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Asymmetric Construction of 3-Azabicyclo[3.1.0]hexane Skeleton with Five Contiguous Stereogenic Centers by Cu-Catalyzed 1,3-Dipolar Cycloaddition of Trisubstituted Cyclopropenes

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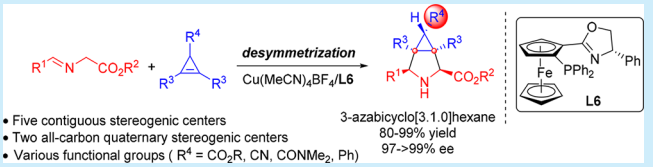
Supporting Information

ABSTRACT: A highly diastereo- and enantioselective desymmetrization of prochiral cyclopropenes via a Cu-$(CH_3CN)_4BF_4$/Ph-Phosferrox complex catalyzed 1,3-dipolar cycloaddition of azomethine ylides was described. A variety of complex 3-azabicyclo[3.1.0]hexane derivatives bearing five contiguous stereogenic centers and two all-carbon quaternary stereogenic centers were directly synthesized as a single isomer in excellent yields (up to 99%) and enantioselectivities (97 → 99% ee). Notably, various functional groups (CO_2R, CN, $CONMe_2$, and Ph) of cyclopropenes were found to be well-tolerated in this transformation. The cycloadduct was conveniently converted to a biologically important GABA derivative via $LiAlH_4$ reduction and subsequent hydrolysis.



Chiral 3-azabicyclo[3.1.0]hexane motifs, especially those bearing bridgehead quaternary carbons, have found utility in a variety of natural products and pharmaceuticals with a broad spectrum of biological activities (Figure 1). For instance, the duocarmycin family of natural products, exemplified by (+)-duocarmycin A, represent one class of the most promising antitumor agents.[1] The selective dopamine D_3 receptor (DRD3) antagonist GSK598809 has been proposed as a medication to treat cocaine use disorder.[2] As a member of the clavine-type ergot alkaloids, (−)-cyclocavine has exhibited potential pesticidal and antiparasitic activities.[3] Procymidone is a commercially available fungicide to control plant diseases.[4] Moreover, the 3-azabicyclo[3.1.0]hexane core is also present in analgesic bicifadine[5a] and drug candidates amitifadine[5b] and centanafadine.[5c] Furthermore, this rigid framework can act as analogues of piperidines, often showing enhanced binding affinities with their targets in medicinal chemistry.[6] However, compared to the well-developed synthetic method of racemic 3-azabicyclo[3.1.0]hexane derivatives,[7,8] the enantioselective synthesis of this scaffold bearing multiple stereogenic centers is very limited. Recently, the group of Cramer[9] employed a Pd-catalyzed cyclopropane C−H functionalization/addition sequence in one-pot processes to access a substituted 3-azabicyclo[3.1.0]hexane with three stereogenic centers (Scheme 1a). Despite this elegant progress, the development of a more efficient and practical method for the convenient synthesis of such a densely substituted bicyclic scaffold particularly containing multiple contiguous stereogenic centers remains a distinct challenge.

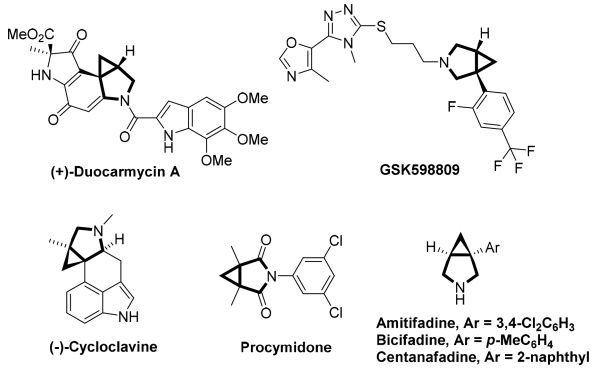


Figure 1. Selected examples of bioactive molecules with 3-azabicyclo[3.1.0]hexane scaffold bearing bridgehead quaternary carbons.

The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with substituted alkenes has become a powerful method for preparing functionalized pyrrolidines with multiple stereogenic centers.[10,11] However, a fully substituted alkene serving as the dipolarophile for the construction of functionalized-pyrrolidines bearing two all-carbon quaternary stereogenic centers at the bridgehead positions still remains challenging. By strain release, the [3 + 2] cycloaddition of azomethine ylides with a trisubstituted cyclopropenes would offer an effective method to form 3-azabicyclo[3.1.0]hexane with two bridgehead all-carbon quaternary centers.[8] Its

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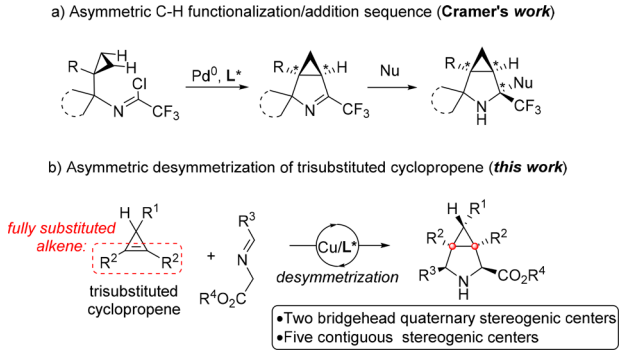
Scheme 1. Enantioselective Synthesis of 3-Azabicyclo[3.1.0]hexane Derivatives

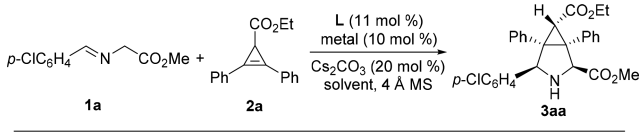


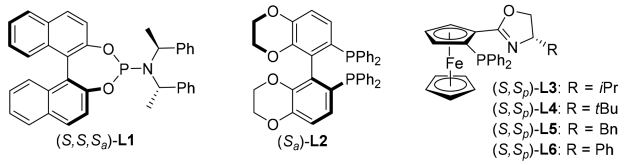
enantioselective version would provide access to chiral pyrrolidines with five contiguous stereogenic centers. In connection with our continuing efforts in structural diversity-oriented synthesis of chiral pyrrolidines through asymmetric cycloaddition of azomethine ylides,[12] we herein describe the first example of a highly efficient and stereoselective synthesis of chiral bicyclic 3-azabicyclo[3.1.0]hexanes via a copper(I)-catalyzed asymmetric [3 + 2] cycloaddition of azomethine ylides with trisubstituted cyclopropenes (Scheme 1b).

Initially, imino ester **1a** and prochiral cyclopropene **2a** were chosen as model substrates for the enantioselective desymmetrization reaction. We carried out our investigation using $Cu(MeCN)_4BF_4$ (10 mol %)/Feringa ligand (S,S,S_a)-**L1** (11 mol %) as the catalyst system, in the presence of 20 mol % of Cs_2CO_3 as the base in CH_2Cl_2 at room temperature (Table 1, entry 1). However, the expected cycloaddition did not occur under the reaction conditions (Table 1, entry 1). Fortunately, bisphosphine ligand (S_a)-**L2** led to a dramatic improvement in yield, affording the desired cycloadduct **3aa** with moderate enantioselectivity (−40% ee) (Table 1, entry 2). Encouraged by this result, the (S,S_p)-Phosferrox ligands **L3**−**L6** were then examined (Table 1, entries 3−6). Interestingly, all the tested ligands promoted this process smoothly within 0.5 h and **L6** exhibited the optimal reaction outcome (95% yield, 97% ee) (Table 1, entry 6). A survey of the solvent effect revealed that THF was the best solvent of choice (Table 1, entries 7−10). Subsequently, no improved results were obtained by varying the bases for this transformation (see Supporting Information (SI) for details). In addition, $Cu(MeCN)_4BF_4$ was the best metal source compared to others tested such as AgOAc and $Cu(OAc)_2$ (Table 1, entries 11 and 12). Furthermore, reducing the temperature to 0 °C resulted in a slight improvement in enantioselectivity (99% ee) (Table 1, entry 13). When a lower catalyst loading (5 mol %) was employed at 0 °C, there was no significant influence on the reaction outcome, and the desired adduct **3aa** was obtained in 97% yield with an excellent ee value (99% ee, Table 1, entry 14).

We then examined the scope of the substrate under the optimal conditions (5 mol % $Cu(MeCN)_4BF_4$, 5.5 mol % **L6**, 20 mol % Cs_2CO_3 in THF at 0 °C) as summarized in Table 2.

Table 1. Optimization of the Reaction Conditions[a]

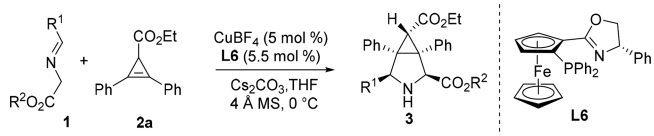




entry	ligand	metal	solvent	yield[b] (%)	ee[c] (%)
1	**L1**	$CuBF_4$	CH_2Cl_2	trace	–
2	**L2**	$CuBF_4$	CH_2Cl_2	97	−40
3	**L3**	$CuBF_4$	CH_2Cl_2	97	96
4	**L4**	$CuBF_4$	CH_2Cl_2	91	96
5	**L5**	$CuBF_4$	CH_2Cl_2	96	92
6	**L6**	$CuBF_4$	CH_2Cl_2	95	97
7	**L6**	$CuBF_4$	THF	98	98
8	**L6**	$CuBF_4$	Et_2O	80	98
9	**L6**	$CuBF_4$	toluene	94	97
10	**L6**	$CuBF_4$	MeCN	93	97
11	**L6**	AgOAc	THF	89	86
12	**L6**	$Cu(OAc)_2$	THF	93	97
13[d]	**L6**	$CuBF_4$	THF	98	99
14[d,e]	**L6**	$CuBF_4$	THF	97	99

[a]All reactions were performed with **1a** (0.12 mmol), **2a** (0.10 mmol) in 1.0 mL of solvent, under an N_2 atmosphere at rt, $CuBF_4$ = $Cu(MeCN)_4BF_4$. [b]Isolated yield. [c]The ee was determined by chiral HPLC analysis. [d]Temp = 0 °C. [e]5 mol % cat., 0.15 mmol scale.

Table 2. Substrate Scope of Azomethine Ylides 1[a]



entry	**1**, R^1/R^2	**3**	yield[b] (%)	ee[c] (%)
1	**1a**, *p*-ClC_6H_4/Me	**3aa**	97	99
2	**1b**, *p*-ClC_6H_4/Et	**3ba**	99	>99
3	**1c**, *p*-ClC_6H_4/*t*-Bu	**3ca**	97	99
4	**1d**, *o*-ClC_6H_4/Me	**3da**	95	98
5	**1e**, *m*-ClC_6H_4/Me	**3ea**	95	99
6	**1f**, *p*-BrC_6H_4/Me	**3fa**	99	99
7	**1g**, *p*-$CO_2MeC_6H_4$/Me	**3ga**	97	>99
8	**1h**, *o*-MeC_6H_4/Me	**3ha**	96	98
9	**1i**, *m*-MeC_6H_4/Me	**3ia**	97	99
10	**1j**, *p*-MeC_6H_4/Me	**3ja**	99	99
11	**1k**, *p*-$MeOC_6H_4$/Me	**3ka**	97	>99
12	**1l**, Ph/Me	**3la**	98	99
13	**1m**, 2-naphthyl/Me	**3ma**	99	>99
14	**1n**, 2-thienyl/Me	**3na**	98	98
15[d]	**1o**, Cy/Me	**3oa**	99	97
16[d]	**1p**, *t*-Bu/Me	**3pa**	95	97

[a]All reactions were performed with **1** (0.18 mmol), **2a** (0.15 mmol) in 1.5 mL of THF, under a N_2 atmosphere at 0 °C, $CuBF_4$ = $Cu(MeCN)_4BF_4$. [b]Isolated yield. [c]The ee was determined by chiral HPLC analysis. [d]10 mol % catalyst and 10 mol % *t*-BuOK was used as base.

Initially, substrate generality was explored by changing the ester groups of imino ester, providing the target cycloadducts in high yields (97−99%), with extremely high enantioselectivities (99 → 99% ee) (Table 2, entries 1−3). Then, a wide range of imino esters (**1d**−**1m**) containing electron-deficient (Table 2, entries 4−7), electron-rich (Table 2, entries 8−11),

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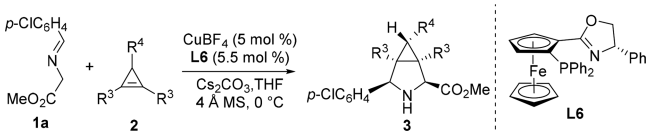
and electron-neutral (Table 2, entries 12−13) substituents on any position of the phenyl ring were employed, and the transformation worked efficiently, affording the corresponding cycloadducts in good yields (95−99%), with excellent enantioselectivities (98 → 99% ee). Noteworthily, the outstanding outcome was still obtained for heteroaromatic 2-thienyl derived imino ester **1n** (Table 2, entry 14). Furthermore, when challenging aliphatic-substituted imino esters **1o**, **1p** were tested, the annulation process could proceed smoothly by employing 10 mol % *t*-BuOK as the base instead of Cs_2CO_3; the desired adducts were obtained in good yields (99% and 95% respectively) with excellent enantioselectivities (both 97% ee) (Table 2, entries 15−16). The absolute configuration of bicyclic cycloadduct **3fa** was determined as (1*S*,2*S*,4*S*,5*R*,6*S*) by X-ray analysis of the single crystal (see the SI).

Next, the scope of enantioselective desymmetrization was further evaluated by a range of prochiral cyclopropenes **2b**−**2i**. Various functional groups on cyclopropenes were examined in this methodology; isopropyl ester and *tert*-butyl ester substituted cyclopropenes (**2b**, **2c**) performed well under the reaction conditions (Table 3, entries 1−2). Notably, the

Table 3. Substrate Scope of Cyclopropenes 2[a]



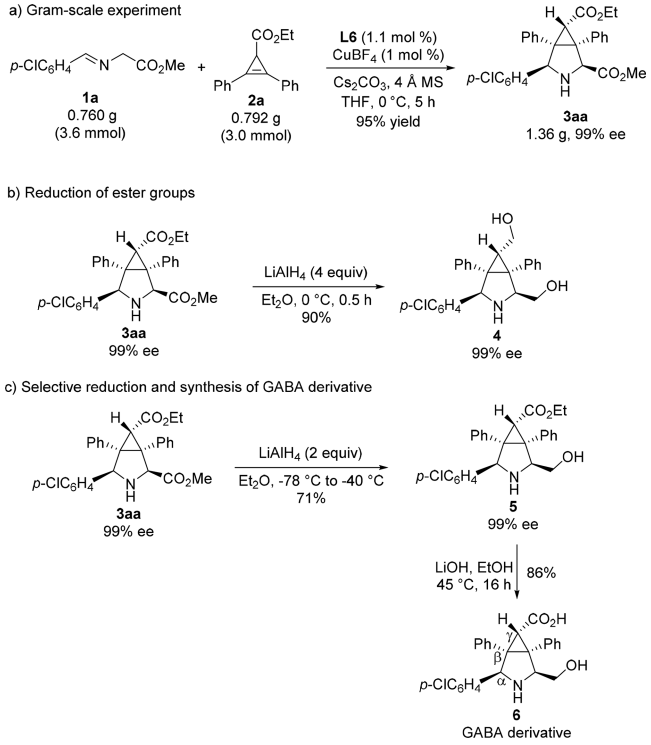
entry	2, R^3/R^4	3	yield[b] (%)	ee[c] (%)
1	**2b**, Ph/CO_2*i*Pr	**3ab**	99	>99
2	**2c**, Ph/CO_2*t*Bu	**3ac**	95	98
3	**2d**, Ph/CN	**3ad**	99	98
4[d]	**2e**, Ph/$CONMe_2$	**3ae**	95	99
5	**2f**, Ph/Ph	**3af**	85	98
6	**2g**, *p*-BrC_6H_4/CO_2Et	**3ag**	95	99
7	**2h**, *p*-MeC_6H_4/CO_2Et	**3ah**	98	99
8[d,e]	**2i**, Me/CO_2Et	**3ai**	80	98

[a]All reactions were performed with **1a** (0.18 mmol), **2** (0.15 mmol) in 1.5 mL of THF, under a N_2 atmosphere at 0 °C, $CuBF_4$ = $Cu(MeCN)_4BF_4$. [b]Isolated yield. [c]The ee was determined by chiral HPLC analysis. [d]10 mol % catalyst and 2 equiv of Cs_2CO_3 was used as base. [e]Temp = 25 °C.

success of this process could be extended to other substituted cyclopropenes, e.g. cyclopropenyl nitrile (**2d**) and cyclopropenyl amide (**2e**), especially unactivated triphenylcyclopropene (**2f**) furnishing the desymmetrized cycloadducts in good yields (85−99%) with excellent ee values (98−99%) (Table 3, entries 3−5). Meanwhile, both electron-donating and -withdrawing substituents on the phenyl ring are well tolerated in the optimal conditions, and products were respectively obtained in 95% and 98% yields both with 99% ee (Table 3, entries 6−7). Noteworthily, aliphatic-substituted cyclopropene **2i** was also tested. Because of the lower reactivity, the reaction was completed by raising the temperature to 25 °C and increasing the amount of Cs_2CO_3 from 20 mol % to 1 equiv giving the target product **3ai** with a slight decrease in yield (80%) but with admirable enantioselectivity (98% ee).

As a further demonstration of the utility of this process, the asymmetric cycloaddition between imino ester **1a** and prochiral cyclopropene **2a** was carried out on a gram scale with a lower catalyst loading (1 mol %), and **3aa** was obtained in 95% yield with 99% ee (Scheme 2a). Then, treatment of **3aa**

Scheme 2. Gram-Scale Synthesis and Synthetic Transformations



with $LiAlH_4$ (4 equiv) led to the reduction of both ester groups without any loss of stereochemical integrity (Scheme 2b). Additionally, selective reduction of the ester group was realized by reducing the amount of $LiAlH_4$ (2 equiv) and lowering the temperature (−78 °C), which was then converted into optically pure γ-amino butyric acid (GABA) derivative **6**[13] by simple hydrolysis (Scheme 2c).

In summary, we have developed a highly efficient desymmetrization process for the asymmetric construction of 3-azabicyclo[3.1.0]hexane derivatives possessing five contiguous stereogenic centers and two bridgehead quaternary stereogenic centers, via a catalytic enantioselective 1,3-dipolar cycloaddition of azomethine ylides with prochiral trisubstituted cyclopropenes. With the Cu(I)/Ph-Phosferrox complex as the catalyst, a wide range of densely functionalized 3-azabicyclo-[3.1.0]hexane derivatives were synthesized in high yields (up to 99%) with excellent levels of stereoselectivity (97 → 99% ee) under mild reaction conditions. Various functional groups (CO_2R, CN, $CONMe_2$) of cyclopropenes, especially an unactivated triphenylcyclopropene, were found to be well-tolerated. This synthetic method offers a straightforward approach to a structurally important chiral 3-azabicyclo[3.1.0]-hexane skeleton for biological research and drug discovery. Further transformation of the bicyclic cycloadducts and asymmetric syntheses of bioactive molecules is underway.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental details, characterization of new compounds, crystallographic data, NMR and HPLC spectra (PDF)

Accession Codes

CCDC 1844508 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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