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Short, Enantioselective Total Synthesis of Aflatoxin B_2 Using an Asymmetric [3+2]-Cycloaddition Step

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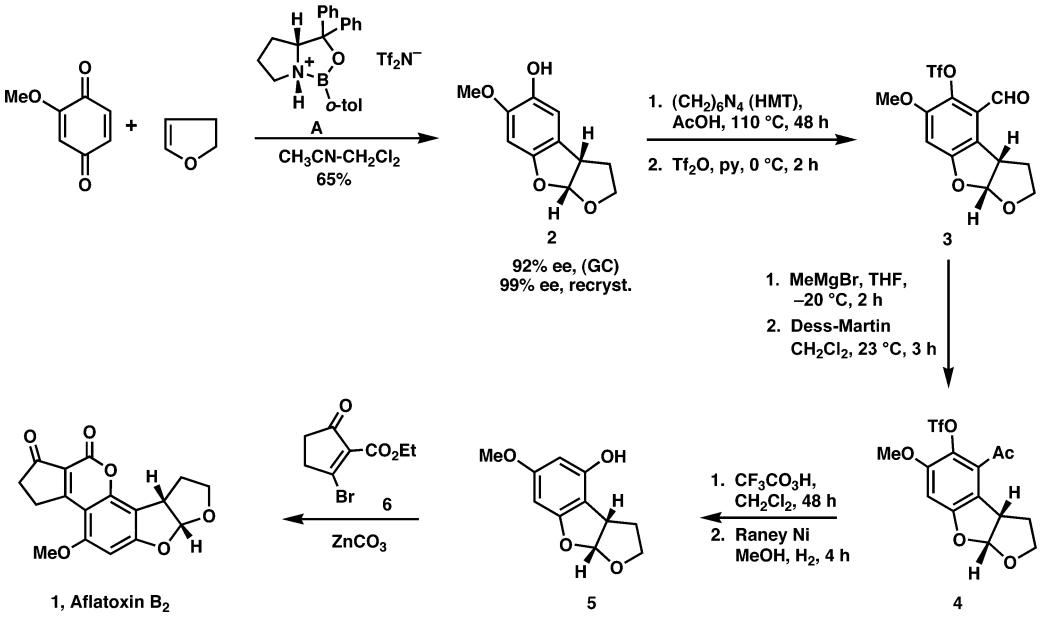
[3+2]-Cycloaddition reactions are among the most powerful tools for chemical synthesis because they provide unique access to numerous five-membered ring systems and allow a rapid buildup of molecular complexity. However, enantioselective versions of these processes have just begun to emerge.[1] We report herein a novel enantioselective addition of 1,4-benzoquinones with vinyl ethers catalyzed by the chiral oxazaborolidinium ion **A** (or the enantiomer; see Scheme 1), a reagent that has previously been shown to be exceedingly effective for the control of absolute stereochemistry for many types of Diels−Alder reactions,[2] and the application of this methodology to a short enantioselective total synthesis of the potent naturally occurring mutagen aflatoxin B_2 (**1**, Scheme 1). Since the first synthesis of racemic aflatoxins by the groups of Büchi and Roberts,[3] there have been numerous syntheses of the racemates,[4] but only recently has an enantioselective route been described.[5]

The synthesis of aflatoxin B_2 is summarized in Scheme 1. Reaction of 2-methoxy-1,4-benzoquinone with 2,3-dihydrofuran (1.5 equiv) in the presence of the (*R*)-oxazaborolidinium triflimide **A** (0.2 equiv) in 1:1 CH_2Cl_2−CH_3CN as solvent at −78 to 23 °C over 7 h produced the [3+2]-cycloadduct **2** as the major product (65% isolated yield) along with the regioisomer produced by [3+2]-cycloaddition to O-1 and C-6 of the quinone as the minor product (32% isolated yield) after chromatography on silica gel.[6−8] The structure and absolute configuration of **2** was determined by X-ray crystallographic analysis both of **2** and the 4-bromobenzoate ester.[6] The enantiomeric purity of **2** was determined to be 92% by GC analysis; after one recrystallization from ether, enantiomerically pure **2**, mp 151−152 °C, $[\alpha]^{23}_D$ −96 (c = 1.0, $CHCl_3$), was obtained. An explanation for the absolute stereochemical course of the formation of **2** is presented in Scheme 2. The phenolic cycloadduct **2** was transformed into the aldehyde **3** by sequential orthoformylation (ca. 40%)[6,7] and triflate ester formation (ca. 80%).[6,7] Conversion of the aldehyde to the corresponding methyl ketone (**4**) was effected by treatment with MeMgBr and subsequent oxidation (85%). Baeyer−Villiger oxidation of **4** and reductive removal of the triflate group together with deacetylation gave the tricyclic phenol **5** (ca. 40% overall).[6,7] Treatment of **5** with the β-bromo-α,β-enone **6** (1.2 equiv) in the presence of $ZnCO_3$ in CH_2Cl_2 as solvent at 23 °C for 24 h produced aflatoxin B_2 (36% yield), having physical properties identical with those reported.[3a,b,6]

A variety of solvents were tested for the critical [3+2]-cycloaddition reaction leading to adduct **2**. Although good enantioselectivity was obtained with toluene or CH_2Cl_2 as solvent, the reactions were slower than with 1:1 CH_2Cl_2−CH_3CN as solvent. The use of CH_3CN or Me_2CHCN as solvent was slightly inferior with regard to product enantiomeric excess than was 1:1 CH_2Cl_2−CH_3CN.

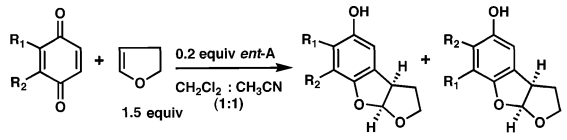
The scope of the [3+2]-cycloaddition reaction was examined with a number of substrates using the *S*-enantiomer of catalyst **A**. The results are summarized in Table 1. The symmetrical quinones, 1,4-benzoquinone and 2,3-dimethyl-1,4-benzoquinone, gave a single [3+2]-cycloadduct, as expected (Table 1, entries 4 and 5). The unsymmetrical quinones shown in entries 1−3 of Table 1 generally

Scheme 1. Synthesis of Aflatoxin B_2



10.1021/ja054503m CCC: $30.25

Table 1. Enantioselective [3+2] Reactions of 1,4-Benzoquinones and 2,3-Dihydrofuran

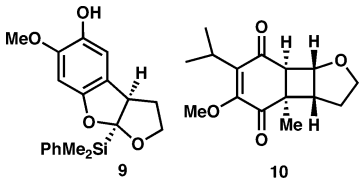


Entry	R_1	R_2	Conditions (°C, h)	% yield[a] (7; 8)[b]	% ee[c]
1	MeO	H	–78 °C, 2 h then, –78 °C to 23 °C, 5 h	65; 32	92; 90
2	MeO		–78 °C, 3 h then, –78 °C to 23 °C, 5 h	75; 15[d]	95
3	MeO	Me	–78 °C, 3 h then, –78 °C to 23 °C, 5 h	68; 29	95
4	H	H	–95 °C, 2 h then, –78 °C to 23 °C, 5 h	63	91
5	Me	Me	–78 °C, 2 h then, –78 °C to 23 °C, 5 h	82	98

[a] Isolated yield. [b] Ratios of regioisomers were determined by ^{1}H NMR analysis at 400 MHz. [c] Enantioselectivities were determined by GC analysis or HPLC analysis using chiral columns.[6] [d] Structures proved by X-ray crystallographic analysis.[6]

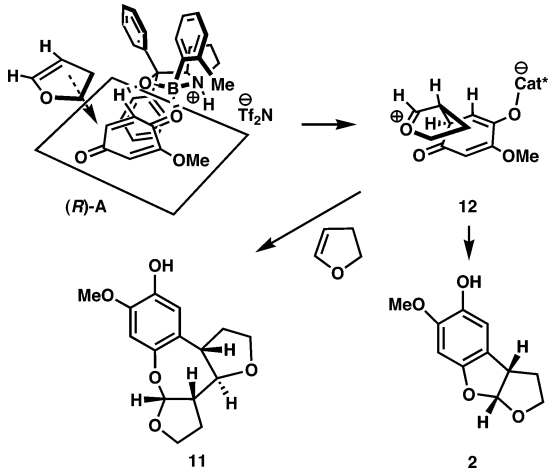
afforded two regioisomers, with the major regioisomer being **7** (corresponding to **2** of Scheme 1). The formation of two regioisomers for entries 1−3 can be understood in terms of two different pathways involving catalyst coordination to each of the two different quinone oxygens. Although coordination to the more basic oxygen may predominate, the other mode of coordination probably leads to a faster [3+2]-cycloaddition rate.[2h] The structures of both adducts of entry 1 were determined unambiguously by X-ray crystallographic analyses, as was the structure of the major adduct of entry 2.

In another example, the reaction of 2-methoxy-1,4-benzoquinone with 5-dimethylphenylsilyl-2,3-dihydrofuran under the standard conditions of Table 1 provided the [3+2]-cycloadduct **9** in 82% yield (only regioisomer formed) and 98% ee. It is clear from this result that additional substitution on the olefinic linkage of the vinyl ether component is tolerated in the cycloaddition process and also that very high regioselectivity is possible with unsymmetrical components. Finally, when the reaction of 2-methyl-5-isopropyl-6-methoxy-1,4-benzoquinone and 2,3-dihydrofuran was carried out with 0.2 equiv of the *S*-catalyst *ent*-**A**, the [2+2]-cycloadduct **10** was obtained as the major product (25% isolated yield, 99% ee).[8]



A mechanistically powerful result for understanding the pathway of the [3+2]-cycloaddition reaction leading to **2** has been obtained by a simple trapping experiment. When the reaction of 2-methoxy-1,4-benzoquinone and 2,3-dihydrofuran was carried out with 10 equiv of the latter and 0.2 equiv of catalyst **A**, the major products were **2** (53% isolated yield, 91% ee) and the 2:1 adduct **11** (41%, 85% ee), with the structure of **11** being fully confirmed by X-ray crystallographic analysis.[6] We believe that the formation of **11** results from the trapping of a 1:1 dipolar intermediate (**12** in Scheme 2) in the [3+2]-cycloaddition process. It is possible that both **2** and **11** are formed from that dipolar intermediate, as shown in Scheme 2 (see also refs 1a−1h).

Scheme 2. Rational Pathway for the Formation of **2** and **11** via **12** with Catalyst **A**



The enantioselective and unusually short synthesis of aflatoxin B_2 shown in Scheme 1 illustrates the utility of the new methodology described herein.

Supporting Information Available: Additional experimental procedures and spectral data for reaction products (22 pages, print/PDF). X-ray crystallographic data for **2**, the 4-bromobenzoate of **2**, **11**, and the products of entries 1 and 2 of Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) See Supporting Information for full details.

(7) Yield not optimized.

(8) For a discussion relevant to the regiochemistry of the [3+2]-cycloaddition reactions reported herein, see ref 2h. For Ti-catalyzed [2+2]-cycloadditions to 1,4-benzoquinones, see: Engler, T. A.; Letavic, M. A.; Rajesh, I.; La Tessa, K. O.; Reddy, J. P. *J. Org. Chem.* **1999**, *64*, 2391−2405.

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