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Cu-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with β-Phenylsulfonyl Enones. Ligand Controlled Diastereoselectivity Reversal

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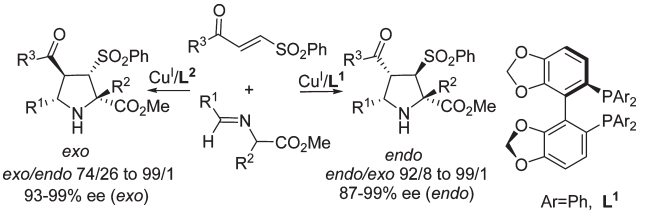

A catalytic asymmetric procedure for the 1,3-dipolar cycloaddition of (E)-β-phenylsulfonyl enones with azomethine ylides to provide highly functionalized pyrrolidine derivatives is described. In the presence of chiral Cu^I-Segphos catalysts the aducts were obtained with high regio-, diastereo-, and enantioselectivity. Interestingly, a switch from *endo* to *exo* selectivity was observed when Segphos or DTBM-Segphos ligand was used.

Pyrrolidine derivatives occupy a prominent place in natural products and medicinal chemistry[1] and have been intensely used as synthetic building blocks and organocatalysts.[2] Although numerous methods have been reported for the preparation of pyrrolidine derivatives,[3] the development of more concise procedures enabling the synthesis of enantiopure highly functionalized examples is a topic of growing interest. In this context, the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to activated alkenes has emerged as an essential tool, which provides a direct access to proline derivatives with good control of the diastereoselectivity and enantioselectivity.[4] Since the pioneering reports in 2002, by Zhang and Jørgersen,[5] several methods based on the use of diverse metal sources and chiral ligands have been developed.[6] Several organocatalytic versions of this reaction have also recently emerged.[7] Practically all of these protocols involve the reaction between azomethine ylides derived from iminoesters and monoactivated (such as acrylates, enones, nitroalkenes, and vinyl sulfones) or symmetrically double activated (such as maleates, fumarates, malemides, and fumaronitriles) dipolarophiles. However, the use of unsymmetrically substituted 1,2-diactivated dipolarophiles, which could lead to the formation of regioisomers, has been seldom explored.[8] In this topic, we have recently developed a general procedure for the catalytic asymmetric 1,3-dipolar cycloaddition of Z-sulfonyl acrylates with azomethine ylides where the regioselectivity of the cycloaddition is mainly controlled

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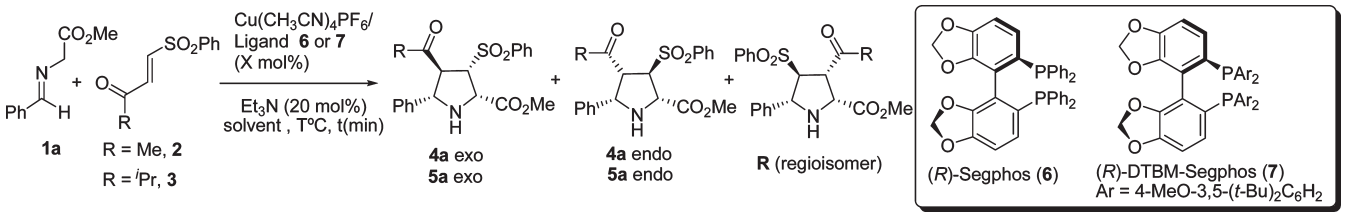
TABLE 1. Optimization Experiments for the Model Reaction



entry	R	ligand	solvent	X	*t* (min)	*T* (°C)	^{1}H NMR ratio[a] *exo*:*endo*:R[b]	yield (%)[c]	yield (%) (major)[d]	ee (%) (major)[e]
1	Me	**6**	THF	10	10	rt	19:71:10	95	66 (*endo*-**4a**)	88
2	Me	**7**	THF	10	10	rt	61:21:18	93	54 (*exo*-**4a**)[f]	≥99[g]
3	Me	**6**	THF	10	240	−78	8:88:4	87	70 (*endo*-**4a**)	97
4	Me	**7**	Et_2O	10	10	rt	81:10:9	93	57 (*exo*-**4a**)[f]	≥99[g]
5	Me	**6**	THF	3	240	−78	5:**92**:3	85	76 (*endo*-**4a**)	94
6	Me	**7**	Et_2O	3	10	rt	**83**:7:10	72	65 (*exo*-**4a**)[f]	≥99[g]
7	^{i}Pr	**6**	THF	3	240	−78	3:**97**:0	99	95 (*endo*-**5a**)	≥99
8	^{i}Pr	**7**	Et_2O	3	240	rt	**98**:1:1	85	84 (*exo*-**5a**)	≥99

[a]By ^{1}H NMR from the crude reaction mixtures. [b]R = 3-ketosubstituted regioisomer. [c]Combined yield in pyrrolidine products after column chromatography. [d]Yield in pure isolated major isomer after column chromatography. [e]Determinated by HPLC, see the Supporting Information for details. [f]Purified by further recrystallization. [g]ee of *exo*-**4a** before recrystallization.

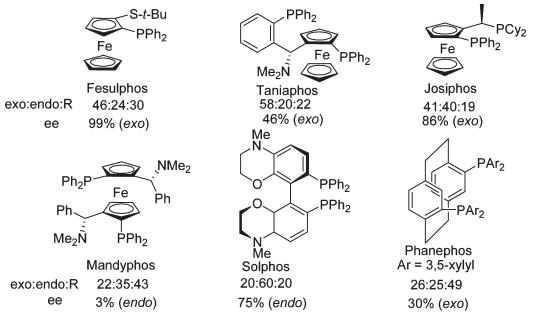
by the sulfonyl group,[9] providing 2,3-dicarboxylate ester pyrrolidines with very high *exo* selectivity and enantioselectivity (80−99% ee). With the aim of expanding the range of 1,2-diactivated dipolarophiles suitable for this reaction, herein we report a highly enantioselective catalytic azomethine ylide dipolar cycloaddition procedure with *β*-phenylsulfonylenones.

To evaluate the viability of the process, we selected the reaction between *N*-benzylidenglycine methyl ester **1a** and (*E*)-4-(phenylsulfonyl)but-3-en-2-one[10] (**2**) as the model system. As a starting point, we carried out the reaction under previously reported Cu-catalyzed conditions for asymmetric dipolar cycloaddition of azomethine ylides with several dipolarophiles[6h] [$Cu(CH_3CN)_4PF_6$ (10 mol %), chiral ligand ligand (10 mol %), and Et_3N (20 mol %) in THF at room temperature]. After screening a variety of chiral ligands,[11] we observed a significant enhancement in the regio- and diastereoselectivity with P,P axially chiral Segphos-type ligands.[12] Under these conditions the regioselectivity of the cycloaddition is mainly controlled by the carbonyl group, leading to the 4-acetyl-substituted pyrrolydines **4a** as the major regioisomer (less than 20% of the minor 3-acetyl regiosomer was observed in all examples studied).[13] Moreover, a remarkable inversion in the *exo*/*endo* diastereoselectivity was observed.[14] Segphos ligand (**6**) afforded the *endo* pyrrolidine **4a** as the major product with 88% ee (Table 1, entry 1), whereas DTBM-Segphos ligand (**7**), with very bulky and electron-donating substituents in the aryl group on the phosphorus atom, gave mainly *exo*-**4a** with ≥99% ee (Table 1, entry 2). Further optimization of the reaction conditions with Segphos-type ligands was then accomplished. The best results with Segphos **6**/$Cu(CH_3CN)_4PF_6$ as the catalyst system were achieved in THF at −78 °C, the aduct *endo*-**4a** being obtained with high yield and 97% ee (entry 3). *exo*-Pyrrolidine **4a** was obtained as the major product with ≥99% ee with DTBM-Segphos **7** as the ligand in Et_2O at room temperature (entry 4). In both cases the catalyst loading could be reduced from 10 to 3 mol % with very similar diastereoselectivity and enantioselectivity (Table 1, entries 5 and 6). When the more sterically demanding isopropyl ketone **3** was used as the dipolarophile, the cycloaddition occurred with a nearly complete control of the regioselectivity and diastereoselectivity, while maintaining an excellent enantiocontrol and opposite *exo*/*endo* selectivities with ligands **6** and **7** (97% *endo* and 93% *exo*, respectively; entries 7 and 8, Table 1).

(9) López-Pérez, A.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 340–343.

(10) *β*-Phenylsulfonyl enones were prepared according to the reported methods: (a) Domínguez, E.; Carretero, J. C. *Tetrahedron* **1990**, *46*, 7197–7206. (b) Leon, F. M.; Carretero, J. C. *Tetrahedron Lett.* **1991**, *32*, 5405–5408. No reaction was observed when the (*Z*)-isomer was used in the cycloaddition.

(11) Fesulphos, Taniaphos, Josiphos, Mandyphos, Solphos, and Phanephos were tested as chiral ligands in this cycloaddition. However, a poor *endo*/*exo* selectivity and regioselectivity was observed with all of them (see Scheme below). In addition, all the cycloadditions occurred with low or moderate enantioselectivity, excepting the case of the reaction with Fesulphos (99% ee for *exo*-**4a**).

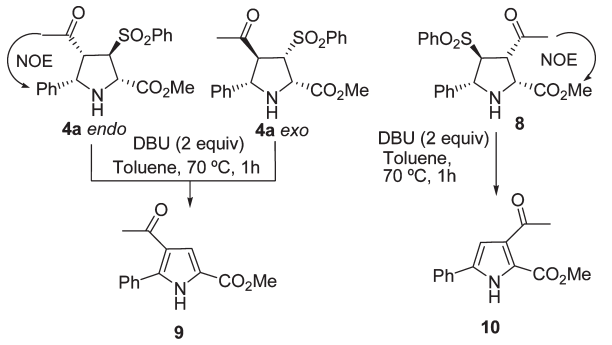


(12) For a review on biaryl-type biphosphine ligands, see: Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405–5432.

(13) From the starting mixture of adducts, formed by the *exo* + *endo* adducts **4a** and the minor 3-acetyl regioisomer, the adduct *endo*-**4a** was isolated pure after standard column chromatography. Although due to their very similar R_f values it was not possible to separate completely *exo*-**4a** and the 3-acetyl regioisomer by column chromatography, pure *exo*-**4a** was obtained after final recrystallization in isopropanol.

(14) For a previous example of a switch in the diastereoselectivity of the 1,3-dipolar cycloaddition of azomethine ylides with nitroalkenes varying the electronic properties of the ligands, see ref 6i.

SCHEME 1. Regiochemistry Determination: Conversion to Pyrroles



The stereochemical and configurational assignment of (+)-*exo*-**4a** was unequivocally established by X-ray diffraction of a recrystallized sample of ≥99% ee.[15] On the other hand, the regiochemistry of aducts **4a** and the minor regioisomer **8** was confirmed by its aromatization to the corresponding pyrroles via basic elimination of the sulfonyl group[16] (Scheme 1). Thus, the treatment of a mixture of *endo* and *exo* **4a** with DBU in toluene afforded exclusively the 2,4,5-trisubstituted pyrrole **9**, whereas the aromatization of the regioisomer **8** led to the 2,3,5-trisubtituted pyrrole **10**. Futhermore, the NOESY spectra of *endo*-**4a** and **8** corroborated these assignments. Hence, important NOESY correlations were observed between the methyl unit of the acetyl group and the ortho protons of the phenyl group in *endo*-**4a**, while the regioisomer **8** showed a significant cross-peak between the acetyl group and the methyl esther unit.

We next studied the scope of the Cu-catalyzed 1,3-dipolar cycloaddition of β-phenylsulfonyl enones with regard to the substitution at the azomethine precursor, in the presence of Segphos ligands **6** or **7** under the previously optimized reaction conditions. Similarly to the behavior of the model phenylimine glycinate, in all cases the regioselectivity of the process was mainly controlled by the carbonyl group of the dipolarophile (3−18% of the regioisomer 3-carbonyl-substituted pyrrolidine was detected in the reaction mixtures).

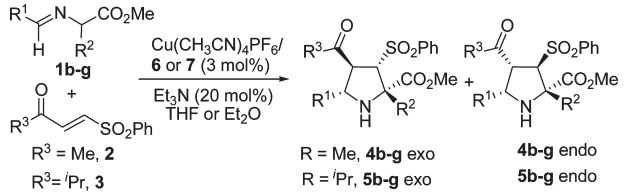
As shown in Table 2 a homogeneous stereochemical behavior was observed. The reaction of aryl- and heteroaryl-substituted glycine derivatives in the presence of ligand **6** afforded the *endo* pyrrolidine as the major stereoisomer with acceptable yields and exceptional enantioselectivities (Table 2, entries 1, 4, 6, 10, and 13), while with DTBM-Segphos ligand **7** the diastereomer *exo*-**4** was selectively obtained also with nearly complete enantioselectivity (Table 2, entries 2, 3, 5, 7, 8, 9, 11, 12, and 14).

Interestingly, this protocol also can be applied to alanine-based dipoles, which lead to pyrrolidines with a quaternary stereocenter in position 2 (R^2 = Me, entries 15 and 16, Table 2), albeit with a slightly lower enantioselectivity.

(15) *Exo* refers to the pyrrolidine with trans stereochemistry at C4−C5. See the Supporting Information for details on the X-ray structure of enantiopure *exo*-**4a**. For the configuration of the *endo* isomer, it has been assumed that the *endo*/*exo* cycloaddition occurs with the same π-facial selectivity on the dipole-Cu complex (pyrrolidine adducts with 2*S*,5*S* configuration).

(16) For a previous example of aromatization of sulfonylpyrrolidines, see: López, A.; Robles-Machín, R.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 9261–9264.

TABLE 2. Scope of the Cu^I/Segphos-Catalyzed 1,3-Dipolar Cycloaddition with β-Phenylsulfonyl Enones



entry	R^1	R^2	R^3	L*	product	*exo*:*endo*[c]	yield[d] (%)	ee (%)[e]
1	*m*-MeC_6H_4	H	Me	**6**[a]	*endo*-**4b**	3:**97**	49	≥99
2	*m*-MeC_6H_4	H	Me	**7**[b]	*exo*-**4b**	**74**:26	59[f]	≥99
3	*m*-MeC_6H_4	H	*i*Pr	**7**[b]	*exo*-**5b**	**99**:1	41	≥99
4	*p*-ClC_6H_4	H	Me	**6**[a]	*endo*-**4c**	8:**92**	64	≥99
5	*p*-ClC_6H_4	H	Me	**7**[b]	*exo*-**4c**	**89**:11	52[g]	≥99
6	*p*-BrC_6H_4	H	*i*Pr	**6**[a]	*endo*-**5c**	2:**98**	54	94
7	*p*-BrC_6H_4	H	*i*Pr	**7**[b]	*exo*-**5c**	**99**:1	59	99
8	thienyl	H	Me	**7**[b]	*exo*-**4d**	**78**:22	63[f]	95
9	thienyl	H	*i*Pr	**7**[b]	*exo*-**5d**	**93**:7	47	≥99
10	*o*-$MeOC_6H_4$	H	Me	**6**[a]	*endo*-**4e**	1:**99**	68	≥99
11	*o*-$MeOC_6H_4$	H	Me	**7**[b]	*exo*-**4e**	**86**:14	46	92
12	*p*-$MeOC_6H_4$	H	*i*Pr	**7**[b]	*exo*-**5e**	**99**:1	71	≥99
13	naphtyl	H	Me	**6**[a]	*endo*-**4f**	8:**92**:	79	≥99
14	naphtyl	H	*i*Pr	**7**[b]	*exo*-**5f**	**98**:2	71	96
15	Ph	Me	Me	**6**[a]	*endo*-**4g**	2:**98**	45	87
16	Ph	Me	*i*Pr	**7**[b]	*exo*-**5g**	**98**:2	61[f]	93

[a]THF, −78 °C. [b]Et_2O, rt, see the Supporting Information for reaction times. [c]By ^1H NMR from the crude reaction mixtures. [d]In pure major isomer after column chromatography. [e]Determined by HPLC (major isomer), see the Supporting Information for details. [f]Containing 5−15% of the 3-ketosubstituted regioisomer. [g]Purified by further recrystallization

In conclusion, (*E*)-phenylsulfonylenones have been studied as novel dipolarophiles in catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. In the presence of Cu^I-Segphos catalysts a high reactivity, selectivity and structural scope were observed, the regioselectivity being controlled by the carbonyl group at the dipolarophile. Remarkably, either the *endo* or the *exo* pyrrolidine aduct can be selectively obtained with Segphos **6** or DTBM-Segphos **7**, respectively.

Experimental Section

Typical Procedure for the Preparation of *exo*-Pyrrolidines: (2*S*,3*S*,4*S*,5*S*)-Methyl 4-Acetyl-5-phenyl-3-(phenylsulfonyl)pyrrolidine-2-carboxylate (*exo*-4a). To a solution of (*R*)-DTBM-Segphos (**7**) (3.7 mg, 3.14×10^{-3} mmol) and $Cu(CH_3CN)_4PF_6$ (1.1 mg, 2.86×10^{-3} mmol) in Et_2O (0.3 mL), under nitrogen atmosphere, at room temperature, were successively added a solution of (*E*)-methyl 2-(benzylideneamino)acetate (**1a**) (20 mg, 0.11 mmol) in Et_2O (0.8 mL) and Et_3N (2.6 μL, 0.019 mmol). The resulting solution was added to a suspension of (*E*)-4-(phenylsulfonyl)but-3-en-2-one (**2**) (20 mg, 0.09 mmol) in Et_2O (0.5 mL). The mixture was stirred for 10 min and filtered through a plug of Celite with the aid of CH_2Cl_2 (5.0 mL), then the solvent was removed under reduced pressure. After silica gel flash chromatography purification (hexane−EtOAc 3:1) a 90:10 mixture of cycloadduct *exo*-**4a** and the 3-ketosubstituted regioisomer (30 mg) was obtained (≥99% ee for *exo*-**4a**). Recrystallization in *i*-PrOH afforded pure *exo*-**4a** (24 mg, 65%, white solid). Mp: 125−126 °C. $[\alpha]_D^{20}$: +41.3 (*c* 0.9, CH_2Cl_2), >99% ee. HPLC: Daicel Chiralpak, *i*-PrOH−hexane 40−60, flow rate 0.7 mL/min (λ = 210 nm). t_R: 18.56 min (2*S*,3*S*,4*S*,5*S*)-*exo*-**4a** and 46.57 min (2*R*,3*R*,4*R*,5*R*)-*exo*-**4a**. ^1H NMR (300 MHz,

$CDCl_3$): δ 7.91−7.88 (m, 2H), 7.69−7.64 (m, 1H), 7.60−7.55 (m, 2H), 7.52−7.49 (m, 2H), 7.45−7.34 (m, 3H), 4.60 (dd, J = 7.34, 5.27 Hz, 1H), 4.15−3.90 (m, 2H), 3.88 (dd, J = 8.10, 5.27 Hz, 1H), 3.63 (s, 3H), 2.95 (br s, 1H), 1.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.7, 168.6, 138.8, 134.1, 129.4, 129.3, 128.9, 128.8, 128.4, 127.4, 68.7, 67.4, 63.1, 61.8, 52.5, 30.2. MS (FAB+): 388.1 ([M + H], 100). HRMS (FAB+): calcd for $C_{20}H_{22}NO_5S$ 388.1219, found 388.1215.

Typical Procedure for the Preparation of *endo*-Pyrrolidines: (2*S*,3*R*,4*R*,5*S*)-Methyl 4-Acetyl-5-phenyl-3-(phenylsulfonyl)pyrrolidine-2-carboxylate (*endo*-4a). To a solution of (*R*)-Segphos (**6**) (2.87 mg, 4.7×10^{-3} mmol) and $Cu(CH_3CN)_4PF_6$ (1.60 mg, 4.3×10^{-3} mmol) in THF (0.5 mL), under nitrogen atmosphere, at −78 °C, were successively added a solution of (*E*)-methyl 2-(benzylideneamino)acetate (**1a**) (30 mg, 0.171 mmol) in THF (0.5 mL) and Et_3N (3.9 μL, 0.029 mmol). The resulting solution was added to a suspension of (*E*)-1-(phenylsulfonyl)but-1-en-3-one (**2**) (30 mg, 0.143 mmol) in THF (0.5 mL). The mixture was stirred for 4 h and filtered through a plug of Celite with the aid of CH_2Cl_2 (5.0 mL), then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexane−AcOEt 3:1) to afford the cycloadduct *endo*-**4a** (43 mg, 76%, white solid). Mp: 125.5−126.8 °C. $[\alpha]_D^{20}$: −62.6 (*c* 1.5, CH_2Cl_2), 94% ee. HPLC: Daicel Chiralpak AD, *i*-PrOH−hexane 40/60, flow rate 0.7 mL/min (λ = 210 nm). t_R: 17.05 min (2*S*,3*R*,4*R*,5*S*)-*endo*-**4a** and 23.24 min (2*R*,3*S*,4*S*,5*R*)-*endo*-**4a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96−7.92 (m, 2H), 7.72−7.66 (m, 1H), 7.62−7.51 (m, 2H), 7.37−7.25 (m, 5H), 4.80 (d, J = 7.56 Hz, 1H), 4.35 (dd, J = 6.05, 3.21 Hz, 1H), 4.25 (d, J = 6.05 Hz, 1H), 4.03 (dd, J = 7.56. 3.02 Hz, 1H), 3.52 (s, 3H), 2.61 (br s, 1H), 1.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.3, 170.2, 137.7, 136.0, 134.2, 129.3, 128.9, 128.8, 128.5, 126.8, 69.2, 66.4, 56.9, 61.5, 52.7, 31.3. MS (FAB+): 388.1 ([M + H], 100). HRMS (FAB+): calcd for $C_{20}H_{22}NO_5S$ 388.1219; found 388.1224.

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Supporting Information Available: Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and X-ray crystallographic data of compound *exo*-**4a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.