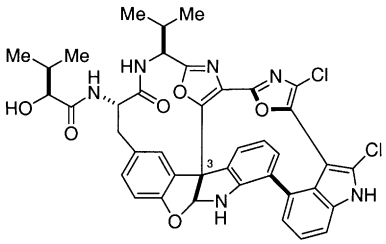
Stereogenic Quaternary Centers

Catalytic Enantioselective Synthesis of Oxindoles and Benzofuranones That Bear a Quaternary Stereocenter**

*Ivory D. Hills and Gregory C. Fu**

A diverse array of indole alkaloids and benzofuran-derived natural products bear quaternary stereocenters in the 3-position of the heterocycle.[1,2] Although noteworthy progress has been described in the development of strategies for the enantioselective synthesis of such compounds,[3] there remains a need for additional approaches.



diazonamide A gelsemine

In 1986, Black et al. reported that 4-dimethylaminopyridine (DMAP) catalyzes the rearrangement of *O*-acylated benzofuranones to give their *C*-acylated isomers [Eq. (1)].[4] During the course of studies directed toward the synthesis of

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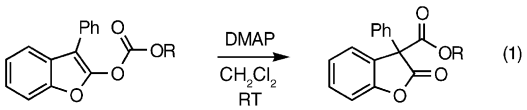
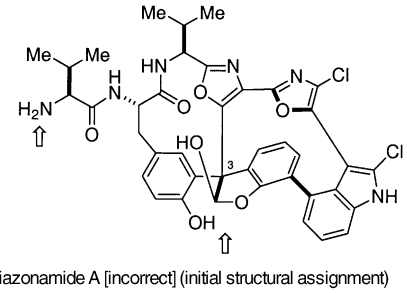
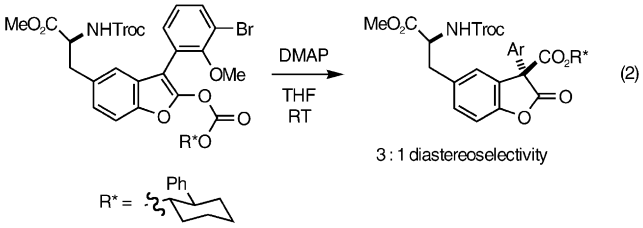


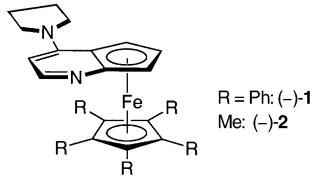
the originally assigned incorrect structure of the potent anticancer agent diazonamide A,[5] Moody et al. employed a non-asymmetric Black-type *C*-acylation to generate the



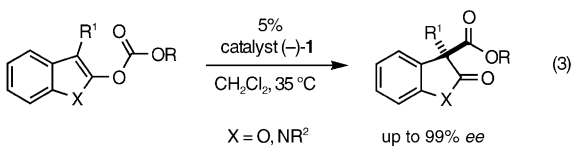
quaternary stereocenter of the benzofuran-derived core.[6] A few years later, also in the context of an approach to the synthesis of the incorrect structure of diazonamide A, Vedejs and Wang described a diastereoselective variant of the Black rearrangement reaction [Eq. (2)] (Troc = trichloroethoxycarbonyl).[7] Notably, for the correct structure of diazonamide A (above), a corresponding *C*-acylation strategy would employ an oxindole rather than a benzofuranone as the substrate.



In recent years, we have been pursuing the development of applications of chiral derivatives of DMAP and PPY (PPY = 4-(pyrrolidino)pyridine; e.g., **1** and **2**) to a range of

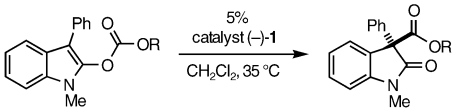


enantioselective nucleophile-catalyzed transformations.[8] In view of the potential significance of the reaction products, we decided to explore the use of these catalysts in asymmetric rearrangements of *O*-acylated benzofuranones and oxindoles. Herein we provide the first examples of enantioselective variants of these processes, demonstrating that catalyst **1** generates the new quaternary stereocenter with very good enantiomeric excess [Eq. (3)].



Our initial studies focused on *O*-acylated oxindoles, a family of compounds that had not previously been explored in the context of O-to-C rearrangements. We generated a representative substrate by treating an oxindole with methyl chloroformate, and we were pleased to discover that PPY derivative **1** did, indeed, catalyze the rearrangement of the resulting carbonate, thus providing a new quaternary stereocenter with promising enantioselectivity (Table 1, entry 1).

Table 1: Effect of the acyl group on the enantioselectivity of O-to-C rearrangements.



Entry	R	*ee* [%][a]
1	Me	58
2	Et	63
3	*t*Bu	–[b]
4		98

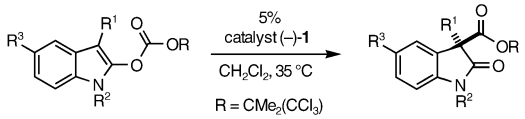
[a] The data are an average of two runs. [b] No rearrangement was observed.

We subsequently determined that an increase in the bulk of the carbonate group (Me→Et) led to an increase in the enantioselectivity (Table 1, entries 1 and 2, 58→63% *ee*). Unfortunately, in the case of a *tert*-butyl substituent, the rearrangement did not proceed, presumably due to a steric effect (Table 1, entry 3). However, we were able to overcome this lack of reactivity through electronic activation, specifically, the use of a trichloro-*tert*-butyl group: rearrangement of this carbonate furnished the desired product with very good enantioselectivity (Table 1, entry 4, 98% *ee*).[9]

With the trichloro-*tert*-butoxycarbonyl substituent as the migrating group, catalyst **1** promotes the rearrangement of a variety of oxindole derivatives with high enantioselectivity (Table 2).[10,11] The reaction proceeds cleanly with either aromatic or heteroaromatic groups in the 3-position (Table 2, entries 1 and 2).[12] 3-Alkyl-substituted *O*-acylated oxindoles can also be employed as substrates, although these rearrangements are slower and require a 10% catalyst loading to obtain a good yield (Table 2, entries 3 and 4). Substitution on the six-membered ring is tolerated, furnishing a product suitable for further functionalization (Table 2, entry 5). Finally, the reaction is not limited to *N*-methyl-substituted oxindoles—catalyst **1** also promoted the rearrangement of an *N*-benzyl-protected heterocycle with high enantioselectivity (Table 2, entry 6).[13]

The conditions that we employed for O-to-C rearrangements of oxindole derivatives (Table 2) are directly applicable to the corresponding reactions of *O*-acylated benzofuranones

Table 2: Catalytic enantioselective rearrangement of oxindole derivatives.

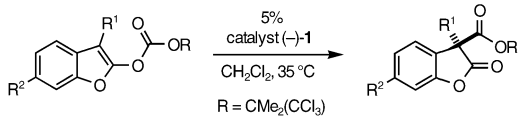


Entry	R^1	R^2	R^3	*ee* [%][a]	Yield [%][a]
1	Ph	Me	H	99	91
2	2-thienyl	Me	H	95	81
3[b]	benzyl	Me	H	94	82
4[b]	Me	Me	H	93	72
5	Ph	Me	I	98	94
6	Ph	Bn	H	98	88

[a] Yield of isolated products. The data are an average of two runs. [b] Catalyst loading: 10%.

(Table 3).[14] Thus, for both 3-aryl- and 3-alkyl-substituted compounds, catalyst **1** promotes the generation of the new quaternary stereocenter with very good enantioselectivity.[15,16]

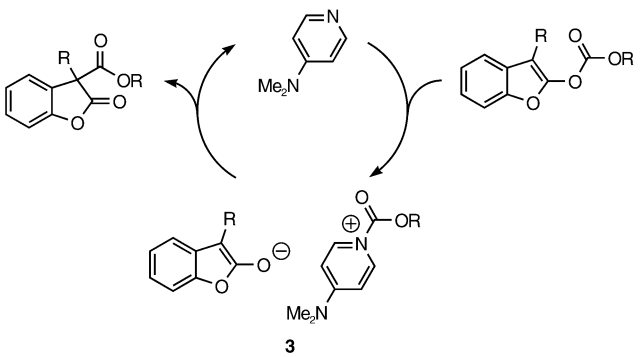
Table 3: Catalytic enantioselective rearrangement of benzofuranone derivatives.



Entry	R^1	R^2	*ee* [%]	Yield [%][a]
1	Ph	H	97	81
2	Bn	H	88	95
3[b]	Me	Me	90	93

[a] Yield of isolated product. [b] This reaction was run at −12 °C with 10% catalyst.

Black et al. suggested that DMAP-catalyzed rearrangements of *O*-acylated benzofuranones proceed through the mechanism illustrated in Scheme 1.[4] We believe that asymmetric reactions of *O*-acylated benzofuranones and oxindoles catalyzed by PPY derivative **1** follow an analogous pathway. Indeed, we have been able to obtain a low-resolution X-ray crystal structure of the ion pair corresponding to **3** (Figure 1).[17–19]



Scheme 1. Proposed mechanism for DMAP-catalyzed rearrangements of *O*-acylated benzofuranones.

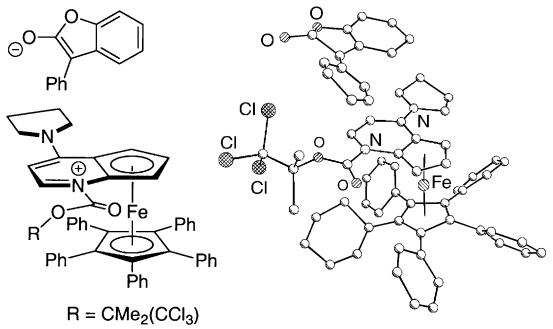


Figure 1. X-ray crystal structure of an ion pair derived from catalyst **1** and an *O*-acylated benzofuranone.

In summary, we have developed the first method for the catalytic enantioselective rearrangement of *O*-acylated benzofuranones and oxindoles, an efficient carbon–carbon bond-forming reaction that generates a quaternary stereocenter. On the mechanistic side, we have crystallographically characterized the presumed intermediate in this process. In view of the abundance of important indole- and benzofuran-derived natural products that bear a quaternary stereocenter in the 3-position of the heterocycle, we believe that this method may prove useful in asymmetric synthesis.

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[1] For a sampling of recent total syntheses, see: a) gelsemine: H. Lin, S. J. Danishefsky, *Angew. Chem.* **2003**, *115*, 38–53; *Angew. Chem. Int. Ed.* **2003**, *42*, 36–51; b) strychnofoline: A. Lerchner, E. M. Carreira, *J. Am. Chem. Soc.* **2002**, *124*, 14826–14827; c) alantrypinone: D. J. Hart, N. A. Magomedov, *J. Am. Chem. Soc.* **2001**, *123*, 5892–5899; d) spirotryprostatin B: L. E. Overman, M. D. Rosen, *Angew. Chem.* **2000**, *112*, 4768–4771; *Angew. Chem. Int. Ed.* **2000**, *39*, 4596–4599.

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[3] For example, the intramolecular asymmetric Heck reaction has proved to be useful; for leading references, see: a) A. D. Lebsack, J. T. Link, L. E. Overman, B. A. Stearns, *J. Am. Chem. Soc.* **2002**, *124*, 9008–9009; b) Y. Donde, L. E. Overman in *Comprehensive Asymmetric Catalysis*; (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**, pp. 675–697.

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[9] 2,2,2-Trichloro-1,1-dimethylethyl chloroformate is commercially available. The trichloro-*tert*-butoxycarbonyl group has been employed in kinetic resolutions of secondary alcohols by an *N*-acylated chiral derivative of DMAP: a) E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1996**, *118*, 1809 – 1810. Catalyst (−)-**2** affords essentially identical enantioselectivity as (−)-**1** (97% *ee*; same enantiomer of the product as (−)-**1**); we chose to focus our studies on catalyst **1**, since it is particularly stable.

[10] The absolute stereochemistry of the product of Table 2, entry 3 was determined by X-ray crystallography (see the Supporting Information); the other configurations were assigned by analogy.

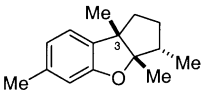
[11] General procedure: The substrate (1.00 equiv) and catalyst (−)-**1** (0.050 equiv) were added, exposed to the air, to a vial that contained a stirrer bar. The vial was sealed with a septum and purged with argon. CH_2Cl_2 ([substrate] = 1.0 M) was then added to the vial through a syringe, and the reaction mixture was heated at 35 °C for 48 h. The reaction mixture was then applied directly to a silica-gel column for purification by flash chromatography (typically, ~85% of the catalyst was recovered).

[12] The slight difference in enantiomeric excess between Table 1, entry 4 and Table 2, entry 1 is due to the difference in the scale of the reactions. See the Supporting Information for additional details.

[13] In preliminary studies, we selectively hydrolyzed (aqueous NaOH) and transesterified (NaOMe) the trichloro-*tert*-butyl ester group.

[14] The absolute stereochemistry of the product of Table 3, entry 1 was determined by X-ray crystallography (see the Supporting Information); the other configurations were assigned by analogy.

[15] We employed the product of Table 3, entry 3 in a formal total synthesis of debromoaplysin (I. D. Hills, unpublished results).



debromoaplysin

[16] Under our standard reaction conditions, the benzofuranone-derived substrates react more rapidly than do the oxindole-derived compounds.

[17] In the original studies of Black et al., a solid was generated under certain conditions and speculated to be the ion-pair intermediate. Unfortunately, the solid could not be characterized.[4]

[18] The quality of the crystal was sufficiently high to unambiguously assign the structure of the ion pair, but not sufficiently high to accurately determine bond lengths. CCDC-208287 contains the supplementary crystallographic data for **3**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[19] The *ee* of the product does not erode with time, indicating that *C*-acylation of the enolate is irreversible; ^{1}H NMR studies show that for the benzofuranone chemistry, the resting state of the catalyst is the *N*-acylated derivative, whereas for the oxindole chemistry, the resting state is the catalyst itself (not acylated).

