A C–H Functionalization Strategy Enables an Enantioselective Formal Synthesis of (–)-Aflatoxin B_2

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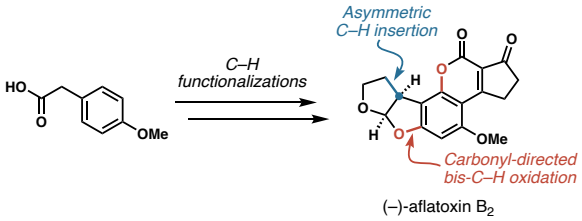
Supporting Information Placeholder



ABSTRACT: An enantioselective formal synthesis of (–)-aflatoxin B_2 from 4-methoxyphenylacetic acid has been achieved by an approach that produces a key carbon–carbon bond, benzylic stereocenter, and two arene carbon–oxygen bonds in the course of three site-selective C–H functionalizations. The carbonyl-directed acetoxylation of two arene C–H bonds described herein is unprecedented in natural products synthesis and occurs under mild conditions that preserve the configuration of a sensitive benzylic stereocenter.

The aflatoxins (**1**–**4**) gained notoriety in the 1960s when it was discovered that they caused the mass turkey death (Turkey X disease) in Great Britain, as well as animal and human deaths during outbreaks of aflatoxicosis in ensuing years.[1–3] These mycotoxins—produced by the pathogenic fungi *Aspergillus flavus, A. versicolor*, and *A. parasiticus*—are dangerous liver carcinogens, afflicting humans and animals that ingest contaminated grain flour, nuts, and corn. In their pure states, aflatoxins B and G fluoresce blue and green, respectively,[4] and their

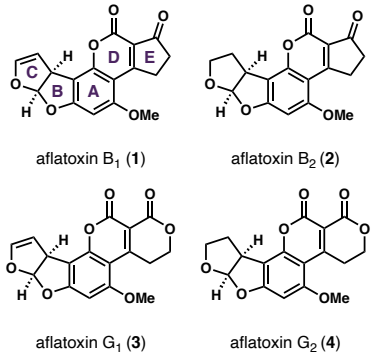
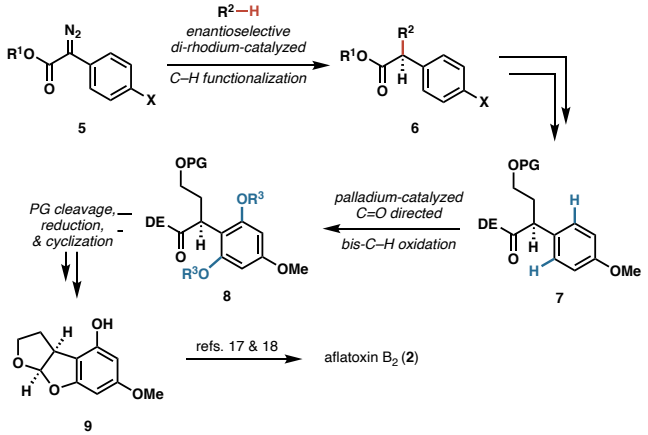


Figure 1. Aflatoxins B_1 (**1**), B_2 (**2**), G_1 (**3**), and G_2 (**4**).

molecular structures were elucidated by the incisive studies of Büchi and coworkers[5–7] and confirmed by X-ray crystallographic analyses.[8] The aflatoxins comprise a substituted coumarin framework annulated to two dihydrofuran rings and either a cyclopentanone ring [e.g. aflatoxins B_1 (**1**) and B_2 (**2**)] or a δ-lactone ring [e.g. aflatoxins G_1 (**3**) and G_2 (**4**)]. The C-ring alkene of aflatoxins B_1 (**1**) and G_1 (**3**) heightens the mutagenicity of these compounds in relation to their dihydro-counterparts.[9]

These biologically active metabolites have engendered several creative efforts in organic synthesis. Since the landmark racemic syntheses by Büchi[10,11] and Roberts,[12] the aflatoxins have served as testing grounds for novel synthetic strategies and methodologies over the last several decades. These efforts have culminated in several enantioselective syntheses,[13–20] many of which rely on the construction of the ABC-tricyclic core, followed by assembly of the D and E rings. In 2003, Trost and Toste achieved an asymmetric synthesis of aflatoxin B_1 in nine total steps, featuring palladium-catalyzed dynamic kinetic asymmetric transformations of γ-acyloxybutenolides to establish the stereochemistry at the ring-junction acetal.[14] The Corey laboratory subsequently reported a concise enantioselective synthesis of (–)-aflatoxin B_2 featuring a remarkable oxazaborolidinium-catalyzed [3+2]-cycloaddition.[17] More recent efforts towards aflatoxin B_2 have targeted tricyclic phenol **9**, which constitutes a formal synthesis of **2**.[15–19] The D and E rings may be annulated in one step through Büchi's Pechmann-type annulation[21] initially described in Corey's synthesis of aflatoxin B_2[17] and later improved by Zu.[19] As a consequence of its highly oxidized nature and sensitive stereogenic centers, furo[2,3-*b*]benzofuran **9** has proven challenging to construct and continues to inspire innovative concepts for synthesis.

Scheme 1. An approach to aflatoxin B_2 enabled by C–H functionalization.[a]

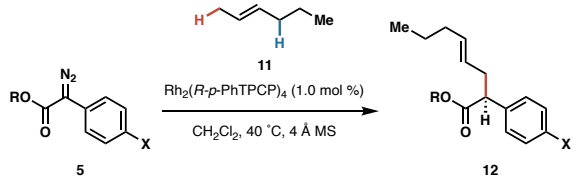


[a]PG = protecting group; DE = directing element.

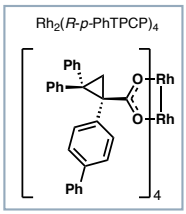
We anticipated that the molecular structures of aflatoxin B_2 (**2**) and its progenitor **9** would challenge the capabilities of emerging methods for transforming C–H bonds[22] and imagined that a synthesis of the aflatoxin core could arise by a sequence of site-selective C–H functionalizations on arylacetic acid derivative **5** (Scheme 1). Specifically, a donor-acceptor carbene C–H insertion mediated by a dirhodium catalyst[23] would construct a needed carbon–carbon bond and establish the associated benzylic stereocenter, while also installing functionality to enable an eventual annulation of rings B and C in compounds **2** and **9**. Enantioenriched **6** could thus be elaborated to key intermediate **7** through traditional functional group manipulations. To complete the oxidation pattern on the aromatic ring, we envisioned a carbonyl-directed bis-C–H palladation/oxidation. Ideally, this pivotal transformation could be facilitated by native functionality in an intermediate towards **9**, eliminating the need for directing group installation and removal.

Among the recent examples of palladium-catalyzed carbonyl-directed *ortho*-C–H oxidations of arylacetic acid derivatives,[24–28] we were drawn to a report from Yu and coworkers describing the C–H acetoxylation of Weinreb amides (DE = –N(OMe)Me), which included a single example of a selective bis-oxidation.[26,29] In light of these results, we reasoned that it might be possible to extend this reactivity platform and achieve a two-fold acetoxylation of the *ortho*-C–H bonds on an intermediate such as **7**. While we understood the challenges associated with this strategy, we were further encouraged by recent developments demonstrating the capacity of pyridine sulfonic acid ligands to lower the barrier for C–H activation of Weinreb amides.[30–32] We thus anticipated that a Weinreb amide could direct both arene C–H oxidations and provide facile access to the aldehyde oxidation state present in the aflatoxins through selective monoreduction. On the foundation of arylacetic acid derivative **5**, a key carbon–carbon bond, benzylic stereocenter, and the pattern of oxidation that distinguishes the aflatoxin A-ring would be rapidly constructed. In the wake of these transformations, we imagined that global protecting group cleavages and a partial reduction of the Weinreb amide moiety would generate a fleeting aldehyde (not shown), which could spontaneously cyclize to afford compound **9**, the penultimate intermediate in syntheses of aflatoxin B_2.[15–19]

Table 1. Enantioselective C–H insertion results for aryl diazoesters **5a**–**5e**.[a]



Entry	R	X	Yield	er	rr
1	CH_2CF_3	Cl (**5a**)	69	96:4	11:1
2	CH_2CCl_3	Cl (**5b**)	51	99:1	13:1
3	CH_2CCl_3	I (**5c**)	96	99:1	> 20:1
4	CH_2CF_3	OMe (**5d**)	59	98:2	11:1
5	CH_2CCl_3	OMe (**5e**)	47	98:2	10:1

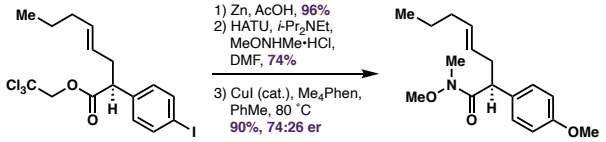


[a]Reactions were performed on a 0.30 mmol scale. Yields are reported as isolated yields following chromatography on silica gel. Enantiomeric ratio was determined by HPLC analysis using a chiral stationary phase. er = enantiomeric ratio; rr = regioisomeric ratio.

The execution of our synthesis commenced with an enantioselective C–H insertion using rhodium carbenes derived from aryldiazoacetates **5a**–**5e** (Table 1). Given the abundance of established methods for enantioselective allylic C–H insertions with donor-acceptor carbenes,[23,33] we investigated the viability of a 2-hexenyl fragment as the precursor to the C-ring in the natural product. A subsequent oxidative cleavage of the olefin and reduction of the resulting aldehyde would then enable the assembly of the furo[2,3-*b*]benzofuran system. This would require selective functionalization of the primary allylic C–H bond (Table 1, red C–H bond) over the more electron-rich secondary allylic position (Table 1, blue C–H bond) in (*E*)-2-hexene (**11**). Early efforts to circumvent issues of regioselectivity using anethole furnished the insertion product in moderate yield (see Supporting Information for details).

Based on prior work from the Davies group,[33,34] reactions of trifluoroethyl and trichloroethyl esters were evaluated with the triarylcyclopropane carboxylate catalyst, Rh_2(*R*-*p*-PhTPCP)$_4$. At the outset, we were concerned that the electron-rich nature of the *p*-methoxyphenyl derivative might cause deleterious dimerization of the rhodium carbene during attempts to perform the C–H insertion and set the benzylic stereocenter. We anticipated that *p*-halo-substituted carbenes **5a**–**5c** would react more efficiently, while also providing a functional handle to introduce the methoxy group at a later stage. This maneuver, albeit less expeditious, would provide additional flexibility if the bis-C(sp^2)–H oxidation proved challenging on an electron-rich *p*-methoxyphenyl intermediate of the type **7**.

Scheme 2. Investigating a C–O coupling strategy[a]

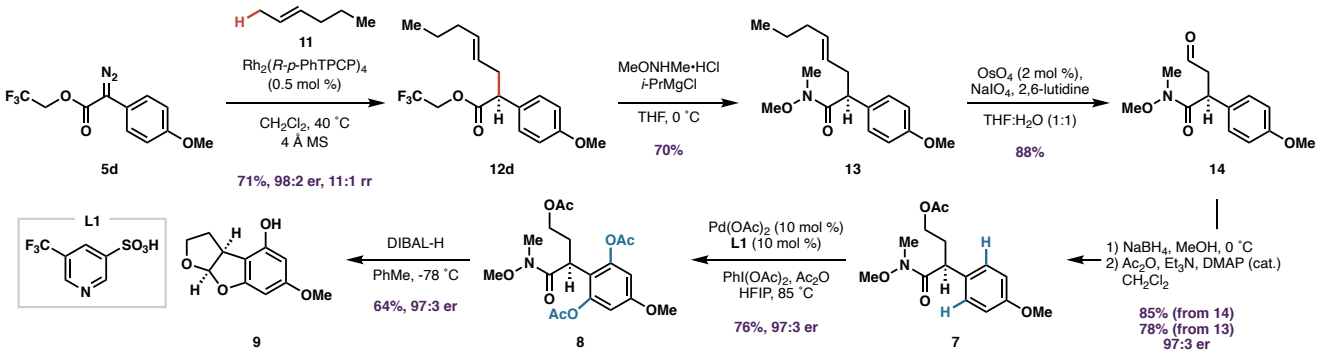


[a]HATU = hexafluorophosphate azabenzotriazole tetramethyl uronium; DMF = *N*,*N*-dimethylformamide; Me_4Phen = 3,4,7,8-tetramethyl-1,10-phenanthroline; er = enantiomeric ratio.

Reactions with *p*-chlorophenyl diazoesters **5a** and **5b** furnished the desired insertion products with moderate to good yields and excellent enantio- and regioselectivity (Table 1, entries 1 and 2). Iodo-substituted derivative **5c** performed exceptionally well under the reaction conditions, providing **12c** in 96% yield and excellent enantioselectivity as a single detectable regioisomer (entry 3). Gratifyingly, reactions with *p*-methoxyphenyl diazoesters also delivered the desired insertion products, albeit with slightly diminished yields (entries 4 and 5). These highly selective transformations highlight the ability of sterically demanding rhodium triarylcyclopropane carboxylate catalysts to achieve catalyst-controlled, site-selective C–H functionalizations. The lower yields obtained with diazoesters **5d** and **5e** demonstrate the sensitivity of this transformation to the electronics of donor-acceptor rhodium carbenes.

The highly efficient and selective C–H insertion with **5c** prompted efforts to install the methoxy group present in the natural product and advance to the bis-C–H oxidation step. Conversion of the trichloroethyl ester moiety to a Weinreb amide was readily achieved using standard conditions (Scheme 2). Although this intermediate could be efficiently converted to the desired *p*-methoxyphenyl derivative via Buchwald's C–O coupling conditions,[35] the sensitive benzylic stereocenter partially racemized under the basic conditions required for the conversion of ester **12c** to **13** (er = 74:26, see Supporting Information). The erosion of enantiopurity while advancing **12c** compelled us to revisit the insertion with *p*-methoxyphenyl diazoester **5d**.

Scheme 3. Completing the enantioselective formal synthesis of (–)-aflatoxin B_2.



[a]DMAP = 4-dimethylaminopyridine; HFIP = 1,1,1,3,3,3-hexafluoroisopropanol; DIBAL-H = diisobutylaluminum hydride; rr = regioisomeric ratio; er = enantiomeric ratio.

Fortunately, we found that the yield of this transformation could be improved to 71% on multigram-scale with 0.5 mol % catalyst loading (Scheme 3).

At this juncture, we turned our attention to the task of oxidizing the arene C–H bonds to access the phloroglucinol core of aflatoxin B_2. To this end, the trifluoroethyl ester of compound **12b** could be directly converted to the Weinreb amide, thereby setting the stage for the palladium-catalyzed C–H acetoxylations (Scheme 3). Anticipating that the olefin in **13** may interfere with attempts to effect this transformation, we elected to elaborate the 2-hexenyl fragment to a suitable precursor to the C-ring in the natural product. Intermediate **13** was unexpectedly sensitive to established oxidative cleavage conditions, and attempts to reductively cleave the olefin (O_3; $NaBH_4$) and directly obtain the corresponding primary alcohol were unsuccessful. Further screening revealed that treatment with catalytic osmium tetroxide and sodium periodate in the presence of 2,6-lutidine afforded aldehyde **14** in 88% yield (see Supporting Information for details).[36]

Unfortunately, early attempts to delay the reduction of the aldehyde to the final cyclization cascade by directly performing the amide-directed C–H acetoxylation on racemic aldehyde **14** under Yu's conditions resulted in complicated mixtures with no detectable amounts of the desired diacetoxylated product. To overcome this, we converted aldehyde **14** to acetate ester **7** in 85% yield by way of a two-stage reductive acetylation sequence prior to oxidation of the aromatic ring. Thus, the stage was set for the pivotal bis-C(sp^2)–H oxidation. Upon exposure to Yu's palladium-catalyzed directed acetoxylation conditions[26] using pyridine sulfonic acid ligand **L1**,[30–32] acetate **7** was smoothly converted to phloroglucinol derivative **8** in 76% yield. This ligand scaffold was particularly effective in promoting the desired two-fold oxidation; other ligands suitable for palladium-catalyzed C–H activation[26,37–40] gave low yields of the desired product (see Supporting Information for details). To the best of our knowledge, this is the first reported example of a two-fold C(sp^2)–H oxidation directed by a native functional group in complex molecule synthesis. With the oxidation of the central aromatic ring set, treatment of **8** with excess diisobutylaluminum hydride (DIBAL-H) at low temperature accomplished a selective monoreduction of the Weinreb amide and reductive cleavage of all three acetates to liberate a putative aldehyde intermediate (not shown); this reactive compound spontaneously cyclized with annulation of rings B and C and afforded **9** in 64% yield, thus completing our formal synthesis of **2**.

A concise formal synthesis of (–)-aflatoxin B_2 (**2**) has been achieved by a strategy that is reliant on three site-selective C–H functionalizations. Key features of this approach include a chiral di-rhodium mediated C–H insertion that not only establishes a key benzylic stereocenter with high margins of enantioselectivity, but also installs functionality appropriate for the annulation of the C-ring in **2**. A carbonyl-directed bis-acetoxylation to site-selectively introduce oxidation eliminated the need for late-stage manipulations on the central aromatic ring and was achieved under mild conditions that preserved a delicate benzylic stereogenic center; we anticipate that this mode of reactivity will find applications in syntheses of other highly oxygenated complex molecules. Together, these pivotal transformations provide direct access to the tricyclic core of **2** and highlight the considerable potential of site-selective C–H functionalizations in natural products synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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