

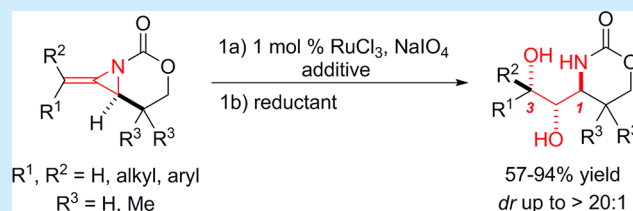
Aminodiols via Stereocontrolled Oxidation of Methyleneaziridines

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S Supporting Information

ABSTRACT: A highly diastereoselective Ru-catalyzed oxidation/reduction sequence of bicyclic methyleneaziridines provides a facile route to complex 1-amino-2,3-diol motifs. The relative *anti* stereochemistry between the amine and the vicinal alcohol are proposed to result from 1,3-bischelation in the transition state by the C1 and C3 heteroatoms.



Aminodiols are ubiquitous in a host of bioactive molecules and natural products (Figure 1).¹ Popular approaches to

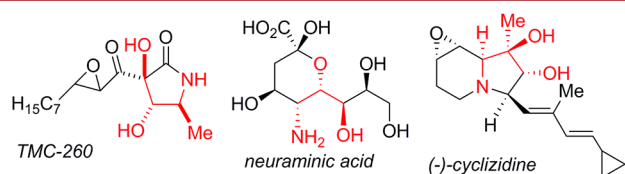


Figure 1. Bioactive molecules containing NOO stereotriads.

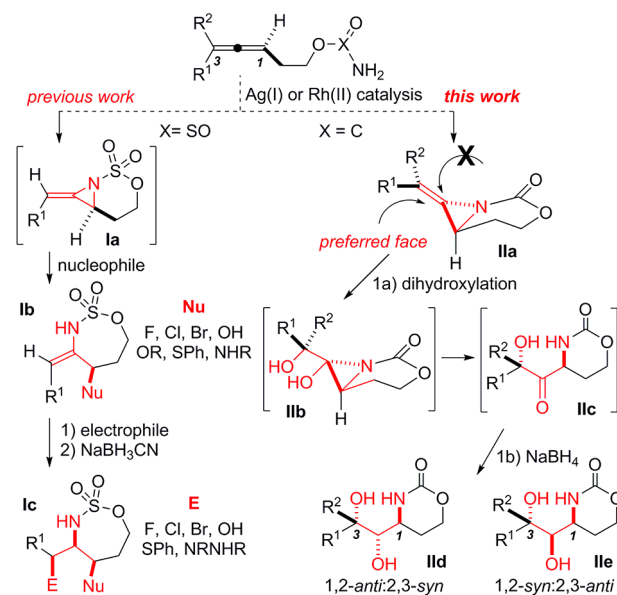
these motifs often employ starting materials from the chiral pool or utilize the ring-opening of chiral epoxy alcohols with amine nucleophiles.^{2,3} These strategies work well when the target aminodiol is relatively simple, but accessing more complex and densely substituted motifs can be difficult. While the dihydroxylation of chiral allylic amines addresses this challenge to some extent, high loadings of OsO₄ and variable dr are drawbacks.⁴

Our group has developed new methods that introduce three new sp³ carbon–heteroatom bonds into an allene in a stereocontrolled manner. Rapid access to C–Nu/C–N/C–E stereotriads (motifs containing three contiguous chiral carbons, **Ic**, Scheme 1) from homoallenic sulfamates is enabled through the intermediacy of bicyclic methyleneaziridines **Ia**.⁵ This method offers diversity in the choices for the Nu and E groups of **Ic** but restricts the placement of nitrogen to the central carbon of the stereotriad. The utility of allene oxidation could be expanded if amine-containing stereotriads of other substitution patterns could be accessed. Herein, we report a highly diastereoselective formation of C–N/C–O/C–O (NOO) triads from simple homoallenic carbamates.

The initial step of our strategy employs allene aziridination to a methyleneaziridine **Ia** (Scheme 1).⁶ The bicyclic nature of **Ia** was expected to promote dihydroxylation to a hemiaminal **Ib** in high dr. Unraveling of **Ib** to a 1,3-hydroxyaminated ketone **Ic**, followed by reduction, would yield either **IId** or **IIE**, depending on the nature of the reductant.

We initially attempted to use homoallenic sulfamates as substrates, but aziridine ring-opening prior to reaction of the

Scheme 1. Allene Functionalization Strategies



exocyclic double bond was problematic. Treatment of homoallenic carbamate **1a** (Table 1) with OsO₄ and NMO gave no reaction; however, a 1 mol % loading of RuCl₃ in the presence of NaIO₄ as the terminal oxidant (“flash dihydroxylation”) cleanly provided the desired ketone **2aE** (**Ic**, Scheme 1 for general structure).⁷ The key to achieving excellent conversion and minimizing oxidative cleavage was to employ CeCl₃ as an additive.^{7d,g} Under these conditions, the ketone **2aE** was obtained as a single diastereomer, indicating excellent facial selectivity in the dihydroxylation. Immediate reduction of the ketone with NaBH₄ in MeOH yielded the 1-amino-2,3-diol **3aE** in >20:1 dr (Table 1, entry 1).

The scope of the reaction was investigated (Table 1).^{5,6} In all cases, the 1-amino-2,3-diol was obtained in >20:1 dr, with both

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Table 1. Stereocontrolled Transformation of *gem*-Dimethyl Bicyclic Methyleneaziridines to NOO Stereotriads

entry	R ¹ , R ²	E:Z	yield ^a	dr ^b	major product	entry	R ¹ , R ²	E:Z	yield ^a	dr ^b	major product
1 ^c	Ph, Me 1a	100:0	94%	>20:1	3aE	6	C ₅ H ₁₁ , Me 1f	70:30	84%	>20:1	3fE
2 ^c	tol, Me 1b	100:0	88%	>20:1	3bE	7	ⁱ Bu, Me 1gE	70:30	74%	>20:1	3gE
3 ^c	4-CF ₃ C ₆ H ₄ Me 1c	100:0	73%	>20:1	3cE		Me, ⁱ Bu 1gZ	70:30	74%	>20:1	3gZ
4	Me, Me 1d	---	70%	>20:1	3d	8	Et, Me 1h	70:30	57%	>20:1	3hE
5	Pr, Pr 1e	---	85%	>20:1	3e	g ^{c,d}	C ₅ H ₁₁ , H 1i	100:0	66%	7.9:1	3iE

^aCombined yield of *E* and *Z*. ^bdr of both the *E* and *Z* products. ^cThe *E* and *Z* methyleneaziridines were separated, and only *E* was used in the reaction. ^d100 mol % CeCl₃ and 3.0 equiv of NaIO₄ were employed in the oxidation, while Zn(BH₄)₂ in Et₂O at 0 °C was used in the reduction.

Table 2. Expanding the Scope of NOO Stereotriad Synthesis*

entry	R ¹ , R ² , R ³	E:Z	yield ^a	dr ^b	major ketone (from <i>E</i>)	major products (from <i>E</i>)	yield 7:8	dr 7:8
1	C ₅ H ₁₁ , Me, H 4a	100:0	98%	>20:1	5a	7a	80%	5.7:1
2	ⁱ Bu, Me, H 4b	3.5:1	55%	>20:1	5b	7b	96%	7.2:1
3	Et, Me, H 4c	2.3:1	66%	2.3:1	5c + 6c	7c	50%	8.3:1 <i>E</i> 7c:8c 7.1:1 <i>E</i> 9c:10c
4	Pr, Pr, H 4d	---	96%	>20:1	5d	7d	88%	6.1:1
5	-(CH ₂) ₅ , H 4e	---	79%	>20:1	5e	7e	96%	8.9:1
6	C ₅ H ₁₁ , Me, Me 4f	2.3:1	80%	>20:1	5f	7f	98%	6.6:1

*Conditions A: 1 mol % of RuCl₃, 50 mol % of AcOH, 1.5 equiv of NaIO₄, 2:1 MeCN/H₂O. Condition B: 1 mol % of RuCl₃, 20 mol % of H₂SO₄, 1.5 equiv of NaO₄, 3:3:1 EtOAc/MeCN/H₂O. ^aYield of the product from the *E* isomer. ^bdr of the product from the *E* methyleneaziridine.

aryl (entries 1–3) and alkyl (entries 4–8) groups tolerated at C3 of the substrate. The presence of an EWG on the arene decreased the yield but did not impact the dr (Table 1, compare entry 3 to entries 1 and 2). The 1-amino-2,3-diols

obtained from *E* methyleneaziridines contained the 1,2-*anti*:2,3-*syn* stereochemistry, as verified by X-ray crystallography of **3cE**. The structures of **3aE** and **3bE** were assigned by analogy to **3cE** (Supporting Information). The *anti* relationship between the

C1 amine and the C2 alcohol was also observed when C3 was achiral (entries 4 and 5). When the two substituents at C3 of the allene were very similar, the mixtures of *E* and *Z* methyleneaziridines were difficult to separate (entries 6–8). However, the reaction could be carried out on the 70:30 *E/Z* mixtures and the resulting isomers separated to give the diastereomeric triads **3f–hE** and **3f–hZ** in excellent dr (*E* shown). Separating ketones **2gE** and **2gZ** and independently subjecting them to reduction clearly showed the dr of the reduction was >20:1. The relative stereochemistries of both **3gE** and **3gZ** were verified by X-ray crystallography as 1,2-*anti*:2,3-*syn* (Supporting Information) for **3gE** and 1,2-*anti*:2,3-*anti* for **3gZ**.

The 1,3-disubstituted methyleneaziridine **1i** (entry 9) was challenging, as overoxidation to the diketone using Ru catalysis was problematic.⁷ Increasing the amount of CeCl₃ improved the selectivity for **2i**, but at the cost of conversion. The use of a full equivalent of CeCl₃ and portionwise addition of 3.0 equiv of NaO₄ gave a 66% yield of the desired product with minimal overoxidation.

To expand the reaction scope and shed light on the factors responsible for stereocontrol in the ketone reduction, methyleneaziridines lacking the *gem*-dimethyl group were explored (Table 2). These compounds were susceptible to ring-opening when the conditions described in Table 1 were employed. Substitution of AcOH or H₂SO₄ for CeCl₃ as the additive improved both the conversions and the yields in the dihydroxylation.

Oxidation of *E*-**4a** (Table 2, entry 1) gave the ketone **5a** in 98% yield as a single diastereomer. Reduction of **5a** with NaBH₄ in MeOH gave the 1,2-*anti*:2,3-*syn* stereoisomer **7a** in 80% yield (verified by X-ray crystallography) and 5.7:1 dr, along with the minor isomer **8a**. The dialkyl-substituted methyleneaziridines **4b** and **4c** were not easily separable, but the diastereomers could be resolved at either the ketone or the 1-amino-2,3-diol stage to give the products in dr of 7.1–8.3:1 (entries 2 and 3). Substrates with identical substituents at C3 (entries 4 and 5) exhibited a 1,2-*anti* relationship between the C1 amine and the C2 alcohol.

The unexpected stereochemical outcomes were initially puzzling. While Felkin–Anh and Cram chelation models are often invoked to explain stereochemical outcomes in the addition of nucleophiles to α -substituted carbonyls, control when a ketone is flanked by two different potential chelating groups is poorly understood.^{8,9} We propose the –NH and the –OH of ketones of the general form **9** (Figure 2) participate in 1,3-bis-chelation to give a *trans* decalin-type intermediate **10**. Reduction of the ketone from the top face should be favored to yield the 1,2-*anti*:2,3-*syn* relationship observed in the products. To determine how well this hypothesis fit our data, the reduction of ketones of several substitution patterns were examined more closely. In the case of **3fE** and **3fZ**, formed from the *E* and *Z* stereoisomers of **2f**, an *anti* relationship between C1 and C2 was noted in both of the products (Table 1, entry 6 and Figure 2, A and B), ruling out stereocontrol of the reduction by C3. The observed results could be rationalized either by our proposed model or by assuming that the amine at C1 is responsible for controlling the reduction outcome. If C1 were solely responsible for stereocontrol of the reduction, the removal of a substituent from C3 of **2i** (Table 1, entry 9 and Figure 2, C) would not be expected to influence the dr. However, we found that the dr of **3iE** decreased to 2.2:1 using NaBH₄ in MeOH. Switching to a less polar solvent and a lower

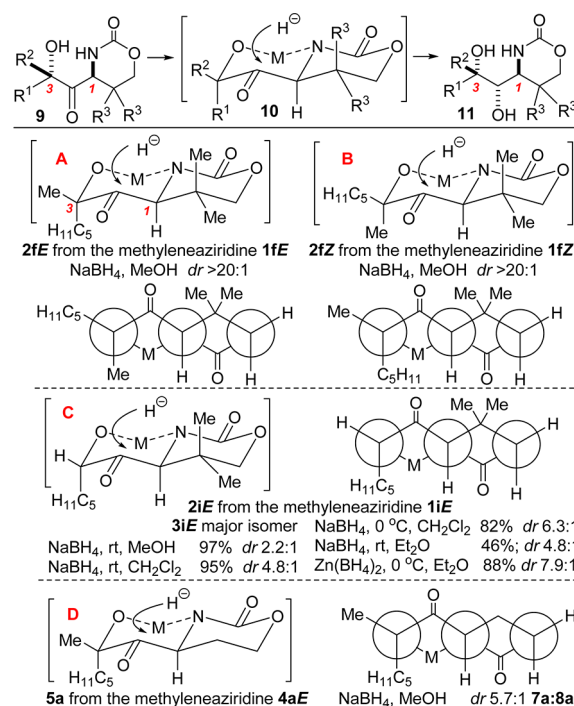


Figure 2. Possible α, α' -chelation models for stereocontrol.

temperature increased the dr, while substitution of Zn(BH₄)₂ for NaBH₄ restored the dr to 7.9:1 with a 1,2-*anti* relationship as verified by X-ray crystallography. Chelation control through the C3 oxygen would be expected to yield the 1,2-*syn*:2,3-*anti* triad; thus, we propose that a tighter transition state exists in C when M = Zn (van der Waal radius of Zn²⁺ = 0.88 Å), as compared to M = Na (Na⁺ = 1.16 Å), leads to an increase in dr. In addition, the *trans* decalin transition state in C is disfavored by the need to place the alkyl group in the pseudoaxial position, a situation that is less favorable in the presence of a highly polar solvent and/or a large cation. Removal of the *gem*-dimethyl groups in **5a** (Figure 2, D) lowered the dr, perhaps due to the lack of assistance from the Thorpe–Ingold effect in enforcing the *trans* decalin transition state.

In conclusion, rapid and diastereoselective conversion of homoallylic carbamates to 1-amino-2,3-diols has been achieved. Stereoselectivity in the reduction of the α, α' -substituted ketones depends on the specific substitution pattern of the substrate but often exhibits dr > 10:1. Coupled with our previous observations that the axial chirality of an allene can be transferred to point chirality, this protocol permits rapid access to densely functionalized, enantioenriched aminodiols.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full characterizations are available for all new compounds. X-ray crystallographic data is available for compounds **3cE**, **3gE**, **3gZ**, **7aE**, and **3iE** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Hanessian, S.; Soma, U.; Dorich, S.; Deschênes-Simard, B. *Org. Lett.* **2011**, *13*, 1048. (b) Ohsaki, A.; Ishiyama, H.; Yonedac, K.; Kobayashi, J. *Tetrahedron Lett.* **2003**, *44*, 3097. (c) Kim, H.; Kang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1827. (d) Azumi, M.; Ogawa, K.; Fujita, T.; Takeshita, M.; Yoshida, R.; Furuai, T.; Igarashi, Y. *Tetrahedron* **2008**, *64*, 6420.

(2) (a) Weber, B.; Kolczewski, S.; Fröhlich, R.; Hoppe, D. *Synthesis* **1999**, *9*, 1593. (b) Hao, L.; He, A.; Falck, J. R.; Liebeskind, L. S. *Org. Lett.* **2011**, *13*, 3682. (c) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Lunazzi, L.; Mazzanti, A.; Mazzanti, G.; Ricci, A.; Varchi, G. *Synlett* **2001**, 995. (d) Weber, B.; Kolczewski, S.; Fröhlich, R.; Hoppe, D. *Synthesis* **1999**, *9*, 1593. (e) Benedetti, F.; Berti, F.; Budal, S.; Campaner, P.; Dinon, F.; Tossi, A.; Radka, A.; Genova, P.; Atanassov, V.; Hinkov, A. *J. Med. Chem.* **2012**, *55*, 3900. (f) Liu, Z.; Byun, H.; Bittman, R. *J. Org. Chem.* **2011**, *76*, 8588.

(3) For selected references, see: (a) Olivier, K. S.; Van Nieuwenhze, M. S. *Org. Lett.* **2010**, *12*, 1680. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (c) Sabitha, G.; Babu, R.; Rajkumar, M.; Yadav, J. S. *Org. Lett.* **2002**, *4*, 343. (d) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

(4) For selected references, see: (a) Noe, M. C.; Letavic, M. A.; Snow, S. L. *Org. React.* **2005**, *66*, 109. (b) Lee, Y.; Kim, M.; Jew, S.; Park, H. *J. Org. Chem.* **2011**, *76*, 740. (c) Csatayova, K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Wilson, D. L. *Org. Lett.* **2011**, *13*, 2606. (d) Krysan, D. J.; Rockway, T. W.; Haight, A. R. *Tetrahedron: Asymmetry* **1994**, *5*, 625.

(5) (a) Adams, C. S.; Boralsky, L. A.; Guzei, I. A.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 10807. (b) Boralsky, L. A.; Marston, D.; Grigg, R. D.; Hershberger, J. C.; Schomaker, J. M. *Org. Lett.* **2011**, *13*, 1924. (c) Weatherly, C. D.; Rigoli, J. W.; Schomaker, J. M. *Org. Lett.* **2012**, *14*, 1704. (d) Rigoli, J. W.; Boralsky, L. A.; Hershberger, J. C.; Marston, D.; Meis, A. R.; Guzei, I. A.; Schomaker, J. M. *J. Org. Chem.* **2012**, *77*, 2446. (e) Weatherly, C. D.; Guzei, I. A.; Schomaker, J. M. *Eur. J. Org. Chem.* **2013**, 3667.

(6) (a) Rigoli, J. W.; Weatherly, C. D.; Vo, B. T.; Neale, S.; Meis, A. R.; Schomaker, J. M. *Org. Lett.* **2013**, *15*, 290. (b) Rigoli, J. W.; Weatherly, C. D.; Alderson, J. M.; Vo, B. T.; Schomaker, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 17238.

(7) (a) Beligny, S.; Eibauer, S.; Maechling, S.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1900. (b) Plietker, B.; Niggemann, M. *Org. Biomol. Chem.* **2004**, *2*, 2403. (c) Plietker, B.; Niggemann, M.; Pollrich, A. *Org. Biomol. Chem.* **2004**, *2*, 1116. (d) Neisius, N. M.; Plietker, B. *J. Org. Chem.* **2008**, *73*, 3218. (e) Plietker, B. *Tetrahedron: Asymmetry* **2005**, *16*, 3453. (f) Plietker, B. *Synthesis* **2005**, 2453. (g) Plietker, B.; Niggemann, M. *J. Org. Chem.* **2005**, *70*, 2402. (h) Plietker, B. *J. Org. Chem.* **2004**, *69*, 8287. (i) Plietker, B. *J. Org. Chem.* **2003**, *68*, 7123. (j) Bataille, C. J. R.; Donohoe, T. J. *Chem. Soc. Rev.* **2011**, *40*, 114. (k) Gourdet, B.; Lam, H. W. *Angew. Chem., Int. Ed.* **2010**, *49*, 8733.

(8) For selected references on the Felkin–Anh and Cram–chelation models, see: (a) Stanton, G. R.; Johnson, C. N.; Walsh, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 4399 and references therein. (b) Guillaume, S.; Ple, K.; Banchet, A.; Liard, A.; Haudrechy, A. *Chem. Rev.* **2006**, *106*, 2355. (c) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191. (d) Tlais, S. F.; Clark, R. J.; Dudley, G. B. *Molecules* **2009**, *14*, 5216. (e) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (f) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. (g) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145. (h) Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 4475. (i) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (j) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. (k) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**,

121, 669. (l) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. *W. J. Am. Chem. Soc.* **1999**, *121*, 686. (m) Atkinson, R. S. *Stereoselective Synthesis*; Wiley: New York, 1995; p 304. (n) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419. (o) Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457. (p) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417.

(9) (a) Zhao, X. Z.; Peng, L.; Tang, M.; Tu, Y. Q.; Gao, S. H. *Tetrahedron Lett.* **2005**, *46*, 6941. (b) Ley, S. V.; Michel, P.; Trapella, C. *Org. Lett.* **2003**, *5*, 4553.