JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

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

Qing-Hua Li, Liang Wei, and Chun-Jiang Wang

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/ja503309u • Publication Date (Web): 29 May 2014

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

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

Qing-Hua Li,[†] Liang Wei,[†] and Chun-Jiang Wang,*[†,‡]

College of Chemistry and Molecular Sciences, Wuhan University, China 430072
State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, China 300071

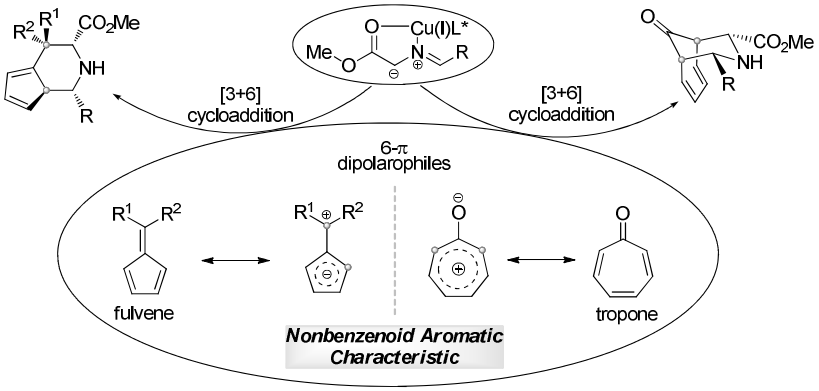
Email: cjwang@whu.edu.cn

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

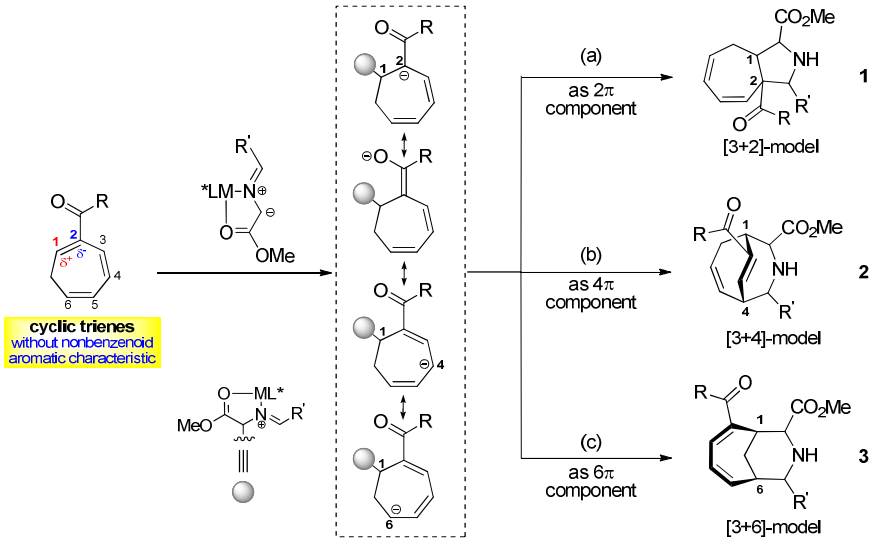
Heterocyclic structures with multiple stereogenic centers are the core elements prevalent in a variety of natural alkaloids and pharmaceutical ingredients exhibiting significant biological activities.[1-3] Metal-catalyzed 1,3-dipolar cycloaddition reaction of azomethine ylides is one of the powerful 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 serving as the three-atom 1,3-dipole units.[5] Recently, fulvenes[6] and tropone[7] 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. 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]

Scheme 1. Reported catalytic asymmetric 1,3-dipolar [3+6]-cycloaddition reactions of azomethine ylides with nonbenzenoid aromatic characteristical compounds as the 6-π dipolarophiles (previous work).



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-π components through varying the electronic property of polyenes, which may not only diversify the existing 1,3-dipolar cycloaddition reaction from the view point 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+2n] cycloaddition have been carried out so far.

Scheme 2. Possible reaction pathways for the designed 1,3-dipolar [3+2n] cycloaddition of azomethine ylides with conjugated cyclic trienes without nonbenzenoid aromatic characteristic.



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-π reaction partner in azomethine ylide-involved 1,3-dipolar [3+2n] 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 was served as 2-π unit ([3+2]-model, Scheme 2a); b) bridged heterocyclic azabicyclo[3.3.2]decadiene **2** in which 2-acyl cycloheptatriene was served as 4-π unit ([3+4]-model, Scheme 2b); and c) bridged heterocyclic azabicyclo[4.3.1]decadiene **3** in which 2-acyl cycloheptatriene was served as 6-π unit ([3+6]-model, Scheme 1c). Therefore, it is a great challenge to control both the exclusive regioselectivity and high stereoselectivity associated with this unknown annulation process.

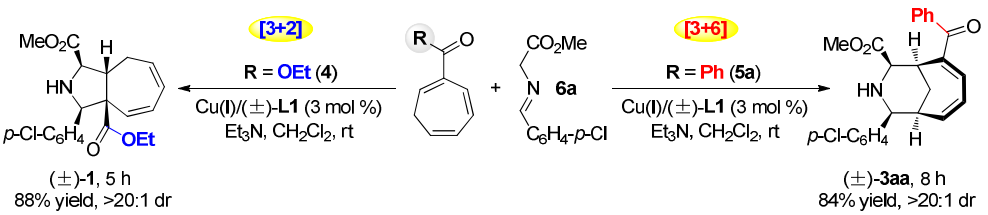
Herein, we report an unprecedented catalytic asymmetric 1,3-dipolar [3+6] cycloaddition of azomethine ylides employing 2-acyl cycloheptatrienes without nonbenzenoid aromatic characteristic as the 6-π components, providing a facile access to a variety of enantioenriched heterocycles containing a unique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

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-complex as the catalysts.

Initially, 5 mol % of $Cu(CH_3CN)_4BF_4/PPh_3$ 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 Cu(I)/*rac*-(±)TF-BiphamPhos complex[9a] as the catalyst, the reactions became very clean and finish smoothly at room temperature. The common [3+2]-reaction pathway was occurred with 2-ethoxycarbonyl cycloheptatriene **4** (Scheme 3, left side) providing the bicyclic pyrrolidine **1** as 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 carbonyl group from CO_2Et to benzoyl, we found that [3+2]-pathway was suppressed and [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.

Scheme 3. Initial results of the 1,3-dipolar [3+2n] 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).



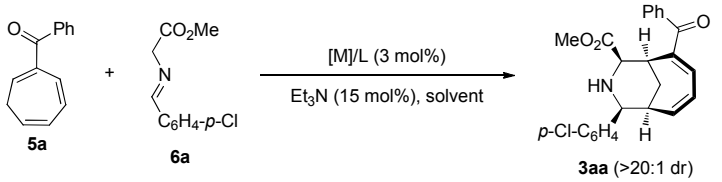
(±)-**1**, 5 h
88% yield, >20:1 dr

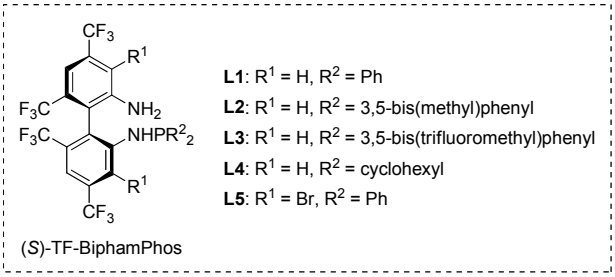
(±)-**3aa**, 8 h
84% yield, >20:1 dr

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 reaction medium had slight effect on this reaction, 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 ^{o}C and -40 ^{o}C, respectively (entries 12 and 13).

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





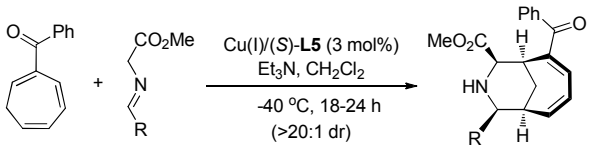
entry	**L1**	[M]	Solvent	*T* (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**(*S*)-L1**	AgOAc	CH_2Cl_2	rt	12	81	39
2	**(*S*)-L1**	$Cu(CH_3CN)_4BF_4$	CH_2Cl_2	rt	8	84	56
3	**(*S*)-L2**	$Cu(CH_3CN)_4BF_4$	CH_2Cl_2	rt	8	75	75
4	**(*S*)-L3**	$Cu(CH_3CN)_4BF_4$	CH_2Cl_2	rt	15	63	43
5	**(*S*)-L4**	$Cu(CH_3CN)_4BF_4$	CH_2Cl_2	rt	12	79	69
6	**(*S*)-L5**	$Cu(CH_3CN)_4BF_4$	CH_2Cl_2	rt	8	85	92
7	**(*S*)-L5**	$Cu(CH_3CN)_4BF_4$	Ether	rt	10	78	88
8	**(*S*)-L5**	$Cu(CH_3CN)_4BF_4$	THF	rt	15	76	87
9	**(*S*)-L5**	$Cu(CH_3CN)_4BF_4$	PhMe	rt	10	83	92
10	**(*S*)-L5**	$Cu(CH_3CN)_4BF_4$	EtOAc	rt	15	79	90
11	**(*S*)-L5**	$Cu(CH_3CN)_4BF_4$	CH_2Cl_2	0	12	81	93
12	**(*S*)-L5**	$Cu(CH_3CN)_4BF_4$	CH_2Cl_2	-20	16	88	95
13	**(*S*)-L5**	$Cu(CH_3CN)_4BF_4$	CH_2Cl_2	-40	20	86	98

[a] All reactions were carried out with 0.23 mmol of **5a** and 0.35 mmol of **6a** in 2 mL of solvent. [b] Yield of the isolated compound **3aa** after purification by column chromatography on silica gel. [c] Ee was determined by HPLC analysis using a chiral stationary phase, and dr was determined by the crude ^{1}H NMR.

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, electron-rich or electron-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, 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 Cs_2CO_3 (entries 13 and 14).

Table 2. Substrate scope of Cu(I)/(*S*)-**L5**-catalyzed asymmetric [3+6] cycloaddition of 2-benzoyl cycloheptatrienes **5a** with imino esters **6**.[a]

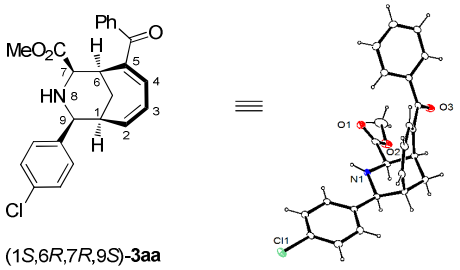


5a **6** **3**

entry	R	Prod.	yield (%)[b]	ee (%)[c]
1	*p*-Cl-C_6H_4 (**6a**)	**3aa**	86	98
2	*o*-Cl-C_6H_4 (**6b**)	**3ab**	82	95
3	*p*-Br-C_6H_4 (**6c**)	**3ac**	85	98
4	*p*-NO_2-C_6H_4 (**6d**)	**3ad**	87	98
5	Ph (**6e**)	**3ae**	83	98
6	*p*-Me-C_6H_4 (**6f**)	**3af**	82	97
7	*o*-Me-C_6H_4 (**6g**)	**3ag**	84	93
8	*m*-MeO-C_6H_4 (**6h**)	**3ah**	77	95
9	*p*-MeO-C_6H_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

[a] All reactions were carried out with 0.23 mmol of **5a** and 0.35 mmol of **6** in 2 mL of CH_2Cl_2. [b] Yield of the isolated compound **3** after purification by column chromatography on silica gel. [c] Ee was determined by HPLC analysis using a chiral stationary phase. Minor diastereomer was not detected on the crude ^{1}H NMR. [d] Inorganic Cs_2CO_3 was employed as the base.

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 analysis[12] (Figure 1). Those of other [3+6]-cycloadducts were deduced based on these results.

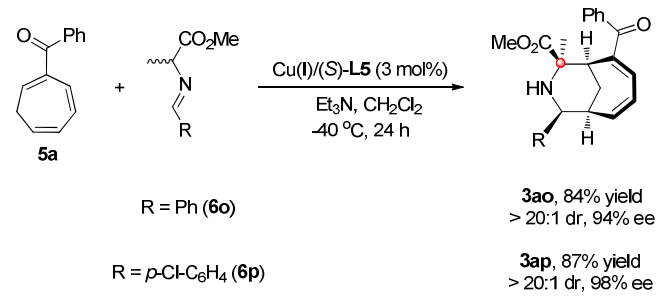


(1*S*,6*R*,7*R*,9*S*)-**3aa**

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 quaternary[13] and three tertiary stereogenic centers, which highlighted the generality of this [3+6] cycloaddition protocol (Scheme 4).

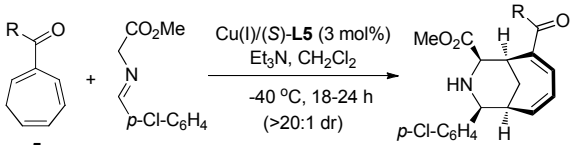
Scheme 4. Cu(I)-Catalyzed asymmetric 1,3-dipolar [3+6] cycloaddition of 2-benzoyl cycloheptatrienes **5a** with imino esters **6** derived from alanine.



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 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). 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 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).

Table 3. Substrate scope of Cu(I)/(*S*)-**L5**-catalyzed asymmetric [3+6] cycloaddition of 2-acyl cycloheptatrienes **5** with imino ester **6a**.[a]



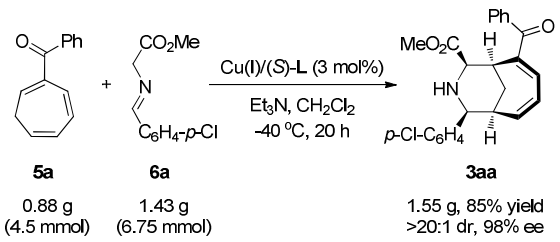
5 **6a** **3**

entry	R	Prod.	yield (%)[b]	ee (%)[c]
1	Ph (**5a**)	**3aa**	86	98
2	*p*-Me-C_6H_4 (**5b**)	**3ba**	81	96
3	*o*-Me-C_6H_4 (**5c**)	**3ca**	84	97
4	*m*-Me-C_6H_4 (**5d**)	**3da**	86	98
5	*p*-MeO-C_6H_4 (**5e**)	**3ea**	78	98
6	*p*-Cl-C_6H_4 (**5f**)	**3fa**	81	97
7	*p*-CF_3-C_6H_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]

[a] All reactions were carried out with 0.23 mmol of **5** and 0.35 mmol of **6a** in 2 mL of CH_2Cl_2. [b] Yield of the isolated compound **3** after purification by column chromatography on silica gel. [c] Ee was determined by HPLC analysis using a chiral stationary phase. Minor diastereomer was not detected on the crude ^{1}H NMR. [d] Data in parentheses was achieved after simple recrystallization in ethyl acetate.

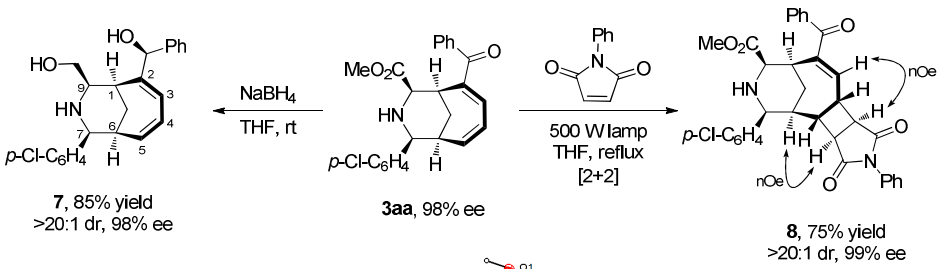
The synthetic utility of this reaction was further investigated. The reaction between **5a** and **6a** was performed on a gram scale to test the scalability of this cycloaddition, and compound **3aa** was obtained in 85% yield and 98% ee (Scheme 5).

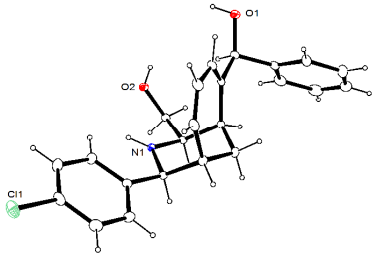
Scheme 5. Scale-up of the 1,3-dipolar [3+6] cycloaddition reaction.



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] annulation[14] to afford enantioenriched compound **8** containing eight stereogenic centers in 75% yield as a single isomer.

Scheme 6. Synthetic transformations.

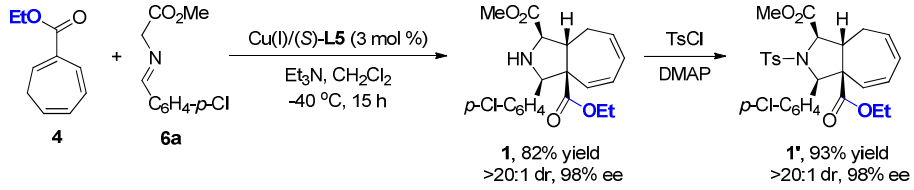


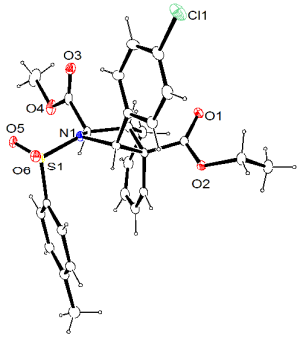


X-ray structure of (*R*)-(1*R*,6*S*,7*S*,9*R*)-**7**

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*,3a*R*,8a*R*) by X-ray analysis of the corresponding *N*-tosylated amide **1'**.

Scheme 7. Cu(I)/(*S*)-**L5**-catalyzed asymmetric 1,3-dipolar [3+2] cycloaddition of imino ester **6a** with 2-ethoxycarbonyl cycoheptatriene **4** and the absolute configuration determination of the corresponding derivative **1'**.



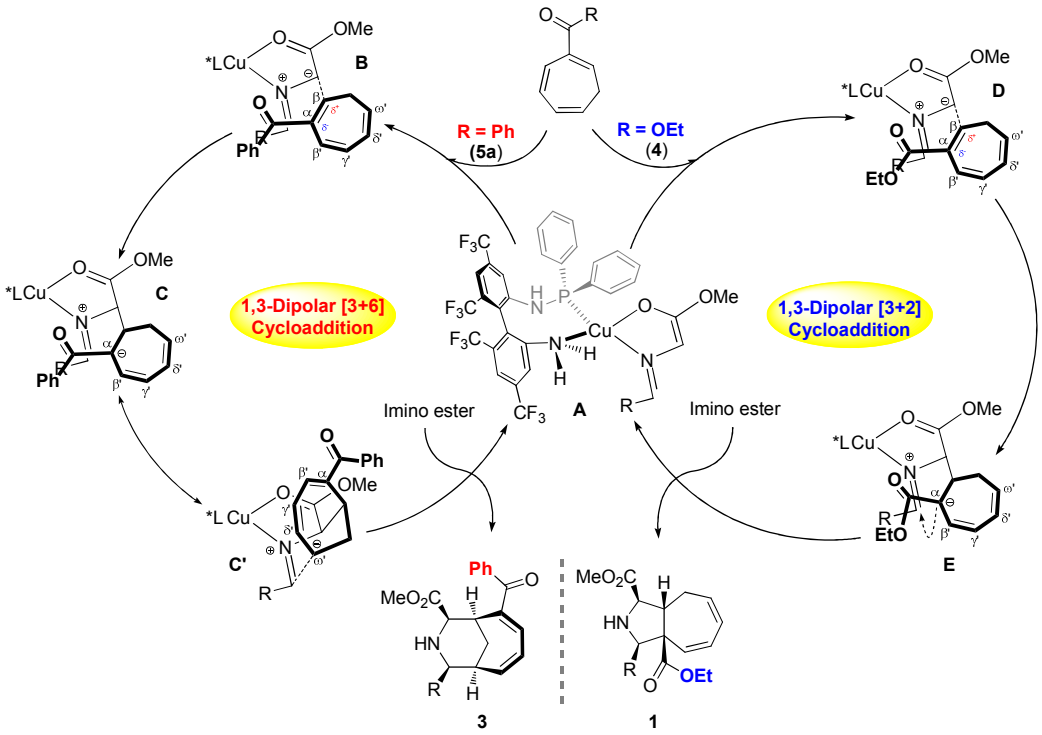


X-ray structure of (1*R*,3*R*,3a*R*,8a*R*)-**1'**

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).

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**.



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 unfavourable 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 pK_a value of the corresponding ω'-proton in C' which could be deduced from the different pK_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]-pathway[15] (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.

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. 2-Acyl group of the cycloheptatriene is the key factor that determines the annulation preferentially through [3+6]-pathway while 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 are currently underway.

EXPERIMENTAL SECTION

General Information. ^{1}H 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 single). ^{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 ^{1}H 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 our previous procedure.[9a] The racemic adducts were obtained by using $Cu(CH_3CN)_4BF_4$/(±)- 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 $Cu(CH_3CN)_4BF_4$ (2.2 mg, 0.0069 mmol) were dissolved in 2 mL of DCM, and stirred at room temperature for about 0.5 h. After imine substrate (0.35 mmol) was added, the mixture was dropped to -40 ^oC. Then, 2-acylcycloheptatrienes (0.23 mmol) and Et_3N (0.03 mmol) was 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 **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%); $[\alpha]^{25}_D$ = -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 $C_{24}H_{22}NO_3Cl + H^+$: 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, λ = 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 $Cu(CH_3CN)_4BF_4$ (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 ^oC. Then, 2-ethoxycarbonyl cycloheptatriene (0.23 mmol, 38 mg) and Et_3N (0.03 mmol) was 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*)-3a-ethyl 1-methyl 3-(4-chlorophenyl)-1,2,3,3a,8,8a-hexahydro-cyclohepta[c]pyrrole-1,3a-dicarboxylate (1) Yield (82%); $[\alpha]^{25}_D$ = -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 $C_{20}H_{22}NO_4Cl + H^+$: 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, λ = 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.

AUTHOR INFORMATION

Corresponding Author

cjwang@whu.edu.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work is supported by 973 Program (2011CB808600), NSFC (21172176, 21372180), NCET-10-0649, and Hubei Province NSF (ZRZ0273). The authors thank all referees for their helpful comments and suggestions.

REFERENCES

(1) (a) Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. in *Progress in Heterocyclic Chemistry, Vol. 19* (Eds.: Gribble, G. W.; Joule, J.), Pergamon: Oxford, **2008**. (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (c) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (d) Aubert, C.; Buisine, O.; Malacria, M.

Chem. Rev. **2002**, *102*, 813. (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (f) Zhao, W. *Chem. Rev.* **2010**, *110*, 1706. (g) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis* Pergamon: Oxford, **1990**, pp. 1−208.

(2) (a) Bindra, J. S.; Manske, R. H. F. *The Alkaloids*, *Vol. 14*, Eds. Academic Press: New York, **1973**. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

(3) (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791.

(4) (a) *1,3-Dipolar Cycloaddition Chemistry*, ed. Padwa, A. Wiley, New York, **1984**. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905. (d) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*, ed. Padwa, A.; Pearson, W. H. Wiley, New York, **2003**.

(5) For recent reviews, see: (a) Nájera, C.; Sansano, J. M.; *Angew. Chem., Int. Ed.* **2005**, *44*, 6272. (b) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174. (c) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (d) Engels, B.; Christl, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7968. (e) Adrio, J.; Carretero, J. C. *Chem. Commun*. **2011**, *47*, 6784. (f) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (g) Chen, Q.-A.; Wang, D.-S.; Zhou, Y.-G. *Chem. Commun*. **2010**, *46*, 4043. (h) Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296. For selected recent examples, see: (i) Huang, J.-Z.; Luo, S.-W.; Gong, L.-Z. *Acta Chim. Sinica* **2013**, *71*, 879. (j) Tong,

M.-C.; Chen, X.; Tao, H.-Y.; Wang, C.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12377. (k) Potowski, M.; Schürmann, M.; Preut, H.; Antonchick, A. P.; Waldmann, H. *Nat. Chem. Biol.* **2012**, 8, 428. (l) He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504. (m) Kim, H. Y.; Li, J.-Y.; Kim, S.; Oh, K. *J. Am. Chem. Soc.* **2011**, *133*, 20750. (n) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (o) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X. *J. Am. Chem. Soc.* **2007**, *129*, 750. (p) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuli K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338. (q) Arai, T.; Yokoyama, N.; Mishiro, A.; Sato, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7895. (r) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schürmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nature Chem.* **2010**, *2*, 735. (s) Nájera, C.; Retamosa, M. D. G.; Sansano, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6055. (t) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174. (u) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979. (v) Knoepfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (w) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, 127, 16394. (x) Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364. (y) Yamashita, Y.; Imaizumi, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 4893.

(6) (a) Potowski, M.; Bauer, J. O.; Strohmann, C.; Antonchick, A. P.; Waldmann, H. *Angew. Chem.*, *Int. Ed.* **2012**, *51*, 9512. (b) He, Z.-L.; Teng, H.-L.; Wang, C.-J. *Angew. Chem.*, *Int. Ed.* **2013**, *52*, 2934.

(7) (a) Teng, H.-L.; Yao, L.; Wang, C.-J. *J. Am. Chem. Soc.* **2014**, *136*, 4075. (b) Liu, H.; Wu, Y.; Zhao, Y.; Li, Z.; Zhang, L.; Yang, W.; Jiang, H.; Jing, C.; Yu, H.; Wang, B.; Xiao, Y.; Guo, H. *J. Am. Chem. Soc.* **2014**, *136*, 2625.

(8) (a) Nakajima, T.; Katagiri, S. *Bull. Chem. Soc. Jpn*. **1962**, *35*, 910. (b) Griffiths, J.; Lockwood, M. *J. Chem. Soc.*, *Perkin Trans. 1*, **1976**, *1*, 48. (c) Dewar, M. J. S. *Nature* (*London*) **1945**, *155*, 50. (d) Dewar, M. J. S. *Nature* (*London*) **1945**, *155*, 141.

(9) (a) Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250. (b) Yan, D.-C.; Li, Q.-H.; Wang, C.-J. *Chin. J. Chem.* **2012**.*30*, 2714. (c) Liu, T.-L.; He, Z.-L.; Tao, H.-Y.; Cai, Y.-P.; Wang, C.-J. *Chem. Commun.* **2011**, *47*, 2616

(10) (a) Wang, M.; Wang, C.-J.; Lin, Z. *Organometallic* **2012**, *31*, 7870. (b) Tong, M.-C.; Li, J.; Tao, H.-Y.; Li, Y.-X.; Wang, C.-J. *Chem. Eur. J.* **2011**, *17*, 12922. (c) Xue, Z.-Y.; Li, Q.-H.; Tao, H.-Y.; Wang, C.-J. *J. Am. Chem. Soc.* **2011**, *133*, 11757.

(11) (a) Kobayashi, J. i.; Hirasawa, Y.; Yoshida, N.; Morita, H. *J. Org. Chem.* **2001,** *66*, 5901. (b) Mu, S.-Z.; Wang, J.-S.; Yang, X.-S.; He, H.-P.; Li, C.-S.; Di, Y.-T.; Wang, Y.; Zhang, Y.; Fang, X.; Huang, L.-J.; Hao, X.-J. *J. Nat. Prod.* **2008,** *71*, 564. (c) Zhang, C.-R.; Liu, H.-B.; Feng, T.; Zhu, J.-Y.; Geng, M.-Y.; Yue, J.-M. *J. Nat. Prod.* **2009,** *72*, 1669. (d) Zhang, C.-R.; Fan, C.-Q.; Dong, S.-H.; Liu, H.-B.; Zhou, W.-B.; Wu, Y.; Yue, J.-M. *Org. Lett.* **2011,** *13*, 2440. (e) Luo, D.-Q.; Zhu, W.-L.; Yang, X.-L.; Liang, S.-J.; Cao, Z.-R. *Helv. Chim. Acta* **2010,** *93*, 1209.

(12) CCDC 951573 (**3aa**), 951574 (**7**) and 987146 (**1'**) contain the supplementary crystallographic data for this paper.

(13) (a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*

Christoffers, J.; Baro, A. Eds. Wiley-VCH: Weinheim, **2005**. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A* **2004**, *101*, 5363.

(14) Mahendar, V.; Oikawa, H.; Oguri, H. *Chem. Commun*. **2013**, *49*, 2299.

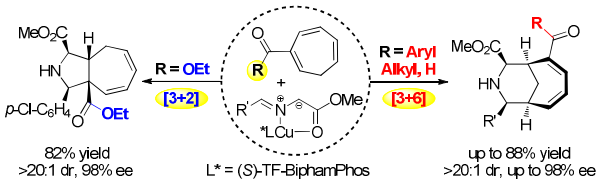
(15) One referee suggested that when 2-ethoxycarbonyl cycloheptatriene **4** is employed as dipolarophile an orbital-controlled concerted pathway might be favored leading to the usual [3+2]-annulation, and we cannot rule out this possibility at the present time.

(16) (a) Blair, J. A.; Tate, C. J. *J. Chem. Soc.* (C), **1971**, 1592; (b) Blair, J. A.; Tate, C. J. *J. Chem. Soc. Chem. Commun*., **1970**, 1319. (c) Oda, M.; Kainuma, H.; Uchiyama, T.; Miyatake, R.; Kuroda, S. *Tetrahedron* **2003**, *59,* 2831.

(17) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucher, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.

(18) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327.

TOC Graphic:


R = OEt
[3+2]
R = Aryl
Alkyl, H
[3+6]
82% yield
>20:1 dr, 98% ee
L* = (S)-TF-BiphamPhos
up to 88% yield
>20:1 dr, up to 98% ee