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A REMOVABLE AUXILIARY FOR AMIDOMERCURATION REACTIONS: THE STEREOCONTROLLED PREPARATION OF VICINAL AMINOALCOHOLS[1]

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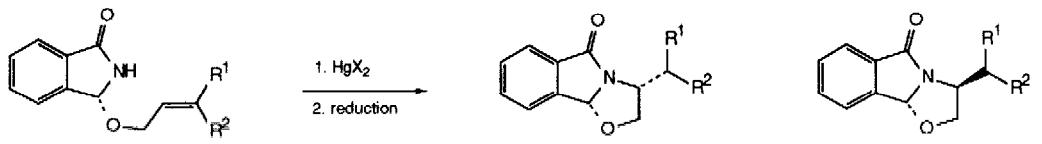
SUMMARY: Unsaturated amidals **1**, derived from allylic alcohols and containing a stereogenic amidal center, undergo amidomercuration with high 1,3-stereoinduction from the amidal center. In substrates derived from secondary allylic alcohols, the influence of the stereogenic amidal center overrides the competing 1,2-stereoinduction from the allylic substituent. Consequently, starting from a single secondary allylic alcohol, the amidal auxiliary enables the selective preparation of either a *syn* or an *anti* vicinal aminoalcohol.

Diastereoselective electrophilic heterocyclization reactions are commonly employed to control the relative stereochemistry in cyclic and, via cleavage of the heterocycle, in acyclic compounds.[2-4] Several practical limitations can be encountered in using this strategy. For example, the level of stereoinduction from the resident stereogenic center may not be acceptable, and only one of the two possible diastereomeric relationships between the resident and the newly created stereocenters can usually be obtained with acceptable selectivity. Also, the strategy is generally best applied to substrates in which the resident stereogenic center resides endocyclic with respect to the newly forming ring. In this letter we describe our preliminary results on the use of a removable phthalimide-derived auxiliary to direct the stereochemical course of the amidomercuration of allylic alcohols.[4]

Harding and co-workers[3] have reported the stereoselective amidomercuration cyclizations of N-acyl amidals derived from N-acetoxymethyl carbamates and chiral secondary allylic and homoallylic alcohols. We were curious as to the relative influence of a resident stereogenic center positioned at the amidal center, adjacent to the nucleophilic amide functionality. Along these lines we investigated the cyclizations of N-acyl amidals **1**. Mercuric acetate promoted cyclization of **1a** followed by borohydride reduction (1. 1.5 eq $Hg(OAc)_2$ / 1.5 eq $NaHCO_3$ /



1a R^1, R^2 = H **1d** R^1 = H, R^2 = Ph
b R^1 = CH_3, R^2 = H **e** R^1 = Ph, R^2 = H
c R^1 = H, R^2 = *n*-Pr

endo **2** *exo* **3**

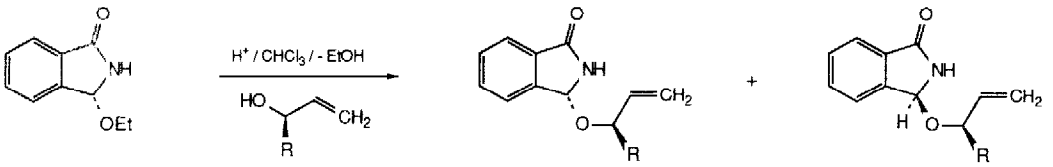
CH_3CN / 25° / 0.5h); 2. excess $NaBH_4$ / satd aq NaOAc) proceeded in good yield (71%) and with high 1,3-stereoinduction from the amidal stereocenter. The crystalline N-acyl oxazolidine product **2** possesses the newly

formed methyl group residing *endo* with respect to the bicyclo[3.3.0] subunit within the molecule. HPLC analysis of the crude reaction mixture showed that less than 1% of the more stable *exo* diastereomer **3** was formed.[5] While the origin of this apparent kinetic[5] stereoselectivity is as yet unclear, it is interesting to note that predominant *endo* diastereomer formation is in accord with the Type B (directing group in tether) Model of Hehre, *et. al.*[6]

Under the reaction conditions described above for the cyclization of **1a**, the *trans*- and *cis*-substituted olefins **1b-d** gave rise to only small amounts of oxazolidine. We examined a number of different mercury salts for the cyclization. It was found that a 1:1 molar mixture of $Hg(OAc)_2$:$Hg(OTFA)_2$ (1.5 eq Hg^{2+} / 2 eq $NaHCO_3$ / CH_3CN / 25° / 1h) effected complete disappearance of starting material within an hour at ambient temperature. Surprisingly, reductive cleavage of the intermediate organomercurial with $NaBH_4$ / satd NaOAc still gave rise to only modest yields (20-30%) of products **2b** and **2c**. In the case of **1d**, no cyclized products were isolated; however, the isomerized *trans*-olefin **1e** was obtained in 68% yield. Apparently under these reduction conditions, ring opening of some reactive intermediate is competitive with reductive cleavage of the C-Hg bond.

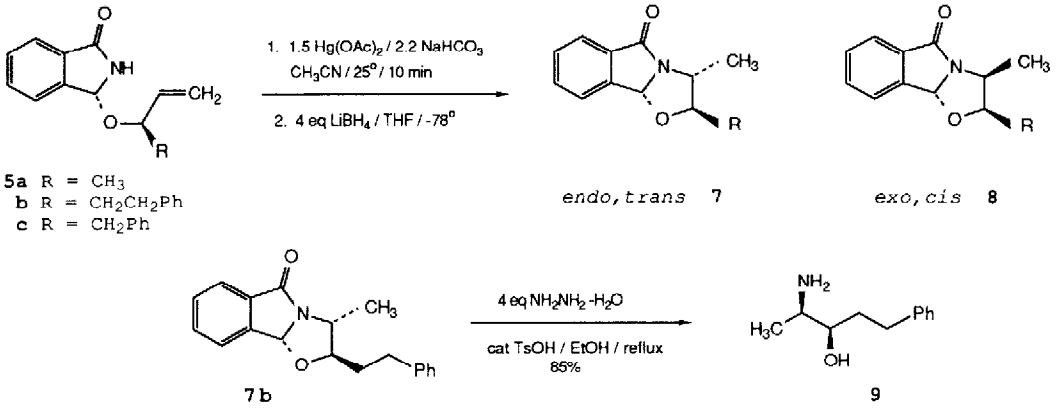
We now employ either of the following two reduction procedures to minimize the competing oxazolidine ring opening. Upon complete Hg^{2+} induced cyclization, the reaction mixture is diluted with an equal volume of THF, cooled to -78°, then treated with 4 molar equivalents of $LiBH_4$ in THF. Using this procedure, compounds **1a-c** were cyclized to oxazolidines **2a-c** in 65, 45, and 60% yields respectively. The 1,3-stereoinduction is in each case quite good (**2a** >200:1; **2b** 40:1; **2c** 12:1). Alternatively, the intermediate organomercurial can be isolated as the mercuric chloride, converted to the alkyl iodide by treatment with iodine (2 eq I_2 / CH_2Cl_2 / 25°), then reduced with tin hydride under standard conditions (4 eq (n-Bu)$_3$SnH / cat AIBN / benzene / 80°). Using this procedure, **1a** was converted to **2a** in 81% yield.

Amidals **1a-d** were prepared via acid catalyzed alcohol exchange between the appropriate allylic alcohol and the ethoxy-substituted amidal **4**. The latter compound was prepared by the $NaBH_4$ reduction of phthalimide in acidic ethanol.[7] The alcohol exchange between compound **4** and a secondary allylic alcohol led to an equilibrium mixture of crystalline diastereomers **5** and **6**, which differ with respect to the stereochemistry at the amidal center. The diastereomers were separated by chromatography on silica and/or fractional crystallization. Either diastereomer can be epimerized to the equilibrium mixture with catalytic *p*-toluenesulfonic acid.



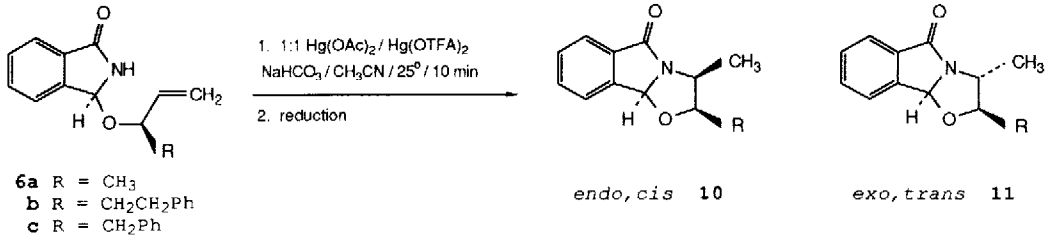
4 5 6

The cyclization of diastereomer **5a** proceeded readily in the presence of $Hg(OAc)_2$. Lithium borohydride reduction afforded the *endo,trans* oxazolidine **7a** in 75% yield. HPLC analysis of the crude reaction mixture showed that less than 0.5% of the *exo,cis* diastereomer **8a** was formed in the cyclization. Analysis of the reaction mixture after short reaction times showed no evidence for epimerization of the amidal stereocenter in either the starting amidal or the product oxazolidine. Compounds **5b** and **5c** were cyclized with similarly high stereoinduction to give the *endo,trans* diastereomer **7** in 93% and 74% yields, respectively. The stereochemical assignment of **7** was confirmed by obtaining a crystal structure of **7c**.[1c]



The *syn* vicinal aminoalcohol is readily liberated by treatment of the oxazolidine with hydrazine hydrate. For example, treatment of **7b** with 4 eq of NH_2NH_2-H_2O (cat *p*-TsOH / EtOH / reflux) gave aminoalocohol **9** in 85% yield. The facility and high stereoselectivity observed in the cyclizations of **5** is not surprising. The resident amidal and allylic stereocenters exert the same sense of 1,3- and 1,2-stereoinduction in directing the stereochemical course of the C-N bond construction.

The cyclizations of diastereomer **6** required more vigorous reaction conditions. In contrast to **5a**, exposure of **6a** to mercuric acetate for periods up to 24h did not effect complete cyclization; however, under the influence of the $Hg(OAc)_2$:$Hg(OTFA)_2$ mixture, cyclization was complete within one hour. Lithium borohydride reduction afforded oxazolidine in 60% yield and with stereoinduction in excess of 50:1 favoring the *endo,cis* diastereomer **10**. The 1,3-stereoinduction from the amidal center overwhelms the influence of the allylic methyl bearing stereocenter. Consequently, starting from a single allylic alcohol (e.g. 1-buten-3-ol), either the *syn*- or *anti*- vicinal aminoalcohol can be obtained selectively via amidal **5** or **6**, respectively. We note that in order to obtain chiral non-racemic aminoalcohols, our approach requires starting with a chiral non-racemic allylic alcohol to resolve the controlling amidal center. Such substrates are readily available by several general routes.[8]



Using the iodine/tin hydride demercuration procedure, **6b** cyclized to a 4.7:1 mixture of **10b** and **11b** in 85% overall yield. The oxazolidines can be deprotected to the corresponding aminoalcohols in 80% yield. Using the lithium borohydride reduction procedure, a 4.2:1 mixture of oxazolidines was obtained in 40% yield. Substrate

6c, possessing a somewhat more sterically demanding allylic substituent, cyclized in 64% yield but with poor stereoselectivity (2.1:1, **10c**:**11c**).

The amidal auxiliary defines a useful strategy for overcoming some of the limitations frequently encountered in amidomercuration cyclization-reactions. The auxiliary is inexpensive, readily available, and easily introduced and removed. More importantly, our initial studies demonstrate that it is feasible to design a removable auxiliary for which the 1,3-stereoinduction from the amidal auxiliary overrides the competing 1,2-stereoinduction of the resident allylic substituent. Further studies on the synthetic utility of amidal auxiliaries and on the consequences of double stereodifferentiation[9] in heterocyclization reactions[10] are in progress.

REFERENCES AND NOTES

[1] a) This work was performed in part at the University of Utah. Financial support of this work by the University of Nebraska-Lincoln and the University of Utah Research Committee is gratefully acknowledged. L. Y. acknowledges the PRC for support as a visiting scholar. b) We thank Professor K. E. Harding (Texas A&M University) for helpful discussions and for sharing experimental results prior to publication. c) We thank Dr. Atta Arif, staff crystallographer in the Department of Chemistry at the University of Utah, for determining the crystal structure of **7c**. d) All new compounds isolated were fully characterized spectroscopically and the elemental composition determined by combustion analysis and/or high resolution mass spectrometry.

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