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Straightforward Stereoselective Synthesis of Spiro-epoxyoxindoles

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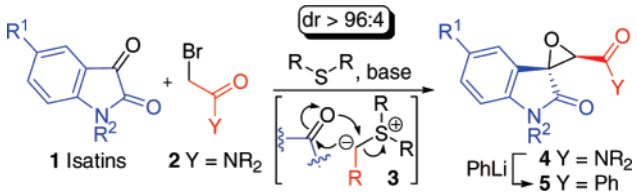
ABSTRACT



The in situ preparation of a sulfonium ylide reagent achieved the highly diastereoselective epoxidation of isatins, so that a new and straightforward access to biologically significant spiro-epoxyoxindoles is provided. The first investigations of an asymmetric version are reported with enantiopure sulfides.

3-Substituted 3-hydroxyoxindoles are common skeletons within both naturally occurring alkaloids and potent bioactive compounds (Figure 1).[1,2] Their construction has stimulated

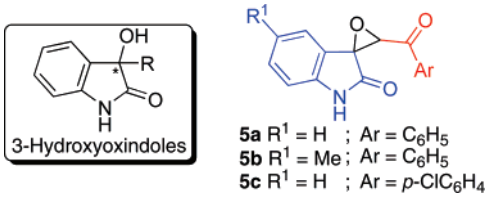


Figure 1. Epoxyoxindoles.

synthetic chemists,[1] and the challenging absolute control of the quaternary center has been recently achieved.[2] Within this family, epoxyoxindoles were also highlighted in medicinal chemistry.[3] For instance, the benzoyl-substituted ones, **5a** and **5b**, were tested as antifungal and antitubercular agents.[3d] Data mining techniques within the NCI database showed the oxirane **5c** effectiveness against both melanoma and leukemia cell classes.[4] The synthesis of these fascinating spiranic frameworks[5] has been tackled via carbene or carbenoid addition to ketones,[6] Darzens-type processes,[7] epoxidation of alkenes,[3d,8] or palladium-mediated cyclization

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(1) For selected recent examples, see: (a) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507. (b) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2006**, *71*, 2346. (c) Suarez-Castillo, O. R.; Sanchez-Zavala, M.; Melendez-Rodriguez, M.; Castelan-Duarte, L. E.; Morales-Rios, M. S.; Joseph-Nathan, P. *Tetrahedron* **2006**, *62*, 3040. (d) Kim, S. C.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 3463.

(2) For selected recent asymmetric examples, see: (a) Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677. (b) Chen, G.; Wang, Y.; He, H.; Gao, S.; Yang, X.; Hao, X. *Heterocycles* **2006**, *68*, 2327. (c) Toullec, P. Y.; Jagt, R. B. C.; De Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2006**, *8*, 2715. (d) Cravotto, G.; Giovenzana, G. B.; Palmisano, G.; Penoni, A.; Pilati, T.; Sisti, M.; Stazi, F. *Tetrahedron: Asymmetry* **2006**, *17*, 3070. (e) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353. (f) Kawasaki, T.; Takamiya, W.; Okamoto, N.; Nagaoka, M.; Hirayama, T. *Tetrahedron Lett.* **2006**, *47*, 5379. (g) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488. (h) Franz, A. Z.; Dreyfuss, P. D.; Schreider, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1020.

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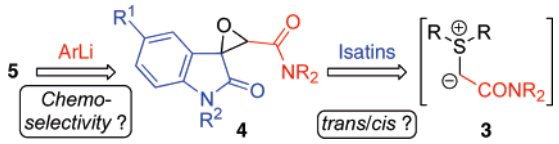
of allenes.[1b] Unfortunately, these racemic methodologies displayed poor substrate scope and moderate trans/cis ratios.[9] However, Dandia and co-workers succeeded in controlling the diastereoselective course of 3-aroylmethylene oxindole epoxidation under microwave irradiation.[3d] Recently, the reaction of 3-diazooxindoles and aromatic aldehydes, catalyzed by $Rh_2(OAc)_4$, afforded *cis* aryl-substituted epoxyoxindoles.[6e]

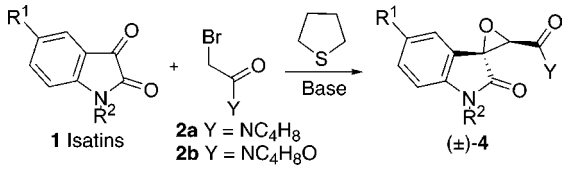
To facilitate a structure−activity relationship investigation of these valuable pharmaceuticals, we sought a concise and connective C−C bond formation synthesis of epoxides **5** and derivatives, from readily available starting materials (Scheme 1). We envisaged an unprecedented diastereoselective sulfonium ylide epoxidation of isatins as a key step,[10] followed by the addition of aryllithium derivatives onto the amide moiety. However, this sequence had to overcome the usually mediocre stereoselectivity for unsymmetrical ketone epoxidation[11,12] and, moreover, the chemo-differentiation of the lactam and amide functions during the aryllithium addition step. We describe herein our first success addressing these selectivity issues.

Scheme 1. Strategy



At the onset of the optimization, we envisaged the epoxidation of *N*-methyl isatin **1a** by readily available α-bromo acetamides **2a** in the presence of thiolane and a base, so that the ylide reagent would be formed in situ (Table 1). Since the pioneering work of Ratts and Yao,[13] amide-stabilized sulfonium ylides **3** proved to be reactive toward aldehydes to give glycidic amides.[14f] However, even with the most efficient recent enantioselective versions,[14] these species are generated by a base from the isolated sulfonium salt, therefore, in a two-step sequence.[11c] The one-pot protocol, allowing a substoichiometric use of sulfide, required α-diazoacetamides, as carbenoid precursors, in the presence of transition metals.[15] To our delight, the isatin **1a** epoxidation took place in a user-friendly one-pot fashion by means of cesium carbonate in acetonitrile (entry 1). Heating at 50 °C was required to secure a complete transformation in 1 day (entry 2), leading diastereoselectively to the new epoxide **4a** in 90% yield (see Supporting Information for further attempts). The high trans/cis ratio (>96:4) is remarkable taking into account that the ylide has to selectively accommodate a rather "flat" molecule (vide infra). The ^{1}H NMR of the crude product revealed other minor compounds (<4% with respect to the *trans*-epoxide), from which we could not rule out the presence of the *cis*-epoxide. Nevertheless, the silica gel purification furnished the pure *trans*-epoxide. Noteworthy was that a substoichiometric amount of sulfide could be used with a longer reaction time (entry 3). This is one of the rare examples of catalytic amide-stabilized sulfonium ylide epoxidation affording glycidic amides in metal-free conditions.[15] It was confirmed that no reaction occurred without sulfide, excluding any Darzens-type mech-

Table 1. Epoxidation of *N*-Methyl Isatin **1a** (R^1 = H; R^2 = Me)[a]



entry	reagents	thiolane (equiv)	temp (°C)	time (h)	yield[b] (%)	dr[c] (trans/cis)
1	**1a**, **2a**	1	20	40	46 (**4a**)	>96:4
2	**1a**, **2a**	1	50	24	90 (**4a**)	>96:4
3	**1a**, **2a**	0.2	50	72	72 (**4a**)	>96:4
4	**1a**, **2a**	0	50	24	0 (**4a**)	–
5	**1a**, **2b**	1	50	24	45 (**4b**)	>96:4

[a] All reactions were performed on 0.75 mmol of *N*-methyl isatin **1a** with α-bromo acetamide **2** (2 equiv), thiolane, and Cs_2CO_3 (2 equiv) in anhydrous acetonitrile. [b] Isolated yield of the *trans*-epoxide after column chromatography. [c] Estimated on the ^{1}H NMR of the crude product.

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(8) (a) Ager, J. W., Jr.; Eastwood, F. A.; Robinson, R. *Tetrahedron, Supplement* **1966**, *7*, 277. (b) Anthony, W. C. *J. Org. Chem.* **1966**, *31*, 77. (c) Kobayashi, G.; Matsuda, Y.; Tominaga, Y.; Ohkuma, M.; Shinoda, H.; Kohno, M.; Mizuno, D. *Yakugaku Zasshi* **1977**, *97*, 1033. (d) Joshi, K. C.; Jain, R.; Garg, S. J. *J. Heterocycl. Chem.* **1984**, *21*, 977. (e) Brunton, S. A.; Jones, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 763.

(9) To our knowledge, there is no enantioselective synthesis of epoxyoxindoles, although an asymmetric substrate-controlled diastereoselective epoxidation has been reported. See: Inoue, M.; Sakazaki, H.; Furukawa, H.; Hirama, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2654.

(10) There is one example of isatin epoxidation by dimethysulfonium methylide having therefore no diastereoselective issue. See: Bravo, P.; Gaudiano, G.; Umani-Ronchi, A. *Gazz. Chim. Ital.* **1970**, *100*, 652.

(11) For reviews, see: (a) Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, 2644. (b) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611. (c) Aggarwal, V. K.; Badine, D. M.; Moorthie, V. A. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; p 1.

(12) For recent successful diastereo- and enantioselective sulfur ylide epoxidation of ketones, see: Aggarwal, V. K.; Bae, I.; Lee, H.-Y.; Richardson, J.; Williams, D. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3274.

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anism (entry 4).[16] Morpholine α-bromo acetamide **2b** could also be employed but gave a lower yield (entry 5).

We evaluated the scope of this one-pot epoxidation protocol to various isatins **1** by α-bromo acetamide **2a** (Table 2).

Table 2. Epoxidation of Various Isatin Derivatives **1**[a]

entry	R^1	R^2	product	yield[b] (%)	dr[c] (trans/cis)
1	H	*p*-MeOBn	**4c**	88	>96:4
2	H	Boc	**4d**	0	-
3	I	Me	**4e**	75	>96:4
4	Br	Me	**4f**	53	>96:4
5	F	Me	**4g**	79	>96:4
6	OCF_3	Me	**4h**	79	>96:4
7	Me	Me	**4i**	88	>96:4
8	NO_2	Me	**4j**	64	95:5

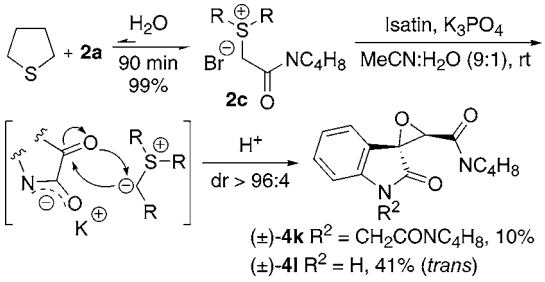
[a] All reactions were performed on 0.75 mmol of isatins **1** with α-bromo acetamide **2a** (2 equiv), thiolane (1 equiv), and Cs_2CO_3 (2 equiv) in anhydrous acetonitrile at 50 °C for 24 h. [b] Isolated yield of the *trans*-epoxides after column chromatography. [c] Estimated on the ^{1}H NMR of the crude product.

The N-benzylated isatin reacted smoothly to afford a crystalline epoxide **4c** (entry 1). An X-ray crystal structure determination proved beyond doubt the trans configuration (see Supporting Information). The *N*-Boc derivative was completely destroyed in these conditions, likely due to its hydrolytic sensitivity (entry 2). Several *N*-methyl isatins, with various groups at C5, were transformed into *trans*-epoxides in good yields and excellent diastereomeric ratios (entries 3−8). For instance, the lipophilic properties could be modulated with fluorine groups (entries 5 and 6).[7d,8d] The 5-bromo **4f** and 5-iodo **4g** adducts offer the opportunity to functionalize via cross-coupling reactions. In general, a decrease in yield was observed with isatins having an electron-withdrawing group at C-5 (entries 4 and 8), compounds likely being prone to ring-opening events during the reaction.[17] Indeed, the epoxidation of isatin **1j**, having a 5-NO_2 group, led to more side products before the purification, which forced us not to predict a dr higher than 95:5. Nevertheless, in all cases, we obtained exclusively these new stable *trans*-oxiranes after column chromatography, from highly diastereoenriched crude products.

To extend the scope of this methodology, we targeted the unprotected isatin epoxidation (Scheme 2).

In regular conditions, however, the expected competitive N-alkylation of the secondary lactam moiety by α-bromo acetamide **2a** took place. So, we devised an alternative approach with the in situ preformation of the sulfonium salt to maximize the concentration of the ylide reagent after deprotonation, thereby favoring the epoxidation. With this purpose, we discovered a practical one-pot protocol. A rapid thiolane alkylation took place in a small amount of water

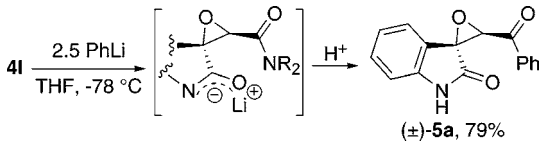
Scheme 2. One-Pot Epoxidation of Isatin



(Scheme 2), resulting in complete sulfonium formation within 90 min (see Supporting Information).[18,19] In fact, the original two-layered mixture became homogeneous along with the salt formation, which is stabilized in such polar aqueous media. Then, we simply added the isatin, the base, and an organic solvent. The facile one-pot process furnished the corresponding *trans*-epoxide **4l** and a small amount of the N-alkylated epoxide **4k** (10% yield). The changes in electronic properties of the transient deprotonated keto-amide did not affect the diastereoselective epoxidation outcome. Although the yield decreased with respect to the *N*-alkyl isatin epoxidation, this expeditious protocol avoids any protection−deprotection sequence from the commercially available isatins.

The new bisglycidic amide **4l**, featuring a secondary lactam, turned out to be useful for further functionalization of the amide moiety (Scheme 3). Preliminary experiments

Scheme 3. Chemoselective Introduction of the Phenyl Moiety



demonstrated that the addition of either phenyllithium[20] or phenyl magnesium bromide was not chemoselective onto *N*-methyl epoxyoxindole **4a** and led to a mixture of products. Nevertheless, we took advantage of the in situ deprotonation of the secondary lactam of **4l**, which acted as a self-protective group against nucleophilic addition events. Thereby, making use of a phenyllithium excess, the benzoyl-functionalized epoxide **5a** was selectively formed with a satisfying 79% yield. This crystal compound was successfully subjected to X-ray analysis, which proved the trans configuration.[21]

(16) Arai, S.; Tokumaru, K.; Aoyama, T. *Tetrahedron Lett.* **2004**, *45*, 1845.

(17) Anthony, W. C. *J. Org. Chem.* **1966**, *31*, 77.

(18) Running the reaction between thiolane and α-bromo acetamide **2a** in an NMR tube showed that only 23% of sulfonium salt was formed after 80 min in a mixture of MeCN−H_2O (9:1).

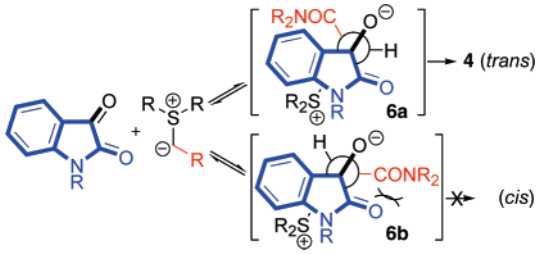
(19) For in situ formation of sulfonium salts for ylide cyclopropanation chemistry, see: Rasmy, O. M.; Vaid, R. K.; Semo, M. J.; Chelius, E. C.; Robey, R. L.; Alt, C. A.; Rhodes, G. A.; Vivenzi, J. T. *Org. Process Res. Dev.* **2006**, *10*, 28. See ref 14 for the the sulfonium salt isolation.

(20) Meth-Cohn, O.; Chen, Y. *Tetrahedron Lett.* **1999**, *40*, 6069.

(21) The ^{1}H NMR of **5a** was already described by Dandia[3d] and assigned as the *cis*-epoxide. We obtained the same ^{1}H NMR spectrum; however, according to the X-ray crystal structure, this is a *trans*-epoxide.

According to recent mechanistic studies,[11a] the sulfonium ylide epoxidation of aldehydes usually proceeds via three chemical steps: (step 1) an addition reaction leading to *cisoid* betaines via a quasi [2+2] approach of the ylide reagent; (step 2) a C−C bond rotation affording *transoid* betaines such as **6** (Scheme 4); and (step 3) the ring-closing process.

Scheme 4. Proposed Epoxidation Model

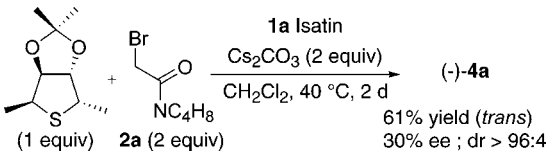


Aggarwal and co-workers investigated the benzaldehyde epoxidation by amide-stabilized sulfonium ylides with DFT computational methods,[14f] revealing that both steps 1 and 2 are endothermic and, therefore, the betaine intermediates easily reverse to the starting materials. The authors found that the ring-closing step (exothermic) was indeed the rate-limiting step and determined the trans/cis ratio. We assume that the isatin epoxidation follows the same pattern. The *transoid* betain **6b**, or the transition state thereof, would suffer from electrostatic repulsions between the two polar amide groups. Therefore, the destabilized betaine **6b** would reverse to the starting sulfonium ylide, itself following the energetically favored *trans*-epoxide pathway (lower energetic barrier from **6a** to the *trans*-epoxide, the amides being opposite to each other).[22]

(22) Recently, a related explanation was proposed to account for the diastereoselective sulfonium ylide cyclopropanation of 3-methylene oxindoles. See: Yong, S. R.; Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron* **2007**, *63*, 1191.

Eventually, we tackled the enantioselective synthesis of these spiro-heterocycles (Scheme 5).[9] A C_2 symmetrical

Scheme 5. Enantioselective Synthesis



sulfide afforded a promising and straightforward entry to the nonracemic epoxyoxindole **4a** with moderate enantioselectivity.[23]

This study has shown that in situ sulfonium ylide formation represents a user-friendly and powerful tool for the diastereoselective elaboration of epoxyoxindoles from readily available isatins. This methodology affords a new and straightforward access to these interesting bioactive compounds and analogues. From the preliminary results therein, this approach should constitute a promising platform toward the development of an asymmetric synthesis of these spiro-epoxides from chiral sulfides.

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Supporting Information Available: Experimental procedures and analytical data for all new products as well as X-ray structural data of **4c** and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070439X

(23) The (*R*,*R*)-2,5-dimethylthiolane afforded the (+)-epoxide **4a** in similar enantioselectivities. For sulfide synthesis, see: Davoust, M.; Brière, J.-F.; Jaffrès, P.-A.; Metzner, P. *J. Org. Chem.* **2005**, *70*, 4166.