# Palladium-Catalyzed Kinetic and Dynamic Kinetic Asymmetric Transformation of 5-Acyloxy-2-(5H)-furanone. Enantioselective Synthesis of (−)-Aflatoxin B Lactone

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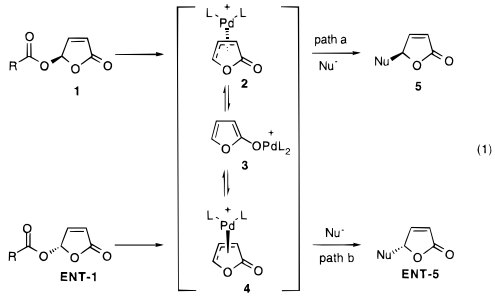
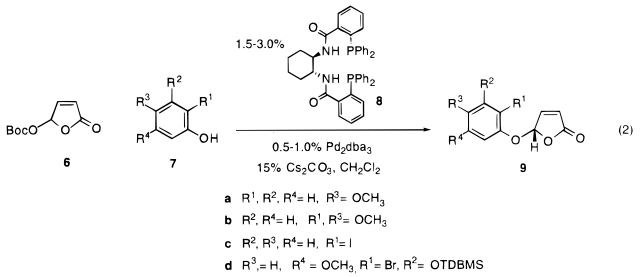
The ability to achieve dynamic kinetic asymmetric transformations is an efficient method for asymmetric synthesis since 100% of the racemic starting material is converted to a single enantiomeric product.[1] In considering this question within the context of asymmetric metal catalyzed allylic alkylations, we were attracted to $\gamma$-acyloxybutenolides as substrates. First, the utility of $\gamma$-alkoxybutenolides as synthons for asymmetric synthesis of natural products has spurred the development of methods for their asymmetric preparation.[2,3] Second, they offer an interesting structural feature that may facilitate the process as illustrated in eq 1. While ionization of racemic **1** initially generates the two




(1)

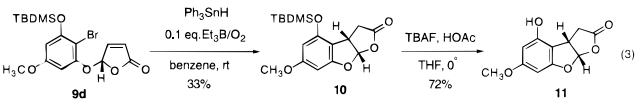
$\pi$-allylpalladium intermediates **2** and **4**, their interconversion through the expediency of a $\sigma$-complex like **3** provides a vehicle for their interconversion. The aromaticity of the furan may serve as a driving force to go from the $\eta^3$ to the $\eta^1$ complex. If interconversion is fast relative to nucleophilic addition and if one of these diastereomeric $\eta^3$-complexes **2** or **4** (in the presence of chiral ligands) undergoes reaction faster than the other, then an effective dynamic kinetic asymmetric transformation would result. In this paper, we explore the behavior of such butenolides in the presence of chiral enantiomerically pure palladium complexes, which demonstrates the feasibility of both kinetic and dynamic kinetic asymmetric transformations and culminates in an efficient strategy for the asymmetric synthesis of the aflatoxin family.[4]

We initiated our studies by examining the chiral recognition in the ionization step. Reaction of **6**[5] with 0.5 equiv of 4-methoxyphenol **7a** in the presence of 5% $Pd_2dba_3$ and 15% chiral ligand **8**[6] in methylene chloride afforded **9a**, however, in only 47% ee (see eq 2). Lowering the catalyst loading to 0.5% $Pd_2dba_3$ and 1.5% **8** resulted in an increase in the enantioselectivity of **9a** to 58%. We conjectured that the moderate enantioselectivity was not due to poor recognition in the ionization step but rather to partial equilibration of the kinetically formed $\pi$-allyl intermediate as conjectured in eq 1. Therefore, we added a base to increase the concentration of deprotonated phenol to increase the rate of nucleophilic attack relative to the equilibration of the kinetically formed intermediate **2** or **3**. Indeed, the addition of 15% cesium carbonate afforded the adduct **9a** in 90% yield (based on **7a** since 2.2 equiv of **6** was employed) in 87−90% ee. The enantiomeric excess of recovered **6** ranged from 16 to 44%.




(2)

Similarly, reaction of 2.2 equiv of **6** with 1 equiv of 3,5-dimethoxyphenol (**7b**) or 2-iodophenol (**7c**) catalyzed by 1% $Pd_2dba_3$ and 3% ligand **8** afforded **9b** and **9c** in 88% ee (82% yield based on **7b**) and 86% ee (88% yield based on **7c**), respectively. Reaction with the more complicated phenol **7d**[7] with **6** under similar conditions afforded adduct **9d** in 70% yield and 87% ee. Triethylborane initiated radical cyclization of **9d** yielded the tricyclic compound **10** (eq 3).[8] Silyl group deprotection of **10**




(3)

affords the Buchi lactone **11**, which constitutes an asymmetric formal synthesis of the aflatoxins.[9,10] The absolute stereochemistry of **11** was established by comparison to the optical rotation reported by Marino.[11]

With these results in hand, our study of the dynamic kinetic asymmetric transformation commenced (eq 2). When the reaction of **6** with **7a**, under the conditions described above, except that equimolar quantities of phenol and butenolide were used, was carried out to conversions of the butenolide greater than 45%, the enantioselectivity dropped significantly (48% ee at 80% conversion, 24% ee at 100% conversion). If the rate of nucleophilic attack was significantly greater than that for interconversion of **2** and **4**, speeding up the latter by, for example, addition of chloride ion to increase the rate of interconversion of **2** and **4**

(1) For a review on dynamic kinetic transformations, see: Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475.

(2) (a) Faber, W. S.; Koh, J.; de Lange, B.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4775. (b) van der Deen, H.; Hof, R. P.; van Oeveren, A.; Feringa, B. L.; Kellogg, R. M. *Tetrahedron Lett.* 8441. (c) van der Deen, H.; Hof, R. P.; van Oeveren, A.; Feringa, B. L.; Kellogg, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 3801. (d) Kinderman, S. S.; Feringa, B. L. *Tetrahedron: Asymmetry* **1998**, *9*, 1215.

(3) For representative examples, see: (a) Krief, A.; Lecomte, Ph.; Demounte, J. P.; Dumont, W. *Synthesis* **1990**, 275. (b) van Oeveren, A.; Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1994**, *59*, 5999 and references therein; c) Harcken, C.; Brückner, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2751.

(4) Schuda, P. F. *Top. Curr. Chem.* **1980**, *91*, 75.

(5) Butenolide **6** is prepared by the reaction of furfural and singlet oxygen (Gollick, K.; Griesbeck, A. *Tetrahedron* **1985**, 2059) followed by reaction of the product alcohol with di-*tert*-butyl dicarbonate.

(6) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *14*, 9327.

(7) The preparation of phenol **7d** (3 steps from phloroglucinol) is detailed in the Supporting Information.

(8) The tributyltinhydride/AIBN method failed to produce any of the desired tricyclic compound **10**. (a) Sloan, C. P.; Cueras, J. C.; Quesnelle, C.; Snieckus, V. *Tetrahedron Lett.* **1988**, *20*, 1685. (b) Hoffmann, H. M. R.; Scmidt, B.; Wolff, S. *Tetrahedron* **1989**, *45*, 6126. (c) Wolff, S.; Hoffman, H. M. R. *Synlett* **1998**, 760.

(9) (a) Buchi, G.; Foulkes, D. M.; Kurone, M.; Mitchell, G. F.; Schneider, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 6745. (b) Buchi, G.; Weinreb, S. M. *J. Am. Chem. Soc.* **1971**, *93*, 746.

(10) For alternative enantioselective formal syntheses of the aflatoxins (aflatoxin $B_2$): see: (a) Rapoport, H.; Civitello, E. H. *J. Org. Chem.* **1994**, *59*, 9, 3775. (b) Bando, T.; Shishido, K. *Synlett* **1997**, 665.

(11) Measured $[\alpha]_D = -137.5$ (87% ee). Reported $[\alpha]_D = -128$ (80% ee). Marino, J. P. *Pure Appl. Chem.* **1993**, *65*, 667.

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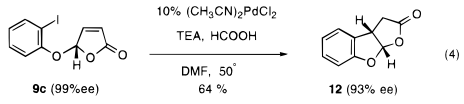
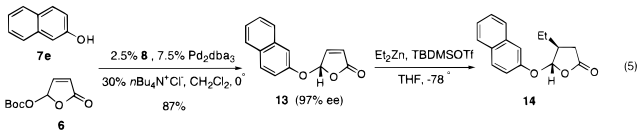
through coordination to palladium which would favor the $\eta^1$-complex **3**[12] should increase the ee. Indeed, addition of 30% tetra-*n*-butylammonium chloride to the reaction mixture resulted in **9a** being isolated in 80% yield and 75% ee, up from 24% ee in the absence of chloride. Slowing the rate of nucleophilic attack by removing the cesium carbonate afforded **9a** in 84% ee (74% yield). Compound **9c** was prepared under identical conditions, in 83% yield and 87% ee, by the reaction of **7c** with **6**. A single recrystallization increases the ee to 99%. Reductive Heck cyclization affords tricyclic lactone **12** in 64% yield without significant deterioration of the enantiomeric excess (93% ee) (eq 4).[13]



(4)

A significant portion of the synthetic utility of $\gamma$-alkoxybutenolides relies on transfer of chirality from the $\gamma$-alkoxy center to the $\alpha$ and $\beta$ carbons.[3] To this end, we prepared butenolide **13** in 97% ee (87% yield), from **6** and 2-naphthol **7e** under our standard palladium-catalyzed conditions for dynamic kinetic asymmetric transformations (eq 5). The steric bulk of 2-naphthol presumably

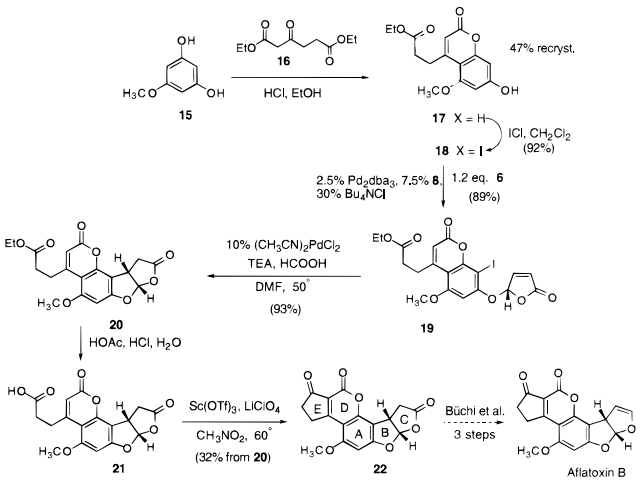


(5)

decreases the rate of nucleophilic attack relative to equilibration and thus may be responsible for the enhanced enantioselectivity. Conjugate addition of diethylzinc promoted by *tert*-butyldimethylsilyl triflate gave a 10:1 ratio of diastereomers in 51% (71% based on recovered **13**) yield.[14] This reaction demonstrates that the 2-naphthyloxy moiety is an efficient auxiliary for this type of chirality transfer.

With these results in hand, we investigated the use of the palladium-catalyzed dynamic kinetic asymmetric transformation toward an enantioselective synthesis of the aflatoxins. Our synthetic plan (see Scheme 1) was to utilize a coumarin as the phenol nucleophile in the allylic alkylation. This would make the synthesis highly convergent and allow for some flexibility in ring E, an important consideration since members of this class of compounds vary at this ring. To this end, we prepared coumarin **17** by the Pechman condensation[15] of monomethyl phloroglucinol **15**[16] with ketoester **16**,[17] which was separated from the 1.4:1 regioisomeric mixture of coumarins by fractional recrystallization ($CH_2Cl_2$−hexane) in 47% yield. Treatment of **17** with iodinemonochloride resulted in regioselective iodination to produce **18** in 92% yield. The sterically demanding coumarin **18** readily participated as the nucleophile in the palladium-catalyzed dynamic

**Scheme 1.** Formal Synthesis of Aflatoxin B




kinetic asymmetric transformation with butenolide **6**, affording the adduct **19** in 89% yield. Unfortunately, at this stage, we were unable to determine its enantioselectivity. Unlike the attempted but failed palladium-catalyzed cyclization of **9d**, subjecting **19** to the standard reductive Heck cyclization conditions afforded the tetracyclic coumarin **20** in 93% yield. At this stage, the enantiomeric excess of **20** was determined to be ≥95% by a $^1$H NMR chiral shift experiment (Eu(hfc)$_3$). In accord with earlier observations, the phenol substituents which are electron-withdrawing, such as the coumarin ring, may be essential for efficient cyclization. Acid-catalyzed hydrolysis of the ethyl ester proceeds smoothly under the conditions reported by Büchi.[9a] Introduction of ring E is accomplished in one step by treatment with scandium triflate and lithium perchlorate.[18] Thus, Büchi's intermediate **22** is available in six steps from two simple building blocks **15** and **16**.

The current study validates the strategy depicted in eq 1 as an efficient approach for the asymmetric synthesis of butenolides. These substitutions occur with excellent ee despite the ease with which the products may racemize due to their propensity toward enolization. Since the nucleophilic substitution event occurs concomitantly with the deracemization event, this strategy is more efficient than performing this transformation as two separate operations.[19] These successes, highlighted by the emergence of an efficient asymmetric synthesis of the aflatoxins, stimulates the exploration of other situations for dynamic kinetic asymmetric transformations.

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**Supporting Information Available:** Experimental procedure and characterization data for **6**, **7d**, **9a**−**d**, **10**−**14**, **17**−**22** (12 pages (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Trost, B. M.; Toste, F. D., *J. Am. Chem. Soc.*, in press. Cf. Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155.
(13) Schmidt, B.; Hoffmann, H. M. R. *Tetrahedron* **1991**, *47*, 9357.
(14) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895.
(15) Asao, T.; Buchi, G.; Abdel-Kader, M. M.; Chang, S. B.; Wick, E. L.; Wogan, G. N. *J. Am. Chem. Soc.* **1965**, *87*, 882.
(16) Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand.* **1991**, *45*, 539.
(17) Wilen, S. H.; Shen, D.; Licata, J. M.; Balwin, E.; Russell, C. S. *Heterocycles* **1984**, *22*, 1747.
(18) Kobayshi, S. Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 4183.
(19) Cuiper, A. D.; Kellogg, R. M.; Feringa, B. L. *Chem. Commun.* **1998**, 655.