Tuning Electronic and Steric Effects: Highly Enantioselective [4+1] Pyrroline Annulation of Sulfur Ylides with α,β-Unsaturated Imines**

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The [4+1] annulation of 1,3-conjugated systems with twoelectron, one-carbon fragments presents a particularly attractive but underexploited strategy to construct naturally occurring and biologically active carbo- and heterocyclopentenes, especially asymmetrically.^[1] In this context, besides carbon monoxide,^[2] isocyanides,^[3] nucleophilic carbenes,^[4] and diazo reagents^[5] used as typical one-carbon units, ylides^[6] have also been gradually developed as functional units and reacted with various electron-deficient conjugated components to provide such scaffolds.^[7] For example, Danheiser and co-workers have shown that sulfur ylides can be used in the [4+1] annulation of yield (trialkylsilyl)vinylketenes to cyclopentenones (Scheme 1, top).^[7a] Recently, by employing a camphor-



Scheme 1. Previous [4+1] annulations of sulfur ylides largely relied upon steric hindrance. Dashed arrows indicate the [2+1] pathway.

derived sulfur ylide, Tang's group developed a highly efficient method to synthesize enantiopure dihydrofuran derivatives from substituted methene-2,4-pentanediones (Scheme 1, bottom).^[7e] However, as analyzed by Sun and Tang,^[6c] the success of these [4+1] routes over competitive [2+1] routes is largely attributed to the steric hindrance at the reactive centers. Herein, independent of this effect, we describe an unprecedented [4+1] annulation of sulfur ylides with α , β -unsaturated imines, which allows efficient construction of pyrroline

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moieties with high chemo- and stereoselectivity (83-99%) yields, up to > 95:5 d.r., and 98% *ee*).

In spite of the remarkable significance of pyrrolines and their derivatives in enantioselective catalysis,^[8] natural products, and pharmaceuticals,^[9] the alternative [4+1] annulation of azadienes has been little used for their synthesis,^[10] compared with the popular [3+2] approach.^[11] To our knowledge, almost all previous endeavors with unstable or semi-stabilized ylides have suffered from the kinetic preference to form aziridines or cyclopropanes (Scheme 2 a).^[12,13] Therefore



Scheme 2. a) Previously reported methods for cyclopropanes and aziridines. b) Realizing the [4+1] pyrroline annulation of sulfur ylides and α , β -unsaturated imines by tuning electronic effects. PMP=*para*-methoxyphenyl, Ts=4-toluenesulfonyl.

the [4+1] annulation between sulfur ylides and α , β -unsaturated imines to synthesize pyrrolines remains a stimulating challenge.

On the basis of our previous study on the chemistry of stable sulfur ylides,^[14] we speculated that the electronic effect could be another potential factor by which to alter the kinetic preference. If we could extend the lifetime of the key zwitterionic intermediates, generated from the Michael addition of sulfur ylides to α , β -unsaturated imines, this would allow formation of the thermodynamic products chemoselectively. Indeed, treatment of phenylacyl sulfur ylide **1** with ester-bearing Ts-protected α , β -unsaturated imine^[15] in CH₂Cl₂ at room temperature (Scheme 2b) produced the desired pyrroline-2-carboxylate in 83% yield within 0.5 hours. In contrast, no reaction occurred when the PMP-protected imine was used. According to these results, we can conclude that the introduction of electron-withdraw-



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ing groups such as tosyl and ester groups is helpful in 1) stabilizing the anionic enamine intermediates and therefore leading to chemoselective pyrroline formation by attack of the nitrogen atom, and 2) it also helps to promote the Michael addition of ylides to unsaturated imines (Ts vs. PMP).

Next, we focused our attention on the asymmetric version of this novel [4+1] annulation. Atropisomeric sulfide 5 was chosen as the element of stereocontrol because of its ease of preparation from cheap and readily available starting materials (both (S)- and (R)-binol).^[16] Treating sulfur ylide 1a with imine 2 (PG = Ts) at -80 °C for 48 hours and subsequently warming to room temperature provided the desired enantioenriched [4+1] cycloadduct with an encouraging result of 93% yield and 81% ee (Table 1, entry 1). Optimization of the reaction conditions led to improved enantioselectivity. Enhancing the size of the ester (Table 1, entry 1 vs. 2), electron deficiency of the protecting group (Table 1, entry 1 vs. 3), solvent polarity (Table 1, entries 4-7), or concentration (Table 1, entry 7 vs. 8) offered no advantage. However, we found that increasing the steric bulk of the sulfonyl group substantially improved the enantioselectivity (Table 1, entries 1 and 4 vs. 9). Owing to the greater repulsive ability of the TIPBS group, a satisfactory result was finally achieved with 95% yield, a d.r. value greater than 95:5, and 98% ee under optimal reaction conditions (Table 1, entry 9).^[17]

Experiments that probed the generality of this asymmetric [4+1] annulation were performed. As summarized in Table 2, the reaction displays a broad scope for sulfur ylides and excellent levels of chemo- and stereoselectivity are achieved. Sulfur ylides having electron-rich (Table 2, entries 2 and 3), electron-neutral (Table 2, entry 1), and electrondeficient substitutents (Table 2, entries 4–6) on the aryl rings all perform well, furnishing products with 88–98% yields, d.r. values greater than 95:5, and 95–98% *ee.* Sub-

 $\textit{Table 1:}\ Optimization of reaction conditions for asymmetric [4+1] annulation. <math display="inline">^{[a]}$

(*R *R	COP =0	^h ⁺ _{Ph} ∕∕	$\underbrace{\overset{\mathbf{N}^{\mathcal{O}^{\mathcal{O}^{\mathcal{O}}}}}_{CO_2R'}}_{CO_2R'} \underbrace{\frac{\text{solvent}}{-80 ^\circ\text{C} \rightarrow \text{RT}}}$	Phoc-N	CO ₂ R'
Entry	1a R'	PG	2 Solvent	3 Yield [%] ^[b]	ee [%] ^[c]
<u>,</u> 1	Me	Ts	toluene/CH ₂ Cl ₂ (4:1)	93	81
2	iPr	Ts	toluene/CH ₂ Cl ₂ (4:1)	70	81
3	Me	Ns	toluene/CH ₂ Cl ₂ (4:1)	82	83
4	Me	TMBS	toluene/CH ₂ Cl ₂ (4:1)	88	85
5	Me	TMBS	toluene	86	86
6	Me	TMBS	CH_2Cl_2	87	33
7	Me	TMBS	toluene/CH ₂ Cl ₂ (9:1)	95	87
8 ^[d]	Me	TMBS	toluene/CH ₂ Cl ₂ (9:1)	85	82
9 ^[e]	Me	TIPBS	toluene/CH ₂ Cl ₂ (9:1)	95	98

[a] Conditions: **1a** (0.25 mmol), **2** (0.20 mmol), and solvent (20 mL), 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 4 mL solvent. [e] Ylide **1a** was reduced to 1.1 equiv of imine **2** and d.r. >95:5, determined by ¹H NMR methods. EWG = electron-withdrawing group, Ns = 4-nitrobenzenesulfonyl, TMBS = 2,4,6-triinethylbenzenesulfonyl, TIPBS = 2,4,6-triisopropylbenzenesulfonyl.

Table 2: Investigating the scope of sulfur ylides in asymmetric [4+1] annulation.^[a]

$= \underbrace{\stackrel{\text{COR}^1}{=}}^{\text{COR}^1} + \underbrace{\stackrel{\text{N}^2}{}}_{\text{Ph}} \underbrace{\stackrel{\text{N}^2}{}}_{\text{2}}$	TIPBS t CO ₂ Me	oluene/CH ₂ Cl ₂ (9:1), 0.01 M –80 °C → RT	Ph, R ¹ OC N TIF 3	CO ₂ Me
1 , R ¹	3	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1 a , Ph	3 a ^[e]	95	> 95 : 5	98
1 b , <i>p</i> -МеОС ₆ Н ₄	3 b	88	>95:5	97
1c, <i>p</i> -MeC ₆ H ₄	3 c	98	>95:5	96
1 d , <i>p</i> -FC ₆ H ₄	3 d	90	>95:5	98
1e, <i>p</i> -ClC ₆ H ₄	3 e	95	> 95 : 5	95
1 f , <i>p</i> -BrC ₆ H ₄	3 f	93	>95:5	97
1g , <i>o</i> -BrC ₆ H ₄	3 g	85	>95:5	97
1 h , <i>m</i> -BrC ₆ H ₄	3 h	91	> 95 : 5	90
1 i , thiophen-2-yl	3 i	96	> 95 : 5	98
1j, Ph-CH≕CH	3 j	99	>95:5	82
1 k , PhCH ₂ CH ₂	3 k	83	>95:5	88
	$\begin{array}{c} \text{COR}^{1} + & \text{Ph} \\ \hline 1 & 2i \\ \hline 1, R^{1} \\ \hline 1a, Ph \\ 1b, p-MeOC_{6}H_{4} \\ 1c, p-MeC_{6}H_{4} \\ 1d, p-FC_{6}H_{4} \\ 1e, p-CIC_{6}H_{4} \\ 1f, p-BrC_{6}H_{4} \\ 1g, o-BrC_{6}H_{4} \\ 1g, o-BrC_{6}H_{4} \\ 1h, m-BrC_{6}H_{4} \\ 1i, thiophen-2-yl \\ 1j, Ph-CH=CH \\ 1k, PhCH_{2}CH_{2} \end{array}$	COR ¹ + Ph CO ₂ Me $\frac{1}{2a}$ 1 2a 1, R ¹ 3 1a, Ph 3a ^[e] 1b, p-MeOC ₆ H ₄ 3c 1c, p-MeC ₆ H ₄ 3d 1e, p-ClC ₆ H ₄ 3d 1e, p-ClC ₆ H ₄ 3d 1e, p-ClC ₆ H ₄ 3f 1g, o-BrC ₆ H ₄ 3f 1g, o-BrC ₆ H ₄ 3f 1g, o-BrC ₆ H ₄ 3f 1g, p-BrC ₆ H ₄ 3g 1g, p-BrC ₆ H ₆ 3g 1g, p-BrC ₆ 3g	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{array}{c c} COR^{1} + & & \\ Ph & & \\ Ph & & \\ CO_{2}Me \end{array} \begin{array}{c} toluene/CH_{2}Cl_{2} \\ (9:1), 0.01 \text{ M} \\ \hline 80 \ ^{\circ}\text{C} \rightarrow \text{RT} \end{array} \begin{array}{c} \text{R}^{1}\text{OC} & & \\ \hline \text{N} \\ \text{TIF} \\ \hline 33 \end{array}$ $\begin{array}{c} 1 & 2a & & \\ \hline 33 \end{array}$ $\begin{array}{c} 1, \text{R}^{1} & & \\ 1 & 2a & & \\ \hline 33 \end{array} \begin{array}{c} \text{Yield} [\%]^{[b]} & d.r.^{[c]} \\ \hline 1a, \text{Ph} & 3a^{[e]} & 95 & >95:5 \\ 1b, p-\text{MeOC}_{6}H_{4} & 3b & 88 & >95:5 \\ 1c, p-\text{MeC}_{6}H_{4} & 3c & 98 & >95:5 \\ 1d, p-\text{FC}_{6}H_{4} & 3d & 90 & >95:5 \\ 1d, p-\text{FC}_{6}H_{4} & 3f & 93 & >95:5 \\ 1f, p-\text{BrC}_{6}H_{4} & 3g & 85 & >95:5 \\ 1g, o-\text{BrC}_{6}H_{4} & 3g & 85 & >95:5 \\ 1h, m-\text{BrC}_{6}H_{4} & 3h & 91 & >95:5 \\ 1i, thiophen-2-yl & 3i & 96 & >95:5 \\ 1j, \text{Ph-CH=CH} & 3j & 99 & >95:5 \\ 1k, \text{PhC}_{2}\text{CH}_{2} & 3k & 83 & >95:5 \end{array}$

[a] Conditions: 1 (0.22 mmol), 2 (0.20 mmol), and toluene/CH₂Cl₂ (9:1, 20 mL), 48 h. [b] Yield of isolated product. [c] Determined by ¹H NMR methods. [d] Determined by HPLC analysis using a chiral stationary phase. [e] The absolute configuration of product **3a** was established by X-ray analysis.

stituents at the *ortho*, *meta*, and *para* positions on the aryl rings are tolerated (Table 2, entries 6–8). In the case of the *meta*-bromo-substituted ylide **1h**, the enantiomeric excess was at a good level although slightly decreased (Table 2, entry 8). Notably, the feasibility of this reaction could also be realized effectively for other stable sulfur ylides, such as heteroaryl- (Table 2, entry 9), alkenyl- (Table 2, entry 10), and alkylacyl-substituted (Table 2, entry 11) substrates.

Additionally, a series of ester-bearing unsaturated imines proved to be suitable for this reaction as highlighted in Table 3. The electronic nature of aromatic substrates (Table 3, entries 1–6) has little effect on the yield and generally,

Table 3: Investigating the scope of unsaturated imines in asymmetric [4+1] annulation.^[a]

(*R *R	$= \underbrace{\overset{\text{COPh}}{\overset{+}}}_{\text{R}^2} \underbrace{\overset{\text{N}}{}}_{\text{R}^2}$,∽TIPBS `CO2R ³ 2	toluene/CH ₂ Cl ₂ (9:1), 0.01 M -80 °C \rightarrow RT	PhOC N ¹	CO ₂ R ³ PBS
Entry	2 , R ²	3	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	2a , Ph	3 a	95	>95:5	98
2	2b , <i>p</i> -MeOC ₆ H₄	31	91	> 95:5	97
3	2c , <i>p</i> -MeC ₆ H ₄	3 m	92	> 95 : 5	98
4	2d , <i>p</i> -FC ₆ H ₄	3 n	99	> 95 : 5	95
5	2e , <i>p</i> -ClC ₆ H ₄	3 o	96	> 95 : 5	95
6	2 f , <i>p</i> -BrC ₆ H₄	3 p	91	>95:5	94
7	2g , <i>o</i> -FC ₆ H ₄	3 q	94	> 95 : 5	86
8	2h , <i>m</i> -BrC ₆ H₄	3 r	89	> 95 : 5	90
9	2i , furan-2-yl	3 s	95	> 95:5	95
10	2j , Ph-CH=CH	3 t	96	> 95 : 5	93
11 ^[e]	2 a , Ph	3 a	93	> 95:5	96

[a] Conditions: **1a** (0.22 mmol), **2** (0.20 mmol), and toluene/CH₂Cl₂ (9:1, 20 mL), 48 h; entries 1–8 and entry 11: $R^3 = Me$; entries 9 and 10: $R^3 = Et$. [b] Yield of isolated product. [c] Determined by ¹H NMR methods. [d] Determined by chiral HPLC analysis. [e] Gram scale: **1a** (2.5 mmol, 1.08 g), **2a** (2.5 mmol, 1.14 g).

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excellent stereoselectivity was achieved (91–99% yields, > 95:5 d.r., 94–98% *ee*). In exploring another dimension by varying the position of the substitution on the aryls rings appended to the imines (Table 3, entries 7 and 8), good results were still achieved (89% yield, >95:5 d.r., \geq 86% *ee*). Furthermore, the heteroaryl- and alkenyl-substituted unsaturated imines can also be employed in this annulation, with excellent yields and high levels of stereoselectivity being achieved (Table 3, entries 9 and 10).^[18] Importantly, the reaction can be carried out on the gram scale without obvious loss in the reaction efficiency (Table 3, entry 11), and with essentially quantitatively recovered sulfide **5** (95% yield).

In addition, the resultant [4+1] cycloadducts could be applied to the synthesis of important building blocks. For instance, two-step deprotection/reduction operations for optically pure **3a** delivered the 4,5-substituted proline ester **6** as a single isomer [Eq. (1); MSA = methanesulfonic acid, TFA = trifluoroacetic acid]. Moreover, the functional group introduced together with the one-carbon unit could be effectively transformed into other moieties. As illustrated in Equation (2), the carbonyl group in **3a** was reduced to a hydroxy group through the acid-assisted Pd-catalyzed hydrogenation with excellent yield and significant diastereoselectivity (>99% yield and 92:8 d.r.).



To better understand the stereoinduction in this asymmetric [4+1] annulation, we additionally collected and analyzed data on the conformations of these ylides in solution. In view of the open character (Scheme 3, top: arvlacyl group away from atropisomeric backbone) and near coplanarity ($\theta = 177.3^{\circ}$ or 167.4°) in the single crystal of 1e',^[19] we supposed a comformer of ylide 1e as shown in Scheme 3 (top, right). The NOE effects and the presence of an intramolecular hydrogen bond for the ylide 1e in solution strongly supports the above proposal. On the basis of this fundamental assumption, we rationalized the important effects responsible for the stereochemical course as follows (Scheme 3, bottom): 1) the unsaturated imines attack the exposed Si face of chiral ylides to avoid the steric repulsion between the TIPBS group in the imine and the naphthalenyl ring in the chiral backbone; 2) this process possibly adopted the cisoid/quasi [4+2]-addition conformation because of favorable Coulombic interactions between the negatively charged N atoms of the unsaturated imines and positively charged S atoms of the stable ylides.^[20] The configuration of cycloadduct 3a was confirmed by X-ray diffraction analysis.

In summary, we have successfully developed a novel [4+1] annulation of stable sulfur ylides with ester-bearing unsaturated imines by manipulating the electronic effects. The low cost, ready availability, and recoverability of the binol-derived



Scheme 3. Rationalizing the origin of stereoselectivity based on conformational analysis of chiral ylides. ClO_4^- counterion omitted for clarity in X-ray crystallographic structure. Thermal ellipsoids are drawn at 30% probability. $\theta =$ dihedral angle ($\theta = C_{37}$ - C_{38} - S_2 - C_{50} , θ was different in dimer).

sulfide lead to an asymmetric process that conveniently provides chiral pyrroline-2-carboxylates with good to excellent results (83–99% yields, up to $98\% \ ee$, >95:5 d.r.). Although detailed investigations of the reaction mechanism and stereochemistry with Gaussian calculations are ongoing, we have rationalized the origin of stereoinduction based on a conformational analysis of chiral ylides; the high stereoselectivity is attributed to steric effects and possible Coulombic interactions. What is more promising is that this work could open up new opportunities for selectively constructing other carbon- and heterocycles beyond traditional small rings.

Experimental Section

Representative procedure: Unsaturated imine 2a (0.2 mmol) and toluene/CH₂Cl₂ (9:1, 20 mL) were added to a 50 mL flask equipped with a magnetic stir bar. After the solution had been stirred at -80 °C for 0.5 h, chiral sulfur vlide 1a (0.22 mmol) was introduced and the mixture stirred for 48 h at the same temperature. The reaction mixture was then slowly warmed to room temperature. Upon completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel [silica: 200-300; eluant: petroleum ether/ethyl acetate $(5:1\rightarrow3:1)$] to provide pure product **3a** in 95% yield. Diastereomeric ratio: >95:5 as determined by ¹H NMR analysis of the reaction mixture. Enantiomeric excess: 98% as determined by HPLC analysis (Daicel Chirapak OD-H, n-hexane/ isopropyl alcohol = 95:5, flow rate 0.7 mLmin⁻¹, T = 25 °C, 254 nm): $t_{\rm R} = 7.51 \, {\rm min}$ $t_{\rm R} = 9.26 \, {\rm min}$ (major), (minor). $[a]_{D}^{33} = -93 \text{ deg cm}^{3} \text{g}^{-1} \text{dm}^{-1} (c = 1.2 \text{ g cm}^{-3}, \text{ CHCl}_{3}).$

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