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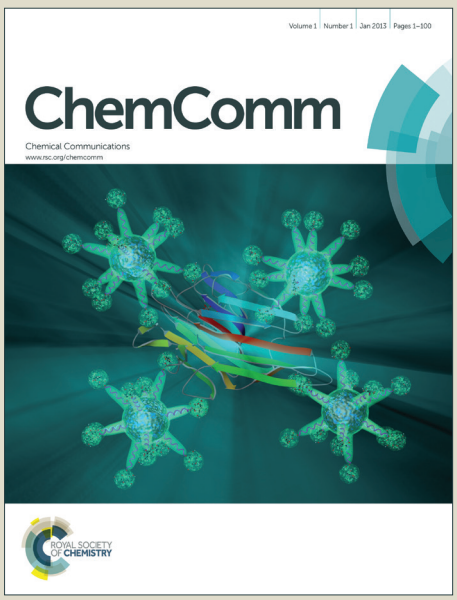

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Copper-catalyzed asymmetric construction of dispiropyrrolidine skeleton *via* 1,3-dipolar cycloaddition of azomethine ylides with α-alkylidene succinimides

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A highly efficient asymmetric 1,3-dipolar cycloaddition of azomethine ylides to α-alkylidene succinimides catalyzed by a novel chiral *N,O*-ligand/Cu(OAc)$_2$ system is reported, affording dispiropyrrolidine derivatives with spiro quaternary stereogenic centers in good to excellent yields (up to 90%), excellent levels of diastereoselectivities (>20:1 dr) and enantioselectivities (up to 97% ee).

As a privileged scaffold for pharmaceutical activity in drug discovery, the pyrrolidinyl-spirooxindole skeleton[1] with multiple contiguous stereogenic centers is the core structure of numerous natural products and pharmaceuticals exhibiting a broad spectrum of biological activities[2] (Fig. 1). For instance, Spirotryprostatin A,[3] isolated from the fermentation broth of *Aspergillus fumigatus*, arrests the cell cycle at the G2/M phase and is an inhibitor of tubulin polymerization. In the past decade, synthetic advances stemming from the vibrant field of natural products chemistry and their corresponding analogues has encouraged the development of more potent and selective bioactive new molecular entities (NMEs).[4] Notably, a synthetic pyrrolidinyl-spirooxindole, MI-219,[5] was found to inhibit the cell cycle with excellent potency and represents a novel non-peptidic, orally active, inhibitor of the p53-MDM2 protein-protein interaction.[5b] Nevertheless, it is noteworthy that the dispiropyrrolidine skeleton, which is a structurally more simpler motif, has the potential to deliver biological activities and better drug-like properties due to lower molecular weight and offers more opportunities for structural diversity.

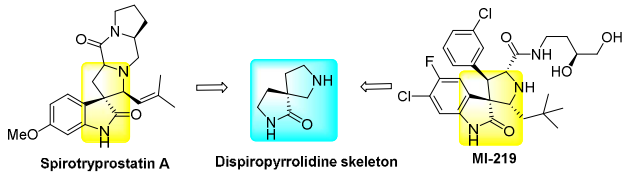
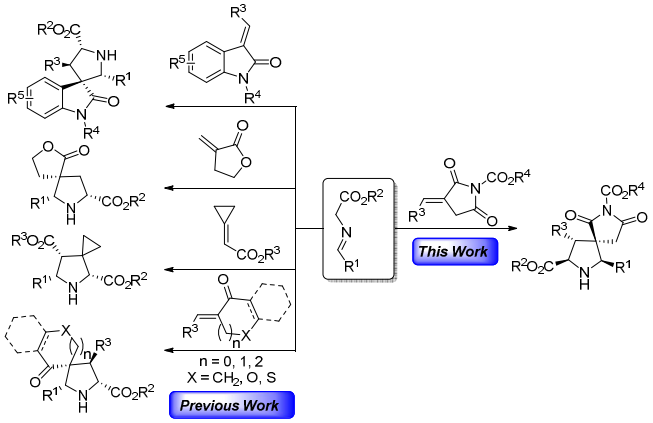


Fig. 1. A selection of natural products and biologically active molecules with dispiropyrrolidine skeletons.

Many efforts have been made developing synthetic methods for the construction of dispiropyrrolidine scaffolds, which have mainly focused on intramolecular cyclization of aminoesters,[6] intramolecular hydroamination of olefins[7] and intermolecular 1,3-dipolar cycloaddition.[8] Among them, catalytic asymmetric 1,3-dipolar cycloaddition[9,10] of azomethine ylides to a variety of electron-deficient alkene dipolarophiles has arguably been one of the most ideal synthetic strategies for the construction of spirocyclic pyrrolidines with spiro quaternary stereogenic centers.[11,12] While dipolarophiles employed in these reactions are mainly 2-oxoindolin-3-ylidenes,[11a-e] cyclopropylidene acetates,[12a] 2-alkylidene-cycloketones,[12b,12c] and α-methylene-γ-butyrolactones,[12d] α-alkylidene succinimides that could be used to directly construct dispiropyrrolidine skeletons have rarely been explored (Scheme 1).[8]



Scheme 1. Asymmetric construction of dispiropyrrolidines *via* 1,3-dipolar cycloaddition of azomethine ylides.

We have recently reported a series of newly designed 1,3-dihydroimidazolpyridine-based *N,O*-ligands with applications in catalytic asymmetric reactions.[13] Among them, chiral *N,O*-ligand/Cu(OAc)$_2$ systems displayed excellent catalytic activity and stereoselectivity in asymmetric 1,3-dipolar cycloaddition of azomethine ylides with alkylidene malonates.[13b] Given the fact that 1,3-dipolar cycloaddition of azomethine ylides to α-alkylidene succinimides would provide a straightforward method to construct structurally novel and potentially biologically important dispiropyrrolidines, we were eager to

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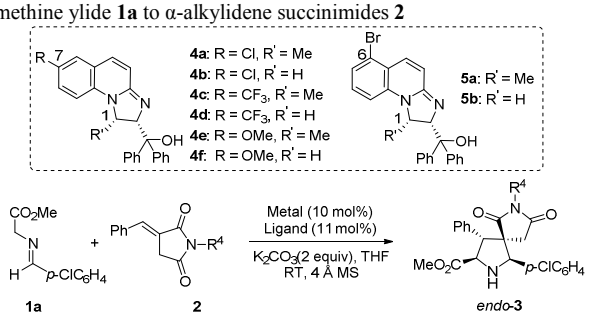
determine if our newly developed *N*,*O*-ligand/$Cu(OAc)_2$ systems could be applied to this new reaction. Herein, we demonstrate the first catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to α-alkylidene succinimides catalysed by chiral *N*,*O*-ligand/$Cu(OAc)_2$ systems, affording dispiropyrrolidine derivatives in good to excellent yields, and excellent levels of diastereoselectivity (> 20:1) and enantioselectivities (up to 97% ee). This catalytic system was further successfully extended to a 1,3-dipolar cycloaddition of azomethine ylides to 2-oxoindolin-3-ylidenes, providing a series of MI-219 analogues in excellent diastereoselectivities (> 99:1) and enantioselectivities (up to 95% ee).

Table 1. Catalyst screening for the asymmetric 1,3-dipolar cycloaddition of azomethine ylide **1a** to α-alkylidene succinimides **2**

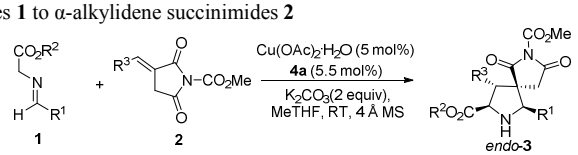


Entry[a]	Metal	Ligand	R^4	Yield (%)[b]	ee (%)[c]
1	$Cu(OAc)_2·H_2O$	**4a**	H (**2a**)	N.R.	-
2	$Cu(OAc)_2·H_2O$	**4a**	CO_2Me (**2b**)	85 (**3ab**)	93
3	$Cu(OAc)_2·H_2O$	**4a**	Cbz (**2c**)	80 (**3ac**)	93
4	$Cu(OAc)_2·H_2O$	**4b**	CO_2Me (**2b**)	40 (**3ab**)	31
5	$Cu(OAc)_2·H_2O$	**4c**	CO_2Me (**2b**)	64 (**3ab**)	93
6	$Cu(OAc)_2·H_2O$	**4d**	CO_2Me (**2b**)	trace	-
7	$Cu(OAc)_2·H_2O$	**4e**	CO_2Me (**2b**)	68 (**3ab**)	93
8	$Cu(OAc)_2·H_2O$	**4f**	CO_2Me (**2b**)	59 (**3ab**)	38
9	$Cu(OAc)_2·H_2O$	**5a**	CO_2Me (**2b**)	72 (**3ab**)	92
10	$Cu(OAc)_2·H_2O$	**5b**	CO_2Me (**2b**)	50 (**3ab**)	35
11	$Cu(CH_3CN)_4BF_4$	**4a**	CO_2Me (**2b**)	85 (**3ab**)	93
12	$Cu(CH_3CN)_4ClO_4$	**4a**	CO_2Me (**2b**)	70 (**3ab**)	93

[a] All reactions were carried out with 0.2 mmol of **1a** and 0.1 mmol of **2** in 1 mL of THF at room temperature. [b] Isolated yield. N.R. = no reaction. [c] Determined by chiral HPLC analysis, and >20:1 dr was determined by ^{1}H NMR of crude product.

We initially chose unprotected α-alkylidene succinimide **2a** as dipolarophile to test the feasibility of 1,3-dipolar cycloaddition with glycine methyl ester **1a** in the presence of chiral *N*,*O*-ligand **4a**/$Cu(OAc)_2·H_2O$ as the catalyst and K_2CO_3 as base in THF at room temperature (Table 1, entry1). Unfortunately, no reaction was observed, perhaps due to the relatively low reactivity of α-alkylidene succinimide. On the other hand, changing the R^4 substituent on the nitrogen of the α-alkylidene succinimide **2** such that it becomes a methyl carbamate, **2b**, gave a substrate that reacted smoothly with glycine methyl ester **1a** under the same conditions to afford *endo*-dispiropyrrolidines **3ab** as the major diastereomer (dr > 20:1) in good yield with excellent level of enantioselectivity, the carbamate group may enhance the polarisability of the dipolarophiles and contributes to the high reactivity. Changing the nitrogen substituent to a Cbz-protecting group, **2c**, gave a similar result in terms of both yield and stereoselectivity. Compound **2b** (the CO_2Me-appended α-alkylidene succinimide) was selected as the dipolarophile and glycine methyl ester **1a** as the dipolar to screen a number of our chiral *N*,*O*-ligands **4**, **5** in this reaction. To compare the effect of substitution on the imidazole ring, ligands **4a** and **4b** (with and without a methyl group adjacently *cis* to the tertiary alcohol respectively) were contrasted. The yield and enantioselectivity were sharply decreased when *N*,*O*-ligand **4b**, which lacks the steric pressure of the methyl group of **4a**, was used (Table 1, entry 4). A buttressing effect of substitution adjacent to the alcohol had been demonstrated in other copper catalyzed reactions reported by us, the present observation is consistent with those previous finding suggesting mechanistic overlap between our previous reports and this work. This "buttressing effect" was also found in other chiral *N*,*O*-ligands **4c-f** and **5** (Table 1, entries 5-10). Electronic effects of substituents on ligand back-bone for methyl appended *N*,*O*-ligands (**4a**, **4c**, **4e**, **5a**) was studied. It transpired that ligands with either electron-withdrawing or -donating groups gave comparable enantioselectivities, and the originally tested ligand **4a** was optimal in terms of achievable yield. Screening of other copper salts as metal sources showed that both $Cu(CH_3CN)_4BF_4$ and $Cu(CH_3CN)_4ClO_4$ gave excellent enantioselectivities, however with a slightly lower yield than for the latter (Table 1, entries 11-12).

Table 2. Substrate scope in the 1,3-dipolar cycloaddition of azomethine ylides **1** to α-alkylidene succinimides **2**



Entry[a]	R^1/R^2	R^3	Yield (%)[b]	ee (%)[c]
1	*p*-ClC_6H_4/Me (**1a**)	Ph (**2b**)	85 (**3ab**)	95
2	*p*-ClC_6H_4/Et (**1b**)	Ph (**2b**)	72 (**3bb**)	92
3	Ph/Me (**1c**)	Ph (**2b**)	83 (**3cb**)	96
4	*o*-ClC_6H_4/Me (**1d**)	Ph (**2b**)	81 (**3db**)	94
5	*m*-ClC_6H_4/Me (**1e**)	Ph (**2b**)	80 (**3eb**)	97
6	*p*-BrC_6H_4/Me (**1f**)	Ph (**2b**)	77 (**3fb**)	95
7	*p*-FC_6H_4/Me (**1g**)	Ph (**2b**)	72 (**3gb**)	95
8	*p*-$CF_3C_6H_4$/Me (**1h**)	Ph (**2b**)	82 (**3hb**)	95
9	*o*-MeC_6H_4/Me (**1i**)	Ph (**2b**)	71 (**3ib**)	93
10	*p*-MeC_6H_4/Me (**1j**)	Ph (**2b**)	77 (**3jb**)	95
11	*p*-$MeOC_6H_4$/Me (**1k**)	Ph (**2b**)	74 (**3kb**)	95
12	2-naphthyl/Me (**1l**)	Ph (**2b**)	74 (**3lb**)	95
13	2-furyl/Me (**1m**)	Ph (**2b**)	90 (**3mb**)	91
14	Cy/Me (**1n**)	Ph (**2b**)	40 (**3nb**)	88
15	*p*-ClC_6H_4/Me (**1a**)	*p*-$MeOC_6H_4$ (**2d**)	77 (**3ad**)	95
16	*p*-ClC_6H_4/Me (**1a**)	*p*-$CF_3C_6H_4$ (**2e**)	68 (**3ae**)	91
17	*p*-ClC_6H_4/Me (**1a**)	*p*-BrC_6H_4 (**2f**)	88 (**3af**)	96
18	*p*-ClC_6H_4/Me (**1a**)	*m*-BrC_6H_4 (**2g**)	85 (**3ag**)	95
19	*p*-ClC_6H_4/Me (**1a**)	2-furyl (**2h**)	60 (**3ah**)	90
20	*p*-ClC_6H_4/Me (**1a**)	*n*-Pr (**2i**)	50 (**3ai**)	94
21	*p*-ClC_6H_4/Me (**1a**)	CH=CHPh (**2j**)	30 (**3aj**)	87

[a] All reactions were carried out with 0.4 mmol of **1** and 0.2 mmol of **2** in 2 mL of MeTHF at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis, and >20:1 dr was determined by ^{1}H NMR of crude product.

The choice of base and solvent was optimized in the presence of 10 mol% of $Cu(OAc)_2·H_2O$ and 11 mol% of chiral *N*,*O*-ligand **4a** (see the Supporting Information, Table S1), K_2CO_3 as base and MeTHF[14] as solvent were found to be optimal in terms of both yield and enantioselectivity (85% yield, 95% ee). Additionally, the higher reactivity in MeTHF permitted lower catalyst loading (5 mol%) in the presence of two equivalents of

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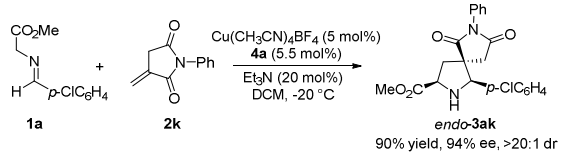
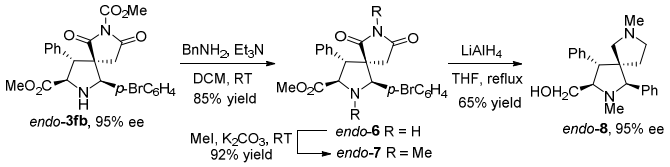
K_2CO_3, which provide the corresponding *endo*-dispiropyrrolidine **3ab** in comparable results (85% yield, 95% ee).

The above optimization identified optimal conditions as: 5 mol% of $Cu(OAc)_2 \cdot H_2O$, 5.5 mol% of chiral *N*,*O*-ligand **4a**, two equivalents of K_2CO_3, and addition of 4 Å MS (50 mg/mL), MeTHF as solvent and room temperature. The generality and substrate scope were then probed using a series of azomethine ylides **1** and α-alkylidene succinimides **2**, as shown in Table 2. Similar diastereo- and enantioselectivities were observed when the methyl ester of azomethine ylide **1a** was replaced by an ethyl ester (Table 2, entries 1-2). Azomethine ylides **1** bearing electron-rich (Table 2, entries 9-11), electronically-neutral (Table 2, entries 3 and 12), and electron-deficient groups (Table 2, entries 1, 2, 4-8) on the aryl ring all reacted with α-alkylidene succinimide **2b** smoothly affording the corresponding products exclusively in good yields (71-85%), excellent diastereoselectivities (>20:1 dr), and excellent enantioselectivities (92-97% ee). It is noteworthy that comparable results were achieved for the sterically hindered *ortho*-chloro and *ortho*-methyl-substituted azomethine ylides **1d** and **1i** (Table 2, entries 4 and 9 respectively). The heteroaryl substituted azomethine ylide **1m** derived from 2-furylaldehyde worked well in this transformation leading to desired product formation in 90% yield and 91% ee (Table 2, entry 13). Additionally, less reactive alkyl substituted azomethine ylide **1n** is also tolerated in this transformation affording *endo*-**3na**, albeit in a slightly lower yield and enantioselectivity (entry 14, 40% yield and 88% ee). We next turned our attention to various substituted α-alkylidene succinimides. α-Alkylidene succinimides **2** with both electron-donating (Table 2, entry 15) and electron-withdrawing substituents (Table 2, entries 16-18) at different positions on the aromatic ring were tolerated, resulting in formation of the corresponding *endo*-**3** products in excellent diastereoselectivities (>20:1 dr) and high enantioselectivities (91-96% ee) (Table 2, entries 15-18). Remarkably, α-alkylidene succinimides **2** with a 2-furyl substituent (Table 2, entry 19) and alkyl substituents (Table 2, entries 20 and 21) were also able to undergo the asymmetric 1,3-dipolar cycloadditions providing the desired *endo*-**3ah-3aj** in excellent enantiomeric excesses (up to 94% ee), however only moderate yields were attained.



Scheme 2. Asymmetric 1,3-dipolar cycloaddition of azomethine ylide **1a** to α-alkylidene succinimide **2k**.

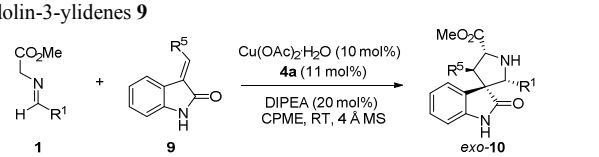


Scheme 3. Transformation of cycloadduct **3fb** into spirocyclic bispyrrolidine *endo*-**8**.

The asymmetric 1,3-dipolar cycloaddition of azomethine ylide **1a** to more reactive terminal alkene substrate **2k** was also investigated (Scheme 2). Thus, *endo*-**3ak** was generated in 90% yield, 94% ee, and >20:1 dr when chiral *N*,*O*-ligand **4a**/$Cu(CH_3CN)_4BF_4$ complex was used as catalyst with Et_3N as base, in DCM at -20 °C. A scaled up asymmetric 1,3-dipolar cycloaddition of azomethine ylide **1f** to α-alkylidene succinimide **2b** demonstrated that chiral *N*,*O*-ligand **4a**/$Cu(OAc)_2$ system was suitable for generating 2.0 g of *endo*-**3fb** in 81% yield, 95% ee, and >20:1 dr (see the Supporting Information, Scheme S1) in one batch. The product *endo*-**3fb** can be easily transformed into *N*-methyl *endo*-dispiropyrrolidine **7** in excellent yield, a subsequent $LiAlH_4$ reduction afforded *endo*-**8** in 65% yield, without loss of stereochemical integrity (Scheme 3, 95% ee). The relative and absolute configuration of the major diastereoisomer of **6** was assigned as *endo*-(1*R*,3*R*,4*R*,5*R*) according to single crystal X-ray diffraction analysis of *endo*-**6** (see the Supporting Information for details).

Furthermore, the chiral *N*,*O*-ligand **4a**/$Cu(OAc)_2$ system was also applicable to the asymmetric 1,3-dipolar cycloaddition of azomethine ylides **1** to 2-oxoindolin-3-ylidenes **9**. After optimization of the reaction conditions, it was found that the reaction proceeded efficiently in the presence of $Cu(OAc)_2 \cdot H_2O$ (10 mol%), chiral *N*,*O*-ligand **4a** (11 mol%), DIPEA (20 mol%), and 4 Å MS (50 mg/mL) in CPME as solvent at room temperature (Table 3). As expected, all reactions proceeded smoothly to afford the desired product *exo*-**10** in good to excellent yields (88-99%), excellent diastereoselectivities (99:1 dr) and high enantioselectivities (92-95% ee), comparable to those obtained in previous reports.[11]

Table 3. Asymmetric 1,3-dipolar cycloaddition of azomethine ylides **1** to 2-oxoindolin-3-ylidenes **9**



Entry[a]	R^1	R^5	Yield (%)[b]	ee (%)[c]
1	*p*-ClC_6H_4 (**1a**)	Ph (**9a**)	95 (**10aa**)	95
2	Ph (**1c**)	Ph (**9a**)	95 (**10ca**)	94
3	*p*-BrC_6H_4 (**1f**)	Ph (**9a**)	93 (**10fa**)	93
4	*p*-FC_6H_4 (**1g**)	Ph (**9a**)	99 (**10ga**)	94
5	*p*-ClC_6H_4 (**1a**)	*p*-ClC_6H_4 (**9b**)	95 (**10ab**)	94
6	*p*-ClC_6H_4 (**1a**)	*p*-MeC_6H_4 (**9c**)	88 (**10ac**)	92

[a] All reactions were carried out with 0.2 mmol of **1** and 0.1 mmol of **9** in 1 mL of CPME at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis, and 99:1 dr was determined by ^1H NMR of crude product.

In conclusion, a highly efficient asymmetric 1,3-dipolar cycloaddition of azomethine ylides **1** to α-alkylidene succinimides **2** catalyzed by a novel chiral *N*,*O*-ligand/$Cu(OAc)_2 \cdot H_2O$ system was developed, affording *endo*-dispiropyrrolidine derivatives **3** in good to excellent yields (up to 90%), excellent level of diastereoselectivities (>20:1 dr) and enantioselectivities (up to 97% ee). This highly efficient chiral *N*,*O*-ligand/$Cu(OAc)_2$ catalytic system was also applicable to the asymmetric 1,3-dipolar cycloaddition of azomethine ylides **1** to 2-oxoindolin-3-ylidenes **9**, affording the corresponding *exo*-dispiropyrrolidines **10** in good to excellent yields (up to 99%), excellent diastereoselectivities (99:1 dr), and high enantioselectivities (up to 95% ee). The highly stereoselective construction of dispiropyrrolidine and pyrrolidinyl-spirooxindole skeletons with excellent diastereo- and enantioselectivities suggests a highly efficient protocol of potential importance tomedicinal chemistry, agrochemicals and diversity-orientedsynthesis. Further investigations in the area of

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spirocyclic pyrrolidine synthesis and applications are ongoing in our laboratories.

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Notes and references

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† Electronic Supplementary Information (ESI) available: experimental procedures, spectral data, and crystallographic data. See DOI: 10.1039/b000000x/

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