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Asymmetric Induction in Cuprate and Photoadditions to 2-t-Butyl-2,6-dimethyl-1,3-dioxin-4-one. Absolute but Opposite Face Selectivities

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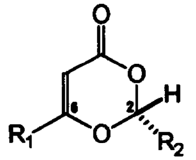
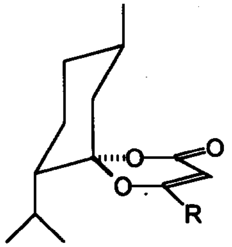
Abstract: Cuprate addition to 2-t-butyl-2,6-dimethyl-1,3-dioxin-4-one (3) results in *exclusive* attack from the *top* face (side opposite the t-butyl group) of the molecule while photoaddition of 3 with cyclohexene or the ethylene ketal of 2-cyclohexenone gives *exclusively* adducts formed by reaction on the *bottom* face of the substrate.

Reactions of 1,3-dioxin-4-ones in the ground or excited state have been extensively investigated for synthetic and mechanistic reasons.[1-5] With 2-monosubstituted dioxinones (e.g. **1a**), reactions such as cuprate additions and catalytic hydrogenation take place almost exclusively from the top face (i.e. the side opposite the t-butyl group).[1] On the other hand, photoaddition of **1b** and cyclopentene at -78° takes place with a modest preference (d.e. 23%) for the bottom face of the dioxinone.[6] Dioxinones such as **2** (and their diastereomers) which have a spirocyclic chiral center at the 2-position, have been prepared from (-)-menthone.[3] Cuprate addition to **2a** and catalytic hydrogenation of **2b** occurred selectively from the top and less hindered face with d.e.'s of 82% and 88%, respectively.[7] Conversely, photoaddition of **2a**[7] and **2b**[3] with cyclopentene occurred preferentially from the *bottom* face with d.e.'s of 72% and 82%, respectively. We wish to report that 2-t-butyl-2,6-dimethyl-1,3-dioxin-4-one (3) reacts *exclusively* with cuprate reagents from one face and undergoes photoadditions with certain alkenes *exclusively* from the *other* face.



1a R_1 = Me, R_2 = t-butyl
1b R_1 = H, R_2 = cyclohexyl



2a R = H
2b R = Me

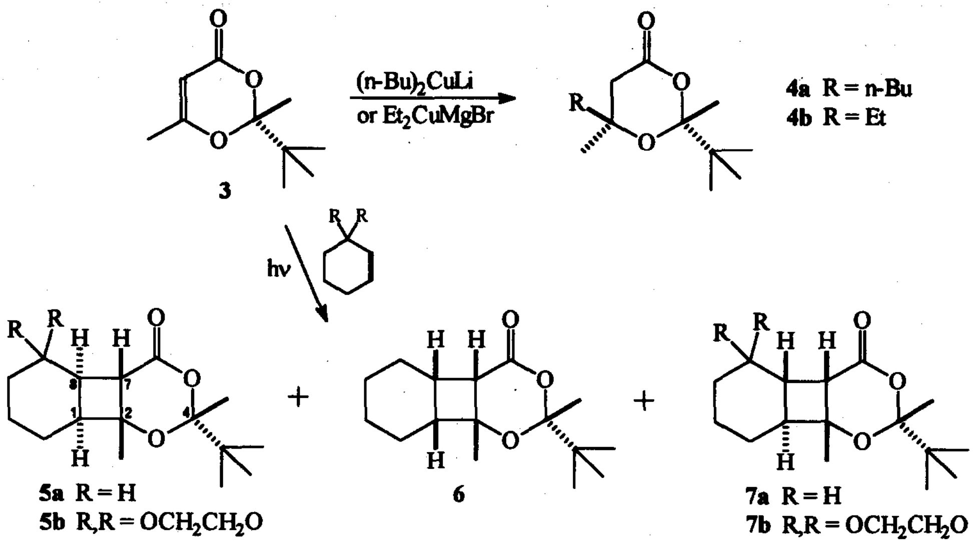
Dioxinone 3 may be prepared in racemic form by reaction of pinacolone with diketene[8] or in optically pure form from the readily available (R)-3-hydroxybutyric acid[9] using a recently described procedure.[10] Reaction of 3 (-78° to -20°C) with $(n\text{-Bu})_2CuLi$ gave **4a** in 73% yield while reaction with $Et_2CuMgBr$ gave **4b** (Scheme 1) in 57% yield (83% based on recovered 3). None of the other diastereomer was observed in the ^1H NMR spectra of the crude or purified products. The stereochemistry of 4 was determined by NOE difference experiments. Thus, in both reactions the only isomer formed was the result of attack of the cuprate reagent from the *top* face of 3.[11]

Photoaddition of 3 and cyclohexene (2 equiv.) in 20% acetone:acetonitrile with a Corex filter[5] gave a mixture of three crystalline adducts: **5a** (54%), **6** (18%) and **7a** (15%) (Scheme 1). The structure of **5a** was determined by single-crystal X-ray analysis.[12] The structures of **6** and **7a** were established by detailed analyses of their ^1H and ^{13}C NMR spectra and by NOE difference experiments.[13] Of particular note was the H-7/H-8 coupling constant of 4.4 Hz in the ^1H NMR spectrum of the *anti* adduct **5a** compared with a coupling of 10.2 Hz in the *syn* adduct **6**. Also, the downfield shift of the cyclobutane carbons in the ^{13}C NMR spectrum of **7a** as compared with **5a** and **6**[14] was indicative of a *trans* ring fusion in the former.[15] Photoaddition of 3 and the ethylene ketal of 2-cyclohexenone gave a mixture of adducts **5b** (35%) and **7b** (14%) (Scheme 1). Thus, in both these irradiations, the only adducts formed were the result of attack from the *bottom* face of 3.

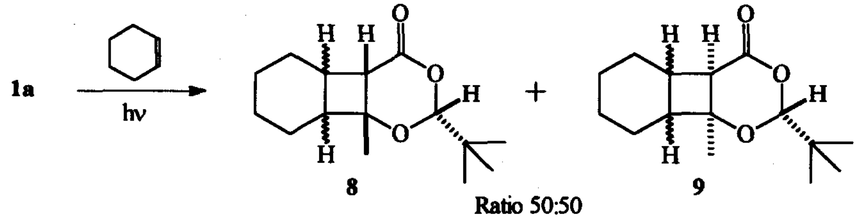
For purposes of comparison, we reinvestigated the photoaddition of **1a** and cyclohexene. This reaction had been mentioned previously[16] but the product distribution was not reported. At least 7 products were present as judged by the number of different H-4 acetal resonances in the 4.7-5.6 ppm region of the ^1H NMR spectrum of the adduct mixture. Detailed examination of the ^1H NMR spectra of fractions obtained by flash chromatography of the mixture,[13] revealed a 50:50 distribution of adducts **8** and **9**[17] (Scheme 2) resulting from attack of cyclohexene on the top and the bottom faces of **1a**.[18]

The photoadditions of **1a** or 3 with cyclopentene were also investigated and compared. Crystalline adducts **10a** (22%), **11** (18%) and **12a** (49%)[19] were formed from **1a** while **10b** (90%) and **12b** (9%)[19] were formed from 3 (Scheme 3). The bottom:top face selectivities of 45:55 for **1a** and 91:9 for 3 further illustrate the effectiveness of the latter dioxinone.

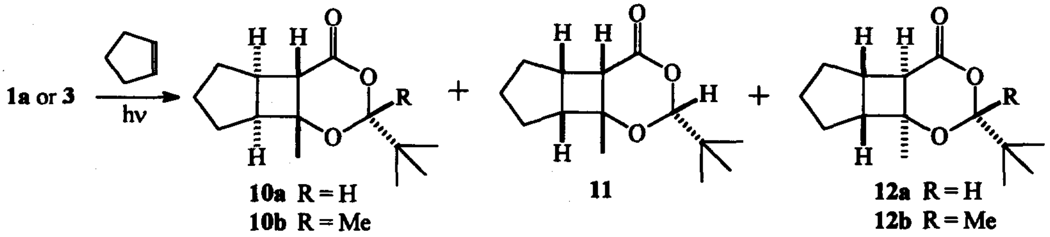
In conclusion, we have shown that substitution of the acetal proton (H-2) in **1a** by a methyl group to give dioxinone 3 dramatically enhances the face selectivity in the photoaddition reactions with alkenes such as cyclohexene and cyclopentene. For example, with **1a** and cyclohexene a 50:50 bottom/top mixture is obtained while with 3 the photoaddition takes place *exclusively* from the bottom face. A previous investigation concluded that monocyclic dioxinones having a chiral acetal carbon show poor face selectivity in intermolecular photoadditions[20] but clearly that is not the case for 3. Apparently the 2-methyl group introduces sufficient steric hindrance to block the photoaddition from the top face of 3. In the cuprate additions, both **1a** and 3 give only products resulting from attack on the top face. These results suggest that pyramidalization of the enone system in the ground state as proposed by Seebach[1] dominates over the additional hindrance of the 2-methyl group in 3. We intend to use the novel dioxinone 3 in asymmetric induction studies directed towards the synthesis of optically active natural products.



Scheme 1



Scheme 2



Scheme 3

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8. Prepared in 76% yield by heating diketene (1 equiv.) with pinacolone (2 equiv.) in presence of p-TsOH as described previously for the synthesis of 2,2,6-trimethyl-1,3-dioxin-4-one: Carroll, M.F.; Bader, A.R. *J. Am. Chem. Soc.* **1952**, *74*, 6305.
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10. Lange, G.L.; Organ, M.G.; Roche, M.R. *J. Org. Chem.* **1992**, *57*, 6000.
11. Hydrogenation of **3** was also investigated using catalysts such as Pd/C, PtO_2 and Rh/alumina at various hydrogen pressures, but the dioxinone either did not react or fragmented.
12. Performed by N.J. Taylor, University of Waterloo.
13. Full details of these analyses will be published in a full paper.
14. ^{13}C NMR chemical shifts of cyclobutane carbons: **5a** - 33.48, 41.95, 45.63, 77.22; **6** - 29.42, 43.50, 46.06, 74.21; **7a** - 38.91, 47.30, 55.68, 77.77.
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17. Both adducts include a mixture of *anti*, *syn* and *trans*-fused isomers.
18. The ^1H NMR chemical shift of the acetal proton (H-4) in these adducts appears to be diagnostic in determining the face selectivity of these cycloadditions. An H-4 resonance in the region 4.7-5.0 ppm indicates that cyclohexene has added from the bottom face of **1a** (same side as the t-butyl group), whereas a resonance in the region 5.2-5.6 ppm shows that cyclohexene has added from the top face. A related example supporting this conclusion has been reported recently[6] and the spectra of adducts **10a**, **11** and **12a** displayed similar resonances.
19. The yields are based on recovered **1a** or **3**, respectively. The actual combined yields were 53% from **1a** and 34% from **3** (not maximized).
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