11H-Benz[4,5]imidazo[1,2-a]indol-11-one as a New Precursor of Azomethine Ylides: 1,3-Dipolar Cycloaddition Reactions with Cyclopropenes and Maleimides

Alexander S. Filatov, Yulia A. Pronina, Stanislav I. Selivanov, Stanislav V. Shmakov, Anton A. Uspenski, Vitali M. Boitsov, and Alexander V. Stepakov

1. Introduction

1,3-Dipolar cycloaddition (1,3-DC) is one of the most versatile methodologies for constructing five-membered heterocycles [1,2]. [3 + 2] Cycloaddition can take place with the participation of various 1,3-dipoles and dipolarophiles; however, these reactions have several features in common: (1) the dipole has a charge, (2) the resulting cycloadduct is uncharged, and (3) the HOMO of the 1,3-dipole reacts with the LUMO of the dipolarophile (a HOMO-controlled reaction). Among the 1,3-dipoles, azomethine ylides (belonging to allyl-type N-centered dipoles) are among the most popular and frequently used in 1,3-dipolar cycloaddition reactions [3,4]. One of the most well-known methods for the preparation of azomethine ylides is the reaction of amines with aldehydes, followed by deprotonation of the iminium cation or a prototropic shift of the imine [5,6]. Amino acids are capable of reacting with aldehydes or ketones to generate intermediate oxazolidinones, which undergo decarboxylation, resulting in the formation of azomethine ylides [7,8]. The other commonly used approaches to generate azomethine ylides rely on thermal ring-opening reactions involving aziridines or 4-oxazolines [9,10]. These and other methods continue to be widely used in synthetic organic chemistry. Reactions of azomethine ylides with alkenes make it possible to obtain highly substituted pyrrolidines containing up to four stereocenters [11,12]. The pyrrolidine ring, isolated or fused, can be attributed to a fundamental structural fragment that is part of a large number of natural...
and synthetic biologically-significant compounds [13]. The analysis of 164 U.S. FDA-approved small-molecule drugs from 2015 to June 2020 revealed that 22 (13%) of them contain a pyrrolidine moiety [14]. At the same time, 17 (8.5%) out of 200 small molecular drugs with the largest retail sales in 2020 contained the pyrrolidine cycle [15]. Nevertheless, despite many achievements in the study of 1,3-dipolar cycloaddition reactions, the search for new carbonyl substrates for the generation of azomethine ylides, which can lead to the construction of new heterocyclic systems containing valuable pharmacophore fragments, is highly desirable. Of the pharmacophore fragments that can be obtained through the [3 + 2] cycloaddition reactions of azomethine ylides, in our opinion, derivatives of 3-azabicyclo[3.1.0]hexane and pyrrolizine deserve special attention (Figure 1). 3-Azabicyclo[3.1.0]hexanes can be characterized as an important class of heterocyclic compounds with diverse pharmacological and biological activities. For example, 3-azabicyclo[3.1.0]hexanes exhibit anti-neuroinflammatory (monoacylglycerol lipase inhibitor, (I) [16], anti-neurodegenerative (dual leucine zipper kinase inhibitor, (II) [17] and antiviral (SARS-CoV-2 main protease inhibitor, (III) [18,19] effects. It is well known that pyrrolizine is the main structural moiety in many organic compounds exhibiting various biological activities, including anticoagulant (serine protease thrombin inhibitor, (IV) [20], anti-cancer (indicine N-oxide, (V), is an antitumor agent for pediatric cancer and solid tumors research) [21] and anti-HIV activities (7,7a-diepialexine, (VI) [21] (Figure 1).

Figure 1. Selected examples of biologically active 3-azabicyclo[3.1.0]hexanes and pyrrolizines.

In previous studies by our research group, cyclopropenes were widely used as dipolarophiles in 1,3-dipolar cycloaddition reactions with azomethine ylides generated from the corresponding ketones and α-amino acids (Scheme 1). We used derivatives of isatin [22], alloxan [23], ninhydrin [24–27], 11H-indeno[1,2-b]quinoxaline-11-one [28], and tryptanthrin [29] as the ketone components. The products of these reactions were pharmacologically interesting spiro-fused 3-azabicyclo[3.1.0]hexanes and pyrrolizines, some of which were identified as exhibiting in vitro antitumor activity [30,31].

As we noted above, the search for new substrates for the generation of azomethine ylides is an urgent task, since it allows introducing new unique poly/spirocyclic systems into the arsenal of heterocyclic chemistry, which may be of interest for pharmacology. With our continued research interest in 1,3-dipolar cycloaddition reactions, herein we present the first example of the generation of azomethine ylides from the tetracyclic ketone 11H-benzo[4,5]imidazo[1,2-a]indol-11-one and an α-amino acids, and also its [3 + 2] cycloaddition with cyclopropenes and maleimides (Scheme 1). It is known that indole-fused heterocycles, such as benzimidazo[1,2-a]indole derivatives, are structural fragments of numerous natural products and pharmacologically active compounds [32–36]. Previously, Lee and coworkers [37,38] described the functionalization of 11H-benzo[4,5]imidazo[1,2-a]indol-11-one, which resulted in compounds of interest for the creation of phosphorescent organic light-emitting devices.
2. Results and Discussion

2.1. Synthesis

In initial studies, the possibility of 1,3-dipolar cycloaddition was investigated by performing a model three component reaction of cyclopropene 1a, 11H-benzo[4,5]imidazo[1,2-a]indol-11-one (2), and L-proline (3a) in various solvents (Table 1). In methanol or ethanol, only trace amounts of cycloadduct 4a/5a could be detected (Table 1, entries 1 and 2); when the reaction was carried out in THF or acetonitrile, the desired product 4a/5a was obtained in 21% or 52%, respectively, after 18 h (Table 1, entries 3 and 4). At the same time, when carrying out the reaction in low-polarity dioxane, it was possible to increase the yield of the target product to 64%; however, in this case, as in all others, a low level of diastereoselectivity was observed (dr 2:1) (Table 1, entry 5). The use of non-polar solvents such as benzene or toluene did not increase the yield (Table 1, entries 6 and 7). Non-polar solvents such as benzene or toluene did not facilitate an increase of the yield (Table 1, entries 6 and 7). Non-polar solvents such as benzene or toluene did not increase the yield (Table 1, entries 6 and 7). Non-polar solvents such as benzene or toluene did not facilitate an increase of the yield (Table 1, entries 6 and 7). Non-polar solvents such as benzene or toluene did not increase the yield (Table 1, entries 6 and 7). Non-polar solvents such as benzene or toluene did not facilitate an increase of the yield (Table 1, entries 6 and 7).

Through the experiments above, we finally confirmed the optimal reaction conditions: 1 (0.3 mmol), 2 (0.3 mmol), 3 (0.6 mmol), and 1,4-dioxane (4 mL) in a sealed tube at 100 °C for 18 h under a nitrogen atmosphere.

To explore the scope of the reaction, a range of cyclopropene dipolarophiles 1a-h was tested in the reaction with azomethine ylide generated from ketone 2 and L-proline (3a) under optimized conditions. The results are summarized in Table 2.
Unsubstituted and methyl-substituted cyclopropenes proved to be ineffective as dipolarophiles in this reaction. In most cases, the diastereomers are chromatographically inseparable. Inseparable mixture of diastereomers.

Table 1. Optimization of the Reaction Conditions.

| Entry | Solvent | T (°C) | Time, h | Yield \(^{b}\) of 4a/5a, % (dr) |
|-------|---------|--------|---------|-------------------------------|
| 1     | EtOH    | 80     | 6       | Trace                         |
| 2     | MeOH    | 60     | 6       | Trace                         |
| 3     | THF     | 70     | 18      | 21 (2.6:1)                    |
| 4     | CH₃CN   | 90     | 18      | 52 (1.8:1)                    |
| 5     | 1,4-dioxane | 100   | 18      | 64 (2:1)                      |
| 6     | benzene | 80     | 18      | 27 (2.2:1)                    |
| 7     | toluene | 110    | 18      | 39 (1.5:1)                    |

\(^a\) Reaction conditions: 1a (1 equiv.), 2 (1 equiv.), 3a (2 equiv.), solvent. \(^b\) Isolated yield. \(^c\) The reaction was carried out in a sealed tube under a nitrogen atmosphere.

Table 2. Synthesis of Racemic Spiro-Adducts 4 via One-Pot Three-Component Reactions of Cyclopropenes 1a-h, Ketone 2 and L-Proline (3a) \(^a,b,c\).

| 1a-h | Solvent | 1,4-dioxane | 100 °C | sealed tube | 4a-h | 5e-h |
|------|---------|-------------|--------|-------------|------|------|
| 4a   | 64% yield \(^c\) | 2:1 dr     | 2:1 dr |
| 4b   | 83% yield \(^c\) | 2.2:1 dr   | 2.2:1 dr |
| 4c   | 64% yield \(^c\) | 2.3:1 dr   | 2.3:1 dr |
| 4d   | 56% yield major diastereomer |
| 5d   | 6% yield minor diastereomer |

\(^a\) Reactions of 1 (0.3 mmol), 2 (0.3 mmol), and 3 (0.6 mmol) were carried out in 1,4-dioxane (4 mL) in a sealed tube at 100 °C for 18 h under a nitrogen atmosphere. \(^b\) Isolated yield. \(^c\) Crystallization of the mixture from methanol gave the major diastereomer 4 as a pure compound. \(^d\) Inseparable mixture of diastereomers. \(^e\) The \(dr\) values were determined by \(^1\)H NMR of the crude mixture.

In addition to product 4a, various cycloadducts can be prepared as mixtures of diastereomers with good conversion and low \(dr\) (Table 2). In most cases, the diastereomers are chromatographically inseparable; however, the major endo-diastereomer 4c can be isolated by crystallization of the mixture from methanol (Table 2, 4a-c,e-h). Only in the case of cycloadduct 4d/5d derived from trimethylsilylcyclopropene 1d were both diastereomers...
4d and 5d successfully separated by preparative TLC. It is important to note that cyclopropenes with both electron-rich and electron-deficient substituents R\(^1\) at the C3 position turned out to be reactive towards this azomethine ylide. The corresponding cycloadducts 4a-h were obtained as mixtures of two diastereomers in overall yields of 58–83% (Table 2). No significant effect of the R\(^1\) substituents on the course of the reactions was observed. The structures of major diastereomers 4 were unambiguously confirmed by NMR spectroscopy and single-crystal X-ray analysis of 4f (Figure 2). The stereochemistry of the minor diastereomer 5d was determined using 2D NMR spectroscopy (see the Supporting Information, Figures S53–S59). As can be seen, the diastereomers 4 and 5 differ from each other in the configuration of the spiro atom. Attempts to carry out this reaction with other secondary a-amino acids such as sarcosine, azetidine-2-carboxylic acid, pipercolic acid, and thiazolidine-4-carboxylic acid were unsuccessful. It is noteworthy that only cyclopropenes containing phenyl substituents at the double bond can be used in this reaction. Unsubstituted and methyl-substituted cyclopropenes proved to be ineffective as dipolarophiles in this reaction.

![Figure 2. ORTEP representation of the molecular structure of 4f (CCDC 2195042).](image)

The trimethylsilyl group of 4d was readily removed by K\(_2\)CO\(_3\) in methanol and ether to obtain cyclopropylacetylene 4i in a 92% yield (Scheme 2).

![Scheme 2. Removal of the trimethylsilyl group from 4d.](image)

Upon further study of the substrate scope, we focused on the a-amino acid component (Table 3). First, we performed a reaction between cyclopropene 1a and azomethine ylide generated in situ from ketone 2 and 2-aminobutanoic acid (3b). As a result, spiro[3-azabicyclo[3.1.0]hexane] 6a was obtained as a chromatographically inseparable mixture of two diastereomers in 46% yield with low dr (2.6:1). The major endo-diastereomer can be obtained in pure form by crystallization from methanol. The reaction between cyclopropene 1a, ketone 2, and different alkyl-substituted amino acids (DL-norvaline (3c), L-methionine (3d), DL-norleucine (3e), and L-leucine (3f)) proceeded smoothly under the optimal reaction conditions and produced the expected spiro cycloadducts 6b–e in moderate isolated yields (42–53%) (Table 3). As in the previous case, these products are formed as a mixture of diastereomers, from which the main component can be isolated by crystallization from methanol. Subsequently, the cyclopropene scope of the 1,3-dipolar cycloaddition was investigated, employing ketone 2 and L-leucine (3f) as precursors of the azomethine ylide.
It should be noted that cyclopropenes 1b–d,f,h give the corresponding products 6f–j in moderate yields, regardless of the electronic effect of the substituent at C3 (Table 3). Summarizing the data given in Table 3, it should be noted that the nature of the substituent at the cyclopropene ring does not significantly affect the yield of the target spiro adducts nor the stereochemistry of cycloaddition. The stereochemistry of the major diastereomer is identical to the stereochemistry of the cycloadducts obtained from cyclopropenes and azomethine ylides based on isatin, 11H-indeno[1,2-b]quinoxalin-11-one, and tryptanthrin (previously described in a series studies) [22,28,29]. In the case of other primary N-amino acids such as glycine, alanine, valine, 2-aminocaprylic acid, phenylglycine, phenylalanine, and tryptophan, the corresponding cycloadducts could not be obtained.

### Table 3. Synthesis of Racemic Spiro-Adducts 6 via One-Pot Three-Component Reactions of Cyclopropenes 1a-d,f,h, Ketone 2 and Primary N-Amino Acids 3b–f a,b,c,d.

| R1 | R2 | Isolated yield | dr | R1 | R2 | Isolated yield | dr |
|----|----|----------------|----|----|----|----------------|----|
| Ph | Ph | 40% yield | 2.6:1 dr | Ph | Ph | 50% yield | 2.1:1 dr |
| CH3 | CH3 | 49% yield | 2.3:1 dr | Ph | Ph | 42% yield | 2.4:1 dr |
| CH3 | CH3 | 53% yield | 2:1 dr |
| CH3 | CH3 | 45% yield | 2.1:1 dr | Ph | Ph | 50% yield | 3.1:1 dr |
| CH3 | CH3 | 50% yield | 2.2:1 dr | Ph | Ph | 55% yield | 1.9:1 dr |
| CH3 | CH3 | 53% yield | 2.1:1 dr |

a Reactions of 1 (0.3 mmol), 2 (0.3 mmol), and 3 (0.6 mmol) were carried out in 1,4-dioxane (4 mL) in a sealed tube at 100 °C for 18 h under a nitrogen atmosphere. b Isolated yield. c Crystallization of the diastereomeric mixture from methanol gave the major diastereomer 6 as a pure compound. d The dr values were determined by 1H NMR of the crude mixture.

As shown above, cyclopropenes can successfully act as dipolarophiles in reactions with azomethine ylides derived from ketones and amino acids, which allowed us to expand the structural diversity of dipoles capable of reacting with cyclopropenes. However, other dipolarophiles are also of interest for studying their reactivity towards new azomethine ylides. We turned our attention to the maleimides, classical dipolarophiles well-studied in many 1,3-dipolar cycloaddition reactions. Various maleimides 7 were tested in the reaction with azomethine ylide generated from 2 and 3a, and the results are summarized in Table 4. Optimization of the reaction conditions showed that the best yield of cycloadducts was achieved when the reactions were carried out in an acetonitrile medium. The three-component reaction involving parent maleimide (7a) proceeded in acetonitrile at 100 °C for 18 h with the formation of endo-product 8a in 78% yield with 1:5:1 diastereoselectivity (Table 4). Reaction of ketone 2, L-proline (3a) and N-methyl maleimide (7b) afforded 8b in 69% yield with low diastereoselectivity (1:7:1 dr). Interestingly, N-phenyl maleimide (7c) resulted in an increase in diastereoselectivity (8c, 9:1 dr). The higher diastereoselectivity can be explained by the π-π interaction between the phenyl group of maleimide 7c and...
the aromatic moiety of azomethine ylide. N-Alkylmaleimides 7d–f also reacted smoothly with the azomethine ylide generated from 2 and 3a to form the desired endo-products 8d–f in high yields (68−89%), albeit with low diastereoselectivity. The structure and relative configuration of 8f were unambiguously determined by X-ray diffraction analysis (Figure 3). In line with the structure of 8f, this relative configuration was assigned to other major cycloadducts 8. The minor diastereomer is an epimer and differs in its spiro atom configuration.

**Table 4.** Synthesis of Racemic Spiro-Adducts 8 via One-Pot Three-Component Reactions of Maleimides 7a–f, Ketone 2 and L-Proline 3a a,b,c.

| a | Reactions of 7 (0.25 mmol), 2 (0.25 mmol), and 3a (0.5 mmol) were carried out in acetonitrile (4 mL) in a sealed tube at 100 °C for 18 h under a nitrogen atmosphere. b | Isolated yield. c | The dr values were determined by 1H NMR of the crude mixture. |

![Chemical structure and reaction scheme](image)

**Figure 3.** ORTEP representation of the molecular structure of 8f (CCDC 2195043).

2.2. **Computational Study**

Given that 11H-benzo[4,5]imidazo[1,2-a]indol-11-one (2) had not previously been studied as a precursor of azomethine ylides, we considered it necessary to carry out a density functional theory (DFT) computational study that would enable obtaining a comprehensive view of the reaction mechanisms of azomethine ylide formation and cycloaddition between
1,2-diphenyl-3-vinylcyclopropene (1c) and azomethine ylide generated from 2 (Figure 4). Moreover, this calculation data may provide further evidence of the relative configuration of both resulting diastereomers 4c and 5c.

Initially, we calculated the Gibbs free energy change for the reactions of azomethine ylide AY-1 (S-shaped) and AY-2 (W-shaped) formation from tetracyclic ketone (2) and L-proline (3a). These reactions are exergonic processes taking place with a decrease in the Gibbs free energy (ΔG = −7.3 kcal/mol for AY-1, ΔG = −6.4 kcal/mol for AY-2). As was established in studies [39,40] regarding the decarboxylative route to azomethine ylides, the first intermediate is an oxazolidin-5-one derivative. The latter is converted into a nitrogen ylide as a result of stereospecific 1,3-dipolar cycloversion. In this case, the condensation reactions involving cyclopropene 1c and ylides AY-1 (ΔG‡1c+AY-1→4c = 7.95 kcal/mol), AY-2 (ΔG‡1c+AY-2→5c = 8.01 kcal/mol) are immediately trapped by cyclopropene 1c, since both ylides are immediately trapped by cyclopropene 1c. It is remarkable that each of these ylides produces only one cycloadduct. According to the calculation data, cycloaddition reactions of 1,2-diphenyl-3-vinylcyclopropene (1c) to both forms of the azomethine ylide, AY-1 and AY-2, occur strictly via endo transition states (ΔG‡1c+AY-1→4c = 7.95 kcal/mol and ΔG‡1c+AY-2→5c = 8.01 kcal/mol), which significantly prevail over exo ones (ΔG‡1c+AY-1→4c = 11.59 kcal/mol and

**Figure 4.** Plausible reaction mechanism for the reaction of 1,2-diphenyl-3-vinylcyclopropene (1c), 11H-benz[4,5]imidazo[1,2-a]indol-11-one (AY-1), and L-proline (3a).
ΔG‡1c + AY - 2c > 5c′ = 11.77 kcal/mol). Of the two endo pathways, the endo approach involving ylide AY-1 is more favorable than the other endo approach (ca. 0.9 kcal/mol). The calculation data are completely consistent with experimental results. Actually, cycloadduct 4c, the precursor of which is the more thermodynamically stable ylide AY-1, predominates in the mixture of diastereomers 4c and 5c. In the meantime, minor diastereomer 5c results from the endo approach of ylide AY-2 to cyclopropane 1c. Probably, these findings hold true for other cycloaddition reactions between cyclopropanes 1 and azomethine ylide generated from 2 and 3a.

2.3. Biological Assay

The antiproliferative activity of some of the synthesized spiro-fused 11H-benzo[4,5]imidazo[1,2-a]indol-11-ones and cyclopropa[a]pyrrolysines 4 or 3-azabicyclo[3.1.0]hexanes 6 against human erythroleukemia (K562) cell line was evaluated in vitro using the standard MTS assay for 24 and 72 h. The results of these investigations are presented in Figure 5. It was found that spiroadducts with the N-isopropylcarbamoyl group at the cyclopropane moiety were more active, while replacement of this group with phenyl one led to a significant decrease in this activity. Thus, it was found that among the tested compounds, spiroadducts 4f and 6i demonstrated a significant activity, with IC₅₀ 5 ± 1 and 12 ± 2 μg/mL, respectively.

Figure 5. Cytotoxicity of Selected Racemic Spiro-Adducts 4 and 6 against the K562 cell line for 24 h (A) and 72 h (B).

3. Materials and Methods

3.1. Chemistry

NMR spectra were recorded with a Bruker Avance 400 spectrometer (400.13 MHz for ¹H and 100.61 MHz for ¹³C). Chemical shifts are reported in ppm relative to residual CHCl₃ (¹H, δ = 7.26 ppm), CDCl₃ (¹³C, δ = 77.17), residual DMSO-d₅ (¹H, 2.50 ppm), and DMSO-d₆ (¹³C, 39.52 ppm) as internal standards. Mass spectra were recorded on a HRMS-ESI-QTOF mass-analyzer, electrospray ionization, positive mode. Single-crystal X-ray diffraction experiments for compounds 4f and 8f were carried out using an Agilent Technologies «Xcalibur» diffractometer with monochromated Mo Kα radiation. Melting points were determined on a melting point apparatus and are uncorrected. 11H-Benzо[4,5]imidazo[1,2-a]indol-11-one was obtained from 11H-benzo[d]imidazole and 2-fluorobenzaldehyde, according to a known method [37]. Cyclopropanes 1a [41], 1b, c [42], 1d [43], 1e [44], 1f, g [45], and 1h [46] were prepared according to the literature data, while α-amino acids 3 were obtained from commercial sources. Maleimides 7e [47] and 7f [48] were synthesized according to previously described procedures, 7a–d were obtained from commercial sources. Crystallographic data for compounds 4f (CCDC 2195042) and 8f (CCDC 2195043) have been deposited at the Cambridge Crystallographic Data Centre and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif (accessed on 5 August 2022). Copies of ¹H and ¹³C NMR spectra of compounds 4–6 and 8 are given at Supporting Informa-
tion, (Figures S1–S52). X-ray crystallographic data for compounds 4f and 8f are given at Supporting Information, (Figures S60, S61 and Tables S1 and S2).

General Procedure A for the One-Pot Three-Component Reaction of 1H-Benz[4,5]-imidazo[1,2-α]indol-11-one, L-Proline, and Cyclopropanes

1H-Benz[4,5]-imidazo[1,2-α]indol-11-one (2, 0.3 mmol), L-proline (3a, 0.6 mmol), cyclopropane (1, 0.3 mmol), and anhydrous 1,4-dioxane (4 mL) were added to a screw-capped tube (Schuett-biotec type). The reaction vessel was closed and the reaction mixture was stirred in a preheated oil bath at 100 °C for 18 h (the reaction progress was monitored by TLC). The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to silica gel PTLC using a mixture of hexane–ethyl acetate as an eluent to give the major diastereomer 4a–h.

(±)-(1'R,1'a'R,2'R,6'a'S,6b'S)-1',1a',6b'-Triphenyl-1'a',4',5',6',6a',6b'-hexahydro-1'H-spirobenzo[4,5]-imidazo[1,2-α]indol-11,2'-cyclopropa[α]pyrrolizine (4a) and (1'R,1'a'R,2'S,6'a'S,6b'S)-1',1a',6b'-triphenyl-1'a',4',5',6',6a',6b'-hexahydro-1'H-spirobenzo[4,5]-imidazo[1,2-α]indol-11,2'-cyclopropa[α]pyrrolizine (5a)

Prepared according to the general procedure A using cyclopropane 1a (85.3 mg, 0.22 mmol), ketone 2 (70.0 mg, 0.32 mmol) and L-proline (3a) (73.2 mg, 0.64 mmol). Purification of the crude (hexane–ethyl acetate, 3:1) furnished 4a and 5a (112 mg, 64%) as an inseparable mixture in ratio 2:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 4a as a pure compound (67 mg; Data for 4a: white solid; mp 170–172 °C; Rf 0.64 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3056, 2963, 2905, 2836, 1609, 1523, 1492, 1472, 1445, 1347, 1306, 1222, 1166, 772, 737, 706, 556, 534 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.89 (t, J = 7.7 Hz, 2 H), 7.61 (d, J = 7.7 Hz, 2 H), 7.49 (d, J = 7.7 Hz, 1 H), 7.40 (t, J = 7.7 Hz, 1 H), 7.33–7.22 (m, 7 H), 7.02 (t, J = 7.7 Hz, 1 H), 6.94 (t, J = 7.7 Hz, 2 H), 6.75 (brs, 2 H), 6.56 (t, J = 7.7 Hz, 1 H), 6.60 (t, J = 7.7 Hz, 2 H), 6.48 (d, J = 7.7 Hz, 2 H), 4.81 (t, J = 7.0 Hz, 1 H), 3.70 (s, 1 H), 3.20 (q, J = 7.0 Hz, 1 H), 2.57 (m, 1 H), 2.20 (m, 1 H), 2.03 (m, 1 H), 1.90–1.80 (m, 2 H).

13C NMR (101 MHz, CDCl3): δ = 162.3, 148.2, 138.9, 137.1, 134.7, 134.4, 134.3, 132.3 (4 C), 131.3, 130.9 (2 C), 129.4, 129.1, 127.7 (2 C), 126.5 (2 C), 126.5, 126.4 (2 C), 126.4, 126.2, 125.0, 123.8, 122.7, 122.1, 120.7, 110.5, 110.2, 75.7, 71.4, 57.6, 46.5, 45.1, 31.3, 26.6, 25.0.

HRMS (ESI): m/z [M+H]+ calcd for C30H32N3: 452.2592; found: 452.2592.

(±)-(1'R,1'a'R,2'R,6'a'S,6b'S)-1'-Ethyl-1'a',6b'-diphenyl-1'a',4',5',6',6a',6b'-hexahydro-1'H-spirobenzo[4,5]-imidazo[1,2-α]indol-11,2'-cyclopropa[α]pyrrolizine (4b) and (±)-(1'R,1'a'R,2'S,6'a'S,6b'S)-1'-ethyl-1'a',6b'-diphenyl-1'a',4',5',6',6a',6b'-hexahydro-1'H-spirobenzo[4,5]-imidazo[1,2-α]indol-11,2'-cyclopropa[α]pyrrolizine (5b)

Prepared according to the general procedure A using cyclopropane 1b (70.5 mg, 0.32 mmol), ketone 2 (70.0 mg, 0.32 mmol), and L-proline (3a) (73.2 mg, 0.64 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished 4b and 5b (131 mg, 83%) as an inseparable mixture in ratio 2:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 4b as a pure compound (81 mg; Data for 4b: white solid; mp 220–222 °C; Rf 0.59 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3056, 2963, 2905, 2836, 1609, 1523, 1492, 1472, 1445, 1347, 1347, 1306, 1222, 1166, 922, 748, 737, 699 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.89 (d, J = 7.5 Hz, 1 H), 7.87–7.80 (m, 1 H), 7.52–7.42 (m, 4 H), 7.36–7.27 (m, 4 H), 7.26–7.18 (m, 3 H), 6.88–6.80 (m, 3 H), 6.76 (t, J = 7.5 Hz, 2 H), 4.79 (brm, 1 H), 3.05–2.98 (m, 1 H), 2.50–2.38 (m, 2 H), 2.33–2.11 (m, 2 H), 2.11–1.99 (m, 1 H), 1.89–1.75 (m, 1 H), 1.63–1.49 (m, 1 H), 1.47–1.34 (m, 1 H), 1.02 (t, J = 7.0 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 162.4, 148.0, 138.9, 137.9, 135.3, 132.7, 131.6 (2 C), 129.9 (2 C), 129.3, 129.1, 127.5 (2 C), 126.7 (2 C), 126.4, 126.0, 125.6, 123.7, 122.6, 122.0, 120.6, 110.5, 110.1, 71.7, 70.5, 54.4, 44.4, 41.7, 29.6, 26.8, 26.6, 19.2, 14.2.

HRMS (ESI): m/z [M+H]+ calcd for C30H32N3: 494.2591; found: 494.2597.

(±)-(1'R,1'a'R,2'R,6'a'S,6b'S)-1'-Ethyl-1'a',6b'-diphenyl-1'a',4',5',6',6a',6b'-hexahydro-1'H-spirobenzo[4,5]-imidazo[1,2-α]indol-11,2'-cyclopropa[α]pyrrolizine (4c) and (±)-
Prepared according to general procedure A using cyclopropene 1c (69.9 mg, 0.32 mmol), ketone 2 (70.0 mg, 0.32 mmol), and L-proline (3a) (73.2 mg, 0.64 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 5:1) furnished 4c and 5c (101 mg, 64%) as an inseparable mixture in a ratio of 2.3:1, respectively.

Data for mixture 4c + 5c: white solid; mp 218–220 °C.

IR (KBr): 3055, 2967, 2910, 2869, 2809, 1610, 1526, 1493, 1473, 1446, 1348, 1223, 1168, 998, 902, 740, 699, 443 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.00 (d, J = 7.5 Hz, 1 H), 7.97 (d, J = 7.5 Hz, 1 H), 7.90 (d, J = 7.5 Hz, 1 H), 7.89 (d, J = 7.5 Hz, 2 H), 7.85 (d, J = 7.5 Hz, 1 H), 7.65 (d, J = 7.5 Hz, 1 H), 7.59 (d, J = 7.5 Hz, 1 H), 7.49 (d, J = 7.5 Hz, 1 H), 7.45–7.21 (m, 8 H(4c + 5c)), 7.17 (d, J = 7.5 Hz, 1 H), 6.97 (d, J = 7.5 Hz, 2 H), 6.82–6.76 (m, 1 H), 6.75–6.65 (m, 2 H(4c + 4 H(5c))), 5.62 (dd, J = 17.0, 2.5 Hz, 1 H(5c)), 5.49 (dd, J = 17.0, 2.5 Hz, 1 H(5c)), 5.16 (dt, J = 17.0, 10.3 Hz, 1 H(4c)), 5.05 (dd, J = 10.3, 2.5 Hz, 1 H(4c)), 5.01 (dd, J = 10.3, 2.5 Hz, 1 H(5c)), 4.95 (dt, J = 17.0, 10.3 Hz, 1 H(5c)), 4.76 (dd, J = 8.5, 6.0 Hz, 1 H(5c + 5e)), 4.12 (brq, J = 7.2 Hz, 1 H(5c)), 3.30 (d, J = 9.6 Hz, 1 H(5c)), 3.25 (d, J = 10.6 Hz, 1 H(5c)), 3.10 (q, J = 7.2 Hz, 1 H(5c)), 2.80 (brt, J = 8.0 Hz, 1 H(5c)), 2.50 (td, J = 8.0, 4.0 Hz, 1 H(4c)), 2.27–1.91 (m, 3 H(4c + 5c)), 1.91–1.73 (m, 2 H(4c + 5c)).

¹³C NMR (101 MHz, CDCl₃): δ = 162.2 (4c), 148.2 (4c), 138.9 (4c), 138.0 (4c), 136.6 (4c), 134.6 (4c), 132.6, 132.1 (2 C (4c)), 131.4 (2 C (4c)), 131.1 (4c), 129.4 (4c), 129.2 (4c), 128.1 (4c), 127.9 (2 C (4c)), 126.8 (4c), 126.7 (2 C), 126.4, 126.3 (4c), 124.3 (5c), 123.8 (4c), 123.3 (5c), 122.7 (4c), 122.4 (5c), 122.1 (4c), 120.8 (5c), 120.7 (4c), 114.1 (5c), 113.3 (4c), 110.5 (4c), 110.4 (5c), 110.2 (4c), 110.1 (5c), 74.3 (4c), 70.9 (4c), 55.2 (4c), 49.4 (4c), 45.0 (4c), 44.9 (4c), 32.2 (5c), 30.7 (4c), 27.8 (5c), 27.2 (5c), 26.6 (4c), 25.1 (4c).

HRMS (ESI): m/z [M+H]+ calc'd for C₃₈H₃₉N₃: 562.2673; found: 562.2679.

(±)-(1'R,1a'R,2'R,6a'R,6b'S)-1a',6b'-diphenyl-1'-vinyl-1a',4',5',6',6a',6b'-hexahydro-1'H-spiro[benzo[4,5]imidazo[1,2-alindole-11,2'-cyclopropa[alpyrro]lizine] (5d)

Prepared according to general procedure A using cyclopropene 1d (92.3 mg, 0.32 mmol), ketone 2 (70.0 mg, 0.32 mmol), and L-proline (3a) (73.2 mg, 0.64 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished 4d and 5d as separated diastereomers.

Data for major diastereomer 4d: yield 101 mg (56%); white solid; mp 189–191 °C; Rᵢ 0.60 (SiO₂, hexane–ethyl acetate, 3:1).

IR (KBr): 3057, 2969, 2835, 2152, 1609, 1526, 1492, 1471, 1446, 1344, 1250, 1223, 849, 840, 735, 697 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.91–7.84 (m, 2 H), 7.65 (d, J = 7.5 Hz, 2 H), 7.52–7.47 (m, 1 H), 7.44 (t, J = 7.5 Hz, 1 H), 7.37–7.20 (m, 7 H), 6.95 (d, J = 7.5 Hz, 2 H), 6.86 (t, J = 7.5 Hz, 1 H), 6.76 (t, J = 7.5 Hz, 2 H), 4.85 (dd, J = 5.0, 9.0 Hz, 1 H), 3.42 (s, 1 H), 3.06–2.82 (m, 1 H), 2.44–2.33 (m, 1 H), 2.22–1.98 (m, 3 H), 1.85–1.70 (m, 1 H), –0.05 (s, 9 H).

¹³C NMR (101 MHz, CDCl₃): δ = 160.9, 147.9, 138.7, 135.2, 134.0, 132.3 (2 C), 130.6, 130.1 (2 C), 129.5, 129.2, 127.1 (2 C), 126.7, 126.5 (2 C), 126.2, 125.9, 124.1, 122.8, 122.1, 122.0, 110.5, 110.2, 104.2, 92.0, 70.7, 69.6, 56.5, 43.6, 43.0, 26.5, 25.3, 19.0, –0.5 (3 C).

HRMS (ESI): m/z [M+H]+ calc'd for C₃₈H₃₉N₃Si: 562.2673; found: 562.2679.

Data for minor diastereomer 5d: yield 11 mg (6%); white solid; mp 242–245 °C; Rᵢ 0.48 (SiO₂, hexane–ethyl acetate, 3:1).

IR (KBr): 3057, 2969, 2954, 2835, 2154, 1609, 1492, 1471, 1344, 1223, 850, 735, 697 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.06–7.99 (m, 1 H), 7.66–7.56 (m, 2 H), 7.50 (d, J = 7.5 Hz, 2 H), 7.43–7.35 (m, 2 H), 7.35–7.25 (m, 3 H), 7.24–7.13 (m, 3 H), 6.87 (t, J = 7.5 Hz, 1 H), 6.75 (t, J = 7.5 Hz, 2 H), 6.68 (d, J = 7.5 Hz, 2 H), 4.97 (brs, 1 H), 3.89 (brs, 1 H), 3.29 (s, 1 H), 2.73 (brs, 1 H), 2.31 (brs, 1 H), 2.22 (brs, 1 H), 2.07 (brs, 2 H), –0.13 (s, 9 H).
**13**C NMR (101 MHz, CDCl₃): δ = 158.0, 147.8, 141.0, 136.6, 135.1, 132.1 (2 C), 131.0, 129.9 (2 C), 129.3, 128.5, 127.3 (2 C), 126.5 (4 C), 125.6, 124.1, 123.4, 122.5, 120.9, 110.5, 110.2, 103.4, 92.1, 73.0, 72.9, 57.6, 48.6, 48.3, 28.5, 27.2, 21.8, −0.6 (3 C).

HRMS (ESI): m/z [M+H]+ calc'd for C₃₅H₃₈N₃Si: 562.2673; found: 562.2672.

(±)-(1′R,1′a′R,2′R,6a′R,6b′S)-Methyl 1′a′,6b′-diphenyl-1′a′,4′,5′,6′,6a′,6b′-hexahydro-1′H-spiro[benzo[4,5]imidazo[1,2-a]indole-11,2′-cyclopropa[α]pyrrolizine]-1′-carboxylate (4e) and (±)-(1′R,1′a′R,2′S,6a′R,6b′S)-methyl 1′a′,6b′-diphenyl-1′a′,4′,5′,6′,6a′,6b′-hexahydro-1′H-spiro[benzo [4,5]imidazo[1,2-a]indole-11,2′-cyclopropa[α]pyrrolizine]-1′-carboxylate (5e)

Prepared according to the general procedure A using cyclopropene 1f (88.8 mg, 0.32 mmol), ketone 2 (70.0 mg, 0.32 mmol), and L-proline (3a) (73.2 mg, 0.64 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished 4f and 5f (112 mg, 67%) as an inseparable mixture in a ratio of 3:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 4f as a pure compound (71 mg).

Data for 4f: white solid; mp 242–244 °C; Rf 0.36 (SiO₂, hexane–ethyl acetate, 3:1).

IR (KBr): 3056, 2949, 2843, 1740, 1609, 1472, 1447, 1357, 1237, 1169, 922, 741, 695, 618 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 8.00–7.90 (m, 2 H), 7.71 (d, J = 7.7 Hz, 2 H), 7.55–7.44 (m, 2 H), 7.42–7.25 (m, 7 H), 6.88 (d, J = 7.7 Hz, 2 H), 6.79 (t, J = 7.7 Hz, 1 H), 6.70 (t, J = 7.7 Hz, 2 H), 4.75 (brs, 1 H), 3.38 (s, 3 H), 3.37 (s, 3 H), 3.08 (m, 1 H), 2.51 (brs, 1 H), 2.14 (m, 1 H), 1.98 (m, 1 H), 1.87–1.75 (m, 2 H).

13C NMR (101 MHz, CDCl₃): δ = 170.0, 161.3, 148.0, 138.9, 134.4, 133.5, 131.6, 130.7 (2 C), 130.5 (2 C), 129.8, 128.9, 127.8 (2 C), 126.8, 126.7, 126.6 (2 C), 126.3, 124.1, 123.1, 122.4, 120.7, 110.8, 110.3, 74.7, 71.1, 58.2, 51.1, 48.3, 45.0, 28.8, 26.5, 25.2.

HRMS (ESI): m/z [M+H]+ calc'd for C₃₅H₃₈N₃SiO: 524.2333; found: 524.2333.

(±)-(1′R,1′a′R,2′R,6a′R,6b′S)-N-Isopropyl-1′a′,6b′-diphenyl-1′a′,4′,5′,6′,6a′,6b′-hexahydro-1′H-spiro[benzo[4,5]imidazo[1,2-a]indole-11,2′-cyclopropa[α]pyrrolizine]-1′-carboxamide (4f) and (±)-(1′R,1′a′R,2′S,6a′R,6b′S)-N-isopropyl-1′a′,6b′-diphenyl-1′a′,4′,5′,6′,6a′, 6b′-hexahydro-1′H-spiro[benzo[4,5]imidazo[1,2-a]indole-11,2′-cyclopropa[α]pyrrolizine]-1′-carboxamide (5f)

Prepared according to the general procedure A using cyclopropene 1f (88.8 mg, 0.32 mmol), ketone 2 (70.0 mg, 0.32 mmol), and L-proline (3a) (73.2 mg, 0.64 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished 4f and 5f (114 mg, 80%) as an inseparable mixture in a ratio of 5:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 4f as a pure compound (105 mg).

Data for 4f: white solid; mp 242–244 °C; Rf 0.69 (SiO₂, hexane–ethyl acetate, 1:2).

IR (KBr): 3423, 3048, 2965, 2844, 1644, 1609, 1532, 1493, 1472, 1446, 1352, 1222, 1168, 930, 764, 716, 699, 668, 668 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 8.05 (d, J = 7.7 Hz, 1 H), 7.94 (d, J = 7.7 Hz, 1 H), 7.88 (d, J = 7.7 Hz, 2 H), 7.80–7.74 (m, 4 H), 7.38–7.22 (m, 6 H), 7.03 (d, J = 7.7 Hz, 2 H), 6.84 (t, J = 7.7 Hz, 1 H), 6.75 (t, J = 7.7 Hz, 2 H), 4.72 (t, J = 6.0 Hz, 1 H), 3.69 (m, 1 H), 3.49 (d, J = 6.0 Hz, 1 H), 3.26 (s, 1 H), 3.19 (m, 1 H), 2.52 (m, 1 H), 2.11 (m, 1 H), 2.00–1.80 (m, 3 H), 0.55 (d, J = 6.5 Hz, 3 H), 0.27 (d, J = 6.5 Hz, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 168.0, 161.5, 138.9, 133.7, 133.3, 131.9 (2 C), 131.5 (2 C), 131.0, 129.8 (2 C), 128.9 (2 C), 128.2 (2 C), 127.5, 127.4, 127.3 (2 C), 126.9, 124.2, 122.9, 122.3, 120.7, 110.6, 110.2, 75.2, 56.0, 47.2, 45.9, 40.7, 31.6, 26.5, 25.4, 21.6, 21.3.

HRMS (ESI): m/z [M+H]+ calc'd for C₃₇H₃₉N₃O: 551.2805; found: 551.2805.

(±)-(1′R,1′a′R,2′R,6a′R,6b′S)-1′a′,6b′-Diphenyl-1′a′,4′,5′,6′,6a′,6b′-hexahydro-1′H-spiro[benzo[4,5]imidazo[1,2-a]indole-11,2′-cyclopropa[α]pyrrolizine]-1′-carboxylate (4g) and (±)-(1′R,1′a′R,2′S,6a′R,6b′S)-1′a′,6b′-diphenyl-1′a′,4′,5′,6′,6a′,6b′-hexahydro-1′H-spiro[benzo[4,5]imidazo[1,2-a]indole-11,2′-cyclopropa[α]pyrrolizine]-1′-carboxylate (5g)

Prepared according to the general procedure A using cyclopropene 1g (69.5 mg, 0.32 mmol), ketone 2 (70.0 mg, 0.32 mmol), and L-proline (3a) (73.2 mg, 0.64 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 2:1) furnished 4g and 5g (91 mg, 58%).
as an inseparable mixture in a ratio of 4:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 4g as a pure compound (35 mg).

Data for 4g: beige solid; mp 247–250 °C; Rf 0.39 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3422, 2962, 2857, 1704, 1491, 1451, 1351, 1230, 1109, 930 cm⁻¹.

HRMS (ESI): m/z [M+H]+ calcd for C38H37N3O3: 554.2784; found: 554.2783.

Cycloadduct 4d (80 mg, 0.142 mmol) was dissolved in ether (1 mL) and methanol gave the major diastereomer 4h as an inseparable mixture in a ratio of 3:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 4h as a pure compound (32 mg).

Data for 4h: white solid; mp 230–231 °C; Rf 0.54 (SiO2, hexane–ethyl acetate, 3:1) as an inseparable mixture in a ratio of 3:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 4h as a pure compound (32 mg).

HRMS (ESI): m/z [M+H]+ calcd for C34H27N4: 491.2230; found: 491.2230.

C12H12NO2 (20.9 mg; 0.151 mmol) was added and the resulting suspension was filtered off and washed with methanol and hexane to afford pure product 4i.

Yield: 64.9 mg (92%); white solid; mp 259–262 °C; Rf 0.43 (SiO2, hexane–ethyl acetate, 1:3).

IR (KBr): 3296, 2956, 2860, 1611, 1528, 1494, 1473, 1447, 1349, 1224, 1169, 926, 742, 704, 644, 624, 550, 442 cm⁻¹.

HRMS (ESI): m/z [M+H]+ calcd for C35H28N3: 505.2325; found: 505.2325.

General Procedure B for the One-Pot Three-Component Reaction of 11H-Benzo[4,5]-imidazo[1,2-alindole-11-one, Primary α-Amino Acids and Cyclopropenes
11H-Benz[4,5]imidazo[1,2-a]indol-11-one (2, 0.3 mmol), primary α-amino acid (3, 0.6 mmol), cyclopropene (1, 0.3 mmol), and anhydrous 1,4-dioxane (4 mL) were added to a screw-capped tube (Schuett-Biotec type). The reaction vessel was closed, and the reaction mixture was stirred in a preheated oil bath at 100 °C for 18 h (the reaction progress was monitored by TLC). The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to silica gel PTLC using a mixture of hexane–ethyl acetate as an eluent to give the spiro-adducts 6a–j.

(±)-(1'R,2'R,4'R,5'S,6'R)-4'-Ethyl-1',5',6'-triphenyl-3'-azaspiro[benezo[4,5]imidazo[1,2-alindole]-11,2'-bicyclo[3.1.0]hexane] (6a)

Prepared according to the general procedure B using cyclopropene 1a (91.5 mg, 0.34 mmol), ketone 2 (75.0 mg, 0.34 mmol), and DL-2-amino-butanolic acid (3b) (70.1 mg, 0.68 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished the corresponding cycloadduct (82 mg, 46%) as an inseparable mixture in a ratio of 2.6:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 6a as a pure compound (35 mg).

Data for 6a: beige solid; mp 226–228 °C; Rf 0.51 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3372, 3049, 3029, 2955, 2928, 2870, 1608, 1496, 1472, 1446, 1344, 1224, 914, 762, 699, 550, 438 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 8.00 (d, J = 7.8 Hz, 1 H), 7.98 (br.d, J = 7.8 Hz, 1 H), 7.63 (d, J = 7.5 Hz, 2 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.40–7.20 (m, 8 H), 7.02 (t, J = 7.5 Hz, 1 H), 6.93 (t, J = 7.5 Hz, 2 H), 6.90–6.50 (br.s, 2 H), 6.73 (t, J = 7.5 Hz, 1 H), 6.59 (br.t, J = 7.5 Hz, 2 H), 6.47 (d, J = 7.5 Hz, 2 H), 4.67 (dd, 4.0, 9.0 Hz, 1 H), 3.85 (s, 1 H), 2.80–2.00 (br.s, 1 H), 1.76–1.60 (m, 2 H), 0.94 (br.t, J = 7.0 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 163.8, 148.1, 138.4, 137.0, 136.8, 134.3, 133.1 (2 C), 132.3 (2 C), 131.0, 130.9 (2 C), 129.4, 129.2, 127.6 (2 C), 126.6 (2 C), 126.4 (4 C), 125.3, 125.0, 124.2, 123.0, 122.7, 120.0, 110.3, 110.2, 71.2, 68.5, 52.0, 47.4, 29.3, 23.7, 11.1.

HRMS (ESI): m/z [M+H]+ calcd for C39H39N3: 530.2591; found: 530.2595.

(±)-(1'R,2'R,4'R,5'S,6'R)-1',5',6'-Triphenyl-4'-propyl-3'-azaspiro[benzo[4,5]imidazo[1,2-alindole]-11,2'-bicyclo[3.1.0]hexane] (6b)

Prepared according to the general procedure B using cyclopropene 1a (91.5 mg, 0.34 mmol), ketone 2 (75.0 mg, 0.34 mmol), and DL-norvaline (3c) (79.7 mg, 0.68 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished the corresponding cycloadduct (92 mg, 50%) as an inseparable mixture in a ratio of 2.1:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 6b as a pure compound (41 mg).

Data for 6b: beige solid; mp 262–264 °C; Rf 0.49 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3372, 3049, 3029, 2955, 2928, 2870, 1608, 1496, 1472, 1446, 1344, 1224, 914, 762, 730, 699, 559, 546 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 8.00 (d, J = 7.8 Hz, 1 H), 7.97 (d, J = 7.8 Hz, 1 H), 7.64 (d, J = 7.5 Hz, 2 H), 7.47 (d, J = 7.7 Hz, 1 H), 7.42–7.18 (m, 8 H), 7.02 (t, J = 7.5 Hz, 1 H), 6.93 (t, J = 7.5 Hz, 2 H), 6.80–6.50 (br.s, 2 H), 6.73 (dd, 3.4, 9.5 Hz, 1 H), 3.84 (s, 1 H), 2.80–2.00 (br.s, 1 H), 1.76–1.60 (m, 2 H), 0.94 (br.t, J = 7.0 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 163.6, 148.1, 138.5, 137.2, 134.4, 133.3 (2 C), 132.4 (2 C), 131.2, 131.0 (3 C), 129.5, 129.3, 127.7 (2 C), 126.7 (2 C), 126.5 (3 C), 125.44, 125.39, 125.2, 124.3, 123.1, 122.3, 120.8, 110.4, 110.3, 71.3, 67.1, 51.9, 47.4, 33.1, 29.3, 20.0, 14.4.

HRMS (ESI): m/z [M+H]+ calcd for C39H39N3: 544.2747; found: 544.2752.

(±)-(1'R,2'R,4'R,5'S,6'R)-4'-2-(Methylthio)ethyl-1',5',6'-triphenyl-3'-azaspiro[benezo[4,5]imidazo[1,2-alindole]-11,2'-bicyclo[3.1.0]hexane] (6c)

Prepared according to the general procedure B using cyclopropene 1a (91.5 mg, 0.34 mmol), ketone 2 (75.0 mg, 0.34 mmol), and L-methionine (3d) (101.5 mg, 0.68 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished the corresponding cycloadduct (96 mg, 49%) as an inseparable mixture in a ratio of 2.3:1, respectively. Crystal-
lization of the mixture from methanol gave the major diastereomer 6c as a pure compound (57 mg).

Data for 6c: white solid; mp 245–247 °C; Rf 0.47 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3447, 3309, 3059, 3026, 2915, 2848, 1608, 1521, 1493, 1472, 1445, 1341, 1218, 1169, 1079, 739, 698 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.79 (d, J = 7.8 Hz, 1 H), 7.79 (d, J = 7.8 Hz, 1 H), 7.64 (d, J = 7.5 Hz, 2 H), 7.47 (d, J = 7.7 Hz, 1 H), 7.41–7.21 (m, 6 H), 7.03 (t, J = 7.5 Hz, 1 H), 6.94 (t, J = 7.5 Hz, 2 H), 6.80–6.40 (brs, 2 H), 6.74 (t, J = 7.5 Hz, 1 H), 6.59 (brt, J = 7.5 Hz, 2 H), 6.47 (d, J = 7.5 Hz, 2 H), 4.81 (t, J = 6.0 Hz, 1 H), 3.87 (s, 1 H), 2.95–2.40 (brs, 1 H), 2.63–2.43 (m, 2 H), 2.03 (s, 3 H), 2.01–1.90 (m, 2 H).

13C NMR (101 MHz, CDCl3): δ = 163.3, 148.0, 138.4, 136.7 (2 C), 133.8, 133.1 (2 C), 132.3 (2 C), 130.9 (3 C), 129.5, 129.2, 127.7 (2 C), 126.8, 126.6 (2 C), 126.4 (3 C), 125.3, 125.2, 124.3, 123.0, 122.3, 120.3, 110.4, 110.2, 71.2, 66.7, 51.7, 47.1, 31.5, 30.5, 29.5, 15.5.

HRMS (ESI): m/z [M+H]⁺ calc for C39H34N3S: 576.2468; found: 576.2470.

(±)-(1'R,2'R,4'R,5'S,6'R)-4'-Butyl-1',5',6'-triphenyl-3'-azaspiro[benzo[4,5]imidazo[1,2-alindole]-11',2',5'-bicyclo[3.1.0]hexane] (6d)

Prepared according to the general procedure B using cyclopropene 1a (91.5 mg, 0.34 mmol), ketone 2 (75.0 mg, 0.34 mmol), and DL-norleucine (3e) (89.2 mg, 0.68 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished the corresponding cycloduct (79 mg, 42%) as an inseparable mixture in a ratio of 2:1, respectively. Crystalization of the mixture from methanol gave the major diastereomer 6d as a pure compound (25 mg).

Data for 6d: white solid; mp 267–270 °C; Rf 0.46 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3306, 3031, 2955, 2929, 1608, 1540, 1493, 1473, 1447, 1364, 1226, 1168, 1032, 944, 807, 749, 738, 698, 551 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.98 (d, J = 7.8 Hz, 1 H), 7.92 (d, J = 7.8 Hz, 1 H), 7.55 (d, J = 7.5 Hz, 1 H), 7.41–7.26 (m, 9 H), 7.20 (d, J = 7.5 Hz, 1 H), 6.96 (t, J = 7.5 Hz, 1 H), 6.89 (t, J = 7.5 Hz, 2 H), 6.85–6.40 (brs, 2 H), 6.76 (t, J = 7.5 Hz, 1 H), 6.62 (brs, 2 H), 6.53 (d, J = 7.5 Hz, 2 H), 4.28 (dd, d = 3.4, 9.5 Hz, 1 H), 3.83 (s, 1 H), 3.20–2.60 (brs, 1 H), 1.76–1.60 (m, 2 H), 1.55–1.43 (m, 1 H), 1.33–1.21 (m, 3 H), 0.83 (s, J = 7.3 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 160.8, 147.4, 140.8, 137.2, 136.8, 134.2, 132.6 (2 C), 132.0, 131.7 (2 C), 130.9 (2 C), 129.5, 128.7, 127.9 (2 C), 126.9 (2 C), 126.8, 126.3 (2 C), 126.2, 124.9 (2 C), 124.4, 123.4, 122.7, 120.6, 110.6, 110.5, 72.8, 71.0, 53.4, 50.2, 30.7, 30.2, 29.3, 22.8, 13.9.

HRMS (ESI): m/z [M+H]⁺ calc for C40H36N3S: 558.2904; found: 558.2905.

(±)-(1'R,2'R,4'R,5'S,6'R)-4'-Isobutyl-1',5',6'-triphenyl-3'-azaspiro[benzo[4,5]imidazo[1,2-alindole]-11',2',5'-bicyclo[3.1.0]hexane] (6e)

Prepared according to the general procedure B using cyclopropene 1a (91.5 mg, 0.34 mmol), ketone 2 (75.0 mg, 0.34 mmol), and L-leucine (3f) (89.2 mg, 0.68 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished the corresponding cycloduct (101 mg, 53%) as an inseparable mixture in a ratio of 2:1, respectively. Crystalization of the mixture from methanol gave the major diastereomer 6e as a pure compound (52 mg).

Data for 6e: white solid; mp 255–257 °C; Rf 0.66 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3421, 3056, 3028, 2960, 2914, 2871, 2840, 1609, 1496, 1472, 1446, 1341, 1226, 1170, 763, 728, 699, 563, 546 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 8.00 (d, J = 7.8 Hz, 1 H), 7.97 (d, J = 7.8 Hz, 1 H), 7.79 (d, J = 7.5 Hz, 2 H), 7.47 (d, J = 7.7 Hz, 1 H), 7.41–7.20 (m, 8 H), 7.02 (t, J = 7.5 Hz, 1 H), 6.94 (t, J = 7.5 Hz, 2 H), 6.85–6.45 (brs, 2 H), 6.73 (t, J = 7.5 Hz, 1 H), 6.59 (t, J = 7.5 Hz, 2 H), 6.48 (d, J = 7.5 Hz, 2 H), 4.80 (dd, d = 3.4, 9.5 Hz, 1 H), 3.80 (s, 1 H), 2.80–1.80 (brs, 1 H), 1.75–1.56 (m, 2 H), 1.42–1.32 (m, 1 H), 0.91 (d, J = 6.3 Hz, 3 H), 0.83 (d, J = 6.3 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 163.5, 148.2, 138.5, 137.1, 134.2, 133.1 (2 C), 132.3 (2 C), 131.1, 130.9 (2 C), 129.4 (2 C), 129.2, 127.8, 127.6 (2 C), 126.6 (2 C), 126.4 (3 C), 125.2, 125.0, 124.2, 122.9, 122.1, 120.8, 110.3, 110.2, 71.4, 65.2, 51.8, 47.5, 39.7, 29.2, 25.4, 23.9, 21.7.
HRMS (ESI): m/z [M+H]+ calcd for C_{40}H_{36}N_{3}: 558.2904; found: 558.2909.

(±)-(1'R,2'R,4'R,5'S,6'R)-6'-Ethyl-4'-isobutyl-1',5'-diphenyl-3'-azaspiro[benzo[4,5]imidazo[1,2-a]indole-11,2'-bicyclo[3.1.0]hexane] (6f)

Prepared according to the general procedure B using cyclopropene 1b (70.0 mg, 0.32 mmol), ketone 2 (70.0 mg, 0.32 mmol), and L-leucine (3f) (83.4 mg, 0.64 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished the corresponding cycloadduct (79 mg, 48%) as an inseparable mixture in a ratio of 2:7:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 6f as a pure compound (31 mg).

Data for 6f: white solid; mp 215–216 °C; Rf 0.60 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3357, 3054, 2951, 2869, 1609, 1495, 1472, 1445, 1338, 1224, 1165, 770, 738, 700 cm⁻¹.  
1H NMR (400 MHz, CDCl₃): δ = 7.98 (d, J = 7.5 Hz, 2 H), 7.94–7.98 (m, 2 H), 7.55–7.40 (m, 4 H), 7.39–7.23 (m, 5 H), 6.84–6.73 (m, 3 H), 6.68 (t, J = 7.5 Hz, 2 H).  
13C NMR (101 MHz, CDCl₃): δ = 163.9, 148.3, 138.7, 138.0, 137.6, 133.8, 131.8 (2 C), 130.7 (2 C), 129.5, 129.4, 128.1 (2 C), 126.8 (2 C), 126.5, 126.1, 125.1, 124.3, 122.8, 122.1, 120.9, 110.6, 70.3, 64.1, 47.2, 44.7, 40.2, 26.4, 25.4, 23.8, 21.9, 20.2, 14.8.

HRMS (ESI): m/z [M+H]+ calcd for C_{39}H_{36}N_{3}: 510.2904; found: 510.2910.

(±)-(1'R,2'R,4'R,5'S,6'R)-4'-Isobutyl-1',5'-diphenyl-6'-vinyl-3'-azaspiro[benzo[4,5]imidazo[1,2-a]indole-11,2'-bicyclo[3.1.0]hexane] (6g)

Prepared according to the general procedure B using cyclopropene 1c (69.4 mg, 0.32 mmol), ketone 2 (70.0 mg, 0.32 mmol), and L-leucine (3f) (83.4 mg, 0.64 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished the corresponding cycloadduct (81 mg, 50%) as an inseparable mixture in a ratio of 3:1:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 6g as a pure compound (29 mg).

Data for 6g: white solid; mp 250–251 °C; Rf 0.59 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3330, 3057, 2954, 2923, 2866, 1607, 1525, 1491, 1470, 1447, 1341, 1223, 1167, 996, 896, 771, 742, 700, 634 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.97 (d, J = 7.5 Hz, 1 H), 7.94 (d, J = 7.5 Hz, 2 H), 7.88 (d, J = 7.5 Hz, 1 H), 7.48 (d, J = 7.5 Hz, 1 H), 7.44–7.36 (m, 3 H), 7.35–7.23 (m, 5 H), 6.93 (d, J = 7.5 Hz, 2 H), 6.78 (t, J = 7.5 Hz, 1 H), 6.70 (t, J = 7.5 Hz, 2 H), 5.49 (dd, J = 17.0, 2.5 Hz, 1 H), 5.33 (dd, J = 17.0, 10.0 Hz, 1 H), 5.04 (dd, J = 10.0, 2.5 Hz, 1 H), 4.74 (dd, J = 3.0, 10.0 Hz, 1 H), 3.33 (d, J = 10.0 Hz 1 H), 2.50–1.90 (br.s, 1 H), 1.66–1.53 (m, 2 H), 1.42–1.32 (m, 1 H), 0.90 (d, J = 6.3 Hz, 3 H), 0.84 (d, J = 6.3 Hz, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 163.5, 148.3, 138.4, 138.2, 136.8, 136.1, 132.9, 132.5, 132.1 (2 C), 132.0 (2 C), 129.4, 129.3, 127.9 (2 C), 126.7 (2 C), 126.6, 126.4, 125.3, 124.2, 122.9, 122.1, 120.7, 110.3, 110.2, 70.8, 64.2, 49.5, 46.1, 39.9, 28.9, 25.4, 23.8, 21.8.

HRMS (ESI): m/z [M+H]⁺ calcd for C_{38}H_{34}N_{3}: 508.2747; found: 508.2755.

(±)-(1'R,2'R,4'R,5'S,6'R)-4'-Isobutyl-1',5'-diphenyl-6'-(trimethylsilyl)ethynyl)-3'-azaspiro[benzo[4,5]imidazo[1,2-a]indole-11,2'-bicyclo[3.1.0]hexane] (6h)

Prepared according to the general procedure B using cyclopropene 1d (91.7 mg, 0.32 mmol), ketone 2 (70.0 mg, 0.32 mmol), and L-leucine (3f) (83.4 mg, 0.64 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 3:1) furnished the corresponding cycloadduct (93 mg, 48%) as an inseparable mixture in a ratio of 2.2:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 6h as a pure compound (42 mg).

Data for 6h: white solid; mp 182–185 °C; Rf 0.62 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3362, 3050, 2956, 2919, 2161, 1608, 1526, 1492, 1471, 1467, 1343, 1251, 1224, 1168, 844, 730, 702, 696, 577, 474 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 8.13 (d, J = 7.5 Hz, 2 H), 7.95 (d, J = 7.5 Hz, 1 H), 7.87 (d, J = 7.5 Hz, 1 H), 7.50 (d, J = 7.5 Hz, 1 H), 7.45–7.36 (m, 3 H), 7.34–7.24 (m, 5 H), 6.95 (d, J = 7.5 Hz, 2 H), 6.78 (t, J = 7.5 Hz, 1 H), 6.70 (t, J = 7.5 Hz, 2 H), 4.80 (dd, J = 3.0, 9.0 Hz, 1 H),
3.34 (s, 1 H), 2.45–1.87 (br.s, 1 H), 1.62–1.71 (m, 2 H), 1.49–1.39 (m, 1 H), 0.89 (d, J = 6.3 Hz, 3 H), 0.85 (d, J = 6.3 Hz, 3 H), -0.1 (s, 9 H).

13C NMR (101 MHz, CDCl3): δ = 163.1, 148.1, 138.4, 136.2, 135.1, 131.9 (2 C), 131.6, 131.2 (2 C), 129.5, 129.3, 127.5 (2 C), 126.7, 126.4 (3 C), 125.4, 124.3, 123.0, 122.2, 120.8, 110.4, 110.3, 105.0, 92.0, 69.9, 62.7, 50.9, 46.5, 40.2, 25.4, 23.7, 21.8, 15.7, –0.6 (3 C).

HRMS (ESI): m/z [M+H]+ calc for C38H40N3Si: 578.2986; found: 578.2994.

(±)-1'(R,2'R,4'R,5'S,6'R)-4'-Isobutyl-1',5'-diphenyl-3'-azaspiro[benzoimidazo[1,2-al]indole-11,2'-bicyclo[3.1.0]hexane]-6'-carboxamide (6i)

Prepared according to the general procedure B using cyclopropene 1f (100.8 mg, 0.36 mmol), ketone 2 (80.0 mg, 0.36 mmol), and L-leucine (3f) (95.3 mg, 0.73 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 2:1) furnished the corresponding cycladduct (112 mg, 55%) as an inseparable mixture in a ratio of 1.9:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 6i with an admixture of the minor 7i (overall 51 mg).

Data for 6i: white solid; mp 214–216 °C; Rf 0.77 (SiO2, hexane–ethyl acetate, 2:1).

IR (KBr): 3422, 3297, 3061, 3025, 2955, 2924, 2868, 1635, 1607, 1535, 1494, 1445, 1348, 1219, 1167, 763, 742, 698 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 8.00 (d, J = 7.7 Hz, 1 H), 7.94 (m, 3 H), 7.72 (d, J = 7.7 Hz, 1 H), 7.55–7.40 (m, 5 H), 7.38–7.25 (m, 4 H), 6.98 (d, J = 7.7 Hz, 1 H), 6.84 (t, J = 7.7 Hz, 1 H), 6.74 (t, J = 7.7 Hz, 1 H), 4.63 (d, J = 7.0 Hz, 1 H), 3.71 (m, 1 H), 3.54 (brs, 1 H), 3.37 (s, 1 H), 2.32 (brs, 1 H), 1.60 (m, 1 H), 0.88 (d, J = 6.5 Hz, 3 H), 0.80 (d, J = 6.5 Hz, 3 H), 0.59 (d, J = 6.5 Hz, 3 H), 0.29 (d, J = 6.7 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 168.2, 148.1, 138.5, 133.3, 132.6 (2 C), 131.4 (2 C), 131.0, 129.9, 129.8, 129.4, 129.1, 128.9, 128.0 (2 C), 127.6, 127.4, 127.3 (2 C), 125.6, 124.6, 123.0, 122.2, 120.8, 110.3, 110.2, 71.2, 65.2, 50.5, 48.0, 40.8, 39.3, 29.2, 25.3, 23.7, 21.6 (2 C).

HRMS (ESI): m/z [M+Na]+ calc for C38H38N4O3Na: 589.2938; found: 589.2938.

(±)-1'(R,2'R,4'R,5'S)-4'-Isobutyl-1',5'-diphenyl-3'-azaspiro[benzo[4,5][imidazo[1,2-al]indole-11,2'-bicyclo[3.1.0]hexane]-6'-carboxamide (6i)

Prepared according to the general procedure B using cyclopropene 1h (61.1 mg, 0.32 mmol), ketone 2 (70.0 mg, 0.32 mmol), and L-leucine (3f) (83.4 mg, 0.64 mmol). Purification of the crude by PTLC (hexane–ethyl acetate, 2:1) furnished the corresponding cycladduct (81 mg, 53%) as an inseparable mixture in a ratio of 2.1:1, respectively. Crystallization of the mixture from methanol gave the major diastereomer 6j as a pure compound (36 mg).

Data for 6j: white solid; mp 180–183 °C; Rf 0.54 (SiO2, hexane–ethyl acetate, 3:1).

IR (KBr): 3364, 3055, 3023, 2952, 2929, 2862, 2836, 1610, 1529, 1492, 1471, 1447, 1337, 1220, 1169, 1048, 1012, 917, 781, 736, 703, 593, 495 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.96 (d, J = 7.5 Hz, 1 H), 7.85 (d, J = 7.5 Hz, 1 H), 7.67 (d, J = 7.5 Hz, 2 H), 7.51 (d, J = 7.5 Hz, 1 H), 7.42–7.23 (m, 7 H), 7.20 (t, J = 7.5 Hz, 1 H), 6.87 (d, J = 7.5 Hz, 1 H), 6.76 (t, J = 7.5 Hz, 1 H), 6.68 (t, J = 7.5 Hz, 2 H), 5.03–4.98 (m, 1 H), 3.51 (s, 2 H), 2.41 (d, J = 4.0 Hz 1 H), 1.68–1.40 (m, 1 H), 0.92 (d, J = 6.3 Hz, 3 H), 0.90 (d, J = 6.3 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 163.6, 148.2, 138.3, 137.8, 137.1, 135.2, 131.3 (2 C), 129.7 (2 C), 129.4, 129.2, 128.0 (2 C), 126.9 (2 C), 126.3, 125.0, 124.1, 122.9, 122.1, 120.8, 110.4, 110.2, 69.9, 60.9, 50.8, 46.9, 41.6, 40.9, 25.5, 23.7, 22.1, 14.4.

HRMS (ESI): m/z [M+H]+ calc for C34H32N3: 482.2591; found: 482.2592.

General Procedure C for the One-Pot Three-Component Reaction of 11H-Benzo[4,5]-imidazo[1,2-al]indole-11-one, L-Proline and Maleimides

11H-Benzo[4,5]imidazo[1,2-al]indole-11-one (2, 0.25 mmol), L-proline (3a, 0.5 mmol), maleimide (7, 0.25 mmol), and anhydrous acetonitrile (4 mL) were added to a screw-capped tube (Schuett-biotech type). The reaction vessel was closed and the reaction mixture was stirred in a preheated oil bath at 100 °C for 18 h (the reaction progress was monitored using TLC). The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to silica gel PTLC using a mixture of
hexane—ethyl acetate as an eluent to give the mixtures of spiro-adducts 8a—f and their minor diastereomers.

(±)-(3a'S,4'R,8a'R,8b'R)-3a',6',7',8',8a',8b'-Hexahydro-1'H-spiro[benzo[4,5]imidazoindole-11,4'-pyrrolo[3,4-alpyrrolizin]-1',3'(2'H)-dione (8a) and (3a'S,4'S,8a'R,8b'R)-3a',6',7',8',8a',8b'-hexahydro-1'H-spiro[benzo[4,5]imidazo[1,2-alindole-11,4'-pyrrolo[3,4-alpyrrolizin]-1',3'(2'H)-dione (8a-minor).

Prepared according to the general procedure C using maleimide 7a (52.5 mg, 0.54 mmol), ketone 2 (85.0 mg, 0.39 mmol), and L-proline (3a) (88.9 mg, 0.77 mmol). Purification of the crude by PTLC (hexane-EtOAc, 1:2) furnished 8a as an inseparable mixture with its minor diastereomer in a ratio of 1.5:1, respectively (113 mg, 78%).

Data for mixture 8a+minor: white solid; mp 244–245 °C.

IR (KBr): 3470, 3152, 3058, 2966, 2765, 1770, 1717, 1609, 1530, 1495, 1474, 1450, 1337, 1304, 1285, 1269, 1246, 1266, 1260, 1114, 1113, 69.0, 65.8, 55.1, 48.6, 48.1, 28.9, 24.6.

HRMS (ESI): m/z [M+H]± calcd for C29H19N4O2: 371.1505; found: 371.1505.

(±)-(3a'S,4'R,8a'R,8b'R)-2'-Methyl-3a',6',7',8',8a',8b'-hexahydro-1'H-spiro[benzo[4,5]imidazo[1,2-alindole-11,4'-pyrrolo[3,4-alpyrrolizin]-1',3'(2'H)-dione (8b) and (±)-3a'S,4'S,8a'R,8b'R)-2'-methyl-3a',6',7',8',8a',8b'-hexahydro-1'H-spiro[benzo[4,5]imidazo[1,2-alindole-11,4'-pyrrolo[3,4-alpyrrolizin]-1',3'(2'H)-dione (8b-minor).

Prepared according to the general procedure C using maleimide 7a (56.5 mg, 0.49 mmol). Purification of the crude by PTLC (hexane-EtOAc, 1:2) furnished 8b as a pure compound (50 mg).

Data for 8b: white solid; mp 238–239 °C; Rf 0.52 (SiO2, hexane—ethyl acetate, 1:2).

IR (KBr): 3064, 2988, 2961, 2949, 2831, 1774, 1700, 1607, 1471, 1433, 1289, 1222, 1194, 743 cm−1.

1H NMR (400 MHz, DMSO-d6): δ = 11.52 (8a) (br.s, 1 H), 10.03 (minor) (br.s, 1 H), 8.12 (8a) (d, J = 7.9 Hz, 1 H), 8.09 (minor) (d, J = 7.9 Hz, 1 H), 7.94 (minor) (d, J = 7.9 Hz, 1 H), 7.91 (8a) (d, J = 7.9 Hz, 1 H), 7.84 (minor) (d, J = 7.9 Hz, 1 H), 7.77 (8a) (d, J = 7.9 Hz, 1 H), 7.73 (minor) (d, J = 7.9 Hz, 1 H), 7.59 (minor) (t, J = 7.9 Hz, 1 H), 7.54 (8a) (t, J = 7.9 Hz, 1 H), 7.44−7.19 (8a+minor) (m, 4 H (8a) + 3 H (minor)), 4.49 (minor) (td, J = 7.0, 2.5 Hz, 1 H), 4.39 (minor) (d, J = 9.8 Hz, 1 H), 4.20 (8a) (q, J = 7.5 Hz, 1 H), 4.08 (minor) (q, J = 5.5 Hz, 1 H), 3.78 (8a) (d, J = 7.5 Hz, 1 H), 3.59 (8a) (t, J = 7.5 Hz, 1 H), 3.17 (8a+minor) (d, J = 5.5 Hz, 1 H), 2.98 (minor) (m, 1 H), 2.57 (minor) (t, J = 7.5 Hz, 1 H), 2.27 (8a) (t, J = 7.5 Hz, 1 H), 2.17 (minor) (m, 1 H), 2.05−1.60 (8a+minor) (m, 4 H (8a) + 1 H (epimer)).

13C NMR (101 MHz, DMSO-d6) for 8a: δ = 177.7, 176.1, 160.6, 147.2, 137.7, 132.4, 130.1, 128.8, 127.3, 124.1, 123.7, 122.8, 120.2, 111.1, 65.1, 64.7, 59.8, 53.9, 44.9, 41.5, 26.0, 22.4.

13C NMR (101 MHz, DMSO-d6) for 8a-minor: δ = 179.2, 176.6, 161.0, 147.0, 138.0, 134.3, 130.4, 128.5, 126.9, 124.6, 126.6, 126.0, 111.4, 111.3, 69.0, 65.8, 55.1, 48.6, 48.1, 28.9, 24.6.

HRMS (ESI): m/z [M+H]+ calcd for C26H19N4O2: 371.1505; found: 371.1505.

(±)-(3a'S,4'R,8a'R,8b'R)-2'-Phenyl-3a',6',7',8',8a',8b'-hexahydro-1'H-spiro[benzo[4,5]imidazo[1,2-alindole-11,4'-pyrrolo[3,4-alpyrrolizin]-1',3'(2'H)-dione (8c) and (±)-3a'S,4'S,8a'R,8b'R)-2'-phenyl-3a',6',7',8',8a',8b'-hexahydro-1'H-spiro[benzo[4,5]imidazo[1,2-alindole-11,4'-pyrrolo[3,4-alpyrrolizin]-1',3'(2'H)-dione (8c-minor).

Prepared according to the general procedure C using maleimide 7c (42.5 mg, 0.23 mmol), ketone 2 (54.0 mg, 0.25 mmol), and L-proline (3a) (56.5 mg, 0.49 mmol). Purification of the
crude by PTLC (hexane-ethyl acetate, 1:2) furnished 8e as an inseparable mixture with its minor diastereomer in a ratio of 9:1, respectively (68.2 mg, 61%).

Data for mixture 8c+minor: light pink color; mp 198–200 °C.

IR (KBr): 3054, 2961, 2924, 2829, 1777, 1709, 1609, 1525, 1494, 1472, 1390, 1371, 1221, 1185, 744, 692, 616 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.89(8c) (d, J = 7.9 Hz, 1 H), 7.79(8c) (d, J = 7.9 Hz, 1 H), 7.60–7.35(8c+minor) (m, 9 H), 7.28(8c) (d, J = 7.9 Hz, 1 H), 7.22(8c) (t, J = 7.9 Hz, 1 H), 4.52(8c) (q, J = 6.5 Hz, 1 H), 4.36(minor) (brs, 1 H), 4.16(minor) (d, J = 8.5 Hz, 1 H), 4.08(8c) (d, J = 7.5 Hz, 1 H), 4.00(minor) (brs, 1 H), 3.81(8c) (t, J = 7.5 Hz, 1 H), 2.77(minor) (br m, 1 H), 2.48(8c+minor) (m, 1 H), 2.18–1.98(8c+minor) (m, 5 H).

13C NMR (101 MHz, CDCl₃) for 8c: δ = 175.1, 173.7, 160.5, 138.4, 132.2, 131.8, 130.1, 129.1 (2 C), 128.6, 127.5, 126.3 (2 C), 124.3, 124.0, 123.0, 120.6, 110.9, 110.7, 66.3, 65.9, 58.7, 43.9, 42.0, 26.4, 22.8.

HRMS (ESI): m/z [M+H]+ calc’d for C₂₃H₂₃N₂O₂: 447.1816; found: 447.1820.

(-)-(3a’S,4’R,8a’R,8b’R)-2’-Benzyl-3a’,6’,7’,8’,8a’,8b’-hexahydro-1’H-spiro[benzo[4,5]imidazo[1,2-alindole-11,4’-pyrrolo[3,4-alpyrrolizine]-1’3’(2’H)-dione (8d)

Prepared according to the general procedure C using maleimide 7d (45.9 mg, 0.25 mmol), ketone 2 (54.0 mg, 0.25 mmol), and L-proline (3a) (56.5 mg, 0.49 mmol). Purification of the crude by PTLC (hexane-ethyl acetate, 1:2) furnished 8d as an inseparable mixture with its minor diastereomer in a ratio of 2.3:1, respectively (103 mg, 89%).

Data for mixture 8d+minor: white solid; mp 164–166 °C.

IR (KBr): 3062, 2961, 2829, 1777, 1702, 1698, 1608, 1494, 1474, 1398, 1343, 1222, 1173, 757, 737, 709, 618 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.85(8d) (d, J = 7.9 Hz, 1 H), 7.75(8d) (d, J = 7.9 Hz, 1 H), 7.70(minor) (d, J = 7.9 Hz, 1 H), 6.67(8d) (d, J = 7.9 Hz, 1 H), 7.62(minor) (br, d, J = 7.9 Hz, 1 H), 7.56(8d+minor) (t, J = 7.9 Hz, 1 H), 7.52(8d+minor) (t, J = 7.5 Hz, 2 H), 7.43(8d+minor) (t, J = 7.5 Hz, 1 H), 7.52(8d+minor) (d, J = 7.5 Hz, 2 H), 7.38–7.22(8d+minor) (m, 4 H), 6.97(8d) (t, J = 7.9 Hz, 1 H), 6.55(8d) (d, J = 7.9 Hz, 1 H), 4.87(8d) (d, J = 13.6 Hz, 1 H), 4.75(minor) (br, m, 1 H), 4.68(8d) (d, J = 13.6 Hz, 1 H), 4.66(minor) (d, J = 14.3 Hz, 1 H), 4.43(8d) (q, J = 6.8 Hz, 1 H), 4.38(minor) (d, J = 14.3 Hz, 1 H), 4.23(minor) (d, J = 9.6 Hz, 1 H), 3.87(8d) (d, J = 7.5 Hz, 1 H), 3.66(8d) (t, J = 7.5 Hz, 1 H), 3.48(minor) (m, 1 H), 2.87(minor) (q, J = 7.5 Hz, 1 H), 2.76(minor) (br, t, J = 7.5 Hz, 1 H), 2.39(minor) (m, 1 H), 2.27(8d) (m, 1 H), 2.15–1.90(8d+minor) (m, 5 H), 8d(8d+3H(minor)).

13C NMR (101 MHz, CDCl₃) for 8d: δ = 175.7, 174.4, 160.5, 147.4, 138.2, 132.5, 132.1, 129.1 (2 C), 128.8, 128.5 (2 C), 128.3, 128.0, 127.8, 124.0, 123.9, 122.9, 120.6, 110.7, 110.6, 66.0, 65.7, 58.4, 44.1, 42.6, 42.0, 26.2, 22.7.

HRMS (ESI): m/z [M+H]+ calc’d for C₂₀H₂₅N₄O₂: 461.1972; found: 461.1978.

(±)-(3a’S,4’R,8a’R,8b’R)-2’-Phenethyl-3a’,6’,7’,8’,8a’,8b’-hexahydro-1’H-spiro[benzol[4,5]imidazo[1,2-alindole-11,4’-pyrrolo[3,4-alpyrrolizine]-1’3’(2’H)-dione (8e)

Prepared according to the general procedure C using maleimide 7e (49.3 mg, 0.25 mmol), ketone 2 (54.0 mg, 0.25 mmol), and L-proline (3a) (56.5 mg, 0.49 mmol). Purification of the crude by PTLC (hexane-ethyl acetate, 1:2) furnished 8e as an inseparable mixture with its minor diastereomer in a ratio of 1.5:1, respectively (95.4 mg, 80%).

Data for mixture 8e+minor: white solid; mp 162–164 °C.

IR (KBr): 3060, 3027, 2956, 2930, 2817, 1772, 1702, 1609, 1496, 1473, 1449, 1400, 1363, 1168, 767, 747, 738, 698 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.86(8e) (d, J = 7.9 Hz, 1 H), 7.77(8e) (d, J = 7.9 Hz, 1 H), 7.72(minor) (d, J = 7.9 Hz, 1 H), 7.70(minor) (d, J = 7.9 Hz, 1 H), 7.64(minor) (br, d, J = 7.9 Hz, 1 H), 7.60–7.52(8e+minor) (m, 1 H), 7.48(8e) (t, J = 7.5 Hz, 1 H), 7.43(8e) (t, J = 7.5 Hz, 1 H), 7.39–7.17(8e+minor) (m, 6 H), 6.8(8e) + 8 H(minor), 7.14(8e)
(t, J = 7.5 Hz, 1 H), 6.73(8e) (d, J = 7.5 Hz, 1 H), 4.79(minor) (br.m, 1 H), 4.40(8e) (m, 1 H), 4.20(8e) (d, J = 9.5 Hz, 1 H), 3.98(8e) (dt, J = 13.4, 8.0 Hz, 1 H), 3.86(8e) (ddd, J = 13.4, 6.0, 8.0 Hz, 1 H), 3.8(8e) (d, J = 7.5 Hz, 1 H), 3.59(8e) (m, 2 H), 3.47(minor) (m, 1 H), 3.13(8e) (dt, J = 13.4, 8.0 Hz, 1 H), 3.02(8e) (ddd, J = 13.4, 6.0, 8.0 Hz, 1 H), 3.0–2.78(minor) (m, 3 H), 2.69(minor) (m, 1 H), 2.43(minor) (m, 1 H), 2.24(8e) (m, 1 H), 2.18–1.88(8e+minor) (m, 4 H(8e) + 5 H(minor)).

13C NMR (101 MHz, CDCl3) for 8e: δ = 176.0, 174.5, 160.4, 147.6, 138.3, 137.6, 131.9, 130.4, 129.9, 129.1 (2 C), 128.4 (2 C), 128.3, 127.7, 126.7, 124.0, 122.9, 120.6, 110.7, 110.6, 65.7, 65.3, 58.3, 43.6, 41.6, 40.3, 33.3, 26.3, 22.8.

HRMS (ESI): m/z [M+H]+ calcld for C38H37N2O2: 547.2129; found: 547.2134.

(±)-(3a′,S,4′R,8a′R,8b′R)-2′-(2,2-Diphenylethyl)-3a′,6′,7′,8′,8a′,8b′-hexahydro-1′H-spiro[benzo[4,5]imidazo[1,2-a]indole-11′,4′-pyrrolo[3,4-a]pyrrolizine]-1′,3′(2′H)-dione (8f) and (±)-(3a′,S,4′S,8a′R,8b′R)-2′-(2,2-diphenylethyl)-3a′,6′,7′,8′,8a′,8b′-hexahydro-1′H-spiro[benzo[4,5]imidazo[1,2-a]indole-11′,4′-pyrrolo[3,4-a]pyrrolizine]-1′,3′(2′H)-dione (8f-minor)

Prepared according to the general procedure C using maleimide 7f (69.3 mg, 0.25 mmol), ketone 2 (54.0 mg, 0.25 mmol), and L-proline (3a) (56.5 mg, 0.49 mmol). Purification of the crude by PTLC (hexane-EtOAc, 1:2) furnished 8f as an inseparable mixture with its minor diastereomer in a ratio of 1:2.1, respectively (93.8 mg, 68%).

Data for mixture 8f+minor: white solid; mp 219–221 °C.

IR (KBr): 3053, 2960, 2926, 2878, 2828, 1773, 1700, 1609, 1492, 1472, 1446, 1398, 1345, 1169, 756, 744, 701 cm⁻¹.

1H NMR (400 MHz, CDCl3) for 8f+minor: δ = 7.84(minor) (d, J = 7.9 Hz, 1 H), 7.76(8f) (d, J = 7.9 Hz, 1 H), 7.74(8f) (d, J = 7.9 Hz, 1 H), 7.70(minor) (d, J = 7.9 Hz, 1 H), 7.60–7.46(8f+minor) (m, 3 H), 7.44–7.32(8f+minor) (m, 11 H), 7.31–7.10(8f+minor) (m, 14 H), 7.52(minor) (d, J = 7.9 Hz, 1 H), 4.83(8f) (t, J = 8.3 Hz, 1 H), 4.69(minor) (br.s, 1 H), 4.59(minor) (t, J = 8.3 Hz, 1 H), 4.38(8f) (br.q, J = 7.5 Hz, 1 H), 4.32(8f) (dd, J = 8.9, 13.5 Hz, 1 H), 4.24(8f) (dd, J = 7.7, 13.5 Hz, 1 H), 4.15(minor) (dd, J = 8.2, 13.2 Hz, 1 H), 4.03(minor) (dd, J = 9.1 Hz, 1 H), 3.85(minor) (dd, J = 9.1, 13.2 Hz, 1 H), 3.67(8f) (d, J = 7.5 Hz, 1 H), 3.53(8f) (t, J = 7.5 Hz, 1 H), 3.29(8f) (br.t, J = 8.0 Hz, 1 H), 2.88–2.73(8f+minor) (m, 2 H), 2.28(8f) (br.q, J = 8.5 Hz, 1 H), 2.18 (brs, 1 H), 2.11–1.80(8f+minor) (m, 8 H).

13C NMR (101 MHz, CDCl3) for 8f+minor: δ = 177.1(8f), 176.4(minor), 174.6(8f), 174.5(minor), 160.6(8f), 150.1(minor), 147.8(8f), 147.5(minor), 141.3(minor), 141.07(8f), 141.05(minor), 140.8(8f), 139.0(minor), 138.3(8f), 131.6(8f+minor), 130.3(minor), 129.9(8f), 129.2(8f), 129.1(minor), 128.48(8f) (2 C), 128.47(minor) (2 C), 128.43(8f) (2 C), 128.35(minor) (2 C), 128.3(8f) (2 C), 128.1(8f), 128.04(minor) (3 C), 128.02(8f) (2 C), 127.96(minor) (2 C), 127.0(minor), 126.8(8f), 126.6(8f+minor), 126.0(minor), 124.2(8f), 123.9(minor), 123.8(8f), 123.6(8f), 122.9(8f), 122.6(minor), 120.9(minor), 120.6(8f), 111.2(minor), 110.6(8f), 110.53(minor), 110.49(8f), 68.9(minor), 66.5(8f), 65.5(8f), 57.7(8f+minor), 54.4(8f), 51.9(minor), 48.1(minor), 47.77(minor), 47.75(8f), 43.79(minor), 43.75(8f), 43.1(minor), 42.0(8f+ minor), 29.4(minor), 26.1(8f), 25.3(minor), 22.9(8f).

HRMS (ESI): m/z [M+H]+ calcld for C36H31N4O2: 551.2442; found: 551.2450.

3.2. Computational Methodology

Full geometry optimization of reactants, products, and transition state structures (TSs) was performed at the DFT/HF level of theory using M11 hybrid exchange-correlation functional [49] and cc-pVDZ basis set [50]. The polarizable continuum model (PCM) was used to calculate solvent effects of 1,4-dioxane [51]. The optimizations were carried out using the Beryn analytical gradient optimization method [52]. All stationary points were described by harmonic vibrational frequency calculations to prove the location of correct minima (only real frequencies) and transition states (only one imaginary frequency). For the transition states, the normal modes corresponding to the imaginary frequencies were related to the vibrations of new developing bonds. IRC calculations were performed to check the energy profiles connecting each TS to the two associated minima of the proposed
mechanism [53]. Thermal corrections to enthalpy and entropy values were evaluated at 298.15 K and 1.0 atm. All calculations were performed using the Gaussian 09 computational program package [54]. Data on energies (a.u.) and cartesian coordinates of stationary points for reactants, intermediates, products and the transition states (M06-2x/cc-pVDZ, PCM = 1,4-dioxane) are given at Supporting Information, (Table S5).

3.3. Cell Culture and Culturing Conditions

The human erythroleukemia (K-562) cell line was obtained from the cell repository “Vertebrate cell culture collection” (supported by the Ministry of Science and Higher Education of the Russian Federation, agreement № 075-15-2021-683, Institute of Cytology, Russian Academy of Sciences, Saint Petersburg, Russia). Cells were grown on RPMI medium (Hyclone, GE Healthcare Life Sciences, Logan, UT, USA) supplemented with 10\% (v/v) fetal bovine serum (Hyclone, GE Healthcare Life Sciences, Logan, UT, USA) and gentamicin (Sigma-Aldrich, St. Louis, MO, USA) at 37 °C in a humidified atmosphere with 5% CO₂.

3.4. Cell Proliferation Assay

To evaluate the in vitro toxicity of the compounds synthesized, cells were seeded into 96-well plates at a density of 5 × 10³ cells per well. On the next day, the tested compounds were added to the wells at concentrations ranging from 1 to 30 mg/mL, followed by incubation for 1 and 3 days. Cell proliferation was determined by adding 20 \( \mu \)L of MTS reagent (BioVision, Milpitas, CA, USA) stock solution per well. The plate was incubated for 2 h at 37 °C in a humidified, 5% CO₂ atmosphere. The plates were then read at 495 nm using a plate spectrophotometer (Multiskan GO, Thermo Fisher Scientific, Waltham, MA, USA). All samples were measured in triplicate. Data on K562 cells viability after the treatment for 24 h and 72h are given at Supporting Information, (Tables S3 and S4).

3.5. Statistical Analysis

Statistical processing of results was performed using Statistica 6.0. All data from the three independent experiments were used for measuring the means ± standard deviation (mean ± SD), which were compared using Student’s t-test or a nonparametric Wilcoxon Mann–Whitney U test.

4. Conclusions

In summary, we have shown for the first time the possibility of generating azomethine ylides from 11H-benzo[4,5]imidazo[1,2-a]indol-11-one and α-amino acids, and we also studied their 1,3-dipolar cycloaddition with cyclopropenes and maleimides. As a result of these reactions, novel spiro[benzo[4,5]imidazo[1,2-a]indole-11,2'-pyrrolidine] frameworks were obtained in moderate to good yields, albeit with low stereoselectivity. With the use of a DFT computational study, the observed poor diastereoselectivity was found to result from the formation of two isomeric azomethine ylides (S- and W-shaped dipoles), which subsequently react with cyclic dipolarophiles in a fully diastereoselective fashion. The results of antiproliferative activity study showed that the spiroadducts with a N-isopropylcarbamoyl group at the cyclopropane moiety were more active, while replacement of this group with a phenyl one led to significant decrease in the activity. It was found that, among the tested compounds, spiroadducts 4f and 6i demonstrated a significant activity, with IC₅₀ 5 ± 1 and 12 ± 2 \( \mu \)g/mL, respectively. Despite its low stereoselectivity, the availability of numerous olefins and amino acids makes this method useful for accessing new hybrid spiro-heterocyclic systems containing simultaneously benzimidazole, indole, and pyrrolidine moieties. Current efforts are focused on increasing the stereoselectivity of cycloaddition reactions involving these new azomethine ylides and other dipolarophiles, as well as studying the biological properties of the products.
Supplementary Materials: The supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms232113202/s1. References [55–64] are cited in the supplementary materials.

Author Contributions: Investigation, A.S.F., Y.A.P., S.I.S., S.V.S., A.A.U., V.M.B. and A.V.S.; Writing, A.V.S. and V.M.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was financially supported by a grant from the Russian Science Foundation, RSF 20-15-00332.

Data Availability Statement: The data are available in the Supplementary Section.

Acknowledgments: This research made use of resources from the X-ray Diffraction Centre, Centre for Magnetic Resonance, Centre for Chemical Analysis and Materials from the Saint-Petersburg State University. S.I.S. acknowledges Saint-Petersburg State University for the research grant 92425251.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Hashimoto, T.; Maruoka, K. Recent Advances of Catalytic Asymmetric 1,3-Dipolar Cycloadditions. Chem. Rev. 2015, 115, 5366–5412. [CrossRef] [PubMed]
2. Breugst, M.; Reissig, H.-U. The Huisgen Reaction: Milestones of the 1,3-Dipolar Cycloaddition. Angew. Chem. Int. Ed. 2020, 59, 12293–12307. [CrossRef] [PubMed]
3. Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A.P.; Waldmann, H. Catalytic Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides for Biology-Oriented Synthesis. Acc. Chem. Res. 2014, 47, 1296–1310. [CrossRef] [PubMed]
4. Cheng, F.; Kalita, S.J.; Zhao, Z.-N.; Yang, X.; Zhao, Y.; Schneider, U.; Shibata, N.; Huang, Y.-Y. Diastereodivergent Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides and β-Fluoroalkyl Vinylsulfones: Low Copper(II) Catalyst Loading and Theoretical Studies. Angew. Chem. Int. Ed. 2019, 58, 16637–16643. [CrossRef] [PubMed]
5. Otero-Fraga, J.; Suárez-Pantiga, S.; Montesinos-Magraner, M.; Rhein, D.; Mendoza, A. Direct and Stereospecific [3 + 2] Synthesis of Pyrrolidines from Simple Unactivated Alkenes. Angew. Chem. Int. Ed. 2017, 56, 12962–12966. [CrossRef]
6. Xu, X.; Bao, L.; Ran, L.; Yang, Z.; Yan, D.; Wang, C.-J.; Teng, H. Synthesis of bioactive fluoropyrrolidines via copper(ii)-catalysed asymmetric 1,3-dipolar cycloaddition of azomethine ylides. Chem. Sci. 2022, 13, 1398–1407. [CrossRef]
7. Shen, P.; Guo, Y.; Wei, J.; Zhao, H.; Zhai, H.; Zhao, Y. Straightforward Synthesis of Succinimide-Fused Pyrrolizidines by a Three-Component Reaction of α-Diketone, Amino Acid, and Maleimide. Synthesis 2021, 53, 1262–1270. [CrossRef]
8. Wang, K.-K.; Li, Y.-L.; Chen, R.; Wang, Z.-Y.; Li, N.-B.; Zhang, L.-L.; Gu, S. Substrate-Controlled Regioselectivity Switchable [3 + 2] Annulations to Access Spirooxindole Skeletons. J. Org. Chem. 2022, 87, 8158–8169. [CrossRef]
9. Chronopoulos, D.D.; Liu, Z.; Suenaga, K.; Yudasaka, M.; Tagmatachis, N. [3 + 2] cycloaddition reaction of azomethine ylides generated by thermal ring opening of aziridines onto carbon nanohorns. RSC Adv. 2016, 6, 44782–44787. [CrossRef]
10. Liao, Y.; Liu, X.; Zhang, Y.; Xu, Y.; Xia, Y.; Lin, L.; Feng, X. Asymmetric [3 + 2] cycloaddition of donor-acceptor aziridines with aldehydes via carbon–carbon bond cleavage. Chem. Sci. 2016, 7, 3775–3779. [CrossRef]
11. Arrastia, I.; Arrieta, A.; Cossio, F.P. Application of 1,3-Dipolar Reactions between Azomethine Ylides and Alkenes to the Synthesis of Catalysts and Biologically Active Compounds. Eur. J. Org. Chem. 2018, 2018, 5889–5904. [CrossRef] [PubMed]
12. Fan, X.; Wang, C.-J. Catalytic asymmetric construction of spiropyrrolidines via 1,3-dipolar cycloaddition of azomethine ylides. Org. Biomol. Chem. 2018, 16, 2591–2601. [CrossRef]
13. Vitaku, E.; Smith, D.T.; Njardarson, J.T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. J. Med. Chem. 2014, 57, 10257–10274. [CrossRef]
14. Bhutani, P.; Joshi, G.; Raja, N.; Bachhav, N.; Rajanna, P.K.; Bhutani, H.; Paul, A.T.; Kumar, R.U.S. FDA Approved Drugs from Simple Unactivated Alkenes. J. Med. Chem. 2020, 63, 1262–1270. [CrossRef]
15. Njardarson, J.T. Top 200 Small Molecule Pharmaceuticals by Retail Sales in 2020. Available online: https://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/Top%20200%20Pharmaceuticals%20Small%20Molecule%202020New.pdf (accessed on 23 June 2022).
16. McAllister, L.A.; Butler, C.R.; Mente, S.; O’Neil, S.V.; Fonseca, K.R.; Piro, J.R.; Cianfrogna, J.A.; Foley, T.L.; Gilbert, A.M.; Harris, A.R.; et al. Discovery of Trifluoromethyl Glycol Carbamates as Potent and Selective Covalent Monosacglycerol Lipase (MAGL) Inhibitors for Treatment of Neuroinflammation. J. Med. Chem. 2018, 61, 3008–3026. [CrossRef]
17. Patel, S.; Meilandt, W.J.; Erickson, R.L.; Chen, J.; Deshmukh, G.; Estrada, A.A.; Fuji, R.N.; Gibbons, P.; Gustafson, A.; Harris, S.F.; et al. Selective Inhibitors of Dual Leucine Zipper Kinase (DLK, MAP3K12) with Activity in a Model of Alzheimer’s Disease. J. Med. Chem. 2017, 60, 8083–8102. [CrossRef]
18. Qiao, J.; Li, Y.-S.; Zeng, R.; Liu, F.-L.; Luo, R.-H.; Huang, C.; Wang, Y.-F.; Zhang, J.; Quan, B.; Shen, C.; et al. SARS-CoV-2 Mpro inhibitors with antiviral activity in a transgenic mouse model. Science 2021, 371, 1374–1378. [CrossRef]
19. Kneller, D.W.; Li, H.; Phillips, G.; Weiss, K.L.; Zhang, Q.; Arnould, M.A.; Jonsson, C.B.; Surendranathan, S.; Parvathareddy, J.; Blakeley, M.P.; et al. Covalent narpalprevir- and boceprevir-derived hybrid inhibitors of SARS-CoV-2 main protease. Nat. Commun. 2022, 13, 2268. [CrossRef] [PubMed]
43. Gilbertson, R.D.; Weakley, T.J.R.; Haley, M.M. Preparation, X-ray Crystal Structures, and Reactivity of Alkynylcyclopropenylum Salts. J. Org. Chem. 2000, 65, 1422–1430. [CrossRef] [PubMed]
44. Belyy, A.Y.; Levin, A.A.; Platonov, D.N.; Salikov, R.F.; Medvedev, M.G.; Tomilov, Y.V. Synthesis of Diazaanorcaradienes and 1,2-Diazepines via the Tandem [4 + 2]-Cycloaddition/Retro-[4 + 2]-Cycloaddition Reaction between Methoxy carbonylcyclopropenes and Dimethoxy carbonyl tetrazine. Eur. J. Org. Chem. 2019, 2019, 4133–4138. [CrossRef]
45. White, E.H.; Winter, R.E.K.; Graeve, R.; Zirngibl, U.; Friend, E.W.; Maskill, H.; Mende, U.; Kreiling, G.; Reisenauer, H.P.; Maier, G. Versuche zur Darstellung von Diphenyltetraedran. Chem. Ber. 1981, 114, 3906–3915. [CrossRef]
46. Li, H.; Praveen Rao, P.N.; Habeeb, A.G.; Knaus, E.E. Design, syntheses, and evaluation of 2,3-diphenylcycloprop-2-en-1-ones and oxime derivatives as potential cyclooxygenase-2 (COX-2) inhibitors with analgesic-antiinflammatory activity. Drug Dev. Res. 2002, 57, 6–17. [CrossRef]
47. Jiang, S.; Tala, S.R.; Lu, H.; Zou, P.; Avan, I.; Ibrahim, T.S.; Abo-Dya, N.E.; Abdelmajeid, A.; Debnath, A.K.; Katritzky, A.R. Design, synthesis, and biological activity of a novel series of 2,5-disubstituted furans/pyrroles as HIV-1 fusion inhibitors targeting gp41. Bioorg. Med. Chem. Lett. 2011, 21, 6895–6898. [CrossRef]
48. Ledovskaya, M.S.; Molchanov, A.P.; Boitsov, V.M.; Kostikov, R.R.; Stepakov, A.V. An efficient synthesis of substituted isoxazolopyrrole isoquinolines via diastereoselective N-acyliminium ion cyclization. Tetrahedron 2015, 71, 1952–1958. [CrossRef]
49. Peveratti, R.; Truhlar, D.G. Improving the Accuracy of Hybrid Meta-GGA Density Functionals by Range Separation. J. Phys. Chem. 1989, 1–4. [CrossRef]
50. Dunning, T.H. Gaussian basis sets for use in correlated molecular calculations. I. The atoms boron through neon and hydrogen. J. Chem. Phys. 1989, 90, 1007–1023. [CrossRef]
51. Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. Energies, structures, and electronic properties of molecules in solution with the C-PCM solvation model. J. Comput. Chem. 2003, 24, 669–681. [CrossRef]
52. Schlegel, H.B. Optimization of equilibrium geometries and transition structures. J. Comput. Chem. 1982, 3, 214–218. [CrossRef]
53. Fukui, K.J. Formulation of the reaction coordinate. J. Chem. Phys. 1970, 74, 4161–4163. [CrossRef]
54. 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.; et al. Gaussian 09, Revision C.01; Gaussian: Wallingford, CT, USA, 2013.
55. Neuhaus, D.; Williamson, M.P. The Nuclear Overhauser Effect in Structural and Conformational Analysis, 2nd ed.; VCH Publishers Inc.: New York, NY, USA, 2000; 619p.
56. Bell, R.A.; Saunders, J.K. Correlation of the nuclear Overhauser effect with internuclear distance. Can. J. Chem. 1970, 48, 1114–1122. [CrossRef]
57. Woessner, D.E. Spin Relaxation Processes in Two-Proton System Undergoing Anisotropic Reorientation. J. Magn. Reson. 1989, 83, 29–43. [CrossRef]
58. Lee, W.; Krishna, N. Influence of conformational exchange on the 2D NOESY spectra of biomolecules existing in multiple conformations. J. Magn. Reson. 1992, 98, 163–175. [CrossRef]
59. Butts, C.P.; Jones, C.R.; Harvey, J.N. High precision NOEs as a probe for low level conformers—second conformation of strychnine. Chem. Commun. 2011, 47, 1193–1195. [CrossRef]
60. Butts, C.P.; Jones, C.R.; Song, Z.; Simpson, T.J. Accurate NOE-distance determination enables the stereochemical assignment of a flexible molecule—Arugosin C. Chem. Commun. 2012, 48, 9023–9025. [CrossRef] [PubMed]