Diastereodivergent Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides and -Fluoroalkyl Vinylsulfones: Low Copper(II) Catalyst Loading and Theoretical Studies

Diastereodivergent Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides and β-Fluoroalkyl Vinylsulfones: Low Cu(II) Catalyst Loading and Theoretical Studies

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Dedicated to Prof. Qing-Yun Chen on the occasion of his 90th birthday

Abstract: We have developed Cu(II)-catalyzed asymmetric 1,3-dipolar cycloadditions using β-fluoroalkyl alkenyl arylsulfones as dipolarophiles and glycine/alanine iminoesters as azomethine ylide precursors. Remarkably, a catalyst loading as low as 0.5 mol% proves to be highly efficient. Accordingly, a wide range of enantioenriched 3-fluoroalkyl pyrrolidines, as well as Δ^2-pyrroline and pyrrole derivatives, are generated in good to excellent yields with high asymmetric induction. This synthetic approach is shown to be diastereodivergent in that *exo*-adducts could be converted to the corresponding *exo'*-adducts via DBU-mediated epimerization at C2 of the pyrrolidine core. The free energy profiles via DFT calculations suggest the Michael addition of the 1,3-dipole to be the rate- and enantiodetermining step, and the origin of stereoselectivity is studied by means of the noncovalent interaction (NCI) analysis.

Introduction

Synthetic efficiency, cost, and environmental impact are three key criteria to evaluate an established synthetic protocol, which means that an ideal reaction system should be highly atom- and step-economic as well as stereoselective with cheap and readily available starting materials being converted under mild reaction conditions. On this basis, the development of stereodivergent asymmetric synthesis from identical starting materials by modifying the reaction conditions is significant and of particular interest, albeit challenging.[1]

Saturated five-membered *N*-heterocycles such as pyrrolidines, especially bearing an ester group at C2, such as proline derivatives, are widely incorporated in catalytically, biologically, and pharmaceutically active molecules.[2] The 1,3-dipolar cycloaddition of azomethine ylides[3] and activated alkenes represents a straightforward, powerful, and highly atom-economic solution to install pyrrolidine frameworks with up to four adjacent stereogenic centers. During the past two decades, the exploration of novel catalytic asymmetric 1,3-dipolar cycloadditions with functionalized alkenes [e.g. C(=O)R, NO_2, SO_2Ph, CN, $P(=O)(OR)_2$)] as dipolarophiles has drawn great attention.[4] Consequently, intensive studies on structure–activity relationships of catalysts and/or substrates have been carried out, accompanied with the enrichment of a library of multi-substituted enantioenriched pyrrolidines to the utmost extent.[5] Despite these tremendous advances, the known synthetic methods still suffer from various problems, such as: (1) high catalyst loading (at least 5 mol%); (2) rarely using cheaper and more stable Cu(II) catalysts in contrast to Cu(I) catalysts;[6] (3) few examples of providing *exo'*-adducts as the major isomers;[7] (4) limited trifluomethylated starting materials.[8]

In recent years, considerable efforts have been devoted to the asymmetric incorporation of fluorine atom/s into organic molecules because such modification can tune the physical, chemical, and biological properties of the corresponding non-fluorinated parent molecules.[9] Among various fluoroalkyl groups, the trifluoromethyl group (CF_3) has received significant attention because of its similar size to the methyl group and its high electronegativity resulting in unique stereoelectronic properties, which may substantially increase the metabolic stability, lipophilicity and thus bioavailability of drug molecules. Indeed, a number of CF_3-substituted pyrrolidines displaying interesting bioactivities have been reported; including insecticide **I**,[10] suicide inhibitor **II**,[11] antibacterial agent **III**,[12] and hepatitis C virus inhibitor **IV**[13] (Figure 1). Therefore, the discovery of efficient approaches to assemble such type of molecules is highly desirable and continues to be an attractive area of research. Some impressive synthetic paradigms including catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to access enantioenriched CF_3-pyrrolidines have been published.[14] Despite these efforts, it is still necessary to devise novel chiral catalytic systems and functionalized dipolarophiles in order to directly access structurally diverse and optically active CF_3-pyrrolidines as well as their much less explored CF_2X- and CFH_2-variants beyond organic chemistry research. Especially, the selective formation of diverse pyrrolidine diastereoisomers from identical starting materials, by simply changing the reaction conditions, would be a substantial advance in this research arena. To the best of our knowledge, only two reports exemplified the diastereodivergent catalytic asymmetric synthesis of enantioenriched non-fluorinated pyrrolidines from nitroalkenes. In 2006, Hou and coworkers developed a chiral ligand-controlled diastereodivergent synthesis of both *endo*- and *exo*-pyrrolidines through asymmetric Cu(I) catalysis (10 mol%) (Scheme 1a).[15] In 2011, Oh and coworkers demonstrated the diastereoselective switch through changing the copper(I) source (10 mol%) (Scheme 1b).[16]

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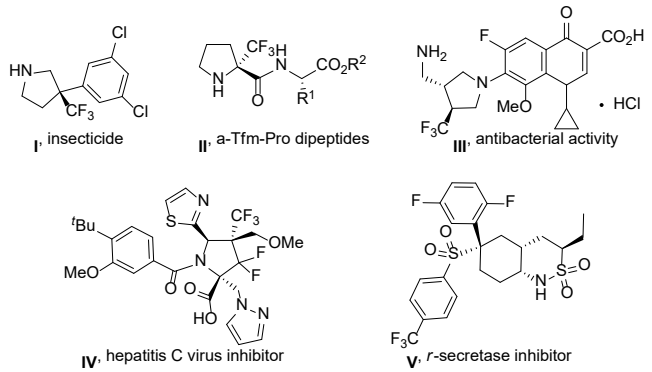
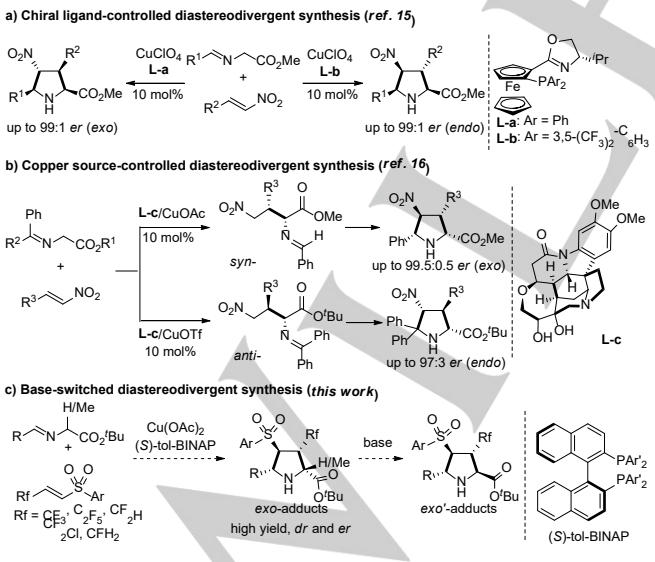


Figure 1. Representative bioactive molecules bearing trifluoromethyl pyrrolidine and/or sulfone motifs.

With this background and in continuation of our efforts on the catalytic asymmetric synthesis of fluorinated heterocycles,[17] electron-deficient alkenes such as β-fluoroalkyl alkenyl arylsulfones **1** were chosen as dipolarophiles because of the synthetic versatility of arylsulfone groups[18] and the structural importance (see compound **V**;[19] Figure 1).[20] A successful asymmetric transformation will give rise to tetrasubstituted pyrrolidine carboxylates with a fluoroalkylated stereogenic center at C3 (Scheme 1c). The challenge consists of controlling both the regioselectivity at the doubly activated unsymmetric C=C double bond as well as the diastereo- and enantioselectivities during the simultaneous creation of four adjacent stereogenic centers in a mild eco-benign process featuring low catalyst loading and high efficiency. Novel strategy is sought to switch the diastereoselectivity of 1,3-dipolar cycloadducts under the asymmetric Cu(II) catalysis.

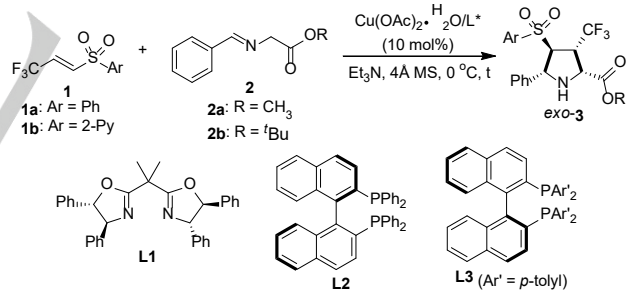


Scheme 1. Diastereodivergent asymmetric synthesis of enantioenriched pyrrolidines.

Results and Discussion

Reaction optimization. At the outset, β-CF_3-vinyl phenylsulfone **1a** (Ar = Ph) and glycine iminoester **2a** (R = Me) were used as reactants in the presence of $Cu(OAc)_2 \cdot H_2O$ (10 mol%) because of its low cost, non-toxicity, high chemical stability and good catalytic activity [Table 1; see also the Supporting Information (SI)]. Ligand screening at 0 °C revealed that chiral BOX ligand **L1** is unsuitable (entry 1), and the use of the more sterically hindered diphosphine ligand **L3** [(*S*)-tol-BINAP] displayed an increased enantiomeric ratio (*er*) than **L2** (BINAP) (entry 3 vs. entry 2). Gratifyingly, the asymmetric induction for the *exo*-product was substantially increased when glycine iminoester **2b** (R = ^{t}Bu) was used instead of **2a** at 0 °C (*dr* = 41:1, *er* = 94:6; entry 4). THF was found to be the best solvent giving product *exo*-**3ab** with a *dr* of 60:1 and an *er* of 97:3 (entry 6 vs. entries 5 and 4). An experiment at –10 °C led to a slight drop in enantioselectivity (entry 7). When the catalyst loading was decreased to 5 mol% and 2.5 mol%, comparable catalytic results were obtained (entries 8 and 9). Although the catalyst loading could be further decreased to 0.5 mol%, a loading of 2.5 mol% was used in the substrate scope exploration for experimental convenience. The use of other potential Lewis acid catalysts such as CuOAc, $Ni(OAc)_2$, and AgOAc provided inferior results in this 1,3-dipolar cycloaddition (entries 10–12). Notably, the use of β-CF_3-vinyl 2-pyridylsulfone **1b** (Ar = 2-py) proved to be well suited for this transformation in terms of yield and asymmetric induction (entry 13). Therefore, the optimized conditions were found to be conducting the reaction in THF at 0 °C using $Cu(OAc)_2 \cdot H_2O$/(*S*)-tol-BINAP (2.5 mol%), and Et_3N (10 mol%) (entries 9 and 13).

Table 1. Optimization of the reaction conditions.[a]

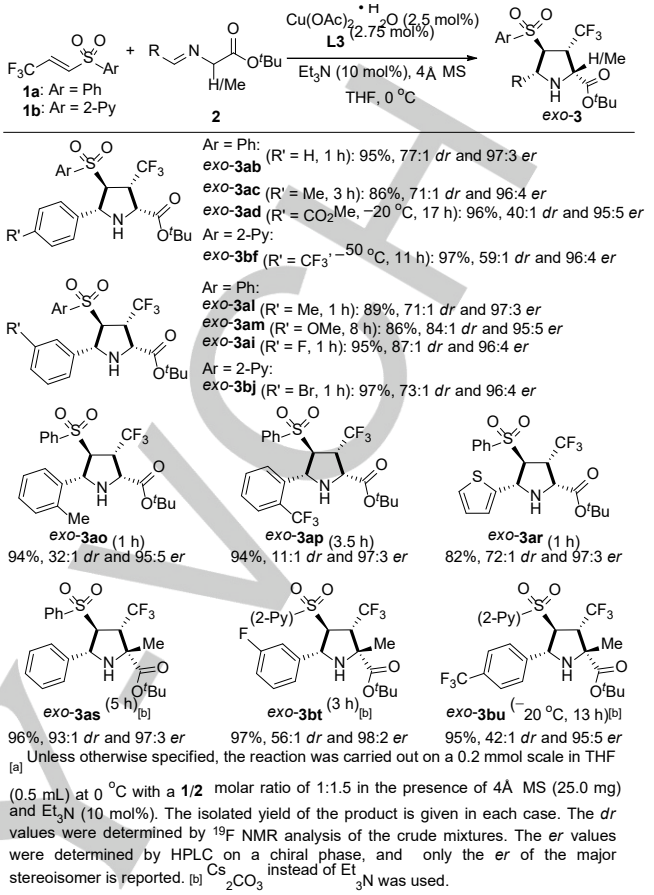


entry	**2**	solvent	L*	t/h	*exo*-**3**	yield (%)[b]	*dr*[c]	*er*[d]
1	**2a**	CH_2Cl_2	**L1**	4	**3aa**	90	13:1	25:75
2	**2a**	CH_2Cl_2	**L2**	6	**3aa**	88	23:1	22:78
3	**2a**	CH_2Cl_2	**L3**	6	**3aa**	83	19:1	87:13
4	**2b**	CH_2Cl_2	**L3**	3	**3ab**	96	41:1	94:6
5	**2b**	Toluene	**L3**	6	**3ab**	94	28:1	93:7
6	**2b**	THF	**L3**	4	**3ab**	84	60:1	97:3
7[e]	**2b**	THF	**L3**	2	**3ab**	91	68:1	95:5
8[f]	**2b**	THF	**L3**	8	**3ab**	96	62:1	96:4
9[g]	**2b**	THF	**L3**	1	**3ab**	95	77:1	97:3

10[g,h]	**2b**	THF	**L3**	6	**3ab**	85	20:1	13:87
11[g,i]	**2b**	THF	**L3**	72	**3ab**	52	9:1	47:53
12[g,j]	**2b**	THF	**L3**	1	**3ab**	96	25:1	68:32
13[g,k]	**2b**	THF	**L3**	1	**3bb**	95	77:1	96:4

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), Lewis acid (10 mol%), L* (11 mol%), 4Å MS (25.0 mg), solvent (0.3 mL), and 10 mol% of Et_3N were used. [b] Isolated yields. [c] Determined by ^{19}F NMR analysis of crude mixtures. [d] Determined by chiral HPLC. [e] The reaction was performed at –10 °C. [f] 5 mol% of catalyst was used. [g] **1** (0.2 mmol), **2** (0.3 mmol), and 2.5 mol% of catalyst was used. [h] CuOAc was used. [i] The reaction was performed with $Ni(OAc)_2$ at rt. [j] AgOAc was used. [k] **1b** was used.

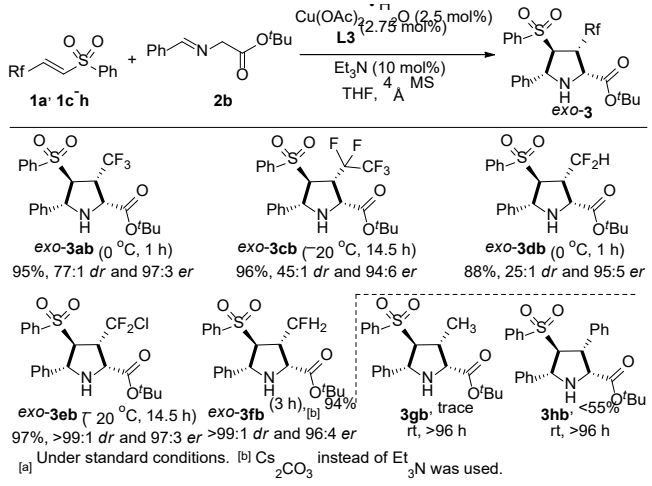
Iminoester scope of cycloaddition. After determining the optimized reaction conditions, the glycine iminoester scope was initially examined (Scheme 2). Firstly, the scope was evaluated with respect to glycine aldimines **2** by cyclizing with trifluoromethylated alkene **1a** or **1b**. Substrates with electron-donating (Me and MeO) and withdrawing groups (CO_2Me and CF_3) in *para*- and *ortho*- positions, as well as electron-donating (Me and MeO) and halide (F and Br) groups at the *meta*-position of phenyl ring were shown to be tolerated, and the respective products *exo*-**3** were isolated in 82–97% yields with high asymmetric induction (*dr* = 11:1 to 87:1; *er* = 95:5 to 97:3). It should be noted that when glycine iminoesters bearing *para*-CO_2Me and CF_3 substituents were used, lower temperature and/or alkene **1b** with a 2-pyridylsulfone group were required to get satisfactory enantiomeric ratios of *exo*-**3ad** and *exo*-**3bf**, respectively. A heteroaromatic glycine iminoester obtained from thiophene-2-carbaldehyde proved to be compatible with the transformation to give product *exo*-**3ar** in 82% yield with 72:1 *dr* and 97:3 *er*. Moreover, enantioenriched trifluoromethylated pyrrolidine *exo*-**3as** bearing an all-carbon quaternary stereocenter at C2 was also successfully synthesized in the presence of Cs_2CO_3 base in 96% yield with 93:1 *dr* and 97:3 *er*., as well as cycloadducts *exo*-**3bt** and *exo*-**3bu** were received from *meta*-F and *para*-CF_3-substituted alanine iminoesters with excellent results.



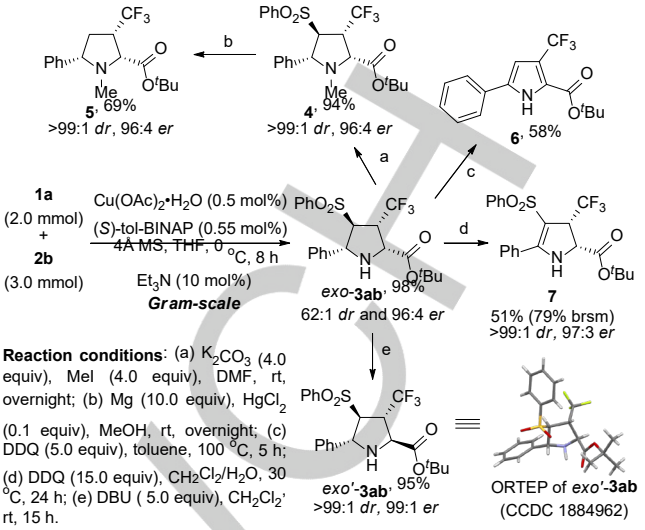
[a] Unless otherwise specified, the reaction was carried out on a 0.2 mmol scale in THF (0.5 mL) at 0 °C with a **1**/**2** molar ratio of 1:1.5 in the presence of 4Å MS (25.0 mg) and Et_3N (10 mol%). The isolated yield of the product is given in each case. The *dr* values were determined by ^{19}F NMR analysis of the crude mixtures. The *er* values were determined by HPLC on a chiral phase, and only the *er* of the major stereoisomer is reported. [b] Cs_2CO_3 instead of Et_3N was used.

Scheme 2. Scope of glycine and alanine iminoesters.[a]

Dipolarophile scope. Next, we turned our attention to explore the scope of various β-fluoroalkyl alkenyl phenylsulfones **1** with glycine iminoester **2b** (Scheme 3). Dipolarophiles **1a** and **1c**–**f** with diverse fluoroalkylated groups such as CF_3, CF_2CF_3, CF_2H, CF_2Cl and CFH_2 were used successfully to give the corresponding enantioenriched pyrrolidines *exo*-**3ab**–**fb** in 88–97% yields with high asymmetric induction (*dr* = 25:1 to >99:1; *er* = 94:6 to 97:3). Interestingly, a much lower reactivity was observed when β-methyl and β-phenyl substrates **1g** and **1h** were examined for comparison. These results support that the strongly electron-withdrawing fluoroalkyl group is critical for the activation of the dipolarophile, thus facilitating the rapid access to diverse 3-fluoroalkylated pyrrolidines.



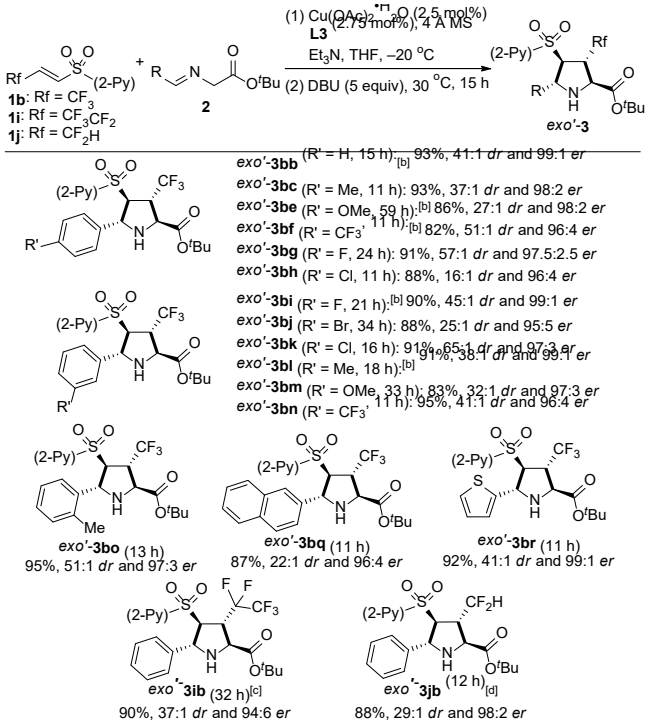
Scheme 3. Scope of dipolarophiles.[a]



Scheme 4. Synthetic transformation of *exo*-**3ab**.

Synthetic applications. The reaction was amenable to a gram-scale experiment at a remarkably low 0.5 mol% catalyst loading to form pyrrolidine *exo*-**3ab** in 98% yield with 62:1 *dr* and 96:4 *er* (Scheme 4). In order to demonstrate the synthetic utility of *exo*-**3ab**, a variety of divergent syntheses was carried out. The *N*-methylation of *exo*-**3ab** gave CF_3-pyrrolidine **4** in 94% yield with >99:1 *dr* and 96:4 *er*, which readily underwent reductive desulfonylation to form CF_3-pyrrolidine **5** without erosion of asymmetric induction (Scheme 4; reactions a and b). Structure **5** has been shown to be of particular interest in medicinal chemistry and peptide sciences;[21] it can thus be made available by avoiding a multi-step synthesis and the use of explosive and flammable 3,3,3-trifluoropropene gas as dipolarophile.[22] The oxidation of *exo*-**3ab** with DDQ at 100 °C and 30 °C gave access to trisubstituted desulfonylated pyrrole **6** and enantioenriched Δ^2-pyrroline **7**, respectively (Scheme 4; reactions c and d). In contrast to the base-induced elimination of a sulfonyl group,[23] treatment of *exo*-**3ab** with 5.0 equiv of DBU at room temperature triggered epimerization at C2 to give the thermodynamically more stable *exo'*-**3ab** with all-*trans* configuration in 95% yield with >99:1 *dr* and 99:1 *er* (Scheme 4; reaction e). This serendipitous discovery of diastereodivergent asymmetric synthesis significantly broadens the library of enantioenriched CF_3-pyrrolidines in a simple and expeditious fashion.

Substrate scope of asymmetric 1,3-dipolar cycloaddition/epimerization. Glycine iminoester scope was again surveyed since the interesting sequential asymmetric 1,3-dipolar cycloaddition/epimerization was discovered. Based on the above study, alkene **1b** with a 2-pyridylsulphone group exhibited better performance than **1a** in some cases, which was therefore utilized in this section. As shown in Scheme 5, lower temperature (–20 °C or –50 °C) enabled superior levels of enantioinduction compared with the results at 0 °C in Schemes 2 and 3. It was also observed that relatively higher *er's* were obtained for glycine iminoesters with electron-donating and halide groups in the phenyl ring than that with electron-withdrawing substituents (*exo*'-**3bf** and *exo*'-**3bn**). Various desired *exo*'-3-CF_3-pyrrolidines including containing 2-naphthyl (*exo*'-**3bq**) and 2-thiophenyl (*exo*'-**3br**) groups at C5 were produced (up to 95% yield, 65:1 *dr* and 99:1 *er*). Furthermore, when pentafluoroethyl alkene **1i** and iminoester **2b** were checked, *exo*'-**3ib** was generated with comparable results to the product *exo*-**3cb**. In the case of difluoromethyl alkene **1j** and iminoester **2b**, the cycloaddition at –20 °C and thereafter epimerization at 50 °C proceeded to produce *exo*'-**3jb** in 88% yield with 29:1 *dr* and 98:2 *er*.



[a] The 1,3-dipolar cycloaddition was carried out under standard conditions except reaction temperature. [b] The 1,3-dipolar cycloaddition was performed at –50 °C. [c] The 1,3-dipolar cycloaddition was performed at –50 °C for 12 h, then –20 °C for 20 h. [d] The epimerization was performed at 50 °C.

Scheme 5. Scope of glycine imines in asymmetric 1,3-dipolar cycloaddition/epimerization.[a]

Mechanism study

Proposed reaction mechanism. In the proposed mechanistic course involving step-wise nucleophilic addition in a head–head and/or tail–tail fashion, initial coordination of glycine iminoester **2b** and the (*S*)-tol-BINAP–Cu(II) complex facilitates the deprotonation by Et_3N to generate a well-organized enantioenriched *N*-metalated azomethine ylide complex **I** (Figure 2). Enantioselective Michael addition of **I** across the C=C double bond of **1a** occurs in a *syn*-selective manner to give zwitterionic intermediate **III**-*exo*. Intramolecular Mannich-type addition within **III**-*exo* from the *Si*-face of the iminium moiety followed by a proton transfer forms product *exo*-**3ab** with regeneration of the chiral copper catalyst.

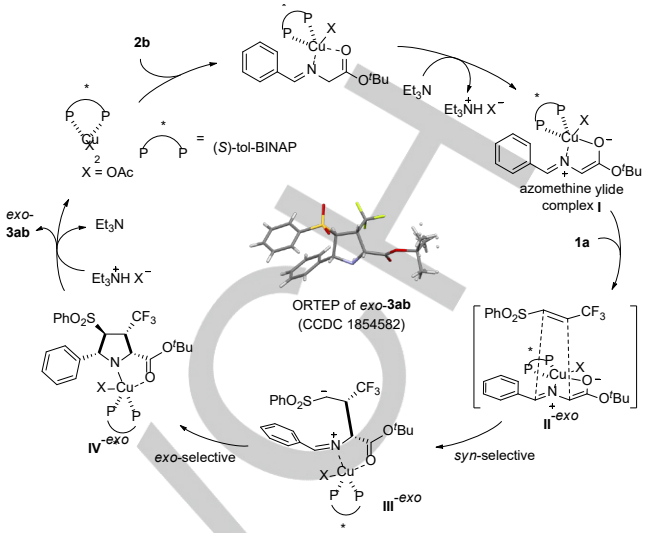


Figure 2. Proposed reaction mechanism.

Computational studies. The absolute configuration of *exo*-**3ab** (CCDC 1854582) was unambiguously determined as (2*R*,3*S*,4*S*,5*R*) by single-crystal X-ray analysis,[24] and the remaining products were assigned by analogy. Non-linear effect study suggests that the active chiral Cu(II) catalyst works as a monomeric species without significant aggregation to form product *exo*-**3ab** with high asymmetric induction (see Figure S1 in SI). In order to shed light on the origin of the preferred diastereo- and enantioselectivity, Density Functional Theory (DFT) calculations have been carried out along the reaction pathways by using the Gaussian 16 suite of program (see the details in SI). For comparison, the reaction pathways for producing *endo*-**3ab** and *enantio*-*exo*-**3ab** were studied as well (Figure 3). For all three pathways, intermediates **I**, **II**, **III** and **IV**, as well as the transition states were considered to understand the stereoselectivity. Based on the Gibbs free energy change profiles depicted in Figure 3, alkene **1a** approaching toward the azomethine ylide complex **I** in a *exo*-selective fashion displays the lowest energy change (**II**-*exo*, ΔG^{o} = 9.68 kcal/mol). During the asymmetric Michael addition to form the intermediate **III**, the free energy of activation and free energy associated with the favorable intermediate **III**-*exo* are 14.68 and 12.74 kcal/mol, respectively, which are both lower than that of another two possible pathways to produce its opposite enantiomer (**III**-*enantio*-*exo*: $\Delta\Delta G^{\ddagger}$ = 17.44 kcal/mol, ΔG^{o} = 13.99 kcal/mol) or *endo*-selective (2*R*,3*R*,4*R*,5*R*)-isomer (**III**-*endo*: $\Delta\Delta G^{\ddagger}$ = 17.44 kcal/mol, ΔG^{o} = 19.93 kcal/mol). Comparing with the energy barrier during the subsequent rapid cycloaddition event ($\Delta\Delta G^{\ddagger}$ = 6.21 kcal/mol), the Michael addition to form the intermediate **III** should be the rate- and enantioselectivity-determining step. The energy barrier difference between **III**-ts-*exo* and **III**-ts-*enantio*-*exo* (2.76 kcal/mol) indicates high propensity to form the desired enantiomer in the experimental findings.

In order to reveal the origin of stereoselectivity, the noncovalent interaction (NCI) analysis[25] has been performed for the transition states of the rate-determining steps of the three pathways using the NCIPLOT software and the M06-L/def2-

TZVPP wavefunctions. The plots of NCI analysis (see Figure S2 in SI) indicate that, in **III**-ts-*exo*, the benzene ring of **1a** has attractive weak interaction with the two polar hydrogen of **2b**, which can be described as C-H···π interactions and helps to stabilize the transition state. On the contrary, in **III**-ts-*enantio-exo*, the benzene ring of **1a** does not have the attractive interactions with **2b**. For **III**-ts-*endo* the interaction is essentially a π-π interaction between the two phenyl rings of the reactants supplemented by a slightly repulsive interaction between one C-H group on **2b** and the SO_2 group. Overall the network of weak interactions in **III**-ts-*exo* is more stabilizing than the network of weak interactions in **III**-ts-*endo*.

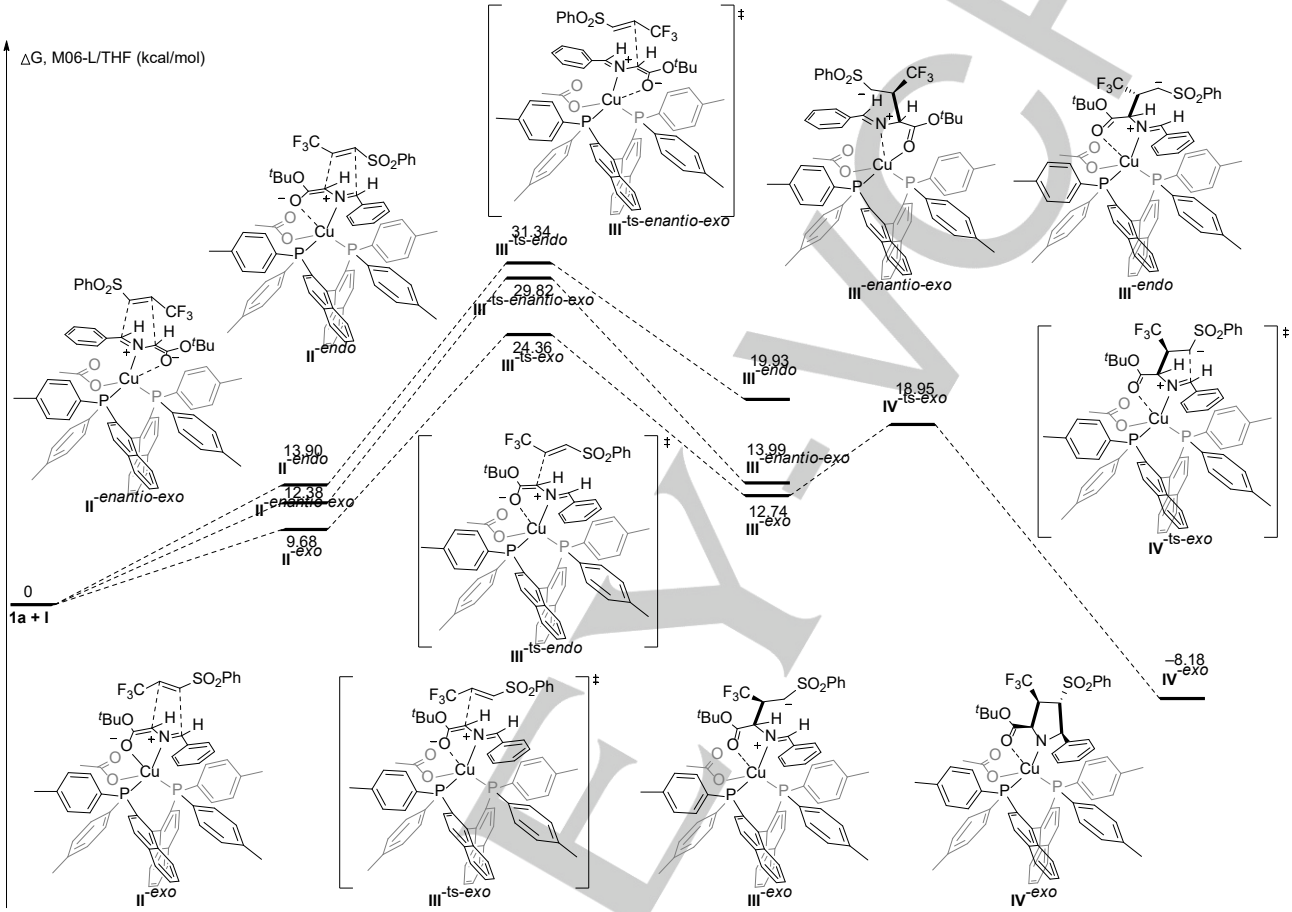


Figure 3. Gibbs free energy change profiles. Relative energies are in kcal/mol and calculated at the M06-L/def2-TZVPP level in THF.

Conclusion

In summary, we have accomplished a highly effective, diastereo- and enantioselective, as well as practical asymmetric 1,3-dipolar cycloaddition using β-fluoroalkyl alkenyl arylsulfones and glycine iminoesters. This protocol features several notable characteristics: 1) a wide array of enantioriched *exo*-3-fluoroalkyl pyrrolidines bearing four adjacent chiral centers were installed (up to 97% yield, >99:1 *dr* and 97:3 *er*); 2) a rare example of using a stable and inexpensive Cu(II) source in combination with a commercially available axially chiral diphosphine ligand; 3) a gram-scale asymmetric synthesis was achieved at the lowest level of catalyst loading (0.5 mol%) among the already established 1,3-dipolar cycloaddition reactions; 4) trifluoromethylated Δ^2-pyrroline and pyrrole derivatives were subsequently prepared with the aid of the phenylsulfone group; 5) the simple sequential addition of 5.0 equiv of DBU results in a remarkable and unprecedented diastereochemical switch to uncommon *exo'*-adducts (up to 95% yield, 65:1 *dr* and 99:1 *er*); and 6) the proposed stepwise reaction pathway catalyzed by a monomeric active Cu(II) species was supported by DFT calculations and non-linear effect study, and the stereochemical results were explained through the NCI analysis. The extensive exploration of fluoroalkylated building blocks in other types of catalytic asymmetric transformations is underway in our laboratory.

Experimental Section

General procedure for the asymmetric 1,3-dipolar cycloaddition. A mixture of (*S*)-tol-BINAP (0.55–2.75 mol%), $Cu(OAc)_2 \cdot H_2O$ (0.5–2.5 mol%) and 4Å MS (25 mg) in THF (0.1 mL) was stirred in a glove box at room temperature for 2 h. β-Fluoroalkyl alkenyl aryl sulfone **1** (0.2 mmol, 1.0 equiv) and a solution of Et_3N (10 mol%) in anhydrous THF (0.2 mL)

were added successively. After drop-wise addition of a solution of azomethine ylide **2** (0.3 mmol, 1.5 equiv) in anhydrous THF (0.2 mL) at 0 °C, the reaction mixture was stirred at 0 °C for the time as indicated. The catalytic process was monitored by TLC analysis. After complete consumption of **1**, the crude mixture was analyzed by ^{19}F NMR spectroscopy to determine the diastereomeric ratio. The crude mixture was purified by flash column chromatography on silica gel to afford the intended product *exo*-**3**. The optical purity of *exo*-**3** was determined by chiral HPLC.

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Keywords: 1,3-dipolar cycloaddition • diastereodivergent • azomethine ylides • low catalyst loading • fluoroalkyl

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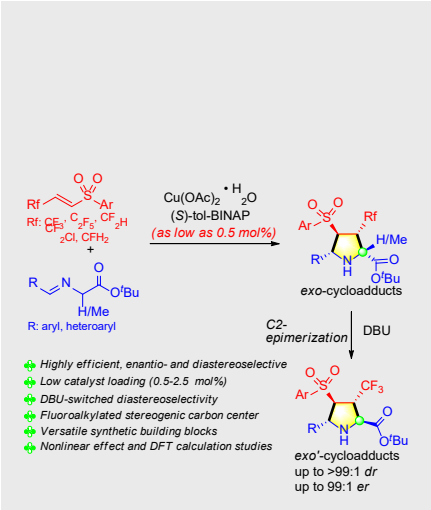
Entry for the Table of Contents (Please choose one layout)

Layout 1:

RESEARCH ARTICLE

The commercially available chiral $Cu(OAc)_2$/(S)-tol-BINAP catalyst exhibited high capacity in the asymmetric 1,3-dipolar cycloaddition of fluoroalkylated building blocks and azomethine ylides, which can be diastereodivergent to get both enantioenriched *exo*- and *exo'*-pyrrolidine derivatives by adding DBU base.



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Diastereodivergent Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides and β-Fluoroalkyl Vinylsulfones: Low Cu(II) Catalyst Loading and Theoretical Studies