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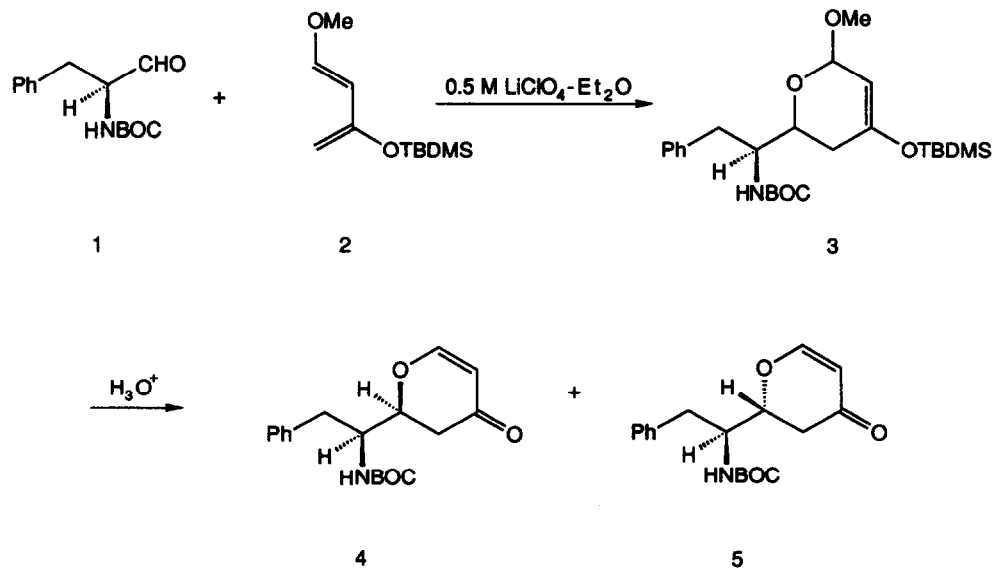
# LITHIUM CATALYZED HETERO DIELS-ALDER REACTIONS

## CYCLOCONDENSATION OF N-PROTECTED α-AMINO ALDEHYDES WITH 1-METHOXY-3-*tert*-BUTYLDIMETHYLSILYLOXYBUTADIENE IN THE PRESENCE OF LITHIUM PERCHLORATE

Paul A. Grieco* and Eric D. Moher[1]
Department of Chemistry, Indiana University
Bloomington, Indiana 47405

**Abstract:** Lithium perchlorate in diethyl ether catalyzes the cyclocondensation of N-BOC protected α-amino aldehydes with 1-methoxy-3-*tert*-butyldimethylsilyloxybutadiene providing, after exposure to acid, dihydropyrones possessing the threo configuration.

The [4+2] cycloadducts derived from the cyclocondensation of N-protected α-amino aldehydes with substituted butadienes (e.g. *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene), represent useful building blocks for the construction of complex amino sugar antibiotics. The limited number of studies in this area has focussed on the use of ultra high pressure[2] and/or conventional Lewis acid catalysis (e.g. $ZnCl_2$, $Et_2AlCl$)[3] to promote hetero Diels-Alder reactions. We wish to report that lithium perchlorate in diethyl ether catalyzes the cycloaddition reaction between N-BOC protected α-amino aldehydes and *trans*-1-



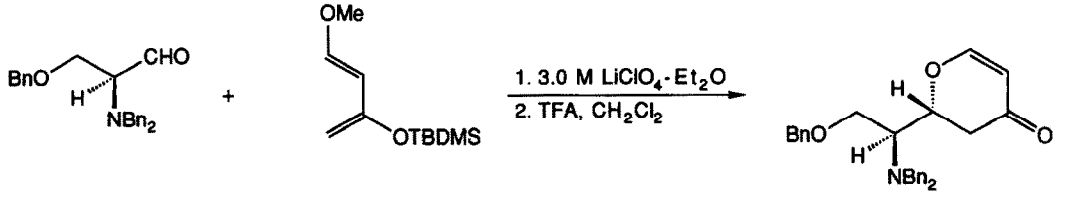

(1)

methoxy-3-silyloxy-1,3-butadienes leading to the formation of dihydropyrones upon exposure of the derived cycloadducts to aqueous acid (cf Equation 1). The formation of major adducts possessing the threo configuration as exhibited by **4** is consistent with a chelation controlled process.

Our initial investigation concentrated on the cyclocondensation of aldehyde **1**[4] with Danishefsky's diene[5] in 0.5 M lithium perchlorate in diethyl ether. Exposure of a 0.2 M solution of **1** in 0.5 M lithium perchlorate-diethyl ether to 2.0 equiv of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene[5] led to the rapid consumption of diene giving rise, after treatment with 1.0 N hydrochloric acid in tetrahydrofuran to a 58% yield of **4** and **5** in a ratio of 5.5:1. Use of the more robust siloxy diene, trans-1-methoxy-3-*tert*-butyldimethylsilyloxy-1,3-butadiene(**2**)[6] led to enhanced diastereoselectivity as well as an improvement in the yield. For example, treatment of a 0.2 M solution of **1** in 0.5 M lithium perchlorate-diethyl ether with 2.0 equiv of **2** at ambient temperature for 11 h afforded, after brief exposure (30 min, 0°C) to 1.0 N hydrochloric acid in tetrahydrofuran (1:2), a 70% yield of **4** and **5** in a ratio of 10:1. No racemization occurred during the cycloaddition reaction as evidenced by $^1$H NMR studies.

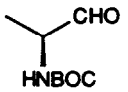
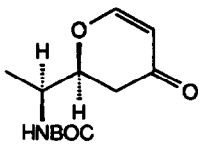
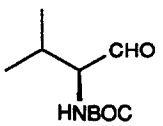
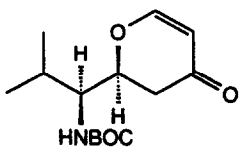
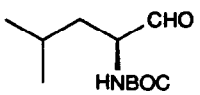
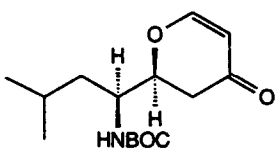
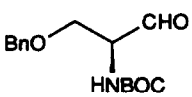
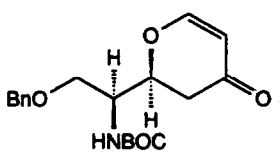
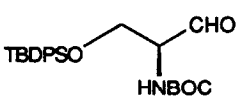
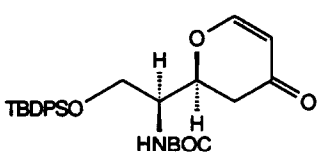
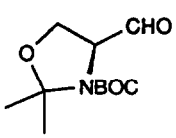
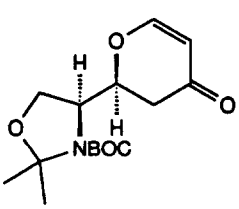
The data obtained from a number of protected α-amino aldehydes[7] are summarized in Table I. The results are in keeping with a chelation controlled process. Note that as one increases the steric bulk of the alkyl substituent on the α-carbon, the diastereoselectivity is enhanced (entries 1-3). In the case of the serine derived aldehydes (entries 4-6), low diastereoselectivity was observed with O-benzyl N-t-BOC serinal (entry 4) due, presumably, to competing β-chelation control. In contrast the corresponding O-*tert*-butyldiphenylsilylether (entry 5) and the N-BOC oxazolidine aldehyde[3b] (entry 6) gave rise to much improved ratio of the threo-erythro diastereomer.

The threo diastereofacial selectivity observed above could be reversed by changing the nature of the protecting group on nitrogen and utilizing 3.0 M lithium perchlorate in diethyl ether as the medium. Best results were obtained with N,N-dibenzyl α-amino aldehydes.[3c,d] For example treatment (2 h) of a 0.2 M solution of aldehyde **6**[8] in 3.0 M lithium perchlorate-diethyl ether with 2.0 equiv of diene **2**




6 2 7

**Table 1.** Cyclocondensation of Protected α-Amino Aldehydes with *trans*-1-Methoxy-3-[(*tert*-butyldimethylsilyl)oxy]-1,3-butadiene[a]

| entry | aldehyde | time, h | threo product | ratio[b] threo-erythro | yield,[c] % |
|---|---|---|---|---|---|
| 1[d] |  | 2.0 |  | 3:1 | 54 |
| 2[d] |  | 23.5 |  | 8:1 | 79 |
| 3 |  | 13.5 |  | 10:1 | 74 |
| 4[e] |  | 1.5 |  | 2.5:1 | 64 |
| 5 |  | 6.5 |  | 8:1 | 79 |
| 6[f] |  | 2.0 |  | 10:1 | 73 |

[a]All reactions were conducted at ambient temperature employing a 0.2 M solution of aldehyde in 0.5 M lithium perchlorate-diethyl ether in the presence of 2.0 equiv of diene followed by brief exposure (0°C, 15 min) to 1.0 N hydrochloric acid-tetrahydrofuran (1:10) unless stated otherwise. [b]Diastereomer ratios were determined by HPLC and/or $^1$H NMR. [c]Isolated yield. [d]1.0 N HCl-THF (1:2), 0°C, 30 min. [e]HOAc-THF (1:1), 0°C → RT, 1.25 h. [f]1.0 N HCl-THF (1:2), RT, 20 min.

followed by brief exposure (25 min) to 3.0 equiv of trifluoroacetic acid in methylene chloride gave rise (66%) to dihydropyrone **7** possessing the erythro configuration which was homogeneous by $^1$H NMR analysis. The corresponding threo diastereomer could not be detected.

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## References

1. Abbott Predoctoral Fellow, 1991-1993.
2. Golebiowski, A.; Izdebski, J.; Jacobsson, U.; Jurczak, J. *Heterocycles*, **1986**, *24*, 1205. Jurczak, J.; Golebiowski, A.; Raczko, J. *Tetrahedron Lett.*, **1988**, *29*, 5975. Jurczak, J.; Golebiowski, A. *Chem. Rev.*, **1989**, *89*, 149. Golebiowski, A.; Raczko, J.; Jacobsson, U.; Jurczak, J. *Tetrahedron*, **1991**, *47*, 1053.
3. (a) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F. *J. Org. Chem.*, **1982**, *47*, 1981.
   (b) Garner, P.; Ramakanth, S. *Ibid*, **1986**, *51*, 2609.
   (c) Midland, M. M.; Afonso, M. M. *J. Am. Chem. Soc.*, **1989**, *111*, 4368.
   (d) Jurczak, J.; Golebiowski, A.; Raczko, J. *J. Org. Chem.*, **1989**, *54*, 2496.
4. Rich, D. H.; Sun, E. T. O.; Ulm, E. *J. Med. Chem.*, **1980**, *23*, 27.
5. Commercially available from Aldrich.
6. Ireland, R. E., Aristoff, P. A.; Hoyng, C. F. *J. Org. Chem.*, **1979**, *44*, 4318.
7. The aldehydes were prepared according to the procedure of Rich: Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.*, **1978**, *43*, 3624.
8. Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew, Chem., Int. Ed. Engl.*, **1987**, *26*, 1141.

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