, 14.3; HRMS(EI) m/z calcd for $C_{21}H_{23}NO_5S$ $(M)^+$ 401.1296, found 401.1308.

*(E)-Ethyl 3-(3-(4-fluorophenyl)-2-methyl-5-(phenylsulfonyl)-isoxazolidin-4-yl)acrylate (**21b**):* pale yellow solid (276 mg, 65%); mp 110−111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 7.5 Hz, 2H), 7.58 (t, J = 7.5 Hz,1H), 7.44 (t, J = 7.5 Hz, 2H), 7.10 (m, 2H), 6.86 (m, 3H), 5.96 (d, J = 15.5 Hz, 1H), 5.17 (t, J = 5.5 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 3.95 (b, 1H), 3.86 (dd,J = 4.5, 5.0 Hz, 1H), 2.59 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 163.8, 161.8, 144.7, 137.7, 134.5, 131.3, 129.8, 129.8, 129.6, 128.5, 122.7, 115.9, 115.7, 79.7, 76.1, 73.5, 60.8, 42.5, 14.3; HRMS(EI) m/z calcd for $C_{21}H_{22}FNO_5S$ $(M)^+$ 419.1202, found 419.1201.

General Procedure for Isoxazolidines 23a,b. A mixture of (2*E*,4*E*)-ethyl 5-(phenylsulfonyl)penta-2,4-dienoate **1** (1 mmol), Oxime **22a,b** (1 mmol), NCS (1.1 mmol), and $KHCO_3$ (1.5 mmol) was stirred in DCM (10 mL) at rt for 16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, water was added, and the reaction mixture was extracted with DCM (3 × 15 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Purification of the residue on a silica gel (230−400 mesh) column chromatograph using 40−50% of ethyl acetate in petroleum ether as eluent furnished analytically pure ((*E*)-ethyl 3-(3-phenyl-5-(phenylsulfonyl)-4,5-dihydroisoxazol-4-yl)-acrylate **23a** and (*E*)-ethyl 3-(3-(4-fluorophenyl)-5-(phenylsulfonyl)-4,5-dihydroisoxazol-4-yl)acrylate **23b**.

*(E)-Ethyl 3-(3-phenyl-5-(phenylsulfonyl)-4,5-dihydroisoxazol-4-yl)acrylate (**23a**):* colorless solid (234 mg, 60%); mp 144.5−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 2.40 Hz, 2H), 7.71 (m, 3H), 7.59 (m, 2H), 7.44 (m, 3H), 7.00 (dd, J = 14.8, 4.0 Hz, 1H), 6.79 (d, J = 14.8 Hz, 1H), 5.63 (t, J = 4.4 Hz, 1H), 4.36 (d,J = 6.0 Hz, 1H), 4.21 (q, J = 6.9 Hz, 2H), 1.20 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 153.9, 140.2, 139.4, 133.8, 133.0, 130.8, 129.4, 128.7, 127.9, 127.5, 127.2, 82.1, 62.6, 58.6, 13.8; HRMS(EI) m/z calcd for $C_{20}H_{19}NO_5S$ $(M)^+$ 385.0983, found 385.0982.

*(E)-Ethyl 3-(3-(4-fluorophenyl)-5-(phenylsulfonyl)-4,5-dihydroi-soxazol-4-yl)acrylate (**23b**):* colorless solid (257 mg, 63%); mp 133−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (m, 2H), 7.69 (m, 3H), 7.57 (m, 2H), 7.12 (m, 2H), 6.97 (dd, J = 14.7, 4.2 Hz, 1H), 6.77 (d, J = 14.7 Hz, 1H), 5.63 (t, J = 4.5 Hz, 1H), 4.35 (d, J = 5.4 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 165.7, 162.4, 152.8, 140.0, 139.4, 133.8, 133.0, 129.4, 129.3, 127.8, 123.8, 123.8, 116.1, 115.8, 82.1, 62.6, 58.5, 13.8; HRMS(EI) m/z calcd for $C_{20}H_{18}FNO_5S$ $(M)^+$ 403.0889, found 403.0888.

General Procedure for the Synthesis of *N*-(Methoxymethyl)-*N*-((trimethylsilyl)methyl)alkylamines 24a−c. (Chloromethyl)-trimethylsilylamine (5 mmol) was added to a solution of benzylamine, cyclopentylamine, *tert*-butylamine (10 mmol) in acetonitrile (150 mL), and the reaction mixture was refluxed for 16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, acetonitrile was removed under reduced pressure, water was added, and the reaction mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to furnish analytically pure product *N*-((trimethylsilyl)methyl)phenylmethanamine, *N*-((trimethylsilyl)-methyl)cyclopentanamine, or *N*-((trimethylsilyl)methyl)-phenylmethanamine, which was used as such for the next step without any purification.To a stirred solution of methanol (12 mmol) and 37% aqueous formaldehyde (12 mmol) at 0 °C was added 2-methyl-*N*-((trimethylsilyl)methyl)propan-2-amine, *N*-((trimethylsilyl)methyl)-cyclopentanamine, or *N*-((trimethylsilyl)methyl)phenylmethanamine (10 mmol) dropwise over a period of 10 min. The resulting mixture was stirred for 2 h, anhydrous K_2CO_3 (2.5 mmol) was added, and the mixture was stirred at 0 °C for 30 min. After completion of the reaction as monitored by TLC, water was added, and the reaction mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to furnished crude product. The pure compound was isolated by fractional distillation to obtain *N*-(methoxymethyl)-*N*-((trimethylsilyl)methyl)-*tert*-butylamine, *N*-(methoxymethyl)-*N*-((trimethylsilyl)methyl)cyclopentanamine, or *N*-(methoxymethyl)-*N*-((trimethylsilyl)methyl)benzylamine **24a−c**. All of the compounds are liquid.

*N-(Methoxymethyl)-N-((trimethylsilyl)methyl)-tert-butylamine (**24a**):* colorless oil (87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (s, 2H), 3.16 (s, 3H), 1.97 (s, 2H), 1.05 (s, 9H), 0.04 (s, 9H).

*N-(Methoxymethyl)-N-((trimethylsilyl)methyl)cyclopentanamine (**24b**):* pale yellow oil (78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (s, 2H), 3.21 (s, 3H), 3.15 (m, 1H), 2.22 (s, 2H), 1.32−1.83 (m, 8H), 0.04 (s, 9H).

*N-(Methoxymethyl)-N-((trimethylsilyl)methyl) benzylamine (**24c**):* pale yellow oil (90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14−7.06 (m, 5H), 4.44 (s, 2H), 3.62 (s, 3H), 3.24 (s, 2H), 1.69 (s, 2H), 0.04 (s, 9H).

General Procedure for the Synthesis of 3,3′-Bis-pyrrolidines 25a−f. TFA (0.1 mmol) was added to a solution of diene **1a** or **1b** (1 mmol) and **24a**, **24b**, or **24c** (3 mmol) in DCM (5 mL). The reaction mixture was stirred at 80 °C in the microwave for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction, water (30 mL) was added to the mixture and then extracted with DCM (2 × 30 mL), the combined organic layer was washed with 10% $NaHCO_3$ (30 mL), water (30 mL), and saturated brine (30 mL), and organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Purification of the residue on a silica gel (230−400 mesh) column chromatograph using 30−60% of ethyl acetate in petroleum ether as eluent furnished an analytically pure inseparable mixture of diastereomers **25a−f** (6:4).

*Ethyl 1-tert-butyl-4-(1-tert-butyl-4-(phenylsulfonyl)pyrrolidin-3-yl)pyrrolidine-3-carboxylate (**25a** and **25a′**):* colorless syrup (350 mg, 75%); ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.91 (m, 2H), 7.65−7.53 (m, 3H), 4.14 (q, J = 7.1 Hz, 2H), 3.82 (m, 1H), 2.42−2.92 (m, 11H), 1.25 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H), δ 0.93 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 174.8, 138.6, 138.5, 133.4, 133.4, 128.9,128.8, 128.7, 66.0, 65.9, 60.6, 60.5, 55.2, 53.7, 52.0, 51.9, 51.7, 50.3, 50.2, 50.0,49.7, 49.5, 49.3, 47.3, 47.1, 46.2, 45.9, 44.2, 44.0, 43.7, 42.6, 42.3, 28.2, 26.9, 25.9, 15.4; HRMS(EI) m/z calcd for $C_{25}H_{40}N_2O_4S$ $(M)^+$ 464.2708, found 464.2705.

*Ethyl 1-cyclopentyl-4-(1-cyclopentyl-4-(phenylsulfonyl)-pyrrolidin-3-yl)pyrrolidine-3-carboxylate (**25b** and **25b′**):* colorless syrup (376 mg, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (m, 2H), 7.64−7.53 (m, 3H), 4.14 (q, 2H), δ 3.76 (m, 1H), 2.32−2.94 (m, 13H), 1.49−1.66 (m, 14H), 1.23 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 138.4, 133.6, 129.1, 128.8, 66.4, 66.2, 65.8, 60.8, 57.5, 56.9, 56.7, 54.1, 46.0, 44.4, 42.5, 31.7, 31.7, 24.0, 24.0, 23.8, 14.2 ppm; HRMS(EI) m/z calcd for $C_{27}H_{40}N_2O_4S$ $(M)^+$ 488.2708, found488.2708.

*Ethyl 1-benzyl-4-(1-benzyl-4-(phenylsulfonyl)pyrrolidin-3-yl)-pyrrolidine-3-carboxylate (**25c** and **25c′**):* colorless syrup (361 mg, 67%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (m, 2H),δ 7.83 (m, 1H), δ 7.53 (m, 2H) 7.30−7.14 (m, 10H), 4.11 (q, 2H), 3.89 (m, 1H), 3.47 (m, 4H, $-CH_2$Ph), 3.04 (m, 1H), 2.84−2.52 (m, 10H), 1.249(t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 174.5, 138.9, 138.7, 138.6, 138.5, 138.4, 133.7, 133.6, 129.3, 129.2, 128.8, 128.7, 128.6, 128.4, 128.3, 127.6, 127.1, 66.3, 66.1, 60.8, 60.8, 60.8, 59.7, 59.7, 59.4, 59.4, 59.2, 58.5, 58.3, 58.0, 57.7, 57.0, 54.9, 54.7, 46.5, 46.0, 45.0, 44.5, 43.5, 42.9, 14.2; HRMS(EI) m/z calcd for $C_{31}H_{36}N_2O_4S$ $(M)^+$ 532.2395, found 532.2394.

*Ethyl 4-(4-(4-methoxyphenylsulfonyl)-1-tert-butylpyrrolidin-3-yl)-1-tert-butylpyrrolidine-3-carboxylate (**25d** and **25d′**):* colorless

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354

syrup (360 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.79 (d, 2H), 6.98 (d, 2H), 4.12 (q, 2H), 3.85 (s, 3H, $-OCH_3$), 3.72 (m, 1H), 2.44−2.92 (m, 11H), 1.25 (t, 3H), 1.03 (s, 9H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 163.5, 130.9, 130.8, 129.9, 129.7, 114.1, 66.0, 60.6, 55.5, 51.7, 50.1, 49.5, 47.4, 47.2, 45.9, 44.30, 44.0, 42.3, 25.5, 13.2; HRMS(EI) m/z calcd for $C_{26}H_{42}N_2O_5S$ $(M)^+$ 494.2814, found 494.2814.

*Ethyl 4-(4-(4-methoxyphenylsulfonyl)-1-cyclopentylpyrrolidin-3-yl)-1-cyclopentylpyrrolidine-3-carboxylate (**25e** and **25e′**):* colorless syrup (367 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 2H), 6.96 (d, 2H), 4.11 (q, 2H), 3.87 (s, 3H, -OCH_3), 3.74 (m, 1H), 2.49−3.09 (m, 13H), 1.46−1.77 (m, 14H), 1.23 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 163.6, 131.0, 130.8, 114.2, 65.9, 65.8, 60.8, 57.5, 55.6, 54.3, 46.1, 44.4, 31.6, 31.5, 24.0, 23.9, 14.1; HRMS(EI) m/z calcd for $C_{28}H_{42}N_2O_5S$ $(M)^+$ 518.2814, found 518.2812.

*Ethyl 4-(4-(4-methoxyphenylsulfonyl)-1-benzylpyrrolidin-3-yl)-1-benzylpyrrolidine-3-carboxylate (**25f** and **25f′**):* colorless syrup (353 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, 2H), 7.05−7.30 (m, 12H), 4.11 (q, 2H), 3.85 (s, 3H), 3.80 (m, 1H), 3.29−3.56 (m, 4H), 2.53−3.04 (m, 11H), 1.17 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 165.5, 139.4, 138.8, 132.0, 130.0, 129.96, 129.3, 129.2, 128.1, 128.0, 115.6, 67.7, 67.3, 61.9, 60.5, 60.0, 58.5, 57.2, 56.3, 55.4, 47.1, 45.6, 44.5, 43.9 14.4 ppm; HRMS(EI) m/z calcd for $C_{32}H_{38}N_2O_5S$ $(M)^+$ 562.2501, found 562.2500.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02845.

X-ray data for **4a** (CIF)
X-ray data for **9a** (CIF)
^{1}H NMR and ^{13}C NMR spectra for all compounds; COESY, HMBC and NOESY spectra for **21b** and **23a**; additional details on computations, including total energies and Cartesian coordinates for computed structures and TS structures (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: subuchem@hotmail.com.
*E-mail: kkbalu@hotmail.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

U.S. dedicates this manuscript to the late Professor R. Uma. HRMS were provided by SAIF IITM.

■ REFERENCES

(1) (a) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vols. *1 and 2*. (b) Huisgen. Kinetics and Mechanism of 1,3-Dipolar Cycloaddition. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633.

(2) Tsuge, O.; Kanemasa, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1989; Vol. *45*, p 231.

(3) Grigg, R.; Sridharan, V. *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: London, 1993; Vol. *3*, p 161.

(4) (a) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235. (b) Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2006**, *2006*, 2873. (c) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (d) Ruck-Braun, K.; Freysoldt, T. H. E.; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507. (e) Kanemasa, S. *Synlett* **2002**, *2002*, 1371.

(5) (a) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105. (b) Harwood, L. M.; Vickers, R. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; p 169. (c) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley−VCH: Weinheim, 2002; Chapter 6, p 211. (d) Karlsson, S.; Hogberg, H. E. *Org. Prep. Proced. Int.* **2001**, *33*, 103. (e) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (f) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.

(6) (a) Daly, J. W.; Spande, T. W.; Whittaker, N.; Highet, R. J.; Feigl, D.; Noshimori, N.; Tokuyama, T.; Meyers, C. W. J. *J. Nat. Prod.* **1986**, *49*, 265. (b) Molineux, R. J. In *Alkaloids: Chemical and Biological Perspective*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Chapter 1. (c) Fujimori, S. Jpn Pat. Appl. 88-2912; *Chem. Abstr.* **1990**, *112*, 98409. (d) Waldmann, H. *Synlett* **1995**, *1995*, 133. (e) Mukherjee, S.; Raunak; Dhawan, A.; Prasad, A. K.; Olsen, C. E.; Cholli, A. S.; Errington, W.; Watterson, A. C.; Parmer, V. S. *Ind. J. Org. Chem.* **2004**, *43B*, 2670.

(7) Bang-Andersen, B.; Ahmadian, H.; Stensbol, T. B.; Madsen, U.; Bogeso, K. P.; Krogsgaard-Larsen, P.; Lenz, S. M. *J. Med. Chem.* **2000**, *43*, 4910.

(8) (a) Carroll, W. A.; Grieco, P. *J. Am. Chem. Soc.* **1993**, *115*, 1164. (b) Earley, W. G.; Oh, T.; Overman, L. *Tetrahedron Lett.* **1988**, *29*, 3785. (c) Ban, Y.; Taga, N.; Oishi, T. *Chem. Pharm. Bull.* **1976**, *24*, 736.

(9) Hilton, S. T.; Ho, T. C.; Pljevaljcic, G.; Jones, K. *Org. Lett.* **2000**, *2*, 2639.

(10) (a) Okita, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 11143. (b) Rosenmund, P.; Hosseini-Merescht, M.; Bub, C. *Leibigs. Ann. Chem.* **1994**, *1994*, 151. (c) Kornet, M. J.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892.

(11) (a) Poornachandran, M.; Raghunathan, R. *Synth. Commun.* **2007**, *37*, 2507. (b) Augustine, T.; Kanakam, C. C.; Vithiya, S. M.; Ramkumar, V. *Tetrahedron Lett.* **2009**, *50*, 5906. (c) Suresh Babu, A. R.; Raghunathan, R.; Satiskumar, B. K. *Tetrahedron Lett.* **2009**, *50*, 2818. (d) Dandia, A.; Jain, A. K.; Laxkar, A. K.; Bhati, D. S. *Tetrahedron Lett.* **2013**, *54*, 3180. (e) Arumugam, N.; Periyasami, G.; Raghunathan, R.; Kamalraj, S.; Muthumary, J. *Eur. J. Med. Chem.* **2011**, *46*, 600. (f) Lanka, S.; Thennarasu, S.; Perumal, P. T. *RSC Adv.* **2014**, *4*, 2263. (g) Lanka, S.; Thennarasu, S.; Perumal, P. T. *Tetrahedron Lett.* **2012**, *53*, 7052. (h) Vadla, R.; Ahmad, A. N.; Chennakesava, R.; Arulananda, B. S. *Synlett* **2012**, *4*, 549.

(12) For review of sulfonyl diene in organic synthesis, see: (a) Backvall, J. E.; Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291. (b) Simpkins, N.S. *Tetrahedron* **1990**, *46*, 6951. (c) Blumberg, L. C.; Costa, B.; Goldstein, R. *Tetrahedron Lett.* **2011**, *52*, 872. (d) Beugelmans, R.; Benadjila, I. L.; Chastanet, J.; Negron, G.; Roussi, G. *Can. J. Chem.* **1985**, *63*, 725.

(13) (a) Raj, A. A.; Raghunathan, R.; SrideviKumari, M. R.; Raman, N. *Bioorg. Med. Chem.* **2003**, *11*, 407. (b) Rusil, I.; Ashraf, A. M.; Choon, T. S.; Shahida, A. N.; Yoon, Y. K.; Raju, S. K.; Hasnah, O. WO2012/99452, 2012. (c) Sahu, D.; Pathak, T.; Ganguly, B. *Org. Lett.* **2014**, *16*, 2100.

(14) (a) Houk, K. N. In *Pericyclic Reactions*; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. *II*, p 203. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.

(15) Sankar, U.; Mahalakshmi, S.; Balasubramanian, K. K. *Synlett* **2013**, *24*, 1533.

(16) (a) Belyk, K. M.; Beguin, C. D.; Palucki, M.; Grinberg, N.; DaSilva, J.; Askin, D.; Yasuda, N. *Tetrahedron Lett.* **2004**, *45*, 3265. (b) Blumberg, L. C.; Costa, B.; Goldstein, R. *Tetrahedron Lett.* **2011**, *52*, 872 and references cited therein for cycloaddition chemistry. (c) Babu, A. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2008**, *49*, 4618.

(17) The X-ray crystal structure data of **4a**and **9a** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposited numbers as follows: CCDC 865207 (**4a**) and CCDC 898323 (**9a**). The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(18) (a) *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis; Novalstrategiesc in Synthesis*, 2nd ed.; Feuer, H., Ed.; Wiley Sons, 2008. (b) Patrick, T.B.; Shadmehr, M.; Khan, A. H.; Singh, R. K.; Asmelash,

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354

B. *J. Fluorine Chem.* **2012**, *143*, 109. (c) Andrade, M. M.; Barros, M. T.; Pinto, R. C. *Tetrahedron* **2008**, *64*, 10521. (d) Hang, X. C.; Chen, Q. Y.; Xiao, J. C. *Synlett* **2008**, *13*, 1989. (e) Lavanya, G.; Mallikarjuna Reddy, L.; Padmavathi, V.; Padmaja, A. *Eur. J. Med. Chem.* **2014**, *73*, 187. (f) de Blas, J.; Carretero, C. J.; Dominguez, E. *Tetrahedron: Asymmetry* **1995**, *6*, 1035. (g) Romanski, J.; Nowak, P.; Maksymiuk, A.; Chapuis, C.; Jurczak, J. *RSC Adv.* **2013**, *3*, 23105.

(19) (a) Hamilton, G. L.; Backes, B. J. *Tetrahedron Lett.* **2006**, *47*, 2229. (b) Li, Q.; Wang, W.; Berst, K. B.; Claiborne, A.; Hasvold, L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1953. (c) Grafton, M.; Mansfield, A. C.; Fray, M. J. *Tetrahedron Lett.* **2010**, *51*, 1026. (d) Srihari, P.; Yaragorla, S.; Basu, D.; Chandrasekhar, S. *Synthesis* **2006**, *2006*, 2646.

(20) (a) Rodriguez Sarmiento, R. M.; Wirz, B.; Iding, H. *Tetrahedron: Asymmetry* **2003**, *14*, 1547.

(21) Takeuchi, H.; Fujimoto, T.; Hoshino, K.; Motoyoshiya, J.; Kakehi, A.; Yamamoto, I. *J. Org. Chem.* **1998**, *63*, 7172.

(22) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785.

(23) Hehre, W. J.; Radom, L.; Schleyer, P. R.; Pople, J. A. *Ab Initio Molecular Orbital theory*; Wiley: New York, 1986.

(24) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J. ; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O. ; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D. Farkas, J.; Foresman, B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision A.02*; Gaussian, Inc.: Wallingford, CT, 2009.

(25) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.

(26) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

(27) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

(28) (a) Domingo, L. R.; Chamorro, E.; Perez, P. *J. Org. Chem.* **2008**, *73*, 4615. (b) Domingo, L. R.; Picher, M. T. *Tetrahedron* **2004**, *60*, 5053.

(29) Padmanabhan, J.; Parthasarathy, R.; Elango, M.; Subramanian, V.; Krishnamoorthy, B. S.; Guitierrez-Oliva, S.; Toro-labbe, A.; Roy, D. R.; Chattaraj, P. K. *J. Phys. Chem. A* **2007**, *111*, 9130.

(30) Perez, P.; Domingo, L. R.; Duque-Norena, M.; Chamorro, E. *J. Mol. Struct.: THEOCHEM* **2009**, *895*, 86.

(31) Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793.

(32) Contini, A.; Leone, S.; Menichetti, S.; Viglianisi, C.; Trimarco, P. *J. Org. Chem.* **2006**, *71*, 5507.

(33) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646−10647.

DOI: 10.1021/acs.joc.5b02845
J. Org. Chem. 2016, 81, 2340−2354