Synthetic Methods

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Highly Diastereoselective Sulfonium Ylide Rearrangements to Quaternary Substituted Indolines**

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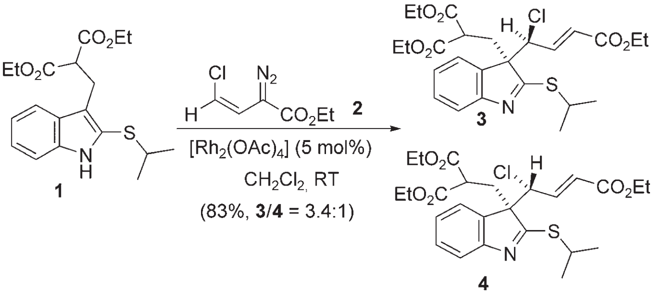
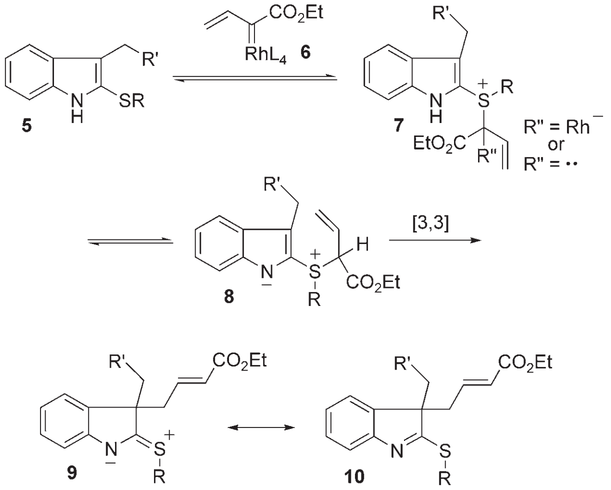
The stereoselective generation of quaternary centers, including quaternary centers at C3 of oxindoles and indolines, remains a challenge for contemporary organic synthesis.[1] To date, a list of the most successful methods addressing the indoline/oxindole problem would include intra- and intermolecular Mannich,[2] Heck,[3] and Mukaiyama aldol condensations,[4] as well as alkylation reactions,[5–7] cycloadditions,[8] π-allyl couplings,[9] cyclopropane ring openings,[10] oxidative couplings, and rearrangements.[11,12]

In the course of our studies aimed at the use of 2-thioindoles as precursors to substituted oxindoles and indolines,[13–15] we became fascinated with the coupling of 2-thio-3-alkylindoles with vinyl diazoacetates in the presence of Rh^{II} salts because the reaction delivered structurally rich quaternary substituted indolines in high yield and the mechanism was mechanistically interesting (Scheme 1).[16] We did not use this reaction in total synthesis endeavors because it was only modestly diastereoselective when monosubstituted vinyl diazoacetates were used as the coupling partners.[17,18]



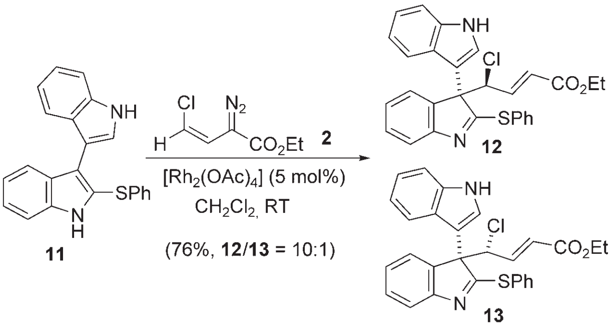
Scheme 1. 2-Thioindole Rh^{II}-vinyl carbenoid couplings.

In terms of the mechanism for the transformation to **3** and **4**, an abundance of indirect evidence suggested a [3,3] rearrangement of an intermediate sulfonium ylide (i.e. **7** or **8** to give **9** and **10**, Scheme 2).[19] Because of the well-established stability of sulfonium ylides, we presumed that Rh^{II} was important in the generation and delivery of the carbenoid to the thioether, but that it was absent during the subsequent sequence leading to C–C bond formation and **10** (cf. **7**, R'' = ••, Scheme 2).[20]



Scheme 2. Working hypothesis for 2-thioindole Rh^{II}-vinyl carbenoid couplings.

Our previous studies resulted in levels of diastereoselectivity that were similar to those seen with **1**, therefore we were surprised when the reaction of bis(thioindole) **11**[21] with **2** gave **12** in relatively high diastereoselectivity (Scheme 3). We became intrigued by the generation of **12** and decided to examine the reaction in more detail by exploring the effect of thioindole substitution on diastereoselectivity. As an aside, the importance of the thioether group in the reaction becomes



Scheme 3. Diastereo- and chemoselective bis(indole) vinyl carbenoid couplings.

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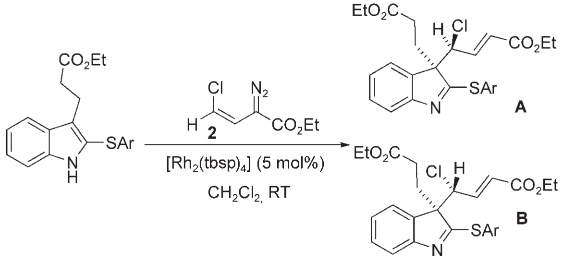
clearer with this example; no products resulting from reaction of the vinyl carbenoid with the indole lacking the thioether unit were isolated.

To determine whether the substituent at C3 of the indole ring was responsible for the enhanced diastereoselectivity with **11**, we examined the effect of a variety of C3 substituents on the reaction (Table 1). Whereas 3-*tert*-butyl-2-thiophenylindole (**16**)[22] gave the highest selectivity (Table 1, entry 4), more subtle structural modifications as exemplified by **14**,[23] **15**,[24] and **17**[25] resulted in little to no change in diastereoselectivity (Table 1, entries 2, 3, and 5).

Table 1: The influence of substitution at C3 on the diastereoselectivity.



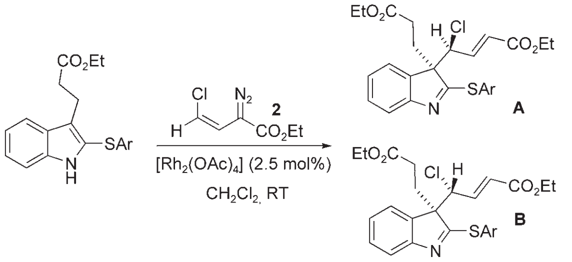
Entry	Indole	R	Indoline	**A/B**	Yield
1	**11**	3′-indole	**12**	10:1[a]	76%
2	**14**	Ph	**18**	8:1[a]	80%
3	**15**	Me	**19**	7:1[a]	75%
4	**16**	*t*Bu	**20**	15:1[a]	91%
5	**17**	$CH_2CH_2CO_2Et$	**21**	8:1[b]	88%

[a] Ratio of diastereomers determined by ^1H NMR spectroscopy of the crude reaction mixture. [b] Ratio of diastereomers determined by HPLC analysis of the crude reaction mixture.

From our perspective the most interesting result from the studies summarized in Table 1 was that 2-thiophenylethers showed enhanced selectivity relative to 2-alkylthioethers (compare Table 1, entry 5 with Scheme 1), implying that substitution on the thioether group might influence the reaction. We examined the effect of the substitution on the thioarene unit to gain more insight (Table 2) into the reaction.[26] Whereas *para* substitution resulted in selectivities that were similar to those obtained with the parent thiophenyl derivative (compare Table 2, entries 1 and 2 with Table 1, entry 5), the reaction was significantly enhanced by substitution *ortho* to the thioether. The diastereoselectivity increased to 11:1 with *ortho*-methyl thioether **26** (Table 2, entry 5) and to 15:1 with 2,6-dimethylphenyl thioether **27** (Table 2, entry 6). The highest selectivity in these studies was obtained with *ortho*-isopropyl indole **28** giving indoline **35** with 18:1 diasteroselectivity. These results along with the lower selectivities seen with *ortho*-methoxy and *ortho*-fluoro thiophenyl ethers **24** and **25**, respectively (Table 2, entries 3 and 4) imply that steric, and not electronic effects are operative here.[27]

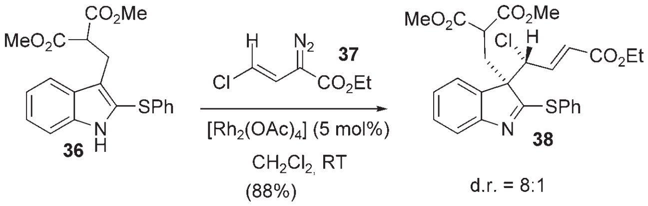
As would be expected for a reaction involving a concerted rearrangement (cf. **8** to **9**, Scheme 2), the reaction is stereospecific; the reaction of **36** with (*E*)-vinylchloride **37** gave indoline **38**, whose structure is analogous to the minor isomer from the reaction of **17** with **2**, as the major product in 88% yield as an 8:1 ratio of diastereomers (Scheme 4).

Table 2: The influence of thioaryl substitution on the diastereoselectivity of the reactions with **2** and **36**.



Entry	Indole	Ar	Indoline	**A/B**	Yield
1	**22**	$4\text{-}OMeC_6H_4$	**29**	7:1	86%
2	**23**	$4\text{-}NO_2C_6H_4$	**30**	7:1	74%
3	**24**	$2\text{-}OMeC_6H_4$	**31**	9:1	74%
4	**25**	$2\text{-}FC_6H_4$	**32**	7:1	81%
5	**26**	$2\text{-}MeC_6H_4$	**33**	11:1	75%
6	**27**	2,6-dimethylphenyl	**34**	15:1	96%
7	**28**	2-*i*PrC_6H_4	**35**	18:1	91%

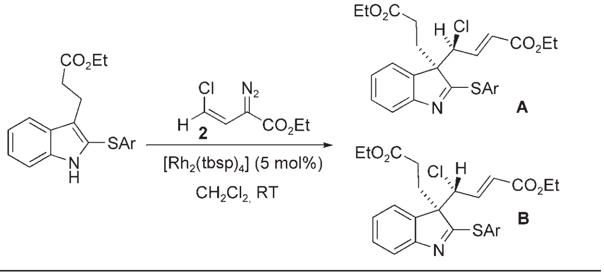
[a] Ratio of diastereomers determined by the integrations of the allylic proton peak in the ^1H NMR spectra of the crude reaction mixture.



Scheme 4. (*E*)-Chlorovinyldiazoacetate coupling.

We next examined the influence of a chiral Rh^{II} complex ($[Rh_2(tbsp)_4]$; tbsp = tetrakis{1-[(4-*tert*-butylphenyl)sulfonyl]-(2*S*-pyrrolidinecarboxylate}) on the reaction.[28] Although the enantioselectivity was low (Table 3),[29] exposure of 2,6-dimethylphenylthioindole **27** to **2** and $[Rh_2(tbsp)_4]$ resulted in an increased diastereoselectivity when compared to the

Table 3: Effect of $[Rh_2(tbsp)_4]$ on the diastereoselective coupling reactions of **2** with 2-arylthioindoles.

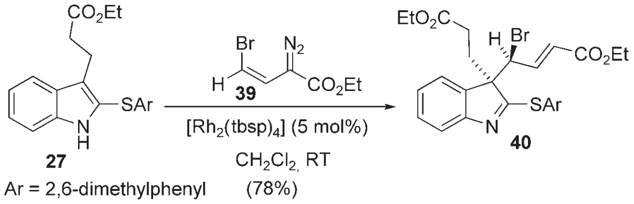


Entry	Indole	Ar	Indoline	**A/B**[a]	Yield
1	**22**	$4\text{-}OMeC_6H_4$	**29**	7:1[b]	94%
2	**27**	2,6-dimethylphenyl	**34**	>95:5[c]	91%

[a] Ratio of diastereomers determined by integration of the of the allylic proton in the ^1H NMR spectrum of the crude reaction mixture. [b] e.r. = 62:38 as determined by chiral HPLC methods. [c] e.r. = 56:44 as determined by chiral HPLC methods.

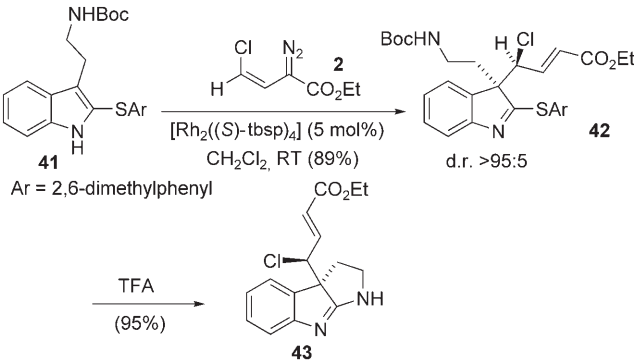
analogous [$Rh_2(OAc)_4$] reaction (compare Table 2, entry 2 with entry 6). Interestingly, there was essentially no change in selectivity for the reaction of *p*-methoxy derivative **22**. Although additional data is clearly needed, from these studies we believe that the metal may be more involved in the reaction than presumed previously. Our current speculation is that it may be present at least up to the proton transfer step (see **7**, $R'' = Rh^-$, Scheme 2).[30,31]

Of additional note is that the reaction is not limited to the use of vinyl chlorides. In addition to the multitude of substituted vinyl diazoacetates previously disclosed,[14,16,19] bromovinyl diazoacetate **39** underwent a stereoselective reaction with 2-arylthioindole **27** to give allylic bromide **40** as a single diastereomer in 78 % yield (Scheme 5).



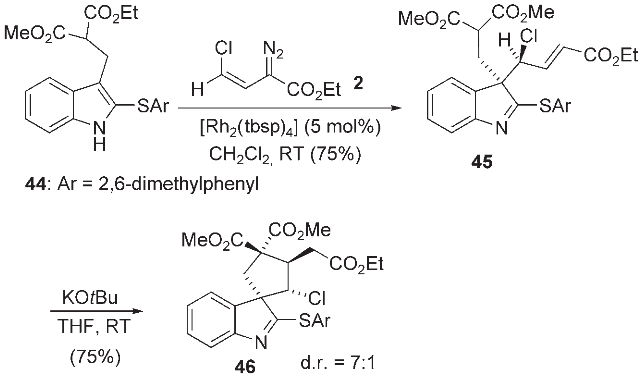
Scheme 5. (*Z*)-Bromovinyldiazoacetate coupling.

Based upon their wealth of interesting functionality, we were hopeful that the products from the reactions outlined above would be amenable to additional derivatization. Thus, we were pleased to generate pyrroloindoline **43** in 95 % yield from the acid mediated cyclization of thioindoline **42** that came from the reaction of **41** with **2** in the presence of [$Rh_2((S)\text{-tbsp})_4$] (Scheme 6).[32]



Scheme 6. Pyrroloindoline synthesis. TFA = trifluoroacetic acid.

The treatment of substituted indoline **45**, having a quaternary C3 center, with a base resulted in a diastereoselective spirocyclization reaction and the generation of **46** in 75 % yield (Scheme 7).[33] The coupling/cyclization sequence outlined here represents a novel approach to halogenated spirocycles.[34]



Scheme 7. Spirocyclopentane synthesis.

In summary, described herein are the unique, high yielding, and diastereoselective coupling reactions involving sulfonium ylide intermediates from halogenated vinyl diazoacetates and 2-thioindoles. These transformations led to the synthesis of structurally interesting substrates that would be difficult to prepare by using other methodologies. Current efforts are focused on the control of the absolute stereochemistry of the products and the application of the reaction to non-indole aromatic thioether substrates.

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