

Catalytic Asymmetric 1,3-Dipolar [3 + 6] Cycloaddition of Azomethine Ylides with 2-Acyl Cycloheptatrienes: Efficient Construction of Bridged Heterocycles Bearing Piperidine Moiety

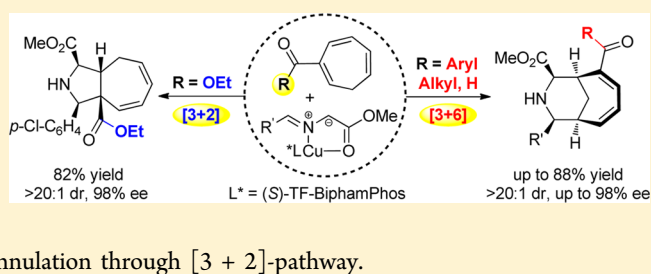
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S Supporting Information

ABSTRACT: Conjugated cyclic trienes without nonbenzenoid aromatic characteristic were successfully employed as fine-tunable dipolarophiles in the Cu(I)-catalyzed asymmetric azomethine ylide-involved 1,3-dipolar [3 + 6] cycloaddition for the first time, affording a variety of bridged heterocycles bearing piperidine moiety in good yield with exclusive regioselectivity and excellent stereoselectivity. 2-Acyl group is the key factor that determines the annulation preferentially through [3 + 6]-pathway, while 2-ester group modulates the annulation through [3 + 2]-pathway.



INTRODUCTION

Heterocyclic structures with multiple stereogenic centers are the core elements prevalent in a variety of natural alkaloids and pharmaceutical ingredients exhibiting significant biological activities.^{1–3} Metal-catalyzed 1,3-dipolar cycloaddition reaction of azomethine ylides is one of the powerful tools for the convergent construction of heterocyclic pyrrolidine frameworks from readily available organic compounds.⁴ However, the intrinsic limitation of 1,3-dipolar cycloaddition reaction is that five-membered heterocycles are normally generated via [3 + 2] reaction model because 2- π olefins are usually served as the two-atom dipolarophile units, while azomethine ylides are served as the three-atom 1,3-dipole units.⁵ Recently, fulvenes⁶ and tropone⁷ were employed as efficient 6- π dipolarophiles in the catalytic asymmetric 1,3-dipolar [3 + 6]-cycloaddition, which provided the direct and efficient approach to enantioenriched nitrogen-containing non-five-membered heterocycles (Scheme 1). The intrinsic nonbenzenoid aromatic characteristic exhibited by the resonance forms of fulvene and tropone provides the driving force for those 1,3-dipolar [3 + 6]-cycloaddition reactions.⁸

As part of our research interest in the asymmetric construction of five-⁹ and non-five-membered^{6b,7b} nitrogen-containing heterocycles via azomethine ylide-involved 1,3-dipolar cycloaddition, we planned to investigate the conjugated polyenes without nonbenzenoid aromatic characteristic as the dipolarophiles to further explore the feasibility of modulating the polyenes as potential different $2n-\pi$ components through varying the electronic property of polyenes, which may not only diversify the existing 1,3-dipolar cycloaddition reaction from the viewpoint of synthetic methodology but also be valuable in the facile and straightforward construction of structurally and stereochemically complex heterocycles. To the best of our knowledge,

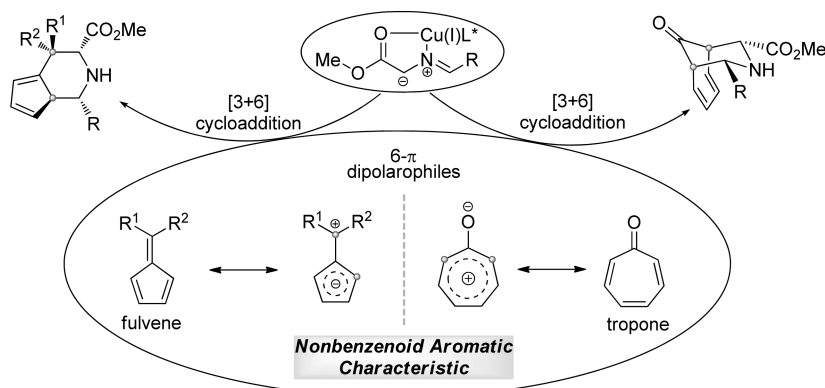
no studies on the substrate-controlled 1,3-dipolar [3 + 2 n] cycloaddition have been carried out so far.

In consideration of that a stepwise mechanism was revealed for the Cu(I) or Ag(I)/TF-BiphamPhos catalytic system developed in this laboratory through both theoretical calculations and experimental results,¹⁰ we envisaged that conjugated cyclic trienes containing an electron-withdrawing carbonyl group at the 2-position are the potential 2, 4 or 6- π components in the metal-catalyzed 1,3-dipolar cycloaddition (Scheme 2). The carboanion in the generated zwitterionic intermediate is stabilized by the delocalization of the negative charge over the adjacent carbonyl and conjugated diene. Having analyzed the electron factor and structural feature of the generated zwitterionic intermediates from the electron-deficient trienes, we are interested in the application of 2-carbonyl substituted cycloheptatrienes as the potential $2n-\pi$ reaction partner in azomethine ylide-involved 1,3-dipolar [3 + 2 n] cycloaddition with the aid of tuning the substituted group at the 2-position of cycloheptatrienes. We envisioned that the subsequent intramolecular cyclization of the generated zwitterionic intermediate might undergo through three possible different pathways and therefore deliver three types of adducts with different regioselectivities: (a) bicyclic heterocycle **1** in which 2-acyl cycloheptatriene served as a 2- π unit ([3 + 2]-model, Scheme 2a); (b) bridged heterocyclic azabicyclo[3.3.2]decadiene **2** in which 2-acyl cycloheptatriene served as a 4- π unit ([3 + 4]-model, Scheme 2b); and (c) bridged heterocyclic azabicyclo[4.3.1]decadiene **3** in which 2-acyl cycloheptatriene served as a 6- π unit ([3 + 6]-model, Scheme 2c). Therefore, it is a great challenge to control both the exclusive

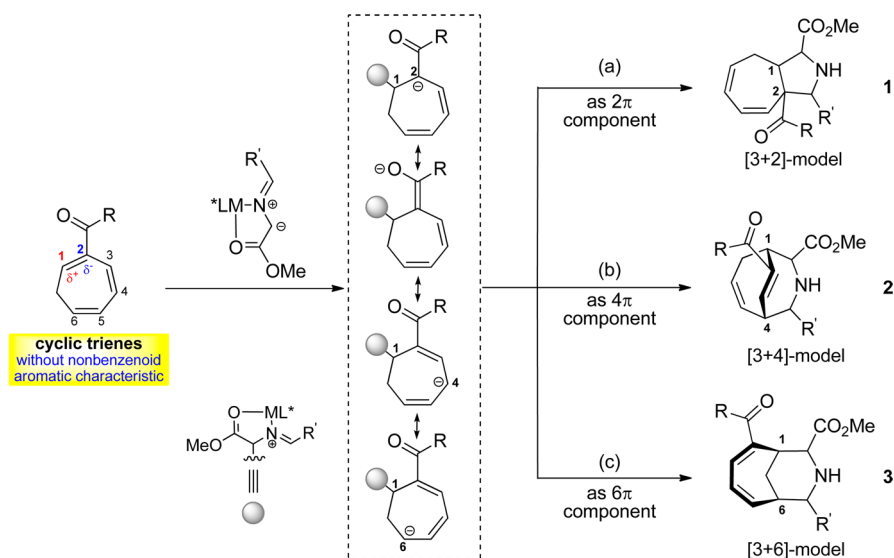
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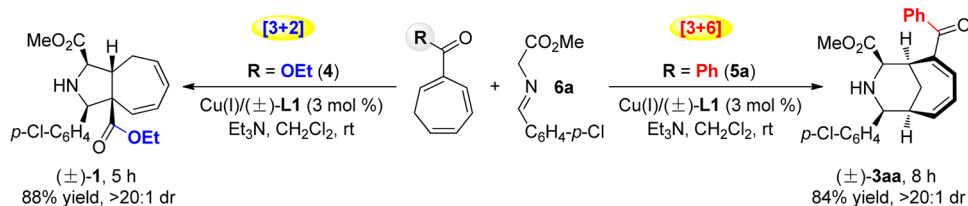
Scheme 1. Reported Catalytic Asymmetric 1,3-Dipolar [3 + 6]-Cycloaddition Reactions of Azomethine Ylides with Nonbenzenoid Aromatic Characteristic Compounds as the 6- π Dipolarophiles (previous work)



Scheme 2. Possible Reaction Pathways for the Designed 1,3-Dipolar [3 + 2*n*] Cycloaddition of Azomethine Ylides with Conjugated Cyclic Trienes without Nonbenzenoid Aromatic Characteristic



Scheme 3. Initial Result of the 1,3-Dipolar [3 + 2*n*] Cycloaddition Reaction Pathway Investigation: [3 + 2]-Model for 2-Ethoxycarbonyl Cycloheptatriene **4** (left side) and [3 + 6]-Model for 2-Benzoyl Cycloheptatriene **5a** (right side)

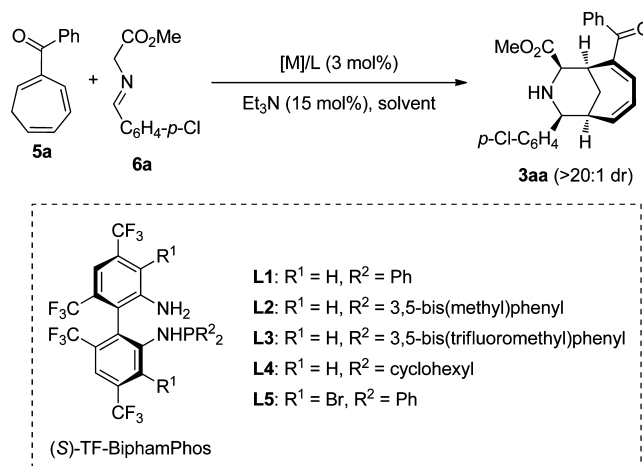


regioselectivity and high stereoselectivity associated with this unknown annulation process.

Herein, we report an unprecedented catalytic asymmetric 1,3-dipolar [3 + 6] cycloaddition of azomethine ylides employing 2-acyl cycloheptatrienes without nonbenzenoid aromatic characteristics as the 6- π components, providing a facile access to a variety of enantioenriched heterocycles containing a unique bridged piperidine moiety,¹¹ which is the core structure of many bioactive molecules. Another attractive feature of the current methodology is that the subtle change in the carbonyl group of conjugated cyclic trienes plays a significant role in controlling the reaction pathway in [3 + 6] or [3 + 2]-models.

RESULTS AND DISCUSSION

At the outset of this study, we examined the reaction of 2-ethoxycarbonyl cycloheptatriene **4** and 2-benzoyl cycloheptatriene **5a** with *N*-(4-chlorobenzylidene)-glycine methyl ester **6a** in the presence of different metal complexes as the catalysts. Initially, 5 mol % of $\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4/\text{PPh}_3$ complex was employed with Et_3N as the base in DCM at room temperature. Although full conversions of both trienes were observed, only unidentified mixtures were generated from the messy reaction systems. To our delight, using $\text{Cu}(\text{I})/\text{rac}(\pm)\text{TF-BiphamPhos}$ complex^{9a} as the catalyst, the reactions became very clean and finished smoothly at room temperature. The common [3 + 2]-

Table 1. Optimization of Cu(I)-catalyzed asymmetric [3 + 6] cycloaddition of 2-benzoyl cycloheptatriene **5a** with imino ester **6a**^a

entry	L1	[M]	solvent	T (°C)	time (h)	yield (%) ^b	ee (%) ^c
1	(S)-L1	AgOAc	CH ₂ Cl ₂	rt	12	81	39
2	(S)-L1	Cu(CH ₃ CN) ₄ BF ₄	CH ₂ Cl ₂	rt	8	84	56
3	(S)-L2	Cu(CH ₃ CN) ₄ BF ₄	CH ₂ Cl ₂	rt	8	75	75
4	(S)-L3	Cu(CH ₃ CN) ₄ BF ₄	CH ₂ Cl ₂	rt	15	63	43
5	(S)-L4	Cu(CH ₃ CN) ₄ BF ₄	CH ₂ Cl ₂	rt	12	79	69
6	(S)-L5	Cu(CH ₃ CN) ₄ BF ₄	CH ₂ Cl ₂	rt	8	85	92
7	(S)-L5	Cu(CH ₃ CN) ₄ BF ₄	ether	rt	10	78	88
8	(S)-L5	Cu(CH ₃ CN) ₄ BF ₄	THF	rt	15	76	87
9	(S)-L5	Cu(CH ₃ CN) ₄ BF ₄	PhMe	rt	10	83	92
10	(S)-L5	Cu(CH ₃ CN) ₄ BF ₄	EtOAc	rt	15	79	90
11	(S)-L5	Cu(CH ₃ CN) ₄ BF ₄	CH ₂ Cl ₂	0	12	81	93
12	(S)-L5	Cu(CH ₃ CN) ₄ BF ₄	CH ₂ Cl ₂	-20	16	88	95
13	(S)-L5	Cu(CH ₃ CN) ₄ BF ₄	CH ₂ Cl ₂	-40	20	86	98

^aAll reactions were carried out with 0.23 mmol of **5a** and 0.35 mmol of **6a** in 2 mL of solvent. ^bYield of the isolated compound **3aa** after purification by column chromatography on silica gel. ^cEe was determined by HPLC analysis using a chiral stationary phase, and dr was determined by the crude ¹H NMR.

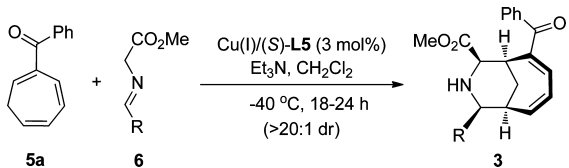
reaction pathway occurred with 2-ethoxycarbonyl cycloheptatriene **4** (Scheme 3, left side) providing the bicyclic pyrrolidine **1** as a single isomer, which was confirmed by X-ray diffraction analysis of the corresponding enantiopure compound later (*vide infra*).¹² Neither [3 + 4] nor [3 + 6] cycloadduct was detected in this process. When switching the carbonyl group from CO₂Et to benzoyl, we found that a [3 + 2]-pathway was suppressed and a [3 + 6]-reaction occurred preferentially affording the bridged adduct azabicyclo[4.3.1]decadiene **3aa** with excellent diastereoselectivity (Scheme 3, right side). Further X-ray diffraction analysis confirmed that an exclusive regioselectivity was achieved in this case,¹² and formation of any [3 + 2] and [3 + 4] cycloadduct was not observed.

The promising results encouraged us to conduct the asymmetric variant of this 1,3-dipolar [3 + 6] cycloaddition with chiral TF-BiphamPhos ligands,^{9a} and the results are tabulated in Table 1. Employing Ag(I)/(S)-(L1) complex as the catalyst, compound **3aa** was separated in 81% yield albeit with moderate ee value (Table 1, entry 1). Better catalytic activity and higher enantioselectivity were exhibited by Cu(I)/(S)-L1 complex. Then, a series of chiral ligands were screened with copper(I) as the metal precursor. Deleterious enantioselectivities were observed for ligand L2-L4 in which the sterically hindered substituents with different electron properties were introduced on the phosphorus atom (entries 3–5). Installing two bromine atom at the 3,3'-position of the biphenyl backbone significantly improved the enantioselectivity, and L5 was shown as the best

chiral ligand in this [3 + 6] annulation affording **3aa** in 85% yield and 92% ee (entry 6) (see Supporting Information for the screening results of other commonly used chiral ligands). Subsequent solvent screening revealed that the reaction medium had a slight effect on this reaction and that dichloromethane and toluene were the best solvents in terms of stereoselectivity and reactivity (Table 1, entries 6–10). Reducing the reaction temperature was beneficial for further enantioselectivity improvement, and 95% and 98% ee were achieved when the cycloaddition was carried out at -20 °C and -40 °C, respectively (entries 12 and 13).

Having established the optimal reaction conditions, we explored various imino esters to examine the substrate scope. The representative results are summarized in Table 2. A wide range of imino esters are compatible with this [3 + 6]-cycloaddition reaction. Aryl imino esters containing different substitution patterns (e.g., *para*-, *meta*-, or *ortho*-) at the phenyl ring were well tolerated, regardless of the electron properties (e.g., electron-neutral, -rich, or -deficient), and the desired adducts **5** were obtained in good yield (77–87%) with high diastereoselectivity (>20:1 dr) and excellent enantioselectivity (93–98%) (Table 2, entries 1–10). It is worth mentioning that excellent diastereoselectivity and enantioselectivity could be maintained with sterically hindered *ortho*-chloro (**6b**), *ortho*-methyl (**6g**), and fused aromatic 1-naphthyl (**6j**) imino esters (entries 2, 7, and 10). This cycloaddition was also compatible with heteroaromatic frameworks as shown in entries 11 and 12,

Table 2. Substrate Scope of Cu(I)/(S)-L5-Catalyzed Asymmetric [3 + 6] Cycloaddition of 2-Benzoyl Cycloheptatrienes 5a with Imino Esters 6^a



entry	R	prod.	yield (%) ^b	ee (%) ^c
1	<i>p</i> -Cl-C ₆ H ₄ (6a)	3aa	86	98
2	<i>o</i> -Cl-C ₆ H ₄ (6b)	3ab	82	95
3	<i>p</i> -Br-C ₆ H ₄ (6c)	3ac	85	98
4	<i>p</i> -NO ₂ -C ₆ H ₄ (6d)	3ad	87	98
5	Ph (6e)	3ae	83	98
6	<i>p</i> -Me-C ₆ H ₄ (6f)	3af	82	97
7	<i>o</i> -Me-C ₆ H ₄ (6g)	3ag	84	93
8	<i>m</i> -MeO-C ₆ H ₄ (6h)	3ah	77	95
9	<i>p</i> -MeO-C ₆ H ₄ (6i)	3ai	83	98
10	1-naphthyl (6j)	3aj	81	96
11	furyl (6k)	3ak	81	98
12	thienyl (6l)	3al	83	94
13 ^d	Pr (6m)	3am	75	91
14 ^d	PhCH=CH (6n)	3an	81	97

^aAll reactions were carried out with 0.23 mmol of 5a and 0.35 mmol of 6 in 2 mL of CH₂Cl₂. ^bYield of the isolated compound 3 after purification by column chromatography on silica gel. ^cEe was determined by HPLC analysis using a chiral stationary phase. Minor diastereomer was not detected on the crude ¹H NMR. ^dInorganic Cs₂CO₃ was employed as the base.

and 98% and 94% ee were observed for 2-furyl (6k) and 2-thienyl (6l) substituted imino esters, respectively. Notably, the substrate scope of this cycloaddition was successfully extended to less reactive aliphatic- and alkenyl-substituted imino esters 6m and 6n, and the desired adducts 3am and 3an were separated in good yield with excellent diastereoselectivity and enantioselectivity in the presence of stronger inorganic base Cs₂CO₃ (entries 13 and 14).

The relative and absolute configuration of the adduct 3aa was unequivocally determined as (1*S*,6*R*,7*R*,9*S*) based on the X-ray diffraction analysis¹² (Figure 1). Those of other [3 + 6]-cycloadducts were deduced based on these results.

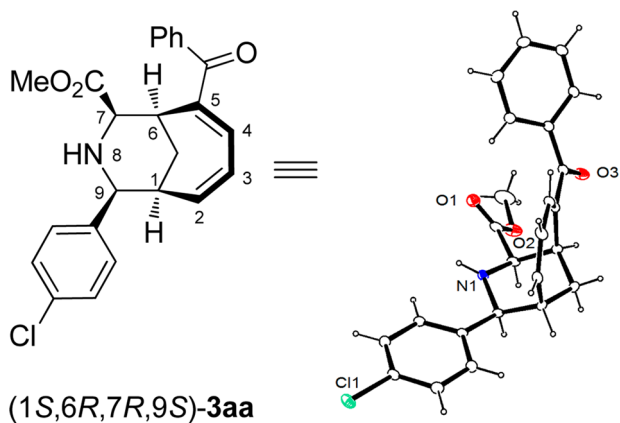
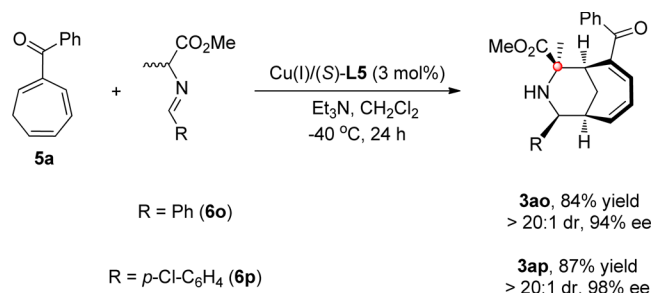


Figure 1. ORTEP representation of (1*S*,6*R*,7*R*,9*S*)-3aa at 10% probability for the drawing of thermal ellipsoids.

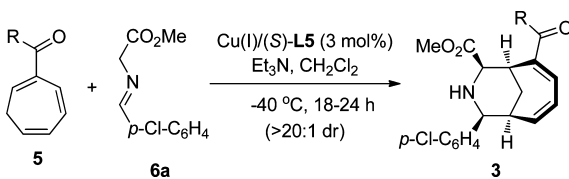
Remarkably, α -substituted imino esters 6o and 6p derived from alanine worked well in this cyclization process, furnishing the corresponding chiral-bridged azabicyclo[4.3.1]decadienes 3ao and 3ap containing one unique quaternary¹³ and three tertiary stereogenic centers, which highlighted the generality of this [3 + 6] cycloaddition protocol (Scheme 4).

Scheme 4. Cu(I)-Catalyzed Asymmetric 1,3-Dipolar [3 + 6] Cycloaddition of 2-Benzoyl Cycloheptatrienes 5a with Imino Esters 6 Derived from Alanine



The substrate scope of this cycloaddition with respect to the cycloheptatrienes was also explored to further investigate the generality of the method. As shown in Table 3, the efficient

Table 3. Substrate Scope of Cu(I)/(S)-L5-Catalyzed Asymmetric [3 + 6] Cycloaddition of 2-Acyl Cycloheptatrienes 5 with Imino Ester 6a^a



entry	R	prod.	yield (%) ^b	ee (%) ^c
1	Ph (5a)	3aa	86	98
2	<i>p</i> -Me-C ₆ H ₄ (5b)	3ba	81	96
3	<i>o</i> -Me-C ₆ H ₄ (5c)	3ca	84	97
4	<i>m</i> -Me-C ₆ H ₄ (5d)	3da	86	98
5	<i>p</i> -MeO-C ₆ H ₄ (5e)	3ea	78	98
6	<i>p</i> -Cl-C ₆ H ₄ (5f)	3fa	81	97
7	<i>p</i> -CF ₃ -C ₆ H ₄ (5g)	3ga	83	96
8	1-naphthyl (5h)	3ha	88	98
9	furyl (5i)	3ia	75	97
10	thienyl (5j)	3ja	81	97
11	Me (5k)	3ka	78	96
12	H (5l)	3la	85	71(99) ^d

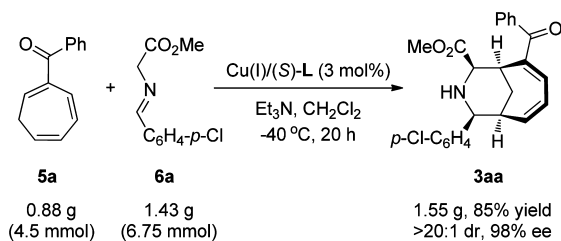
^aAll reactions were carried out with 0.23 mmol of 5 and 0.35 mmol of 6a in 2 mL of CH₂Cl₂. ^bYield of the isolated compound 3 after purification by column chromatography on silica gel. ^cEe was determined by HPLC analysis using a chiral stationary phase. Minor diastereomer was not detected on the crude ¹H NMR. ^dData in parentheses were achieved after simple recrystallization in ethyl acetate.

catalytic system is amenable to a variety of 2-acyl cycloheptatrienes including aromatic (entries 1–8), heteroaromatic (entries 9–10), and aliphatic groups (entry 11), affording the desired cycloadducts in good yields (75–88%) with high diastereoselectivities (>20:1 dr) and excellent enantioselectivities (96–98% ee). The electron-deficient (entries 6 and 7) and electron-rich (entries 2–5) phenyl ring in the acyl moiety of

cycloheptatrienes had negligible influence on the results of asymmetric induction. Substitution at the *para*-, *meta*-, or *ortho*-positions of the phenyl ring in 2-acyl cycloheptatrienes could also be well tolerated without effect on the enantioselectivity. Notably, aliphatic 2-acyl cycloheptatriene **5k** worked well in this process as a viable 6- π -component, producing the desired cycloadduct **3ka** in 78% yield with 96% ee (entry 11). 2-Formyl cycloheptatriene **5l** could also be compatible in this [3 + 6] cycloaddition affording the desired adduct **3la** in good yield with high diastereoselectivity albeit moderate enantioselectivity. Fortunately, the enantiopure **3la** can be easily achieved by simple crystallization (entry 12).

The synthetic utility of this reaction was further investigated. The reaction between **5a** and **6a** was performed on a gram scale to test the scalability of this cycloaddition, and compound **3aa** was obtained in 85% yield and 98% ee (Scheme 5).

Scheme 5. Scale-Up of the 1,3-Dipolar [3 + 6] Cycloaddition Reaction



The adduct **3aa** contains functional groups that are feasible toward synthetic transformations as exemplified in Scheme 6. Treatment of **3aa** with NaBH_4 led to the reduction of both carbonyl and ester groups providing the diol (*R*)-(1*R*,6*S*,7*S*,9*R*)-**7** in good yield with high diastereoselectivity. In addition, irradiation of **3aa** with *N*-phenyl maleimide using a 500 W lamp underwent excellent regioselective and diastereoselective [2 + 2] annulation¹⁴ to afford enantioenriched compound **8** containing eight stereogenic centers in 75% yield as a single isomer.

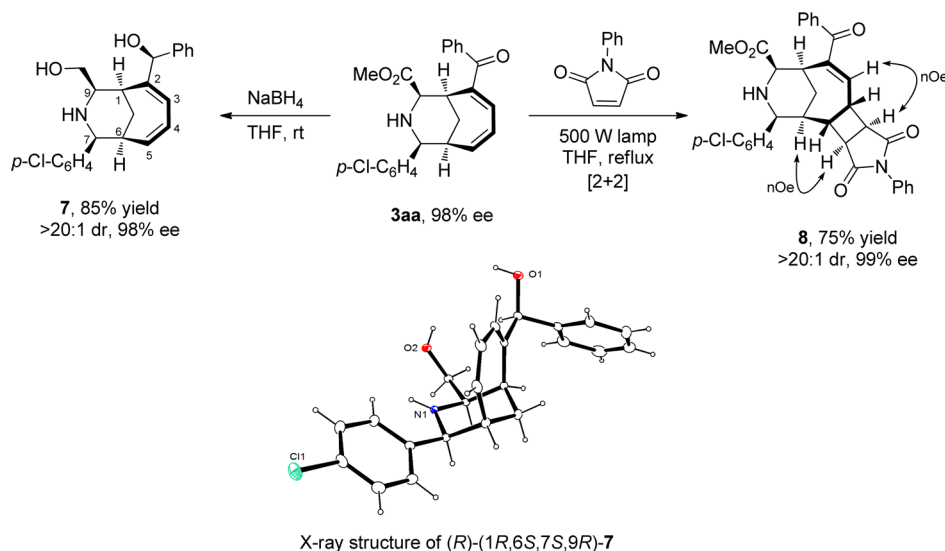
The asymmetric variant of 1,3-dipolar [3 + 2] cycloaddition with 2-ethoxycarbonyl cycloheptatriene **4** as the 2- π dipolarophiles was also carried out under the established optimal

reaction condition for the above [3 + 6]-cycloaddition, and the results are listed in Scheme 7. Employing Cu(I)/(S)-(L5) complex as the catalyst and *N*-(4-chlorobenzylidene)-glycine methyl ester **6a** as the dipole precursor, the [3 + 2]-cycloadduct **1** was separated in 82% yield with high diastereoselectivity and excellent enantioselectivity. The absolute configuration of **1** achieved by Cu(I)/(S)-L5 was unequivocally determined to be (1*R*,3*R*,3*aR*,8*aR*) by X-ray analysis of the corresponding *N*-tosylated amide **1'**.

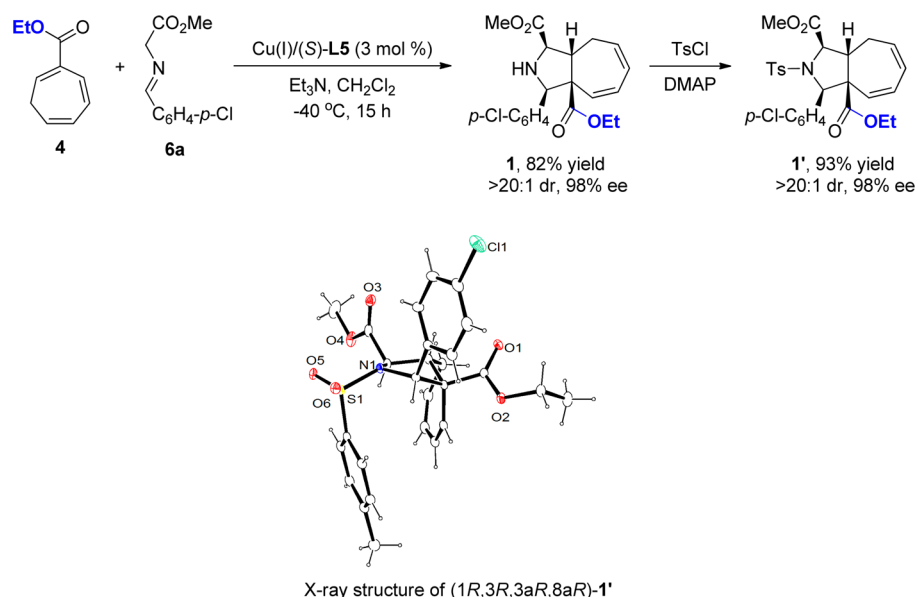
Based on the X-ray structure and the absolute configuration of the cycloadducts **3aa** and **1'**, a plausible stepwise mechanism is proposed to rationalize the regioselectivity and stereoselectivity of [3 + 6]- and [3 + 2]-cycloaddition (Scheme 8).

The catalytically active species is the distorted tetrahedral Cu(I) -species **A** formed by the coordination of the chiral ligand and the *in situ*-formed azomethine ylide in such manner to avoid otherwise unfavorable steric repulsion.^{10a} The back side of the azomethine ylide is shielded by the bulky PPh_2 group. The initial Michael addition of ylide **A** to the positively charged β -position of **5a** and **4** via *Re* face attack generate the zwitterionic intermediates **C** and **E**, respectively. The more electron-deficient benzoyl group of the species **C** renders the carboanion more stable than ester group of **E** does, which favors greater weight to its resonance form **C'**. The negative charge at α -position in **C** is more easily delocalized to ω' -position than that in **E** because of the lower $\text{p}K_a$ value of the corresponding ω' -proton in **C'** which could be deduced from the different $\text{p}K_a$ values of the α -proton in acetophenone (24.7)¹⁷ and in ethyl acetate (30.5).¹⁸ Subsequent intramolecular Mannich addition of the carboanion to the *Si* face of the imino moiety prefers to adopt a six-membered chair-like transition state, undergoing [3 + 6]-reaction pathway with exclusive regioselectivity and excellent stereoselectivity (Scheme 8, left side). On the contrary, the less stable anion of the intermediate **E** is believed to undergo the subsequent intramolecular cyclization directly through [3 + 2]-pathway¹⁵ (Scheme 8, right side). The proposed transition-state model is fully consistent with the observed regio- and stereochemical outcome. Nevertheless, a precise understanding of the real mechanism for the current 1,3-dipolar [3 + 6] cycloaddition system awaits further study.

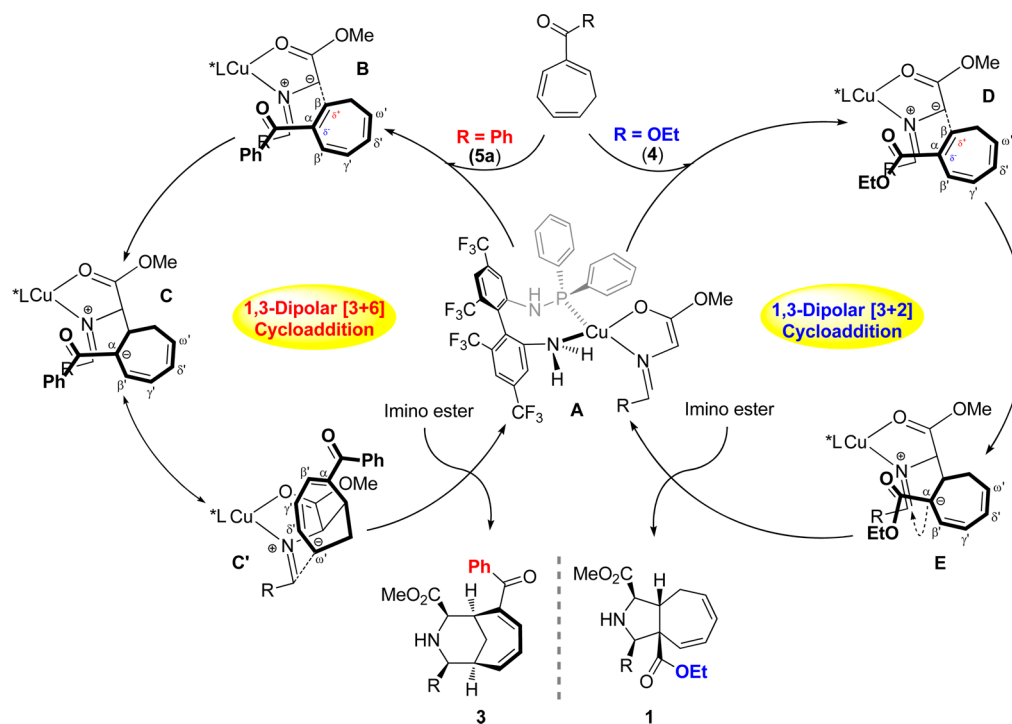
Scheme 6. Synthetic Transformations



Scheme 7. Cu(I)/(S)-L5-Catalyzed Asymmetric 1,3-Dipolar [3 + 2] Cycloaddition of Imino Ester 6a with 2-Ethoxycarbonyl Cycloheptatriene 4 and the Absolute Configuration Determination of the Corresponding Derivative 1'



Scheme 8. Postulated Catalytic Cycle for Cu(I)/TF-BiphamPhos-Catalyzed 1,3-Dipolar [3 + 6] Cycloaddition of Azomethine Ylide with 2-Benzoyl Cycloheptatriene 5a and 1,3-Dipolar [3 + 2] Cycloaddition with 2-Ethoxycarbonyl Cycloheptatriene 4



CONCLUSION

In summary, we have developed an unprecedented substrate-controlled catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides employing 2-substituted cycloheptatrienes without nonbenzenoid aromatic characteristic as the fine-tunable dipolarophiles for the first time. A variety of enantiopure heterocycles bearing a bridged piperidine moiety were achieved in generally good yield with exclusive regioselectivity and excellent stereoselectivity. The 2-acyl group of the cycloheptatriene is the key factor that determines the annulation preferentially through [3 + 6]-pathway, while the 2-ester group

modulates the annulation through [3 + 2]-pathway. Subsequent synthetic transformation of the cycloadduct provided facile access to synthetically useful compounds with diverse functionality. Further investigation of mechanism and synthetic application is currently underway.

EXPERIMENTAL SECTION

General Information. ^1H NMR spectra were recorded on a VARIAN Mercury 300 MHz spectrometer in CDCl_3 . Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as (s = single, d = double, t = triple, q =

quartet, m = multiple or unresolved, and brs = broad singlet). ^{13}C NMR spectra were recorded on a Bruker 75 MHz spectrometer in CDCl_3 . Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Commercially available reagents were used without further purification. All reactions were monitored by TLC with silica gel-coated plates. Diastereomeric ratios were determined from crude ^1H NMR or HPLC analysis. Enantiomeric ratios were determined by HPLC, using a chiralpak IB-H column, a chiralpak AD-H column, or a chiralcel OD-H column with hexane and *i*-PrOH as solvents, and 2-substituted cycloheptatrienes were prepared according to the literature procedure.¹⁶ Imino esters **2** and chiral ligands **L1-L5** were prepared according to our previous procedure.^{9a} The racemic adducts were obtained by using $\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4/(\pm)\text{-TF-BiphamPhos}$ as the catalyst.

General Procedure for Cu(I)/(S)-L5-Catalyzed Asymmetric 1,3-Dipolar [3 + 6] Cycloaddition of Azomethine Ylides with 2-Acyl Cycloheptatrienes 5. Under argon atmosphere, (S)-TF-BiphamPhos (**L5**) (6.1 mg, 0.0076 mmol) and $\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4$ (2.2 mg, 0.0069 mmol) were dissolved in 2 mL of DCM and stirred at room temperature for about 0.5 h. After an imine substrate (0.35 mmol) was added, the mixture was dropped to -40°C . Then, 2-acylcycloheptatrienes (0.23 mmol) and Et_3N (0.03 mmol) were added sequentially. Once the starting material was consumed (monitored by TLC), the organic solvent was removed, and the residue was purified by column chromatography to give the cycloaddition product **3**, which was then directly analyzed by HPLC analysis to determine the enantiomeric excess.

(1*S*,6*R*,7*R*,9*S*)-methyl 5-benzoyl-9-(4-chlorophenyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (**3aa**, Table 2, entry 1). Yield (86%); $[\alpha]_D^{25} = -461.2$ (c 0.74, CHCl_3); ^1H NMR (CDCl_3 , TMS, 300 MHz) δ 7.67 (d, $J = 7.2$ Hz, 2H), 7.52–7.41 (m, 3H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.25 (d, $J = 8.1$ Hz, 2H), 6.79 (d, $J = 7.8$ Hz, 1H), 6.11 (dd, $J_1 = 7.8$ Hz, $J_2 = 11.7$ Hz, 1H), 5.70 (dd, $J_1 = 7.8$ Hz, $J_2 = 11.7$ Hz, 1H), 4.24 (m, 1H), 4.16 (m, 1H), 4.04 (m, 1H), 3.45 (s, 3H), 3.11 (m, 1H), 2.50–2.45 (m, 1H), 1.80–1.66 (m, 2H); ^{13}C NMR (CDCl_3 , TMS, 75 MHz) δ 198.3, 172.3, 140.7, 139.8, 139.7, 139.3, 138.4, 132.5, 131.3, 129.4, 128.2, 127.9, 127.2, 125.8, 65.0, 64.1, 51.7, 40.7, 34.0, 27.7; HRMS: calcd for $\text{C}_{24}\text{H}_{22}\text{NO}_3\text{Cl} + \text{H}^+$: 408.1361, found: 408.1374. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak IB-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, $\lambda = 254$ nm); $t_r = 13.54$ and 17.38 min.

Procedure for Cu(I)/(S)-L5-Catalyzed Asymmetric 1,3-Dipolar [3 + 2] Cycloaddition of Azomethine Ylide 6a with 2-Ethoxycarbonyl Cycloheptatriene 4. Under argon atmosphere, (S)-TF-BiphamPhos (**L5**) (6.1 mg, 0.0076 mmol) and $\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4$ (2.2 mg, 0.0069 mmol) were dissolved in 2 mL of DCM and stirred at room temperature for about 0.5 h. After imino ester **6a** (0.35 mmol, 74 mg) was added, the mixture was dropped to -40°C . Then, 2-ethoxycarbonyl cycloheptatriene (0.23 mmol, 38 mg) and Et_3N (0.03 mmol) were added sequentially. Once starting material was consumed (monitored by TLC), the organic solvent was removed, and the residue was purified by column chromatography to give the cycloaddition product **1** in 82% yield, which was then directly analyzed by HPLC analysis to determine the enantiomeric excess.

(1*R*,3*R*,3*aR*,8*aR*)-3*a*-ethyl 1-methyl 3-(4-chlorophenyl)-1,2,3,3*a*,8*a*-hexahydro-cyclohepta[*c*]pyrrole-1,3*a*-dicarboxylate (**1**). Yield (82%); $[\alpha]_D^{25} = -14.3$ (c 0.86, CHCl_3); ^1H NMR (CDCl_3 , TMS, 300 MHz) δ 7.27 (m, 4H), 6.34–6.30 (m, 1H), 6.15–6.01 (m, 3H), 4.37 (s, 1H), 3.95 (d, $J = 11.8$ Hz, 1H), 3.83 (s, 3H), 3.76–3.68 (m, 2H), 3.42–3.38 (m, 1H), 2.52–2.37 (m, 2H), 0.96 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , TMS, 75 MHz) δ 173.5, 172.5, 137.0, 133.7, 133.0, 128.4, 128.2, 128.1, 127.0, 72.8, 64.3, 63.4, 61.0, 57.4, 52.2, 28.9, 13.6; HRMS: calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_4\text{Cl} + \text{H}^+$: 376.1310, found: 376.1311. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AS-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/min, $\lambda = 240$ nm); $t_r = 15.94$ and 25.86 min.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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