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HIGHLY DIASTEREOSELECTIVE ADDITION TO A NOVEL CHIRAL OXAZINONE. FURTHER APPROACHES TO CHIRAL QUATERNARY CARBON COMPOUNDS.

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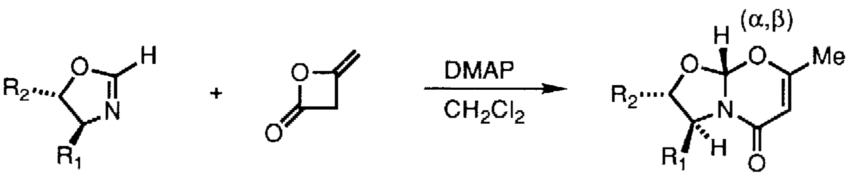
Summary: The chiral bicyclic oxazinone **2d**, readily obtained, show high diastereoselective 1,4-addition of cuprates and catalyzed hydrogenation.

Our studies on developing asymmetric C-C bond forming reactions with novel chiral auxiliaries have now been extended to a new system **2**. We have examined the cyclocondensation of various 2-H chiral oxazolines **1(a-d)**[1,2] with diketene and found that the bicyclic oxazinones



1a, R_2 = Ph, R_1 = CH_2OMe
1b, R_2 = H, R_1 = CH_2Ph
1c, R_2 = H, R_1 = i-Pr
1d, R_2 = H, R_1 = t-Bu

	β:α	(%)
2a	70:30	(80)
2b	93 7	(75)
2c	96:4	(88)
2d	>99:1	(91)

2(a-d)[3] can be obtained in good yields. However, all but the t-butyl oxazoline **1d**[4] gave varying mixtures of diastereomeric products in **2**. The **syn** relationship of angular hydrogen to the alkyl substituent was confirmed by X-ray crystallographic analysis, as well as NOE studies. It was felt that **2d** obtained in good yield and as a single diastereomer would be an interesting substrate with which to carry out various asymmetric additions and thus provide a potentially useful chiral auxiliary for further synthetic efforts.

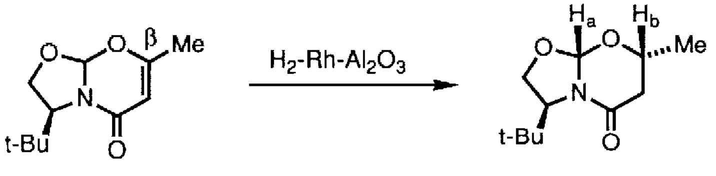
The first reaction attempted was hydrogenation of **2d** using rhodium-on-alumina as a catalyst. The reduction was performed at atmospheric pressure and after 5 h gave a 97% yield of **3** as a single diastereomer (by ^{1}H-NMR, ^{13}C-NMR, GLC). The hydrogen (H_b) on the β-face was confirmed by NOE which showed a 12% enhancement with the angular hydrogen (H_a).

A number of conjugate additions to **2d** were next attempted since conjugated amides are well known to undergo 1,4-addition by a variety of nucleophiles.[5] However, when a variety of cuprates of standard order (e g. EtMgBr CuI, $Bu_2Li{\cdot}CuI$, i-PrMgBr CuBr Me_2S, etc.) were introduced into THF or ether solutions of **2d**, little or no addition occurred When the cuprates were added to **2d** and TMSCl, according to the method of Kuwajima,[6] the additions took place at -78°C and very good yields of the adducts **4 as a single diastereomer** were obtained [7] The diastereoselectivity was seen as 97-99.5% by ^{1}H-NMR and GLC analyses, respectively, of the crude reaction mixture, thus, no inadvertent separations occurred during chromatographic purification. In an attempt to produce a useable amount of the other diastereomer for identification purposes, the cuprate-TMSCl addition was performed at 0°C. Once again, **no other diastereomer could be detected** (NMR, GLC). The nucleophile, therefore, entered from the β-face, **syn** to the t-butyl group, to give **4** and this was confirmed by single crystal X-ray analysis. In view of the lability of **4** to aqueous acids and copper sulfate and other reductive or hydrolytic agents, this result has potential synthetic utility in reaching chiral β-alkyl, β-hydroxy acids, amides, or esters.[8]

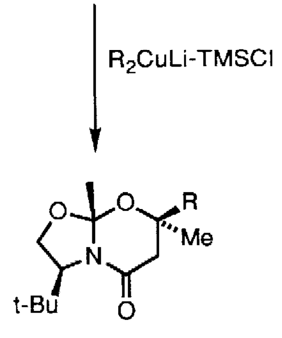
The underlying cause for this high degree of diastereofacial addition from the β-face is presently unknown but appears to be related to the direction of pyramidalization of the trigonal β-carbon in the unsaturated amide portion of **2**. Thus, the methyl group in **2d** is tilted downward (toward the α-face) due to the distortion from planarity of the π-bond. This is clearly seen from our X-ray structure of **2d** which shows a slight degree of pyramidalization on the sp^2 carbon bearing the methyl group. This would agree with the observation and notion set forth by Seebach in his dioxinone series[8] where he states that the nucleophile enters the α,β-unsaturated system (dioxin-4-one) from the same direction as the pyramidalization and reasons for both phenomena may be related.

Additionally, the reasons for the high stereoselectivity could also have their origin in the relief of torsional angle strain which has also been invoked as a cause of stereodifferentiation, but due to the uncertainty of the degree of CH_3-H torsion angles from X-ray data, we must await more accurate measurements.[9] At this point of our studies, our results appear to be another example in accord with Seebach's insightful explanation.

Further studies on the synthetic and stereochemical aspects of this oxazinone system are in progress.



2d **3**



4 (a-e)

R_2CuLi	% Yield	mp°C	$[\alpha]_D$
4a, Bu	85	44-45	+39.2°
4b, Et	98	72-73	+49.2°
4c, i-Pr	91	124-126	+47.1°
4d, 	87	140-141	+37.0°
4e, Ph 	87	81-82	+34.6°

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References

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2. Previous cyclocondensations of 2-H oxazolines with dichloroketene, albeit in poor yield (~5%) have been reported; Johnson, P. Y ; Caldwell, J W. *J. Org. Chem.* **1974**, *40*, 2408 For reactions of imines with diketene to give oxazinones see Maujean, A , Chuche, J *Tet. Lett.* **1976**, *33*, 2905.

3 This bicyclic oxazinone system has been described earlier by condensation of simple oxazolines with acetyl Meldrum's acid, Yamamoto, Y ; Watanabe, Y.; Morita, Y.; Narita, M. *Ann. Rep. Tohoku Coll. Pharm.* **1986**, 41; *Chem. Abstr. 108* (15), 13175 h.

4. Mp 110-112°C, $[\alpha]_D^{24}$ -168° (c 1.64, $CHCl_3$). Satisfactory spectral and combustion analyses were obtained.

5. Mpango, G. B.; Mahalanabis, K. K.; Mahdari, Z , Snieckus, V. *Tet Lett.* **1980**, *21*, 4823, Baldwin J E.; DuPont, W. A. *ibid* 1881; Alexakis, A.; Berlan, J.; Besace, Y. *Tet. Lett.* **1986**, *27*, 1047, and earlier references cited.

6. Matzuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45,* 349, and references therein.

7 Procedure for cuprate addition to **2d**: A solution of n-BuLi (3.0 eq) was added to a suspension of CuI (1.5 eq) in 2 mL THF at -78°C, warmed to -40°C for 20 min HMPA (3.0 eq) was added and stirred for 10 min and the dark green solution cooled to -78°C. The oxazinone (1 mmol) and TMSCl (0.36 mL) in 1.5 mL THF was added *via* cannula to the cuprate solution and stirred for 1h The mixture was warmed to -40°C and maintained for 4 h and then allowed to reach room temperature. To this was added 5 mL of pH 7 buffer solution, the volatiles evaporated and the residue diluted with 30 mL ether and 15 mL 10% NH_4OH. After layer separation, extraction (CH_2Cl_2), washing (brine) and drying (Na_2SO_4), the solvent was evaporated and the residue filtered through a plug of silica gel with ethyl acetate. Purification was accomplished *via* radial chromatography (chromatron) using 30% ethyl acetate-hexane, to give 217 mg (85% of **4a**) as white crystals. The analytical sample was prepared by recrystallization from pentane.

8 Seebach, D.; Zimmerman, J.; Gysel, U ; Ziegler, R., Ha, T K. *J. Am. Chem Soc.* **1988**, *110*, 4763.

9. We are in the process of obtaining accurate C-H angles to assess 2-H to 3-CH_3 torsional angles in **2d** using neutron diffraction techniques, and we have prepared the appropriate deuterated analog of **2d**, for this purpose. (O. P. Anderson and M. A. Thomson, research in progress).

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