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A Removable Auxiliary For Amidomercuration Reactions: The Stereoselective Preparation Of Substituted N-Acyl Pyrrolidines And Piperidines[1]

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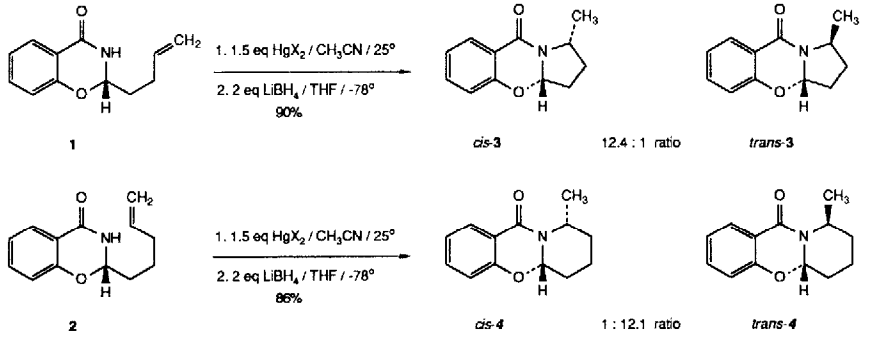
Summary: Salicylamide condenses with γ,δ- or δ,ε-unsaturated aldehydes to give cyclic amidals which readily undergo diastereoselective mercury(II)-mediated amidocyclization. The resulting products serve as versatile intermediates for further elaboration as nitrogen heterocycles.

Diastereoselective electrophilic heterocyclization reactions are commonly employed to control the relative stereochemistry in cyclic and, via cleavage of the heterocycle, in acyclic compounds.[3] We have been interested in the consequences of double stereodifferentiation[4] in electrophilic amidocyclizations, particularly as it relates to the design of practical auxiliaries to control the stereochemical course of the cyclization. We have recently reported amidomercuration cyclizations that are directed by a phthalimide-derived auxiliary as a route to vicinal aminoalcohols.[5] The stereogenic amidal center provides the dominant influence on the stereochemical course of these cyclizations.[6] We now wish to report our preliminary investigations into the utility of the salicylamide-derived amidal auxiliary as a stereochemical directing group for the conversion of unsaturated aldehydes into a variety of substituted N-acyl pyrrolidines and piperidines.

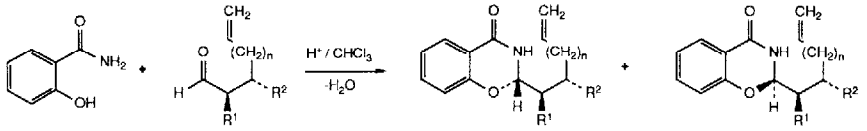
Salicylamide undergoes acid catalyzed reaction with 4-pentenal or 5-hexenal under the conditions of azeotropic removal of water (cat TsOH / $CHCl_3$ / -H_2O) to yield the crystalline amidals **1** and **2** (70-85%). The cyclizations of these parent substrates assess the sense and strength of the stereogenic amidal center in directing the stereochemical course of the C-N bond construction. Amidal **1** undergoes rapid cyclization mediated by mercuric acetate/mercuric trifluoroacetate (a. 1.5 eq of a 1:1 mixture of $Hg(OAc)_2$-$Hg(O_2CCF_3)_2$ / CH_3CN / 25° / 10 min; b. aq NaCl), a mixture of mercury(II) salts that we found to be effective in the phthalimide cyclizations. The intermediate organomercurial chloride can be reductively cleaved (2 eq $LiBH_4$ / THF / -78°) to give a 12.4:1



cis:trans ratio of diastereomeric amidals in 90% yield. Pure diastereomer *cis*-**3** can be isolated by chromatography and recrystallization. Alternatively, the organomercurial intermediate can be efficiently cleaved by iodine (2 eq I_2 / CH_2Cl_2 / 0° / 99%). Similarly, unsaturated amidal **2** undergoes facile cyclization/reduction to give a 1:12.1 *cis:trans* mixture of crystalline amidals in 86% yield. The degree of stereoinduction is comparable in the parent

five- and six-membered ring cyclizations, however the sense of stereoinduction differs in the two ring systems. The five-membered ring cyclization affords the thermodynamically less stable diastereomer (*cis*-**3**).[7a] The six-membered ring cyclization yields the thermodynamically more stable diastereomer (*trans*-**4**).[7b] The newly formed methyl substituent resides in a pseudo-axial orientation in this latter compound.

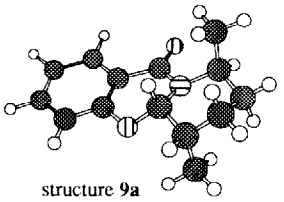
Chiral aldehydes, substituted at the α- or β-positions, can be obtained in high optical purity by asymmetric alkylation, conjugate addition, and related methodologies. Condensation of salicylamide with such an unsaturated aldehyde gives rise to a mixture of diastereomeric amidals **5** and **6**. The crystalline amidals, diastereomeric at the amidal center, can be separated by chromatography and/or fractional crystallization, and either diastereomer can be epimerized to the original mixture. In the cyclization of **5** or **6**, the resident R^1- or R^2-bearing stereocenter is expected to either reinforce or compete with the influence of the amidal stereocenter in directing the stereochemical course of the C-N bond construction. The consequences of double stereodifferentiation in the mercury(II)-mediated cyclization/LiBH4 reduction of several amidals of the type **5** and **6** provided some rather surprising results (Table I).



5a (n=1), **b** (n=0) **6a** (n=1), **b** (n=0)

The diastereomeric amidals derived from 2-methyl-5-hexenal (**5a** and **6a**, $R^1 = CH_3$, $R_2 = H$; Table I entries 1-2) were separated, then individually cyclized via the procedure described above. There is no evidence for epimerization of the amidal center under the reaction conditions. One diastereomer (**5a**) cyclizes with poorer stereoselectivity (3.6:1 **8a**:**7a**, 60%) than the parent compound **2**, which cyclizes with 12.1:1 stereoselectivity under these conditions. The other diastereomer (**6a**) reacts with higher selectivity (14.1:1 **9a**:**10a**, 71%) than **2**.

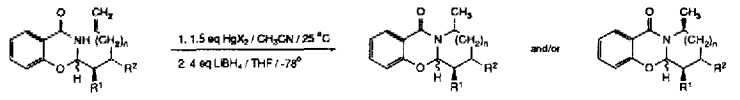
At first glance, these results seemingly fulfill our intuition about double stereodifferentiation. However, the structures of **8a** and **9a** proved to be somewhat surprising. As expected from the cyclization of **2**, both diastereomers **8a** and **9a** have the newly formed methyl-substituent in the pseudo-axial orientation. Compound **8a**, formed more slowly in the mercury-mediated cyclization (4-5 h vs 10 min) and with lower stereoselectivity (3.6:1 vs 14.1:1), has the resident methyl-(R^1-)substituent in the pseudo-equatorial orientation. Compound **9a**, the diastereomer produced with the highest selectivity, has the resident methyl-substituent in the pseudo-axial orientation. A result quite the opposite of what would be reasonably expected based upon the efficiency and relative rates of cyclization of the two diastereomers. (Structure **9a** was confirmed by single crystal x-ray analysis.) These observations raise interesting questions about the nature of the cyclization transition state. It is also noteworthy that the stereochemical relationship generated in compound **9a** would not be expected from a heterocyclization without the influence of the salicylamide auxiliary.



structure **9a**

Several other substitution patterns of **5** and **6** were examined. With the exception of entry 4, all of the cyclizations proceed readily; that is, reaction times for complete amidomercuration are less than 15 minutes at ambient temperature and overall chemical yields are 84-99%. In cases where the influence of the resident stereogenic center reinforces the influence of the amidal stereocenter (entries 3, 6, 8) good-to-excellent levels of stereoinduction are observed. In entry 5, competing stereochemical influences yield overall low diastereoselectivity. In entry 7 the influence of the adjacent cyclohexyl-substituent strongly predominates over that of the more remote amidal center and overall excellent stereoinduction is observed. Entry 4 presents an interesting limiting case. Amidocyclization of substrate **6a** ($R^1 = H$, $R^2 = c\text{-}C_6H_{11}$) would have led to a six-membered ring in which the resident cyclohexyl-substituent was forced into a pseudo-axial orientation. No

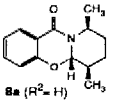
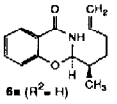
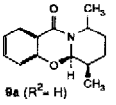
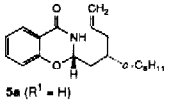
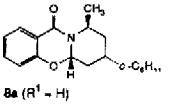
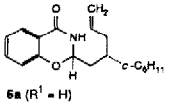
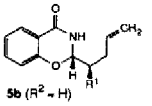
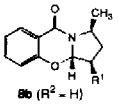
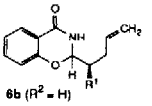
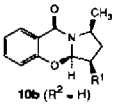
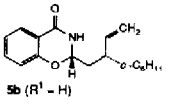
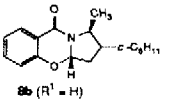
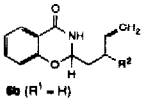
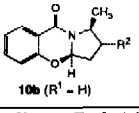
Table I. The Diastereoselective Amidomercuration Cyclizations of Substituted Amidals **5a-b** and **6a-b**.[a]



5 (β-H) a (n = 1), b (n = 0)
6 (α-H) a (n = 1), b (n = 0)

7a,b (β-H, cis)
9a,b (α-H, trans)

8a,b (β-H, trans)
10a,b (α-H, cis)

entry	substrate	major product	% yield	isomer ratio (RHgCl ratio)[b]
1	 **5a** (R^2 = H)	 **8a** (R^2 = H)	60%	3.6 : 1 (3.5 : 1)
2	 **6a** (R^2 = H)	 **9a** (R^2 = H)	71%	14.1 : 1 (11 : 1)
3	 **5a** (R^1 = H)	 **8a** (R^1 = H)	91%	> 50 : 1 (>20 : 1)
4	 **6a** (R^1 = H)	----	----	----
5	 **5b** (R^2 = H)	 **8b** (R^2 = H)	93%, R^1 = CH_2Ph 89%, R^1 = c-C_6H_{11}	2.4 : 1 (2.3 : 1) 2.1 : 1
6	 **6b** (R^2 = H)	 **10b** (R^2 = H)	95%, R^1 = CH_2Ph 88%, R^1 = c-C_6H_{11}	12.0 : 1 (10 : 1) 6 - 9 : 1 (12 : 1)
7	 **5b** (R^1 = H)	 **8b** (R^1 = H)	95%	> 50 : 1 (> 20 : 1)
8	 **6b** (R^1 = H)	 **10b** (R^1 = H)	89%, R^2 = CH_2CH_2Ph 99%, R^2 = c-C_6H_{11}	10.0 : 1 > 50 : 1 (> 20 : 1)

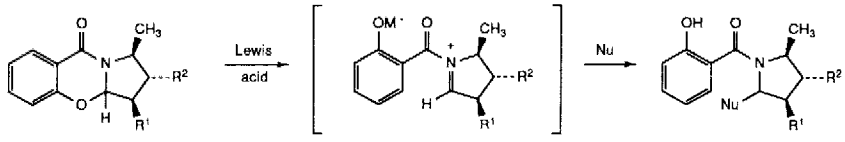
a) Compounds **5a-b** (**a** n=1, **b** n=0) cyclize to **7a-b** (cis) and/or **8a-b** (trans). Compounds **6a-b** (**a** n=1, **b** n=0) cyclize to **9a-b** (cis) and/or **10a-b** (trans). b) The ratio in parentheses gives the ^{1}HNMR integration of amidal protons in the crude mixture of organomercurials prior to $LiBH_4$ reduction.

cyclization products are observed from this substrate under the typical reaction conditions. After prolonged reaction times, only products from intermolecular reaction are isolated.

In each of the cases reported in Table I, the ratio of diastereomeric amidals was measured for both the reduced products **7** - **10** and the intermediate organomercurials. In general, there is a reasonable correlation between the two values. In a few cases, however, a slight discrepancy is observed. For example, in entry 6 (R^2 = c-C_6H_{11}) the ratio of diastereomeric organomercurials is reproducibly about 12:1. After reduction, the

stereoselectivity varied from experiment to experiment, and a ratio of diastereomeric amidals as low as 6.7:1 was observed. While the effect is admittedly small, it may be of some significance. The loss of stereochemistry in the reduction step does not arise via epimerization of the amidal center. Under such circumstances a different set of diastereomers would have been produced. The overall chemical yields are excellent (85-90%). The selective destruction of one diastereomer cannot account for the change in the ratio. The loss of stereoselectivity must arise via ring opening, reclosure, and subsequent trapping during the course of the reduction. A facile amide radical cyclization, with selective trapping on carbon, may account for the observed results.[1d,8]

The heterocycles generated in the amidomercuration reaction should prove to be useful intermediates for further chemical transformations. For example, the salicylamide derivatives could serve as useful N-acyliminium ion[9] precursors. In this manner compounds **10b** ($R^1 = C_6H_{11}$, $R^2 = H$ or $R^1 = H$, $R^2 = CH_2CH_2Ph$) are reduced by $(TFA)_2BH$[10] to the N-acyl pyrrolidine **11** (65-70%).



10 11 (Nu = H)

In summary, we find that certain substitution patterns (i.e. those leading to 2,4- and 2,5- *trans*-dialkyl substituted piperidines and *trans*-2,3- and *cis*-2,4-dialkyl substituted pyrrolidines) can be formed efficiently and with practical levels of stereoselectivity using the salicylamide auxiliary. Some of these stereochemical relationships are difficult to generate using other heterocyclization strategies.[11] In addition, these cyclized products should be useful as intermediates for further chemical elaboration. Further studies on the stereochemical consequences of chiral auxiliaries and double stereodifferentiation in heterocyclization reactions are in progress.

References and Notes.

1 a) Financial support for these investigations from the University of Nebraska Research Council and NIH Biomedical Research Support Grant RR-07055 are gratefully acknowledged. Mass spectral analyses were performed by the Midwest Center for Mass Spectrometry, which is supported by the NSF. 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 Beckie E. Takacs for preparing some of the intermediates used in these studies. d) We thank Professor M.E. Newcomb (Texas A&M University) for helpful mechanistic discussions alerting us to the possible involvement of nitrogen-centered radical cyclizations in our chemistry. e) All stable new compounds were characterized spectroscopically and the elemental composition determined by combustion analysis and/or high resolution mass spectrometry.

2 The author to whom questions regarding the crystal structure determinations should be directed.

3 Bartlett, P.A. in *Asymmetric Synthesis, Vol. 3*; Morrison, J.D., Ed.; Academic: New York, 1984; pp 411-54.

4 a) Masamune,S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed., Engl.* **1985**, *24*, 1-76; b) Heathcock, C.H.; White, C.T.; Morrison, J.J.; VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 1296-1309; c) Kurth, M.J.; Brown, E.G. *J. Am. Chem. Soc.* **1987**, *109*, 6844-45.

5 Takacs, J.M.; Helle, M.A.; Yang, L. *Tetrahedron Lett.* **1989**, *30*, 1777-80.

6 For a leading reference on the cyclizations of non-stereogenic amidal-containing substrates see: Harding, K.E.; Jones, M.W. *Heterocycles* **1989**, *28*, 663-8. b) For the report of a chiral amidal auxiliary, see: Harding, K.E., Hollingsworth, D.R., Reibenspies, J. *Tetrahedron Lett., in press.* c) For another chiral auxiliary see: Jew, S-s.; Terashima, S.; Koga, K. *Tetrahedron* **1979**, *35*, 2345-52.

7 a) The stereochemistry of *cis*-**3** was assigned in analogy to compound **10b** ($R^1 = H$, $R^2 = CH_2CH_2Ph$) for which a crystal structure was determined, and is consistent with the acid catalyzed epimerization of the amidal center in pure (±) *cis*-**3** or (±) *trans*-**3** to a mixture slightly enriched in the more stable (±) *trans*-**3** (*cis:trans* 1:1.3). b) The stereochemistry of *trans*-**4** was assigned in analogy to compound **9a** for which a crystal structure was determined, and is consistent with the acid catalyzed epimerization of the amidal center in (±) *cis*-**4** or (±) *trans*-**4** gives a mixture enriched in the more stable (±) *trans*-**4** (*cis:trans* 1:9.4). *Cis*-**4** is apparently thermodynamically disfavored due to an unfavorable $A_{1,3}$-type interaction between the carbonyl oxygen and the pseudo-equatorial methyl substituent as has been noted in similar systems (see reference 11a).

8 a) Mackiewicz, P.; Furstoss, R. *Tetrahedron* **1978**, *34*, 3241-60; b) Chow, Y.L.; Perry, R.A. *Can. J. Chem.* **1985**, *63*, 2203-10; c) Newcomb, M.E.; Marquardt, D.J. *Heterocyles* **1989**, *28*.

9 Speckamp, W.N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367-416.

10 Maryanoff, B.E.; McComsey, D.F.; Nortey, S.O. *J. Org. Chem.* **1981**, *46*, 355-60.

11 a) Harding, K.E.; Marman, T.H. *J. Org. Chem.* **1984**, *49*, 2838-40; b) Williams, D.R.; Osterhout, M.H.; McGill, J.M. *Tetrahedron Lett.* **1989**, *30*, 1327-30; and references therein.

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