Stereoselective Construction of *trans*-Disubstituted Azabicycles Using Oxauracil as a Novel Free Radical Acceptor

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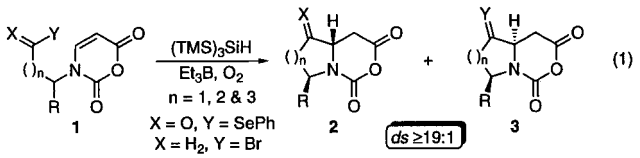
Intramolecular free radical cyclizations have been studied extensively in which the factors that control and influence selectivity are well understood.[1,2] Recent advances in asymmetric catalysis have added the enantioselective manifold to this transformation, for which excellent selectivities have been obtained in a variety of *intermolecular* radical additions.[3] The construction of cyclic ethers using intramolecular radical cyclizations provides a versatile and diastereoselective method;[4,5] however, the transposition of this information to cyclic amines has proven problematic.[6] Preliminary studies with acyclic vinylogous carbamates demonstrated that the intramolecular acyl radical cyclization reactions furnish the corresponding cyclic amines in modest yield and with poor diastereoselectivity, albeit favoring the *trans*-diastereoisomer.[7] The poor selectivity was attributed to $A^{1,3}$-strain between the *N*-protecting group and the incipient α-amino stereogenic center and/or the vinylogous carbamate resulting in poor rotamer discrimination. We envisioned that a cyclic acceptor that could incorporate the protecting group component would eliminate the steric congestion and should lead to improved diastereocontrol.[8]



(1)

Herein, we describe the stereoselective intramolecular addition of acyl and alkyl radicals to the new free radical acceptor oxauracil,[9] for the construction of *trans*-disubstituted azabicycles (eq 1). We anticipate that this template will provide a versatile synthon for the construction of a variety of biologically important cyclic amines and β-amino acid derivatives.[10]

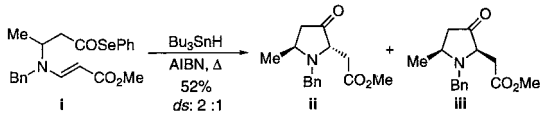
Table 1: Intramolecular Radical Cyclizations with the Acyl Selenides and Alkyl Bromides **1a**−**l**

entry		acyl selenide and alkyl bromide precursor **1**[a,b]				ratio of **2**: **3**[c]	yield (%)[d]
1	**a**	X = O	Y = SePh	*n* = 1	R = Me	≥19:1	92
2	**b**	"	"	"	R = Ph	≥19:1	89
3	**c**	X = H_2	Y = Br	"	R = Me	≥19:1	97
4	**d**	"	"	"	R = Ph	≥19:1	94
5	**e**	X = O	Y = SePh	*n* = 2	R = Me	≥19:1	98
6	**f**	"	"	"	R = Ph	≥19:1	85
7	**g**	X = H_2	Y = Br	"	R = Me	≥19:1	94
8	**h**	"	"	"	R = Ph	≥19:1	88
9	**i**	X = O	Y = SePh	*n* = 3	R = Me	≥19:1	87
10	**j**	"	"	"	R = Ph	≥19:1	68
11	**k**	X = H_2	Y = Br	"	R = Me	≥19:1	58
12	**l**	"	"	"	R = Ph	≥19:1	52

[a] All the cyclizations were carried out on a 1 mmol reaction scale. [b] $(TMS)_3SiH$, Et_3B, PhH, 0 °C to RT.[11] [c] Ratios of diastereoisomers determined by 400 MHz ^1H NMR integration.[12,13] [d] Isolated yields.

Table 1 summarizes the results for the acyl and alkyl radical cyclization reactions. Treatment of acyl selenides and alkyl bromides **1** with tris(trimethylsilyl)silane[14] and triethylborane, in the presence of air, furnished the corresponding azabicycles **2**/**3** as a ≥19:1 mixture of diastereoisomers, favoring **2** (entries

(7) Treatment of the acyl selenide **i** with tributyltin hydride and AIBN in refluxing benzene furnished the pyrrolidin-3-ones **ii/iii** in 52% yield, as a 2:1 mixture of diastereoisomers favoring **ii**.



(8) For a related example of a stereoselective free radical cyclization where a similar nonbonding interaction is invoked to rationalize the *trans*-diastereoselectivity, see: Beckwith, A. L. J.; Joseph, S. P.; Mayadunne, R. T. A. *J. Org. Chem.* **1993**, *58*, 4198.

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(10) For representative articles on the importance of β-amino acids in the formation of secondary structures, see: (a) Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem Commun.* **1997**, 2015. (b) DeGrado, W. F.; Schneider, J. P.; Hamuro, Y. *J. Pept. Res.* **1999**, *54*, 205. (c) Gademann, K.; Hinterman, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905. (d) Wang, X.; Espinosa, J. F.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 4821 and references therein.

(11) *Representative Cyclization Procedure*: The acyl selenide or alkyl bromide **1** (1.0 mmol, azeotroped with anhydrous benzene) were dissolved in anhydrous benzene (0.02, 0.01, and 0.005 M for 5-, 6-, and 7-exo radical cyclizations respectively) and cooled with stirring to 0 °C, protected from moisture by a drying tube packed with Drierite. Triethylborane (2.0 mL, 2.0 mmol, 2.0 equiv of a 1 M solution in hexane) was added *via* syringe, followed by the addition of *tris*(trimethylsilyl)silane (636 μL, 2.0 mmol, 2.0 equiv). The reaction mixture was then allowed to warm to room temperature and stirred under an atmosphere of dry air (tlc control). The solvent was then removed in vacuo to afford a crude solid, which was recrystallized using 5% diethyl ether/hexane to furnish the *azabicycles* **2** (see Table 1) as white crystalline solids.

† To whom all correspondence regarding the *X*-ray crystal structures should be addressed.

(1) For general reviews on radical reactions, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon*−*Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (c) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: San Diego, 1992. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1992; Vol. 4, pp 715, 779 and references therein.

(2) For recent reviews on acyl radical reactions, see: (a) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (b) Chatgiliagloglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991 and references therein.

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(4) For some recent examples of the stereoselective construction of cyclic ethers *via* intramolecular radical cyclizations, see: (a) Dulcère, J.-P.; Dumez, E.; Faure, R. *J. Chem. Soc., Chem. Commun.* **1995**, 897. (b) Maiti, G.; Adhikari, S.; Roy, S. C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 927. (c) Srikrishna, A.; Viswajanani, R.; Yelamaggad, C. V. *Tetrahedron Lett.* **1995**, *36*, 1127. (d) Hartung, J.; Gallou, F. *J. Org. Chem.* **1995**, *60*, 6706. (e) Lee, E.; Park, C.-P.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017. (f) Ihara, M.; Katsumata, A.; Setsu, F.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 677. (g) Engman, L.; Gupta, V. *J. Org. Chem.* **1997**, *62*, 157. (h) Beckwith, A. L. J.; Page, D. M. *J. Org. Chem.* **1998**, *63*, 5144. (i) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811 and references within.

(5) (a) Evans, P. A.; Roseman, J. D. *Tetrahedron Lett.* **1995**, *36*, 31. (b) Evans, P. A.; Roseman, J. D. *J. Org. Chem.* **1996**, *61*, 2252. (c) Evans, P. A.; Roseman, J. D.; Garber, L. T. *J. Org. Chem.* **1996**, *61*, 4880. (d) Evans, P. A.; Roseman, J. D. *Tetrahedron Lett.* **1997**, *38*, 5249. (e) Evans, P. A.; Manangan, T. *Tetrahedron Lett.* **1997**, *38*, 8165. (f) Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 3175. (g) Evans, P. A.; Manangan, T. *J. Org. Chem.* **2000**, *65*, 4523.

(6) For a recent review that highlights the challenges of azacycle construction *via* radical cyclizations, see: Esker, J. L.; Newcombe, M. *Adv. Heterocycl. Chem.* **1993**, 58, 1. For some recent examples of radical mediated azacycle construction, see: (a) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1383. (b) Sato, T.; Chono, N.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1115. (c) Schultz, A. G.; Guzzo, P. R.; Nowak, D. M. *J. Org. Chem.* **1995**, *60*, 8044. (d) Goodall, K.; Parsons, A. F. *Tetrahedron Lett.* **1997**, *38*, 491. (e) Lee, E.; Jeong, E.; Min, S. J.; Hong, S.; Lim, J.; Kim, S. K.; Kim, H. J.; Choi, B. G.; Koo, K. C. *Org. Lett.* **2000**, *2*, 2169 and references therein.

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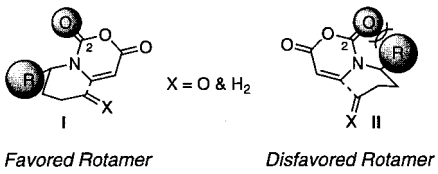
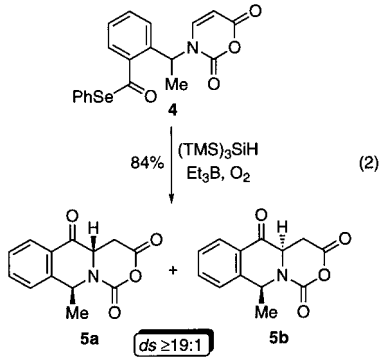


Figure 1.

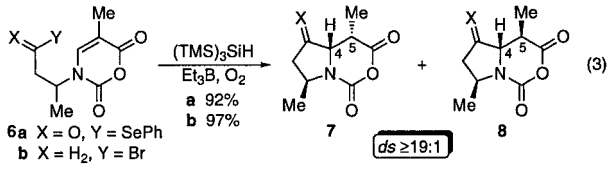
1−12).[15] The acyl radical cyclizations proceed efficiently for each ring size examined, whereas reduction becomes competitive with the rate of cyclization for the 7-exo alkyl radical additions (entries 11 and 12). This study confirms previous findings that demonstrated that the rate of decarbonylation can be suppressed by lowering the temperature and indicates the acyl radical is less prone to reduction.[5b] The excellent diastereoselectivity obtained for each cyclization was rationalized in the following manner. Figure 1 illustrates the origin for rotamer preference, which translates to diastereoselectivity, **I** versus **II**, to nonbonding interactions between the C-2 carbonyl of the oxauracil and the incipient α-amino stereogenic center.

Isoquinolines are ubiquitous to a variety of biologically important molecules and thus represent important templates for target-directed synthesis.[16] Treatment of the aryl acyl selenide **4**



under the standard reaction conditions furnished the corresponding isoquinoline **5a**/**b** in 84% yield as a ≥19:1 mixture of diastereoisomers, favoring **5a**. The inherent versatility of this transformation is evident from the ability to substitute various aryl groups and heterocycles, which are expected to facilitate the synthesis of related derivatives.

The oxathymine derivative was expected to expand the synthetic scope of the transformation through the introduction of an additional stereogenic center in the cyclization. We anticipated that the conformational bias of the azabicycle upon cyclization would result in the stereoselective reduction of the incipient free radical. Treatment of the acyl selenide **6a** and alkyl bromide **6b** under standard cyclization conditions furnished the corresponding azabicycles **7a**/**8a** and **7b**/**8b** in excellent yield as a ≥19:1 mixture of diastereoisomers respectively (eq 3). The stereochemistry of



the major stereoisomer was confirmed with the aid of a NOESY NMR experiment, which established the *syn*-relationship of the protons at C-4 and C-5 in **7**.

In conclusion, we have demonstrated the first examples of the intramolecular addition of acyl and alkyl radicals to oxauracil, for the stereoselective construction of 5,6-, 6,6-, and 7,6-azabicycles. The oxauracil derivative provides a versatile template for post-cyclization functionalization that should prove useful for the construction of biologically important *trans*-disubstituted cyclic amines and *β*-amino acids.[10] The ability to modify this protocol for the construction of isoquinoline derivatives and the introduction of an additional stereogenic center at C-5 using oxathymine highlights the immense synthetic potential of this methodology for target-directed synthesis.

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Supporting Information Available: Spectral data for **1/2a**−**l**, **4**, **5a**, **6a/b**, and **7a/b** including ORTEP plots of **10a**−**c** (PDF). X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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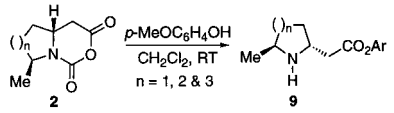
(12) The diastereoselectivity was determined in the following manner, due to the hydrolytic and thermal instability of the azabicycles **2**, which deemed them unsuitable for analysis by GLC and HPLC. Treatment of **2c**, **2g**, and **2k** with *p*-methoxyphenol at room temperature furnished the amino esters **9a**−**c** with diastereoselectivities of 37:1 (**a**; $n = 1$), 29:1 (**b**; $n = 2$) and 24:1 (**c**; $n = 3$) respectively (determined by HPLC[13]).



(13) To determine the selectivity at higher temperature, the oxauracil derivative **1c** was subjected to standard tributyltin hydride and AIBN in refluxing benzene to afford the azabicycles **2c**/**3c**, which upon treatment with *p*-methoxyphenol at room temperature furnished the amino ester with 10:1 diastereoselectivity by HPLC.[12]

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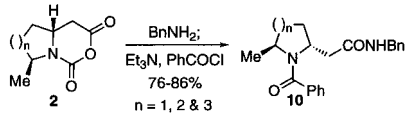
(15) The stereochemistry of the azabicycles **2c**, **2g**, and **2k** was confirmed through X-ray crystallographic analysis on the dipeptides **10a**−**c** which were prepared in 76−86% overall yield.



For $C_{21}H_{24}N_2O_2$ (**10a**, $n = 1$): monoclinic, *Pc*, $a = 15.2634(6)$ Å, $b = 6.7949(2)$ Å, $c = 9.3479(3)$ Å, $\beta = 104.269(2)°$, $V = 939.59(6)$ Å^3, $Z = 2$, $Z' = 1$, $T = 228(2)$ K, $D_{calc} = 1.189$ g cm^{-1}, colorless plate, $GOF = 1.023$, $R(F) = 4.65\%$ for 2505 observed independent reflections ($4° \le 2\theta \le 56°$). For $C_{22}H_{26}N_2O_2$ (**10b**, $n = 2$): monoclinic, $P2_1/n$, $a = 10.5766(1)$ Å, $b = 9.7748(2)$ Å, $c = 19.1768(4)$ Å, $\beta = 98.416(1)°$, $V = 1961.23(6)$ Å^3, $Z = 4$, $Z' = 1$, $T = 213(2)$ K, $D_{calc} = 1.187$ g cm^{-1}, colorless block, $GOF = 1.071$, $R(F) = 5.05\%$ for 3967 observed independent reflections ($4° \le 2\theta \le 56°$). For $C_{23}H_{28}N_2O_2$ (**10c**, $n = 3$): triclinic, *P1*, $a = 10.000(6)$ Å, $b = 10.5047(6)$ Å, $c = 11.5559(6)$ Å, $\alpha = 68.821(1)$, $\beta = 86.902(1)$, $\gamma = 65.525(1)°$, $V = 1023.65(10)$ Å^3, $Z = 2$, $Z' = 1$, $T = 213(2)$ K, $D_{calc} = 1.182$ g cm^{-1}, colorless plate, $GOF = 1.057$, $R(F) = 6.57\%$ for 4354 observed independent reflections ($4° \le 2\theta \le 56°$).

(16) For related examples of the intramolecular addition of aryl and alkyl radicals to uracil derivatives, see: (a) Yoshimura, Y.; Otter, B. A.; Ueda, T.; Matsuda, A. *Chem. Pharm. Bull.* **1992**, *40*, 1761. (b) Zhang, W.; Pugh, G. *Tetrahedron Lett.* **1999**, *40*, 7591 and references therein.