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Extending Pummerer Reaction Chemistry. Asymmetric Synthesis of Spirocyclic Oxindoles via Chiral Indole-2-sulfoxides

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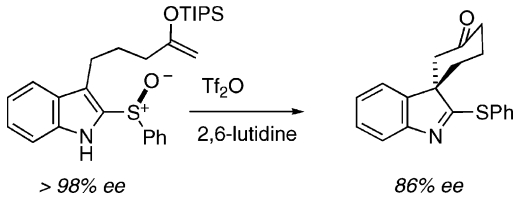
ABSTRACT

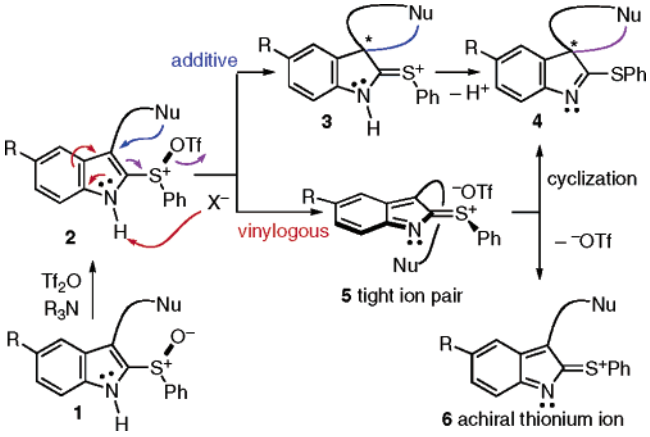


The conversion of (S_S)-3-(ω-allylsilane and silyl enol ether)indole-2-sulfoxides to spirocyclic indolenines and then to oxindoles proceeds, in favorable cases, with moderate levels of chirality transfer from sulfur to C(3) of the indole core. A mechanistic model, which features either an Sn2′-like additive Pummerer sequence or a tight ion pair generated by an Sn1-like vinylogous Pummerer transform, is proposed to rationalize the sense of asymmetric induction.

Recent advances in the Pummerer chemistry of heteroarenes, including imidazoles,[1] furans,[2] benzofurans,[2b] and thiophenes,[2] in addition to indole-2-sulfoxides,[3] have documented that these processes are effective and efficient methods for achieving formal oxidative nucleophilic additions to the heterocyclic core with complete control of regiochemistry and with complete avoidance of product overoxidation. In contrast to the furan, benzofuran, and thiophene series, the Pummerer reaction of 3-substituted indole-2-sulfoxides (cf. **1**, Scheme 1) is not accompanied by rearomatization, and the generation of a new stereogenic center at C(3) raises the possibility of chirality transfer from sulfur-to-carbon in these systems.

The asymmetric synthesis of C−Nu bonds via the Pummerer reaction of chiral sulfinate substrates has had an uneven history, with notable successes recorded by Marino,[4] Kita,[5] García Ruano,[6] and Padwa[6] amidst many failed

Scheme 1. Additive and Vinylogous Pummerer Mechanisms for a Chiral Indole-2-sulfoxide



(1) Feldman, K. S.; Skoumbourdis, A. P. *Org. Lett.* **2005**, *7*, 929−931.
(2) (a) Akai, S.; Kawashita, N.; Satoh, H.; Wada, Y.; Kakiguchi, K.; Kuriwaki, I.; Kita, Y. *Org. Lett.* **2004**, *6*, 3793−3796. (b) Padwa, A.; Nara, S.; Wang, Q. *Tetrahedron Lett.* **2006**, *47*, 595−597.
(3) Feldman, K. S.; Vidulova, D. B.; Karatjas, A. G. *J. Org. Chem.* **2005**, *70*, 6429−6440.

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attempts.[7] As exemplified with the chiral indole-2-sulfoxide **1**, significant sulfur-to-carbon transfer of stereochemical information is possible only if the intermediacy of an achiral thionium ion **6** can be avoided. In earlier studies on other systems, both concerted bond-breaking/bond-making schemes[4] and, in independent work, tight ion pairs that preserve (planar) chirality[5,6] have been invoked as the means to steer reaction away from an achiral thionium ion.

With unsaturated sulfoxide substrates, the course of the Pummerer reaction embodies a mechanistic dichotomy: rearrangement via either an *additive* or a *vinylogous* pathway, as exemplified with the indole-2-sulfoxide substrate in Scheme 1. The additive pathway offers an intrinsic conduit for passing stereochemical information from sulfur to the newly forming C−Nu_1 bond (**2**→**3**), at least in principle (cf. Marino's work[4]). On the other hand, the vinylogous alternative can proceed either with loss of stereochemistry through an achiral thionium ion **6** or with preservation of stereochemical information via a planar chiral tight ion pair **5**. In the case of the indole-2-sulfoxides, the nucleophilic addition products derived from either pathway are identical, preventing a simple assignment of mechanism based on the product formed.

Six chiral indole-2-sulfoxides **7a**/**b**, **8a**/**b**, and **9a**/**b** were chosen to study the possibility of S → C chirality transfer, Figure 1 (see the Supporting Information for syntheses). The

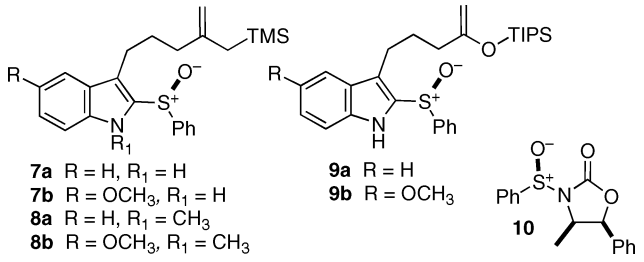
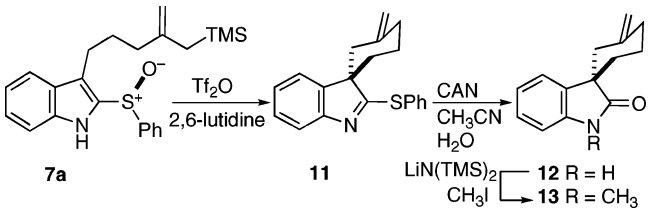


Figure 1. Chiral indole-2-sulfoxide substrates for Pummerer-mediated oxidative cyclization.

key transformation in each of these substrate syntheses involved the sulfinylation of an indole C(2) anion with the chiral sulfoxide transfer reagent **10** introduced by Evans,[8] following the protocols described in the pioneering studies of Marino.[4] The enantiomeric excesses (>98%, detection limit) of the chiral sulfoxides **7a**/**b** were verified by chiral shift reagent studies with $Eu(tfc)_3$, whereas the enantiomeric excesses of the ketone precursors to **9a**/**b** were assayed at > 98% by the chiral shift reagent (*S*)-2,2,2-trifluoroanthryl ethanol, as expected by the use of enantiopure **10**.

The Pummerer chemistry commenced with the simple allylsilane-bearing sulfoxide **7a**, Table 1. Unfortunately, ^1H

Table 1. Pummerer-Initiated Cyclization of the Allylsilane-Bearing Chiral (*S*)-Indole-2-sulfoxide **10a**



entry	solvent	polarity[a] (viscos)[b]	T (°C)	yield **13** (%)	ee[c] (%)
1	CF_3CH_2OH	59.8 (2.0)	−40	18	0
2	n-$C_5H_{11}OH$	49.1 (25.4)	−78	17	0
3	$C_2H_2Cl_4$	39.4 (3.7)	−40	17	26
4	CH_2Cl_2	40.7 (0.73)	−78	57	38
5	Et_2O	34.5 (0.28)	−78	39	49
6	toluene	33.9 (1.2)	−78	41	55
7	toluene		−90	NR	
8	Et_2O		−110	NR	

[a] $E_T(30)$ values (kcal/mol) from: Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319−2358. [b] Centipoise, from: *CRC Handbook of Chemistry and Physics*, 85th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, 2004; 2004−2005. [c] Average of two independent trials.

NMR chiral shift reagent studies with thioimidate **11** did not lead to identification of a characteristic signal that permitted differentiation of the enantiomers. Only upon conversion of **11** into **13** were the enantiomers distinguishable by use of $Eu(tfc)_3$ (see the Supporting Information), but the absolute configuration of the newly formed quaternary stereogenic center could not be assigned at this time.

Both yield and enantiomeric excess with **7a** responded to solvent variation, as the less polar solvents led to product in both higher yield and greater ee. The alcohol solvents performed poorly by any criteria, although the role of competitive solvent sulfonylation in diverting the reaction was not assessed. Switching to the non-hydroxylic and less polar solvents $C_2H_2Cl_4$ and CH_2Cl_2 provided the first glimpse of success by delivering product in modest ee. By switching to the slightly less polar but more viscous toluene as solvent, the maximum ee (55%) was observed. Temperatures lower than −78 °C did not lead to productive reaction for these substrates.

Examination of **7b** (R = OCH_3) was undertaken with the expectation that the electronic character of R would have little impact on a Pummerer reaction proceeding through an additive Sn2′-like path but might exert some influence on the reaction through the vinylogous Sn1-like path as a consequence of a Hammond postulate-type argument. Greater incursion of the vinylogous path from **7b** might promote reaction through achiral **6**, leading to a drop in ee's compared

(4) (a) Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643−7644. (b) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566−5572.

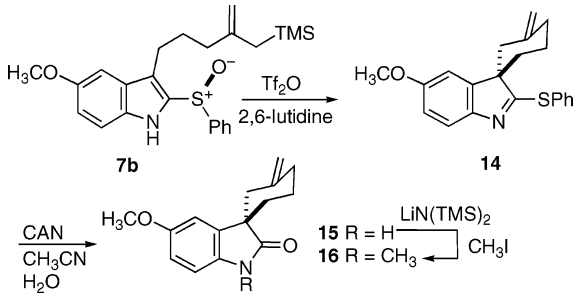
(5) Kita, Y.; Shibata, N.; Fukui, S.; Masahiko, B.; Fujita, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1763−1767.

(6) (a) García Ruano, J. L.; Alemán, J.; Aranda, M. T.; Arévalo, M. J.; Padwa, A. *Org. Lett.* **2005**, *7*, 19−22. (b) García Ruano, J. L.; Alemán, J.; Aranda, M. T.; Arévalo, M. J.; Padwa, A. *Phosphorus, Sulfur, Silicon* **2005**, *180*, 1497−1498. (c) García Ruano, J. L.; Alemán, J.; Padwa, A. *Org. Lett.* **2004**, *6*, 1757−1760.

(7) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003−5034.

(8) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977−5985.

Table 2. Pummerer-Initiated Cyclization of the Allylsilane-Bearing Chiral (*S*)- Indole-2-sulfoxide **7b**

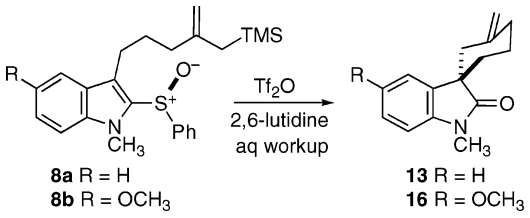


			yield (%)			
entry	solvent	T (°C)	**14**	**15**	**16**	ee (%)
1	CH_2Cl_2	−78	47	50	44	10
2	Et_2O	−78	47	50	50	28
3	toluene	−78	42	82	60	56

with the less cation-stabilizing case **7a**. The data (Table 2) do sustain this line of thinking, with lower ee's attending reaction of **7b** compared with **7a** in both CH_2Cl_2 and Et_2O, although no effect was seen in toluene. In practice, better overall yields of the *N*-methyl oxindole **16** (and **13**, Table 1) result from the use of crude reaction products in each step.

The *N*-methylallylsilane substrates **8a** and **8b** represent a stringent test for thionium ion formation, as the absence of a labile N−H proton guarantees that any material passing through a vinylogous Pummerer pathway must access a presumably high-energy dicationic thionium ion intermediate $=N^+(CH_3)-C=S^+Ph$.[3] These substrates delivered the oxindole products **13** and **16**, respectively, directly through in situ hydrolysis of a putative C(3)-cyclized thionium ion intermediate, Table 3. For the R = H case **8a**, the yields do not vary as per solvent polarity (CH_3CN $E_T(30)$ = 45.6 kcal/mol), but the ee's do, with the greater ee attending reaction in the more polar solvent. For the R = OCH_3 case **8b**, both yields and ee's slightly increase in response to increasing solvent polarity, and again, the ee is maximized in CH_3CN.

Table 3. Pummerer-Initiated Cyclization of the Allylsilane-Bearing Chiral (*S*)-*N*-methylindole-2-sulfoxides **8a** and **8b**

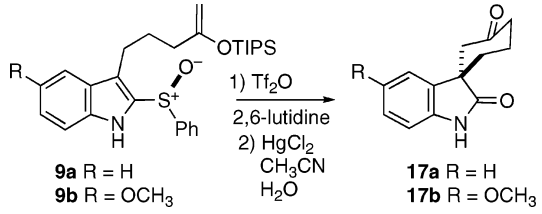


entry		solvent	T (°C)	yield **13/16** (%)	ee[a] (%)
1	**8a**	CH_2Cl_2	−78	63	7
2	**8a**	CH_3CN	−40	63	46
3	**8b**	toluene	−78	41	20
4	**8b**	Et_2O	−78	45	28
5	**8b**	CH_3CN	−40	59	32

[a] Average of two or three independent trials.

The final substrates chosen for study, the silyl enol ethers **9a** and **9b** (Table 4), represent a marked change in reactivity

Table 4. Pummerer-Initiated Cyclization of the Allylsilane-Bearing Chiral (*S*)-Indole-2-sulfoxides **9a** and **9b**



entry		solvent	T (°C)	yield **17a/b** (%)	ee[a] (%)
1	**9a**	CH_2Cl_2	−78	33	43
2	**9a**	toluene	−78	33	67
3	**9a**	Et_2O	−78	60	51
4	**9a**	Et_2O	−110	58	86
5	**9b**	CH_2Cl_2	−78	80	13
6	**9b**	toluene	−78	76	38
7	**9b**	Et_2O	−78	80	43
8	**9b**	Et_2O	−110	33	74

[a] Average of two or three independent trials.

of the pendant nucleophile (Mayr *N* values: allylsilane ~ 1.8; silyl enol ether ~ 5.4).[9] For these compounds, enantiomeric excesses were measured on the oxindoles **17a**/**b** that were prepared by hydrolysis of the first-formed thioimidates. For the R = H substrate **9a**, reasonable ee's were obtained in all solvents tested. However, it was gratifying to observe that by the simple expedient of dropping the temperature to −110 °C, the transformation proceeded smoothly to furnish thioimidate and then oxindole product both in good yield and in relatively high ee (^{1}H NMR, (*S*)-2,2,2-trifluoromethylanthryl ethanol; see the Supporting Information). The R = OCH_3 substrate **9b** proceeded with lower ee under comparable conditions (−78 °C). At the low-temperature limit of −110 °C, however, even this compound delivered Pummerer product with significantly improved ee.

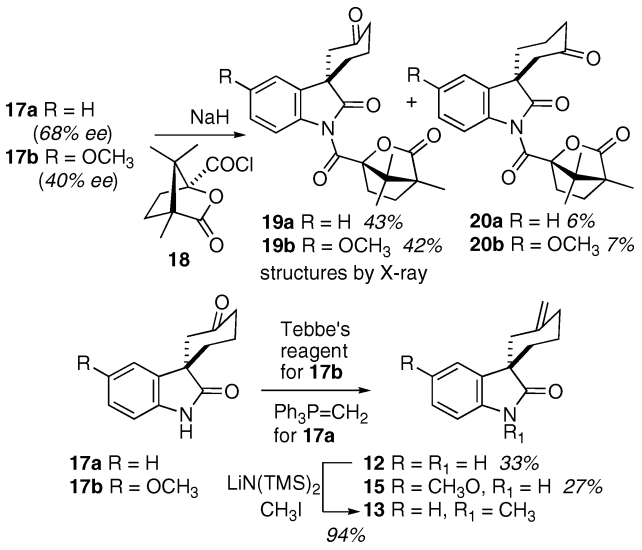
A clear benefit can be ascribed to the silyl enol ether nucleophile terminator compared to the allylsilane analogue in terms of both chemical reactivity (compare with Table 1, entries 7 and 8) and enantiomeric excess obtained. The lack of reactivity of allylsilane indole-2-sulfoxide **7a** at −110 °C is curious, as it is not clear why the remote nucleophile should have any influence on the ability of the sulfoxide's oxygen to react with Tf_2O. Perhaps this unexpected observation can be rationalized if either (1) the initial sulfonylation step (**1** → **2**) is reversible, or (2) the triflate is hydrolyzed

(9) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

from unreactive **2** upon workup to reform **1**. Under these speculative scenarios, further reaction by any pathway from **2** then depends on the ability of the pendant nucleophile (silyl enol ether ≫ allylsilane) to satisfy the burgeoning electron demand by participation.

The absolute stereochemistries at C(3) of the oxindole products **17a**/**b**, **13**, and **15** were determined by a combination of derivatization and X-ray crystallography, Scheme 2.

Scheme 2. Determination of Absolute Stereochemistry at C(3) in the Oxindole Products



The absolute configuation at C(3) for both major enantiomers formed from the Pummerer sequence is (*S*) as shown. The absolute configurations of the oxindoles derived from the allylsilane terminator systems **7a**, **7b**, **8a**, and **8b** were established by chemical correlation, **17a** → **12** → **13**, and **17b** → **15**. In all cases, the (*S*) absolute configuration at C(3) was found.

Revisiting the mechanistic picture depicted in Scheme 1 in light of the results described above permits some refinement, but ultimately does not allow any definitive conclusions to be drawn. At the very least, these results provide indisputable evidence that these Pummerer reactions cannot be proceeding exclusively or even predominantly through the commonly cited but achiral free thionium ion intermediate (cf. **6**). The most compelling evidence in support of the additive Sn2′-like pathway can be found in the results of the N−CH_3 allylsilane series **8a**/**8b**, where (1) the yield is insensitive to R (R = H or R = OCH_3), (2) the ee's are marginally higher when R = H compared with R = OCH_3, and (3) the ee's increase (again, marginally) as the solvent polarity increases.

With the N−H allylsilane series **7a**/**7b**, the ee vs solvent polarity trends are just the opposite of those seen with the N−CH_3 analogues **8a**/**8b**, an observation suggestive of different mechanisms operating with the two types of substrates. By process of elimination, the spotlight then focuses on a vinylogous pathway/tight ion pair (cf. **2** → **5**) for **7a**/**7b** as a means to generate thioimidate product with high ee. This speculation is supported by the observation that with solvents of nearly identical polarity (Et_2O and toluene), the more viscous of the two (toluene), which presumably differentially retards dissociation of chiral **5** into achiral **6**, provides product with higher ee. In addition, the observed solvent polarity trends fall within the scope of this explanation to the extent that the more polar solvents should accelerate the conversion of **5** into **6** and thus provide product with lower ee. None of these data, however, rule out the additive Sn2′ process for **7a**/**7b**.

The yield and ee trends with the enol ether substrates **9a**/**9b** do not lend themselves to ready interpretation. The fact that the "nucleophilicity" of the nucleophile seems to matter (yields and ee's of **17a**/**17b** are higher than those of the allylsilane analogues **11**/**14** under identical conditions) argues for a role in the rate determining step for this unit, a picture consistent with the Sn2′-like additive pathway. On the other hand, the greater yields but lower ee's of the R = OCH_3 species **9b** compared to the R = H analogue **9a** lend weight to a mechanistic argument relying on the vinylogous pathway through a thionium ion (**5** or **6**). Thus, the mechanistic path(s) taken by the enol ether substrates cannot be disentangled at this point.

In summary, the formation of 3,3-spirocyclic oxindole products in modest-to-moderate enantiomeric excess by Pummerer-mediated oxidative cyclization of chiral indole-2-sulfoxides has been observed. Evidence in support of two distinct mechanistic paths, depending upon the substrate's structural details, was garnered. Efforts to incorporate these Pummerer methodology advances in natural product synthesis are ongoing, and results will be reported in due course.

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Supporting Information Available: Experimental procedures for **7a**/**b**−**9a**/**b**, **13**−**17a**/**b**, and **19a**/**b**; copies of ^1H and ^{13}C NMR spectra for **7b, 8b, 9b**, **14**−**17b**, and **19a**/**b**; X-ray data for **19a** and **19b**; ee determinations for **13**, **16**, **17a**, and **17b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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