Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 3584–3598

C_2-Symmetric nitroxides and their potential as enantioselective oxidants

Benjamin Graetz, Scott Rychnovsky,* Wen-Hao Leu, Patrick Farmer* and Rong Lin

Department of Chemistry, University of California, Irvine, 516 Rowland Hall, Irvine, CA 92697-2025, USA

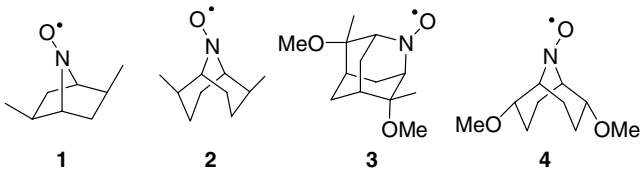
Received 20 July 2005; accepted 9 September 2005
Available online 10 November 2005

Abstract—The synthesis and evaluation of four C_2-symmetric nitroxides are presented. The nitroxides were evaluated for their ability to mediate the oxidation of several alcohols and found to have good catalytic activity. One enantioenriched nitroxide was found to kinetically resolve selected secondary alcohols with very modest selectivities.

1. Introduction

Nitroxyl radical catalyzed enantioselective oxidations of alcohols have great potential for synthetic utility due to the ubiquitous need for enantiomerically pure secondary alcohols. One of the difficult challenges facing nitroxide mediated enantioselective oxidations is generating a nitroxide that has both good catalytic activity and high enantioselectivity. The design and rationale for selectivity in nitroxide mediated oxidations has been established in several literature reports.[1] Many categories of nitroxides have been used in oxidation chemistry, such as azepines,[1d] pyrrolidines,[2] piperidines,[3] morpholines,[4] piperazinones,[4] piperazines,[4] and isoindoles.[5] One common theme among these synthetic efforts centers around nitroxides with bis(tetralkyl) substituents α to the nitrogen. This constraint for bis(tetralkyl) substituents is due to rapid disproportionation to produce a nitrone and a *N*-hydroxylamine, which generally occurs when hydrogens α to the nitrogen are present.

There are examples, however, of bicyclic nitroxide systems in which the nitrogen resides at the bridgehead of the bicyclic system.[6] These bridgehead nitroxides, while containing α-hydrogens, will still obey Bredt's rule,[7] thereby reducing or eliminating rapid decomposition of the nitroxide to a nitrone with a bridgehead olefin. Most of the reported bridgehead nitroxides were achiral, and none of the chiral bridgehead nitroxides were prepared in enantiomerically enriched form. We decided to investigate the preparation, stability, and utility of chiral bridgehead nitroxides (Fig. 1) as enantioselective oxidation catalysts, and the results of this investigation are described herein.



1 2 3 4

Figure 1. Synthesized nitroxides.

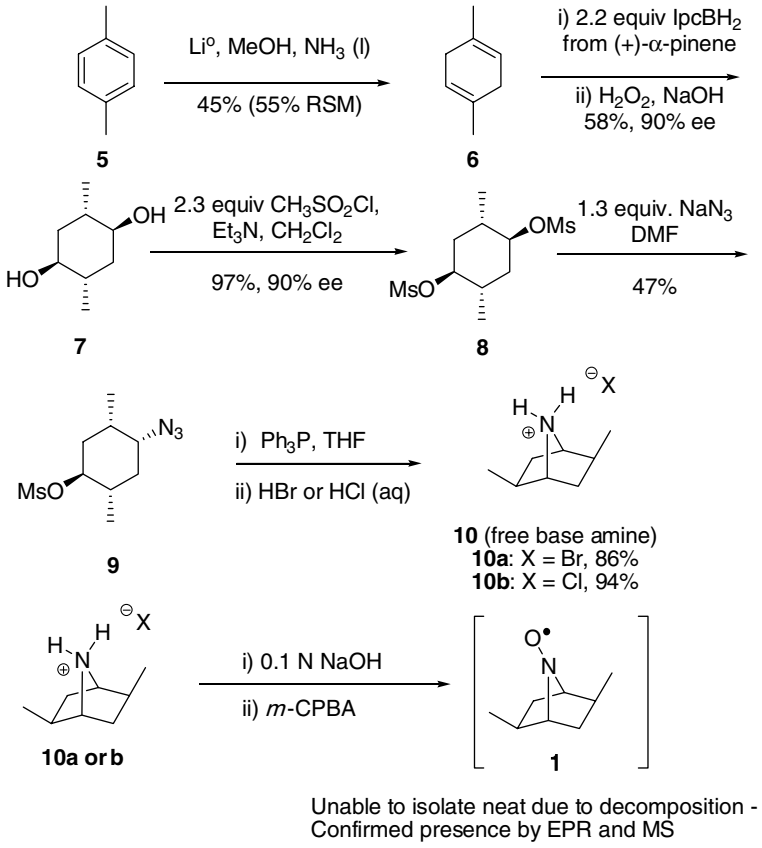
2. Results and discussion

2.1. Synthesis of nitroxides

The synthesis of **1** is based on the work of Zhang et al. and Halterman et al. with slight modifications to their procedures.[8] Synthesis of **1** began with a Birch reduction of *para*-xylene[9] with lithium in liquid ammonia in the presence of methanol to give **6** in 45% yield, with the remaining 55% as unreacted starting material (Scheme 1). The low yield in this step may be due to the poor solubility of *para*-xylene in liquid ammonia, making reduction of the precipitate by lithium difficult. However, attempts to enhance solvation of *para*-xylene by the addition of THF did not improve the yield. Compound **6** could not be separated from *para*-xylene and was used as a mixture. Enantiomerically pure isopinocampheylborane ($IpcBH_2$) was prepared according

* Corresponding authors. Tel.: +1 949 824 8292; fax: +1 949 824 6379; e-mail: srychnov@uci.edu

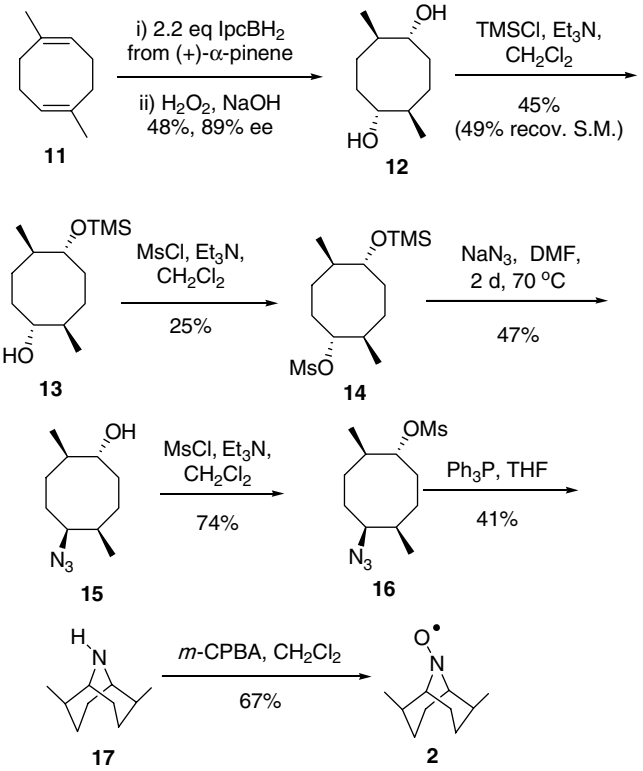
0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.09.016



Scheme 1. Synthesis of [2.2.1] nitroxide **1**.

to a Brown procedure[10] using (+)-α-pinene. Treatment of **6** with $IpcBH_2$ followed by oxidation with alkaline hydrogen peroxide gave a mixture of C_2- and C_1-symmetric diols in a 3:1 ratio. Separation of the diols by flash chromatography gave the C_2-symmetric diol **7** in 58% yield with 90% ee, as determined by the specific rotation.[8b] The diol was treated with methanesulfonyl chloride and triethylamine in CH_2Cl_2, to provide bis(methanesulfonate) ester **8** in 97% yield. Monodisplacement with sodium azide in DMF[11] afforded **9** in 47% yield. Treatment of **9** with triphenylphosphine[12] effectively reduced the azide with concomitant cyclization to the bicyclic [2.2.1] secondary amine **10**, which was isolated as the amine salt with aqueous HBr or HCl, providing **10a** and **10b** in 86% and 94% yield, respectively. Isolation of the free amine **10** was difficult due to its apparent low boiling point but it could be generated in a solution of CH_2Cl_2 as needed by treatment of **10a** or **10b** with 0.1 M NaOH and extraction with CH_2Cl_2. The free-based amine was used to generate nitroxide **1** by treatment with *m*-CPBA. The isolation of the nitroxide itself was not possible due to its apparent instability (vide infra); however, oxidations with nitroxide **1** could be carried out if the nitroxide was generated immediately before use in the oxidation studies.

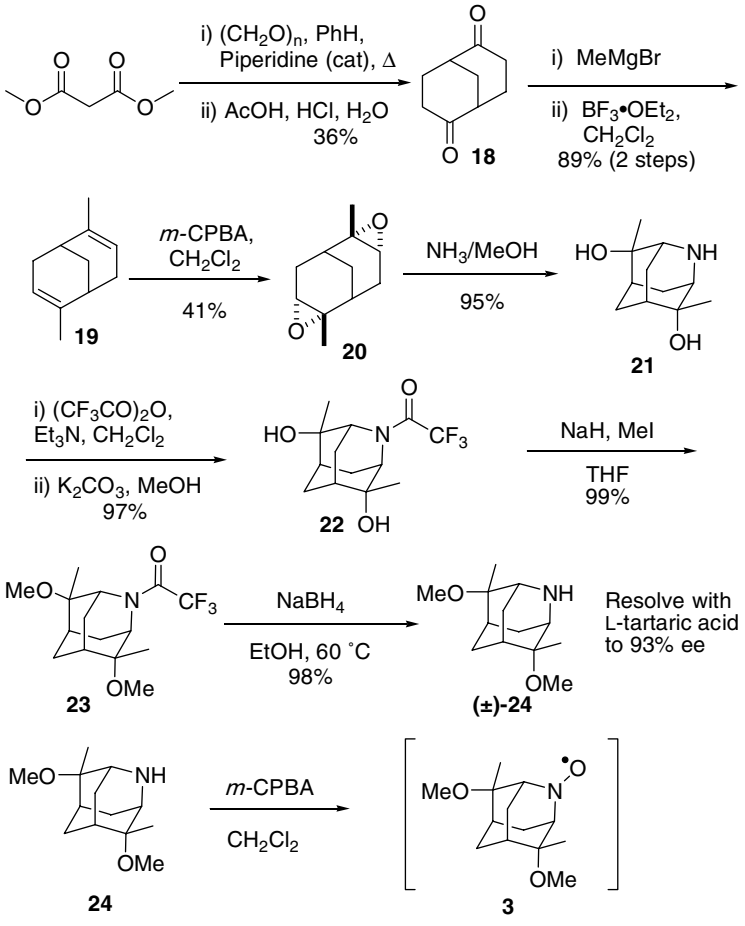
We set out to synthesize the analogous [3.3.1] nitroxide **2** in the same fashion as **1**; however, the reaction sequence used for **1** could not be directly applied. The successful synthesis is outlined in Scheme 2. The initial strategy



Scheme 2. Synthesis of [3.3.1] nitroxide **2**.

translated onto this substrate well with an asymmetric hydroboration of commercially available 1,5-dimethyl-1,5-cyclooctadiene using Brown's $IpcBH_2$ to produce diol **12** in 48% yield and 89% ee, determined by specific rotation (Scheme 2).[13] The remaining sequence, however, required a stepwise approach. Starting with diol **12**, protection of one of the alcohols with TMSCl provided silyl ether **13** in 45% with the remaining material recovered as unreacted starting material. Alcohol **13** was treated with methanesulfonyl chloride and provided a separable mixture of two products. One product was the TMS ether **14**, isolated in 25% yield. The remaining isolated material (61%) arose from deprotection of the labile TMS ether during the work up. Each product was separately treated with sodium azide in DMF to provide azide **15** by removal of any remaining TMS ether in the acidic workup. Azide **15** was converted to methanesulfonate **16** in 74% yield. Treatment of **16** with triphenylphosphine[12] effectively reduced the azide with concomitant cyclization to the bicyclic [3.3.1] secondary amine **17** in 41% yield. While amine **17** was higher in molecular weight than amine **10**, the volatility of amine **17** accounted for the modest yield in the reduction. A stable and isolable nitroxide **2** was produced in 67% yield when amine **17** was treated with *m*-CPBA.

A racemic C_2-symmetric aza-adamantyl amine was synthesized as a precursor to nitroxide **3** (Scheme 3). The synthesis of amine **24** began with the preparation of Meerwein's ester[14] by a condensation reaction of dimethyl-malonate and formaldehyde in refluxing benzene while removing water with a Dean Stark trap. The crude intermediate tetraester was decarboxylated in refluxing acetic acid, hydrochloric acid, and water to produce dione **18**.[15] Grignard addition to the dione gave 47% of isolated C_2-symmetric diol, which when treated with $BF_3{\cdot}OEt_2$, gave diene **19**. If the crude diol from the Grignard reaction was treated with $BF_3{\cdot}OEt_2$, the yield for the two steps could be improved to 89%. From the ^{13}C NMR spectrum of the crude intermediate diol, several alcohol bearing carbon atoms were observed, suggesting multiple diastereomers were present. Each of the diastereomers would eliminate to produce diene **19**, accounting for the improved yield. Treatment of **19** with *m*-CPBA gave 41% of the racemic, C_2-symmetric bis-epoxide **20**. Other epoxide diastereomers were produced in the reaction but were separated during chromatography. Heating **20** in methanol saturated with ammonia provided **21**, the aza-adamantyl core in 95% yield.[16] Protection of the amine with trifluoroacetic anhydride gave a peracylated intermediate



Scheme 3. Synthesis of nitroxide **3**.

that could be deprotected selectively by treatment with potassium carbonate in methanol to provide trifluoroacetamide **22** in 97% yield. Diol **22** was converted to the dimethyl ether in 99% yield by treatment with sodium hydride and methyl iodide. Deprotection of the amine with sodium borohydride in refluxing ethanol cleanly afforded racemic amine **24** in 98% yield.

Amine **24** could be resolved by complexation with L-tartrate and an unoptimized recrystallization from ethanol and ether to provide a low yield of a white precipitate. These crystals were treated with 0.1 M NaOH, and analysis of the remaining amine by GC on a chiral column indicated an enantiomeric excess of 93%.

Amine **24** was used to generate nitroxide **3** by treatment with *m*-CPBA. The isolation of the nitroxide itself was not possible due to its apparent instability (vide infra); however, oxidations with nitroxide **3** could be carried out if the nitroxide was generated immediately before use in the oxidation studies.

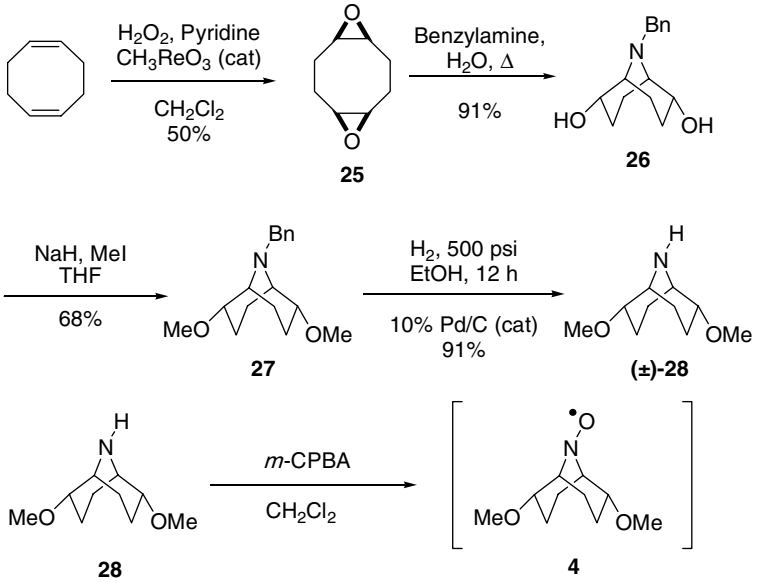
A final synthesis of a second [3.3.1] bicyclic system was undertaken. It was believed that the [3.3.1] nitroxide system may impart some unusual stability that allowed for the isolation of nitroxides such as **2**. A facile synthetic entry into such a [3.3.1] system, amine **26**, was reported by Michel and Rassat.[17]

The synthesis began with a rhenium catalyzed hydrogen peroxide oxidation of 1,5-cyclooctadiene to provide the *syn*-bis-epoxide **25** in 50% yield with the remaining material as the mono-epoxide (Scheme 4). Simple refluxing of **25** with benzylamine in water provided the [3.3.1] bicyclic amine core in 91% yield. The resultant diol **26** was converted to dimethyl ether **27** in 68% yield by treatment with sodium hydride and methyl iodide. The benzyl protection of the amine was removed by hydrogen reduction with palladium on carbon in 91% yield to provide amine **28**. Racemic amine **28** was used to generate nitroxide **4** by treatment with *m*-CPBA. The isolation of the nitroxide itself was not possible due to its apparent instability (vide infra); however, oxidations with nitroxide **4** could be carried out if the nitroxide was generated immediately before use in oxidation studies.

2.2. EPR analysis for nitroxide conformation

Only nitroxide **2** was stable enough to be isolated. To evaluate each of the nitroxides ability to catalyze the oxidation of alcohols, it became imperative to establish that a nitroxide was in fact generated from each amine precursor. The remaining nitroxides gave fleeting evidence for their formation, such as turning a solution of CH_2Cl_2 red or pink upon the addition of *m*-CPBA. This color change would fade over minutes to hours depending on the nitroxide. While this was supportive evidence, it was hardly diagnostic. NMR spectroscopy could not be used to observe any transient nitroxide present, due to the paramagnetic broadening of the NMR signals. Electron paramagnetic resonance (EPR) spectroscopy is a direct method to observe nitroxides. The EPR of a typical nitroxide is characterized by three sharp lines that are separated by 13–15 Gauss. We set out to study nitroxides **1**–**4** by EPR spectroscopy.

When each of the amine precursors was dissolved in CH_2Cl_2, placed in an EPR tube, and treated with *m*-CPBA, a nitroxide signal was immediately observed (Fig. 2). These EPR experiments were carried out at room temperature. Control experiments with *m*-CPBA in CH_2Cl_2 or the amine in CH_2Cl_2 gave no observable EPR signal. The nitroxide signals were then observed over time to determine the lifetimes of nitroxides **1**–**4**.



Scheme 4. Synthesis of [3.3.1] nitroxide **4**.

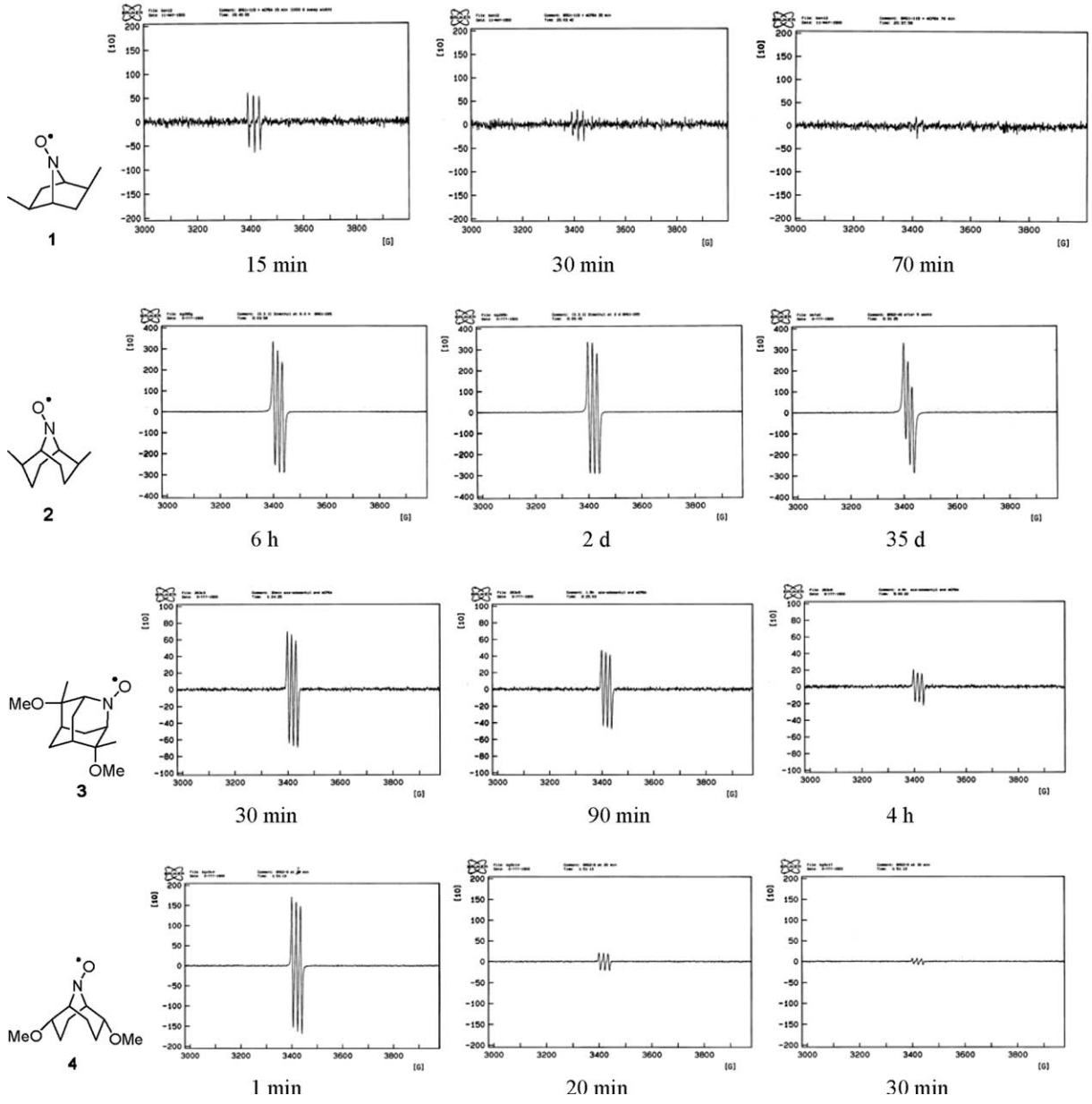


Figure 2. EPR spectra of nitroxides **1**–**4** over time.

As can be seen in Figure 2, the characteristic triplet of a nitroxide was observed for structure **1**. After 30 min from the time of addition of *m*-CPBA, the triplet signal had already decreased significantly in strength. By 70 min from the time of addition of *m*-CPBA, almost all evidence of a nitroxide signal had faded into the noise.

The fate of nitroxide **2** is quite different from that of the other nitroxides. Upon addition of *m*-CPBA to amine **17**, a strong EPR signal was observed. After 6 h this signal remained unchanged with essentially the same in intensity. Two days later, the same characteristic triplet was observed with no loss of intensity. The sample was then stored in a freezer (−15 °C) for five weeks. After warming back to room temperature and observing the EPR signal, again a characteristic triplet was observed with approximately the same intensity. Nitroxide **2** was indefinitely stable at reduced temperature.

Azaadamantyl nitroxide **3** presents a strong EPR signal that diminished slowly over several hours at room temperature. After 30 min, the characteristic triplet remained as a strong signal but diminished somewhat from its previous high intensity. After 90 min, the signal had decreased to approximately half of its original intensity. The signal, however, remained for several additional hours and at 4 h is still quite clear. After about 7 h the signal was completely lost, diminishing into background noise.

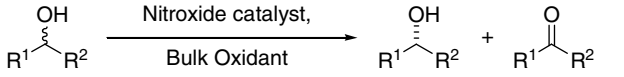
The final [3.3.1] nitroxide **4**, presented an interesting contrast to structure **2**, the other [3.3.1] nitroxide reported. A strong triplet was immediately observed

upon the addition of *m*-CPBA to amine **24**. This signal, however, faded rapidly at room temperature. Within 20 min the signal had decreased to approximately 20% of its original intensity, and by 30 min, the signal had almost completely disappeared. This [3.3.1] nitroxide represented the least stable of the four synthesized nitroxides. There are two major differences between nitroxide **2** and nitroxide **4**. The methyl ether substituents on nitroxide **4** are oriented equatorially, while the methyl substituents of nitroxide **2** are axial. In addition, the methyl ethers are electron withdrawing substituents compared to the methyl substituents of nitroxide **2**. However, these structural and electronic differences do not provide an obvious explanation for the disparity in stability between **2** and **4**.

Since the intensity of the EPR signal is proportional to the concentration of nitroxide, we can estimate a half-life for each of the nitroxides in solution at room temperature. Nitroxide **1** had a half-life of ca. 20 min. Nitroxide **3** had a half-life of ca. 90 min. Nitroxide **4** had a half-life of ca. 7 min.

With confirmation that each of the four nitroxides was in fact capable of being generated, even if for limited times, it was appropriate to evaluate whether these nitroxides would act as catalysts in the oxidations of alcohols. If the compound showed catalytic activity, the enantiopurity of the remaining alcohol would be determined, thereby evaluating each nitroxide for both catalytic efficiency and enantioselectivity.

2.3. Oxidation of alcohols using nitroxide catalysts



(1)

Oxidations were carried out under kinetic resolution conditions (Eq. 1), in which the progress of the oxidation is controlled by the limiting reagent, in this case the bulk oxidant. A series of secondary alcohols were required as test substrates for oxidations. Four alcohols were chosen based on availability and ease of separation of the enantiomers by GC on a chiral column. Separation of the oxidized ketone product from the remaining alcohol by GC also was a requisite. Commercially available *sec*-phenylethanol **29** and 2-octanol **30** were chosen. Additionally, 2′-chloro-*sec*-phenylethanol **31** and 2′-methyl-*sec*-phenylethanol **32** were synthesized by simple $LiAlH_4$ reduction of commercially available 2′-chloroacetophenone and 2′-methylacetophenone (Fig. 3).

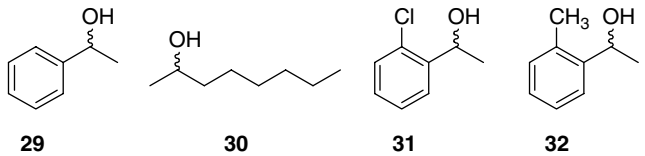


Figure 3. Alcohols used in oxidations.

Anelli's procedure is a useful and widely used TEMPO catalyzed oxidation of alcohols. Anelli's conditions[18] for the oxidation of alcohols utilized a nitroxide catalyst, an alcohol, KBr, and a buffered bleach solution (pH ~ 8.6) as the bulk oxidant. *m*-CPBA has also been used as a bulk oxidant in TEMPO oxidations. Previous research by Rychnovsky et al. evaluated the role of halide ions in TEMPO catalyzed oxidation of alcohols using *m*-CPBA as the bulk oxidant.[19] These studies demonstrated that redox-active counterions have a significant effect on the oxidation reaction. The counterion could, in some systems, increase the amount of oxidation observed. A procedure was then developed using the hydrobromide salt of 2,2,6,6-tetramethylpiperidine (TMP·HBr).[19] An alcohol mixed with 1 equiv of *m*-CPBA as the bulk oxidant and catalytic TMP·HBr (1 mol %) converted the alcohol to its corresponding ketone. Additionally, a phase transfer catalyst, such as Bu_4NBr, could be used to facilitate the biphasic reaction. An adaptation of this procedure, using *m*-CPBA as the bulk oxidant, was selected to evaluate nitroxide **1** as an oxidation catalyst.

Since nitroxide **1** was generated from HCl or HBr salts of the amine precursor, this method of starting from the HCl and HBr salts seemed ideal for evaluating nitroxide **1**. Following the reported procedure, nitroxide salt **10a** or **10b** was dissolved in CH_2Cl_2 and added to a solution of an alcohol and *m*-CPBA (Table 1). Control experiments in Table 1 (entries 1, 4, 5, 10, 11, and 14) have the catalyst and/or the additive omitted to identify any background oxidation.

From Table 1, several general trends appear. First, the addition of **1** or **10a** as a catalyst increases the amount of oxidation compared to *m*-CPBA alone. This suggests the catalyst is acting in some fashion to mediate the oxidation, and in the case of entries 12 and 13, the catalyst is resolving alcohol **31** with minimal selectivity. There is no increase in resolution or conversion when increasing

Table 1. Oxidation of alcohols with *m*-CPBA, 1% catalyst, and additive

Entry	Alcohol	Catalyst	Additive	% Conversion[a]	% ee alcohol
1	**29**	None	None	14	—
2	**29**	**1**	None	34	0
3	**29**	**1**	Bu_4NBr	53	0
4	**30**	None	None	12	—
5	**30**	None	Bu_4NBr	10	—
6	**30**	None	*t*-BuOH[b]	14	—
7	**30**	**1**	Bu_4NBr	40	0
8	**30**	**10a**	Bu_4NBr	36	0
9	**30**	**10a**	None	35	0
10	**31**	None	Bu_4NBr	15	—
11	**31**	None	BHT	17	—
12	**31**	**10a**	Bu_4NBr	30	9
13	**31**	**10a**[c]	Bu_4NBr	33	9
14	**32**	None	Bu_4NBr	15	—
15	**32**	**10a**	Bu_4NBr	40	0

[a] Conversion determined by GC.
[b] 0.5 equiv of *t*-BuOH.
[c] 2.5% Catalyst.

the catalyst from 1% to 2.5% (cf. entry 12 vs 13). It is also apparent from Table 1 that *m*-CPBA alone provides significant background oxidation (entries 1 and 4). Minisci et al. have shown that *m*-CPBA will also oxidize simple alcohols, such as cyclohexanol and 2-heptanol, in up to 83% yield at elevated temperatures (40 °C, 24 h).[20] Minisci et al. was able to suppress the oxidation using *t*-BuOH as solvent; however, entry 6 shows that with 0.5 equiv of *t*-BuOH, background oxidation persisted in this system. Minisci proposed a radical mechanism for the oxidations of alcohols by *m*-CPBA; however, addition of the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT) also failed to inhibit background oxidation (entry 11). The high background oxidation observed with *m*-CPBA and Bu_4NBr or *m*-CPBA alone makes it difficult to determine the true amount of oxidation mediated by the nitroxide; therefore, another method for one evaluation of the oxidation ability of the nitroxides was needed.

A bulk oxidant that gave minimal background oxidation was required to elucidate the catalytic activities of **1**–**4** and better determine their abilities to resolve alcohols. Procedures are known that generate a nitroxide from an amine or amine hydrobromide salt such as oxidation with basic peroxide,[21] sodium tungstate,[22] or in situ generation of dimethyl dioxirane from Oxone® and acetone.[23] Each of these methods was attempted (Table 2). While there was little or no background oxidation for each of these methods in the absence of **10**, there was also no oxidation of the alcohol observed when **10** was added. Presumably, these reaction conditions failed to further oxidize any nitroxide generated to *N*-oxoammonium salt, the active oxidizing species, even though the literature reported isolation of the *N*-oxoammonium salt in selected cases.[21,22] The redox-active halogen counterion appears to be oxidizing the alcohol, as reported by Rychnovsky and Vaidyanathan,[19] in the case of entries 8 and 9 since there was no significant oxidation observed without the counterion present (cf. entries 6 vs 8 and 7 vs 9).

Margarita et al.[24] developed a method using a hypervalent iodide species to mediate the oxidation of alcohols to carbonyl compounds. The procedure uses catalytic TEMPO in combination with [bis(acetoxy)iodo]benzene (BAIB) as the bulk oxidant. Following this precedent, various alcohols were dissolved in CH_2Cl_2 with one half an equivalent of BAIB (Table 3). In a separate flask, amine **10** was oxidized with *m*-CPBA to the nitroxide since BAIB was not reported to generate a nitroxide from an amine.[24] This hypothesis was tested and confirmed by the use of amine **10** (entry 2), in which no oxidation was observed. The nitroxide solution was then added to the alcohol mixture, and the oxidation of the alcohol monitored. Without nitroxide (entries 1, 2, 4, and 6), oxidation did not occur, indicating that there was no background oxidation. Therefore, the choice of BAIB as a bulk oxidant should help elucidate oxidations that are directly mediated by the nitroxide catalyst without contamination by background oxidations. Each of the alcohols was oxidized to high conversion of the theoretical 50% possible based on 0.5 equiv of BAIB, suggesting **1** is an efficient oxidation catalyst. A small amount of kinetic resolution occurred as indicated by the % ee of the recovered alcohols and the very modest calculated *S*-values in entries 3, 5, and 7.

With the proper choice of bulk oxidant now realized, screening the remaining catalysts was a straightforward process (Table 4). To be consistent in the evaluation of the alcohols, the same method of preparation presented earlier was utilized. Specifically, various alcohols were dissolved in CH_2Cl_2 with 0.5 equiv of BAIB at 0 °C. In a separate flask, the amine precursor to the nitroxide was oxidized with *m*-CPBA, generating the nitroxide. The nitroxide was then transferred to the alcohol solution to initiate oxidation at 0 °C.

The long lived [3.3.1] nitroxide **2** (entries 1–4) displays good catalytic activity with yields ranging from 78% to

Table 2. Oxidation of **31** with various bulk oxidants

Entry	Bulk oxidant	Catalyst	% Conversion[a]
1	H_2O_2/NaOH	None	0
2	H_2O_2/NaOH	**10**	0
3	$Na_2WO_4{\cdot}2H_2O$	None	0
4	$Na_2WO_4{\cdot}2H_2O$	**10**	0
5	Oxone/acetone	None	0
6	Oxone/acetone	**10**	3
7	Oxone/acetone	TMP	0
8	Oxone/acetone	**10a**	40
9	Oxone/acetone	TMP·HBr	43

[a] Conversion determined by GC.

Table 3. Oxidation of alcohols with 0.5 equiv BAIB and 1% cat. at 0 °C

Entry	Alcohol	Catalyst	% Conversion[a]	% ee	*S*-Value
1	**31**	None	0	—	—
2	**31**	**10**	0	—	—
3	**31**	**1**	46	22	2.1
4	**32**	None	0	—	—
5	**32**	**1**	50	7	1.2
6	**29**	None	0	—	—
7	**29**	**1**	43	4	1.2
8	**30**	**1**	41	0	—

[a] Conversion determined by GC.

Table 4. Oxidation of alcohols with 0.5 equiv BAIB, 1% cat. at 0 °C

Entry	Alcohol	Catalyst	% Conversion[a]	% ee alcohol
1	**29**	**2**	46	0
2	**30**	**2**	39	0
3	**31**	**2**	43	0
4	**32**	**2**	46	0
5	**29**	**3**	48	0
6	**30**	**3**	44	0
7	**31**	**3**	47	0
8	**32**	**3**	49	0
9	**29**	**4**	30	—
10	**30**	**4**	19	—
11	**31**	**4**	28	—
12	**32**	**4**	28	—

[a] Conversion determined by GC.

94% based on 0.5 equiv of BAIB, the limiting reagent; however, no kinetic resolution was observed. The enantioenriched azaadamantyl nitroxide **3**, which had been resolved to 93% ee by crystallization with L-tartaric acid, consistently shows the best conversions compared to the other nitroxides with a lowest yield for 2-octanol at 88% of theory (entries 5–8). Unfortunately, again, no kinetic resolution was observed for any of the alcohols. Finally, the racemic [3.3.1] nitroxide **4** showed moderate catalytic activity with yields from 40 to 60%. This is presumably due to the shorter lifetime of the nitroxide as shown by the EPR studies (Fig. 2). While nitroxides **1**, **3**, and **4** all had lifetimes ranging from hours to weeks, nitroxide **4** lasted for only about 30 min. These oxidation reactions, while fast, are run for 30–45 min, a length of time long enough for the decay of **4** to become a factor.

In 2000, Tanaka et al. reported a strong temperature dependence in the kinetic resolution of alcohols.[25] In Tanaka's work, an electro-oxidative kinetic resolution of *sec*-alcohols mediated with a catalytic amount of a nitroxide was performed by use of an undivided cell under constant current conditions. The *S*-values increased markedly when the reaction was performed at lower temperatures. Varying the temperature from room temperature to −15 °C produced *S*-values increasing from 1.6 (room temperature), to 6.3 (−5 °C), to 16.4 (−15 °C). Tanaka's work was limited to −15 °C because of the aqueous biphasic experimental design. Temperatures below −15 °C solidified the aqueous phase.

This low temperature enhancement of kinetic resolution seemed ideal for our nitroxides, as BAIB in CH_2Cl_2 should be amenable to low temperature oxidations. Herein, only the enantioenriched catalysts **1**, **2**, and **4** were evaluated (Table 5). The catalyst loading was reduced to 0.5%, and the amount of BAIB was increased to 0.6 equiv (0.8 equiv in the case of **2**). The temperature was lowered to −35 °C. Nitroxide **1** continued to display good catalytic activity even at the lower catalyst loading (entries 1–3). Additionally, a nominal increase in the kinetic resolution was observed with *S*-values increasing slightly. Nitroxide **2** also showed high catalytic activity at the lower temperature; however, no resolution of the remaining alcohol was observed (entries 4–6). In an unexpected result, azaadamatyl nitroxide **4**, which was previously shown to have the best catalytic activity, was an inefficient catalyst at low temperature (entries 7–9). Additionally, no kinetic resolution was observed for nitroxide **4**. Racemic **4** was then evaluated at higher catalyst loading (2%) to determine if 0.5% was an insufficient amount. Conversions with 2% catalyst loading remained effectively unchanged as seen from entries 7–9. When the temperature was lowered to −55 °C, the only tested nitroxide, **1**, showed no increase in enantioselectivity compared to the results at −35 °C.

Table 5. Oxidation of alcohols with 0.6 equiv BAIB, 0.5% cat. at −35 °C

Entry	Alcohol	Catalyst	% Conversion[a]	% ee alcohol	*S*-Value
1	**29**	**1**	45	27	2.5
2	**31**	**1**	56	30	2.1
3	**32**	**1**	48	16	1.6
4	**29**	**2**	74[b]	0	—
5	**31**	**2**	71[b]	0	—
6	**32**	**2**	61[b]	0	—
7	**29**	**4**[c]	10	0	—
8	**31**	**4**[c]	5	0	—
9	**32**	**4**[c]	3	0	—

[a] Conversion determined by GC.
[b] 0.8 equiv of BAIB used.
[c] Additional attempts with 2% catalysts did not improve conversions.

2.4. Oxidative stability cyclic voltammetry

Electrochemical characterization of the nitroxides by cyclic voltammetry yielded information on both the oxidation potential and stability of the catalytically active *N*-oxo ammonium salts. The voltammograms of nitroxides **1**–**4**, Figure 4, showed that while the nitroxides vary in little in oxidation potential, there is large variation in the stability of their corresponding *N*-oxo ammonium species. A measure of the stability of the oxidized forms were obtained by comparison of the reversibility (or symmetry) of the voltammometric scans under identical conditions; a loss of current in the reverse scan, measured by the ratio of the cathodic and anodic peak currents, i_{pa}/i_{pc}, indicates that the oxo ammonium ion is being depleted via a competing pathway before it can be reduced back to the nitroxide.

The same nitroxides that were observed to decay over time by EPR **1**, **3**, and **4** also showed enhanced irreversibility by cyclic voltammetry. The implication is that in each of these cases **1**, **3**, and **4**, both the nitroxide and the oxo-ammonium appear to decay by pathways that have not been elucidated. In the case of nitroxide **2**, a reversible CV was observed with a reversibility factor $i_{pa}/i_{pc} = 1.06$ or nearly unity.

We have previously evaluated a series of nitroxide catalysts under Alleli's conditions and shown that effective nitroxide catalysts have oxidation potentials between 638 and 807 mV, whereas the ineffective catalysts have oxidation potentials above 852 mV.[26] The oxidation potential of **2** (E°) obtained by voltammetry ($E^\circ = (E_{pa} + E_{pc})/2$) is 657 mV. It has already been demonstrated that nitroxides **1**, **3**, and **4** are catalytically active suggesting they are turning over through a redox cycle to oxidize alcohols. Although electrochemically irreversible, the oxidation potentials of these nitroxides can be estimated from the potential of the initial anodic current peak, and are approximated as: **1** ≈ 700 mV, **3** ≈ 550 mV, and **4** ≈ 650 mV. It is noteworthy that all of these potentials are similar to TEMPO at ca. 640 mV. Interestingly, the stability of the *N*-oxo ammonium species does not correlate with the catalytic efficiency or the enantioselectivity of these catalysts.

3. Conclusions

We have prepared a number of bicyclic nitroxides with α-hydrogens and explored their utility as enantioselective

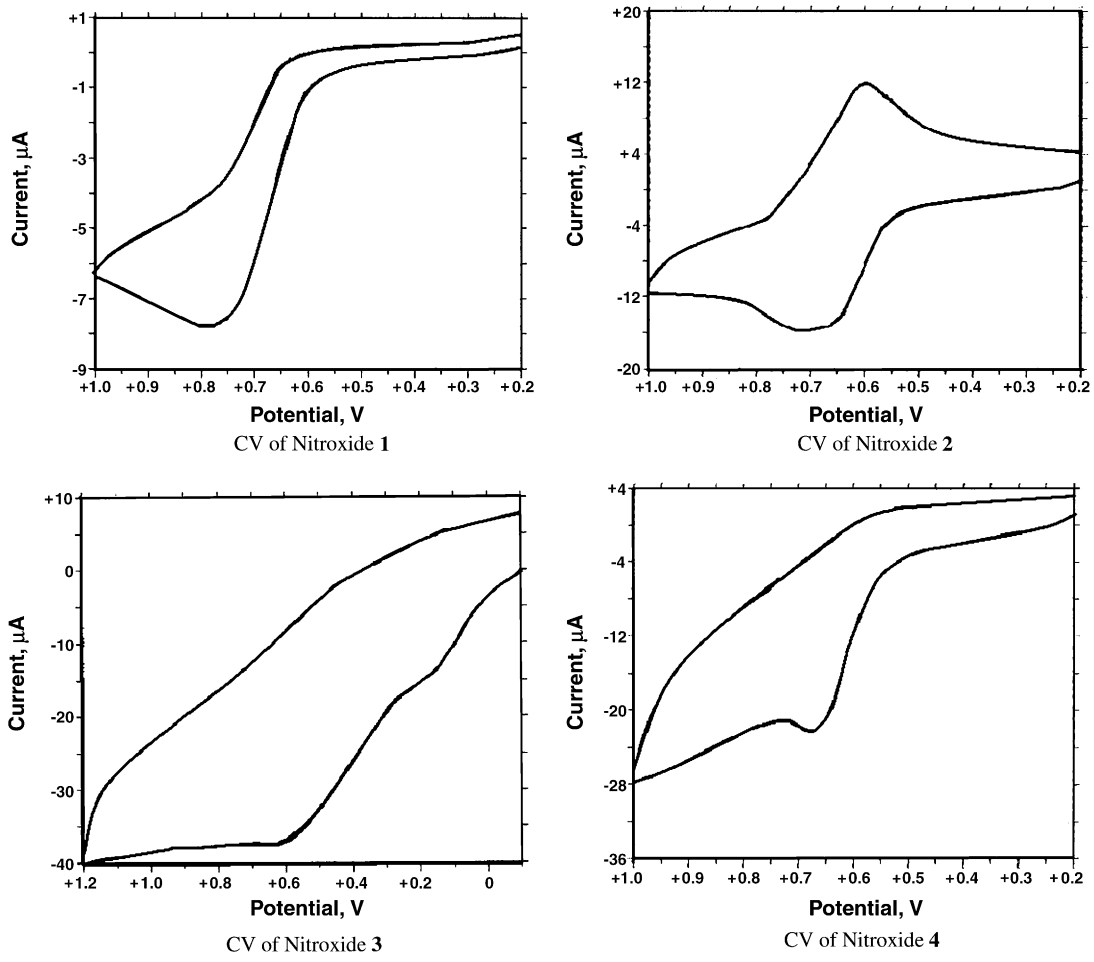


Figure 4. Cyclic voltammograms of nitroxides **1**–**4**.

alcohol oxidation catalyst. Nitroxide **2** was indefinitely stable, but the other three nitroxides showed lifetimes of 40 min to 7 h at room temperature in CH_2Cl_2. Three of the nitroxides, **1**, **2**, and **3**, showed high efficiency and good turnover as catalysts for the oxidation of alcohols. Only catalyst **1** showed any enantioselectivity in the oxidation of alcohols, and the selectivities were modest. The rationale for poor selectivity is not obvious at this time but could be attributed to the simply alkyl methyl substituents around the nitroxide not providing enough steric interaction to induce selectivity. This is the first report of the synthesis of enantiomerically active bicyclic nitroxides, and the first example of α-hydrogen nitroxide as catalyst for alcohol oxidations. Considering the wide variety of nitroxides that are not effective catalysts for the oxidation of alcohols, it is remarkable that three of the four bicyclic nitroxides prepared in our study showed very good catalytic efficiency.

4. Experimental

4.1. General procedures

All moisture- and air-sensitive reactions were carried out in flame- or oven-dried glassware using magnetic stirring under a positive pressure of nitrogen or argon gas. Reaction solvents were distilled or obtained from alumina filtration system when necessary. Thin layer chromatography was performed on Whatman silica gel PE SIL G/UV plates. Concentration in vacuo was performed using a Büchi rotary evaporator. Flash chromatography was performed on EM Science 230–400 mesh silica gel. Melting points were determined using an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a MIDAC Grams/Prospect FT-IR. NMR spectra were recorded on a Brüker GN500, a Brüker Omega 500, and a Brüker DRX 400 MHz FTNMR instruments. Proton NMR spectra were obtained using $CDCl_3$ as solvent, unless otherwise noted, and referenced to residual protiated solvent (δ 7.26 ppm) or to a TMS standard (δ 0.0 ppm). Carbon NMR spectra were recorded in ppm relative to the residual solvent signal: $CDCl_3$ (δ 77.00 ppm). Mass spectra were determined on an AE2-MS 30, a PG 7070E-HF, a CG Analytical 7070E, or a Fisions autospec spectrometer. Optical rotations were measured with a Jasco DIP-370 digital polarimeter. Tetrahydrofuran, diethylether, toluene, and methylene chloride were dried by filtration through alumina according to the procedure by Grubbs.[27] Capillary GC analysis was performed on a Hewlett Packard Model 6890 instrument equipped with a FID detector. Chiral capillary GC analysis was performed on a Hewlett Packard Model 5890 instrument

equipped with a FID detector and beta-cyclodextrin permethylated hydroxypropyl column. All cyclic voltammetry studies were performed in the laboratories of Professor Patrick Farmer, at UC, Irvine. A BAS 100W electrochemistry system was used for CV. The three-electrode cell employed a Pt wire counter electrode. All CV experiments were performed at room temperature. The electrodes were immersed in dichloromethane solutions containing 0.1 M tetrabutyl-ammonium hexafluorophosphate. Scan rates were 100 mV/s. Electron paramagnetic resonance experiments were performed on a Brüker ESP 300 E. All reagents were purchased from Aldrich Chemical Co. or Acros and were used as received, unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ).

4.2. 1,4-Dimethylcylohexa-1,4-diene 6

Compound **6** was prepared using a modified Kwart procedure.[9] A solution of methanol (6.87 g, 214 mmol) and *p*-xylene (25.0 mL, 204 mmol) in 500 mL of ammonia was cooled to −78 °C, and lithium wire (3.54 g, 510 mmol) was added in five portions over 1 h. After stirring for 24 h, the ammonia was allowed to evaporate. Methanol (250 mL) was slowly added to the resulting residue, while the flask was immersed in a 0 °C bath. The solution was warmed to room temperature and water (150 mL) was added. The aqueous layer was extracted with hexane (4 × 120 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated in vacuo to give 20.8 g of an unpurified oil, as a mixture of 1,4-dimethylcylohexa-1,4-diene **6** and *p*-xylene (45:55). The oil was taken on as a mixture: IR (neat) 2965, 2818, 1517, 1458, 1385, 948, 795 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.40 (s, 2H), 2.56 (s, 4H), 1.67 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.2, 118.6, 31.7, 20.9.

4.3. (1*S*,2*S*,4*S*,5*S*)-(+)-2,5-Dimethylcyclohexane-1,4-diol 7

Compound **7** was prepared according to Halterman's procedure.[8b] To a solution of $2IpcBH_2{\cdot}TMED$ (16.6 mL, 0.47 M, 7.8 mmol) in THF was added $BF_3{\cdot}OEt_2$ (2.1 mL, 17 mmol) dropwise. The flask was swirled to mix the solution, then allowed to stand for 3 h undisturbed, during which time a translucent precipitate of $2BF_3{\cdot}TMED$ was formed. The supernatant was collected in a separate flask by anhydrous filtration of the precipitate followed by washing the precipitate with cold THF (3 × 8 mL). The collected supernatant containing (+)-$IpcBH_2$ was cooled to −78 °C, and the 1,4-dimethylcylohexa-1,4-diene and *p*-xylene mixture (1.81 g of diene/*p*-xylene, 45:55, 7.5 mmol of **6**) was added slowly. The mixture was placed in a refrigerator at 5 °C for ca. 30 h, then cooled with an ice bath and treated with 1 mL of methanol dropwise (H_2 was evolved). The solution of organoboranes was oxidized by successive slow addition of aqueous sodium hydroxide (4.0 M, 13.4 mL, 54 mmol) and hydrogen peroxide (30% in water, 5.96 g, 54 mmol). The solution was warmed to 35 °C for 4 h to ensure complete oxidation. Two layers were separated after cooling. The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give ca. 4 g of an unpurified oil. Purification on silica gel (2% hexane/ethyl acetate) removed the nonpolar pinanol and provided a mixture of the C_2 and C_i-symmetric diols. Further purification on silica gel (diethyl ether) provided diol **7** as a white solid (0.63 g, 58%): mp 121 °C; $[\alpha]_D^{23} = +29.7$ (*c* 0.51, CH_2Cl_2); IR (neat) 3280, 2930, 2860, 1450, 1420, 1256, 1094, 1064, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.54 (m, 2H), 1.88 (ddd, $J = 13.2$, 6.7, 6.6 Hz, 2H), 1.74 (ddd, $J = 13.4$, 7.2, 4.5 Hz, 2H), 1.54 (ddd, $J = 13.5$, 7.4, 3.4 Hz, 2H), 1.32 (d, $J = 4.5$ Hz, 2H), 1.00 (d, $J = 7.0$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.4, 35.5, 35.2, 17.9. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.53; H, 10.97.

4.4. (1*S*,2*S*,4*S*,5*S*)-(+)-2,5-Dimethylcyclohexane-1,4-diol bis(methanesulfonate) 8

To a solution of diol **7** (0.48 g, 3.1 mmol) and dry triethylamine (0.65 g, 6.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added dropwise a solution of methanesulfonyl chloride (0.73 g, 6.4 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at 0 °C for 30 min and then at room temperature for 1 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, and concentrated in vacuo to give 0.935 g of an unpurified oil. Purification on silica gel (diethyl ether) provided **8** as a white solid (0.903 g, 97%): mp 68–82 °C; $[\alpha]_D^{23} = +29.8$ (*c* 1.025, CH_2Cl_2); IR (neat) 3020, 2950, 1460, 1330, 1119, 996, 890, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.57 (m, 2H), 3.04 (s, 6H), 2.22 (ddd, $J = 14.0$, 7.0, 3.5 Hz, 2H), 2.07 (ddd, $J = 14.0$, 7.1, 4.5 Hz, 2H), 1.81 (ddd, $J = 13.9$, 7.2, 3.4 Hz, 2H), 1.08 (d, $J = 7.0$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.5, 38.8, 33.9, 33.2, 17.4; HRMS (CI/isobutane) *m*/*z* calcd for $C_{10}H_{21}O_6S_2$ $[M+H]^+$ 301.0781, found: 301.0778. Anal. Calcd for $C_9H_{20}O_6S_2$: C, 39.99; H, 6.71. Found: C, 40.05; H, 6.85.

4.5. Azide 9

To a solution of **8** (2.5 g, 8.2 mmol) in DMF (15 mL) was added sodium azide (701 mg, 10.8 mmol). The mixture was heated to 85 °C and stirred for 9 h, then allowed to cool to room temperature. Water (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo to give 1.5 g of an unpurified oil. Purification on silica gel (8% ethyl acetate/hexane) provided **9** (955 mg, 47%) as a white solid: mp 52 °C; $[\alpha]_D^{23} = +27.6$ (*c* 2.30, CH_2Cl_2); IR (neat) 2944, 2867, 2100, 1350, 1172, 1258, 1080, 963, 890 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.49 (ddd, $J = 9.3$, 9.3, 4.1 Hz, 1H), 3.67 (ddd, $J = 10.4$, 4.4, 4.4 Hz, 1H), 2.69 (m, 1H), 2.10 (ddd, $J = 13.4$, 4.4, 4.4 Hz, 1H), 1.90 (ddd, $J = 13.6$, 3.3,

3.3 Hz, 1H), 1.83 (m, 1H), 1.76 (ddd, $J = 14.0$, 10.0, 4.4 Hz, 1H), 1.54 (ddd, $J = 10.3$, 10.3, 3.3 Hz, 1H), 1.12 (d, $J = 6.7$ Hz, 3H), 1.02 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.4, 61.3, 38.7, 35.8, 35.6, 31.9, 29.7, 18.3, 13.5; HRMS (CI/isobutane) m/z calcd for $C_9H_{16}NO_3S$ $[M-2N+H]^+$ 220.1007, found: 220.1010. Anal. Calcd for $C_9H_{17}N_3O_3S$: C, 43.71; H, 6.93. Found: C, 43.92; H, 6.88.

4.6. Amine 10a

To a solution of **9** (190 mg, 0.77 mmol) in THF (10 mL) was added triphenylphosphine (227 mg, 0.87 mmol). The mixture was stirred at room temperature for 2 d, then aqueous 2 M NaOH (5 mL) was added. The aqueous layer was extracted with diethyl ether (3×3 mL). The combined organic phases were extracted with aqueous 2 N HBr (4×4 mL). The aqueous acid was washed consecutively with CH_2Cl_2 (2×6 mL) then toluene (2×6 mL). The aqueous acid was concentrated in vacuo to give ca. 150 mg of crude crystals. The crystals were recrystallized from THF to give **10a** (136 mg, 86%) as white crystals: $[\alpha]_D^{23} = +17.0$ (c 0.705, MeOH); IR (neat) 2870, 1610, 1600, 1195, 947, 820, 805, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (br s, 2H), 3.90 (d, $J = 4.5$ Hz, 2H), 1.93 (m, 4H), 1.78 (ddd, $J = 12.4$, 4.6, 4.6 Hz, 2H), 1.30 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 65.1, 36.8, 34.5, 20.2. HRMS (EI) m/z calcd for $C_8H_{15}N$ $[M-HBr]^+$ 125.1204, found: 125.1207.

4.7. Amine 10b

To a solution of **9** (133 mg, 0.54 mmol) in THF (8 mL) was added triphenylphosphine (161 mg, 0.62 mmol). The mixture was stirred at room temperature for 3 d, then aqueous 2 N NaOH (5 mL) was added. The aqueous layer was extracted with diethyl ether (3×3 mL). The combined organic phases were extracted with aqueous 2 M HCl (4×4 mL). The aqueous acid was washed consecutively with CH_2Cl_2 (2×6 mL) and then toluene (2×6 mL). The aqueous acid was concentrated in vacuo to give ca. 100 mg crude crystals. The crystals were recrystallized from THF to give **10b** (82 mg, 94%) as white crystals: $[\alpha]_D^{23} = +32.1$ (c 0.570, MeOH); IR (neat) 2870, 1610, 1600, 1190, 942, 846, 808, 770 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (br s, 2H), 3.85 (d, $J = 4.5$ Hz, 2H), 1.92 (m, 4H), 1.73 (ddd, $J = 12.4$, 4.6, 4.6 Hz, 2H), 1.28 (d, $J = 7.0$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.8, 37.0, 34.6, 20.0.

4.8. Diol 12

To a solution of 2IpcBH$_2$·TMED (50.0 mL, 0.47 M, 23.5 mmol) in THF was added BF_3·OEt_2 (3.0 mL, 24 mmol) dropwise. The flask was swirled to mix the solution, then allowed to stand for 3 h undisturbed, during which time a translucent precipitate of 2BF_3·TMED formed. The supernatant was collected in a separate flask by anhydrous filtration of the precipitate followed by washing the precipitate with cold THF (3×20 mL). The collected supernatant containing (+)-IpcBH$_2$ was cooled to -78 °C, and 1,5-dimethylcyloocta-1,5-diene (3.96 g, 29.1 mmol) was added slowly. The mixture was placed in a freezer at -15 °C for 4 d then cooled with an ice bath and treated with 4 mL of methanol dropwise (H_2 evolved). The solution of organoboranes was oxidized by successive slow addition of aqueous sodium hydroxide (4.0 M, 30 mL, 120 mmol) and hydrogen peroxide (30% in water, 8.0 mL, 71 mmol). The solution was warmed to 35 °C for 4 h to ensure complete oxidation. Two layers were separated after cooling. The aqueous layer was extracted with diethyl ether (4×75 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give ca. 14 g of an unpurified oil. Purification on silica gel (2% hexane/ethyl acetate) removed the less polar pinanol and provided a mixture of the C_2 and C_i-symmetric diols. Further purification on silica gel (diethyl ether) provided diol **12** as a white solid (1.96 g, 48%): mp 130–132 °C; $[\alpha]_D^{23} = +8.1$ (c 0.15, THF); IR (neat) 3280, 2996, 2881, 2819, 1450, 1420, 1093, 947, 708 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.35 (dt, $J = 10.9$, 8.6 Hz, 2H), 1.89 (m, 2H), 1.72 (m, 6H), 1.40 (s, 2H), 1.35 (m, 2H), 1.04 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.0, 40.7, 34.4, 29.0, 20.4; HRMS (EI) m/z calcd for $C_{10}H_{19}O$ $[M-OH]^+$ 155.1436, found: 155.1436. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.53; H, 11.62.

4.9. Alcohol 13

To a solution of diol **12** (0.172 g, 1.00 mmol) and dry triethylamine (0.142 g, 1.40 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise a solution of trimethylsilyl chloride (0.108 g, 1.00 mmol) in CH_2Cl_2 (2 mL). The mixture was warmed to room temperature and stirred for 5 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (4×5 mL). The combined organic phases dried over $MgSO_4$, and concentrated in vacuo to give 110 mg of an unpurified oil. Purification on silica gel (10% ethyl acetate/hexane) provided **13** as a clear oil (111 mg, 45%) and recovered **12** (85 mg, 49%); IR (neat) 3260, 2994, 2965, 2886, 1420, 1268, 1121, 940, 772 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32 (m, 2H), 2.93 (m, 1H), 1.80 (m, 4H), 1.68 (m, 4H), 1.44 (s, 1H), 1.30 (m, 2H), 1.47 (m, 2H), 1.05 (d, $J = 6.8$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.0, 78.4, 41.1, 41.0, 35.1, 34.9, 29.8, 29.3, 21.1, 20.8, 0.7.

4.10. Methanesulfonate 14

To a solution of alcohol **13** (640 mg, 2.62 mmol) and dry triethylamine (1 mL) in CH_2Cl_2 (20 mL) at 0 °C was added dropwise a solution of methanesulfonyl chloride (363 mg, 3.17 mmol) in CH_2Cl_2 (5 mL). The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organics were dried over $MgSO_4$, and concentrated in vacuo to give 880 mg of an unpurified oil. Purification on silica gel (5–50% ethyl acetate/hexanes) provided **14** as a clear oil (212 mg,

25%); IR (neat) 3020, 2950, 1480, 1456, 1374, 1330, 1258, 1123, 1025, 892, 825 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.42 (dt, $J = 9.0$, 2.5 Hz, 1H), 3.30 (dt, $J = 8.0$, 2.0 Hz, 1H), 2.97 (s, 3H), 2.05 (m, 1H), 1.94 (m, 2H), 1.78 (m, 3H), 1.65 (m, 2H), 1.31 (m, 2H), 1.01 (d, $J = 6.5$ Hz, 3H), 0.92 (d, $J = 6.5$ Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 89.4, 77.8, 39.8, 38.7, 37.7, 33.3, 32.1, 28.4, 28.2, 20.6, 20.2, 0.3.

4.11. Azide 15

To a solution of **14** (212 mg, 0.657 mmol) in DMF (5 mL) was added sodium azide (53 mg, 0.82 mmol). The mixture was heated to 70 °C and was stirred for 48 h, then allowed to cool to room temperature. Water (2 mL) and saturated aqueous $NaHCO_3$ solution (2 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3×2 mL). The combined organic phases were dried over $MgSO_4$, and concentrated in vacuo to give an unpurified oil. Purification on silica gel (5–10% ethyl acetate/hexane) provided **15** as a clear oil (87 mg, 47%): $[\alpha]_D^{23} = +25.6$ (c 0.31, CH_2Cl_2); IR (neat) 3375, 2926, 2871, 2094, 1480, 1456, 1373, 1278, 1191, 1011, 952, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (dt, $J = 9.5$, 3.5 Hz, 1H), 3.28 (dt, $J = 9.0$, 3.5 Hz, 1H), 2.04 (m, 2H), 1.86 (m, 1H), 1.74 (m, 2H), 1.58 (m, 4H), 1.41 (m, 2H), 1.07 (d, $J = 6.0$ Hz, 3H), 0.97 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.9, 63.7, 38.5, 36.0, 33.1, 28.9, 28.4, 28.0, 21.7, 17.7. ESMS m/z calcd for $C_{10}H_{19}N_3ONa$ $[M+Na]^+$ 220.15 found 220.09.

4.12. Azidemethanesulfonate 16

To a solution of alcohol **15** (87 mg, 0.35 mmol) and dry triethylamine (200 μL) in CH_2Cl_2 (10 mL) at 0 °C was added dropwise a solution of methanesulfonyl chloride (49 mg, 0.43 mmol) in CH_2Cl_2 (0.5 mL). The mixture was allowed to warm to room temperature and stirred for 2 d. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2×8 mL). The combined organic were dried over $MgSO_4$, and concentrated in vacuo to give an unpurified oil. Purification on silica gel (10% ethyl acetate/hexanes) provided **16** as a clear oil (70 mg, 74%); IR (neat) 2988, 2940, 2876, 2101, 1353, 1170, 1254, 1087, 966, 891, 777, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.46 (dt, $J = 8.0$, 2.0 Hz, 1H), 3.75 (dt, $J = 8.0$, 3.0 Hz, 1H), 3.00 (s, 3H), 2.50 (tt, $J = 13.6$, 2.5 Hz, 1H), 2.09 (m, 1H), 1.95–1.88 (m, 3H), 1.79–1.70 (m, 2H), 1.58–1.47 (m, 3H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H).

4.13. Amine 17

To a solution of **16** (177 mg, 0.64 mmol) in THF (10 mL) was added triphenylphosphine (200 mg, 0.76 mmol). The mixture was stirred at room temperature overnight, then warmed to 45 °C for 2 d. The reaction mixture then had 2 M HCl (aq) (10 mL) added and the organic layer separated. The aqueous layer was washed with CH_2Cl_2 (3×5 mL), then made basic with aqueous 4 M NaOH. The basic aqueous layer was extracted with CH_2Cl_2 (3×8 mL). The combined organic phases were dried over $MgSO_4$, and concentrated in vacuo to give 78 mg of an unpurified oil. Purification of the oil by Kugelrohl distillation provided **17** as a clear oil (40 mg, 41%): IR (neat) 3424, 3057, 2936, 2874, 1438, 1345, 1191, 1119, 1070, 1040, 997, 905, 756, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.68 (br s, 2H), 2.50 (br s, 1H), 2.08 (ddd, $J = 22.0$, 12.0, 5.0 Hz, 2H), 1.98 (ddd, $J = 22.0$, 12.0, 5.0 Hz, 2H), 1.65 (br s, 2H), 1.34 (m, 2H), 1.30 (m, 2H), 1.11 (d, $J = 7.2$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.4, 32.4, 27.1, 25.2, 20.4. HRMS (CI/isobutane) m/z calcd for $C_{10}H_{20}N$ $[M+H]^+$ 154.1597, found: 154.1591.

4.14. Diene 19

To a solution of methyl magnesium bromide (3 M, 30 mL, 90 mmol) in diethyl ether was added dropwise dione **18**[15,16] (3.515 g, 23.10 mmol) dissolved in THF (100 mL). The mixture was heated at reflux for 24 h, then cooled to 0 °C. The cooled reaction mixture was quenched by slow addition of saturated aqueous ammonium chloride (100 mL) and water (100 mL). The aqueous layer was extracted with ethyl acetate (4×150 mL). The combined organic phases were washed with brine (2×20 mL), dried over $MgSO_4$, and concentrated in vacuo to give ca. 4.5 g of an unpurified solid. The unpurified solid was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. To the solution was added dropwise $BF_3{\cdot}OEt_2$ (9.0 mL, 73 mmol). The mixture was allowed to stir for 1 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution (50 mL) and water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic phases were dried over $MgSO_4$, and concentrated in vacuo to give ca. 4 g of an unpurified oil. Purification on silica gel (hexane) provided **19** as a clear oil (3.03 g, 89%); IR (neat) 3000, 2961, 2910, 2832, 1670, 1443, 1377, 1198, 1143, 1012, 803 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.32 (q, $J = 1.5$ Hz, 2H), 2.23 (m, 1H), 2.19 (m, 3H), 1.96 (m, 1H), 1.92 (m, 1H), 1.69 (q, $J = 1.4$ Hz, 6H), 1.66 (t, $J = 7.9$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 119.2, 32.4, 30.4, 29.6, 22.4.

4.15. Bisepoxide 20

To a solution of *m*-CPBA (1.03 g (70 wt %), 4.18 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added dropwise a solution of **19** (204 mg, 1.38 mmol) in CH_2Cl_2 (5 mL). The mixture was warmed to room temperature and allowed to stir for 9 h. The reaction mixture was diluted in diethyl ether (50 mL) and sequentially washed with $NaHSO_3$ (10% aqueous, 3×20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), water (10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, and concentrated in vacuo to give 208 mg of an unpurified oil. Purification on silica gel treated with 2% triethylamine (10% ethyl acetate/hexane) provided **20** as a white solid (99 mg, 41%): mp 44–45 °C; IR (neat) 2980, 2890, 1435, 1379, 1097, 1006, 848, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.96 (d, $J = 4.1$ Hz, 2H), 2.12 (dd, $J = 16.0$, 6.6 Hz, 2H), 2.06 (dd, $J = 16.2$,

3.3 Hz, 2H), 1.89 (s, 2H), 1.54 (s, 2H), 1.33 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 59.7, 57.4, 29.5, 26.5, 21.3, 21.3. HRMS (FAB) m/z calcd for $C_{11}H_{17}O_2$ $[M+H]^+$ 181.1228, found: 181.1222.

4.16. Aminediol 21

To a solution of bisepoxide **20** (176 mg, 0.976 mmol) in MeOH (1 mL) was added ammonia saturated MeOH (3 mL) in a sealed tube. The tube was heated to 120 °C for 36 h. The reaction mixture was concentrated in vacuo to give 194 mg of an unpurified solid. Recrystallization from acetone provided **21** as a brown solid (182 mg, 95%): mp 162 °C; IR (neat) 3440, 3370, 2885, 1445, 1105, 1034, 989, 931, 900, 607 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.48 (s, 1H), 2.63 (s, 2H), 2.30 (dq, $J = 16.5$, 2.5 Hz, 2H), 2.06 (t, $J = 3.5$ Hz, 2H), 1.85 (d, $J = 16.5$ Hz, 2H), 1.70 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.3, 55.3, 37.5, 29.9, 27.2, 26.6. HRMS (FAB) m/z calcd for $C_{11}H_{20}NO_2$ $[M+H]^+$ 198.1494, found: 198.1489.

4.17. Amidediol 22

To a solution of aminediol **21** (154 mg, 0.78 mmol) and triethylamine (730 mg, 7.26 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added trifluoroacetic anhydride (604 mg, 2.88 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched by addition of water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 7 mL). The combined organic phases were dried over $MgSO_4$, and concentrated in vacuo to give ca. 0.5 g of an unpurified oil. The unpurified oil was dissolved in MeOH (8 mL) and had ca. 250 mg K_2CO_3 added. The mixture was stirred at room temperature for 30 min, then diluted with ethyl acetate (10 mL), and water (8 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic phases were dried over $MgSO_4$, and concentrated in vacuo to give an unpurified oil. Purification on silica gel (30% ethyl acetate/hexane) provided **22** as a white solid (222 mg, 97%): mp 172–174 °C; IR (neat) 3423, 2999, 2881, 1675, 1460, 1197, 1145, 1099, 923, 906, 707 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) (mixture of rotamers) δ 4.31 (s, 1H), 3.73 (s, 1H), 3.33 (s, OH), 2.38 (t, $J = 14.8$ Hz, 2H), 2.09 (s, 2H), 1.75 (t, $J = 14.9$ Hz, 2H), 1.68 (s, 2H), 1.24 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 156.8 (q, $J = 35.0$ Hz), 118.2 (q, $J = 285$ Hz), 71.1, 70.7, 58.6, 55.3, 38.0, 37.7, 28.9, 27.2, 27.0, 25.7. HRMS (FAB) m/z calcd for $C_{13}H_{19}F_3NO_3$ $[M+H]^+$ 294.1317, found: 294.1306.

4.18. Amidediether 23

To a solution of amidediol **22** (153 mg, 0.522 mmol) in THF (10 mL) was added sodium hydride (89 mg, 3.71 mmol), which was washed with hexanes (5 mL). To the reaction mixture was added iodomethane (340 mg, 2.4 mmol). The mixture was allowed to stir for 5 h. The reaction mixture was cooled to 0 °C and quenched by the addition of methanol dropwise until H_2 evolution stopped and then water added (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic phases were dried over $MgSO_4$, and concentrated in vacuo to give an unpurified oil. Purification on silica gel (5% ethyl acetate/hexane) provided **23** as a clear oil (186 mg, 99%): IR (neat) 2940, 2909, 2831, 1690, 1450, 1221, 1199, 1137, 1073, 1010, 916, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ 4.54 (s, 1H), 3.81 (s, 1H), 3.23 (s, 3H), 3.22 (s, 3H), 2.34 (dt, $J = 13.4$, 1.0 Hz, 1H), 2.27 (dt, $J = 13.4$, 1.0 Hz, 1H), 1.93 (m, 2H), 1.88 (m, 2H), 1.71 (dt, $J = 13.4$, 3.4 Hz, 1H), 1.65 (dt, $J = 13.4$, 3.4 Hz, 1H), 1.23 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7 (q, $J = 35.0$ Hz), 116.7 (q, $J = 287$ Hz), 74.3, 74.0, 55.8, 55.8, 51.9, 48.3, 48.3, 33.4, 32.1, 29.7, 27.6, 25.9, 25.6, 19.2, 18.6. HRMS (FAB) m/z calcd for $C_{15}H_{23}F_3NO_3$ $[M+H]^+$ 322.1629, found: 322.1623.

4.19. Aminediether 24

To a solution of amidediether **23** (186 mg, 0.522 mmol) in ethanol (10 mL) was added sodium borohydride (80 mg, 2.11 mmol). The mixture heated to 60 °C and allowed to stir for 8 h. The reaction mixture was concentrated in vacuo to ca. 1 mL and quenched by addition of water added (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, and concentrated in vacuo to give **24** (121 mg, 98%): IR (neat) 3345, 2900, 2819, 1451, 1374, 1351, 1186, 1097, 957, 889 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.19 (s, 6H), 2.70 (s, 2H), 2.21 (dt, $J = 10.9$, 2.1 Hz, 1H), 1.86 (m, 5H), 1.73 (dt, $J = 10.9$, 2.0 Hz, 1H), 1.36 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 74.7, 53.7, 47.7, 33.3, 29.0, 26.6, 19.8. HRMS (FAB) m/z calcd for $C_{13}H_{24}NO_3$ $[M+H]^+$ 226.1807, found: 226.1812.

4.20. Aminediether 27

To a suspension of hexanes washed (15 mL) sodium hydride (317 mg, 13.2 mmol) in THF (50 mL) cooled to 0 °C was added dropwise a solution of amidediol **26**[17] (1.487 g, 6.01 mmol) in THF (15 mL). The reaction mixture was stirred at 0 °C for 30 min, then to the reaction mixture was added iodomethane (1.87 g, 13.1 mmol). The mixture was allowed to stir overnight at room temperature. The reaction mixture was cooled to 0 °C and quenched by addition of methanol dropwise until H_2 evolution stopped then water was added (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, and concentrated in vacuo to give an unpurified oil. Purification on silica gel (10% ethyl acetate/hexane) provided **27** as a clear oil (1.125 g, 68%): IR (neat) 3054, 2935, 2874, 1490, 1450, 1438, 1190, 1038, 996, 758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, $J = 7.2$, 2H), 7.30 (t, $J = 7.3$ Hz, 2H), 7.23 (t, $J = 7.2$, 1H), 3.94 (q, $J = 13.9$, 2H), 3.64 (ddd, $J = 11.0$, 11.0, 5.3 Hz, 2H), 3.27 (s, 6H), 2.88 (t, $J = 4.9$ Hz, 2H), 2.00 (ddd, $J = 13.0$, 13.0, 6.4 Hz, 2H), 1.90 (dd, $J = 14.0$, 6.9 Hz, 2H), 1.81 (ddd, $J = 14.0$, 13.4, 6.4 Hz, 2H), 1.65 (ddd, $J = 14.0$, 13.4, 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 128.2, 127.9, 126.8, 76.5,

56.6, 55.7, 51.9, 27.1, 20.2. HRMS (CI/isobutane) m/z calcd for $C_{17}H_{25}NO_2$ $[M+H]^+$ 276.1965, found: 276.1973.

4.21. Amine 28

Argon was bubbled through a solution of **27** (515 mg, 1.87 mmol), acetic acid (470 μL, 8.25 mmol), and 10% palladium on carbon (130 mg) in ethanol (3 mL) in a Parr bomb. The resultant suspension was pressurized with hydrogen (500 psi) and stirred at room temperature overnight. After filtration through Celite, the solution was taken up in CH_2Cl_2 (15 mL). The organic layer was washed with 1 M NaOH (10 mL), the organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo to give an unpurified oil. The unpurified amine was diluted with CH_2Cl_2 (10 mL) and extracted with 2 M HCl (10 mL). The aqueous layer was washed with CH_2Cl_2 (2×8 mL), and then made basic with 4 M NaOH. The basic aqueous layer was extracted with CH_2Cl_2 (4×10 mL). The combined organic phases were dried over $MgSO_4$, and concentrated in vacuo to give **28** as a clear oil (317 mg, 91%). IR (neat) 3283, 2933, 2819, 1451, 1374, 1351, 1186, 1097, 957, 889 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.46 (ddd, $J = 11.1$, 11.1, 5.5 Hz, 2H), 3.35 (s, 6H), 3.09 (t, $J = 4.8$, 2H), 2.05 (dd, $J = 12.8$, 4.6 Hz 2H), 1.98 (q, $J = 6.7$ Hz, 2H), 1.72–1.60 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.7, 56.0, 47.6, 27.3, 23.8. HRMS (CI/isobutane) m/z calcd for $C_{10}H_{20}NO_2$ $[M+H]^+$ 186.1495, found: 186.1499.

4.22. General procedures used in oxidations

Catalyst **10** was prepared according to the following procedure: To **10b** dissolved in CH_2Cl_2 (1 mL) was added aqueous 0.1 N NaOH (1.5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×0.5 mL). The combined organic phases were dried over $MgSO_4$ and added to reactions calling for **10**.

Catalyst **1**, **2**, **3**, and **4** were prepared according to the following procedure:**10** was made as described above. To **10**, **17**, **24**, or **28** was added 1 equiv of *m*-CPBA in CH_2Cl_2 (~0.1 M). The solution was stirred for 15 min, during which time it turned faint red. This solution was added to reactions calling for **1**, **2**, **3**, or **4**.

Alcohols were resolved by chiral GC using a Hewlett Packard Model 5890 instrument equipped with a FID detector and β-cyclodextrin permethylated hydroxypropyl column. *sec*-Phenethyl alcohol (**2**): Initial temperature—65 °C (5 min), rate—0.7°/min, final temperature—150 °C (25 min). Retention times: 26.01, 29.66 min. 2-Ocatanol **30**: Initial temperature—60 °C (5 min), rate—0.5°/min, final temperature—150 °C (25 min). Retention times: 15.35, 17.22 min. 2′-Chloro-*sec*-phenethyl alcohol **31**: Initial temperature—90 °C (5 min), rate—1.3°/min, final temperature—150 °C (25 min). Retention times: 38.22, 40.80 min. 2′-Methyl-*sec*-phenethyl alcohol **32**: Initial temperature—80 °C (5 min), rate—1.0°/min, final temperature—150 °C (25 min). Retention times: 41.84, 44.23 min.

4.23. General procedures for oxidation of alcohols using *m*-CPBA as the bulk oxidant

The *m*-CPBA used was first purified according to standard protocol.[28] A solution of the alcohol (1 mmol) in CH_2Cl_2 (0.5 mL) and any additive and/or catalyst (0.01 mmol) was cooled to 0 °C. A solution of *m*-CPBA (0.5 mmol) in CH_2Cl_2 (1.5 mL) cooled to 0 °C was added dropwise over a few minutes. The reaction mixture was stirred at 0 °C for 20 min, then was allowed to warm to room temperature and stirred for another 30 min. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (3 mL), and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×1 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The resulting oil was analyzed by GC and NMR for any oxidation and enantiomeric excess of unreacted alcohol.

4.24. General procedures for oxidation of alcohols using H_2O_2/NaOH as the bulk oxidant

A solution of the alcohol (1 mmol) in 0.5 mL of THF and catalyst (0.01 mmol) was cooled to 0 °C. A solution of H_2O_2 (30% in water, 0.5 mmol) and aqueous 1 M NaOH in THF (1.5 mL) cooled to 0 °C was added dropwise over a few minutes. The reaction mixture was stirred at room temperature for 1 d. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (3 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×1 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The resulting oil was analyzed by GC and NMR for any oxidation and enantiomeric excess of unreacted alcohol.

4.25. General procedures for oxidation of alcohols using $Na_2WO_4 \cdot 2H_2O$, H_2O_2 as the bulk oxidant

A solution of the alcohol (1 mmol) in CH_2Cl_2 (0.5 mL) and catalyst (0.01 mmol) was cooled to 0 °C. A solution at 0 °C of $Na_2WO_4 \cdot 2H_2O$ (0.2 mmol), H_2O_2 (0.5 mmol) in CH_2Cl_2 (1.5 mL), and Bu_4NHSO_4 (0.04 mmol), as a phase transfer catalyst, was added dropwise over a few minutes. The reaction mixture was stirred at room temperature for 1 d. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (3 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×1 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The resulting oil was analyzed by GC and NMR for any oxidation and enantiomeric excess of unreacted alcohol.

4.26. General procedures for oxidation of alcohols using Oxone®/acetone as the bulk oxidant

A solution of the alcohol (1 mmol) in CH_2Cl_2 (0.5 mL), catalyst (0.01 mmol), and Bu_4NHSO_4 (0.06 mmol), as a phase transfer catalyst was cooled to 0 °C. A solution at 0 °C of phosphate buffer (1 mL, pH 8.0), acetone (1 mL), Oxone® (0.5 mmol), in water (1.5 mL) was added dropwise over a few minutes. The reaction

mixture was stirred at room temperature for 1 d. The reaction mixture was quenched by addition of saturated $NaHCO_3$ (3 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×1 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The resulting oil was analyzed by GC and NMR for any oxidation and enantiomeric excess of unreacted alcohol.

4.27. General procedures for oxidation of alcohols using BAIB as the bulk oxidant

A solution of the alcohol (1 mmol) in CH_2Cl_2 (0.5 mL) and catalyst (0.01 mmol) was cooled to 0 °C. A solution at 0 °C of BAIB in CH_2Cl_2 (1 mL) was added dropwise over a few minutes. The reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (3 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×1 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The resulting oil was analyzed by GC and NMR for any oxidation and enantiomeric excess of unreacted alcohol.

4.28. General procedure for electrochemical characterization of nitroxides

The experiments were performed in CH_2Cl_2, using SCE as the reference electrode.[29] Therefore, all potentials reported are in reference to SCE. Tetrabutylammonium hexafluoro-phosphate was used as the supporting electrolyte. The potentials were recorded at a scan rate of 100 mV/s.

Acknowledgements

Support was provided by the Schering-Plough Research Institute and by the University of California Irvine.

References

1. (a) Semmelhack, M. F.; Schmid, C. R.; Chou, C. S.; Cortes, D. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374–3376; (b) Ma, Z.; Bobbitt, J. M. *J. Org. Chem.* **1991**, *56*, 6110–6114; (c) Ma, Z.; Huang, Q.; Bobbit, J. M. *J. Org. Chem.* **1993**, *58*, 4837–4843; (d) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996**, *61*, 1194–1195.
2. (a) Keana, J. F. W.; Cuomo, J.; Lex, L.; Seyedrezai, S. *J. Org. Chem.* **1983**, *48*, 2647–2654; (b) Hankovszky, H. O.; Hideg, K.; Lovas, M. J.; Jerkovich, G.; Rockenbauer, A.; Györ, M.; Sohár, P. *Can. J. Chem.* **1989**, *67*, 1392–1400; (c) Benfaremo, N.; Steenbock, M.; Klapper, M.; Müllen, K.; Enkelmann, V.; Cabrera, K. *Liebigs Ann. Chem.* **1996**, 1413–1415; (d) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Gautier-Luneau, I.; Pierre, J.-L. *J. Org. Chem.* **1997**, *62*, 9385–9388; (e) Rockenbauer, A.; Mercier, A.; LeMoigne, F.; Olive, G.; Tordo, P. *J. Phys. Chem. A* **1997**, *101*, 7965–7970.
3. (a) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Durif, A.; Averbuch, M.-T.; Pierre, J.-L. *Tetrahedron Lett.* **1998**, *39*, 2565–2568; (b) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Chem. Soc., Chem. Commun.* **1995**, 1029–1030.
4. Rychnovsky, S. D.; Beauchamp, T.; Vaidyanathan, R.; Kwan, T. *J. Org. Chem.* **1998**, *63*, 6363–6374.
5. Braslau, R.; Chaplinski, V.; Goodson, P. *J. Org. Chem.* **1998**, *63*, 9857–9864.
6. (a) Dupeyre, R. M.; Rassat, A. *J. Am. Chem. Soc.* **1966**, *88*, 3180–3181; (b) Mendenhall, G. D.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 6390–6394; (c) Mendenhall, G. D.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 6395–6400.
7. For reviews see: (a) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683–1715; (b) Buchanan, G. L. *Chem. Soc. Rev.* **1974**, *3*, 41–63.
8. (a) Xiao, D.; Zhang, Z.; Jiang, Q.; Zhang, X. *Tetrahedron Lett.* **1998**, *39*, 5331–5334; (b) Halterman, R. L.; Chen, Z.; Eriks, K. *Organometallics* **1991**, *10*, 3449–3458.
9. Kwart, H.; Conley, R. *J. Org. Chem.* **1973**, *38*, 2011–2016.
10. Brown, H. C.; Jadhav, A. K.; Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074–5083.
11. Bates, R. B.; Gangwar, S. *Tetrahedron: Asymmetry* **1993**, *4*, 69–72.
12. Murahashi, S. I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *45*, 3292–3303.
13. (a) Langrand, G.; Secchi, M.; Buono, G.; Baratti, J.; Triantaphylides, C. *Tetrahedron Lett.* **1985**, *26*, 1857–1860; (b) Langrand, G.; Baratti, G.; Buono, G.; Triantaphylides, C. *Tetrahedron Lett.* **1986**, *27*, 29–32.
14. Meerwein, H.; Schurmann, W. *Annalen* **1913**, 196–242.
15. Schaefer, J. P.; Honig, L. M. *J. Org. Chem.* **1968**, *33*, 2655–2659.
16. Henkel, J. G.; Faith, W. C.; Hane, J. T. *J. Org. Chem.* **1981**, 3483–3486.
17. Michel, P.; Rassat, A. *J. Org. Chem.* **2000**, *65*, 2572–2573.
18. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562.
19. Rychnovsky, S. D.; Vaidyanathan, R. *J. Org. Chem.* **1999**, *64*, 310–312.
20. Minisci, F.; Bravo, A.; Bjorsvik, H.-R.; Fontana, F.; Serri, A. *J. Org. Chem.* **1996**, *61*, 6409–6416.
21. Hudson, A.; Hussain, H. A. *J. Chem Soc. (b).* **1961**, *35*, 1507–1509.
22. Lebedev, O. L.; Khiedekel, M. L.; Razuvaev, G. A. *Dok. Akad. Nauk. SSSR.* **1961**, *140*, 1327–1329.
23. Brik, M. E. *Tetrahedron Lett.* **1995**, *36*, 5519–5522.
24. Margarita, R.; Mico, A.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.
25. Kuroboshi, M.; Yoshihisa, H.; Cortona, M. N.; Kawakami, Y.; Gao, Z.; Tanaka, H. *Tetrahedron Lett.* **2000**, *41*, 8131–8135.
26. Rychnovsky, S. D.; Vaidyanathan, R.; Beauchamp, T.; Lin, R.; Farmer, P. J. *J. Org. Chem.* **1999**, *64*, 6745–6749.
27. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
28. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: New York, 1988; p 123.
29. Professor Patrick Farmer's laboratory, University of California, Irvine and Dr. Rong Lin are gratefully acknowledged for conducting the CV experiments.