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Catalytic Asymmetric Vinylogous Mannich Reaction of *N*-(2-Thienyl)sulfonylimines

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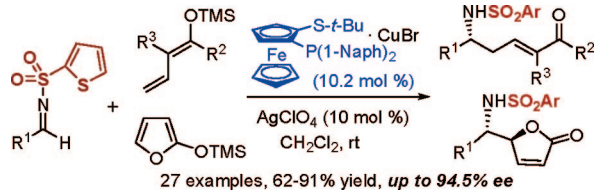
ABSTRACT



Both cyclic and acyclic silyl dienol ethers participate efficiently in the asymmetric vinylogous Mannich reaction of *N*-2-thienylsulfonylimines catalyzed by copper(I) complexes of Fesulphos ligands. This procedure displays wide imine and nucleophile versatility, high enantiocontrol, and complete γ-regioselectivity in most cases examined. The mild sulfonamide deprotection allows the resulting products to be readily transformed into optically active δ-lactams or 5-hydroxy-2-piperidone derivatives.

The γ-addition of dienolate equivalents to imines, known as vinylogous Mannich-type reaction (VMR), provides rapid access to δ-amino-α,β-unsaturated carbonyl derivatives, a valuable class of intermediates for the synthesis of alkaloids and other nitrogen-containing compounds.[1] However, in contrast to the much more developed vinylogous aldol reaction,[2] the catalytic asymmetric variant of this transformation has been little explored. The first report by Martin et al.[3] on VMR of 2-silyloxy furans was later improved by Hoveyda, Snapper, and Carswell[4] using chiral silver-based catalysts and by Akiyama et al.[5] with a binol-based phosphoric acid catalyst. The direct reaction of γ-butenolides with imines has been achieved by Shibasaki et al.[6] combining Brönsted acid and chiral metal catalysis. The groups of Chen[7] and Jorgensen[8] have reported asymmetric organocatalytic protocols for the γ-selective addition of α,α-dicyanoolefins to imines. Aside from these elegant approaches leading to optically active butenolides and dicyanoolefins, there is plenty of room for the development of asymmetric protocols showing high nucleophile versatility, especially with more general and truly vinylogous enolate equivalents such as acyclic silyl dienol ethers. Very recently, Schneider's group[9] has described the first VMR of an acyclic, ester derived, silyl dienolate using a binol-based phosphoric acid catalyst, which occurs with complete γ-site regiocontrol and high asymmetric

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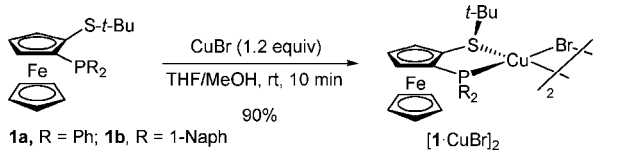
induction (80−90% ee). This work prompted us to disclose our own results in this area.

Herein, we report an efficient metal-catalyzed asymmetric VMR procedure compatible with both cyclic and acyclic silyl dienol ethers that relies on the use of *N*-(2-thienyl)sulfonylimines as substrates and Cu^{I}−Fesulphos complexes as catalysts. Wide imine and nucleophile versatility, high enantiocontrol, and complete γ-site selectivity are key features of this method.

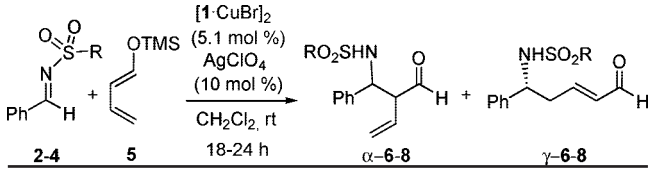
We have recently reported that the readily available Cu^{I} complex of the bulky Fesulphos ligand[10] **1b** ([**1b**·CuBr]$_2$, Scheme 1) is a very efficient catalyst for Mannich[11] and formal

Scheme 1. Synthesis of the Copper(I) Complexes [**1**·CuBr]$_2$



aza Diels−Alder reactions[12] of *N*-sulfonylimines. On the other hand, *N*-(2-thienyl)sulfonylimines were previously found by others[13] and us[11] to provide enhanced reactivity and selectivity toward Mannich-type reactions compared to typically substituted sulfonylimines such as *N*-tosylimines. Both the superiority of the *N*-(2-thienyl)sulfonyl group and the higher performance of phosphine **1b** over the parent ligand **1a** was confirmed in the model reaction of the *N*-sulfonylimines **2**−**4** with the commercially available silyloxy-1,3-butadiene **5** under our optimized conditions[11] [combination of [**1**·CuBr]$_2$ (5.1 mol %) and $AgClO_4$ (10 mol %) in CH_2Cl_2 at rt]. As depicted in Table 1, the

Table 1. Cu^{I}−Fesulphos-Catalyzed Asymmetric VMR of *N*-Sulfonylimines **2**−**4** with Silyl Dienol Ether **5**



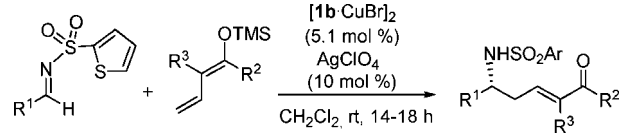
entry	R (imine)	ligand	α-:γ- [a]	product	yield[b] (%)	ee[c] (%)
1	*p*-Tol (**2**)	**1a**	34[d]:66	**6**	37	30
2	*p*-Tol (**2**)	**1b**	25[d]:75	**6**	44	42
3	2-thienyl (**3**)	**1a**	<2:>98	**7**	65	78
4	2-thienyl (**3**)	**1b**	<2:>98	**7**	85	94
5	2-pyridyl (**4**)	**1a** or **1b**	NR	**8**		

[a] Determined by NMR from the crude reaction mixture. [b] Isolated yield of the γ-isomer after chromatography. [c] Of the γ-isomer, by chiral HPLC. [d] As a mixture of diastereomers.

2-thienylsulfonyl group was essential for achieving high reactivity and δ-regioselectivity (entries 3 and 4), while the copper(I) complex of the bulky ligand **1b** was superior to **1a** in terms of enantiocontrol (entry 4). Thus, the combined choice of substrate **3** and ligand **1b** led to the corresponding vinylogous Mannich adduct **7** with complete γ-selectivity in 85% isolated yield and 94% ee. In contrast, no reaction was observed in the case of the 2-pyridylsulfonylimine **4**[14] (entry 5).

Complete γ-addition selectivity and good yields were also observed in the reaction of the silyl dienolate **5** with a survey of *N*-(2-thienyl)sulfonylimines (**9**−**16**, entries 1−8 in Table 2). In all cases, the corresponding α,β-unsaturated δ-(2-

Table 2. Catalytic Asymmetric VMR of Acyclic Silyl Dienol Ethers[a]



entry	R[1] (imine)	R[2]	R[3]	diene	product	yield[b] (%)	ee[c] (%)
1	*m*-ClC$_6$H$_4$ (**9**)	H	H	**5**	**17**	84	91
2	*p*-OMeC$_6$H$_4$ (**10**)	H	H	**5**	**18**	62	94
3	*o*-MeC$_6$H$_4$ (**11**)	H	H	**5**	**19**	68	93
4	1-Naph (**12**)	H	H	**5**	**20**	81	89
5	2-Naph (**13**)	H	H	**5**	**21**	66	92
6	PhCH=CH (**14**)	H	H	**5**	**22**	83	90 (99)[d]
7	Cy (**15**)	H	H	**5**	**23**	83	65
8	*i*-Pr (**16**)	H	H	**5**	**24**	72	66 (99)[d]
9	Ph (**3**)	OMe	H	**25**	**27**	72	83
10	*p*-OMeC$_6$H$_4$ (**10**)	OMe	H	**25**	**28**	62[e]	95
11	1-Naph (**12**)	OMe	H	**25**	**29**	70	91
12	2-Naph (**13**)	OMe	H	**25**	**30**	74	78 (95)[d]
13	PhCH=CH (**14**)	OMe	H	**25**	**31**	83	80 (99)[d]
14	Cy (**15**)	OMe	H	**25**	**32**	84	75
15	2-thienyl (**26**)	OMe	H	**25**	**33**	76	66
16	Ph (**3**)	O*i*-Pr	Me	**34**	**35**	91	71
17	Ph (**3**)	OMe	Me	**37**	**38**	75	80
18	2-Naph (**13**)	OMe	Me	**37**	**39**	85	77
19	1-Naph (**12**)	OMe	Me	**37**	**40**	87	80
20	*p*-CF$_3$C$_6$H$_4$ (**36**)	OMe	Me	**37**	**41**	86	75
21	Cy (**15**)	OMe	Me	**37**	**42**	88	82

[a] 2−4 equiv of dienol ether was used. [b] After chromatographic purification. [c] Determined by chiral HPLC. [d] After a single recrystallization [e] 14% of the α-addition product was also obtained (see the Supporting Information).

thienyl)sulfonylamino aldehyde (**17**−**24**) was the only regioisomer detected by NMR in the reaction mixture. High enantiocontrol (89−94% ee) was consistently achieved with aromatic imines of varied electronic and steric nature (entries 1−5). Notably, α,β-unsaturated imines (entry 6), yet unexplored in VMR, and aliphatic imines (entries 7 and 8), which have been seldom used in VMR,[5−7] did also participate in the VMR quite efficiently, although the enantioselectivity was significantly lower in the case of the aliphatic imines.

Other silyl dienol ethers with additional substituents at C-1 (R^2) or C-2 (R^3) of the 1,3-diene moiety proved also to be suitable nucleophiles. For instance, the more electronically

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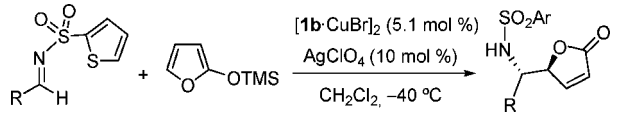
biased methyl ester-derived silyl enol ether **25**[15] underwent smooth VMR with a variety of aromatic and aliphatic imines to afford with complete γ-selectivity the corresponding α,β-unsaturated δ-amino esters (**27**−**33**) in good yield (72−84%) and high enantioselectivity (75−95% ee, Table 2, entries 9−15). The only exceptions to this general trend were the electron-rich imine **10**, leading to a small amount of the α-addition product (entry 10), and the decreased asymmetric induction observed in the case of the heteroaryl imine **26** (R^1 = 2-thienyl, 66% ee, entry 15). In contrast, the silyl dienolate **34**, derived from a more sterically encumbered ester, provided a lower asymmetric induction than the parent methyl ester (compare entries 9 and 16). The presence of an additional substituent at C-2 (diene **37**)[16] led to similar results in terms of γ-selectivity and chemical yields, although with slightly lower enantiocontrol (77−82% ee, entries 17−21). Among the reactions performed with diene **37**, the aliphatic imine **15** provided the highest asymmetric induction (82% ee, entry 21). Most of the sulfonamide products are crystalline solids, and its enantiopurity can be significantly enhanced by a single recrystallization (from 66−90% ee to 95−99% ee, entries 6, 8, 12, and 13).[17]

To further extend the scope of this protocol, a cyclic diene, the 2-trimethylsilyloxyfuran, was also examined. As shown in Table 3, the higher reactivity of this nucleophile allowed the reaction to be performed at −40 °C, giving the corresponding chiral aminoalkyl γ-substituted γ-butenolides in excellent yields and high diastereocontrol (from 81:19 to 93:7). The major isomer was isolated in 79−87% yield and high enantiocontrol (80−94.5% ee) after chromatography. The reaction of the α,β-unsaturated imine **14** provided the product **48**, with an additional double bond susceptible of further functionalization, with 94.5% ee (entry 5). The enantiopurity of **44** and **48** was raised to >99% ee upon single recrystallization.[17]

Table 3. Catalytic Asymmetric VMR of 2-Trimethylsilyloxyfuran

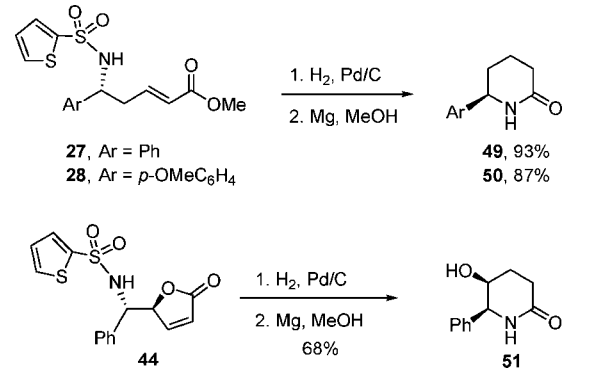


entry	R (imine)	product	dr[a]	yield[b] (%)	ee[c] (%)
1	Ph (**3**)	**44**	93:7	85	88 (99)[c]
2	*p*-$OMeC_6H_4$ (**10**)	**45**	81:19	79	94
3	*p*-ClC_6H_4 (**43**)	**46**	90:10	87	90
4	2-Naph (**13**)	**47**	93:7	84	89
5	PhCH=CH (**14**)	**48**	91:9	87	94.5 (>99)[c]

[a] Determined by NMR from the crude reaction mixture. [b] Of the major diastereomer after chromatography. [c] Of the major diastereomer, determined by chiral HPLC. [d] After a single recrystallization.

A synthetically relevant advantage of using the 2-thienylsulfonyl group is the facile deprotection of the sulfonamide products by simple treatment with Mg in MeOH. For example, adducts **27** and **28** were converted to the δ-lactams **49**[18] and **50**,[19] respectively, by hydrogenation of the double bond and subsequent deprotection (Scheme 2). In a similar fashion, γ-butenolide **44** was transformed into the 5-hydroxy-2-piperidone (+)-**51**[20] in 68% yield through the hydrogenation/deprotection sequence. The preparation of the known piperidines (+)-**49** and (+)-**51** allowed us to establish the absolute configuration of the starting adducts **27** and **44** and, by analogy, that of the rest of VMR products.

Scheme 2. Amine Deprotection and Chemical Correlations



In summary, we have developed a catalytic asymmetric VMR procedure applicable to both acyclic and cyclic silyl dienol ethers. The high enantiocontrol and nearly complete γ-selectivity displayed by the combination of Cu^I−Fesulphos catalyst and *N*-(2-thienyl)sulfonylimines provides a ready access to optically active α,β-unsaturated δ-amino carbonyl derivatives in good yields.

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Supporting Information Available: Experimental procedures and characterization data of new compounds; copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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