Synthetic Methods

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The Phenylsulfonyl Group as a Temporal Regiochemical Controller in the Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides**

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Pyrrolidine derivatives are a significant group of heterocycles which are present in an array of natural and synthetic biologically active products.[1] Furthermore, proline analogues have applications as chiral ligands and as organocatalysts in asymmetric synthesis.[2] This synthetic and biological relevance has encouraged the development of efficient routes for the stereoselective and enantioselective preparation of substituted pyrrolidines.[3] In this context, the metal-catalyzed asymmetric [3+2] cycloaddition of stabilized azomethine ylides with electron-deficient alkenes has emerged as one of the most convergent and atom-economical tools for the enantioselective synthesis of pyrrolidine and proline-type derivatives.[4,5]

The regioselectivity in the cycloaddition of stabilized N-metalated azomethine ylides (usually derived from glycine esters) with unsymmetrically substituted electron-deficient olefins is controlled by electronic effects, leading to pyrrolidine rings, which are substituted at the 2- and 4-positions, as the sole product.[6] However, this excellent regiocontrol hampers the preparation of the regioisomeric pyrrolidine rings with electron-withdrawing substituents at the 2- and 3-positions. This type of structural unit is frequently found in natural, and biologically active compounds. For instance, 2,3-dicarboxylic acid substituted pyrrolidine units are potent and selective inhibitors of glutamate receptors and glutamate transporters,[7] and they have been used in the design of new peptides and constrained peptidomimetics.[8] Taking into account that most methods currently used in the preparation of pyrrolidines with 2,3-dicarboxylic acid substitution are based on multistep approaches from α-amino acid precursors,[9] the development of more convergent synthetic strategies is highly desirable.

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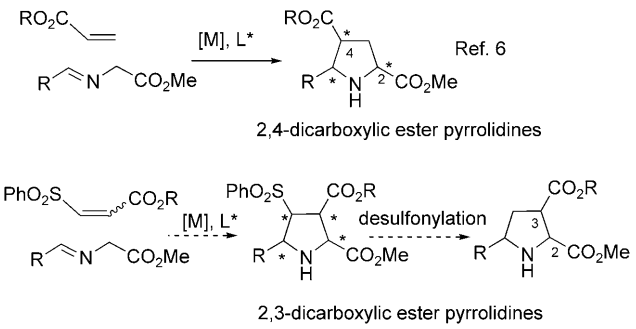
We have recently reported that unsubstituted vinyl sulfones[10] and bis(sulfonyl)ethylenes[11] are excellent dipolarophiles in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. Bearing in mind the excellent properties of the sulfonyl group both as a powerful electron-withdrawing group and as an easily removed substituent,[12] we envisaged that the regioselectivity of the catalytic asymmetric reaction of sulfonyl acrylates with azomethine ylides derived from iminoesters could be controlled by the sulfonyl moiety rather than the ester group,[13] and lead to the regioselective and stereoselective formation of 2,3-dicarboxylic acid substituted pyrrolidines (Scheme 1). Herein, we

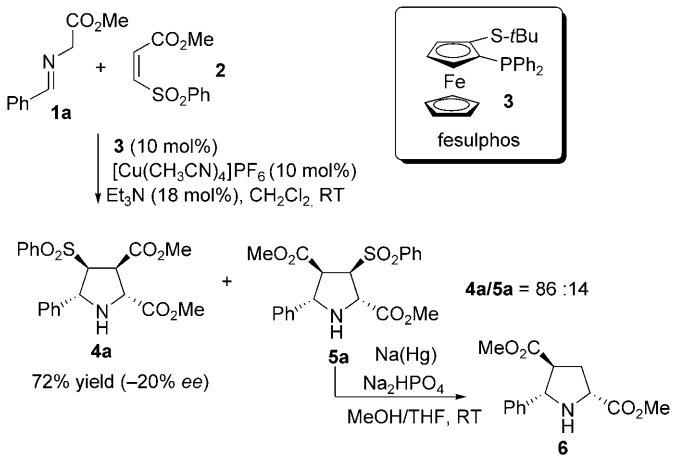


Scheme 1. Strategy for the enantioselective synthesis of 2,3-dicarboxylic ester substituted pyrrolidines.

describe the scope of this strategy and its application to the enantioselective synthesis of a variety of 2,3-dicarboxylic ester substituted pyrrolidines and derivatives.

First, we carried out the reaction of methyl (*E*)-3-phenylsulfonylpropenoate and *N*-benzylideneglycine methyl ester (**1a**) under the optimal reaction conditions previously reported by us for the copper-catalyzed 1,3-dipolar cycloaddition of azomethine ylides and bis(sulfonyl)ethylenes.[11] However, under these reaction conditions [[$Cu(CH_3CN)_4$]PF_6 (10 mol%), fesulphos ligand (**3**; 10 mol%), and Et_3N (18 mol%) in CH_2Cl_2 at room temperature] we observed the formation of a complex mixture of isomers.[14] In an attempt to improve the selectivity of the cycloaddition we next turned to using the diastereoisomeric dipolarophile, methyl (*Z*)-3-phenylsulfonylpropenoate (**2**).[15]

Gratifyingly, under the same reaction conditions this dipolarophile cleanly afforded a mixture of two isomers in an 86:14 ratio (Scheme 2). After chromatographic separation of the isomers the regiochemical and stereochemical assignment of each of the products was first determined by NMR



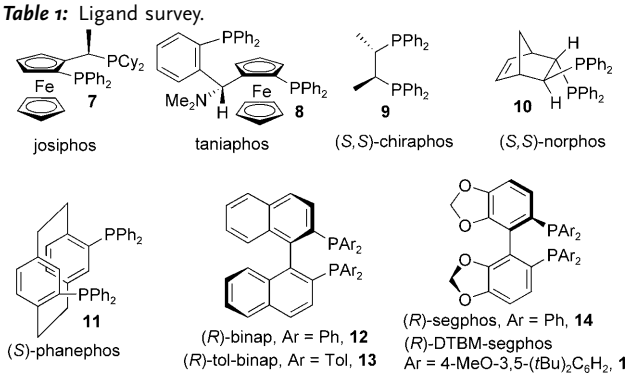
Scheme 2. Copper/fesulphos-catalyzed asymmetric cycloaddition of azomethine ylide **1a** with sulfonylacrylate **2**.

spectroscopy and later confirmed by X-ray diffraction analysis of an enantiomerically pure sample of (+)-**4a**[16] and by chemical correlation of the minor isomer (**5a**) to the known pyrrolidine 2,4-dicarboxylic ester **6**[5k] (obtained by reductive elimination of the sulfonyl group).

Two main conclusions can be drawn from this reaction: a) The structure of the major isomer, **4a**, with 2,3-dicarboxylic ester substitution, shows that the regioselectivity of the 1,3-dipolar cycloaddition is mainly controlled by the sulfonyl group. b) For both regioisomers there is perfect control of the *endo*/*exo* stereoselectivity, such that there is exclusive formation of the *exo* isomer. However, concerning the enantioselectivity of the process, the optical purity of the main product **4a** was very low (20% *ee*).[17] Therefore, to identify a more efficient chiral catalyst system we next screened a structurally varied set of commercially available chiral ligands (Table 1).

Interestingly, the regioselectivity in favor of (+)-**4a** was similar with all the ligands tested (**7**–**15**), indicating that the regiocontrol exerted by the sulfonyl group is hardly dependent on the nature of the chiral ligand. In contrast, as expected, this set of ligands provided very different enantioselectivities. Ferrocene ligands, such as josiphos (**7**) and taniaphos (**8**) (Table 1, entries 1 and 2), or the P,P-bidentate ligands chiraphos (**9**), norphos (**10**), and phanephos (**11**) (Table 1, entries 3–5) provided low enantioselectivities. The most interesting results were obtained with the P,P axially chiral ligands **12**–**15**. The low enantioselectivity achieved with (*R*)-binap (Table 1, entry 6) was improved to 35% *ee* with (*R*)-segphos (Table 1, entry 8), and to 40% *ee* with (*R*)-tol-binap (Table 1, entry 7). To our delight, the ligand DTBM-segphos (**15**), which has a bulky substituted phosphine and a minor dihedral angle,[18] produced a dramatic enhancement in the asymmetric induction, leading to (+)-**4a** in 96% *ee* (80% yield). The catalyst loading could be decreased from 10 to 5 mol% with similar reactivity and enantioselectivity (Table 1, entry 10). However, an additional reduction in the catalyst loading to 3 mol% resulted in a somewhat lower diastereoselectivity and enantioselectivity (Table 1, entry 11). The stereochemical and configurational assignment of (+)-(2*R*,3*R*,4*S*,5*R*)-**4a** was unequivocally established by X-ray diffraction analysis of a recrystallized sample of greater than 99% *ee*.[16]

Table 1: Ligand survey.



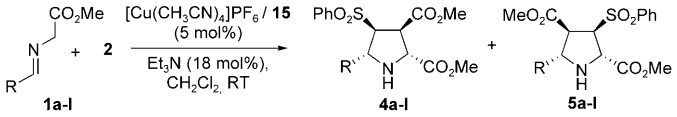
Entry[a]	Ligand	**4a**/**5a**[b]	Yield **4a** [%][c]	*ee* **4a** [%][d]
1	**7**	84:16	78	20 (–)
2	**8**	85:15	24	13 (–)
3	**9**	83:17	40	14 (+)
4	**10**	87:13	43	5 (+)
5	**11**	87:13	60	13 (+)
6	**12**	84:16	58	20 (+)
7	**13**	86:14	63	40 (+)
8	**14**	73:27	61	35 (–)
9	**15**	86:14	81	96 (+)
10[e]	**15**	86:14	80	96 (+)
11[f]	**15**	82:18	70	91 (+)

[a] Reaction conditions: Ligand (10 mol%), $[Cu(CH_3CN)_4]ClO_4$ (10 mol%), Et_3N (18 mol%), CH_2Cl_2, RT. [b] Determined by ^1H NMR analysis of the crude reaction mixtures. [c] Adduct (+)-**4a** after purification by using column chromatography. [d] Determined by HPLC methods, see the Supporting Information for details. [e] 5 mol% of $[Cu(CH_3CN)_4]PF_6$ was used. [f] 3 mol% of $[Cu(CH_3CN)_4]PF_6$ was used.

With these optimal reaction conditions in hand, we next examined the scope of the 1,3-dipolar cycloaddition with regard to the α-iminoester (Table 2). A rather homogeneous regioselectivity (from 78:22 to 90:10) and high enantioselectivity (80–99% *ee*) was observed regardless of the *ortho*, *meta*, or *para* substituents on the aromatic ring, as well as the electron-withdrawing or electron-donating nature of the substituents (Table 2, entries 1–8). In all cases the major regioisomer **4** was isolated in good yield (65–80% yield) after silica gel chromatographic purification of the crude reaction mixture. Similar results were also obtained for heteroaromatic α-iminoesters (Table 2, entries 9 and 10). α,β-Unsaturated azomethine ylides are also suitable substrates for this reaction, providing the major regioisomer **4k** with excellent enantioselectivity (Table 2, entry 11). Unfortunately, no cycloaddition was observed when an alkyl iminoester was tested under the same reaction conditions (Table 2, entry 12). From a practical point of view it is interesting to note that similar chemical yields and enantioselectivities were obtained in reactions performed on a 0.3 to 3.0 mmol scale, and that the enantiopurity of the major product **4** can be enhanced to more than 99% *ee* by simple recrystallization from isopropanol (Table 2, entries 1, 8, and 10).

To highlight the versatility of sulfonylpyrrolidines **4** in the preparation pyrrolidine-2,3-dicarboxylate derivatives, we

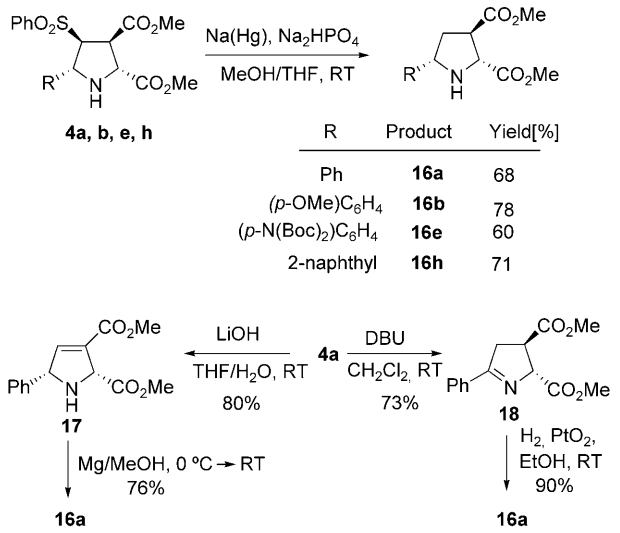
Table 2: Copper/DTBM-segphos catalyzed 1,3-dipolar cycloaddition of iminoesters **1a–l**.



Entry	R	**4**/**5**[a]	Product	Yield **4** [%][b]	*ee* **4** [%][c]
1	Ph	86:14	**4a**	80	96 (99)[d]
2	(*p*-OMe)C_6H_4	87:13	**4b**	73	96
3	(*m*-F)C_6H_4	78:22	**4c**	75	99
4	(*p*-Br)C_6H_4	82:16	**4d**	71	88
5	(*p*-N(Boc)$_2$)C_6H_4	>98:2	**4e**	75	88
6	(*p*-COMe)C_6H_4	80:20	**4f**	65	99
7	(*o*-Me)C_6H_4	90:10	**4g**	70	99
8	2-naphthyl	86:14	**4h**	70	80 (99)[d]
9	2-thiophenyl	85:15	**4i**	78	88
10	2-pyrryl	>98:2	**4j**	62	84 (99)[d]
11	CH=CH-Ph	86:14	**4k**	67	99
12	Cy	–	**4l**	–	–

[a] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [b] Product after purification by using column chromatography. [c] Determined by HPLC methods, see the Supporting Information for details. [d] The *ee* value after recrystallization.

explored some desulfonylation reactions (Scheme 3). The reductive cleavage of the sulfonyl group was performed by straightforward treatment with Na(Hg), leading to the



Scheme 3. Reductive and basic elimination of the sulfonyl group.

corresponding 2,3-dicarboxylic ester pyrrolidines (2*R*,3*R*,5*S*)-**16** (60–78% yield) and without any detectable epimerization. In contrast, the elimination of the sulfonyl of (+)-**4a** under basic conditions selectively provided either the Δ^3-pyrroline **17** (80% yield) or the Δ^1-pyrroline **18** (73% yield) depending on the base used (LiOH or DBU, respectively). The subsequent reduction of the C=C bond of **17** (Mg/MeOH) or the C=N bond of **18** (H_2, PtO_2) afforded the same 2,3-dicarboxylic ester **16a**, showing that in both cases the elimination of the sulfonyl group occurred without epimerization at the C2-position.[19]

In conclusion, a general procedure for the catalytic asymmetric 1,3-dipolar cycloaddition of (*Z*)-sulfonyl acrylates with azomethine ylides has been developed. Interestingly, the regioselectivity of the cycloaddition is mainly controlled by the sulfonyl group, providing 2,3-dicarboxylic ester substituted pyrrolidines with very high *exo* selectivity and enantioselectivity (80–99% *ee*) using Cu^I/DTBM-segphos as the catalyst system. The desulfonylation of the adducts highlights the versatility of this protocol in the enantioselective synthesis of substituted pyrrolidines (and pyrrolines) with opposite regioselectivity to that obtained using typical acrylate dipolarophiles.

Experimental Section

Typical procedure for asymmetric 1,3-dipolar cycloaddition of azomethine ylides: A solution of methyl (*E*)-*N*-benzylideneglycinate **1a** (468 mg, 2.60 mmol) in CH_2Cl_2 (5.0 mL), Et_3N (83 μL, 0.59 mmol), and a solution of methyl (*Z*)-3-(phenylsulfonyl)acrylate **2** (500 mg, 2.20 mmol) in CH_2Cl_2 (5.0 mL) were successively added to a solution of DTBM-segphos **15** (130.0 mg, 0.11 mmol) and $[Cu(CH_3CN)_4]PF_6$ (41 mg, 0.11 mmol) in CH_2Cl_2 (5.0 mL) under nitrogen atmosphere. After stirring at room temperature for 5 h, the mixture was filtered through a plug of Celite with the aid of CH_2Cl_2 (5.0 mL), and then the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromathography (hexanes/EtOAc 2:1) to afford the adduct (+)-**4a** (712 mg, 80%, white solid, m.p. = 156–157 °C) in 96% *ee*. The enantiopurity of (+)-**4a** was enhanced to more than 99% *ee* by recrystallization from isopropanol.

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[1] For reviews, see: a) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139–165; b) S. G. Pyne, A. S. Davis, N. J. Gates, K. B. Lindsay, T. Machan, M. Tang, *Synlett* **2004**, 2670–2680; c) Y. Cheng, Z.-T. Huang, M. X. Wang, *Curr. Org. Chem.* **2004**, *8*, 325–351; d) D. Enders, C. Thiebes, *Pure Appl. Chem.* **2001**, *73*, 573–578.

[2] For selected reviews on proline catalysis, see: a) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; b) B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557; c) E. N. Jacobsen, *Science* **2002**, *298*, 1904–1905; d) B. List, *Synlett* **2001**, 1675–1686.

[3] For selected recent methods of asymmetric pyrrolidine syntheses not based on dipolar cycloadditions of azomethine ylides, see: a) S. K. Jackson, A. Karadeolian, A. B. Driega, M. A. Kerr, *J. Am. Chem. Soc.* **2008**, *130*, 4196–4201; b) M. G. Unthank, B. Tavassoli, V. K. Aggarwal, *Org. Lett.* **2008**, *10*, 1433–1436; c) J. M. Schomaker, S. Bhattachriee, J. Yan, B. Borhan, *J. Am. Chem. Soc.* **2007**, *129*, 1996–2003; d) B. M. Trost, D. B. Horne, M. J. Woltering, *Chem. Eur. J.* **2006**, *12*, 6607–6620.

[4] For recent reviews, see: a) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887–2902; b) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235–3285; c) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484–4517; d) T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* **2006**, 2873–2888; e) M. Bonin, A Chauveau, . L. Micouin, *Synlett* **2006**, 2349–2363; f) S. Husinec, V. Savic, *Tetrahedron: Asymmetry* **2005**, *16*, 2047–2061; g) I. Coldham,

R. Hufton, *Chem. Rev.* **2005**, *105*, 2765 – 2809; h) C. Nájera, J. M. Sansano, *Angew. Chem.* **2005**, *117*, 6428 – 6432; *Angew. Chem. Int. Ed.* **2005**, *44*, 6272 – 6276.

[5] For recent references, see: a) C. Nájera, M. de Gracia Retamosa, J. M. Sansano, *Angew. Chem.* **2008**, *120*, 6144 – 6147; *Angew. Chem. Int. Ed.* **2008**, *47*, 6055 – 6058; b) J.-W. Shi, M.-X. Zhao, Z.-Y. Lei, M. Shi, *J. Org. Chem.* **2008**, *73*, 305 – 308; c) S.-I. Fukuzawa, H. Oki, *Org. Lett.* **2008**, *10*, 1747 – 1750; d) W. Zeng, Y.-G. Zhou, *Tetrahedron Lett.* **2007**, *48*, 4619 – 4622; e) C. Nájera, M. de Gracia Retamosa, J. M. Sansano, *Org. Lett.* **2007**, *9*, 4025 – 4028; f) W. Zeng, G.-Y. Chen, Y.-G. Zhou, Y.-X. Li, *J. Am. Chem. Soc.* **2007**, *129*, 750 – 751; g) S. Cabrera, R. Gómez Arrayás, B. Martín-Matute, F. P. Cossío, J. C. Carretero, *Tetrahedron* **2007**, *63*, 6587 – 6602; h) B. Martín-Matute, S. I. Pereira, E. Peña-Cabrera, J. Adrio, A. M. S. Silva, J. C. Carretero, *Adv. Synth. Catal.* **2007**, *349*, 1714 – 1724; i) J.-W. Shi, J. W. Shi, *Tetrahedron: Asymmetry* **2007**, *18*, 645 – 650; j) X.-X. Yan, Q. Peng, Y. Zhang, K. Zhang, W. Hong, X.-L. Hou, Y.-D. Wu, *Angew. Chem.* **2006**, *118*, 2013 – 2017; *Angew. Chem. Int. Ed.* **2006**, *45*, 1979 – 1983; k) O. Dogan, H. Koyuncu, P. Garner, A. Bulut, W. J. Youngs, M. Panzner, *Org. Lett.* **2006**, *8*, 4687 – 4690. For organocatalytic asymmetric versions of this reaction, see: l) M.-X. Xue, X.-M. Zhang, L.-Z. Gong, *Synlett* **2008**, 691 – 694; m) C. Guo, M.-X. Xue, M.-K. Zhu, L.-Z. Gong, *Angew. Chem.* **2008**, *120*, 3462 – 3465; *Angew. Chem. Int. Ed.* **2008**, *47*, 3414 – 3418; n) X.-H. Chen, W.-Q. Zhang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 5652 – 5654; o) I. Ibrahem, R. Rios, J. Vesely, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 6252 – 6257; p) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem.* **2007**, *119*, 5260 – 5262; *Angew. Chem. Int. Ed.* **2007**, *46*, 5168 – 5170; q) C. Alemparte, G. Blay, K. A. Jorgensen, *Org. Lett.* **2005**, *7*, 4569 – 4572.

[6] K. V. Gothelf in *Cycloaddition Reactions in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2002**, chap. 5. For catalytic asymmetric 1,3-dipolar cycloaddition between azomethine ylides and acrylates, see references: [5a,c,g,k,q]. For examples before 2005, see reference [4h].

[7] a) K. Shimamoto, Y. Shigeri, *Cent. Nerv. Syst. Agents Med. Chem.* **2006**, *6*, 59 – 71; b) H. Bräuner-Osborne, L. Bunch, N. Chopin, F. Couty, G. Evano, A. A. Jensen, M. Kusk, B. Nielsen, N. Rabaso, *Org. Biomol. Chem.* **2005**, *3*, 3926 – 3936; c) C. L. Willis, D. L. Dauenhauer, J. M. Humphrey, A. R. Chamberlin, A. L. Buller, D. T: Monaghan, R. J. Bridges, *Toxicol. Appl. Pharmacol.* **1997**, *144*, 44 – 55.

[8] See for instance: a) J. M. Ndungu, J. P. Cain, P. Davis, S.-W. Ma, T. W. Vanderah, J. Lai, F. Porreca, V. J. Hruby, *Tetrahedron Lett.* **2006**, *47*, 2233 – 2236; b) R. B. Perni, L. J. Farmer, K. M. Cottrell, J. J. Court, L. F. Courtney, D. D. Deininger, C. A. Gates, S. L. Harbeson, J. L. Kim, C. Lin, Y.-P. Luong, J. P. Maxwell, M. A. Murcko, J. Pitlik, B. G. Rao, W. C. Schairer, R. D. Tung, J. H. Van Drie, K. Wilson, J. A. Thomson, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1939 – 1942; c) D. Damour, F. Herman, R. Labaudinière, G. Pantel, M. Vuihorge, S. Mignani, *Tetrahedron* **1999**, *55*, 10135 – 10154.

[9] For selected examples, see: a) C. Flamant-Robin, Q. Wang, A. Chiaroni, A. N. Sasaki, *Tetrahedron* **2002**, *58*, 10475 – 10484; b) N. A. Sasaki, M. Dockner, A. Chiaroni, C. Riche, P. Potier, *J. Org. Chem.* **1997**, *62*, 765 – 770; c) I. B. Parr, S. K. Boehlein, A. B. Dribben, S. M. Shuster, N. G. Richards, *J. Med. Chem.* **1996**, *39*, 2367 – 2378; d) R. Pauly, C. Fontain, A. Chiaroni, C. Riche, P. Potier, *Tetrahedron Lett.* **1994**, *35*, 241 – 244; e) M. W. Hollanday, W. L. Lin, C. S. May, D. S. Garvey, D. G. Witte, T. R. Miller, C. A. W. Wolfram, A. M. Nadzam, *J. Med. Chem.* **1991**, *34*, 457 – 461.

[10] T. Llamas, R. Gómez Arrayás, J. C. Carretero, *Synthesis* **2007**, 950 – 956.

[11] A. López-Pérez, J. Adrio, J. C. Carretero, *J. Am. Chem. Soc.* **2008**, *130*, 10084 – 10085.

[12] a) N. S. Simpkins, *Sulfones in Organic Synthesis*, Pergamon, Oxford, **1993**. For a review on desulfonylation reactions, see: b) C. Nájera, M. Yus, *Tetrahedron* **1999**, *55*, 10547 – 10658.

[13] For regiochemical control in Diels–Alder reactions of β-sulfonylacrylates, see: A. D. Buss, G. C. Hirst, P. J. Parsons, *J. Chem. Soc. Chem. Commun.* **1987**, 1836 – 1837.

[14] The Cu/fesulphos-catalyzed reaction of glycinate **1a** with dipolarophile (*E*)-**2** provided a 38:33:29 mixture of isomers that could not be separated by chromatography.

[15] Dipolarophile (*Z*)-**2** was easily prepared in one step by addition of sodium benzenesulfinate to methyl propiolate: G. C. Hirst, P. J. Parsons, *Organic Synthesis Coll. Vol. 8*, p. 458; *Coll. Vol. 69*, pp. 169–171, 460.

[16] See the Supporting Information for details. CCDC 705120 contains the supplementary crystallographic data for (+)-**4a** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] The use of other solvents (THF, toluene, or CH_3CN) or metal salts ($[Cu(CH_3CN)_4]ClO_4$, $Zn(OTf)_2$, AgOTf) resulted in similar or even lower stereoselectivities.

[18] For a recent review on biaryl-type bisphosphine ligands, see: H. Shimizu, I. Nagasaki, T. Saito, *Tetrahedron* **2005**, *61*, 5405 – 5432.

[19] Both Δ^1 and Δ^3-pyrrolines are interesting heterocycles because of their biological relevance and their versatility as synthetic intermediates. For biological properties, see: a) S. Castellano, H. D. G. Fiji, S. S. Kinderman, M. Watanabe, P. de Leon, F. Tamanoi, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 5843 – 5845; b) A. Stapon, R. Li, C. A. Townsend, *J. Am. Chem. Soc.* **2003**, *125*, 8486 – 8493; c) Y. Lee, K.-Q. Ling, X. Lu, R. B. Silverman, E. M. Shepard, D. M. Dooley, L. M. Sayre, *J. Am. Chem. Soc.* **2002**, *124*, 12135 – 12143. For their interest as synthetic intermediates, see: d) A. L. L. Garcia, M. J. S. Carpes, A. C. B. M. de Oca, M. A. G. dos Santos, C. C. Santana, C. R. D. Correia, *J. Org. Chem.* **2005**, *70*, 1050 – 1053; e) T. J. Donohoe, H. O. Sintim, J. Hollinshead, *J. Org. Chem.* **2005**, *70*, 7297 – 7304; f) A. Goti, S. Cicchi, V. Mannucci, F. Cardona, F. Guarna, P. Merino, T. Tejero, *Org. Lett.* **2003**, *5*, 4235 – 4238; g) M. Lombardo, S. Fabbroni, C. Trombini, *J. Org. Chem.* **2001**, *66*, 1264 – 1268.

