



Diastereoselective synthesis of quaternary substituted thioindolines from sulfur ylide intermediates

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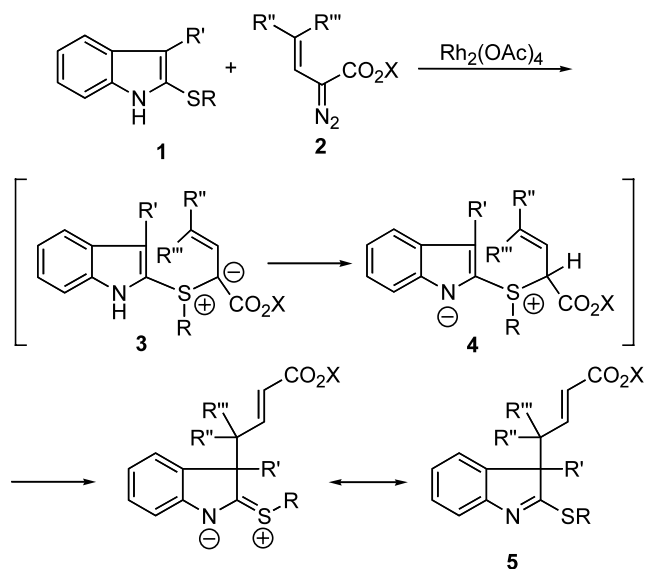
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Abstract—We have examined the coupling reactions of 2-thioindoles with vinyl diazoacetates in the presence of Rh(II) catalysts. While attempted enantio- and/or diastereoselective couplings using chiral catalysts and/or chiral auxiliaries on the vinyl diazoacetate have been largely unsuccessful, substrates having resident chirality on fused thiopyrans gave thioindolines with moderate to high diastereoselectivities. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The presence of C(3) quaternary substitution in a variety of indolines containing natural and non-natural products has inspired a number of groups, including ours, to develop new and improved routes for their synthesis.^{1–3} Our interest in this area is the result of our ability to generate quaternary substituted thioindolines from the coupling of vinyl diazoacetates with 2-thio-3-alkylindoles in the presence of Rh(II) (Scheme 1).⁴



Scheme 1.

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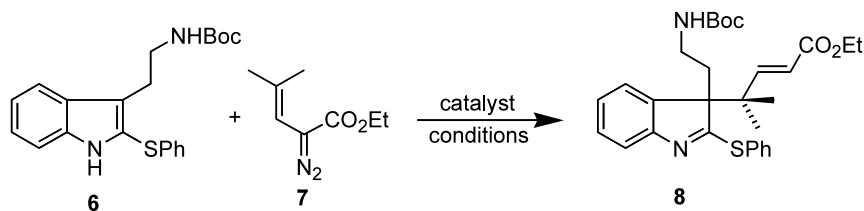
Presumably, **5** results from a [3,3]-sigmatropic rearrangement of sulfur ylide **4**.^{5,6}

While pleased with our results thus far, we realized that the application of the **1**→**5** transformation to the synthesis of interesting indoline containing targets was dependent upon our ability to extend its scope to include the synthesis of diastereomerically and/or enantiomerically enriched substrates. Herein, we report the results of our preliminary efforts to address this issue through the use of chiral substrates and chiral catalysts.

In spite of the fact that only modest levels of enantioselectivity have been observed when chiral catalysts have been used in related oxygen and sulfur ylide-induced [2,3]-sigmatropic rearrangements,⁷ we decided to explore the effect of chiral catalysts on our coupling reaction. As outlined in Table 1, chiral Rh(II) and Cu(I) catalysts gave disappointing results; we isolated indoline **8** in moderate to low yields and with low levels of enantioselectivity when **6** was exposed to **7**⁸ and Rh₂(DOSP)₄ **9**,⁹ Rh₂(S-TBSP)₄ **10**,⁹ or Cu(I)bisoxazoline (from Cu(CH₃CN)PF₆ and bisoxazoline **11**).¹⁰

In addition to chiral catalysts, we have also examined the effect of chiral substrates on the coupling reaction. As depicted in Table 2, when tryptamide **6** was exposed to pantolactone vinyl diazoester **12**¹¹ and either Rh₂(OAc)₄ or Rh₂(TBSP)₄, we isolated indoline **13** as a less than satisfactory 2:1 mixture of diastereomers, which could not be improved upon regardless of the reaction conditions.

Table 1.



Catalyst	Conditions		Yield (%)	e.r. ^a	Catalyst	Conditions		Yield (%)	e.r. ^a
	Solvent	Temp.				Solvent	Temp.		
Rh ₂ (OAc) ₄	CH ₂ Cl ₂	Rt	83	–	Rh ₂ (<i>S</i> -TBSP) ₄	CH ₂ Cl ₂	Rt	28	62:38
Rh ₂ (<i>S</i> -DOSP) ₄	CH ₂ Cl ₂	Rt	68	62:38	Rh ₂ (<i>S</i> -TBSP) ₄	PhCH ₃	Rt	0	–
Rh ₂ (<i>S</i> -DOSP) ₄	CH ₂ Cl ₂	0°C	36	61:39	Rh ₂ (<i>S</i> -TBSP) ₄	PhCl	Rt	60	62:38
Rh ₂ (<i>S</i> -DOSP) ₄	CH ₂ Cl ₂	–30°C	0	–	Rh ₂ (<i>S</i> -TBSP) ₄	CHCl ₃	Rt	41	58:42
Rh ₂ (<i>S</i> -DOSP) ₄	PhH	Rt	21	–	Rh ₂ (<i>S</i> -TBSP) ₄	CH ₃ CN	Rt	5	62:38
Rh ₂ (<i>S</i> -DOSP) ₄	PhCl	Rt	59	62:38	Rh ₂ (<i>S</i> -TBSP) ₄	THF	Rt	0	–
Rh ₂ (<i>S</i> -DOSP) ₄	CHCl ₃	Rt	50	59:41	Rh ₂ (<i>S</i> -TBSP) ₄	Et ₂ O	Rt	62	59:41
Rh ₂ (<i>S</i> -DOSP) ₄	CH ₃ CN	Rt	65	63:37	Cu(CH ₃ CN)PF ₆ , 11	PhH	Rt	9	53:47
Rh ₂ (<i>S</i> -DOSP) ₄	Et ₂ O	Rt	45	60:40	Cu(CH ₃ CN)PF ₆ , 11	CH ₂ Cl ₂	Rt	10	53:47
Rh ₂ (<i>S</i> -DOSP) ₄	THF	Rt	0	–	Cu(CH ₃ CN)PF ₆ , 11	CH ₃ CN	Rt	24	53:47

^a Measured using a Chiralcell OD HPLC column.

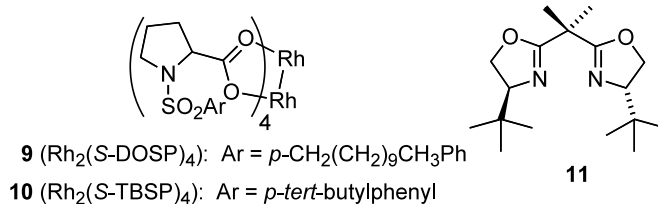
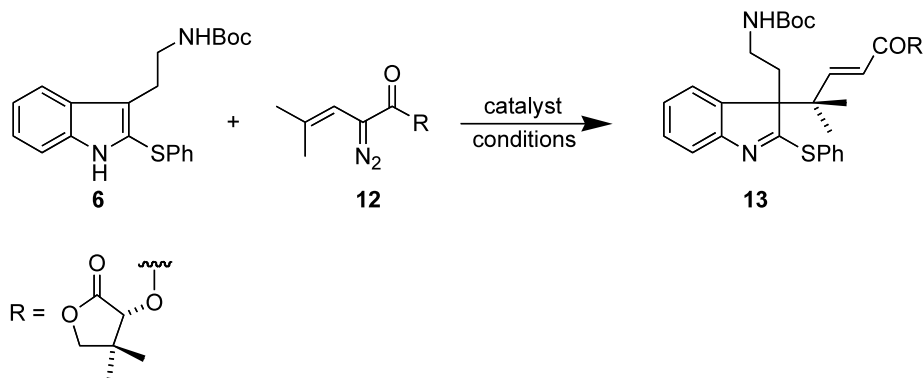


Table 2.



Catalyst	Conditions		Yield (%)	d.r. ^a
	Solvent	Temp.		
Rh ₂ (OAc) ₄	CH ₂ Cl ₂	Rt	16	2:1
Rh ₂ (OAc) ₄	ClCH ₂ CH ₂ Cl	83°C	89	2:1
Rh ₂ (<i>S</i> -TBSP) ₄	CH ₂ Cl ₂	Rt	29	2:1
Rh ₂ (<i>R</i> -TBSP) ₄	CH ₃ CN	Rt	21	5:3

^a Ratio was determined from integration of the vinyl signals in the crude ¹H NMR spectra.

Having had little success with chiral catalysts or chiral vinyl diazoacetates,¹² we opted to investigate chiral indoles where the chirality would reside on a thiopyran ring fused to the indole (e.g. **14**). These studies were made all the more compelling by the ready availability of thiopyran ring systems having substitution α -, β -, and γ - to sulfur and by the notion that the thiopyran might prove useful in its own right subsequent to the coupling reaction (Fig. 1).¹³

Our initial experiments examined the coupling of a β -substituted thiopyran, tryptophan derivative **15**.¹⁴ The coupling of **15** with vinyl diazoacetate **7** in the presence of $\text{Rh}_2(\text{OAc})_4$ resulted in the generation of indolines **16** and **17** as a 2:1 mixture of diastereomers in 90% overall yield (Scheme 2).^{15–17}

From the notion that the position of the stereogenic center might be important, we also examined γ -substituted thiopyran **18**.¹⁸ The coupling of **18** with **19** gave a

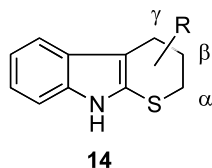
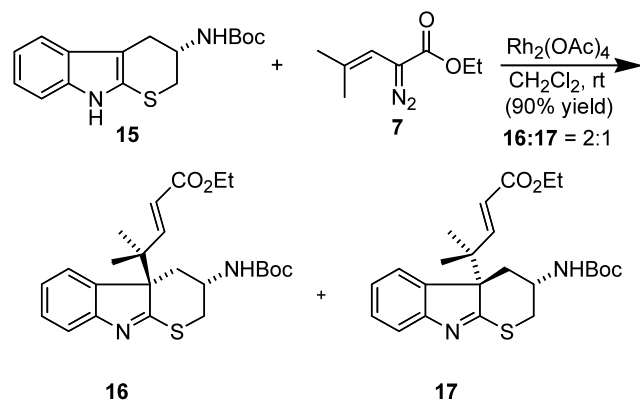


Figure 1.

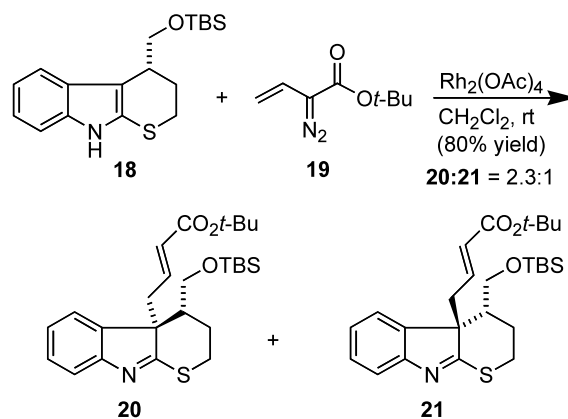


Scheme 2.

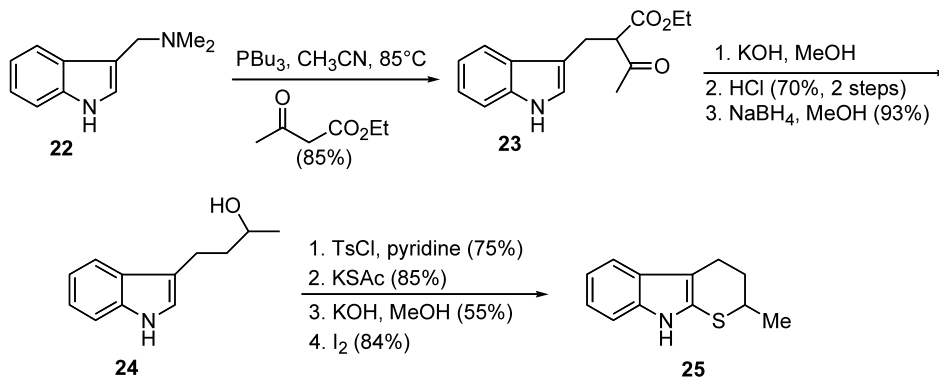
2.3:1 mixture of indolines **20** and **21** in 82% overall yield.¹⁹ Surprisingly, the vinyl group was positioned *syn* to the thiopyran substituent in the major diastereomer (Scheme 3).²⁰

Having examined β - and γ -substituted thiopyrans, we next investigated the influence of substitution at the position α - to sulfur. Clearly, if the selectivity was dependent upon the diastereoselective formation of a sulfur ylide intermediate, α -substitution should have an impact. In order to test this notion, the previously unknown α -methyl thiopyran **25** was synthesized in racemic form via the route outlined in Scheme 4. Alkylation of ethyl acetoacetate with gramine²¹ was followed by decarboxylation and reduction to give **24**.²² Displacement of the mesylate from **24** with KSAc gave **25** following hydrolysis²³ and oxidative cyclization of the resulting acyclic thiol using I_2 in DMF.

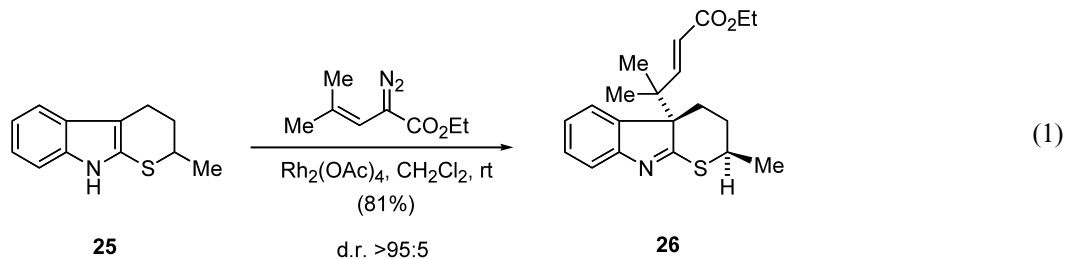
Thioindole **25** was subjected to vinyl diazoacetate **7** and $\text{Rh}_2(\text{OAc})_4$ at rt (Eq. (1)). We were extremely pleased to isolate thioindoline **26** as a >95:5 mixture of diastereomers in 81% yield (Eq. (5)).^{24,25} The success of this experiment is exciting to us for two reasons: firstly, it demonstrates that thioindole-vinyl diazoacetate coupling reactions can be used to generate indolines with high stereoselectivity and secondly, from this result it appears likely that the mechanism presented in Scheme 1 is accurate. This finding will undoubtedly play a significant role in our use of this transformation in chemical synthesis.



Scheme 3.



Scheme 4.



2. Conclusions

In conclusion, the coupling of thioindoles with vinyl diazoacetates in the presence of Rh(II) gives the corresponding indolines in high yield and high diastereoselectivity depending upon the substrate. While we have been unable to find a chiral catalyst or a chiral diazoester capable of influencing the enantio- or diastereoselectivity of the reaction, we have found a successful method by utilizing a chiral thiopyran. We are continuing to explore these reactions and will report our efforts in due course.

Acknowledgements

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- In light of the similar size of each of the thioether substituents in **6**, it is probably not surprising that we have observed low levels of stereoselectivity with chiral catalysts and chiral diazoacetates. Assuming that the selectivity is determined during the ylide forming step and because of the similar environment about both sides of sulfur, the chiral carbenoid is unable to distinguish between the two diastereotopic sulfur lone pairs. We are currently testing this notion by examining thioethers having more and less sterically demanding substituents attached to sulfur.
- The thiol from hydrolysis of the thioindoline should be amenable to a number of transformations including coupling and oxidation reactions.
- 15** is available in five steps from L-tryptophan. See: Ishizuka, N.; Sato, T.; Yasuo, M. *Chem. Pharm. Bull.* **1990**, *38*, 1396.
- Ratio determined from the relative integration of the vinyl signals in the crude ¹H NMR spectrum.
- The 2:1 ratio represents a slight improvement over our experiments with 2-thiotryptophan where we had isolated a 1:1 mixture of diastereomers. See Ref. 4b.

17. The relative stereochemistry shown for **16** was assumed based upon the notion that the major ylide intermediate would have the allyl group on the face opposite the amino group.
18. **18** is available in eight steps from L-malic acid. See: Ishizuka, N.; Shiro, M.; Mukisumi, Y. *J. Chem. Soc. Perkin 1* **1990**, 4, 827.
19. The diastereomeric ratio of **20:21** was determined spectroscopically by integration of the vinyl signals in the ¹H NMR spectrum of the crude reaction mixture. The relative stereochemistry of **20** and **21** was also determined spectroscopically using the following rationale: (a) NOEs were observed between the vinyl ester and the siloxy CH₂ in the major diastereomer **20**; (b) an NOE was observed between the TBSOCH₂CH proton and the vinyl ester in the minor diastereomer **21**.
20. We are currently exploring this phenomenon; we do not currently have a reasonable explanation for the predominance of the *syn* isomer from this experiment.
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22. Presumably, optically active **24** would form from asymmetric reduction of the ketone that arises from decarboxylation of **23**.
23. We believe that the relatively low yield from the thioester hydrolysis is due to the formation of a by-product in 30% yield. Although we have little structural proof at this point, we have tentatively assigned the by-product to be a disulfide dimer. Reduction of the by-product with LiAlH₄ followed by oxidative cyclization also gave **25**.
24. The 95:5 ratio represents a lower limit; we observed none of the other diastereomer by 300 MHz ¹H NMR.
25. The relative stereochemistry about **26** was elucidated spectroscopically; NOEs were observed between the hydrogen adjacent to sulfur and: (a) the olefin hydrogens; (b) one of the methyl groups at the allylic position.