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Exoselective 1,3-Dipolar [3 + 6] Cycloaddition of Azomethine Ylides with 2-Acylcycloheptatrienes: Stereoselectivity and Mechanistic Insight

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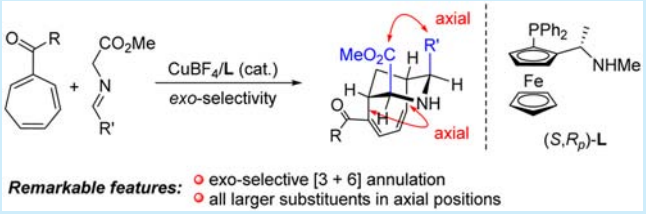
Supporting Information

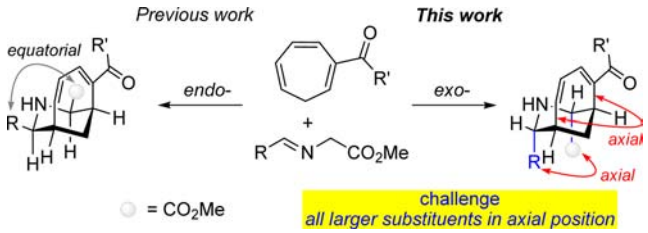
ABSTRACT: A highly *exo*-selective 1,3-dipolar [3 + 6] cycloaddition of azomethine ylides with 2-acylcycloheptatrienes was realized with a Cu(I)/(S,R_p)-PPF-NHMe complex as the catalyst, leading to a diverse range of bridged piperidines with multiple functionalities in good yield with excellent stereoselectivity control. Theoretical calculations indicated a stepwise mechanism for this *exo*-selective [3 + 6] annulation, which accounts for the remarkable feature of this annulation: all of the larger substituent groups occupy the axial positions in the six-membered chairlike conformation of the piperidine ring.



Nitrogen-containing heterocycles are frequently found in many biologically active natural products and pharmaceuticals.[1] Among the developed methodologies for heterocycle synthesis, the 1,3-dipolar cycloaddition reaction is one of the most powerful tools for the convergent construction of five-membered heterocycles in organic synthesis[2] due to the diverse and readily available 1,3-dipoles (three-atom, 4π systems) and dipolarophiles (two-atom, 2π systems). In view of the five-membered heterocycles normally generated, a 1,3-dipolar cycloaddition reaction was referred to as the [3 + 2] cycloaddition reaction as well.[3] Being coordinated with a chiral ligand, the in situ formed metalated azomethine ylides have received much attention in catalytic asymmetric 1,3-dipolar cycloaddition reactions, providing an expedient approach to enantioenriched pyrrolidine derivatives in the last decades.[4,5] However, the 1,3-dipolar cycloaddition reaction has been seldom utilized for synthesis of non-five-membered N-containing heterocycles. Having utilized fulvenes[6] and tropone[7] as 6-π dipolarophiles in the azomethine ylide involved 1,3-dipolar cycloaddition reaction, we recently disclosed that with Cu(I)/TF-BiphamPhos as the catalyst 2-acylcycloheptatrienes[8] could also serve as 6-π partners for constructing bridged piperidines with multiple functionalities via exclusive *endo* selectivity control. The six-membered heterocycles were each identified as having a chairlike conformation in which the two substituents from ylides occupy two equatorial positions and the *cis*-butadiene moieties from cycloheptatrienes are in two axial positions (Scheme 1, left side).

In view of the significance of access to any of the diastereomers of chiral compounds with high diastereo-/enantioselectivity and to further diversify synthetic methods for biologically important piperidines,[9] we decided to investigate the feasibility of realizing the [3 + 6]-annulation in an exclusively *exo*-selective manner (Scheme 2). Formation of the *exo*-cycloadduct is challenging and mechanistically intriguing considering that the two substituents from ylides would have to be arranged in the seemingly energy-disfavored axial positions, in view of the fact that the *cis*-butadiene moiety from cycloheptatrienes has no choice but to occupy the axial positions in the chairlike conformation because of ring strain. In this paper, we present our results on the *exo*-selective 1,3-dipolar [3 + 6] cycloaddition of azomethine ylides with 2-acylcycloheptatrienes in high yields and excellent enantioselectivities catalyzed by the Cu(I)/(S,R_p)-PPF-NHMe complex. The remarkable feature of this annulation, different from the case of *endo*-selective 1,3-dipolar [3 + 6] cycloaddition, is that we managed to generate piperidines in which the substituent groups occupy the axial positions of the six-membered chairlike conformation of the piperidine ring.

Scheme 1. Conformation Analysis for *Endo*- and *Exo*-Selective Construction of Bridged Piperidines via 1,3-Dipolar [3 + 6] Cycloaddition



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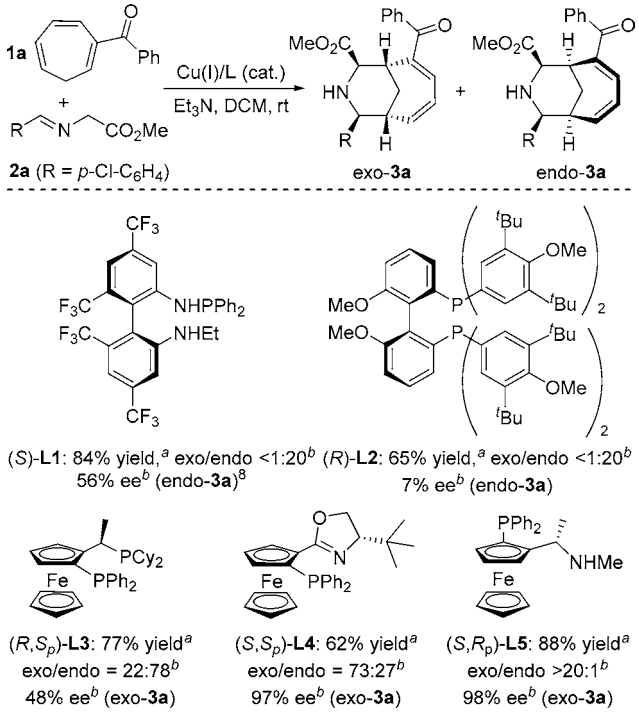
Scheme 2. Investigation of *Exo*-Selective 1,3-Dipolar [3 + 6] Cycloaddition



[a]Yield of the isolated compound **3a**. [b]ee and dr were determined by HPLC analysis using a chiral stationary phase.

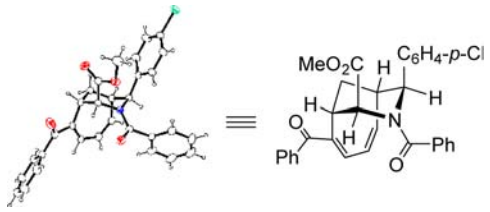
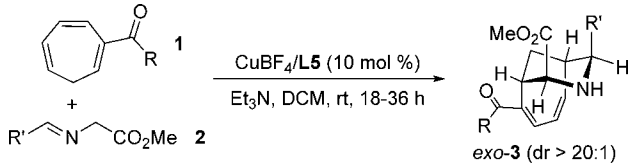


Figure 1. X-ray structure of (1*R*,6*S*,7*R*,9*S*)-*exo*-**4**.

Considering the crucial role of chiral ligands in asymmetric catalysis,[10] screening of some readily available and privileged chiral ligands to investigate the potential variation of stereoselective control would be desirable and practicable. We started our investigation by employing 2-benzoylcycloheptatriene **1a** and imine ester **2a** as the model substrates. DTBM-Biphep (**L2**) was first tested as the chiral ligand at room temperature with CH_2Cl_2 as the solvent. Although excellent *exo* selectivity was achieved with **L2** in our previously reported Cu(I)-catalyzed 1,3-dipolar [3 + 2] cycloaddition,[11] only the same *endo* selectivity was unexpectedly detected in this case. When (R,S_p)-**L3** was next screened in this transformation, partial inversion of diastereoselectivity was observed, but the desired *exo* adduct was formed as the minor isomer (22:78 dr) with only 48% ee. Inspired by this promising result, we turned our attention to a ferrocene-based ligand. The Cu(I)/(S,R_p)-^{t}Bu-Phosferrox (**L4**) catalyst,[12] giving high *exo* selectivity for 1,3 dipolar [3 + 2] cycloaddition of azomethine ylide,[13] was then evaluated in this higher order cycloaddition. The cycloadduct was produced in moderate yield favoring exoisomer in 73:27 dr, and the enantioselectivity was remarkably enhanced to 97% ee. Following the trend observed for the ferrocene-based chiral P,N-ligand, (S,R_p)-PPF-NHMe (**L5**),[7a] which contains similar

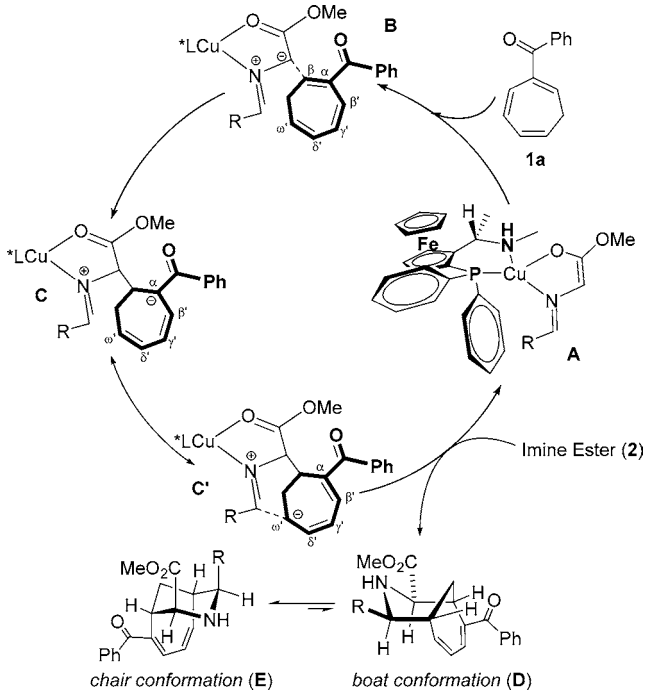
Table 1. Substrate Scope for Catalytic *Exo*-Selective 1,3-Dipolar [3 + 6] Cycloaddition of Azomethine Ylides 2 with 2-Acylcycloheptatrienes 1[a]



entry	R	R′	3	yield[b] (%)	ee[c](%)
1	Ph (**1a**)	*p*-ClC_6H_4 (**2a**)	**3a**	88	98
2	Ph (**1a**)	*o*-ClC_6H_4 (**2b**)	**3b**	78	99
3	Ph (**1a**)	*m*-ClC_6H_4 (**2c**)	**3c**	82	99
4	Ph (**1a**)	*p*-CNC_6H_4 (**2d**)	**3d**	73	>99
5	Ph (**1a**)	Ph (**2e**)	**3e**	74	99
6[d]	Ph (**1a**)	*p*-$MeOC_6H_4$ (**2f**)	**3f**	56	99
7[e]	Ph (**1a**)	*p*-MeC_6H_4 (**2g**)	**3g**	65	98
8	Ph (**1a**)	*m*-MeC_6H_4 (**2h**)	**3h**	72	>99
9	Ph (**1a**)	2-naphthyl (**2i**)	**3i**	81	>99
10	Ph (**1a**)	2-furyl (**2j**)	**3j**	72	99
11	Ph (**1a**)	PhCH=CH (**2k**)	**3k**	63	97
12	Ph (**1a**)	Et (**2l**)	**3l**	65	94
13	*p*-ClC_6H_4 (**1b**)	*p*-ClC_6H_4 (**2a**)	**3m**	79	96
14	*m*-ClC_6H_4 (**1c**)	*p*-ClC_6H_4 (**2a**)	**3n**	85	97
15	*p*-$MeOC_6H_4$ (**1d**)	*p*-ClC_6H_4 (**2a**)	**3o**	77	99
16	2-furyl (**1e**)	*p*-ClC_6H_4 (**2a**)	**3p**	75	97
17	2-thienyl (**1f**)	*p*-ClC_6H_4 (**2a**)	**3q**	92	99
18	Me (**1g**)	*p*-ClC_6H_4 (**2a**)	**3r**	75	98
19[e]	H (**1h**)	*p*-ClC_6H_4 (**2a**)	**3s**	72	98

[a]All reactions were carried out with 0.45 mmol of **1** and 0.30 mmol of **2** in 2.0 mL of CH_2Cl_2. $CuBF_4$ = $Cu(MeCN)_4BF_4$. [b]Isolated yield. Around 10% yield of the byproduct was separated, which was formed via [3 + 2] cycloaddition[14] (see the Supporting Information for details). [c]ee was determined by HPLC analysis. [d]dr = 4:1. [e]dr = 5:1.

Scheme 3. Postulated Catalytic Cycle



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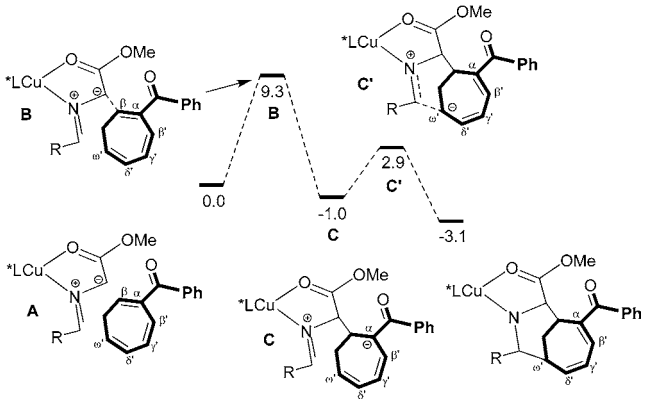

Figure 2. Free energy profile calculated for the 1,3-dipolar [3 + 6] cycloaddition of imine ester **2a** with 2-benzoylcycloheptatriene **1a** on the basis of the proposed mechanism shown in Scheme 3. The relative free energies are given in kcal/mol.

chelating atoms as the Phosferrox ligand, was subsequently employed in order to identify a more efficient catalyst in terms of both *exo* selectivity and enantioselectivity control. To our gratification, **L5** not only displayed a great improvement on the *exo* selectivity (dr >20:1) but also afforded a perfect enantioselectivity of 98% ee. The absolute configuration of cycloadduct **3a** was determined as (1*R*,6*S*,7*R*,9*S*) by X-ray analysis of the single crystal of its *N*-benzoylated derivative **4** (Figure 1), which validates the *exo* selectivity and confirms the occupation of larger substituents in the axial positions of the six-membered chairlike heterocyclic ring.

We next investigated the scope and generality of this *exo*-selective catalytic system with regard to both azomethine ylide precursors and 2-acylcycloheptatrienes. The representative results of the investigation are summarized in Table 1. In general, various imine esters **2** derived from aromatic aldehydes, which bear electron-deficient (Table 1, entries 1−4), electron-neutral (entries 5), or electron-rich substituents (entries 6−10), afforded the desired *exo* adducts in good yields with good to high diastereoselectivities and excellent enantioselectivities. The substituent patterns on the aromatic ring have a marginal effect on the diastereo-/enantioselectivity. Excellent stereoselectivity was also observed for the sterically hindered *o*-chloro-substituted imino ester **2b** with the same reactivity being maintained (entry 2). Imine esters **2i** and **2j** derived from 2-naphthyl aldehyde and heteroaromatic 2-furyl aldehyde, respectively, were also compatible in this transformation, giving rise to the expected *exo*-**3i** and -**3j** in good yield with 99% ee (entries 9 and 10). α,β-Unsaturated cinammyl imino ester **2k** also worked well in this process, producing the desired *exo*-**3k** with 97% ee (entry 11). Remarkably, less reactive aliphatic imino ester **3l** was also proved to be a viable substrate in this process, producing *exo*-**3l** in an acceptable yield with excellent diastereoselectivity and 94% ee (entry 12). The generality of dipolarophile partners was further explored. In general, various 2-acyl cycloheptatrienes bearing both aromatic and aliphatic groups were well tolerated in this reaction (Table 1, entries 13−18). The consistently high diastereoselectivity and excellent enantioselectivity observed with 2-formylcycloheptatriene **1h** is noteworthy (entry 19); as such, a triene was shown to be a relatively challenging dipolarophile affording only moderate enantioselectivity in our previously reported *endo*-selective [3 + 6] cycloaddition reaction.[8]

With all the experimental results discussed above, we propose a stepwise reaction mechanism (Scheme 3) that explains the selectivities of the reaction. In the proposed mechanism, a two-step process is involved during the cycloaddition reaction. We expect that, as also suggested in previous work,[15] the imine ester will readily undergo deprotonation and coordinate to the metal center, and the resulting metalated azomethine ylide acts as the active catalyst (**A**) in the reaction. The reaction thus involves the attack of the metalated azomethine ylide onto the *Si*-face of dipolarophile unit. The electron-rich end of the azomethine ylide dipole (**B**) first attacks the electron-deficient β-carbon on the cycloheptatriene ring. Upon formation of the intermediate **C**, the electron density shifts to the ω' carbon through the 6-π system on the 7-membered ring. At this point, the second attack takes place from the ω' carbon to the positive end of the azomethine ylide dipole and closes the ring. Due to the chirality of the (S,R_p)-PPF-NHMe ligand, the back side (with respect to the scheme) of the azomethine ylide is blocked by the NHMe group, and it is this steric hindrance that gives rise to the stereoselectivity of the reaction. Subsequent protonation affords the bridged piperidine adduct in boat conformation (**D**) with regeneration of the catalyst. Due to the larger number of eclipsing interactions existed in boat conformation (**D**), the six-membered heterocyclic ring swiftly adopts the final chair conformation (**E**), in which all the larger substituent groups occupy the seemingly energy-disfavored axial positions.

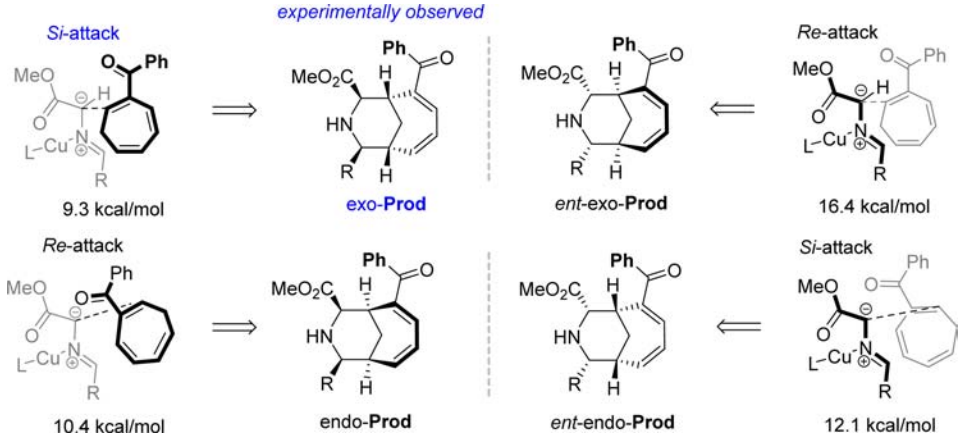

Figure 3. Examination of the possibilities of different attacking modes leading to *exo* and *endo* cycloadducts. Energy reference point is taken to be the van der Waals complex of the dipolarophile and metalated azomethine ylide on the pathway that gives rise to the experimentally observed *exo* cycloadduct.

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From DFT calculations, we can find support for our mechanistic arguments given above. We have chosen the cycloaddition reaction that gives rise to **3a** as our model system in our DFT calculations. The DFT calculation results (Figure 2) indicate that the proposed mechanism is energetically very reasonable. We have also calculated the transition states for other attacking modes leading to *exo* and *endo* cycloadduct as well as different enantiomers (Figure 3, and see the Supporting Information for more details). From these calculations, we indeed found out that the barriers for other pathways are higher than the one shown in Figure 2, thus explaining the high selectivity observed experimentally. Meanwhile, the eclipsing interactions in boat form force the heterocyclic ring to adopt the chair conformation (Scheme 3, **E** was calculated to be 0.6 kcal/mol lower in free energy than **D**).

In conclusion, we have successfully developed a rapid and divergent approach to enantioenriched piperidine derivatives via Cu(I)/(S,R_p)-PPF-NHMe-catalyzed *exo*-selective 1,3-dipolar [3 + 6] cycloaddition of azomethine ylides with 2-acylcycloheptatrienes. The great importance of the bioactive piperidines bearing multiple stereogenic centers makes the methodology particularly interesting in organic synthesis. Theoretical calculations indicated a stepwise mechanism for this *exo*-selective 1,3-dipolar [3 + 6] cycloaddition, which accounts for all the larger substituent groups occupying the axial positions in the six-membered chairlike conformation of the piperidine ring.

■ 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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