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Cu(I)/DTBM-BIPHEP-catalyzed *exo*-selective 1,3-dipolar cycloaddition of azomethine ylides with *cis*-trifluorocrotonate for asymmetric construction of trifluoromethylated pyrrolidines

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ABSTRACT

A direct and facile access to highly substituted *exo*-pyrrolidines bearing a unique trifluoromethyl group is developed via Cu(I)/DTBM-BIPHEP-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with *cis*-4,4,4-trifluorocrotonate for the first time.

Five-membered nitrogen heterocycles, especially the highly substituted pyrrolidines are observed widely in pharmaceuticals, natural alkaloids, organocatalysts, and also useful building blocks in synthetic chemistry.[1] As a consequence, extensive studies have been conducted on the exploitation of the efficient methods for the asymmetric synthesis of biologically active pyrrolidines over the past decade.[2] Among these, the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides generated from readily available imino esters and electron-deficient alkenes has proven to be one of the most powerful and diversity-oriented synthesis (DOS)[3] for the construction of such compounds.[4] Recently, fluorinated organic compounds play a unique and significant role in the pharmaceutical, agrochemical, and material sciences.[5] Chiral trifluoromethylated compounds have attracted considerable attention, mainly due to the fact that the trifluoromethyl group often brings remarkably changes in the physical, chemical, and biological properties of the parent molecules, such as enhanced binding selectivity, higher lipophilicity, and increased metabolic stability.[6]

One such example is (3*R*,4*S*)-7-(3-aminomethyl-4-trifluoromethyl-1-pyrro-lidinyl)-8-ethoxyfluoroquinolone (Fig. 1), in which the key trifluoromethylated pyrrolidine moiety was achieved through TFA-mediated 1,3-dipolar cycloaddition of azomethine ylide with *trans*-4,4,4-trifluorocrotonate.[7] It has been revealed that the stereogenic carbon center bearing a unique CF_3 group on the pyrrolidine ring plays a significant role in the structure-activity relationship and exhibits superior activity against quinolone and methicillin-resistant *Staphylococcus aureus* with low side effect potential.[7] Although various methods have been established for the synthesis of enantioenriched pyrrolidines, however, for the trifluoromethylated pyrrolidines, to our knowledge, only limited racemic examples have been reported employing stoichiometric amount of catalyst.[8] In this topic, we have recently developed a general procedure for the asymmetric approach to trifluoromethylated pyrrolidines with excellent *endo*-selectivity via Cu(I)/(*S*)-TF-BiphamPhos-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with 4,4,4-trifluorocrotonates.[9] Because it is important to synthesize any of the desired diastereomers of cycloadducts with both high diastereoselectivity and enantioselectivity, an investigation of construction for the *exo*-selective trifluoromethylated pyrrolidines is in a high demand. To further diversify bioactive trifluoromethylated

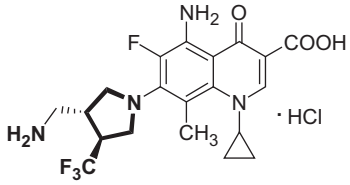

Figure 1. Fluoroquinolone antibacterial agent bearing the key trifluoromethylated pyrrolidine moiety: (3*R*,4*S*)-S-34109.

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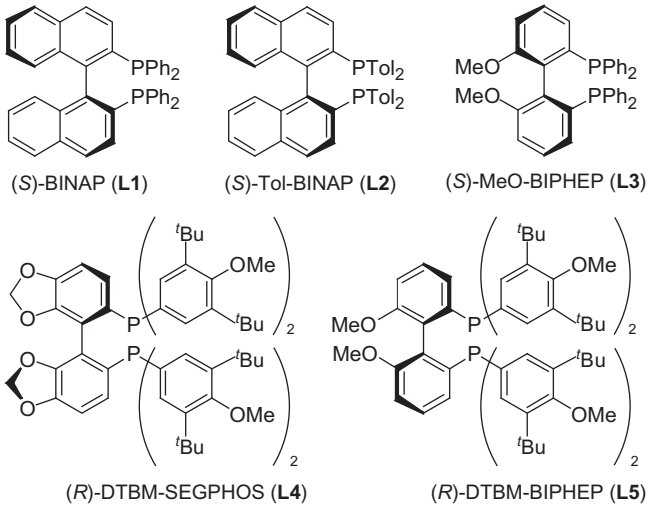


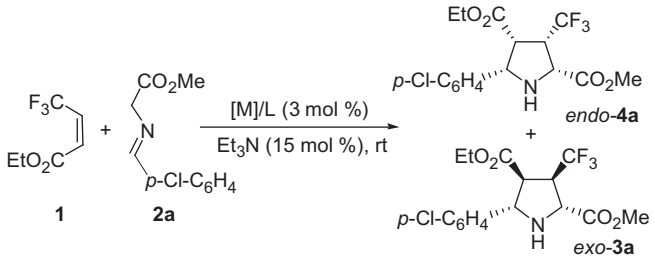
Figure 2. Screened chiral ligands.

pyrrolidine derivatives, the screening of some commercially-available chiral bisphosphine ligands would be desirable and practicable considering good to excellent *exo*-selectivity delivered by the bisphosphine/metal complexes for the cycloaddition of azomethine ylides with some commonly-used electron-deficient alkenes such as acrylates, maleates, maleimides, and vinyl sulfones.[10] Herein, we reported the asymmetric *exo*-selective 1,3-dipolar cycloaddition of azomethine ylides to *cis*-trifluorocrotonate with high yield and excellent enantioselectivity catalyzed by Cu(I)/(*R*)-DTBM-BIPHEP complex.

To explore the feasibility of the diastereoselectivity control for this 1,3-dipoar cycloaddition process, reaction of *cis*-ethyl trifluorocrotonate (**1**) with *N*-(4-chlorobenzyli-dene)-glycine methyl ester (**2a**) was carried out in dichloromethane at room temperature in the presence of silver or copper salts with several commercially-available chiral bisphosphine ligands (Fig. 2). Our initial study showed that AgOAc/(*S*)–BINAP complex successfully catalyzed this cycloaddition, and *exo*-adduct was obtained as the major diastereomer (*exo*/*endo* = 67:33) although the corresponding enantioselectivity was unsatisfactory (Table 1, entry 1). Next studies showed that using $Cu(CH_3CN)_4BF_4$ as the metal precursor gave better results than AgOAc in terms of reactivity and diastereo-/enantioselectivity (entry 2). It is well known that subtle changes in conformation, steric, and electronic properties of the chiral axially bisphosphine ligands can often lead to dramatic variation of reactivity and enantioselectivity, hence, further ligand survey was performed with $Cu(CH_3CN)_4BF_4$ as the metal precursor. A little higher diastereoselectivity but lower enantioselectivity was observed when the phenyl group on the phosphorous atom of BINAP was replaced by the *p*-tolyl group (**L2**) (entry 3). Axially biphenyl ligand (*S*)-MeO-BIPHEP (**L3**) was tested in this transformation leading to the same diastereoselectivity as (*S*)-BINAP (**L1**) but higher enantioselectivity (entry 4). To our delight, the more bulky and electron-donating biphenyl ligands (*R*)-DTBM-SEGPHOS (**L4**) and (*R*)-DTBM-BIPHEP (**L5**) not only exhibited a significant improvement on the diastereo-selectivity (>98:2) but also gave almost perfect enantioselectivity[11] (98% ee and >99% ee, respectively, entries 5 and 6). A study of reaction with $Cu(CH_3CN)_4BF_4$/(*R*)-**L5** in various solvents revealed that CH_2Cl_2 was the best one in terms of yield and enantioselectivity. (entries 6–10).

With the optimal reaction conditions in hand, the scope of this *exo*-trifluoromethylated pyrrolidine formation was demonstrated with various imino esters. As summarized in Table 2, a variety of imino esters **2** derived from aromatic aldehydes, which bear electron-deficient (Table 2, entries 1–7), electron-neutral (entries 8, 14 and 15), or electron-rich groups (entries 9–12) on the phenyl ring, reacted smoothly with *cis*-ethyl 4,4,4-trifluorocrotonate **1** to afford the desired *exo*-adducts in high yields (73–87%), excellent diastereoselectivities (>98:2 dr) and enantioselectivities (92 to >99% ee). It is noteworthy that comparable results were still achieved for the sterically hindered *ortho*-substituted and 1-naphthyl-substituted imino esters **2c, 2e, 2f,** and **2n** in terms of diastereo-/enantioselectivity and reactivity (entries 3, 5, 10 and 14). Additionally, heteroaromatic 2-furyl imino ester **2m** derived from

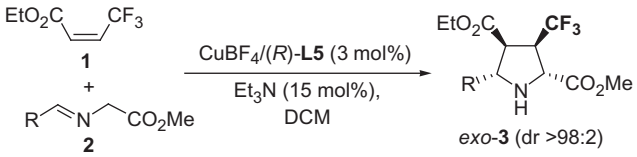
Table 1
Screening studies of the catalytic asymmetric 1,3-dipolar cycloaddition of imino ester **2a** with *cis*-ethyl trifluorocrotonate **1**[a]



Entry	L	(M)	Solvent	*t* (h)	**3a**/**4a**	Yield[b] (%)	ee[c] (%)
1	**L1**	AgOAc	DCM	5	67:33	53	−15
2	**L1**	$CuBF_4$	DCM	3	86:14	65	−27
3	**L2**	$CuBF_4$	DCM	3	92:8	70	−20
4	**L3**	$CuBF_4$	DCM	3	90:10	72	−40
5	**L4**	$CuBF_4$	DCM	3	>98:2	79	98
6	**L5**	$CuBF_4$	DCM	3	>98:2	82	>99
7	**L5**	$CuBF_4$	Et_2O	3	>98:2	88	95
8	**L5**	$CuBF_4$	THF	5	>98:2	64	95
9	**L5**	$CuBF_4$	CH_3CN	8	>98:2	38	94
10	**L5**	$CuBF_4$	PhMe	6	>98:2	78	95

[a] All reactions were carried out with 0.23 mmol of **1** and 0.35 mmol of **2a** in 2 mL solvent. $CuBF_4 = Cu(CH_3CN)_4BF_4$.
[b] Isolated yield.
[c] Ee was determined by chiral HPLC analysis.

Table 2
Substrate scope of $CuBF_4$/**L5**-catalyzed *exo*-selective 1,3-DC of various imino esters **2** with *cis*-ethyl trifluorocrotonate **1**[a]

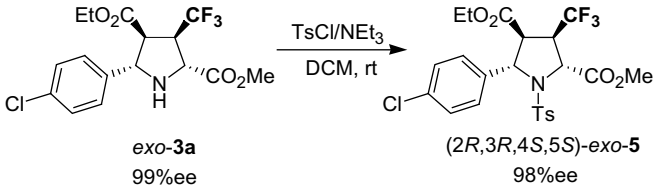


Entry	R	3	Yield[b] (%)	ee[c] (%)
1	*p*-Cl-Ph (**2a**)	**3a**	82	>99
2	*m*-Cl-Ph (**2b**)	**3b**	83	95
3	*o*-Cl-Ph (**2c**)	**3c**	82	99
4	*p*-F-Ph (**2d**)	**3d**	80	98
5	*o*-F-Ph (**2e**)	**3e**	80	92
6	*p*-CF3-Ph (**2f**)	**3f**	85	99
7	*p*-Br-Ph (**2g**)	**3g**	78	97
8	Ph (**2h**)	**3h**	81	96
9	*p*-Me-Ph (**2i**)	**3i**	85	97
10	*o*-Me-Ph (**2j**)	**3j**	86	92
11	*m*-Me-Ph (**2k**)	**3k**	78	95
12	*p*-MeO-Ph (**2l**)	**3l**	73	98
13	2-furyl (**2m**)	**3m**	81	95
14	1-Naphthyl (**2n**)	**3n**	87	98
15	2-Naphthyl (**2o**)	**3o**	83	94
16	PhCH=CH (**2p**)	**3p**	68	>99

[a] All reactions were carried out with 0.23 mmol of **1** and 0.35 mmol of **2** in 2 mL DCM.
[b] Isolated yield.
[c] Ee was determined by chiral HPLC analysis.

2-furylaldehyde also works in this transformation leading to 81% yield and 95% ee (entry 13). Noticeably, α,β-unsaturated imino ester **2p** derived from cinammyl aldehyde also proved to be viable substrates in this process, producing the desired *exo*-**3p** with excellent diastereoselectivity and >99% ee (entry 16). However, no cycloaddition was observed when alkyl substituted imino ester was tested under the same reaction conditions.

The relative and absolute configuration of *exo*-**3a** achieved by $Cu(CH_3CN)_4BF_4$/(*R*)-DTBM-BIPHEP (**L5**) was unequivocally determined by X-ray analysis of its corresponding *N*-tosylated derivative **5**, and it was assigned as (2*R*,3*R*,4*S*,5*S*)[12] (Fig. 3). Those of other cycloadducts were tentatively proposed on the basis of these results.



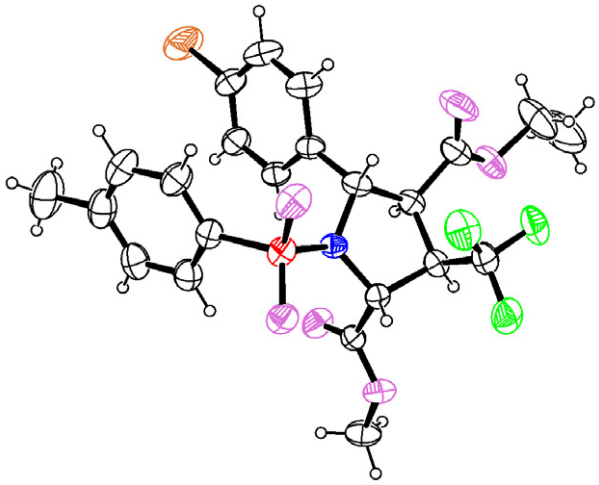


Figure 3. X-ray structure of *exo*-(2*R*,3*R*,4*S*,5*S*)-**5**.

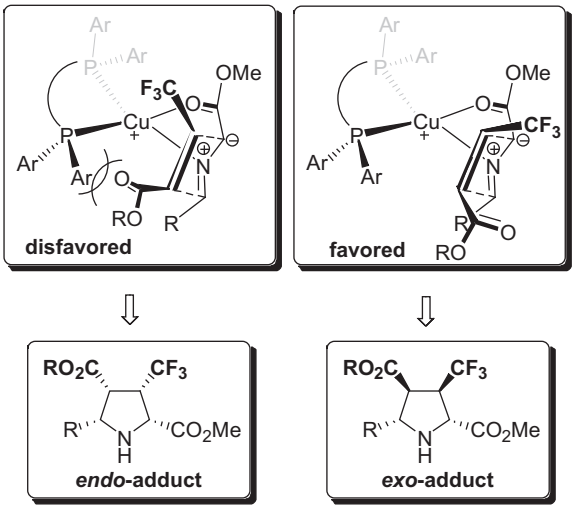


Figure 4. Proposed transition states leading to exo-cycloadduct.

Based on the relative and absolute configuration of the cycloadducts **3**, the high *exo*-selectivity observed in the Cu(I)/(*R*)-DTBM-BIPHEP (**L5**) catalyzed asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylide with *cis*-ethyl 4,4,4-trifluorocrotonate can be rationalized by the proposed transition states in Figure 4. The active species is a copper(I) complex having bulky and electron-donating bisphosphine (*R*)-DTBM-BIPHEP and an in situ-formed azomethine ylide in tetrahedral configuration.[10f] An *exo* approach of *cis*-ethyl 4,4,4-trifluorocrotonate to the copper(I) complex occurred predominantly because of the disfavored steric repulsion between the substituents of *cis*-ethyl 4,4,4- trifluorocrotonate and

the large bulky aryl group on the phosphorus atom of the chiral ligand corresponding to the *endo* approach.

In conclusion, we have successfully developed a facile and practical approach to the catalytic asymmetric synthesis of the *exo*-pyrrolidines bearing a unique trifluoromethyl group for the first time. An appropriate combination of a bulky and electron-donating bisphosphine ligand DTBM-BIPHEP with copper(I) salt led to excellent diastereoselectivity and high enantioselectivity control. The ready availability of the starting materials and the great importance of the chiral trifluoromethylated pyrrolidines make the current methodology particularly interesting in synthetic chemistry. Efforts are currently underway to elucidate the mechanistic details and the scope and limitations of this reaction, and the results will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterisation data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.021.

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11. The Cu(I)/DTBM-BIPHEP(**L5**)-catalyzed reaction of *trans*-ethyl 4,4,4-trifluorocrotonate with imino ester **2a** delivered racemic *endo*-adduct in moderate yield.
12. Crystal data for (2*R*,3*R*,4*S*,5*S*)-**5**: $C_{23}H_{23}ClF_3NO_6S$, $M_r = 533.94$, $T = 293$ K, Orthorhombic, space group $P2_12_12_1$, $a = 10.1514(18)$, $b = 12.640(2)$, $c = 20.255(4)$ Å, $V = 2599.0(8)$ Å^3, $Z = 4$. CCDC 847014 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/re-trieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).