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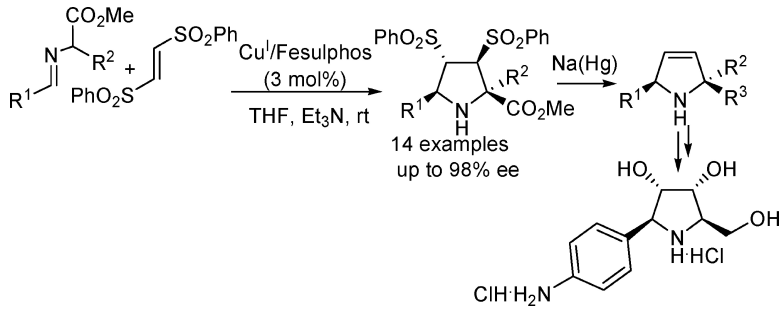

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Bis-Sulfonyl Ethylene as Masked Acetylene Equivalent in Catalytic Asymmetric [3 + 2] Cycloaddition of Azomethine Ylides

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The metal-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides derived from α-iminoesters with alkenes is a very practical and atom-economical method for the enantioselective synthesis of highly substituted pyrrolidines.[1] In recent years, an outstanding progress has been achieved in this field, with a variety of efficient protocols involving Zn,[2] Ag,[3] Cu,[4] and Ni[5] chiral complexes of bidentate chiral ligands having been developed. One of the intrinsic scope limitations of this approach is that it is only applicable to low LUMO dipolarophiles, mainly electron-deficient conjugated alkenes such as α,β-unsaturated esters, imides, nitriles, sulfones, and nitro compounds, restricting severely the substitution pattern at the pyrrolidine ring. For instance, acetylene and simple alkynes are unreactive dipolarophiles in this reaction, which hampers the catalytic asymmetric preparation of 3-pyrrolines.[6] However, this heterocyclic unsaturated ring system is a very appealing and widely used intermediate in the preparation of substituted pyrrolidines,[7] especially hydroxylated pyrrolidines which present outstanding biological activities.[8] To overcome this limitation, an indirect strategy for the catalytic asymmetric synthesis of 3-pyrrolines could be the use of an electron-deficient alkene acting as a masked acetylene equivalent.

We describe herein that commercially available *trans*-1,2-bisphenylsulfonyl ethylene can efficiently play this role by means of a highly enantioselective Cu^{I}−Fesulphos-catalyzed 1,3-dipolar cycloaddition with azomethine ylides, followed by reductive elimination of both sulfonyl groups[9] (Figure 1).

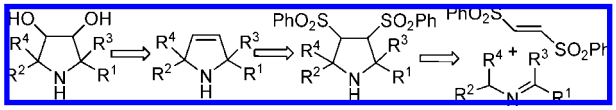
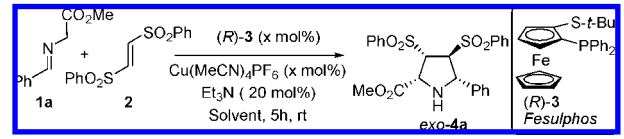


Figure 1. Strategy for the enantioselective synthesis of 3-pyrrolines and substituted pyrrolidines.

On the basis of our recent results on the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with typical electron-deficient alkenes catalyzed by Cu^{I}/Fesulphos,[4b,g] we chose this catalyst system for the study of the model reaction of *N*-benzylidenglycine methyl ester **1a** with *trans*-1,2-bisphenylsulfonyl ethylene **2**.[10] Gratifyingly, in the first experiment carried out with 10 mol % of $Cu(MeCN)_4PF_6$ and ligand Fesulphos (*R*)-**3** in the presence of Et_3N (20 mol %) as base, the disulfonylated pyrrolidine **4a** was obtained in good yield (85%), complete exoselectivity, and high enantioselectivity (Table 1, entry 1, 93% ee). Its configurational and stereochemical assignment was unequivocally established by X-ray diffraction.[11] A brief study of solvents showed a significant improvement of the asymmetric induction when the reaction was performed in THF (Table 1, entry 3, 98% ee). The catalyst loading could be reduced to 3 mol % with very similar reactivity and enantioselectivity (Table 1, entry 4, 98% ee). However, a further reduction in the catalyst loading to 1 mol % (Table 1, entry 5) resulted in a lower chemical yield and enantioselectivity.

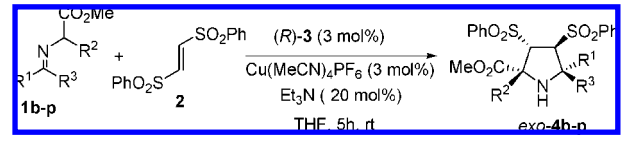
Table 1. Reaction Conditions for the Model Reaction



entry	*x*	solvent	yield (%)[a]	ee (%)[b]
1	10	CH_2Cl_2	85	93
2	10	toluene	83	96
3	10	THF	90	98
4	3	THF	90 (88)[c]	98 (94)[c]
5	1	THF	65	90

[a] Isolated yield after column chromatography. [b] By HPLC. [c] Reaction from *N*-benzylidenglycine ethyl ester.

Table 2. Scope of the Asymmetric Fesulphos−Cu-Catalyzed Cycloaddition of Azomethine Ylides with Sulfonylethylene **2**



entry	R^1	R^2	R^3	product	yield (%)[a]	ee (%)[b]
1	(*p*-OMe)C_6H_4	H	H	**4b**	79	92
2	(*m*-Me)C_6H_4	H	H	**4c**	93	94
3	(*m*-F)C_6H_4	H	H	**4d**	90	97
4	(*o*-Me)C_6H_4	H	H	**4e**	83	95
5	(*p*-*N*-(Boc)$_2$)C_6H_4	H	H	**4f**	82	85
6	2-naphtyl	H	H	**4g**	91	95
7	2-furyl	H	H	**4h**	74	96
8	CH=CH-Ph	H	H	**4i**	77	85 (99)[c]
9	Cy	H	H	**4j**	78	30
10	*t*-Bu	H	H	**4k**	65	26
11	Ph	Me	H	**4l**	81	98
12	(*p*-OMe)C_6H_4	Me	H	**4m**	90	96
13	CH=CH−Ph	Me	H	**4n**	65	97
14	Ph	H	Ph	**4o**	0	−
15	Ph	H	Me	**4p**	0	−

[a] Isolated yield after column chromatography. [b] By HPLC. [c] Enantiomeric excess after recrystallization.

With these optimal reaction conditions in hand, Table 2 shows the scope of the 1,3-dipolar cycloaddition with regard to the substitution at the azomethine ylide. Except in the case of the ketimine dipole precursors (entries 14 and 15), which proved to be unreactive, in all cases, a single diastereomer was detected and isolated (65−93% yield). All aryl- and heteroaryl-substituted glycine derivatives (R^2 = H) provided an excellent enantiocontrol regardless of the electronic nature of the substituent (85−95% ee, entries 1−7). The procedure can also be applied to α,β-unsaturated imines (entry

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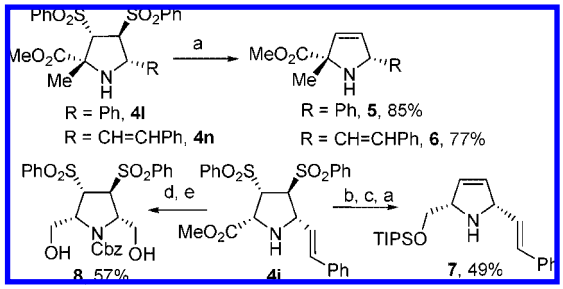
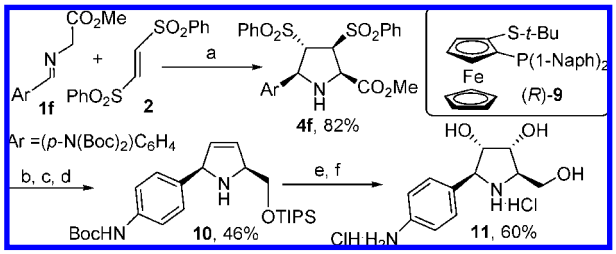
Scheme 1. Enantioselective Synthesis of 3-Pyrrolines and Hydroxymethyl Pyrrolidines[a]



[a] Conditions: (a) Na(Hg), Na_2HPO_4, MeOH/THF, rt; (b) $LiAlH_4$, THF, 0 °C; (c) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) CbzCl, K_2CO_3, CH_3CN; (e) O_3, CH_2Cl_2, then $NaBH_4$, 0 °C.

Scheme 2. Synthesis of Schramm's C-Azanucleoside[a]



[a] Conditions: (a) $Cu(MeCN)_4PF_6$ (3 mol %), (*R*)-**9** (3 mol %), Et_3N (20 mol %), CH_2Cl_2, 48 h, −78 °C; 94% ee; (b) $LiAlH_4$, THF, 0 °C; (c) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) Na(Hg), Na_2HPO_4, MeOH/THF; (e) OsO_4, TMEDA, CH_2Cl_2, −78 °C; (f) HCl/MeOH, rt.

8) and alanine base dipoles (R^2 = Me, entries 11−13) with similar enantioselectivities. In contrast, the reaction of alkyl imines was much less enantioselective (entries 9 and 10).

The straightforward application of this [3 + 2] cycloaddition methodology to the asymmetric synthesis of 3-pyrrolines and hydroxymethyl pyrrolidines is shown in Scheme 1. Direct reductive elimination of the vicinal sulfonyl groups of pyrrolidines **4l** and **4n** by treatment with Na(Hg)[12] gave rise to 3-pyrrolines **5** and **6** in 85 and 77% yields, respectively, without any observable epimerization. Similarly, the ester reduction of pyrrolidine **4i** with $LiAlH_4$, protection of the hydroxyl group as TIPS ether, and desulfonylation afforded the 3-pyrroline **7** in 49% overall yield.[13] On the other hand, ozonolysis of the Cbz derivative of **4i**, followed by reductive treatment ($NaBH_4$), afforded the bishydroxymethyl pyrrolidine **8** in 57% overall yield.

Applying these chemical transformations, Schramm's C-azanucleoside[14] (**11**), a promising trypanosomal nucleoside hydrolase inhibitor, was readily prepared in six steps[15] (Scheme 2). The Cu-catalyzed 1,3-dipolar cycloaddition between the azomethine ylide precursor **1f** and dipolarophile **2** in the presence of (*R*)-**3** afforded the pyrrolidine **4f** in 82% yield and 85% ee (Table 1, entry 5). A similar yield but higher enantioselectivity (94% ee) was achieved by performing the reaction at −78 °C in the presence of the bulkier Fesulphos ligand (*R*)-**9**. Further reduction of the ester moiety ($LiAlH_4$), protection of the alcohol as TIPS, and reductive elimination of the sulfonyl groups afforded the 3-pyrroline **10** (46% overall yield). Finally, the completely stereoselective dihydroxylation of **10** with OsO_4/TMEDA at −78 °C, followed by acid cleavage of the protecting groups, provided **11** in 60% yield.

In summary, we have described a practical approach to the catalytic asymmetric synthesis of 3-pyrrolines. This method is based on the highly enantioselective Fesulphos−Cu-mediated 1,3-dipolar cycloaddition of azomethine ylides with *trans*-1,2-bisphenylsulfonyl ethylene, followed by reductive desulfonylation. The application of this protocol to the enantioselective synthesis of a biologically active trihydroxylated pyrrolidine is also described.

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Supporting Information Available: Experimental procedures, characterization data of new compounds, copies of NMR spectra, and X-ray crystallography data of *exo*-**4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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