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Regioselective Synthesis of Aniline-Derived 1,3- and C_i-Symmetric 1,4-Diols from *trans*-1,4-Cyclohexadiene Dioxide

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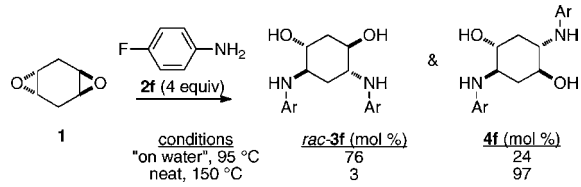
ABSTRACT

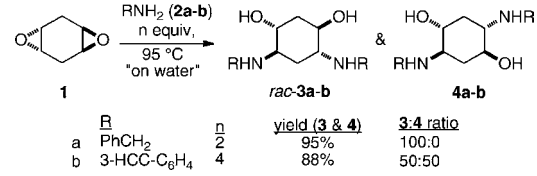


***trans*-Diepoxide 1 is well-known to react with aliphatic amines and the azide ion to give exclusively the 1,3-diol products. However, we observed that by judicious choice of conditions, reaction with anilines can give predominantly the 1,3-diol (3) or the heretofore rarely seen C_i-symmetric 1,4-diol (4). Synthesis of an unsymmetrical 1,4-diol from two different anilines is also demonstrated. These studies demonstrate that an intramolecular anilino−NH hydrogen bond donor can direct Fürst−Plattner epoxide opening.**

Ring-opening of *trans*-1,4,-cyclohexadiene dioxide **1** with aliphatic 1°- and 2°-amines,[1] ammonia,[1b] pyrazole,[2] and azide[1b,3] nucleophiles is well-known to give 1,3-diol products in high selectivity due to Fürst-Plattner[4] control of the second ring-opening. As a case in point, reaction of **1** with benzylamine **2a** "on water"[5] exclusively provides the 1,3-diol **3a** in 95% yield (Scheme 1).

In the context of a BACE1 inhibitor discovery program,[6] we carried out the analogous reaction of **1** with 3-ethynylaniline **2b** (Scheme 1). To our surprise, a 1:1 mixture of the desired 1,3-diol **3b** and the 1,4-diol regioisomer **4b** was obtained. The two regioisomers are easily separable on silica gel, and their structures were assigned by ^{1}H and ^{13}C NMR spectroscopy, based on the time-averaged C_2 symmetry of **3b**, and the instantaneous C_i-symmetry of **4b** (see Supporting Information).

Scheme 1. Opening of *trans*-Diepoxide **1** with Benzylamine **2a** and 3-Ethynylaniline **2b**



Centrosymmetric 1,4-diols derived from **1** and nitrogen nucleophiles have been characterized previously in only one case, as a minor (<5%) byproduct in chiral Lewis acid-catalyzed reactions with $TMSN_3$.[3c,d] Aside from the interest-

(1) (a) Craig, T. W.; Harvey, G. R.; Berchtold, G. A. *J. Org. Chem.* **1967**, *32*, 3743–3749. (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021. (c) Scheunemann, M.; Sorger, D.; Kouznetsova, E.; Sabri, O.; Schliebs, R.; Wenzel, B.; Steinbach, J. *Tetrahedron Lett.* **2007**, *48*, 5497–5501.

(2) Barz, M.; Glas, H.; Thiel, W. R. *Synthesis (Stuttg.)* **1998**, 1269–1273.

(3) (a) Kavadias, G.; Droghini, R. *Can. J. Chem.* **1979**, *57*, 1870–1876. (b) Gruber-Khadjawi, M.; Hönig, H.; Illaszewicz, C. *Tetrahedron: Asymmetry* **1996**, *7*, 807–814. (c) Clique, B.; Ironmonger, A.; Whittaker, B.; Colley, J.; Titchmarsh, J.; Stockley, P.; Nelson, A. *Org. Biomol. Chem.* **2005**, *3*, 2776–2785. (d) Ironmonger, A.; Stockley, P.; Nelson, A. *Org. Biomol. Chem.* **2005**, *3*, 2350–2353.

(4) Fürst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275–283.

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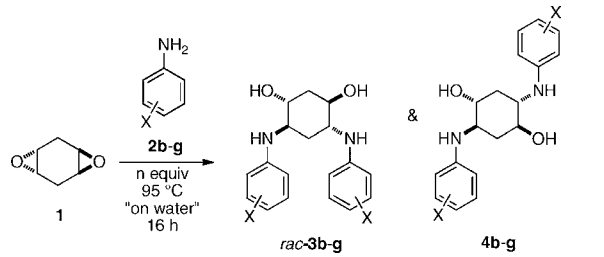
ing C_i-symmetry of **4b**, we viewed that the complete lack of 1,3-diol regioselectivity seen in reaction with **2b** merited further investigation. It seemed likely that electronic effects played a significant role in the ring-opening regioselectivity. Thus we performed reactions of **1** with five other anilines **2c**-**g** under the same conditions (Table 1). Anilines bearing

Table 1. Reactions of **1** with Anilines **2b**−**g** "On Water"



entry	aniline	n	X	sigma value[7]	**3:4**[a]	% yield of major isomer[b]
1	**2c**	2	p-CH_3	−0.14	100:0	96
2	**2d**	2	p-OCH_3	−0.12	100:0	90
3	**2e**	2	H	0.0	84:16	60 (71)
4	**2f**	4	p-F	0.15	76:24	62 (81)
5	**2b**	4	m-CCH	0.21	50:50	44 (88)
6	**2g**	8	m-Cl	0.37	22:78	56 (72)

[a] Crude product ratios measured by ^{1}H NMR spectroscopy before purification. [b] Chromatographed yield of the major regioisomer (note: in entry 5, the yield of **3b** is given). The value in parentheses indicates % recovery of this isomer from the crude product mixture.

electron-donating substituents (e.g., **2c**,**d**) gave the 1,3-diols **3c** and **3d** in 100% regioselectivity (entries 1 and 2). Unsubstituted aniline **2e** gave a 84:16 mixture of regioisomers (entry 3), and anilines bearing electron withdrawing substituents (e.g., **2f**, **2b**, **2g**, entries 4−6) evidenced increasing amounts of the 1,4-diol. As Table 1 illustrates, selectivity for the 1,4-diol increases with the sigma value of the substituent; *m*-chloroaniline **2g** gives a 22:78 ratio of the 1,3- and 1,4-diols. Finally, whereas reaction with electron-rich anilines **2c**,**d** was complete within 4 h at 95 °C, the electron deficient anilines required high equivalency and prolonged reaction time (16 h) to give complete conversion.

On the basis of these results we reasoned that interplay of the relatively weak nucleophilicity and enhanced hydrogen bond donating ability of anilines (relative to aliphatic amines) was responsible for the formation of the 1,4-diols **4** in reactions with **2b** and **2e**−**g**. A unified mechanism for formation of both regioisomers is given in Scheme 2. Opening of **1** with one equivalent of amine gives epoxy aminoalcohol *rac*-**5**. According to the accepted stereoelectronic requirements for epoxide opening, **5** should be formed in the diaxial-conformation (diax-*rac*-**5**). In this conformation it is possible for the newly installed amino substitutent at C4 to donate a hydrogen bond to the epoxide oxygen, thereby activating it for attack. If the second epoxide opening proceeds directly via transition state **4***, the Fürst-Plattner effect will favor amine opening at C1, giving 1,4-diol **4**. We describe this route to **4** as "NH-directed Fürst−Plattner." Note that a similar directing effect of a pendant *cis-hydroxyl* group has been invoked in ring-opening of cyclohexene oxides,[8] and in Li^+/Yb^{3+}-catalyzed opening of cyclitol epoxides.[9] However, if **5** relaxes from its diaxial conformation to the more stable diequatorial conformation (dieq-*rac*-**5**) prior to the second attack, the Fürst-Plattner effect would favor opening at C6 via transition state **3***, giving 1,3-diol **3**. In this case, hydrogen bond assistance of the second epoxide opening is likely provided by water.

Since aliphatic amines like **2a** are poor hydrogen bond donors relative to water, the second ring-opening is expected to proceed via the diequatorial transition state **3***, giving 1,3-diol opening products in high selectivity. (Scheme 1). As mentioned earlier, this standard Fürst−Plattner mechanism also accounts for the high 1,3-diol selectivity seen in reaction of **1** with azide ion[1b,3] and pyrazoles.[2] However, the substantially increased acidity of anilines relative to amines[10] should make them competent hydrogen bond donors, rendering the 1,4-diol pathway transition state **4*** similar in energy to transition state **3***. Furthermore, one would expect that the 1,4-pathway would become increasingly viable with electron deficient anilines, just as Table 1 demonstrates.

In addition, as depicted in Scheme 2, partitioning between the 1,3- and 1,4-diol pathways also depends on the concentration and competence of intermolecular hydrogen bond donors BH (Scheme 2). In "on water" conditions, interfacial water likely plays a dominant role in epoxide activation,[5a] though dissolved water could also play a role. A logical approach to further improve 1,4-selectivity would thus be to perform reactions under conditions where the concentration of such intermolecular hydrogen bond donors is minimized.

Our first attempts to achieve this goal involved running the reactions in aprotic solvents at elevated temperatures ([**1**] = 0.5 M, [**2b**] or [**2d**] = 1 M, in acetonitrile (reflux), DMF (95 °C), and mesitylene (150 °C)). Interestingly no reaction was observed in any of these cases after 16 h, illustrating the importance of hydrogen-bond assistance for the first ring-opening to give *rac*-**5**.

(5) (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279. (b) Azizi, N.; Saidi, M. *Org. Lett.* **2005**, *7*, 3649–3651. (c) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492–502. (d) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270–2274.

(6) Carlier, P. R.; Monceaux, C. J.; Matsuoka, Y.; Hirate-Fukae, C. *Abstract of Papers*, 236th National Meeting of the American Chemical Society, Philadelphia, PA, August 17−21, 2008; American Chemical Society: Washington, DC, 2008; MEDI-300.

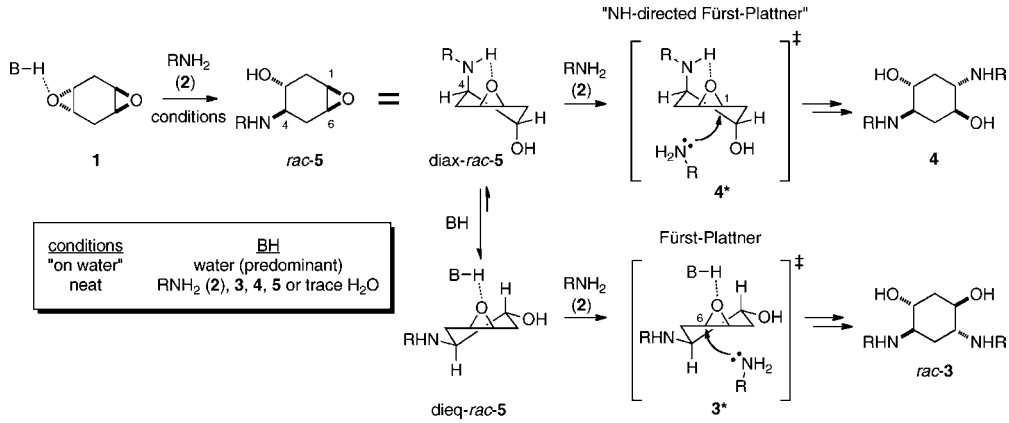
(7) Carey, F. A.; Sundberg, R. J., *Advanced Organic Chemistry. Part A, Structure and Mechanisms*, 5th ed.; Springer: New York, 2007.

(8) For example, *cis*-1,4-cyclohexadiene dioxide reacts with 2 equiv benzylamine **2a** under neat reaction conditions to give only the 1,3-diol (see ref 1b, footnote 46).

(9) (a) Serrano, P.; Llebaria, A.; Delgado, A. *J. Org. Chem.* **2002**, *67*, 7165–7167. (b) Serrano, P.; Llebaria, A.; Vásquez, J.; de Pablo, J.; Anglada, J. A.; Delgado, A. *Chem.*−*Eur. J.* **2005**, *11*, 4465–4472.

(10) Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 2964–2968.

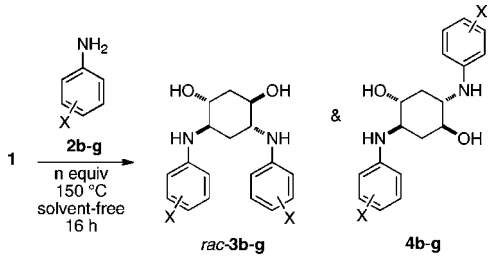
Scheme 2. Proposed Mechanistic Pathways for Formation of 1,3- and 1,4-Diols (**3** and **4**, Respectively)



However, success was realized under neat (solvent-free) conditions at 150 °C (16 h, Table 2). Under these conditions we envision that high reactant concentrations and hydrogen-bonding assistance from a second aniline molecule (or trace water) initially facilitates the first ring-opening to give the epoxy aminoalcohol *rac*-**5**.[11] As hoped, under neat conditions, all the anilines showed a predominance of 1,4-diol **4** (Table 2). Note that the 1,4-selectivity is greatest for the electron-deficient anilines **2b**, **f**−**g** and unsubstituted aniline **2e** (cf. Table 2, entries 3−7). This observation is consistent with the expected enhanced acidity and hydrogen-bonding ability of these anilines (Scheme 2). The low yield seen in the solvent-free reaction of **2b** reflects competing side reactions, perhaps due to the reactivity of the acetylene unit at 150 °C; nevertheless high 1,4-selectivity was seen (8:92, Table 2, entry 5). The fact that selectivity for the 1,4-diol is not absolute under solvent-free conditions points to the participation of a second epoxy aminoalcohol **5** and diols **3**, **4** as intermolecular hydrogen bond donors (BH) in the 1,3-diol pathway.[12] This competing pathway would be most problematic in reaction with electron-rich anilines **2c**−**2d**, since the corresponding pendant anilino groups in **5c**−**5d** are poor H-bond donors relative to the alcohol groups present in **3**−**5.** This reasoning also accounts for the observation that neat reaction of **1** with benzylamine **2a** (4 equiv) affords 1,3-diol **3a** as the sole product (94% yield).

To provide a further test of the key role of intramolecular H-bonding from the pendant aniline in 1,3- vs 1,4-diol selectivity, reactions were performed using *N*-methyl aniline **2h**. In this case, the epoxy aminoalcohol intermediate **5h** would lack an amino hydrogen, and thus the 1,4-diol pathway should not be viable. As hoped, these experiments confirmed our mechanistic hypothesis: both under neat and "on water" conditions, opening of **1** with *N*-methylaniline **2h** exclusively provided the 1,3-diol **3h** (Table 3).

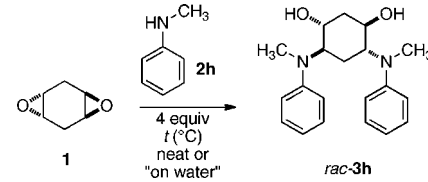
Table 2. Neat (Solvent-Free) Reactions of **1** with Anilines **2b**−**g**



entry	aniline	n	X	sigma value	**3**:**4**[a]	% yield of major isomer[b]
1	**2c**	4	*p*-CH_3	−0.14	40:60	42 (70)
2	**2d**	4	*p*-OCH_3	−0.12	40:60	51 (87)
3	**2e**	4	H	0.0	20:80	45 (55)
4	**2f**	4	*p*-F	0.15	3:97	74 (76)
5	**2b**	8	*m*-CCH	0.21	8:92	28 (30)
6	**2g**	8	*m*-Cl	0.37	10:90	84 (93)

[a] Crude product ratios measured by ^{1}H NMR spectroscopy before purification. [b] Chromatographed yield of the major regioisomer; the value in parentheses indicates % recovery of this isomer from the crude product mixture.

Table 3. Opening of **1** with *N*-methylaniline **2h**

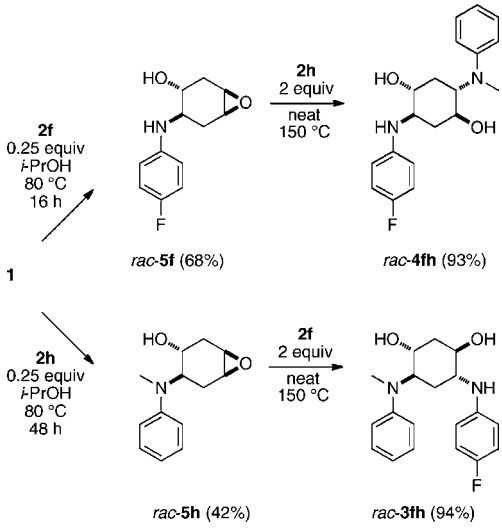


entry	aniline	regime	*t* (°C)	**3h**:**4h**[a]	% yield[b]
1	**2h**	neat	150	100:0	91
2	**2h**	"on water"	95	100:0	97

[a] Product ratios measured by ^{1}H NMR. [b] Chromatographed yield.

To further confirm the role of the pendant amino NH of **5** on the regioselectivity of the second epoxide opening, we designed two experiments to arrive at unsymmetrical 1,3- and 1,4-diols. Scheunemann has previously reported synthesis of unsymmetrical 1,3-diols from **1** via the intermediacy of epoxy aminoalcohols (e.g., **5a**),[1c] but prior to our work, preparation of the corresponding unsymmetrical 1,4-diols had not been possible. Treatment of **1** with 0.25 equiv of anilines **2f** and **2h** in refluxing isopropanol gave epoxy aminoalcohols *rac*-**5f** and **5h** in 68 and 42% yield respectively (Scheme 3). By virtue of its pendant *p*-fluoroanilino group, **5f** is poised to react with an incoming aniline under solvent-free conditions to give the 1,4-diol product. Thus *rac*-**5f** was treated with *N*-methylaniline **2h**, and the unsymmetrical 1,4-diol *rac*-**4fh** was obtained in 93% yield. Conversely, epoxy aminoalcohol *rac*-**5h** cannot react in the 1,4-manifold, since it lacks an intramolecular hydrogen bond donor. Thus treatment of *rac*-**5h** with *p*-fluoroaniline **2f** under solvent-free conditions affords the 1,3-diol *rac*-**3fh** in 94% yield.

Scheme 3. Regiocontrolled Route to Unsymmetrical 1,3- or 1,4-Diols



In conclusion, we have shown that previously inaccessible C_i-symmetric 1,4-diols can be prepared from *trans*-1,2,4,5-diepoxycyclohexane **1** and anilines. The 1,3-:1,4-diol product ratio in reactions of **1** with anilines was found to be sensitive to both electronic effects in the aniline, and to the nature of the reaction conditions. Highest selectivities for the 1,4-diol products **4** are obtained with electron-poor anilines under neat conditions (Table 2). Highest selectivities for the 1,3-diol products **3** are obtained with electron-rich anilines using "on water" conditions (Table 1). The superior hydrogen-bonding ability of a pendant anilino group (relative to an aliphatic amino) in the epoxy aminoalcohol intermediate **5** is proposed to allow access to the 1,4-diol regioisomer via intramolecular H-bond stabilized transition state **4*** (Scheme 2). To the best of our knowledge, the potential of an appropriately acidic intramolecular NH hydrogen bond donor to direct ring-opening of cyclohexene oxides has not previously been recognized in the literature.[13] Finally, by judicious choice of reactant order and reaction conditions, it is possible to synthesize unsymmetrical 1,3- and 1,4-diols from **1** and anilines in high selectivity and yield (Scheme 3). Further mechanistic and synthetic work is in progress and will be reported in due course.

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Supporting Information Available: Synthetic procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) As illustrative examples, in the case of entry 3, [**1**] = 2.1 M, [**2e**] = 8.3 M; for entry 6 [**1**] = 0.9 M, [**2g**] = 7.1 M (all reactants assumed to have density = 1 g/mL). These aniline concentrations are 7- to 8-fold higher than those employed in the acetonitrile, DMF, and mesitylene reactions described above.

(12) Autocatalysis in epoxide ring-opening under neat conditions has been proposed by Sharpless and co-workers (refs 1b, 5a).

(13) Note, however, that this effect can explain some of the results observed in: Kiss, L.; Forró, E.; Martinek, T. A.; Bernáth, G.; De Kimpe, N.; Fülöp, F. *Tetrahedron* **2008**, *64*, 5036–5043.