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Imidazolidinone Nitroxides as Catalysts in the Aerobic Oxidation of Alcohols, en Route to Atroposelective Oxidative Desymmetrization

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New chiral nitroxides based on the imidazolidin-4-one skeleton, and the corresponding hydroxylamines, have been prepared from cyclic nitrones by a straightforward reaction sequence. They were evaluated as catalysts in the aerobic oxidation of benzyl alcohol using different co-catalysts. Both the imidazolidinone nitroxides and hydroxylamines were proven to catalyze the reaction, with the ring substituent having an effect depending on the co-catalytic system. In some cases, rapid oxidation to benzaldehyde was accomplished at room temperature under an atmospheric O_2 pressure. Moreover, atroposelective desymmetrization was achieved during the aerobic oxidation of a diol catalyzed by an enantiopure imidazolidinone nitroxide. Finally, the electrochemical behavior of the new hydroxylamines and nitroxides was investigated by cyclic voltammetry, which gave insights into the observed catalytic properties.

Introduction

The nitroxide-catalyzed oxidation of alcohols with molecular oxygen has received considerable attention over the past decade.[1] The use of O_2 in oxidation reactions is particularly advantageous in terms of cost, atom economy, and environmental impact.[2] The combination of O_2, TEMPO [2,2,6,6-tetramethylpiperidin-1-yloxyl (**I**), Figure 1], and a co-catalyst has rapidly emerged as the most sustainable oxidation method.[2] Most of the work so far has been devoted to the nature of the co-catalyst: Many Cu- or Fe-based systems have been reported,[3] as well as metal-free co-catalysts that generally act as NO_x sources.[4] Conversely, stable nitroxyl radicals other than piperidin-1-yloxyls have seldom been investigated in the aerobic oxidation of alcohols (Figure 1): Iwabuchi and co-workers reported that several AZADO-type nitroxides (**II**) are highly active catalysts in the presence of $NaNO_2$ and acetic acid,[5] Stahl and co-workers applied ABNO-type nitroxides (**III**) either with a Cu-based[6] or a NO_x[7] co-catalyst, and Gartshore and Lupton studied the scope of TOXYL-type nitroxides (**IV**)[8] under the oxidation conditions developed by Sheldon and co-workers.[9] Several other types of nitroxides have been described in the literature, some of which have been used as catalysts in nonaerobic alcohol oxidation.[10] In addition, chiral nitroxides have been employed in oxidative kinetic resolutions and diol desymmetrizations.[11]

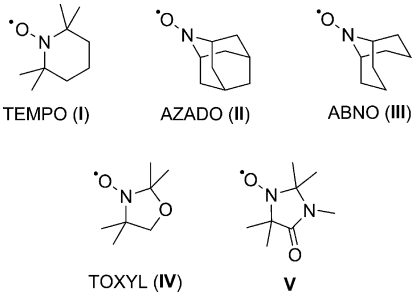

Figure 1. Nitroxides **I**–**IV** employed in the aerobic oxidation of alcohols and imidazolidin-4-one-based nitroxide **V**.

Nitroxides of the general structure **V** with an imidazolidin-4-one skeleton were first prepared in the early 1970s (Figure 1).[12] Their use in various applications, including nitroxide-mediated polymerization[13] and organic batteries,[14] has been investigated.[15] To the best of our knowledge, however, the properties of imidazolidin-4-one-based nitroxides as oxidation catalysts have never been reported.

Our work on imidazolidinone-based nitrones of general formula **1**[16] led us to report the direct C–H arylation of cyclic nitrones.[17] This reaction allows the preparation of a variety of new α,α,α′,α′-tetrasubstituted hydroxylamines in only two steps. In particular, when this transformation was applied to the chiral nitrone MiPNO (**1a**; R^1 = Me, R^2 = *i*Pr), available in both enantiopure forms,[18] enantiopure hydroxylamines **4a** were readily obtained (Scheme 1).

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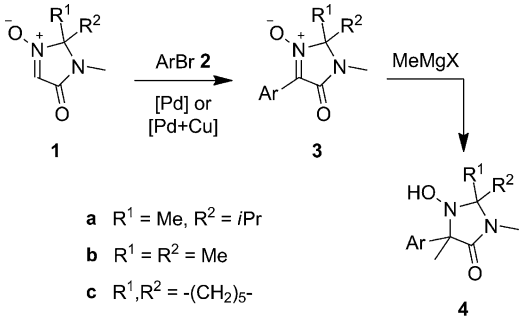


Scheme 1. Direct arylation of nitrones **1** and synthesis of α,α,α′,α′-tetrasubstituted hydroxylamines **4**.

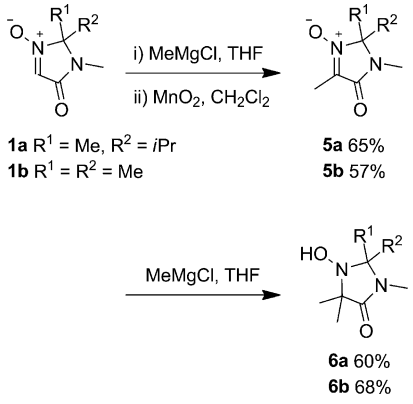
We wondered, i. whether these imidazolidinone-based hydroxylamines **4** could be used as nitroxide precursors for the catalysis of the aerobic oxidation of alcohols, ii. what would be the effect of the nature of the α,α′-substituents, and iii. whether enantiodifferentiation could be achieved. We herein present our first investigations on this subject, combining synthesis, catalytic oxidation experiments, and electrochemical characterization of the species involved.

Results and Discussion

Synthesis of Nitroxide Precursors

In addition to the chiral nitrone MiPNO (**1a**) with isopropyl/methyl substitution,[18] we selected two other imidazolidinone-based nitrones to investigate the influence of substituents at the α position of the nitroxide: **1b** bearing two methyl substituents and **1c** with a spiro-cyclohexane moiety (Scheme 1).

At the α′ position of the nitroxide, we chose to have one methyl group in all cases, together with either an aryl ring (*p*-tolyl or 2-pyridyl in compounds **3** and **4**, Scheme 1, and nitroxides **7**) or a second methyl group (compounds **5** and **6**, Scheme 2, and nitroxides **8**).



Scheme 2. Preparation of bis-methylated hydroxylamines **6**.

Arylnitrones **3** and hydroxylamines **4** were synthesized according to Scheme 1 and the relevant reaction data are presented in Table 1. The palladium-catalyzed coupling of nitrones **1** with *p*-tolyl bromide (**2a**) in the presence of 20 mol-% pivalic acid (Method A), and with 2-bromopyridine (**2b**) in the presence of 5 mol-% copper bromide[17] (Method B), provided arylnitrones **3** in excellent yields. Methylation with excess methyl Grignard reagents (Method C or D) then gave access to hydroxylamines **4** in yields of 40–89%. In the case of chiral nitrones **3aa** and **3ab**, the diastereoselectivity of the addition reactions was excellent, as previously encountered:[17] Only one diastereomer was detected by ^{1}H NMR analysis of the crude reaction mixtures. The relative configurations of **4aa**[17] and **4ab**[19] (Figure 2) were determined by X-ray diffraction analysis: The methyl group was transferred *anti* to the bulky isopropyl group.

Table 1. Preparation of arylnitrones **3** and hydroxylamines **4**.

Nitrone **1**	ArBr **2**	**3**	Yield[a] (Method)[b]	**4**	Yield[a] (Method)[c]
1a	**2a**	**3aa**	99% (A)	**4aa**	89% (C)
1a	**2b**	**3ab**	97% (B)	**4ab**	73% (C)
1b	**2a**	**3ba**	99% (A)	**4ba**	40% (D)
1b	**2b**	**3bb**	81% (B)	**4bb**	89% (C)
1c	**2a**	**3ca**	88% (A)	**4ca**	55% (D)

[a] Isolated yield. [b] Reagents and conditions for direct arylation: ArBr (1.1 equiv.), K_2CO_3 (1.5 equiv.), anisole (1 M), 150 °C, 0.5–2 h. Method A: Pd (2 mol-%), PPh_3 (2 mol-%), PivOH (20 mol-%). Method B: Pd (2 mol-%), PPh_3 (2 mol-%), CuBr·DMS (5 mol-%), 1,10-phenanthroline (5 mol-%). [c] Reagents and conditions for methylation, Method C: MeMgCl (1.5–2.0 equiv.), THF, 15 min. Method D: MeMgI (2.0–3.5 equiv.), diethyl ether, 0 °C, 30 min.

The bis-methylated analogues **6a** and **6b** were prepared in moderate yields by an addition/oxidation/addition reaction sequence (Scheme 2).

There are literature precedents for the direct use of hydroxylamines as oxidation catalysts in place of their nitroxide counterparts.[20] Nevertheless, nitroxides **7aa**, **7ab**, **7ba**, and **8b** were prepared quantitatively by MnO_2 or *m*CPBA oxidation of the corresponding hydroxylamines **4aa**, **4ab**, **4ba**, and **6b**.[21] In the case of **7aa**, crystals suitable

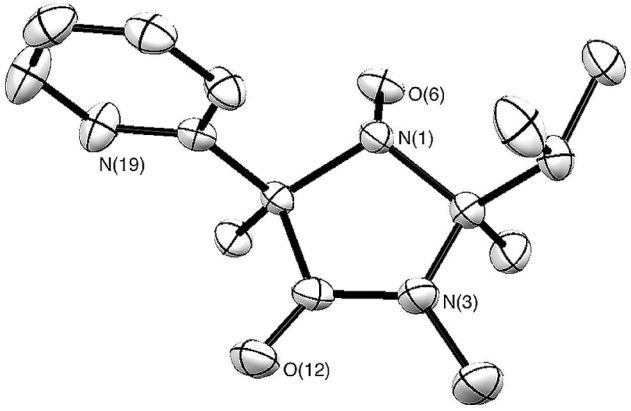


Figure 2. ORTEP drawing of hydroxylamine **4ab**. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.

for X-ray diffraction analysis were obtained (Figure 3).[22] The nitroxide N–O bond length is consistent with literature[23,13d] values (1.271 Å), but it is worth noting that the out-of-plane angle (between the N–O bond and the C–N–C plane) is 14.4°.[24] In previously reported crystal structures of five-membered cyclic nitroxides,[23,25] this angle ranges from 0 to 8°, with one exception, the geometrically strained bicyclic 1,5-dimethyl-8-azabicyclo[3,2,1]octan-3-one-8-oxyl (24.8°).[26] This suggests that nitroxide **7aa** could be geometrically strained as well because of the steric repulsion between the bulky isopropyl group and the aryl group.

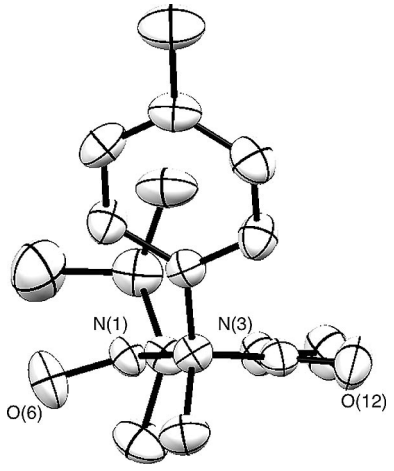


Figure 3. ORTEP drawing of nitroxide **7aa**. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.

Aerobic Oxidation of Benzyl Alcohol

The prepared hydroxylamines and nitroxides (Figure 4) were evaluated as catalysts in the oxidation of benzyl alcohol by molecular oxygen. We selected several co-catalysts that had been developed with TEMPO. Particular attention was paid to the oxidative capacity of these co-catalysts in the absence of nitroxide, as it could be detrimental to enantioselective oxidation. Representative results are presented in Table 2.

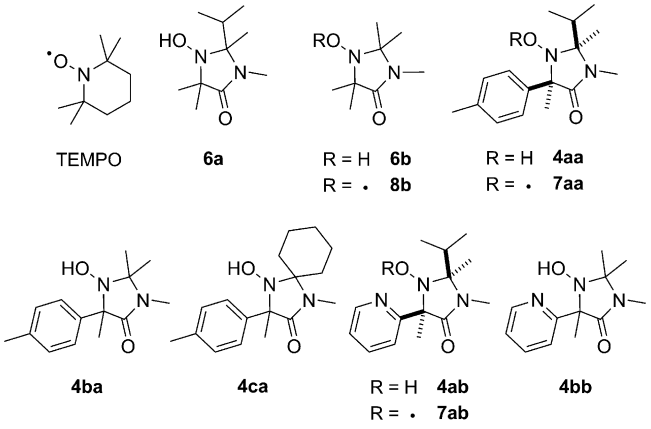


Figure 4. Hydroxylamines and nitroxides evaluated in the aerobic oxidation of benzyl alcohol.

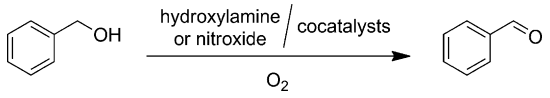
Co-catalytic System $CuBr_2$/*t*BuOK/bipy (Method E)

We started our study by using the conditions developed by Sheldon and co-workers (Method E),[9] namely a Cu^{II} salt with 2,2′-bipyridine as a ligand and KO*t*Bu as base. At 20–30 °C and under 1–4 bar O_2, the oxidation of benzyl alcohol was much slower in the presence of imidazolidinone-based hydroxylamines **6a** and **6b** than with TEMPO (Table 2, compare entries 7 and 9 vs. 1 and 2). When the reaction was performed at 80 °C under 4 bar O_2, with MiPNO-derived hydroxylamine **6a**, the reaction started sluggishly and stalled after a few hours (entry 8). On the other hand, **6b** and the corresponding nitroxide **8b** were found to catalyze cleanly the oxidation of benzyl alcohol to benzaldehyde: complete conversion was reached in less than 4 h (compare entries 11 and 12 vs. 6).

The same trends were observed with aryl-substituted hydroxylamines **4**. At ambient temperature, the oxidation of benzyl alcohol was slow (entries 16 and 23). At 80 °C, the catalysis was inefficient with isopropyl-bearing compounds **4aa** and **4ab** (entries 14 and 21), but led to complete conversion within a few hours with permethylated analogues **4ba** and **4bb** (entries 18 and 25). The case of hydroxylamine **4ca** with a spiro-cyclohexane moiety is intermediate: the reaction does not stall but is slower than with **4ba** (compare entries 19 vs. 18).

Interestingly, with 2-pyridyl-substituted **4bb**, and contrary to what is known with TEMPO,[9,27] the oxidation occurs even in the absence of the 2,2′-bipyridine ligand (entry 26), albeit slowly. A similar result was observed by Gartshore and Lupton with oxazolidine nitroxyl radicals.[8] It is believed that the pyridinyl nitrogen atom coordinates to the copper to help stabilize the active species.[28]

Table 2. Aerobic oxidation of benzyl alcohol using imidazolidinone-based hydroxylamine or nitroxide catalysts and different co-catalysts.



Entry	Cat.[a]	Method E[b] $CuBr_2$/*t*BuOK/bipy				Method F[c] $CuBr_2$/$NaNO_2$				Method G[d] HBr/TBN			
		T [°C]	*P* [bar]	*t* [h]	Conv.[e] [%]	*T* [°C]	*P* [bar]	*t* [h]	Conv.[e] [%]	*T* [°C]	*P* [bar]	*t* [h]	Conv.[e] [%]
1	TEMPO	20	P_{atm}	0.3	97	20	P_{atm}	3	89	20	P_{atm}	3	78
								5	100			5	100
2		30	4	0.3	100								
3		80	4	<1	100	80	4	1	100	80	4	1	100
4	None	20	P_{atm}	23	4	20	P_{atm}	24	3	20	P_{atm}	5	9
												21	11
5		30	4	14	3					30	4	14	6
6		80	4	14	<1	80	4	14	4	80	4	14	73
7	**6a**	30	4	14	10[f]					30	4	14	1
8		80	4	14	12[f]	80	4	14	6[f]				
9	**6b**	20	P_{atm}	5	8	20	P_{atm}	5	2	20	P_{atm}	3	88
				23	13			23	4			5	97
								48	7			21	100
10										30	4	14	100
11		80	4	3.5	100	80	4	14	49				
12	**8b**	80	4	3.5	100								
13	**4aa**									30	4	14	2
14		80	4	14	12[f]	80	4	14	6[f]				
15	**7aa**					80	4	14	8[f]				
16	**4ba**	20	P_{atm}	5	8	20	P_{atm}	5	2	20	P_{atm}	3	62
				23	13			23	4			5	82
								48	6			21	98
17										30	4	14	96
18		80	4	6	98	80	4	14	44				
19	**4ca**	80	4	14	70	80	4	14	32				
20	**4ab**									30	4	14	1
21		80	4	14	0	80	4	14	25[f]				
22	**7ab**					80	4	14	24[f]				
23	**4bb**	20	P_{atm}	5	9	20	P_{atm}	5	19	20	P_{atm}	3	3
				23	14			23	25			5	4
								48	37			21	9
24										30	4	14	5
25		80	4	6	91	80	4	4	100				
26		80	4	14	56[g]								

[a] Hydroxylamine or nitroxide used. [b] Method E: benzyl alcohol (1 mmol), catalyst (5 mol-%), $CuBr_2$ (5 mol-%), *t*BuOK (5 mol-%), 2,2′-bipyridine (5 mol-%) in MeCN/H_2O (2:1, 1 M). [c] Method F: benzyl alcohol (1 mmol), catalyst (5 mol-%), $CuBr_2$ (5 mol-%), $NaNO_2$ (5 mol-%) in $PhCF_3$ (1 M). [d] Method G: benzyl alcohol (1 mmol), catalyst (5 mol-%), HBr (5 mol-%), TBN (5 mol-%) in MeCN (1 M). [e] Conversion of benzyl alcohol, determined by GC analysis. [f] According to the monitoring of O_2 uptake, the reaction stalls within 1–3 h. [g] Reaction performed without 2,2′-bipyridine.

Co-catalytic System $CuBr_2$/$NaNO_2$ (Method F)

To further study the impact of a coordinating atom on the nitroxide activity, we investigated a copper-based co-catalytic system deriving from literature results:[29] $CuBr_2$/$NaNO_2$ (Method F). The TEMPO-catalyzed oxidation of benzyl alcohol proved efficient at room temperature as well as at 80 °C (Table 2, compare entries 1 vs. 4 and 3 vs. 6).[30]

The oxidation was less rapid in the presence of imidazolidinone-based hydroxylamines. After 14 h at 80 °C, only a modest 32% conversion was reached with **4ca** (entry 19). The reaction proved again to stall rapidly with isopropyl-bearing compounds **4/6/7a** (entries 8, 14, 15, 21, and 22), a maximum 25% conversion being obtained with **4/7ab**. Finally, the best results were found with **4/6b** (R^1 = R^2 = Me; entries 11, 18, and 25) with a striking beneficial effect of the 2-pyridyl group: Oxidation to benzaldehyde was complete in 4 h.[31]

Oxidation at room temperature under an atmospheric O_2 pressure was investigated with hydroxylamines **4/6b** (entries 9, 16, and 23) and proved much slower: A maximum 37% conversion was attained in 48 h with 2-pyridyl-substituted **4bb**.

Co-catalytic System HBr/TBN (Method G)

We sought a co-catalyst that would allow a faster oxidation of benzyl alcohol under mild conditions (20 °C, P_{atm}), and found that a combination of HBr and *tert*-butyl

nitrite (TBN; Method G)[32] was effective. When the oxidation of benzyl alcohol was carried out at 80 °C as originally described,[32] we observed a high level of background oxidation over time (entries 3 and 6). On the other hand, oxidation was limited at ambient temperature, whereas the conversion was complete in 5 h in the presence of TEMPO (entries 1, 4, and 5). Hardly any reaction occurred with isopropyl-substituted hydroxylamines **4/6a** (entries 7, 13, and 20), whereas complete conversion of benzyl alcohol was achieved within a day with hydroxylamines **6b** and **4ba** (entries 9, 16, and 17).

Imidazolidinone Nitroxides as Oxidation Catalyts − Conclusions

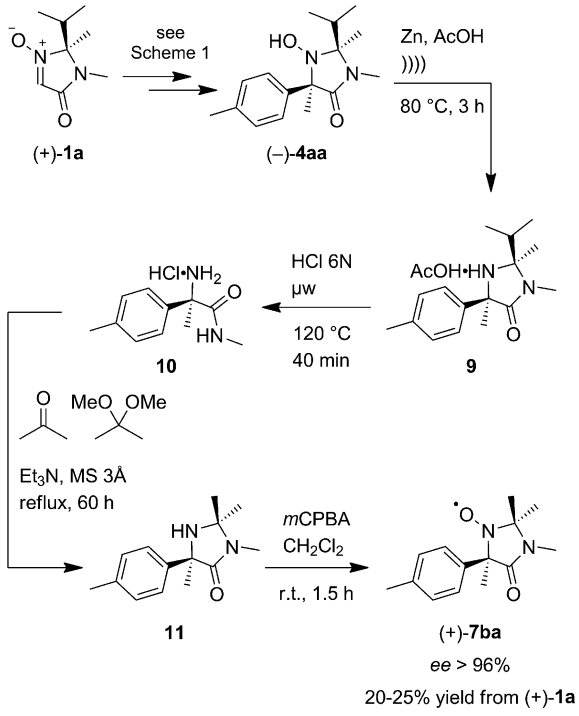
Several conclusions can be drawn from the above results. i. Imidazolidinone nitroxides or their hydroxylamine precursors are indeed able to catalyze the aerobic oxidation of benzyl alcohol. ii. The effect of nitroxide structure (piperidine vs. imidazolidin-4-one) and α,α′-substitution strongly depends on the co-catalytic system used. iii. The nature of the alkyl substituents at the α position is important for catalytic capability; the isopropyl group proved detrimental. iv. Compounds with an aryl group at the α′ position can be as efficient as their permethylated analogues, and even more efficient in the case of a 2-pyridyl group.

Moreover, the best results for the oxidation of benzyl alcohol at room temperature under an atmospheric O_2 pressure were obtained with the HBr/TBN co-catalytic system (Method G). These conditions were therefore selected for the first study of asymmetric oxidation.

Is Enantioselective Oxidation Possible with Imidazolidinone Nitroxides?

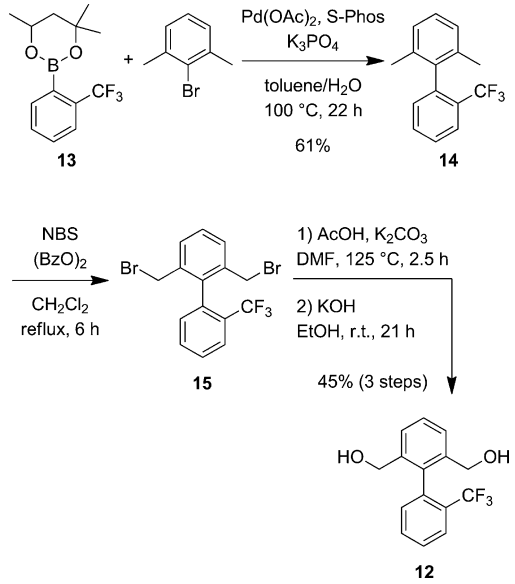
The above conclusions show that one of the original goals of this study, the application of enantiopure compounds **4a**, readily available from enantiopure MiPNO (**1a**), to enantioselective aerobic oxidation, could not be achieved directly. Nevertheless, hydroxylamines **4b** are also chiral, very easily accessed in racemic form, and resolution can be considered. We previously proposed a successful strategy for the resolution of such chiral hydroxylamines by *O*-acylation.[33] We therefore sought to obtain **4ba** in enantiopure form. However, our attempts towards resolution so far have failed. We therefore turned to a less elegant but straightforward synthesis of the corresponding nitroxide **7ba** (Scheme 3).

Enantiopure (+)-**3aa** and (–)-**4aa** were prepared from (+)-MiPNO (**1a**) according to Scheme 1. The N–O bond was reduced by using zinc in acetic acid under sonication and hydrolytic cleavage of the resulting aminal was performed over 40 min under microwave irradiation to cleanly give amino amide **10**. Subsequent reaction with acetone reinstalled the imidazolidinone ring. Finally, amine oxidation with *m*CPBA gave enantiopure nitroxide (+)-**7ba**. The global yield starting from (+)-**1a** was 20–25%.



Scheme 3. Preparation of enantiopure nitroxide (+)-**7ba**.

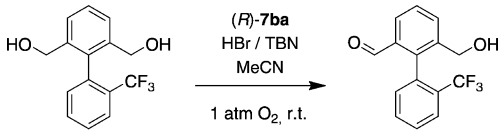
The increasing interest in atropisomerism in drug discovery[34] led us to investigate the atroposelective oxidative desymmetrization of a diol[35,36] to evaluate the enantiodifferentiating ability of imidazolidinone-based nitroxide (+)-**7ba**. Diol **12** was selected as a model and its synthesis is depicted in Scheme 4. Suzuki–Miyaura coupling[37] of readily prepared boronic ester **13**[38] and 2-bromo-*m*-xylene led to biaryl **14** in 61% unoptimized yield. Bromination of both benzylic positions followed by hydrolysis[39] gave diol **12** in 45% yield over three steps.



Scheme 4. Preparation of symmetrical diol **12**.

We then submitted diol **12** to oxidation in the presence of 5 mol-% **7ba**, HBr, and TBN under atmospheric O_2 pressure at room temperature (Table 3).

Table 3. Aerobic oxidation of diol **12** catalyzed by nitroxide (*R*)-**7ba**.[a]



12 **16**

Entry	Amount of (*R*)-**7ba** [mol-%]	Time [h]	Conv. of **12**[b] [%]	*ee* of **16**[c] [%]
1	0	24	2	–
		48[d]	4	–
		96[d]	8	–
2	5	24	12	36
		96[d]	39	24
3	20	24	22	44

[a] Reagents and conditions: Diol **12** (0.2 mmol), (*R*)-**7ba** (5 mol-%), HBr (5 mol-%), TBN (5 mol-%) in MeCN (0.2 M). [b] Conversion determined by ^{19}F NMR spectroscopy. [c] Enantiomeric excess determined by HPLC analysis. [d] Additional HBr (5 mol-%) and TBN (5 mol-%) were introduced into the reaction mixture every 24 h.

The reaction proved much slower than benzyl alcohol oxidation, and stalled after 1 day with 12% conversion and 36% *ee* (entry 2). Notably, daily additions of the same amounts of HBr and TBN caused the conversion to rise slowly to 39%.[40] The slight decrease in *ee* after 4 d is consistent with the occurrence of limited oxidation in the absence of **7ba** (entry 1). Another experiment with 20 mol-% of nitroxide **7ba** confirmed the trend (entry 3): The reaction stalled within a day, but having achieved a higher conversion (22 vs. 12%) and with a slight increase in the *ee*.[41] Thus, it is likely that the prime limitation of this catalytic system is the loss of the nitrogen oxide species that allows the reoxidation of the hydroxylamine by O_2 and thus the catalytic cycle to start again.[42] We are currently investigating other co-catalysts. A major conclusion, however, is that chiral imidazolidinone-based nitroxides can induce enantioselectivity in aerobic oxidation reactions.

Cyclic Voltammetry Study

The electrochemical behavior of nitroxide **8b** and hydroxylamines **4** and **6** (and TEMPO for comparison) was investigated by cyclic voltammetry (CV). Experiments were conducted under an inert atmosphere in a classical three-electrode cell with a glassy carbon disk as working electrode. Measurements were performed in acetonitrile/water (95:5, v/v) containing sodium perchlorate (0.2 M) as supporting electrolyte. 2,6-Lutidine was also added (8 equiv.) to be consistent with catalytic experiments (see below). The cyclovoltammetric data are listed in Table 4.

The CV curve of the nitroxyl radical **8b** (Figure 5, a) displays one reversible oxidation and one irreversible reduction at $E_{1/2}$ = +0.8 V and E_{pc} = –1.6 V, respectively. By analogy with reported studies of other nitroxyl radicals,[43] the oxidation wave has been assigned to the formation of the corresponding oxoammonium cation following a one-electron transfer (Scheme 5, a). Compared with TEMPO, the reversible $N{=}O^+/N{-}O^{\cdot}$ couple of **8b** appears at a significantly higher potential (Table 4, compare entries 2 vs. 1). This result is consistent with the presence of an electron-withdrawing group[43c,44] and also corroborates previous studies in which five-membered cyclic nitroxides were found to be more difficult to oxidize than six-membered-ring nitroxides.[43c] The reduction of **8b** at low potential has been attributed to the formation of the deprotonated hydroxylamine (Scheme 5, a).[45] It is known that this process strongly depends on the experimental conditions (pH, electrode material, solvent) because it can involve proton transfer coupled to electron exchange.[46,47]

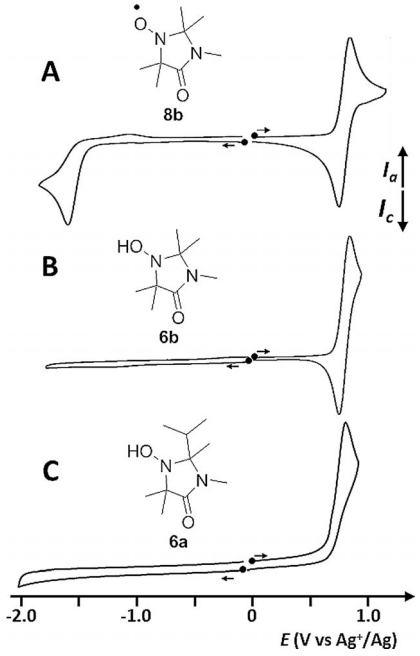
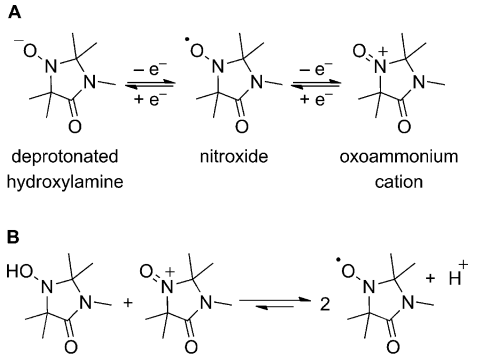


Figure 5. Cyclic voltammograms of a) **8b**, b) **6b**, and c) **6a** in 0.2 M $NaClO_4$ in acetonitrile/water (95:5, v/v) in the presence of 2,6-lutidine (8 equiv.). Working electrode: vitreous carbon; scan rate: 100 mV s^{-1}.

The cyclic voltammograms of the hydroxylamines **4** and **6** each exhibit only one oxidation process in the –2 to +1 V range, which has been attributed to the formation of the oxoammonium cation. The potentials of these oxidation signals logically vary with the nature and substitution of the rings, but remain close to +0.8 V (see Table 4 for data). However, as illustrated in Figure 5b,c, two different types of electrochemical behavior can be clearly identified, depending on the nature of the substituents.

In the case of the dimethyl- (**6b**, **4ba**, and **4bb**) and cyclohexyl-substituted (**4ca**) compounds, the oxidation process appears reversible with a well-defined reduction wave during the reverse scan and a peak separation ($E_{pa} - E_{pc}$) close



Scheme 5. a) One-electron oxidation and reduction of nitroxide **8b** and b) comproportionation reaction to give the nitroxyl radical.

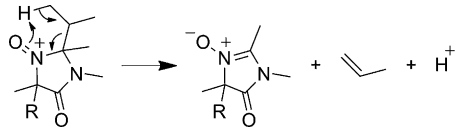
Table 4. Oxidation potentials for nitroxides, hydroxylamines, and TEMPO.

Entry	Compound	$E_{1/2}$ (ΔE_P)[a,b]
1	TEMPO	0.317 (0.085)
2	**8b**	0.800 (0.095)
3	**6b**	0.790 (0.085)
4	**4ba**	0.840 (0.075)
5	**4bb**	0.835 (0.080)
6	**4ca**	0.770 (0.075)
7	**6a**	0.843[c]
8	**4aa**	0.840[c]
9	**4ab**	0.846[c]

[a] $E_{1/2}$ [V] vs. $Ag/AgNO_3$, 10^{-2} M in CH_3CN. [b] $E_{1/2} = (E_{pa} + E_{pc})/2$ at 0.1 Vs^{-1}; $\Delta E_p = E_{pa} - E_{pc}$. [c] Oxidation peak potential (E_{pa}, irreversible process).

to 80 mV (see, for example, Figure 5, b). It is also important to note that the oxidation wave for **6b** appears at the same potential as the oxidation signal of the corresponding nitroxide **8b**. This behavior corroborates previous results,[43d,46,48] and can be explained by comproportionation reactions between the electrogenerated oxoammonium cations and the hydroxylamine moieties leading to the corresponding nitroxyl radical (Scheme 5, b). These results are in accordance with our catalytic experiments (Table 2) revealing that hydroxylamines **4** and **6** or their corresponding nitroxyl radicals **7** and **8** could be used indifferently as oxidation catalysts.

In contrast, the CV curves of the isopropyl-substituted compounds **6a**, **4aa**, and **4ab** exhibit one fully irreversible oxidation wave (see, for example, Figure 5, c) irrespective of the scan rate (voltammograms up to 10 Vs^{-1} have been recorded). Such irreversibility indicates that the electrogenerated isopropyl-containing oxoammonium cations are chemically unstable under the experimental conditions on the CV timescale because of the presence of chemical reactions coupled with electron transfer.[43b,43c,49] An analogous decrease in the stability of an oxoammonium cation when the α substituent is changed from methyl to ethyl or higher alkyl groups was recently pointed out by Coote and co-workers.[49] The proposed explanation[49] could be applied to our study; it would involve the evolution of propene and a new nitrone[50] (Scheme 6). We mentioned above that the isopropyl unit interacts sterically with the neighboring groups on the ring; elimination of propene would therefore be favored by steric decompression. The same elimination from the less encumbered spiro derivative **4ca** would be less favorable enthalpically and entropically. This instability of the oxoammonium unit is in total agreement with the poor catalytic properties of the isopropyl-containing systems.



Scheme 6. Hypothetical mechanism for the decomposition of the oxoammonium cation in the **4/6a** series.

To support our catalytic results, the influence of benzyl alcohol on the electrochemical behavior of the dimethyl- (**6b**, **4ba**, **4bb**) and cyclohexyl-substituted (**4ca**) hydroxylamines was examined. An example of the response is given in Figure 6. As expected, in all cases, upon addition of benzyl alcohol, the oxidation wave corresponding to the formation of the oxoammonium unit became fully irreversible and a gradual increase in the current was observed.[51] This behavior is typical of electrocatalytic processes,[52] that is, the electrogenerated oxoammonium rapidly reacts chemically with benzyl alcohol (this reaction being faster than the CV timescale) to regenerate the nitroxide moiety, which then re-enters the electrocatalytic cycle. Further investigations beyond the scope of this paper are underway to determine the kinetic parameters.

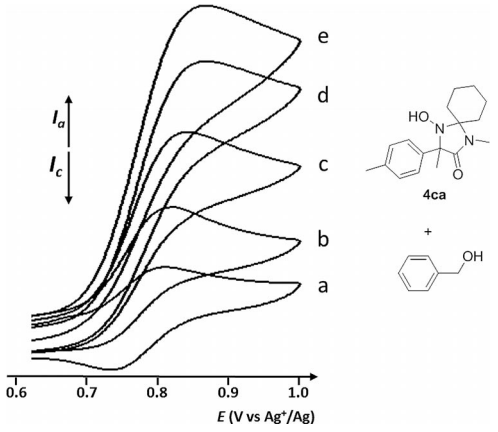


Figure 6. Cyclic voltammograms of **4ca** in the presence of a) 0 equiv., b) 0.5 equiv., c) 2 equiv., d) 5 equiv., and e) 8 equiv. of benzyl alcohol. Data were recorded in 0.2 M $NaClO_4$ in acetonitrile/water (95:5, v:v) in the presence of 2,6-lutidine (8 equiv.). Working electrode: vitreous carbon; scan rate: 100 mVs^{-1}.

Conclusions

Various hydroxylamines and nitroxides with an imidazolidin-4-one skeleton have been prepared from cyclic nitrones in a straightforward reaction sequence. Both types of species catalyze the aerobic oxidation of benzyl alcohol. In some cases, rapid oxidation to benzaldehyde could even be achieved at room temperature under atmospheric O_2 pressure. Regarding the substitution of the imidazolidinone

ring, and by comparison with the permethylated analogue, an aryl group is viable. The catalyst can be readily modified by the direct C–H arylation of nitrones **1**.[17] On the other hand, an isopropyl substituent seems detrimental to the reaction. A cyclic voltammetry study indicated poor stability of the corresponding oxoammonium cation, which could explain its poor catalytic properties. It should be underlined, however, that the extent of the substituent effect was dependent on the co-catalytic system used. In particular, an interesting synergy between a 2-pyridyl substituent and a Cu-based co-catalyst was observed. Work is underway to take advantage of this cooperative effect. Finally, in the case of an enantiopure imidazolidinone nitroxide, very promising results were obtained in the atroposelective oxidative desymmetrization of a diol.

Experimental Section

General: All experiments were carried out under nitrogen in oven-dried glassware equipped with a magnetic stirring bar. Standard inert-atmosphere techniques were used to handle all air- and moisture-sensitive reagents. THF and Et_2O were freshly distilled from sodium benzophenone ketyl, and CH_2Cl_2 and DMF from CaH_2. Anisole was washed with 10% aqueous NaOH and water, dried with magnesium sulfate, distilled, stored, and handled under N_2. Palladium sources were stored in a desiccator and weighed out in air. All other reagents and solvents were purchased from commercial sources and used as received.

Product purifications by dry-column vacuum chromatography[53] were performed using Macherey–Nagel silica gel 60 (0.015–0.04 mm) and gradient elution: cyclohexane/ethyl acetate (10:0 to 0:10), then ethyl acetate/ethanol (10:0 to 9:1).

For optical rotations [*a*], the corresponding concentration is given in g per 100 cm^{-3}. IR spectra were recorded by using ATR (attenuated total reflection). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (standard for ^1H spectra: tetramethylsilane, $\delta_H = 0.0$ ppm; standard for ^{13}C spectra: $CDCl_3$, $\delta_C = 77.16$ ppm) or [D_4]MeOH (standard for ^1H NMR spectra: CHD_2OD $\delta_H = 3.31$ ppm). Multiplicities are given as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), sept (septet), m (multiplet), br. (broad). Coupling constants (*J*) are given in Hertz.

Preparation of Nitrones 1: Nitrones **1** were prepared by using a previously described sequence,[18] starting from a glycine derivative and a ketone. The synthesis of **1b** is reported below, the preparations of **1a**[18b] and **1c**[16d] have been described elsewhere.

1,2,2-Trimethyl-5-oxo-2,5-dihydro-1*H*-imidazole 3-Oxide (1b): In a 250-mL round-bottomed flask, glycine ethyl ester hydrochloride (40.7 g, 0.292 mol) was added in one portion to a 40% aqueous solution of methylamine (102 mL) and the solution was stirred overnight. Excess methylamine and water were eliminated by repeated co-evaporations with EtOH to yield a white sticky solid (51 g). Acetone (100 mL) and triethylamine (60 mL) were added, and the flask was fitted with a Soxhlet extractor filled with activated molecular sieves (4 Å, 110 g). After heating at reflux for 3 h, the reaction mixture was concentrated, and then EtOAc (200 mL) and triethylamine (3 mL) were added. The precipitate (triethylamine hydrochloride) was filtered and rinsed with EtOAc. Concentration of the filtrate yielded 2,2,3-trimethylimidazolidin-4-one as a brown oil (43.8 g). EtOH (100 mL) and a solution of $Na_2WO_4{\cdot}2H_2O$ (4.4 g) in water (6 mL) was added. The flask was plunged into a water bath at 15 °C and a 35% solution of H_2O_2 in water (75 mL) was added dropwise over 3 h, keeping the reaction temperature below 50 °C. Stirring was continued for 1 h and then small portions of MnO_2 were added to destroy the excess peroxides until the end of O_2 evolution. EtOH was evaporated, the mixture was dissolved in EtOAc (400 mL), decanted, and washed with brine. After drying over Na_2SO_4 and concentration, nitrone **1b** was recovered as a yellow solid (35.1 g, 85%). Recrystallization in acetone yielded analytically pure **1b** (m.p. 103–104 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.04 (s, 1 H, *H*C=N), 3.02 (s, 3 H, CH_3N), 1.64 (s, 6 H, CH_3C) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.6 (*C*O), 123.9 (*C*H=N), 89.7 [*C*$(CH_3)_2$], 25.3 (*C*H_3N), 23.8 [(*C*H_3)$_2$C] ppm. IR: $\tilde{\nu}$ = 3120, 3092, 2990, 1690, 1561 cm^{-1}. LRMS (ESI^+): *m*/*z* = 143 $[M + H]^+$, 165.0 $[M + Na]^+$. $C_6H_{10}N_2O_2$ (142.16): calcd. C 50.68, H 7.10, N 19.71; found C 50.25, H 7.02, N 19.87.

Preparation of Arylnitrones 3: Arylnitrones **3** were prepared by direct C–H arylation of nitrones **1** using Method A or B. The preparations of **3aa** and **3ab** have been described elsewhere.[17]

Method A – Coupling Reactions Between Nitrones 1a–c and 4-Bromotoluene (2a): A Schlenk flask under N_2 was charged with nitrone **1**, 4-bromotoluene (**2a**; 1.1 equiv.), [Pd_2(dba)$_3$] (1 mol-%; i.e., 2 mol-% Pd), triphenylphosphine (2 mol-%), pivalic acid (0.2 equiv.), and K_2CO_3 (1.5 equiv.). The flask was evacuated and purged with N_2, and anisole was added to give a 1.0 M solution. The Schlenk flask was plunged into a 150 °C preheated oil bath, and the reaction was monitored by ^1H NMR analysis of small aliquots. After completion of the reaction (<2 h), the crude solution was purified over silica gel to give the arylnitrone.

Method B – Coupling Reactions Between Nitrones 1a–c and 2-Bromopyridine (2b): A Schlenk flask under N_2 was charged with nitrone **1**, 2-bromopyridine (**2b**; 1.1 equiv.), [Pd_2(dba)$_3$] (1 mol-%; i.e., 2 mol-% Pd), triphenylphosphine (2 mol-%), CuBr·DMS (5 mol-%), 1,10-phenanthroline (5 mol-%), and K_2CO_3 (1.5 equiv.). The flask was evacuated and purged with N_2, and anisole was added to give a 1.0 M solution. The Schlenk flask was plunged into a 150 °C preheated oil bath, and the reaction was monitored by ^1H NMR analysis of small aliquots. After completion of the reaction (<2 h), the crude solution was purified over silica gel to give the arylnitrone.

1,2,2-Trimethyl-5-oxo-4-(*p*-tolyl)-2,5-dihydro-1*H*-imidazole 3-Oxide (3ba): The title compound was prepared according to Method A from **1b** (1.42 g, 10 mmol) and 4-bromotoluene (**2a**; 1.88 g, 11 mmol) to give a yellow solid (2.30 g, 99%), m.p. 117–118 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 8.4 Hz, 2 H, C$H_{ar\ ortho}$), 7.27 (d, *J* = 8.4 Hz, 2 H, C$H_{ar\text{-}m}$), 3.10 (s, 3 H, CH_3N), 2.40 (s, 3 H, CH_3-Ar), 1.69 (s, 6 H, CH_3C) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.1 (*C*O), 141.5 (C_{ipso}-Me), 129.9 (*C*=N), 129.1 (*C*$H_{ar\text{-}o}$), 127.6 (*C*$H_{ar\text{-}m}$), 123.6 (C_{ipso}), 86.7 [*C*$(CH_3)_2$], 25.5 (*C*H_3N), 24.3 [(*C*H_3)$_2$C], 21.9 (*C*H_3-Ar) ppm. IR: $\tilde{\nu}$ = 3075, 2995, 2932, 2910, 1701, 1550, 1501, 1435, 1355 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{17}N_2O_2$ $[M + H]^+$ 233.1285; found 233.1289.

1,2,2-Trimethyl-5-oxo-4-(pyridin-2-yl)-2,5-dihydro-1*H*-imidazole 3-Oxide (3bb): The title compound was prepared according to Method B from **1b** (156 mg, 1.1 mmol) and 2-bromopyridine (**2b**; 158 mg, 1.0 mmol) as a yellow solid (166 mg, 81%), m.p. 125–126 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.89–8.82 (m, 1 H, CH_{ar}-N), 8.44 (dt, *J* = 7.9, 0.9 Hz, 1 H, C$H_{ar\text{-}o}$), 7.82 (td, *J* = 7.9, 1.8 Hz, 1 H, C$H_{ar\text{-}m}$), 7.34 (ddd, *J* = 7.9, 4.8, 1.1 Hz, 1 H, C$H_{ar\text{-}p}$), 3.12 (s, 3 H, CH_3N), 1.72 (s, 6 H, CH_3C) ppm. ^{13}C NMR (101 MHz,

$CDCl_3$): δ = 160.9 (*C*O), 150.2 (*C*H$_{ar\text{-}o}$), 145.7 (C_{ipso}), 136.4 (*C*H$_{ar\text{-}p}$), 130.2 (*C*=N), 124.60 (*C*H$_{ar}$), 124.57 (*C*H$_{ar}$), 88.0 [*C*-(CH$_3$)$_2$], 25.6 (*C*H$_3$N), 24.3 [(*C*H$_3$)$_2$C] ppm. IR: $\tilde{\nu}$ = 3110, 3060, 2993, 2933, 2790, 1698, 1574, 1548, 1428, 1385, 1358 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{14}N_3O_2$ [M + H]$^+$ 220.1081; found 220.1085.

4-Methyl-3-oxo-2-(*p*-tolyl)-1,4-diazaspiro[4.5]dec-1-ene 1-Oxide (3ca): The title compound was prepared according to Method A from **1c** (1.00 g, 5.5 mmol) and 4-bromotoluene (**2a**; 0.85 g, 5 mmol) as a beige solid (1.20 g, 88%), m.p. 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 8.4 Hz, 2 H, C*H*$_{ar\text{-}o}$), 7.27 (d, *J* = 8.4 Hz, 2 H, C*H*$_{ar\text{-}m}$), 3.17 (s, 3 H, C*H*$_3$N), 2.39 (s, 3 H, C*H*$_3$-Ar), 2.33–2.20 (m, 2 H, C*H* cy), 2.19–2.07 (m, 2 H, C*H* cy), 1.94–1.83 (m, 2 H, C*H* cy), 1.83–1.66 (m, 3 H, C*H* cy), 1.59–1.46 (m, 1 H, C*H* cy) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.6 (*C*O), 141.2 (C_{ipso}-Me), 129.7 (*C*=N), 129.0 (*C*H$_{ar\text{-}o}$), 127.6 (*C*H$_{ar\text{-}m}$), 123.6 (C_{ipso}), 86.8 (C_{spiro}), 34.0 (*C*H$_2$ cy), 26.6 (*C*H$_3$N), 23.9 (*C*H$_2$ cy), 21.84 (*C*H$_3$-Ar), 21.76 (*C*H$_2$ cy) ppm. IR: $\tilde{\nu}$ = 3034, 2947, 2925, 2865, 1685, 1559 cm^{-1}. LRMS (DCI): *m*/*z* = 273.3 [M + H]$^+$. $C_{16}H_{20}N_2O_2$ (272.35): calcd. C 70.55, H 7.42, N 10.29; found C 70.80, H 7.58, N 10.44.

Preparation of Hydroxylamines 4: Hydroxylamines **4** were prepared by methylation of arylnitrones **3** using Method C or D.

Method C − Nitrone Methylation with MeMgCl in THF: MeMgCl (1.5–2.0 equiv.) in THF was rapidly added to a stirred solution of nitrone **3** in anhydrous THF (0.5–1.0 M) at room temperature (water bath) under N_2. The mixture was stirred for 15 min and quenched by the addition of a saturated ammonium chloride solution. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified over silica gel to give the desired hydroxylamine.

Method D − Nitrone Methylation with MeMgI in Diethyl Ether: MeMgI (2.0–3.5 equiv.) in Et_2O was added dropwise to a stirred solution of nitrone **3** in anhydrous Et_2O (0.1 M) at 0 °C under N_2 and immediate precipitation took place. The mixture was stirred for 30 min at room temperature and quenched by the addition of a saturated ammonium chloride solution. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified over silica gel to give the desired hydroxylamine.

(*rac*)-(2*S,5*R**)-1-Hydroxy-2-isopropyl-2,3,5-trimethyl-5-(*p*-tolyl)-imidazolidin-4-one (4aa):** The title compound was prepared according to Method C from **3aa** (2.42 g, 9.3 mmol) and methylmagnesium chloride (2.6 M, 7.2 mL, 18.6 mmol) as a pale-yellow solid (2.28 g, 89% yield), m.p. 160–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.3 Hz, 2 H, C*H*$_{ar\text{-}o}$), 7.16 (d, *J* = 8.3 Hz, 2 H, C*H*$_{ar\text{-}m}$), 4.36 (s, 1 H, O*H*), 2.81 (s, 3 H, C*H*$_3$N), 2.33 (s, 3 H, C*H*$_3$-Ar), 2.00–1.83 (m, 1 H, C*H* *i*Pr), 1.71 (s, 3 H, C*H*$_3$-C-Ar), 1.56 (s, 3 H, C*H*$_3$-C-*i*Pr), 1.10 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$ *i*Pr), 0.84 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$ *i*Pr) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.9 (*C*O), 139.9 (C_{ipso}), 136.4 (C_{ipso}-Me), 128.5 (*C*H$_{ar\text{-}m}$), 126.2 (*C*H$_{ar\text{-}o}$), 83.7 [*C*(Me)-*i*Pr], 68.8 [*C*(Me)-Ar], 36.9 (*C*H *i*Pr), 25.4 (*C*H$_3$N), 20.7 (*C*H$_3$-Ar), 19.9 (*C*H$_3$-C-Ar), 17.9 (*C*H$_3$-C-*i*Pr), 17.6 (*C*H$_3$ *i*Pr), 16.7 (*C*H$_3$ *i*Pr) ppm. IR: $\tilde{\nu}$ = 3319, 2971, 2938, 1666, 1429, 1368 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{25}N_2O_2$ [M + H]$^+$ 277.1911; found 277.1914.

Compound (2*S*,5*R*)-**4aa** was prepared according to Methods A and D from (*S*)-**1a** (1.4 g, 9.9 mmol) and 4-bromotoluene (**2a**; 1.88 g, 11 mmol) as a yellow-white solid (1.95 g, 76%), m.p. 168–169 °C. $[\alpha]_D^{20}$ = –111.7 (*c* = 0.46, $CHCl_3$).

(*rac*)-(2*S,5*R**)-1-Hydroxy-2-isopropyl-2,3,5-trimethyl-5-(pydridin-2-yl)imidazolidin-4-one (4ab):** The title compound was prepared according to Method C from **3ab** (2.29 g, 9.3 mmol) and methylmagnesium chloride (2.6 M, 5.3 mL, 13.9 mmol) as a brown solid (1.79 g, 73%), m.p. 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 4.3 Hz, 1 H, C*H*$_{ar}$-N), 7.70 (d, *J* = 8.0 Hz, 1 H, C*H*$_{ar\text{-}o}$), 7.66–7.59 (m, 1 H, C*H*$_{ar\text{-}m}$), 7.19–7.09 (m, 1 H, C*H*$_{ar\text{-}p}$), 5.32 (s, 1 H, O*H*), 2.85 (s, 3 H, C*H*$_3$N), 1.98–1.84 (m, 1 H, C*H* *i*Pr), 1.77 (s, 3 H, C*H*$_3$-C-Ar), 1.57 (s, 3 H, C*H*$_3$-C-*i*Pr), 1.07 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$ *i*Pr), 0.77 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$ *i*Pr) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.6 (*C*O), 162.0 (C_{ipso}), 149.0 (*C*H$_{ar}$-N), 136.4 (*C*H$_{ar\text{-}m}$), 122.2 (*C*H$_{ar\text{-}o}$), 120.7 (*C*H$_{ar\text{-}p}$), 83.9 [*C*(Me)-*i*Pr], 70.6 [*C*(Me)-Ar], 36.0 (*C*H *i*Pr), 25.7 (*C*H$_3$N), 19.7 (*C*H$_3$-C-Ar), 18.1 (*C*H$_3$-C-*i*Pr), 17.7 (*C*H$_3$ *i*Pr), 16.8 (*C*H$_3$ *i*Pr) ppm. IR: $\tilde{\nu}$ = 3271, 2986, 2936, 2885, 1675, 1470, 1425, 1372 cm^{-1}. LRMS (ESI$^+$): *m*/*z* = 564.1 [M + H]$^+$. $C_{14}H_{21}N_3O_2$ (263.34): calcd. C 63.84, H 8.05, N 15.96; found C 63.82, H 8.03, N 15.81. On storage, spontaneous recrystallization by sublimation provided white crystals suitable for X-ray analysis.[19]

1-Hydroxy-2,2,3,5-tetramethyl-5-(*p*-tolyl)imidazolidin-4-one (4ba): The title compound was prepared according to Method D from **3ba** (117 mg, 0.5 mmol) and methylmagnesium iodide (1.0 M, 1.00 mL, 1.0 mmol) as a yellow solid (50 mg, 40%), m.p. 146–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.1 Hz, 2 H, C*H*$_{ar\text{-}o}$), 7.14 (d, *J* = 8.1 Hz, 2 H, C*H*$_{ar\text{-}m}$), 5.22 (br. s, 1 H, O*H*), 2.87 (s, 3 H, C*H*$_3$N), 2.32 (s, 3 H, C*H*$_3$-Ar), 1.71 (s, 3 H, C*H*$_3$-C-Ar), 1.49 (s, 3 H, C*H*$_3$C), 1.31 (s, 3 H, C*H*$_3$C) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6 (*C*O), 139.3 (C_{ipso}), 137.2 (C_{ipso}-Me), 129.0 (*C*H$_{ar\text{-}m}$), 126.9 (*C*H$_{ar\text{-}o}$), 81.1 [*C*(CH$_3$)$_2$], 69.8 [*C*(Me)-Ar], 26.0 (*C*H$_3$-C-CH$_3$), 25.3 (*C*H$_3$N), 22.0 (*C*H$_3$-C-Ar), 21.1 (*C*H$_3$-Ar), 20.6 (CH$_3$-C-*C*H$_3$) ppm. IR: $\tilde{\nu}$ = 3285, 2987, 2936, 2860, 1666, 1434, 1402, 1379, 1362 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{21}N_2O_2$ [M + H]$^+$ 249.1598; found 249.1601.

1-Hydroxy-2,2,3,5-tetramethyl-5-(pyridin-2-yl)imidazolidin-4-one (4bb): The title compound was prepared according to Method C from **3bb** (811 mg, 3.7 mmol) and methylmagnesium chloride (2.5 M, 2.2 mL, 5.6 mmol) as an orange oil (777 mg, 89%) that crystallized upon standing, m.p. 116–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (br. s, 1 H, O*H*), 8.45 (d, *J* = 4.6 Hz, 1 H, C*H*$_{ar}$-N), 7.77–7.58 (m, 2 H, C*H*$_{ar}$), 7.23–7.07 (m, 1 H, C*H*$_{ar\text{-}p}$), 2.86 (s, 3 H, C*H*$_3$N), 1.77 (s, 3 H, C*H*$_3$-C-Ar), 1.48 (s, 3 H, C*H*$_3$C), 1.27 (s, 3 H, C*H*$_3$C) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1 (*C*O), 162.4 (C_{ipso}), 147.3 (*C*H$_{ar}$), 136.9 (*C*H$_{ar}$), 122.2 (*C*H$_{ar}$), 121.8 (*C*H$_{ar}$), 80.1 [*C*(CH$_3$)$_2$], 67.9 [*C*(Me)-Ar], 25.0 (*C*H$_3$N), 23.7 (*C*H$_3$-C-Ar), 23.2 (*C*H$_3$-C-CH$_3$), 22.7 (CH$_3$-C-*C*H$_3$) ppm. IR: $\tilde{\nu}$ = 3153, 3003, 2865, 1682, 1594, 1425, 1400, 1366 cm^{-1}. LRMS (ESI$^+$): *m*/*z* = 236.2 [M + H]$^+$, 258.1 [M + Na]$^+$. $C_{12}H_{17}N_3O_2$ (235.29): calcd. C 61.24, H 7.30, N 17.86; found C 60.76, H 7.38, N 17.79.

4-Hydroxy-1,3-dimethyl-3-(*p*-tolyl)-1,4-diazaspiro[4.5]decan-2-one (4ca): The title compound was prepared according to Method D from **3ca** (136 mg, 0.5 mmol) and methylmagnesium iodide (1.7 M, 1.03 mL, 1.75 mmol) as a yellow solid (80 mg, 55%), m.p. 180–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.1 Hz, 2 H, C*H*$_{ar\text{-}o}$), 7.08 (d, *J* = 8.1 Hz, 2 H, C*H*$_{ar\text{-}m}$), 5.03 (s, 1 H, O*H*), 2.82 (s, 3 H, C*H*$_3$N), 2.44–2.24 (m, 1 H, C*H* cy), 2.30 (s, 3 H, C*H*$_3$-Ar), 1.84–1.46 (m, 6 H, C*H* cy), 1.62 (s, 3 H, C*H*$_3$-C-Ar), 1.41–1.06 (m, 2 H, C*H* cy), 0.98–0.88 (m, 1 H, C*H* cy) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.6 (*C*O), 141.9 (C_{ipso}), 136.7 (C_{ipso}-Me), 129.0 (*C*H$_{ar\text{-}o}$), 125.6 (*C*H$_{ar\text{-}m}$), 84.5 (C_{spiro}), 73.1 [*C*(Me)-Ar], 33.5 (*C*H$_2$ cy), 31.7 (*C*H$_2$ cy), 25.8 (*C*H$_3$N), 25.08 (*C*H$_2$ cy), 25.04 (*C*H$_3$-C-Ar), 23.2 (*C*H$_2$ cy), 22.7 (*C*H$_2$ cy), 21.1 (*C*H$_3$-Ar) ppm. IR: $\tilde{\nu}$ =

3368, 2977, 2922, 2857, 1672, 1474, 1403, 1360 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{25}N_2O_2$ $[M + H]^+$ 289.1911; found 289.1910.

Preparation of Methylnitrones 5

2-Isopropyl-1,2,4-trimethyl-5-oxo-2,5-dihydro-1*H*-imidazole 3-Oxide (5a): MiPNO (**1a**; 2.55 g, 15 mmol) was methylated with methylmagnesium chloride (2.6 M, 6.35 mL, 16.5 mmol) according to Method C. The crude hydroxylamine was dissolved in CH_2Cl_2 (13 mL) and MnO_2 (2.73 g, 31.5 mmol) was added. The reaction mixture was stirred for 1.5 h and then the solvent was removed under reduced pressure. The crude material was purified over silica gel to give the desired nitrone as a yellow oil (1.52 g, 65%). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.03 (s, 3 H, CH_3N), 2.41–2.28 (m, 1 H, C*H* *i*Pr), 2.12 (s, 3 H, CH_3-C=N), 1.65 (s, 3 H, CH_3-C-*i*Pr), 0.98 (d, J = 6.7 Hz, 3 H, CH_3 *i*Pr), 0.94 (d, J = 6.8 Hz, 3 H, CH_3 *i*Pr) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.5 (*C*O), 134.6 (*C*=N), 92.0 [*C*(Me)-*i*Pr], 34.4 (*C*H *i*Pr), 26.5 (*C*H_3N), 21.3 (*C*H_3-C-*i*Pr), 16.2 (*C*H_3 *i*Pr), 15.6 (*C*H_3 *i*Pr), 7.6 (CH_3-C=N) ppm. IR: $\tilde{\nu}$ = 3556, 2968, 2875, 1701, 1590, 1252 cm^{-1}. HRMS (ESI): calcd. for $C_9H_{17}N_2O_2$ $[M + H]^+$ 185.1285; found 185.1290.

1,2,2,4-Tetramethyl-5-oxo-2,5-dihydro-1*H*-imidazole 3-Oxide (5b): Compound **1b** (2 mmol) was methylated with methylmagnesium chloride (1.33 M, 2.3 mL, 3 mmol) according to Method C. The crude hydroxylamine was dissolved in CH_2Cl_2 (15 mL) and MnO_2 (0.435 g, 5 mmol) was added. The reaction mixture was stirred overnight, filtered through Celite, and the filtrate concentrated. The crude material was purified over silica gel to give the desired nitrone as a yellow oil (0.179 g, 57%) that crystallized upon standing, m.p. 123–125 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.04 (s, 3 H, CH_3N), 2.13 (s, 3 H, CH_3-C=N), 1.62 [s, 6 H, (CH_3)$_2$C] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (*C*O), 133.8 (*C*=N), 87.7 [*C*(CH$_3$)$_2$], 25.4 (*C*H$_3$N), 23.9 [(CH$_3$)$_2$C], 8.0 (*C*H$_3$-C=N) ppm. IR: $\tilde{\nu}$ = 2990, 1693, 1597 cm^{-1}. HRMS (ESI): calcd. for $C_7H_{13}N_2O_2$ $[M + H]^+$ 157.0972; found 157.0975.

Preparation of Hydroxylamines 6

1-Hydroxy-2-isopropyl-2,3,5,5-tetramethylimidazolidin-4-one (6a): The title compound was prepared according to Method C from **5a** (523 mg, 2.8 mmol) in THF (10 mL) and methylmagnesium chloride (2.6 M, 3.6 mL, 9.3 mmol) as a beige solid (936 mg, 60%), m.p. 97–98 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.53 (s, 1 H, O*H*), 2.75 (s, 3 H, CH_3N), 1.89–1.77 (m, 1 H, C*H* *i*Pr), 1.45 (s, 3 H, CH_3-C-*i*Pr), 1.30 [s, 3 H, (CH_3)$_2$C], 1.29 [s, 3 H, (CH_3)$_2$C], 1.03 (d, J = 6.9 Hz, 3 H, CH_3 *i*Pr), 0.77 (d, J = 6.6 Hz, 3 H, CH_3 *i*Pr) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.9 (*C*O), 83.8 [*C*(Me)-*i*Pr], 64.4 [*C*(CH$_3$)$_2$], 35.5 (*C*H *i*Pr), 25.6 (*C*H$_3$-C-CH$_3$), 25.4 (*C*H$_3$N), 20.4 (CH$_3$-C-*C*H$_3$), 17.9 (*C*H$_3$-C-*i*Pr), 17.7 (*C*H$_3$ *i*Pr), 16.3 (*C*H$_3$ *i*Pr) ppm. IR: $\tilde{\nu}$ = 3354, 2970, 2932, 2879, 1663, 1479, 1400 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{21}N_2O_2$ $[M + H]^+$ 201.1598; found 201.1600.

1-Hydroxy-2,2,3,5,5-pentamethylimidazoldin-4-one (6b): The title compound was prepared according to Method C from **5b** (2.34 g, 15 mmol) and methylmagnesium chloride (3.0 M, 6.0 mL, 18 mmol) as a yellow-brown solid (1.45 g, 68%), m.p. 173–174 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.86 (br. s, 1 H, O*H*), 2.82 (s, 3 H, CH_3N), 1.38 [s, 6 H, (CH_3)$_2$-C-N], 1.31 [s, 6 H, (CH_3)$_2$-C-CO] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9 (*C*O), 79.7 (N-*C*-N), 63.4 (*C*-CO), 24.4 (*C*H$_3$N), 23.4 [(*C*H$_3$)$_2$-C-N], 22.5 [(*C*H$_3$)$_2$-C-CO] ppm. IR: $\tilde{\nu}$ = 3178, 2983, 2932, 2856, 1666, 1501, 1438, 1405, 1365 cm^{-1}. LRMS (ESI^+): m/z = 173.1 $[M + H]^+$, 195.0 $[M + Na]^+$. $C_{12}H_{17}N_3O_2$ (235.29): calcd. C 55.80, H 9.37, N 16.27; found C 55.73, H 9.33, N 16.70.

Preparation of Nitroxides 7 and 8

Oxidation of Hydroxylamines to Nitroxides

Method 1: The hydroxylamine (0.5 mmol) and *m*CPBA (0.5 mmol) were dissolved in CH_2Cl_2 (5 mL) and stirred at 20 °C for 1 h. MnO_2 (50 mg) was added and stirring was continued for 15 min to destroy the excess peroxides and the solvent was evaporated. The residue was taken up in EtOAc (20 mL) and washed with a saturated aqueous solution of K_2CO_3. The organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield the nitroxide.

Method 2: MnO_2 (1 mmol) was added to a solution of hydroxylamine (0.5 mmol) in CH_2Cl_2 (5 mL). The suspension was stirred at room temperature for 16 h, diluted in CH_2Cl_2 (15 mL), filtered through Celite, and concentrated under reduced pressure to yield the nitroxide.

(*rac*)-(2*S,5*R**)-2-Isopropyl-2,3,5-trimethyl-5-(*p*-tolyl)imidazolidin-4-one-1-oxyl (7aa):** The title compound was prepared according to Method 1 from **4aa** (138 mg, 0.5 mmol) as a yellow oil (120 mg).[54] The product was used directly in the oxidation reactions. Slow evaporation of a solution **7aa** in ethanol yielded crystals suitable for X-ray analysis.[22] HRMS (ESI): calcd. for $C_{16}H_{24}N_2O_2$ $[M + H]^{\cdot+}$ 276.1832; found 276.1835.

(*rac*)-(2*S,5*R**)-2-Isopropyl-2,3,5-trimethyl-5-(pyridin-2-yl)imidazolidin-4-one-1-oxyl (7ab):** The title compound was prepared according to Method 2 from **4ab** (526 mg, 2 mmol) as a red oil (522 mg).[54] The product was used directly in the oxidation reactions. HRMS (ESI): calcd. for $C_{14}H_{21}N_3O_2$ $[M + H]^{\cdot+}$ 263.1628; found 263.1636.

2,2,3,5,5-Pentamethylimidazolidin-4-one-1-oxyl (8b): The title compound was prepared according to Method 2 from **6b** (142 mg, 1 mmol) as an orange solid (140 mg), m.p. 65–66 °C.[54] The product was used directly in the oxidation reactions. HRMS (ESI): calcd. for $C_8H_{16}N_2O_2$ $[M + H]^{\cdot+}$ 172.1206; found 172.1211.

(*R*)-2,2,3,5-Tetramethyl-5-(*p*-tolyl)imidazolidin-4-one-1-oxyl [(*R*)-7ba]: Four consecutive steps were telescoped to synthesize the desired product from hydroxylamine (2*S*,5*R*)-**4aa**.

Zinc dust (8.10 g, 124 mmol) was added to a solution of (2*S*,5*R*)-**4aa** (1.71 g, 6.2 mmol) in glacial AcOH (10 mL). The suspension was sonicated at 80 °C for 3 h, filtered through Celite, and the filtrate was evaporated under reduced pressure to obtain (2*R*,5*R*)-2-isopropyl-2,3,5-trimethyl-5-(*p*-tolyl)imidazolidin-4-one acetate (**9**) as a yellow oil (1.20 g). ^1H NMR (400 MHz, [D$_4$]MeOH): δ = 7.62 (d, J = 8.1 Hz, 2 H, C$H_{ar\text{-}o}$), 7.10 (d, J = 8.1 Hz, 2 H, C$H_{ar\text{-}m}$), 2.79 (s, 3 H, CH_3N), 2.30 (s, 3 H, CH_3-Ar), 1.99 (s, 6 H, AcOH), 1.87 (sept, J = 6.8 Hz, 1 H, C*H* *i*Pr), 1.59 (s, 3 H, CH_3-C), 1.51 (s, 3 H, CH_3-C), 0.98 (d, J = 6.8 Hz, 3 H, CH_3 *i*Pr), 0.51 (d, J = 6.8 Hz, 3 H, CH_3 *i*Pr) ppm.

A solution of crude **9** in aqueous HCl (6 N, 10 mL) was exposed to microwave irradiation at 120 °C for 40 min to afford (*R*)-2-amino-*N*-methyl-2-(*p*-tolyl)propanamide hydrochloride (**10**) as a colorless oil (1.21 g). ^1H NMR (400 MHz, [D$_4$]MeOH): δ = 7.40 (d, J = 8.3 Hz, 2 H, C$H_{ar\text{-}o}$), 7.31 (d, J = 8.3 Hz, 2 H, C$H_{ar\text{-}m}$), 2.73 (s, 3 H, CH_3N), 2.37 (s, 3 H, CH_3-Ar), 1.97 (s, 3 H, CH_3-C-Ar) ppm.

The crude **10**, acetone (20 mL), 2,2-dimethoxypropane (20 mL), and triethylamine (0.63 g, 6.2 mmol) were introduced into a 100 mL flask fitted with a Soxhlet extractor filled with activated 3 Å molecular sieves (50 g). The reaction mixture was heated at reflux for 60 h and then the solvent was evaporated under reduced pressure. The crude product was taken up in ethyl acetate (60 mL), washed with concentrated NaOH (10 mL), and the aqueous phase

extracted with ethyl acetate (4× 25 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford (*R*)-2,2,3,5-tetramethyl-5-(*p*-tolyl) imidazolidin-4-one (**11**; 672 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.2 Hz, 2 H, C$H_{ar\text{-}o}$), 7.12 (d, *J* = 8.2 Hz, 2 H, C$H_{ar\text{-}m}$), 2.80 (s, 3 H, CH_3N), 2.31 (s, 3 H, CH_3-Ar), 2.00 (br. s, N*H*), 1.61 (s, 3 H, CH_3-C), 1.45 (s, 3 H, CH_3-C), 1.16 (s, 3 H, CH_3-C) ppm.

*m*CPBA (1.07 g, 4.3 mmol) was added portionwise to a solution of crude **11** in CH_2Cl_2 (5 mL). The mixture was stirred for 1.5 h at room temperature and then quenched with dilute aqueous NaOH (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2× 50 mL) and the combined organic layers dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a red oil. Purification over silica gel gave (*R*)-**7ba** as an orange oil that crystallized upon standing [407 mg, 30% from (2*S*,5*R*)-**4aa**], m.p. 70–71 °C. $[\alpha]_D^{20}$ = +86.3 (*c* = 0.24, $CHCl_3$). HRMS (ESI): calcd. for $C_{14}H_{20}N_2O_2$ $[M + H]^+$ 248.1519; found 248.1522.

A sample of (*rac*)-**7ba** was prepared according to Method 1 from **4ba** (38 mg, 0.15 mmol) as a low-melting beige solid (35 mg).

The enantiomeric purity of (*R*)-**7ba** (≥96% *ee*) was determined by SFC on a Daicel Chiralpak IA-3 column, 4.6 ×100 mm, eluent $scCO_2$/MeOH, 80:20, 1.7 mL/min, 37 °C, UV detection (220 nm), retention time 2.9 min for (*R*)-**7ba** and 3.5 min for (*S*)-**7ba**.

Preparation of Diol 12

2,6-Dimethyl-2′-(trifluoromethyl)-1,1′-biphenyl (14): A 10 mL Schlenk flask under nitrogen was charged with 1-bromo-*m*-xylene (1.85 g, 10.0 mmol), 4,4,6-trimethyl-2-[2-(trifluoromethyl)phenyl]-1,3,2-dioxaborinane (**13**;[38] 4.08 g, 15 mmol), $Pd(OAc)_2$ (22.0 mg, 0.1 mmol), S-Phos (82 mg, 0.2 mmol), and K_3PO_4 (6.37 g, 30 mmol). The flask was evacuated, purged with nitrogen, and a toluene/water mixture (1:0.18; 12 mL) was added. The Schlenk was then plunged into a 100 °C preheated oil bath and the reaction was stirred for 22 h. Purification over silica gel gave **14** (1.52 g, 61%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.7 Hz, 1 H, CH_{ar} 3′), 7.60 (t, *J* = 7.7 Hz, 1 H, CH_{ar} 4′), 7.47 (t, *J* = 7.7 Hz, 1 H, CH_{ar} 5′), 7.22–7.14 (m, 2 H, CH_{ar} 4,6′), 7.08 (d, *J* = 7.7 Hz, 2 H, CH_{ar} 3,5), 1.94 (s, 6 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.2 (*C*$_{ar}$ 1′), 138.8 (*C*$_{ar}$ 1), 136.4 (*C*$_{ar}$ 2), 132.2 (*C*H$_{ar}$ 3′), 131.3 (*C*H$_{ar}$ 5′), 128.8 (q, ^2J = 29.8 Hz, *C*$_{ar}$ 2′), 127.8 and 127.4 (*C*H$_{ar}$ 4,6′), 127.0 (*C*H$_{ar}$ 3), 126.5 (q, ^3J = 5.3 Hz, *C*H$_{ar}$ 3′), 124.1 (q, ^1J = 273.9 Hz, *C*F$_3$), 20.6 (*C*H$_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.3 ppm. IR: $\tilde{\nu}$ = 3065, 3022, 2926, 1311, 1123, 1108 cm^{-1}. LRMS (ESI$^+$): *m*/*z* = 232.1 $[M + H]^+$, 254.1 $[M + Na]^+$.

2,6-Bis(bromomethyl)-2′-(trifluoromethyl)-1,1′-biphenyl (15): Benzoyl peroxide (15 mg, 0.05 mmol) was added to a solution of *N*-bromosuccinimide (1.66 g, 9.4 mmol) and **14** (1.17 g, 4.7 mmol) in CH_2Cl_2 (35 mL). The reaction mixture was heated at reflux for 6 h, and then the solvent was evaporated under reduced pressure. Diethyl ether was added, a precipitate of succinimide was filtered off, and the filtrate evaporated to yield crude **15** (1.95 g) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.7 Hz, 1 H, CH_{ar} 3′), 7.70 (t, *J* = 7.7 Hz, CH_{ar} 4′), 7.60 (t, *J* = 7.7 Hz, 1 H, CH_{ar} 5′), 7.54 (d, *J* = 7.7 Hz, 1 H, CH_{ar} 6′), 7.51–7.39 (m, 3 H, CH_{ar} 3,4,5), 4.30 (d, *J* = 10.4 Hz, 2 H, 2 C*H*H-Br), 3.90 (d, *J* = 10.4 Hz, 2 H, CH*H*-Br) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.7 (*C*$_{ar}$ 1), 137.1 (*C*$_{ar}$ 2,6), 134.9 (q, ^3J = 3.0 Hz, *C*$_{ar}$ 1′), 132.6 (*C*H$_{ar}$), 132.0 (*C*H$_{ar}$), 130.5 (*C*H$_{ar}$ 3,5), 129.5 (*C*H$_{ar}$), 128.9 (*C*H$_{ar}$), 127.5 (q, ^2J = 29.5 Hz, *C*$_{ar}$ 2′), 125.1 (q, ^3J = 5.5 Hz, *C*H$_{ar}$ 3′), 122.7 (q, ^1J = 274.1 Hz, *C*F$_3$), 31.5 (*C*H$_2$-Br) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –60.3 ppm. IR: $\tilde{\nu}$ = 3149, 3066, 1311, 1172, 1160 cm^{-1}.

[2′-(Trifluoromethyl)-1,1′-biphenyl-2,6-diyl]dimethanol (12): K_2CO_3 (2.41 g, 17.1 mmol) was added to a solution of crude **15** (1.74 g) and glacial AcOH (0.98 mL, 17.1 mmol) in DMF (10 mL). The reaction mixture was stirred at 125 °C for 2.5 h and then treated with H_2O (5 mL). The aqueous phase was extracted with Et_2O (2× 20 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl (10 mL), dried with Na_2SO_4, and evaporated under reduced pressure. The crude diacetate was dissolved in EtOH (20 mL) and KOH (1.19 g, 21.3 mmol) was added. The reaction mixture was stirred at room temperature for 21 h, treated with H_2O (15 mL), and the aqueous phase extracted with CH_2Cl_2 (2× 20 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure. Purification over silica gel gave **12** (540 mg, 45% from **14**) as a yellow solid, m.p. 84–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.9 Hz, 1 H, CH_{ar} 3′), 7.61 (t, *J* = 7.2 Hz, 1 H, CH_{ar}), 7.57–7.45 (m, 4 H, CH_{ar}), 7.25 (d, *J* = 6.8 Hz, 1 H, CH_{ar} 6′), 4.32 (d, *J* = 13.1 Hz, 2 H, 2 C*H*H-OH), 4.23 (d, *J* = 13.1 Hz, 2 H, 2 CH*H*-OH), 1.51 (br. s, 2 H, O*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 139.3 (*C*$_{ar}$ 2,6), 136.7 (*C*$_{ar}$ 1′), 135.6 (*C*$_{ar}$ 1), 132.1 (*C*H$_{ar}$ 4′), 131.9 (*C*H$_{ar}$ 6′), 129.0 (*C*H$_{ar}$ 4), 128.8 (q, ^2J = 29.5 Hz, *C*$_{ar}$ 2′), 128.3 (*C*H$_{ar}$ 5′), 126.7 (*C*H$_{ar}$ 3,5), 126.6 (q, ^3J = 5.2 Hz, *C*H$_{ar}$ 3′), 124.0 (q, ^1J = 273.9 Hz, *C*F$_3$), 63.0 (*C*H$_2$-OH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –60.3 ppm. IR: $\tilde{\nu}$ = 3301, 2929, 2876, 1310, 1122, 1109 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{13}F_3O_2Na$ $[M + Na]^+$ 305.0760; found 305.0761.

Oxidation of Alcohols

General: Oxidation reactions under high pressures of O_2 were performed in a High Pressure ChemSCAN II – HEL apparatus equipped with eight 16 mL stainless-steel reactors. Reactions were performed at 4 bar O_2 and stirred magnetically at 1000 rpm.

Reactions under atmospheric O_2 pressure were performed in a 10 mL flask equipped with a balloon of O_2 and stirred with an orbital shaker (1000 rpm) to provide a large vortex.

Method E – $CuBr_2$/*t*BuOK/bipy: The indicated amounts of reagents were added as solids or as solutions in CH_3CN/H_2O (2:1): benzyl alcohol (1 mmol, 1 M), catalyst (5 mol-%), $CuBr_2$ (5 mol-%), *t*BuOK (5 mol-%), and 2,2′-bipyridine (5 mol-%).

Method F – $CuBr_2$/$NaNO_2$: The indicated amounts of reagents were added as solids or as solutions in $PhCF_3$: benzyl alcohol (1 mmol, 1 M) or diol **12** (0.2 mmol, 0.2 M), catalyst (5 mol-%), $CuBr_2$ (5 mol-%), and $NaNO_2$ (5 mol-%).

Method G – HBr/TBN: The indicated amounts of reagents were added as solids or as solutions in CH_3CN: benzyl alcohol (1 mmol, 1 M) or diol **12** (0.2 mmol, 0.2 M), catalyst (5 mol-%), HBr (5 mol-%), TBN (5 mol-%).

Oxidation of Benzyl Alcohol: The oxidation reaction was performed under the conditions of Method E, F, or G. The pressure, temperature, and reaction time are indicated in Table 2 for each particular example. The reaction was monitored by GC analysis.

GC analyses were performed with a Shimadzu C17 apparatus equipped with a flame ionization detector and a BPX5 column (30 m × 0.25 mm, SGE; 100 °C; carrier H_2; velocity 29 m s^{-1}). Retention times: benzaldehyde, 1.52 min; benzyl alcohol, 2.01 min.

Oxidation of Diol 12: The oxidation reaction was performed under the conditions of Method G under an atmospheric O_2 pressure at room temperature. The reaction was monitored by ^{19}F NMR spectroscopy.

Characterization Data for 6-(Hydroxymethyl)-2′-(trifluoromethyl)-1,1′-biphenyl-2-carbaldehyde (16): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (s, 1 H, C*H*O), 7.95 (d, J = 7.8 Hz, 1 H, CH_{ar}), 7.87 (d, J = 7.7 Hz, 1 H, CH_{ar}), 7.83 (d, J = 7.5 Hz, 1 H, CH_{ar}), 7.70–7.47 (m, 4 H, CH_{ar}), 7.31 (d, J = 7.4 Hz, 1 H, CH_{ar}), 4.37 (d, J = 13.6 Hz, 1 H, C*H*H-OH), 4.31 (d, J = 13.6 Hz, 1 H, CH*H*-OH) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –59.7 ppm.

Characterization Data for 2′-(Trifluoromethyl)-1,1′-biphenyl-2,6-dicarbaldehyde (17): Compound **17** is issued from the double oxidation of diol **12** in experiments not reported here; see ref.[40] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (s, 2 H, C*H*O), 8.26 (d, J = 7.7 Hz, 2 H, CH_{ar}-C-CHO), 7.94–7.87 (m, 1 H, CH_{ar}-C-CF_3), 7.74 (t, J = 7.7 Hz, 1 H, CH_{ar}-CH-C-CHO), 7.70–7.63 (m, 2 H, CH_{ar}), 7.45–7.37 (m, 1 H, C$H_{ar\text{-}o}$) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –59.1 ppm.

The enantiomeric purity of **16** was determined by HPLC using a Chiralcel OD-H column (25 m × 0.46 cm, 10% EtOH/hexane, 0.5 mL/min, UV detection at 289 nm); retention times: major enantiomer, 8.70 min; minor enantiomer, 9.46 min.

Electrochemical Measurements: Electrochemical measurements were conducted at 293 K under argon in a standard one-compartment, three-electrode electrochemical cell using a CH-Instrument 660B potentiostat. Investigations were carried out with 2 mM solutions of compounds in acetonitrile/water (95:5, v:v) containing sodium perchlorate (0.2 M) as supporting electrolyte and 2,6-lutidine (8 equiv.) as base. An automatic ohmic drop compensation procedure was systematically implemented prior to recording CV data. CH-Instrument vitreous carbon (Ø = 3 mm) working electrodes were polished with 1 μm diamond paste before each recording. The reference electrode was $Ag/AgNO_3$ (10 mM in CH_3CN containing 0.1 M TBAP). The potential of the regular ferrocene/ferrocenium (Fc/Fc^+) redox couple in acetonitrile was 0.07 V under our experimental conditions. A platinum wire was used as the counter electrode.

Supporting Information (see footnote on the first page of this article): Determination of the optical purity of (*R*)-**7ba**, UHPLC/MS analyses of **4/7ba**, ^{1}H and ^{13}C NMR spectra of **1b**, **3ba**, **3bb**, **3ca**, **4**–**6**, **12**, **14**, and **15**.

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[52] See, for example, ref.[43d,45b] and: a) Y. Hahn, S. K. Song, *Anal. Sci.* **1997**, *13 (suppl.)*, 329–332; b) D. Liaigre, T. Breton, E. M. Belgsir, *Electrochem. Commun.* **2005**, *7*, 312–316; c) M. Barbier, T. Breton, K. Servat, E. Grand, B. Kokoh, J. Kovensky, *J. Carbohydr. Chem.* **2006**, *25*, 253–266.
[53] D. S. Pedersen, C. Rosenbohm, *Synthesis* **2001**, 2431–2434.
[54] The sample did not produce any NMR signal. After the addition of hydrazine hydrate to the NMR tube, signals of the corresponding hydroxylamine protons were observed.

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