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Enantioselective [4 + 1] Annulation Reactions of α-Substituted Ammonium Ylides To Construct Spirocyclic Oxindoles

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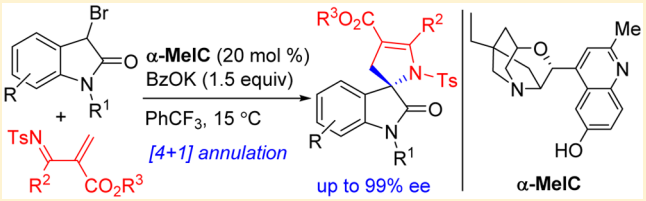
Supporting Information

ABSTRACT: Ammonium ylides have a long history in organic synthesis, but their application in asymmetric catalysis is still underdeveloped in regard to both substrate scope and reaction pathways compared with phosphorus and sulfur ylides. Here a previously unreported asymmetric [4 + 1] annulation reaction of 3-bromooxindoles and electron-deficient 1-azadienes has been developed through ammonium ylide catalysis of a newly designed 2′-methyl α-isocupreine (α-MeIC), efficiently delivering spirocyclic oxindole compounds incorporating a dihydropyrrole motif in excellent enantioselectivity (up to 99% ee). To the best of our knowledge, this work represents the first example of asymmetric catalysis of ammonium ylides bearing α-substitutions, and the catalytic [4 + 1] annulation pathway of ammonium ylides is also unprecedented. Moreover, ^{1}H NMR, mass spectroscopy, and computational calculation studies were conducted, and the catalytic cycle and a tentative explanation of the enantioselective mechanism have been successfully elucidated.



INTRODUCTION

The catalytic functionalization of a carbonyl compound in an enantioselective manner is a fundamental process in asymmetric synthesis and continues to trigger interest even in modern organic chemistry. While significant progress has been made by utilizing previously modified Mukaiyama enolate silyl ethers,[1] recent studies, especially in the upcoming organocatalytic field, have revealed that direct enantioselective α-functionalization of aldehydes or ketones can be efficiently realized by in situ generation of enamine species with a chiral secondary or primary amine. By employing the principle of vinylogy, such an enamine activation strategy can be expanded to the remote γ- or even ε-site of unsaturated carbonyl compounds.[2] In addition, the direct application of carboxylic acids or esters in asymmetric catalysis has been successfully established through the formation of acyl ammoniums[3] or acyl NHC (*N*-heterocyclic carbene) intermediates[4] followed by the isomerization to the corresponding enolates. Nevertheless, the above-mentioned organocatalytic protocols are inapplicable to other types of carbonyl derivatives, such as amides; thus, an alternative method must be adopted.

α-Halo carbonyl compounds, including amides, can form stabilized nucleophilic ylides with a sulfide, tertiary phosphine, or amine in the presence of a base, which provides an effective strategy for the development of diverse annulation or addition reactions, especially stereoselectively. In comparison with the extensively explored phosphorus or sulfur ylides,[5] the asymmetric reactions mediated by ammonium ylides, however, have been minimally investigated.[6] While very limited examples were presented in asymmetric epoxidation or aziridination reactions with simple aryl aldehydes or aldimines, respectively,[7] the Gaunt group made a significant breakthrough in asymmetric cyclopropanation reactions with ammonium ylides either in an inter- or intramolecular pattern.[8] Unfortunately, almost no further development has been reported in the field of ammonium ylides. Very recently, Jubault and co-workers presented the synthesis of racemic fluorinated cyclopropanes by combining α-bromo-α-fluoroacetamides and activated alkenes in the presence of an equivalent amount of DABCO, but without any asymmetric investigation.[9] Thus, the potential application of more complex α-substituted α-halogenated precursors, which would construct a challenging quaternary chiral center, has not succeeded. On the other hand, the development of new annulation modes with ammonium ylides other than the [2 + 1] pathway is also in high demand.

In response to such unexplored problems in the catalysis with ammonium ylides, we describe here a highly enantioselective [4 + 1] annulation reaction[10] of 3-bromooxindoles and electron-deficient 1-azadienes catalyzed by a newly developed cinchona alkaloid derivative, to efficiently construct chiral 3,2′-pyrrolidinylspirooxindole skeletons, which are ubiquitous in a number of biologically important compounds (Figure 1)[11] but with relatively few asymmetric catalytic strategies[12] to access in comparison with 3,3′-pyrrolidinylspirooxindoles.[13] Moreover, a comprehensive catalytic mechanism survey, including ^{1}H NMR, mass spectroscopy study, and computational calculations, has

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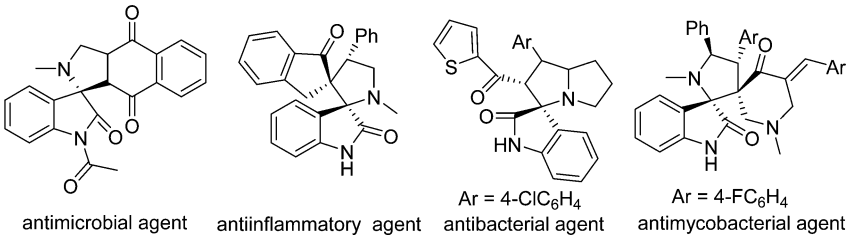
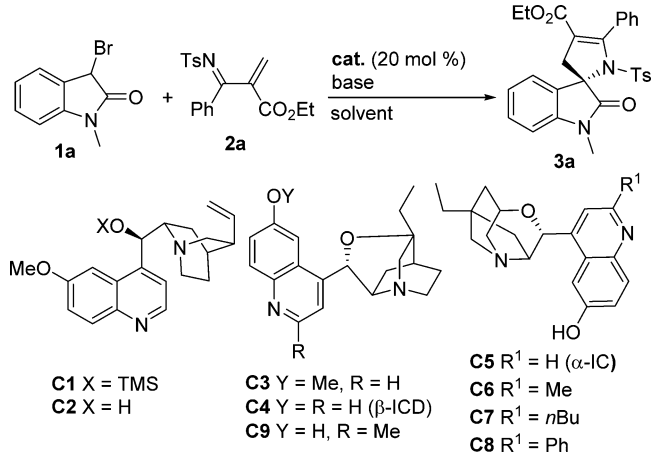


Figure 1. Representative bioactive spirocyclic oxindoles incorporating a pyrrolidine motif.

Table 1. Screening Conditions for [4 + 1] Annulation Reaction Involving 3-Bromooxindole 1a and 1-Azadiene 2a[a]



entry	cat.	base	solvent	T (°C)	t (h)	yield[b] (%)	ee[c] (%)
1	/	Cs_2CO_3	CH_3CN	15	13	10[d]	/
2	/	DIPEA	CH_3CN	15	13	15[d]	/
3	DABCO	Cs_2CO_3	CH_3CN	15	16	75	/
4	**C1**	Cs_2CO_3	CH_3CN	15	24	30	15
5	**C1**	$KHCO_3$	CH_3CN	15	48	50	30
6	**C2**	$KHCO_3$	CH_3CN	15	48	47	24
7	**C3**	$KHCO_3$	CH_3CN	15	48	43	44
8	**C4**	$KHCO_3$	CH_3CN	15	48	50	67
9	**C5**	$KHCO_3$	CH_3CN	15	48	57	58
10	**C5**	AcOK	CH_3CN	15	48	60	60
11	**C5**	AcOK	toluene	15	48	62	65
12	**C5**	AcOK	$PhCF_3$	15	48	63	71
13	**C5**	AcOK	$PhCF_3$	35	8	76	80
14	**C5**	AcONa	$PhCF_3$	35	10	67	74
15	**C5**	*t*-$BuCO_2K$	$PhCF_3$	35	8	70	70
16	**C5**	BzOK	$PhCF_3$	35	8	68	83
17	**C5**	BzOK	$PhCF_3$	15	48	68	89
18	**C4**	BzOK	$PhCF_3$	15	52	69	57
19[e]	**C5**	BzOK	$PhCF_3$	15	48	71	93
20[e,f]	**C5**	BzOK	$PhCF_3$	15	48	73	95
21[e,f]	**C6**	**BzOK**	**$PhCF_3$**	**15**	**48**	**75**	**98**
22[e,f]	**C7**	BzOK	$PhCF_3$	15	48	60	73
23[e,f]	**C8**	BzOK	$PhCF_3$	15	120	40	63
24[e,f]	**C9**	BzOK	$PhCF_3$	15	48	65	63
25[e,f,g]	**C6**	BzOK	$PhCF_3$	15	48	60	97

[a]Unless noted otherwise, the reaction was performed with 0.05 mmol of **1a**, 0.05 mmol of **2a**, 20 mol % of catalyst, and 0.05 mol of base in 0.5 mL of solvent. [b]Isolated yield. [c]By chiral HPLC analysis. [d]By ^{1}H NMR analysis using $Cl_2CHCHCl_2$ as the internal standard. [e]Reaction was performed with 0.075 mmol of **1a**, 0.05 mmol of **2a**, 20 mol % of catalyst, and 0.075 mol of base in 1.0 mL of solvent. [f]1-Azadiene **2a** was added in three portions. [g]With 10 mol % of **C6**.

been conducted to elucidate the unprecedented annulation process of ammonium ylides with α-substitutions.

RESULTS AND DISCUSSION

Enantioselective [4 + 1] Annulation Survey. We initialized our investigation using *N*-methyl 3-bromooxindole[14] **1a** and 1-azadiene 2-[phenyl(*p*-tosylimino)methyl]acrylate[15] **2a** as the model substrates. It was found that the apparent conversion (75%) of the starting materials was observed with the inorganic base Cs_2CO_3 in acetonitrile at 15 °C for 13 h, but the desired [4 + 1] annulation product was detected in low yield, along with a few unidentified products (Table 1, entry 1). Using a

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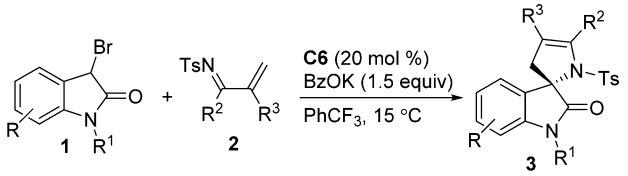
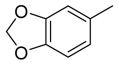
Table 2. Substrate Scope of Enantioselective [4 + 1] Annulation Reaction[a]



entry	R	R^1	R^2	R^3	*t* (h)	yield[b] (%)	ee[c] (%)
1	H	Me	Ph	CO_2Et	48	**3a**, 75	98[d]
2[e]	H	Bn	Ph	CO_2Et	52	**3b**, 54	90
3	H	Ph	Ph	CO_2Et	48	**3c**, 60	90
4	5-Cl	Me	Ph	CO_2Et	60	**3d**, 71	89
5	6-Cl	Me	Ph	CO_2Et	48	**3e**, 61	87
6	7-F	Me	Ph	CO_2Et	48	**3f**, 62	82
7	5-Me	Me	Ph	CO_2Et	48	**3g**, 70	99
8	5-MeO	Me	Ph	CO_2Et	48	**3h**, 66	96
9	5,7-$(Me)_2$	Me	Ph	CO_2Et	48	**3i**, 74	99
10	H	Me	Ph	CO_2Me	53	**3j**, 74	99
11[e]	H	Me	Ph	CO_2tBu	56	**3k**, 67	93
12	H	Me	Ph	Ph	48	/	/
13	H	Me	4-FC_6H_4	CO_2Et	36	**3l**, 73	96
14	H	Me	3-ClC_6H_4	CO_2Et	60	**3m**, 63	97
15	H	Me	4-ClC_6H_4	CO_2Et	52	**3n**, 70	93
16	H	Me	4-BrC_6H_4	CO_2Et	50	**3o**,67	96
17	H	Me	3-MeC_6H_4	CO_2Et	60	**3p**, 66	95
18	H	Me	4-MeC_6H_4	CO_2Et	50	**3q**, 73	97
19	H	Me	4-$MeOC_6H_4$	CO_2Et	48	**3r**, 64	97
20	H	Me		CO_2Et	60	**3s**, 73	97
21	H	Me	3,5-$(MeO)_2C_6H_3$	CO_2Et	48	**3t**, 74	99
22	H	Me	2-naphthyl	CO_2Me	56	**3u**, 73	92
23	H	Me	2-furyl	CO_2Et	60	**3v**, 55	93
24	H	Me	2-thienyl	CO_2Et	60	**3w**, 60	93
25	H	Me	*t*Bu	CO_2Et	48	/	/
26[f]	H	Me	Ph	CO_2Et	50	**3x**, 65	90

[a]Unless noted otherwise, reaction was performed with 0.15 mmol of **1**, 0.1 mmol of **2**, 20 mol % of catalyst **C6**, and 0.15 mol of BzOK in 2.0 mL $PhCF_3$, while 1-azadiene **2** was added in three portions. [b]Isolated yield. [c]By chiral HPLC analysis. [d]The absolute configuration of chiral **3a** was determined by X-ray analysis. The other products were assigned by analogy. [e]Catalyst **C5** was used. [f]*N*-Ns imine substrate was used.

non-nucleophilic organic base DIPEA gave a slightly better yield (15%) but with poorer conversion (34%, entry 2). In contrast, racemic **3a** was isolated in 75% yield under the catalysis of DABCO in the presence of Cs_2CO_3 (entry 3).[10m,n] These experiments suggested that this reaction could proceed more efficiently via an ammonium ylide intermediate than a

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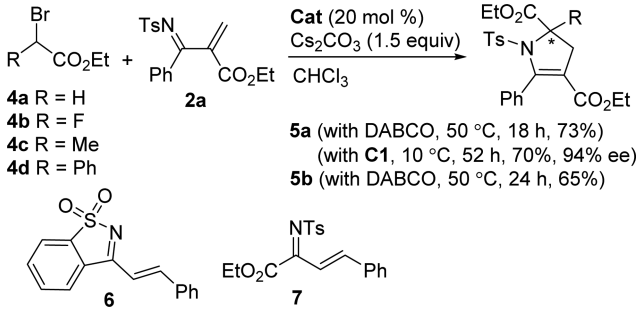
base-promoted domino deprotonation, Michael-type addition, and intramolecular substitution sequence.[14a] Consequently, we conducted the potential asymmetric version by using cinchona alkaloid-based catalysts. *O*-TMS quinine **C1** exhibited low catalytic activity, and the enantioselectivity was very disappointing (entry 4), while better data were obtained by using a weaker base $KHCO_3$ (entry 5). Quinine **C2** delivered poor results too (entry 6). A higher ee value was attained with *O*-Me *β*-isocupreidine (*β*-ICD) **C3** (entry 7), while both yield and enantiocontrol were significantly improved by using *β*-ICD **C4**, indicating that the hydrogen-bonding interaction of the OH group is beneficial for the enantioselectivity (entry 8). Although *α*-isocupreine (*α*-IC) **C5** is generally considered as an enantiocomplementary catalyst of *β*-ICD **C4**,[16] it was surprising that two different chiral catalysts gave the same enantiomer of the product (entry 9).[17] As a cleaner reaction was observed with **C5**, we explored more catalytic parameters with amine **C5** in order to improve the catalytic efficacy. Replacing $KHCO_3$ with AcOK gave a better ee value (entry 10), and the data could be further improved in toluene (entry 11) or $PhCF_3$ (entry 12). It was interesting that a better yield and enantioselectivity could be attained at a higher temperature of 35 °C (entry 13). Subsequently, we screened a variety of base components in $PhCF_3$ (entries 14−16) and found that 83% ee was produced by using $PhCO_2K$ (entry 16), while the enantioselectivity was further improved to 89% ee at 15 °C, though the reaction time had to be dramatically extended (entry 17). In comparison, we conducted the catalytic reaction with *β*-ICD **C4** under the same conditions, but it only afforded a moderate ee value (entry 18). In addition, using excess ylide precursor **1a** and base could slightly improve both yield and enantioselectivity by the catalysis of **C5** (entry 19), and gratifyingly, excellent enantiocontrol (95% ee) was achieved by adding 1-azadiene **2a** in three portions (entry 20). Moreover, considering that the quinoline nitrogen atom of **C5** might affect the chiral ammonium ylide catalysis,[8d] we designed and prepared a new 2′-methylated *α*-IC derivative (*α*-MeIC) **C6** and pleasingly found that a slightly higher yield and enantioselectivity could be obtained under the optimized conditions (entry 21). Nevertheless, amine **C7** and **C8** with larger 2′-substitutions[18] produced poorer data (entries 22 and 23). We also used *β*-MeICD derivative **C9** but still obtained inferior results (entry 24). Finally, it was found that the reaction proceeded smoothly with retained enantioselectivity by using 10 mol % of catalyst **C6**, albeit with a lower yield (entry 25).

Reaction Scope of Enantioselective [4 + 1] Annulation Reaction. After optimizing the catalytic conditions, we investigated the reactions with a variety of 3-bromooxindoles **1** and 1-azadienes **2** in the presence of the tertiary amine **C6** (20 mol %) and BzOK in $PhCF_3$ at 15 °C. The results are summarized in Table 2. At first, 3-bromooxindoles **1** with diverse substitutions were explored. Both yield and enantioselectivity were slightly decreased when *N*-benzyl or *N*-phenyl substituted precursors were applied (Table 2, entries 2 and 3).[19] Electron-withdrawing groups on the aryl ring also have some detrimental effects on the enantiocontrol, while over 80% ee values could be obtained (entries 4−6). In contrast, excellent enantioselectivity was produced by employing 3-bromooxindoles with electron-donating substitutions (entries 7−9). On the other hand, the substitution patterns of electrophilic partners were tested. Acrylates with either a methyl or bulky *tert*-butyl group smoothly gave the [4 + 1] products in outstanding enantioselectivity (entries 10 and 11), but replacing the ester moiety with a phenyl group completely killed the reaction due to the decreased electrophilicity (entry 12). Pleasingly, excellent ee values were attained for 1-azadienes with diversely substituted aryl or heteroaryl groups, and the yields were generally moderate to good (entries 13−24). 1-Azadiene with a 2-*tert*-butyl group could be prepared, but exhibited inert reactivity (entry 25). In addition, an *N*-Ns substituted electrophile also provided good data in reaction with 3-bromooxindole **1a** (entry 26).

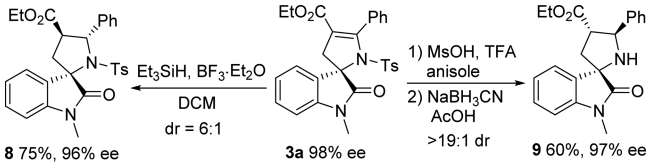
Apart from cyclic ammonium ylide precursors such as **1**, we also explored some acyclic *α*-bromo substituted esters. As outlined in Scheme 1, simple 2-bromoacetate **4a** exhibited the same [4 + 1] annulation reaction pattern with 1-azadiene **2a** catalyzed by DABCO in the presence of a stronger base Cs_2CO_3. Importantly, the enantioselective version could be smoothly realized by employing amine **C1** as the inducer, affording product **5a** with 94% ee and in 70% yield. *α*-Bromo-*α*-fluoroacetate[9] **4b** also showed good reactivity to produce 2-fluoro-subtituted dihydropyrrole **5b** catalyzed by DABCO; unfortunately, the enantioselective attempts were not successful when a number of catalysts illustrated in Table 1 were tested. In addition, other *α*-bromoesters with *α*-substitution, such as **4c** and **4d**, and the previously reported *β*-substituted 1-azadienes **6** and **7**,[20] could not be applied in the [4 + 1] annulation reactions, probably due to the steric hindrance and the relatively lower reactivity.

Scheme 1. Exploration of More Ammonium Ylide Precursors and 1-Azadienes



The resultant [4 + 1] annulation product could be applied to some synthetic transformations. The enamide functionality of **3a** could be efficiently reduced by Et_3SiH and $BF_3{\cdot}Et_2O$ in good diastereoselectivity, delivering separable *N*-Ts protected pyrrolidine derivative **8** in a good yield (Scheme 2). Furthermore, the *N*-Ts group of **3a** could be smoothly removed using MsOH, TFA, and anisole, and a free pyrrolidine compound **9**, which might be more useful in organic synthesis and medicinal chemistry, could be obtained after reduction with $NaBH_3CN$ in AcOH, interestingly with different diastereoselectivity.

Scheme 2. Transformations of Spirocyclic Product 3a



Proposed Catalytic Mechanism and Observation of Key Intermediates. Based on the early experimental studies that the inorganic base and non-nucleophilic organic base such as DIPEA could not efficiently promote the [4 + 1] annulation reaction of 3-bromooxindole **1a** and 1-azadiene **2a**, we proposed a plausible reaction cycle via ammonium ylide catalysis of *α*-IC **C5**.

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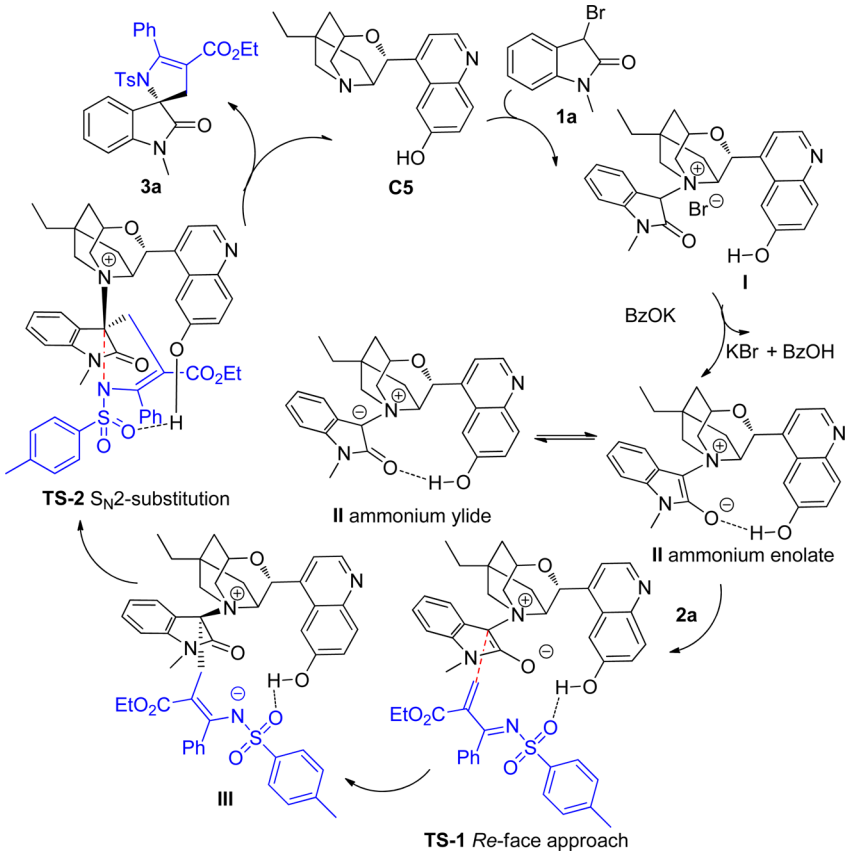
Scheme 3. Proposed Catalytic Mechanism of [4 + 1] Annulation Reaction



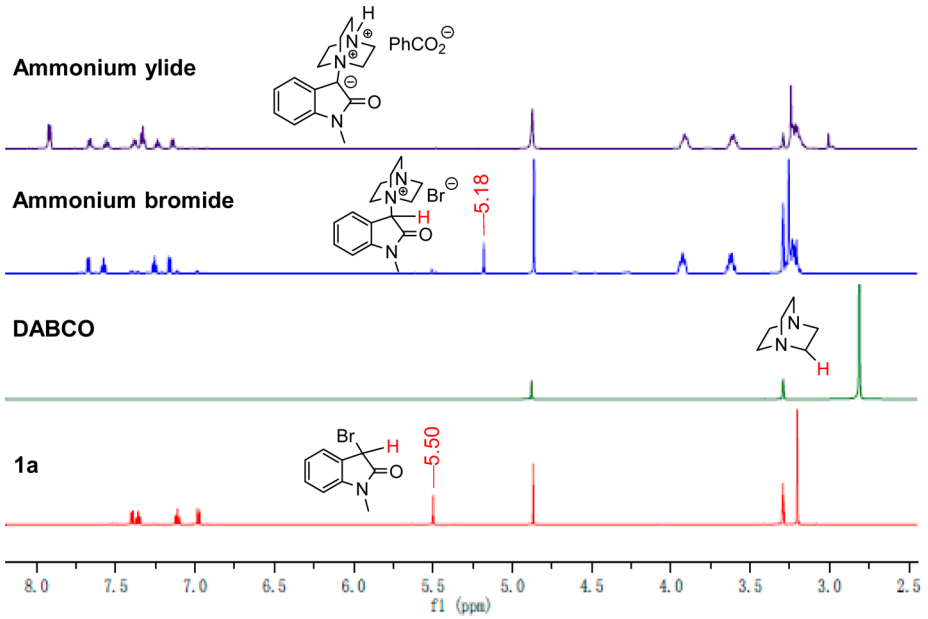


Figure 2. ^{1}H NMR studies on the formation of ammonium ylide from **1a** and DABCO.

As outlined in Scheme 3, **C5** first reacts with 3-bromooxindole **1a** to generate ammonium salt **I** and subsequently produces nucleophilic ammonium ylide or enolate intermediate **II** after deprotonation. The key *Re*-face selective Michael-type addition to electrophilic 1-azadiene **2a** would proceed in a concerted activation mode, via hydrogen-bonding interaction of the OH group of **C5** as illustrated in **TS-1**, delivering zwitterionic intermediate **III**. Finally, an intramolecular S_N2-subsitution of sulfonamide anion via **TS-2** would generate the desired chiral spirocycle **3a** with (*S*)-absolute configuration.

Subsequently, the ^{1}H NMR studies on an equimolar mixture of 3-bromooxindole **1a** and DABCO were conducted. It was found that the corresponding ammonium bromide was easily generated and precipitated from $CDCl_3$; thus we obtained the ^{1}H NMR spectra of **1a**, DABCO, and ammonium bromide, respectively, in CD_3OD. As illustrated in Figure 2, the clear

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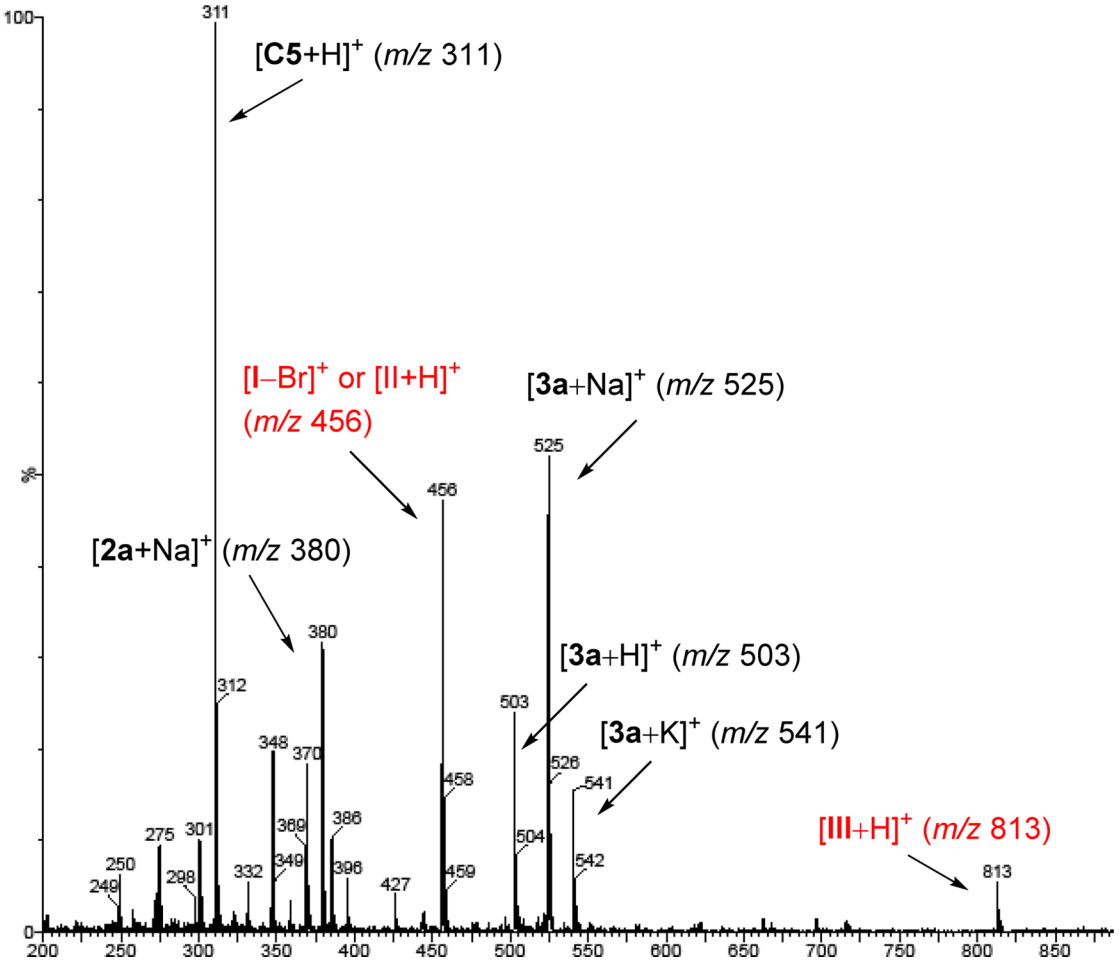

Figure 3. Mass spectroscopy study on the catalytic reaction mixture of **1a**, **2a**, and **C5**.

formation of ammonium bromide from **1a** and DABCO was observed, and the C3 proton signal of **1a** shifted from 5.50 to 5.18 ppm. In addition, the signals of DABCO were also apparently split. Importantly, the subsequent treatment with BzOK led to the clean formation of the corresponding ammonium ylide intermediate, in which the C3 proton signal at 5.18 ppm completely disappeared.

In order to gain more insight into the catalytic mechanism, we also conducted a mass spectroscopy study on the **C5**-catalyzed reaction. As shown in Figure 3, we smoothly detected the ammonium cation of salt **I** or ammonium ylide **II** ($[\mathbf{I} - \mathrm{Br}]^+$ or $[\mathbf{II} + \mathrm{H}]^+$ m/z 456).[21] Importantly, we also successfully observed the key zwitterionic intermediate **III** ($[\mathbf{III} + \mathrm{H}]^+$ m/z 813), which demonstrated that the current [4 + 1] annulation reaction would proceed via an ammonium ylide or enolate pathway.[22]

Computational Calculations To Rationalize the Enantioselectivity. On the other hand, we further conducted comprehensive computational calculations to elucidate the realization of an enantioselective addition and a subsequent annulation reaction. According to the initial computational explorations on the conformation of 1-azadiene **2a**, the formation of ammonium ylide, and approach of Michael-type addition,[23] in addition to previous reports of a *transoid* approach[24] between ammonium enolate and *N*-Ts imino group being considered as a more favorable state due to the steric hindrance from amine **C5**, both *Re*-face and *Si*-face attacks by different poses, corresponding to **path A**–**D**, were considered, as shown in Scheme 4. All transition states (**TSs**) and intermediates involved a hydrogen-bonding interaction between the OH of **C5** and the oxygen atom of the *N*-Ts imine or ester group,[23] which is consistent with the experimental results that the OH group of the catalyst is crucial for enantiocontrol. For the attack orientation, the *Re*-face attack via **TS1A** and **TS1B** forms the same chiral intermediate (*R*)-**IIIA** or (*R*)-**IIIB**, and complex (*S*)-**3aA** or (*S*)-**3aB** would be produced through a Walden inversion S_N2 reaction. Similarly, complex (*R*)-**3aC** or (*R*)-**3aD** could be obtained through path **C** and **D** by *Si*-face attack. These transition states had been confirmed by their normal vibration mode corresponding to the imaginary frequency and the IRC analysis. At the M05-2X/6-311+G(2d,p)//6-31G(d) level using toluene as the solvent, the relative Gibbs free energy barriers of **TS1A**, **TS1B**, **TS1C**, and **TS1D**, whose computationally optimized structures were illustrated in Figure 5, were 18.5, 19.2, 32.7, and 23.1 kcal/mol, respectively (Figure 4). The higher energies of **TS1C** and **TS1D** may result from the steric repulsion, as the shortest distances between H atoms at different carbons in **TS1C** and **TS1D** (1.90 and 1.95 Å, respectively; Figure 5) were shorter than those of **TS1A** and **TS1B** (2.08 and 2.05 Å, respectively). The $\pi-\pi$ interaction between the aryl ring and 1-azadiene was considered as another reason for the low energies of the *Re*-face attack. The dihedral angles between double bonds (C1–C2 and C3–N1) in **TS1A** and **TS1B** were −27.9 and −13.1, respectively, which were smaller than those in **TS1C** and **TS1D**, −39.2 and −31.8, respectively. Moreover, the more coplanar structures of **TS1A** and **TS1B** may be preferable for the conjugation of 1-azadiene

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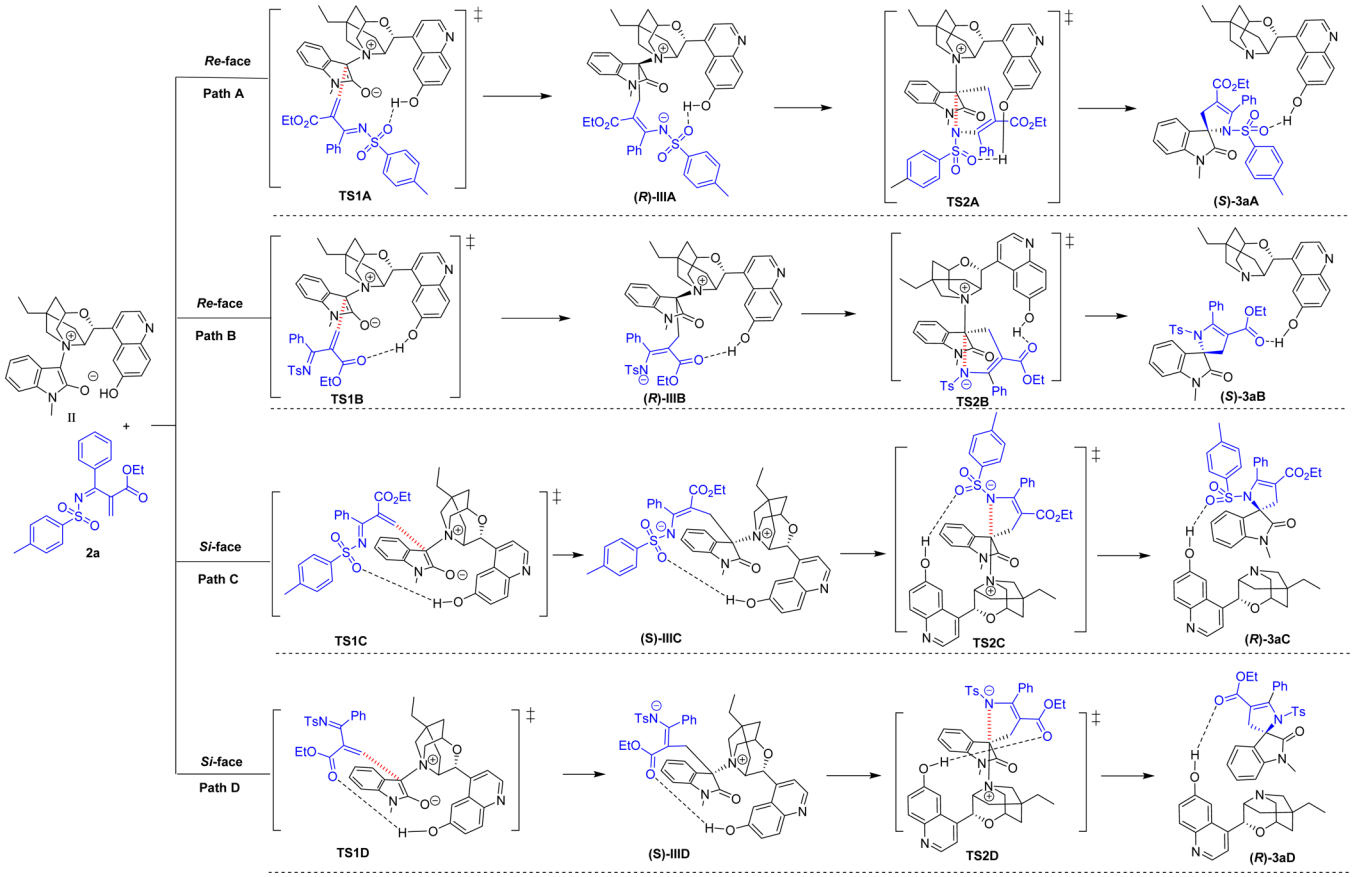
Scheme 4. Different Approaches of [4 + 1] Annulation Reaction to Produce the Corresponding Stereochemical Outcomes



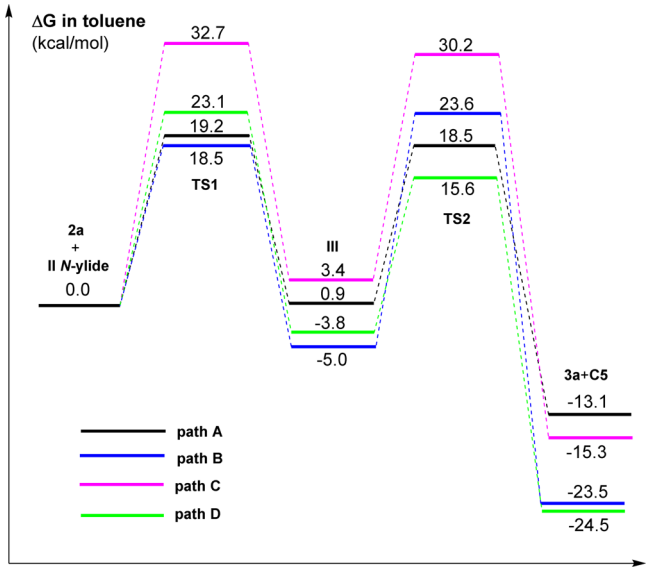


Figure 4. Computed potential energy surface for [4 + 1] annulation reaction.

to achieve the electronic transformation of the anion from the carbanion of ylide to the nitrogen of *N*-Ts imine (N1 atom) and formation of a double bond between C2−C3. These results indicated that **TS1A** and **TS1B** leading to the final product with (*S*)-configuration were the more favorable transition state structures.

After C−C formation by a carbanion attack, the resulted intermediates **IIIA−D** would further conduct a Walden inversion S_N2 reaction to form the chirality-inversed five-membered ring. The transition states **TS2A−D** were depicted in Scheme 4. These **TSs** had also been confirmed by their normal vibration mode corresponding to the imaginary frequency and the IRC analysis, and the optimized structures were shown in Figure 6. As shown in Figure 4, **TS2A** and **TS2D** were considered as the more favorable transition states owing to their lower Gibbs free energy barriers, 17.6 and 19.4 kcal/mol, respectively, while those of **TS1B** and **TS1C** were higher, with 28.6 and 26.8 kcal/mol, respectively. As shown in Figure 6, the breaking of the C4−N2 bond and the formation of the new bond (C4−N1) occur simultaneously through **TS2A−D**, in which the carbon under nucleophilic attack is pentacoordinate and approximately sp^2 hybridized. In **TS2A** and **TS2D**, the nucleophile (N1) attacks the carbon at almost 180° (171.7° and 169.1°, respectively) to the leaving group (N2) with similar distances (about 2.2 Å), since this provides the best overlap between the lone pair of the nitrogen anion (N1) and the σ^* antibonding orbital of C4−N2. However, the **TS2B** and **TS2C** have longer C4−N1 and C4−N2 distances and smaller C4−N1 and C4−N2 bond angles, which results in less overlap between the lone pair and σ^* antibonding orbital. This explained the favorable **TSs** in this S_N2 reaction were **TS2A** and **TS2D**.

Therefore, the computational calculations clearly supported that the most favorable pathway of the α-IC **C5**-catalyzed [4 + 1] annulation reaction was **path A**, via two rate-limiting steps of **TS1A** and **TS2A**. The hydrogen-bonding interaction between the OH of α-IC **C5** and the oxygen atom of *N*-Ts imine may play an important role in the enantioselective annulations.

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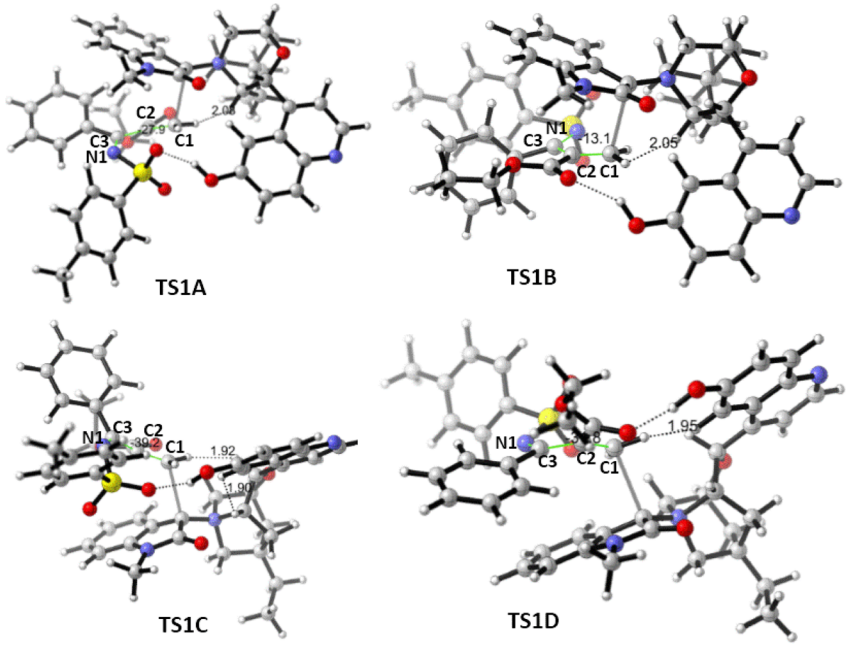

Figure 5. Optimized structures of **TS1A–D**. The bond distances of the optimized structures are in angstroms. The dihedral angle between double bonds, C1–C2 and C3–N1, was marked in green and labeled.

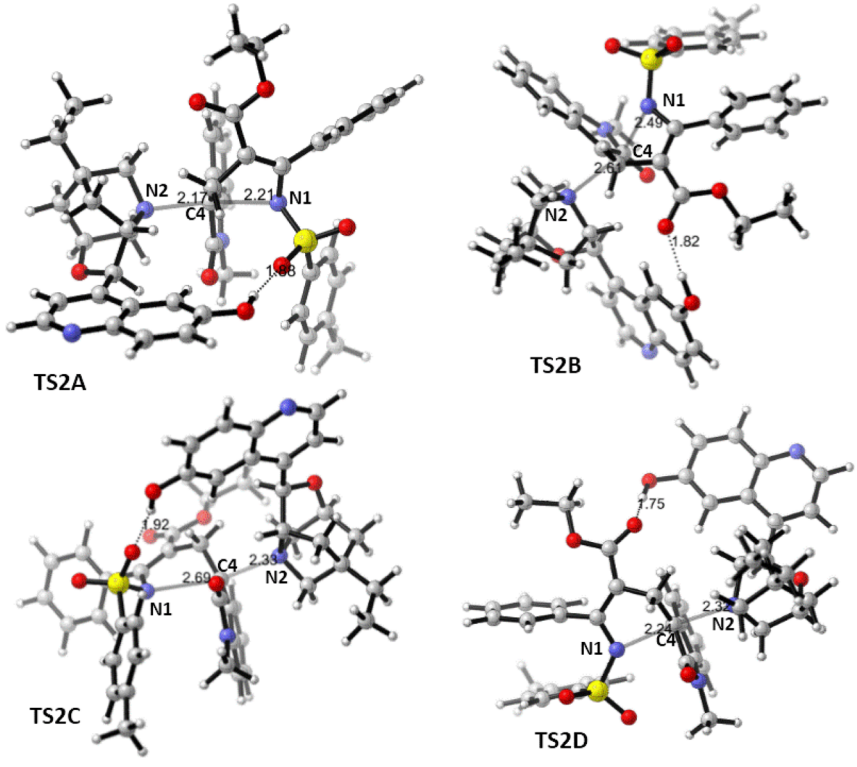

Figure 6. Optimized structures of **TS2A–D**. The bond distances of the optimized structures are in angstroms. The angles of N1–C4–N2 in **TS2A–D** were 171.7°, 167.3°, 157.1°, and 169.1°, respectively.

CONCLUSION

We have developed a highly enantioselective [4 + 1] annulation reaction of 3-bromooxindoles and 2-[aryl(*p*-tosylimino)methyl]-acrylate-type 1-azadienes to construct spirocyclic oxindoles incorporating a dihydropyrrole motif. This process employed a newly designed 2′-methyl α-isocupreine (α-MeIC) as the chiral tertiary amine catalyst and involved the asymmetric Michael-type addition of in situ generated ammonium ylides followed by an intramolecular S_N2 substitution with chirality inversion. Mass spectroscopy studies verified the reaction cycle of ammonium ylide catalysis, and comprehensive computational calculations were conducted to elucidate the catalytic mechanism of enantiocontrol. To the best of our knowledge, this work represents the first example of asymmetric catalysis with challenging ammonium ylides bearing α-substitutions, and the [4 + 1] annulation pathway of ammonium ylides is also unprecedented, though currently the

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substrate scope has some limitations and remains to be expanded. We believe that this study would arouse more research interest in the less-developed ammonium ylide catalysis in comparison with more fruitful phosphorus and sulfur ylide chemistry. More results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization of new products, ^{1}H NMR and mass spectroscopy studies on ammonium ylide intermediates, more computational calculation studies, CIF file of enantiopure product **3a**, NMR spectra and HPLC chromatograms. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04792.

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Notes

The authors declare no competing financial interest.

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