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Authors Alexander Stepakov, Alexander Filatov, Olesya Khoroshilova, Anna Larina and Vitaly Boitsov

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ORCID® iDs Alexander Stepakov - <https://orcid.org/0000-0001-6551-0042>;
Alexander Filatov - <https://orcid.org/0000-0002-4093-4225>; Anna Larina - <https://orcid.org/0000-0002-3029-4930>; Vitaly Boitsov - <https://orcid.org/0000-0002-4857-2046>

Synthesis of bis-spirocyclic derivatives of 3-azabicyclo[3.1.0]hexane via cyclopropene cycloadditions to the stable azomethine ylide derived from Ruhemann's Purple

Alexander S. Filatov¹, Olesya V. Khoroshilova¹, Anna G. Larina¹, Vitali M. Boitsov² and Alexander V. Stepanov*^{1,3}

Address:

¹Saint-Petersburg State University, Universitetskaya nab. 7/9, 199034, St. Petersburg, Russian Federation

²Saint-Petersburg National Research Academic University of the Russian Academy of Sciences, ul. Khlopina 8/3, 194021, St. Petersburg, Russian Federation

³Saint-Petersburg State Institute of Technology, Moskovskii pr. 26, 190013, St. Petersburg, Russian Federation

Email: Alexander V. Stepanov* - alstep@yandex.ru

* Corresponding author

Abstract

A reliable method for the synthesis of bis-spirocyclic derivatives of 3-azabicyclo[3.1.0]hexane through the 1,3-dipolar cycloaddition (1,3-DC) reactions of cyclopropenes to the stable azomethine ylide – protonated form of Ruhemann's Purple

(PRP) has been developed. Both 3-substituted and 3,3-disubstituted cyclopropenes reacted with PRP, affording corresponding bis-spirocyclic 3-azabicyclo[3.1.0]hexane cycloadducts in moderate to good yields with high diastereofacial selectivity. Moreover, several unstable 1,2-disubstituted cyclopropenes were successfully trapped by the stable 1,3-dipole under mild conditions. The mechanism of cycloaddition reactions of cyclopropenes with PRP has been thoroughly studied using density functional theory (DFT) methods at the M11/cc-pVDZ level of theory. The cycloaddition reactions have been found to be $\text{HOMO}_{\text{cyclopropene}} - \text{LUMO}_{\text{ylide}}$ controlled while transition-state energies for the reaction of 3-methyl-3-phenylcyclopropene with PRP are fully consistent with the experimentally observed stereoselectivity.

Keywords

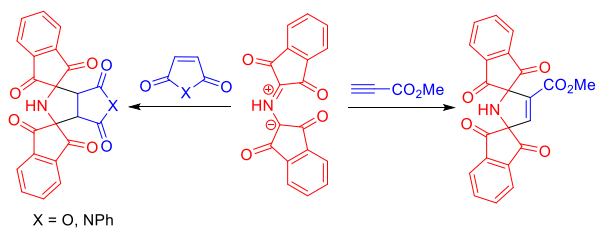
azomethine ylides, cycloaddition, cyclopropenes, DFT calculations, spiro heterocycles

Introduction

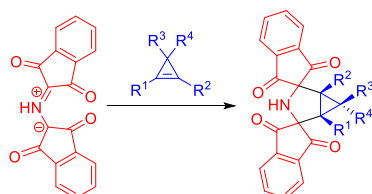
Spiro compounds (molecules containing at least two rings with only one common atom) are an important class of both synthetic and naturally occurring substances. Many biologically active natural products have a spirocyclic skeleton in their structure [1,2]. There is also great interest in studying heterocyclic spiro compounds for drug discovery. This is due to their wide range of biological activities, of which mention should be made of antioxidant [3], anticancer [4], antidiabetic [5] and antibacterial [6] activities. It is also worth noting that spiro compounds have found application in agriculture as fungicides [7], as well as in materials science as organic semiconductors [8]. The 3-azabicyclo[3.1.0]hexane framework is a valuable structural fragment found in numerous natural compounds [9-11]. It is used in pharmaceuticals [12-15] and key intermediates [16,17]. Compounds containing an 3-azabicyclo[3.1.0]hexane moiety

are antagonists of morphine-induced antinociception [18], histone deacetylase inhibitors [13], and opioid receptor antagonists [15]. In our recent studies, much attention has been paid to the development of methods for the synthesis of spiro[3-azabicyclo[3.1.0]hexanes] based on 1,3-dipolar cycloaddition reactions involving azomethine ylides and cyclopropene dipolarophiles, and also the *in vitro* activity of some synthesized compounds has been explored [19-24]. As demonstrated in these studies, the strategy based on azomethine ylide cycloadditions to cyclopropenes enables the concise stereocontrolled synthesis of a broad number of spiro-fused 3-azabicyclo[3.1.0]hexanes. Inspired by our recent achievements, we have focused on developing an approach to the synthesis of bis-spiro[3-azabicyclo[3.1.0]hexanes] (compounds containing spiro units at 2,4-positions of the 3-azabicyclo[3.1.0]hexane moiety), which are a new class of spirocyclic compounds previously undescribed in the literature. When considering a synthetic approach to obtaining such compounds, we have turned our attention to tetrasubstituted azomethine ylide - *N*-protonated Ruhemann's Purple (PRP). This stable ylide was first utilized as a 1,3-dipole in cycloaddition reactions by Grigg and co-workers [25]. This research group demonstrated that the reactions of PRP with dipolarophiles such as *N*-phenylmaleimide, maleic anhydride and methyl propiolate resulted in the formation of corresponding bis-spirocyclic cycloadducts (Scheme 1a). As seen from the above, PRP has been studied in reactions with a small number of dipolarophiles, which makes it impossible to fully evaluate its synthetic potential. Positioning the current study as a continuation of a series of works in which cyclopropenes had been utilized as dipolarophiles, we described the development of a synthetic route to bis-spirocyclic derivatives of 3-azabicyclo[3.1.0]hexane through cyclopropene cycloadditions to stable azomethine ylide PRP (Scheme 1b).

(a) Previous study (Ref. 25):



(b) This study:

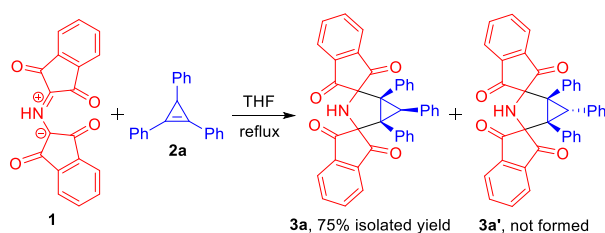


Scheme 1: *N*-Protonated Ruhemann's Purple (PRP) in the 1,3-dipolar cycloaddition reactions.

Results and Discussion

The study commenced with testing the feasibility of the cycloaddition reaction between protonated Ruhemann's purple (PRP, **1**) [26,27] and cyclopropene dipolarophiles **2**. 1,2,3-Triphenylcycloprop-1-ene (TPC, **2a**) [28] was chosen as a model substrate since this alkene had worked well in cycloaddition reactions with various stabilized azomethine ylides [19-24]. Initially, we considered the reaction conditions suggested by Grigg and co-workers in the study [25]. An equimolar mixture of **1** and **2a** were dissolved in tetrahydrofuran (THF), and the resulting mixture was maintained at reflux. After heating only for 2 h, completion of the reaction was indicated by both the colour change of the reaction mixture and TLC (thin layer chromatography) analysis. The proposed cycloadduct was isolated after recrystallization from methanol (MeOH) in 75% yield. Eventually, the structure of meso compound **3a** was unambiguously corroborated by NMR spectra. Given the results of previous studies [22,23] concerning cycloadditions of ninhydrin-derived azomethine ylides to cyclopropenes, it has been suggested that the stable azomethine ylide **1** appears to react diastereoselectively with

TPC (**2a**), resulting in the formation of bis-spirocyclic meso compound **3a** in which the three phenyl substituents attached to the cyclopropane ring are oriented in the same direction (Scheme 2). Another possible diastereomer **3a'** bearing the opposite configuration at the C6' position has been not found by ¹H NMR analysis of the crude mixture. This suggests that the diastereomer **3a** resulting from the approach of the 1,3-dipole **1** from the less-hindered face of TPC (**2a**) is more favorable than opposite stereoisomer **3a'** (Scheme 2).

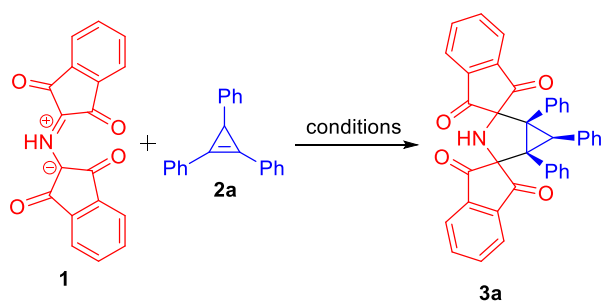


Scheme 2: The pilot experiment aimed at studying the cycloaddition reaction between protonated form of Ruhemann's purple (**1**) and 1,2,3-triphenylcyclopropene (**2a**).

Subsequently, our efforts have focused on optimization the reaction conditions for improving the yield of the cycloadduct **3a**. A broad range of solvents was screened at different temperatures. As presented in Table 1, aprotic polar solvents such as 1,4-dioxane, acetonitrile and dimethylformamide (DMF) at 65 °C favored the formation of desired cycloadduct **3a**. 3-Azabicyclo[3.1.0]hexane derivative **3a** was obtained after recrystallization from MeOH in yields 67, 70 and 61%, respectively (Table 1, entries 2–4). In contrast to aprotic solvents, alcohols such as methanol (MeOH) and ethanol (EtOH) were absolutely unsuitable for carrying out this reaction owing to incompatibility of 1,3-dipole **1** with this medium (Table 1, entries 5–6). PRP (**1**) was found to immediately undergo an acid-base reaction with alcohols to form the stabilized aza-allylic anion known as Ruhemann's purple. Using dichloromethane as a solvent, the reaction took place at reflux. However, in this case, the yield of **3a** significantly

diminished to 42% due to incomplete conversion of **1** and **2a** (Table 1, entry 7). Also, we attempted to carry out this transformation in aprotic solvents at room temperature. Unfortunately, even after 12 h, we failed to completely convert reactants **1** and **2a** into product **3a** in both cases (Table 1, entries 8–9). Accordingly, it has been concluded that tetrahydrofuran is the most appropriate solvent for carrying out the cycloaddition reaction between **1** and **2a**. To reach full conversion of reactants, it is necessary to conduct the reaction at reflux for 2 h (Table 1, entry 1).

Table 1: Optimization of the reaction conditions^{a,b}.



Entry	Solvent	T (°C)	Time (h)	Yield of 3a (%) ^c
1	THF	reflux	2	75
2	1,4- dioxane	65	2	67
3	CH ₃ CN	65	2	70
4	DMF	65	2	61
5	MeOH	reflux	2	NR ^d
6	EtOH	65	2	NR ^d
7	CH ₂ Cl ₂	reflux	12	42
8	THF	RT	12	44

9	CH ₃ CN	RT	12	47
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^aAbbreviations: NR – no reaction, RT – room temperature. ^bReaction conditions: **1** (1 equiv.), **2** (1 equiv.), solvent. ^cIsolated yield. ^dAzomethine ylide **1** exclusively underwent deprotonation in protic solvents.

With the optimized conditions in hand, 1,2-diphenylcyclopropenes differently substituted at the C3 position **2b–g** were tested as dipolarophiles to evaluate the effect of C3-substituents on the 1,3-DC reaction (Scheme 3). 1,2-Diphenylcyclopropene (**2b**) [29] smoothly underwent a cycloaddition reaction to azomethine ylide **1** to form bis-spiro 3-azabicyclo[3.1.0]hexane **3b** in 78% yield (Scheme 3). Remarkably, the structure of cycloadduct **3b** was additionally verified by X-ray analysis (see Supporting Information, Figure S25, Table S1). The reaction of cyclopropene **2c** [30] with PRP (**1**) also proceeded with full diastereofacial selectivity, giving the corresponding cycloadduct **3c** in acceptable yield (72%). On treatment of cyclopropenes **2d** [30], **2e** [31] containing two multiple bonds with stable azomethine ylide **1**, the 1,3-DC reaction occurred in a highly chemo- and diastereoselective manner and brought about the formation of 3-azabicyclo[3.1.0]hexane cycloadducts **3d** and **3e** in 69% and 91% yields, correspondingly (Scheme 3). It is noteworthy that we managed to determine the relative configuration of cycloadduct **3e** by carrying out the corresponding X-ray structural analysis (Figure 3). As anticipated, the azomethine ylide **1** cycloaddition to cyclopropene **3e** led to the formation of diastereomer with three substituents (at the cyclopropane ring) oriented in the same direction.

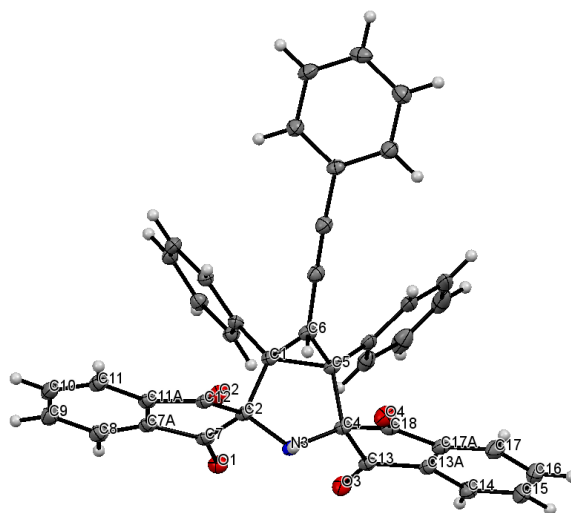
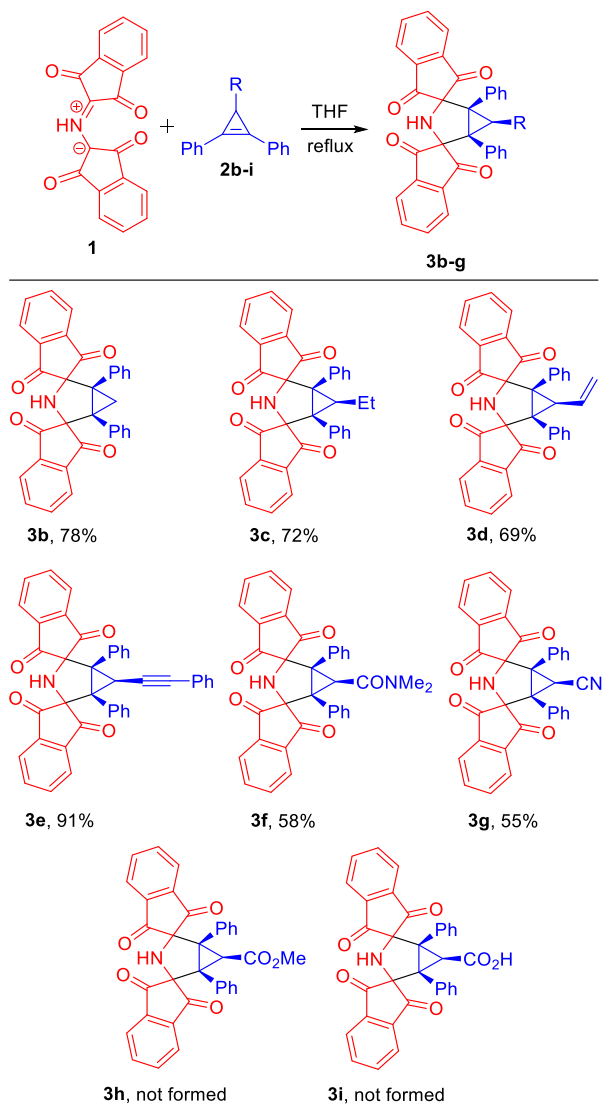


Figure 1: ORTEP representation of the molecular structure of **3e**.

A notable substituent effect on the reactivity of cyclopropene dipolarophiles **2** was observed for the reactions between PRP (**1**) and derivatives of 2,3-diphenylcycloprop-2-ene-1-carboxylic acid **2f–i**. Amide **2f** and nitrile **2g** [32] were found to be less active dipolarophiles towards the azomethine ylide **1** than hydrocarbons **2a–e**. And as a result, the corresponding cycloadducts **2f** and **2g** were obtained in moderate yields (58% and 55%, respectively) as single diastereomers (Scheme 3). Notably, it took more time (6 h) for achieving full consumption of **1** while significant amounts of alkenes **2f** and **2g** remained unreacted. In turn, both ester **2h** and acid **2i** [33] have proven to be totally unreactive towards PRP (**1**) under optimized reaction conditions (THF, reflux). Based on these observations, we have concluded that electronic properties of the substituent at the C3 position of a cyclopropene ring have a major impact on reactivity. A more detailed discussion of this issue is presented in the section devoted to the DFT (density functional theory) computational study. The structures of cycloadducts **3b–g** have been confirmed by the analysis of ^1H and ^{13}C NMR spectra. In line with the structure of meso compound **3e**, the relative configuration, that is shown in Scheme 3, has been assigned to cycloadducts **3a**, **3c**, **3d**, **3f** and **3g**. Thus, the cycloadditions of 3-*R*-1,2-diphenylcyclopropenes **2a**, **2c–g** to azomethine ylide **1** were

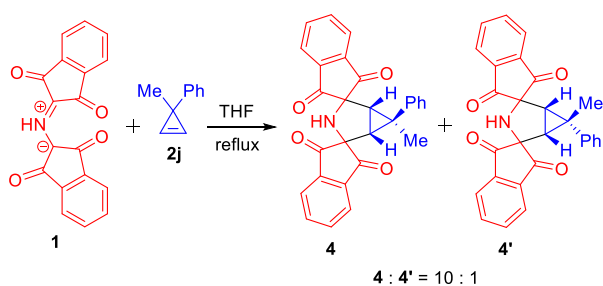
found to exclusively proceed by a pathway in which PRP (**1**) approaches cyclopropenes **2** from the more sterically available side of **2a**, **2c–g** (from the side containing a hydrogen substituent).



Scheme 3: Synthesis of meso 3'-azadispiro[indene-2,2'-bicyclo[3.1.0]hexane-4',2''-indene] derivatives **3b–g** via 1,3-DC reactions of *N*-protonated Ruhemann's purple (**1**) with 3-substituted 1,2-diphenylcyclopropenes **2b–g**.

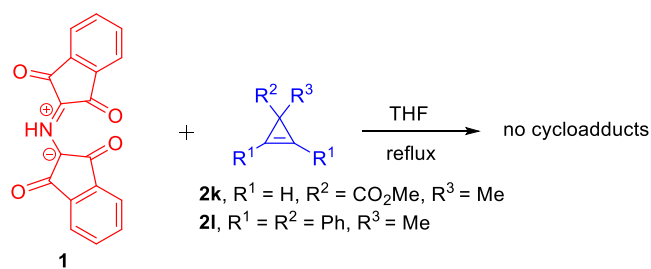
Next, unsymmetrically 3,3-disubstituted cyclopropenes **2j–l** were studied in the reaction with **1** to determine whether these 1,3-DC reactions would similarly proceed with high diastereofacial selectivity. The reaction of 3-methyl-3-phenylcyclopropene (**2j**) [34] with ylide **1** resulted in the formation of 1:1 adduct. The cycloaddition with 3,3-

disubstituted cyclopropene **2j** occurred at slower rates than with 3-monosubstituted 1,2-diphenylcyclopropenes. Approximately 6 h at reflux were needed to complete the reaction. The analysis of ^1H NMR spectrum of the crude mixture revealed that cycloadduct was formed as mixture of diastereomers **4** and **4'** in ratio 10:1 (Scheme 4). Subsequent purification of the crude mixture by recrystallization from MeOH enabled to obtain pure major diastereomer **4** in 62% yield. The structure and relative configuration of cycloadduct **4** were unequivocally established on the basis of its two-dimensional (2D) NMR spectrum (^1H - ^1H nuclear Overhauser effect spectroscopy (NOESY), see Supporting Information, Figure S17). There is a key cross peak between protons of the methyl group and H -(N3') which clearly indicates that the phenyl substituent occupies relative *cis* disposition in respect to two equivalent hydrogen atoms attached to the cyclopropane ring. This experiment has shown that azomethine ylide **1** also predominantly cycloadds to prochiral cyclopropene **2j** from the less-hindered side. This is consistent with previous experiments in which 3-R-1,2-diphenylcyclopropenes have been utilized as dipolarophiles.



Scheme 4: The reaction of protonated Ruhemann's purple (**1**) with 3-methyl-3-phenylcyclopropene (**2j**).

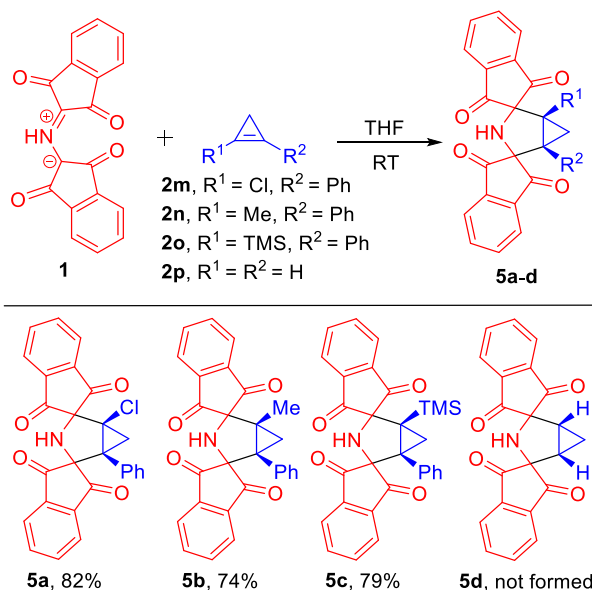
Regretfully, neither methyl 1-methylcycloprop-2-enecarboxylate (**2k**) [35] nor 3-methyl-1,2,3-triphenylcycloprop-1-ene (**2l**) [28] reacted with ylide **1** in THF at reflux (Scheme 5). Inactivity of **2k** appears to be caused by electronic effects while tetrasubstituted cyclopropene **2l** seems to be too bulky to undergo a cycloaddition reaction with **1**.



Scheme 5: Attempts to carry out cycloaddition reactions between 3,3-disubstituted cyclopropenes **2k**, **2l** and azomethine ylide **1**.

To the best of our knowledge, PRP (**1**) is one of the few stable azomethine ylides. This fact prompted us to test this azomethine ylide **1** as an effective trap for capturing unstable cyclopropenes (Scheme 6). At first, 1-chloro-2-phenylcyclopropene (**2m**) [36] that is stable only in dilute, has been studied as a dipolarophile in reaction with **1**. A freshly prepared carbon tetrachloride solution of 1-chloro-2-phenylcyclopropene (**2m**) was treated with PRP (**1**) in THF medium. To avoid cyclopropene decomposition, in this case the reaction was carried out at room temperature with stirring. Twelve hours later, we were pleased to note that azomethine ylide **1** was fully consumed as a result of the cycloaddition reaction with cyclopropene **2m**. The corresponding bis-spiro compound **5a** was readily isolated in 82% yield after recrystallization from ethanol. Certainly, cycloadduct **5a** was obtained as a racemate rather than as a meso compound due to unsymmetrical substitution at the cyclopropane ring. Similarly, we have succeeded in carrying out reactions between unsymmetrically 1,2-disubstituted cyclopropenes **2n**, **2o** and PRP (**1**). 1-Methyl-2-phenylcyclopropene (**2n**) and 1-phenyl-2-(trimethylsilyl)cyclopropene (**2o**) synthesized from reliable precursor 1,1,2-tribromo-2-phenylcyclopropane [37,38] were immediately added to the THF solution of nitrogen ylide **1** at room temperature, resulting in the formation of cycloadducts **5b** and **5c** in satisfactory yields (74% and 79%, respectively). Finally, we make an effort to trap parent cyclopropene (**2p**) as a cycloadduct with PRP (**1**). In one of our previous studies

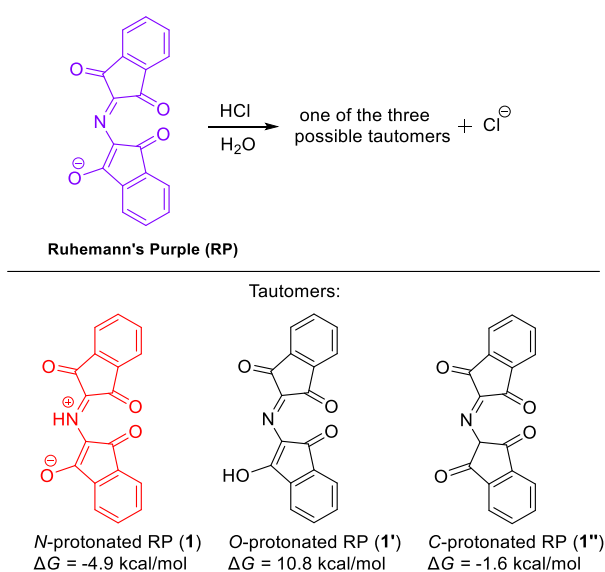
[22], we have demonstrated that stable ninhydrin-derived azomethine ylide – DHPO (2-(3,4-dihydro-2*H*-pyrrolium-1-yl)-1-oxo-1*H*-inden-3-olate) is an excellent chemical trap for detecting parent cyclopropene. Having carried out the experiment with ylide **1** as a trap in a similar fashion, we have found that PRP (**1**) is unreactive towards parent cyclopropene (**2p**) under these conditions. Cyclopropene **2p** generated *in situ* from allyl chloride [39] and driven into a chilled tube containing PRP(**1**) was probably more prone to undergo free-radical polymerization than to react with 1,3-dipole (**1**) by gradually increasing the reaction temperature to 25 °C. Despite this failed experiment, in general, PRP (**1**) has established itself as a highly reactive 1,3-dipole towards cyclopropene dipolarophiles **2**.



Scheme 6: The reactions of protonated Ruhemann's purple (**1**) with unstable cyclopropenes **2m–p**.

In this study, we did not confine ourselves exclusively to carrying out laboratory experiments and also turned to DFT calculations (M11 density functional theory) [40-44] to interpret experimental results. At the beginning of the computational study, we have evaluated the relative stability of the prototropic tautomers which are formed during protonation of Ruhemann's Purple. Although there was conclusive evidence of

the structure of PRP (**1**) in the Grigg's study (proven by X-ray analysis) [25], we aimed to establish the stability order of the tautomers on the basis of calculated relative values of Gibbs free energy. Upon treatment of Ruhemann's Purple with hydrochloric acid, three tautomers **1**, **1'**, **1''** may be theoretically formed, i.e., protonation could occur at the nitrogen atom, the oxygen atom or the carbon atom, respectively (Scheme 7). According to literature data [25], the nitrogen atom of Ruhemann's Purple is considered to be the most basic site in a molecule. We carried out the full geometry optimization of both all possible tautomers **1**, **1'**, **1''** and aza-allylic anion Ruhemann's Purple to calculate the Gibbs free energy change for the corresponding acid-base reactions (Scheme 7). As expected, the calculation data have shown that the betaine form **1** is the most thermodynamically stable of all tautomers ($\Delta G = -4.9$ kcal/mol). It is also not surprising that *O*-protonated form **1'**, which is both a ketone and an enol, is found to be the most unfavorable ($\Delta G = 10.8$ kcal/mol). In contrast to *O*-protonated tautomer **1'**, both *N*-protonated **1** and *C*-protonated **1''** tautomers do not contain an enol functional group. It is therefore likely that the lowest stability of *O*-protonated form **1'** compared to tautomers **1** and **1''** is due to the favorability of the $C=O$ double bond over the $C=C$ double bond.



Scheme 7: The acid-base reaction of Ruhemann's Purple with hydrochloric acid and relative Gibbs free energy change (ΔG , kcal/mol) for acid-base reactions resulting in the formation of three protonated forms of Ruhemann's Purple.

Next, using the equations recommended by Parr [45] and Domingo [46], we have calculated global electrophilicity indexes (GEI, ω) for both PRP (**1**) and cyclopropenes **2** to determine which the type of electron demand takes place during cycloaddition reactions. The global value of electrophilicity index for azomethine ylide **1** (1.29 eV) has revealed that this compound displays a moderate electrophilicity (Table 2, entry 1). By comparing global electrophilicity indexes of reactants **1**, **2a–p** (Table 2, entries 1–17), we have reached conclusion that cyclopropene cycloadditions to PRP (**1**) appear to be inverse electron-demand reactions, i.e., they may be considered as the interaction of the lowest unoccupied molecular orbital (LUMO) of azomethine ylide **1** with the highest occupied molecular orbital (HOMO) of cyclopropenes **2**. It follows that the greater nucleophilicity of cyclopropene substrate **2** is, the higher its reactivity towards 1,3-dipole **1** is. In fact, during experiments, 1,2-diphenylcyclopropenes **2a–e** containing either an alkyl or an alkenyl substituent at the C3 position are found to demonstrate high reactivity in 1,3-DC reactions with PRP (**1**). In contrast to substrates **2a–e**, cyclopropene dipolarophiles **2f–i** bearing electron-withdrawing groups are less nucleophilic. This is evidenced both by fairly large ω values of these cyclopropenes (Table 2, entries 7–10) and by reaction outcomes. Introducing electron-withdrawing groups at the C3 position of 1,2-diphenylcyclopropene framework instead of alkyl or alkenyl substituents results in a decrease in the HOMO and LUMO energies of such cyclopropenes, thereby increasing the $\text{HOMO}_{\text{cyclopropene}} - \text{LUMO}_{\text{ylide}}$ energy gap (Table 2, entries 7–10). In practice, this has an impact on the cyclopropene reactivity towards azomethine ylide **1**. For example, the reactions of 2,3-diphenylcyclopropene-1-carboxylic acid derivatives **2f–i** with PRP (**1**) either bring about the formation of

corresponding cycloadducts **3** in poor yields or result in the formation of complex mixtures. Thus, having carried out an analysis of the global reactivity descriptors, we have found a correlation between the structure of cyclopropene substrates **2** and their reactivity towards PRP (**1**).

Table 2. FMO energies (a.u.), electronic chemical potential (μ , eV), chemical hardness (η , eV) and global electrophilicity index (ω , eV) for PRP (**1**) and cyclopropenes **2**.^{a,b}

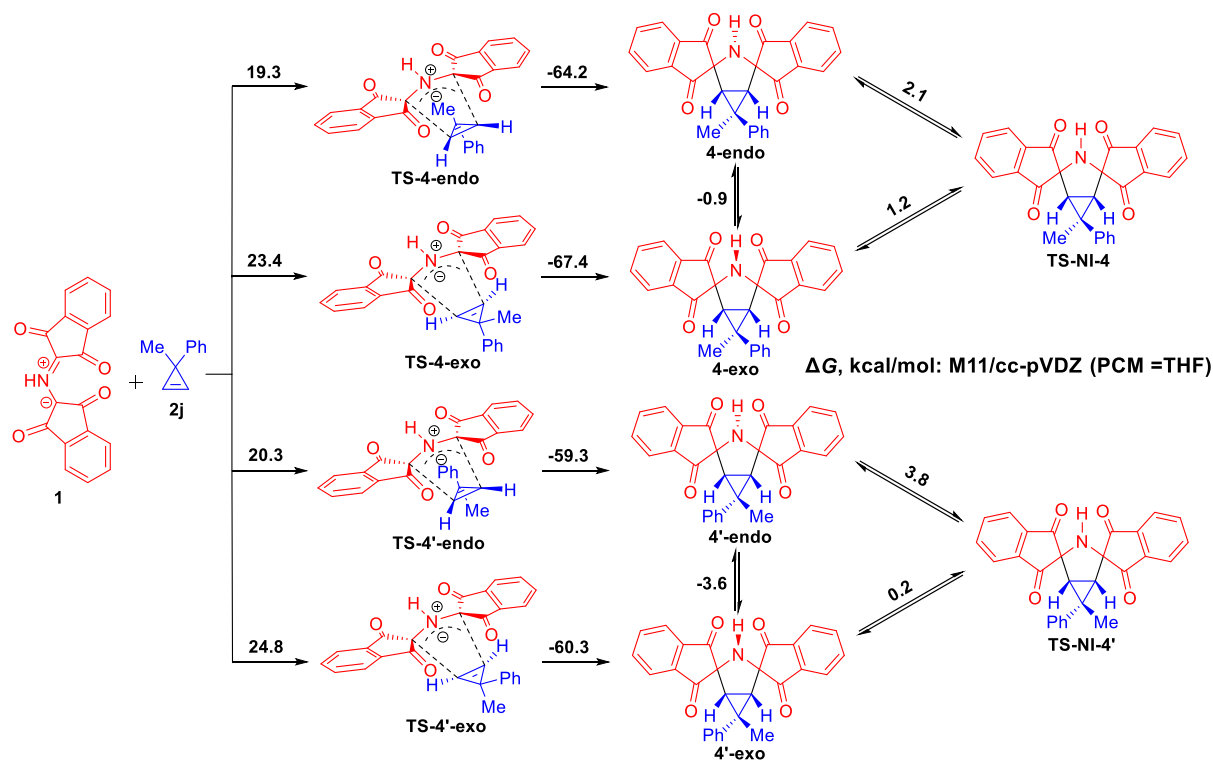
Entry	Comp-d	HOMO	LUMO	μ	η	ω	NED	IED	ED
1	1	-0,3110	-0,0207	-4,51	7,90	1,29	-	-	-
2	2a	-0,2867	0,0614	-3,06	9,47	0,50	10,13	7,24	IED
3	2b	-0,2815	0,0637	-2,96	9,39	0,47	10,19	7,10	IED
4	2c	-0,2802	0,0650	-2,93	9,39	0,46	10,23	7,06	IED
5	2d	-0,2860	0,0612	-3,06	9,45	0,50	10,13	7,22	IED
6	2e	-0,2910	0,0591	-3,16	9,53	0,52	10,07	7,35	IED
7	2f	-0,2925	0,0557	-3,22	9,47	0,55	9,98	7,39	IED
8	2g	-0,2996	0,0526	-3,36	9,58	0,59	9,89	7,59	IED
9	2h	-0,2935	0,0581	-3,20	9,56	0,54	10,04	7,42	IED
10	2i	-0,2947	0,0571	-3,23	9,57	0,55	10,02	7,45	IED
11	2j	-0,3179	0,1212	-2,68	11,95	0,30	11,76	8,09	IED
12	2k	-0,3805	0,1350	-3,34	14,03	0,40	12,14	9,79	IED
13	2l	-0,2853	0,0618	-3,04	9,44	0,49	10,14	7,20	IED
14	2m	-0,3107	0,0820	-3,11	10,68	0,45	10,69	7,89	IED
15	2n	-0,2972	0,0944	-2,76	10,66	0,36	11,03	7,52	IED
16	2o	-0,3019	0,0824	-2,99	10,46	0,43	10,70	7,65	IED
17	2p	-0,3574	0,1556	-2,74	13,96	0,27	12,70	9,16	IED

^a FMO energy (eV) were computed by using HF/6-311g single point calculation on the M11/cc-pVDZ optimized geometries. ^b Energy gaps for both possible HOMO–LUMO interactions between PRP (**1**) and cyclopropenes **2** are given in eV.

In the next step, we concentrated on studying the mechanism of 1,3-DC reactions between PRP (**1**) and cyclopropenes **2**. At first, it was planned to explore the mechanism of 1,3-DC reactions involving cyclopropenes substituted at the C3 position. It is precisely for these cyclopropenes that two diastereomeric cycloadducts that differ from each other only in the configuration of the pseudo-asymmetric C6' carbon atom may be theoretically obtained. In fact, only one of the two epimers is formed, i.e., the cycloaddition reaction proceeds with the complete diastereofacial stereoselectivity in almost all cases. Our goal has been to identify the nature of transition states associated with two theoretically possible diastereomers and to find out if the experimentally observed diastereomer is more kinetically favorable than opposite one.

The reaction between 3-methyl-3-phenylcyclopropene (**2j**) and PRP (**1**) that led to the stereoselective formation of cycloadduct **4** was studied in detail for this purpose (Scheme 8). In analyzing the potential energy surface (PES) of this cycloaddition reaction using the M11 functional together with the cc-pVDZ basis set, we could locate four transition state structures **TS-4-endo**, **TS-4-exo**, **TS-4'-endo**, **TS-4'-exo** that were associated with a concerted mechanism of 1,3-dipolar cycloaddition. Two of them **TS-4-endo** and **TS-4-exo** correspond to two nitrogen invertomers **4-endo** and **4-exo** of cycloadduct **4** while two other **TS-4'-endo** and **TS-4'-exo** associate with nitrogen invertomers **4'-endo** and **4'-exo** of cycloadduct **4'**, respectively. Next, we have determined the Gibbs energy of activation for nitrogen inversion in cycloadducts **4** and **4'** to figure out if the invertomers undergo rapid interconversion. Having carried out the full geometry optimization of both the transition states **TS-4-NI** and **TS-4'-NI**

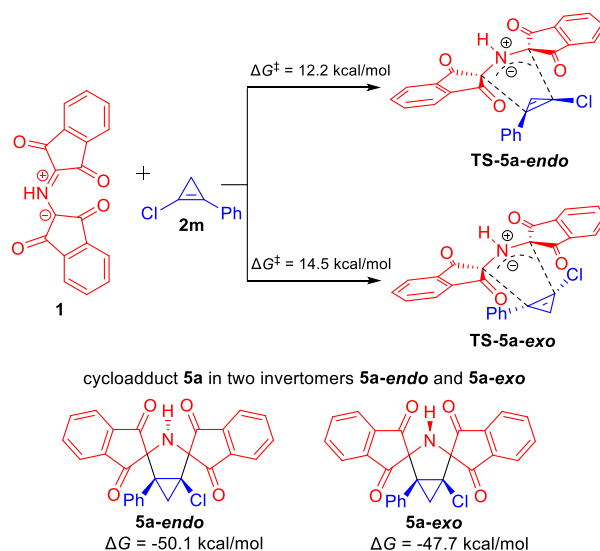
corresponding to pyramidal inversion in cycloadducts **4** and **4'** and two pairs of invertomers, we have found that each of the diastereomers **4** and **4'** is a mixture of two easily interconverting invertomers ($\Delta G^\ddagger_{4\text{-exo}\rightarrow 4\text{-endo}} = 1.2$ kcal/mol and $\Delta G^\ddagger_{4\text{-endo}\rightarrow 4\text{-exo}} = 2.1$ kcal/mol, $\Delta G^\ddagger_{4'\text{-exo}\rightarrow 4'\text{-endo}} = 0.2$ kcal/mol and $\Delta G^\ddagger_{4'\text{-endo}\rightarrow 4'\text{-exo}} = 3.8$ kcal/mol). Since rapid interconversion takes place, it does not matter via which transition state (**TS-4-endo** or **TS-4-exo**) cycloadduct **4** is formed. The same pattern is consistent with cycloadduct **4'**. It should be mentioned that the endo approaches ($\Delta G^\ddagger_{1+2j\rightarrow 4\text{-endo}} = 19.3$ kcal/mol and $\Delta G^\ddagger_{1+2j\rightarrow 4'\text{-endo}} = 20.3$ kcal/mol) are much more profitable than exo ones ($\Delta G^\ddagger_{1+2j\rightarrow 4\text{-exo}} = 23.4$ kcal/mol and $\Delta G^\ddagger_{1+2j\rightarrow 4'\text{-exo}} = 24.8$ kcal/mol). It follows that cycloadducts **4** and **4'** appear to be formed via **TS-4-endo** and **TS-4'-endo**, respectively. In turn, the Gibbs energies of activation corresponding to the endo approaches indicate that cycloadduct **4** ($\Delta G^\ddagger_{1+2j\rightarrow 4\text{-endo}} = 19.3$ kcal/mol) is more kinetically favorable than its epimer **4'** ($\Delta G^\ddagger_{1+2j\rightarrow 4'\text{-endo}} = 20.3$ kcal/mol). The small free energy difference (1.0 kcal/mol) between two competing pathways is in good agreement with experimental data and explains the reason why the cycloaddition reaction does not result in the exclusive formation of **4**.



Scheme 8: Plausible mechanism of the 1,3-DC reaction of protonated Ruhemann's Purple (**1**) with 3-methyl-3-phenylcyclopropene (**2j**) and corresponding DFT calculations (relative Gibbs free energy change between reagents, transition states and possible products are given in kcal/mol).

Additionally, the reaction of PRP (**1**) with 1-chloro-2-phenylcyclopropene (**2m**) was investigated to calculate the Gibbs energy of activation for this cycloaddition reaction and compare this value with the Gibbs free energy barrier calculated for the reaction between **1** and **2j** (Scheme 9). The azomethine ylide **1** cycloaddition to chloro-substituted cyclopropene **2m** has been also found to proceed by a one-step mechanism via two transition states **TS-5a-endo** and **TS-5a-exo** that bring about invertomers **5a-endo** and **5a-exo** of cycloadduct **5a**, respectively. According to the values of Gibbs energy of activation, the endo cycloaddition ($\Delta G^\ddagger = 12.2$ kcal/mol) significantly prevails over the exo one ($\Delta G^\ddagger = 14.5$ kcal/mol). When comparing the values of Gibbs energies of activation calculated for above-mentioned reactions, it has been established that the reaction involving **1** and **2m** ($\Delta G^\ddagger = 12.2$ kcal/mol) should

proceed significantly faster than the cycloaddition between **1** and **2j** ($\Delta G^\ddagger = 19.3$ kcal/mol). Thus, the calculation data are in full accordance with experimental results, taking into consideration the fact that the reaction between **1** and **2m** smoothly occurs at room temperature while the reaction involving 3-methyl-3-phenylcyclopropene (**2j**) requires harsher conditions.



Scheme 9: Plausible mechanism of the 1,3-DC reaction of protonated Ruhemann's Purple (**1**) with 1-chloro-2-phenylcyclopropene (**2m**) and corresponding DFT calculations (relative Gibbs free energy change between reagents, transition states and possible invertomers are given in kcal/mol).

Conclusion

In conclusion, we have developed a convenient method for the synthesis of bis-spirocyclic derivatives of 3-azabicyclo[3.1.0]hexane through cycloaddition reactions of stable azomethine ylide - protonated Ruhemann's Purple to cyclopropenes. The reaction was found to feature a broad scope of cyclopropene dipolarophiles, high diastereoselectivity and mild conditions. DFT calculations have revealed that the cycloaddition reactions are under kinetic control and belong to the class of inverse electron-demand 1,3-DC reactions. We believe that the outcome of this work will be

serve as a baseline for developing synthetic approaches to other bis-spirocyclic derivatives of 3-azabicyclo[3.1.0]hexane on the basis of cycloadditions of tetrasubstituted azomethine ylides to cyclopropenes.

Supporting Information

Supporting Information File 1:

Experimental details for the synthesis and characterization of all compounds, copies of ^1H NMR and ^{13}C NMR spectra, X-ray data and calculations details.

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