Asymmetric Catalysis

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Fulvenes as Effective Dipolarophiles in Copper(I)-Catalyzed [6+3] Cycloaddition of Azomethine Ylides: Asymmetric Construction of Piperidine Derivatives**

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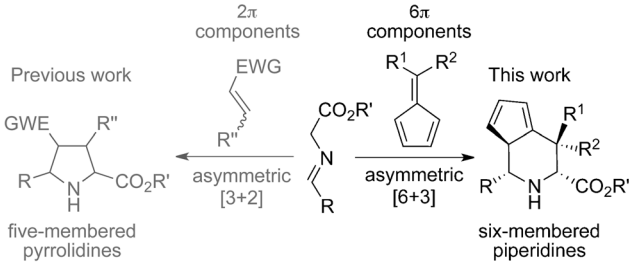
Catalytic asymmetric [3+2] cycloaddition of azomethine ylides is one of the best methods for constructing enantioenriched heterocyclic pyrrolidines,[1] and extensive studies have been conducted on the use of various electron-deficient alkenes as the 2π synthons over the past decade.[2] However, although there are elegant and creative azomethine-ylide-involved cycloaddition reactions toward the construction of five-membered pyrrolidine architectures,[1,2] the direct catalytic asymmetric approach to enantioenriched six-membered heterocyclic piperidines, which are prevalent scaffolds that serve as the core structures of natural alkaloids and bioactive molecules,[3] has met with little success,[4] and we believe this represents a considerable challenge.

In 2003, Hong et al.[5] reported a [6+3] cycloaddition of azomethine ylides with fulvenes[6], in which fulvenes served as 6π components, thus leading to the synthesis of racemic six-membered piperidine derivatives. However, there is a lack of catalytic asymmetric [6+3] cycloadditions which tolerate variations in both the azomethine ylides and fulvenes. Stimulated by the biological significance of piperidine derivatives and the challenging synthetic difficulties associated with enantio- and diastereoselectivity control, we questioned whether fulvenes containing no electron-withdrawing groups could be employed as efficient 6π dipolarophiles and provide a straightforward and asymmetric approach to enantioenriched piperidines. Very recently, one example on the asymmetric cycloaddition of unsymmetrical fulvenes and azomethine ylides has been published concurrently with the preparation of the present manuscript.[7] Herein, we report the Cu^I/TF-BiphamPhos-catalyzed asymmetric synthesis of highly substituted piperidines by the [6+3] cycloaddition of azomethine ylides with various fulvenes (Scheme 1, right), and subsequent transformations which allow facile access to enantioenriched fused polycyclic piperidine derivatives without loss in diastereoselectivity and enantioselectivity.



Scheme 1. Catalytic asymmetric [3+2] cycloaddition reactions using electron-deficient alkenes as 2π components (previous work) and [6+3] cycloaddition using fulvenes as 6π components (this work). EWG = electron-withdrawing group.

For our initial studies, the readily available fulvene **2a**[8] was chosen as the model 6π component. Initially we began our investigations by examining the ability of Cu^I/TF-BiphamPhos and Ag^I/TF-BiphamPhos[9] complexes to probe the possibility of an asymmetric variant of this challenging [6+3] cycloaddition reaction employing the *N*-(4-chlorobenzylidene)glycine methyl ester **3a** as the dipole precursor (Table 1). To our delight, the reaction was completed in less than 24 hours with AgOAc/(*S*)-TF-BiphamPhos (**1a**) as the catalyst and Et_3N as the base in dichloromethane at room temperature, thus yielding the expected six-membered heterocyclic piperidine **4a** with excellent diastereoselectivity and 36% *ee* (Table 1, entry 1). Neither [3+2] nor regioisomeric [6+3] cycloadducts were observed although the by-product[10] formed by self-cycloaddition of **3a** was isolated in 10% yield. The cycloadduct **4a** is formed exclusively and no [1,5] H-shift[11] occurred, probably because most of the substituents on the six-memebered piperidine ring are placed at thermodynamically favored equatorial positions of the chairlike conformation (see X-ray analysis of **4o** below). **4a** is moderately stable, and can be kept at −10 °C for 2–3 weeks without dimerization or oligomerization.[12] Studies showed that using a copper(I) salt as the metal precursor gave better results than a silver(I) salt in terms of the yield and enantioselectivity (entry 2). Encouraged by these results, $Cu(CH_3CN)_4BF_4$ was selected as the model metal source for additional ligand, solvent, and base screening. The ligand **1b**, bearing the bulkier and electron-donating xylyl group on the phosphorus atom, had detrimental effects on the enantioselectivity (entry 3), while **1c**, bearing 3,5-a bis(trifluoromethyl)phenyl group was totally inactive (entry 4). Further ligand tuning revealed that **1d** with two bromine atoms at the

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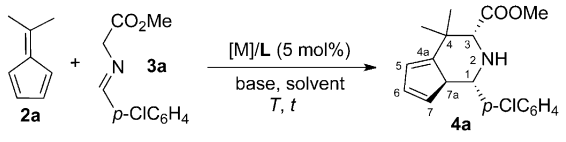
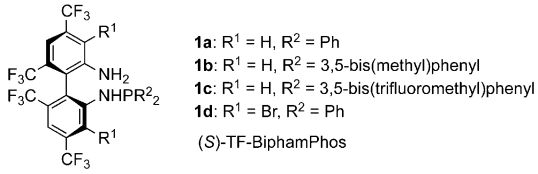
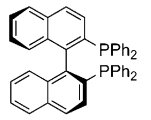
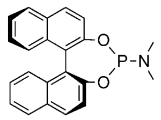
Table 1: Optimization of catalytic asymmetric [6+3] cycloaddition of imino ester **3a** with fulvene **2a**.[a]



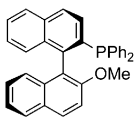




(*S*)-binap (**1e**)



(*S*)-Monophos (**1f**)



(*R*)-Mop (**1g**)

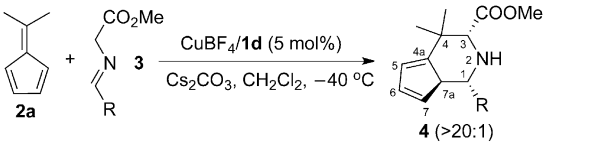
Entry	L	[M]	Base	Solvent	*T* [°C]	*t* [h]	Yield [%][b,c]	*ee* [%][d]
1	**1a**	AgOAc	Et_3N	CH_2Cl_2	RT	24	70	36
2	**1a**	$CuBF_4$	Et_3N	CH_2Cl_2	RT	24	74	64
3	**1b**	$CuBF_4$	Et_3N	CH_2Cl_2	RT	24	73	35
4	**1c**	$CuBF_4$	Et_3N	CH_2Cl_2	RT	24	trace	–
5	**1d**	$CuBF_4$	Et_3N	CH_2Cl_2	RT	24	78	83
6	**1e**	$CuBF_4$	Et_3N	CH_2Cl_2	RT	24	trace	–
7	**1f**	$CuBF_4$	Et_3N	CH_2Cl_2	RT	24	trace	–
8	**1g**	$CuBF_4$	Et_3N	CH_2Cl_2	RT	24	62	25
9	**1d**	$CuBF_4$	Et_3N	THF	RT	24	75	67
10	**1d**	$CuBF_4$	Et_3N	PhMe	RT	24	63	80
11	**1d**	$CuBF_4$	Et_3N	Et_2O	RT	24	58	84
12	**1d**	$CuBF_4$	Et_3N	MeCN	RT	24	49	73
13	**1d**	$CuBF_4$	Cs_2CO_3	CH_2Cl_2	RT	6	78	82
14	**1d**	$CuBF_4$	Cs_2CO_3	CH_2Cl_2	−20	12	72	89
15	**1d**	$CuBF_4$	Cs_2CO_3	CH_2Cl_2	−40	24	77	94

[a] All reactions were carried out with 0.5 mmol of **2a** and 0.25 mmol of **3a** in 1.5 mL of CH_2Cl_2. $CuBF_4 = Cu(CH_3CN)_4BF_4$. [b] Yield of isolated product. [c] The coupling constant $J_{ax\text{-}ax}$ for H^1-H^{7a} in **4a** is 10.4 Hz. [d] The *ee* and > 20:1 d.r. values were determined by HPLC analysis. The minor diastereomer was not detected in the ^1H NMR spectrum of the crude reaction mixture. THF = tetrahydrofuran.

3,3′-position of TF-BIPHAM backbone was the most effective ligand (entry 5). Other commercially available ligands are either ineffective or provide relatively poor enantiomeric excess (entries 6–8). Dichloromethane was shown to be the best solvent in terms of the yield and enantioselectivity (entries 5 and 9–12). Examination of various organic and inorganic bases disclosed that Cs_2CO_3 was the optimal base and could accelerate the reaction without loss of diastereoselectivity and enantioselectivity (entry 13). The cycloaddition performed well at temperatures as low as −40 °C with Cs_2CO_3 as the base, thus leading to full conversion with excellent diastereoselectivity and 94 % *ee* within 24 hours (entry 15).

With the optimal reaction conditions established, the scope of piperidine formation was demonstrated with various imino esters. In general, the reaction proceeded well to afford the desired products exclusively in good yields and excellent diastereo- and enantioselectivity. As shown in Table 2, aromatic imino esters bearing different electronic properties

Table 2: Substrate scope for catalytic asymmetric [6+3] cycloaddition of various imino ester **3** with fulvene **2a**.[a]



Entry	R	**4**	Yield [%][b,c]	*ee* [%][d]
1	*p*-ClC_6H_4 (**3a**)	**4a**	77	94
2	Ph (**3b**)	**4b**	80	90
3	*m*-ClC_6H_4 (**3c**)	**4c**	87	93
4	*p*-BrC_6H_4 (**3d**)	**4d**	69	94
5	*p*-$CF_3C_6H_4$ (**3e**)	**4e**	87	99
6	*o*-FC_6H_4 (**3f**)	**4f**	72	90
7	*p*-MeC_6H_4 (**3g**)	**4g**	75	99
8	*p*-$MeOC_6H_4$ (**3h**)	**4h**	81	96
9	2-naphthyl (**3i**)	**4i**	78	92
10	2-thienyl (**3j**)	**4j**	72	86
11	Cy (**3k**)	**4k**	73	95
12	*i*Bu (**3l**)	**4l**	68	91

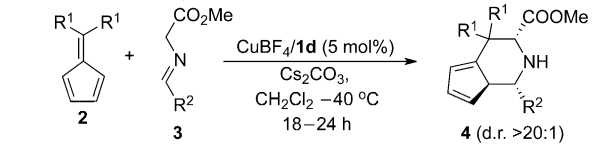
[a] All reactions were carried out with 0.5 mmol of **2a** and 0.25 mmol of **3** in 1.5 mL of CH_2Cl_2. [b] Yield of isolated product. [c] All the coupling constants J_{ax-ax} for H^1-H^{7a} in **4** are greater than 9.0 Hz. [d] Determined by HPLC analysis.

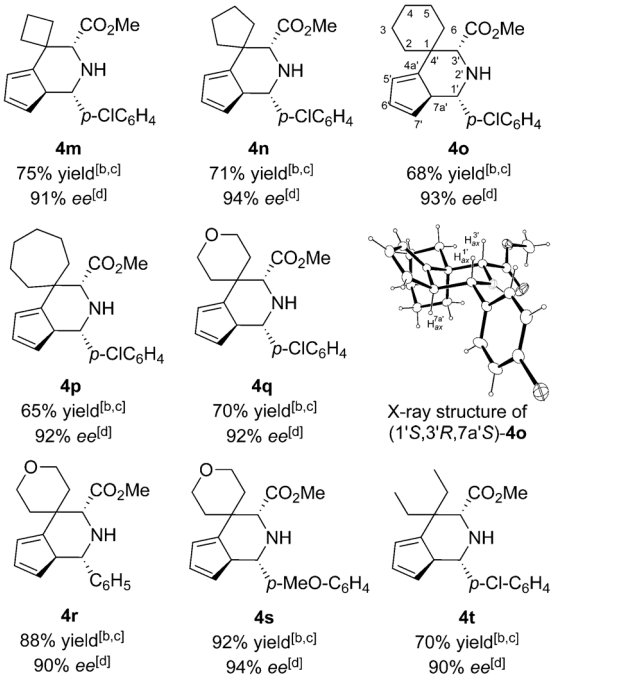
on the aryl rings all work well and provide the corresponding products in high yields (69–87 %), excellent diastereoselectivities (d.r. > 20:1), and enantioselectivities (90–99 % *ee*; Table 2, entries 1–9). The substitution pattern of the arene had little effect on the selectivity of the cycloaddition reaction, and the *ortho*-substituted imino ester **3f** underwent this transformation, thus leading exclusively to the desired piperidine with 90 % *ee* (entry 6). Additionally, the heteroaryl-substituted imino ester **3j** derived from 2-thenaldehyde also works in this transformation leading to 72 % yield and 86 % *ee* (entry 10). Noticeably, the less reactive imino esters **3k** and **3l** from aliphatic aldehydes also proved to be viable substrates in this process, thereby producing the corresponding cycloadducts in good yields with 95 and 91 % *ee*, respectively (entries 11 and 12).

Next, we evaluated symmetrical fulvenes with different ring sizes. As shown in Table 3, fulvenes bearing four-to seven-membered rings did not influence the reaction outcomes, thus delivering their respective spiropiperidines in good yields with 91–94 % *ee* (**4m**–**p**). A cyclic fulvene derived from tetrahydro-4*H*-pyran-4-one was also a viable 6π dipolarophile, thereby furnishing the corresponding spirocycles (**4q**–**s**) with excellent enantioselectivities. Additionally, good yield and high diastereo- and enantioselectivity (**4t**) were achieved for the symmetric acyclic fulvene **2g** derived from pentan-3-one. The relative and absolute configuration of the spiropiperidine **4o**, using Cu^I/(*S*)-**1d**, was unequivocally determined as (1′*S*,3′*R*,7a′*S*) by X-ray crystallographic analysis.[13]

Having succeeded in the stereoselective [6+3] cycloaddition reaction of imino esters with symmetrical fulvenes, we investigated unsymmetrical fulvenes derived from aldehydes which can generate an additional tertiary stereogenic center on the piperidine ring along with the other three tertiary stereogenic centers. The scope of the reaction of the unsym-

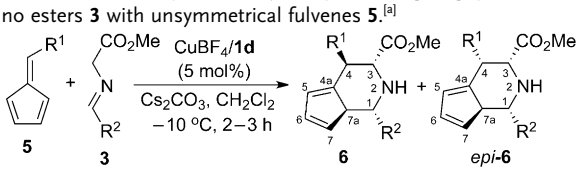
Table 3: Substrate scope for catalytic asymmetric [6+3] cycloaddition of imino ester **3** with symmetrical fulvenes **2**.[a]

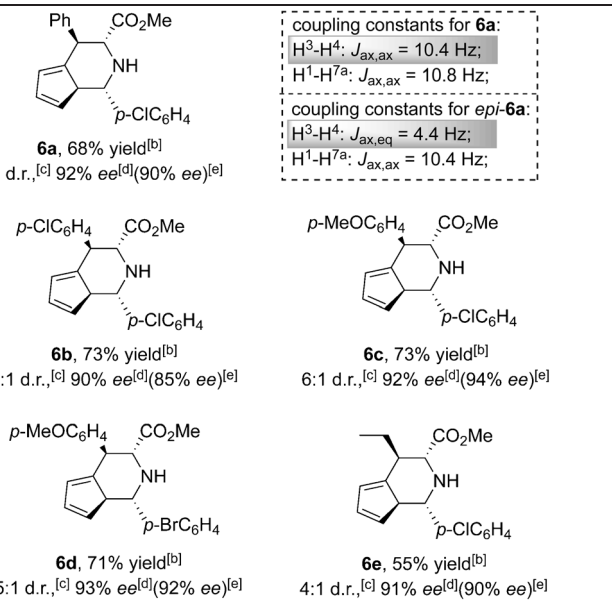




[a] All reaction were carried out with 0.5 mmol of **2** and 0.25 mmol of **3** in 1.5 mL of CH_2Cl_2. [b] Yield of isolated product. [c] All the coupling constants $J_{ax\text{-}ax}$ for $H^{1'}$-$H^{7a'}$ in **4** are greater than 9.0 Hz. [d] Determined by HPLC analysis.

Table 4: Substrate scope for catalytic asymmetric [6+3] cycloaddition of imino esters **3** with unsymmetrical fulvenes **5**.[a]



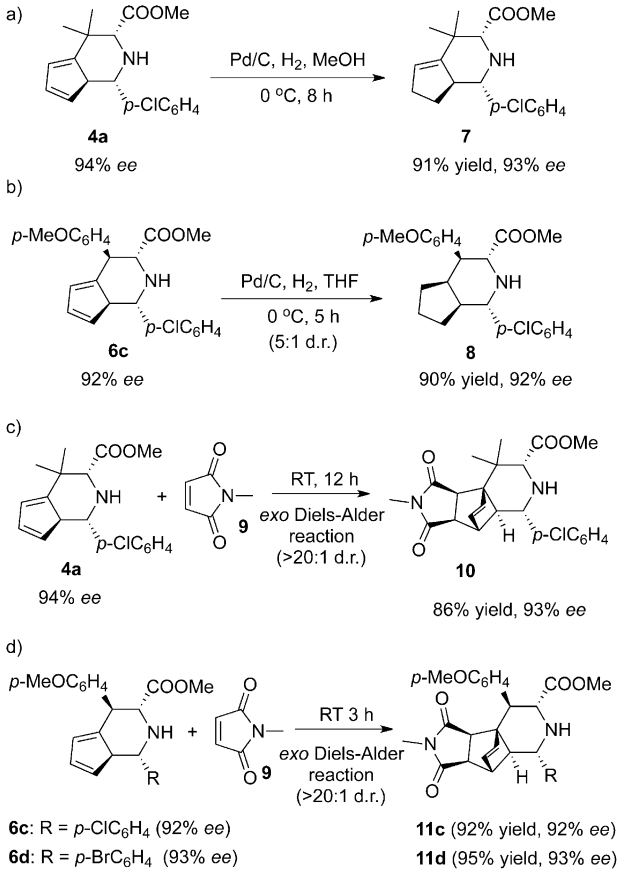


[a] All reactions were carried out with 0.75 mmol of **5** and 0.5 mmol of **3**. [b] Yield of pure isolated **6**, and the yield of pure isolated *epi*-**6** has been included in the Supporting Information. [c] The d.r. value was determined by ^{1}H NMR analysis of the crude reaction mixture and additionally confirmed by the yields of isolated **6** and *epi*-**6**. All the coupling constants $J_{ax\text{-}ax}$ for H^1-H^{7a} in **6** and *epi*-**6** are greater than 9.0 Hz; the coupling constants $J_{ax\text{-}ax}$ for H^3-H^4 in **6** are greater than 9.0 Hz; the coupling constants $J_{ax\text{-}eq}$ for H^3-H^4 in *epi*-**6** are less than 5.0 Hz. [d] The *ee* value was determined by HPLC analysis. [e] The number in bracket is the *ee* value of the minor isomer *epi*-**6**.

metrical fulvenes **5** with imino esters is summarized in Table 4. Indeed, all tested unsymmetrical fulvenes have proven to be excellent substrates in this cycloaddition reaction, thus giving rise to the desired cycloadducts as two diastereomers in good yields with good diastereoselectivities and excellent enantioselectivities (**6a–e**). In general, much higher reactivity was exhibited by unsymmetrical fulvenes compared with symmetrical ones probably because of the reduced steric hindrance. Noticeably, the 3,4-*trans*-substituted piperidine **6** was formed as the major isomer according to the H_{ax}^3-H_{ax}^4 coupling constant (> 10.0 Hz) in the corresponding ^{1}H NMR spectra, and was additionally confirmed by X-ray analysis of the derived **11d**[13] (see below). The minor isomer *epi*-**6** was determined to have a 3,4-*cis*-configuration based on a less than 5.0 Hz coupling constant between H^3 and H^4, and assigned as a $J_{ax\text{-}eq}$ value for H_{ax}^3-H_{eq}^4. Additionally, the consistently excellent diastereo- and enantioselectivity (**6e**) obtained for the cycloaddition of the fulvene **5e** derived from aliphatic aldehyde is noteworthy as such a reaction partner was shown to be relatively challenging substrate in previous studies.[5,7]

The optically active piperidines can be readily converted into synthetically useful compounds. The direct hydrogenation of **4a** in the presence of Pd/C specifically reduced the less bulky disubstituted double bond, thus affording **7** while the bulky trisubstituted double bond adjacent to the quaternary carbon center remains untouched (Scheme 2a). Both double bonds in **6c** could be reduced efficiently because of the absence of an adjacent bulky quaternary center, thus delivering **8** with acceptable diastereoselectivity (Scheme 2b). Conjugated double bonds in the cycloadducts render those piperidine derivatives suitable dienes for a Diels–Alder reaction. Compounds **4a**, **6c**, and **6d** can be readily converted into the corresponding fused piperidines **10**, **11c**, and **11d**, bearing seven to eight stereogenic centers, by a facile catalyst-free Diels–Alder reaction in highly diastereoselective manner (Scheme 2c,d). An X-ray analysis of a single crystal of **11d**[13] showed an *R* configuration for the stereogenic center at the 4-position of the piperidine ring, and thus also corresponding to the moiety in **6d** (Figure 1).

A plausible transition-state model is proposed as a well-defined tetrahedral catalyst/azomethine ylide complex, in which the in situ formed azomethine ylide is coordinated to the copper center of the active species bearing (*S*)-TF-BiphamPhos because of the unfavorable steric repulsion between the phenyl group in the ylide and the phenyl ring on



Scheme 2. Synthetic transformations.

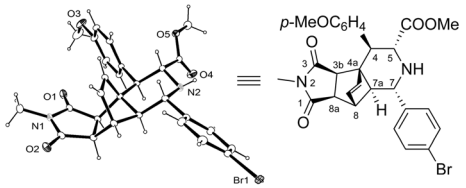


Figure 1. X-ray structure of (3a*R*,3b*S*,4*R*,5*R*,7*S*,7a*S*,8*R*,8a*R*)-**11d**.

the phosphorus atom of the chiral ligand.[14] The highly steric congestion imposed by the latter effectively blocks the unsymmetrical fulvene approach from the back side of the coordinated azomethine ylide, and results in excellent enantiofacial differentiation. As depicted, the coordinated azomethine ylide was assumed to attack the Re face of the fulvene so that the two substituents of ylide moiety and the phenyl group of the unsymmetrical fulvene are placed at the equatorial positions in a chairlike configuration (Figure 2). The proposed transition-state model is fully consistent with the observed stereochemical outcome.

In summary, we have described a novel asymmetric [6+3] cycloaddition of imino esters with various readily available fulvenes catalyzed by Cu^{I}/TF-Biphamphos under mild reaction conditions with good yields, excellent diastereoselectiviyies, high enantioselectivities, and broad substrate scope. Notably, this methodology and subsequent transformations presented herein could open up new prospects for straightforwardly constructing structurally and stereochemically rich piperidines, a valuable structural motif for drug discovery. Efforts are currently underway to elucidate the mechanistic details, and the scope and limitations of this reaction, the results of which will be reported in due course.

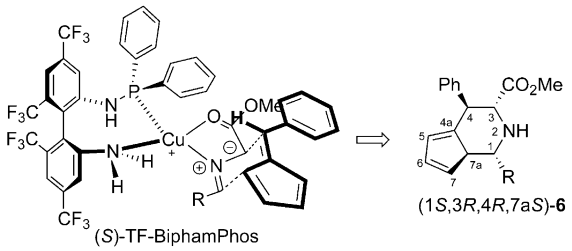


Figure 2. Proposed transition state leading to (1*S*,3*R*,4*R*,7a*S*)-**6**.

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