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Free-Radical Hydroxylation Reactions of Alkylboronates

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The radical hydroxylation of *B*-alkylcatecholboranes, easily prepared by hydroboration of olefins, has been investigated. When molecular oxygen was used as oxidizing agent, the corresponding alcohols were obtained directly without alkaline treatment. The presence of Lewis base additives such as Et_3N or DABCO has a benefic effect on the selectivity and yield. Alternatively, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) reacts cleanly with *B*-alkylcatecholboranes to afford alkyl radicals that can be trapped by a second equivalent of TEMPO to give alkoxyamines. Reduction of the alkoxyamines with zinc in acetic acid affords the desired alcohols. The whole procedure is particularly mild and does not require any basic condition. The two approaches presented in this paper are valuable and represent mild alternatives to the classical alkaline oxidation of organoboranes to alcohols.

Introduction

The conversion of alkenes into alcohols via hydroboration followed by oxidative workup is characterized by a predictable and high degree of stereoselectivity, high chemical yields, and mild and simple experimental conditions which are compatible with a large variety of chemical functions.[1] For the oxidation of the intermediate alkylboranes or alkylboronates, a great number of oxidizing agents have been developed such as alkaline hydrogen peroxide,[2] sodium perborate,[3] amine *N*-oxides,[4] perbenzoic acid,[5] sodium percarbonate,[6] sodium hypochlorite,[7] or Oxone.[8] According to the general consensus, these reagents mediate the oxidation via a polar mechanism.[9] It is worth noting that only a few efforts have been made to develop radical hydroxylation reactions as they are considered less selective and low-yielding methods. In the wake of our ongoing program on the use of organoboranes in radical chemistry,[10−12] the scope of a radical hydroxylation was studied.[11] We report here simple and preparatively useful methods to convert olefins into alcohols via the corresponding *B*-alkylcatecholboranes. Preliminary results have been published as communications and a full account of this work is presented here.[12] *B*-Alkylcatecholboranes react with persistent oxyl radicals such as molecular oxygen, or 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), to afford alkyl radicals which can be trapped by a second equivalent of the reagent to give, after reduction, alcohols.[12]

Results

Oxidation of Alkylboronates with Molecular Oxygen. Reaction of molecular oxygen with organometallic and metalloïd derivatives may generate carbon-centered radicals via a chemically induced electron transfer (ET) process. The formed carbon-centered radical may be trapped by a second molecule of oxygen giving rise to a new C−O bond.[13−16] Although the oxidation by

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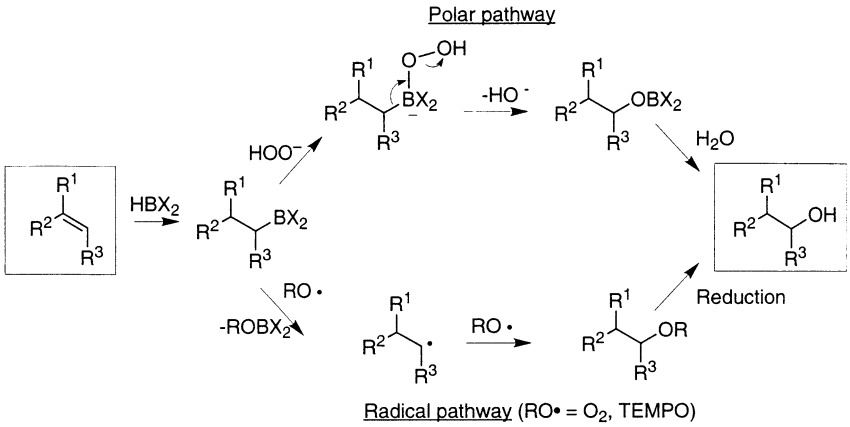
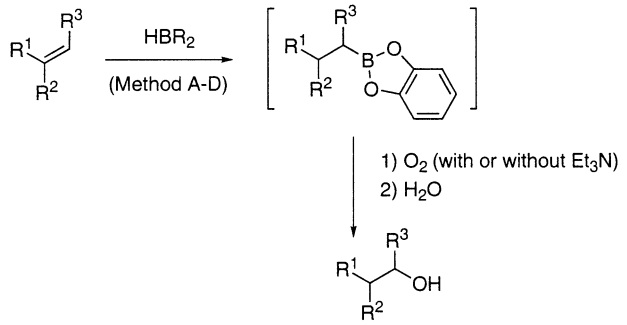
SCHEME 1



air (autoxidation) of main group organoelements, in particular organolithium and organomagnesium compounds leading to hydroperoxides and alcohols, has been longtime recognized, the method did not gain general interest. The insertion of dioxygen into transition metal hydrides to form hydroperoxo complexes has been noted for compounds such as Co(III),[13] Rh(III),[14] Ir(III),[14,15] and Pt(II).[16] In these cases, both polar rearrangement involving oxygen binding and rearrangement as well as the radical chain pathway involving radical addition fragmentation−recombination have been suggested. The vigorous reactivity of organoboranes with oxygen was demonstrated in 1860 by Frankland with the green flame of burning triethylborane.[17] Several mechanistic investigations of the autoxidation of organoboranes were performed and strongly supported a radical mechanism.[18,19] Brown has reported that all three alkyl groups of trialkylboranes are efficiently converted into alcohols in good yields upon treatment with 1.5 equiv of oxygen. This reaction however has not found many synthetic applications.[20] More recently, Knochel has reported that the direct oxidation of organoboranes with oxygen in perfluoroalkanes affords the corresponding alcohols with retention of configuration.[21] This stereochemical outcome is rationalized by an oxygen insertion mechanism rather than by a radical chain mechanism.

For our study, the required alkylboronate intermediates were prepared by hydroboration of different alkenes by reaction with BH_3·THF followed by Et_3N/catecholborane (Method A), BH_3·Me_2S followed by Et_3N/catechol (Method B), catecholborane/$RhCl(PPh_3)_3$[22,38b] (Method C), and catecholborane/*N*,*N*-dimethylacetamide[23] (Method D). The oxygenation reactions were performed at room temperature in the presence or in the absence of Lewis base additives such as Et_3N or *N*,*N*-dimethylacetamide.

SCHEME 2



(a) Free-Radical Hydroxylation of Substituted Cyclic Olefins. The oxygen-mediated radical hydroxylation was investigated first with the cyclic alkenes **1**−**3** and the results are summarized in Table 1. Due to the fast rate of radical recombination, the reactions of radicals with oxygen are expected to give only moderate stereoselectivity.[24] However, we were pleased to notice that the oxidation of alkylboronic esters derived from 2-methylindene (**1**) (Method A), using molecular oxygen, in the presence of triethylamine afforded **4** in 71% yield as a 10 to 1 *trans*/*cis* mixture of diastereomers (Table 1, Entry 1). The reaction mixture was contaminated with a small amount of ketone (<5%).[25] In a parallel experiment when triethylamine was omitted only traces of hydroxylated product **4** were formed and the corresponding ketone (10%) was isolated. The addition of catechol was not necessary although beneficial to the reaction, as in the absence of catechol, the organoborane intermediate gave rise to the desired alcohol **4** (65%; Table 1, Entry 2) with a considerable amount of ketone (19%). The hydroxylation reaction with BH_3·SMe_2 complex (Method B) as hydroborating agent and molecular oxygen afforded slightly better yield (85%) and the selectivity in favor of

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(24) For examples of moderately stereoselective radical oxygenations, see: Kihara, N.; Ollivier, C.; Renaud, P. *Org. Lett.* **1999**, *1*, 1419−1422.

(25) The selectivity of the reactions was measured by GC-MS.

TABLE 1. Free-Radical Hydroxylation of Cyclic Alkenes 1−3

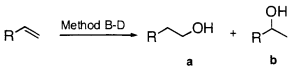
Entry	Alkene	Method[a]	Alcohol	Yield (%) (*trans*/*cis*) with Et_3N	Yield (%) (*trans*/*cis*) without Et_3N
1	 **1**	A	 **4**	71% (10 : 1)	traces
2		A[b]		65% (10 : 1)	traces
3		B		85% (10 : 1)	10% (10 : 1)
4	 **2**	B	 **5**	64% (9 : 1)	12% (9 : 1)
5	 **3**	B	 **6**	46% (4 : 1)	12% (4 : 1)

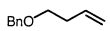
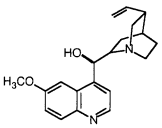
[a] Key: Method A: (i) BH_3·THF (1.2 equiv), rt, 4 h; (ii) Et_3N (1.5 equiv), then catechol (1.2 equiv), THF, 0−5 °C then rt, 2.5 h; (iii) O_2, rt, 12 h. Method B: (i) BH_3·SMe_2 in THF (1.2 equiv), 0−5 °C, then rt, 4 h; (ii) Et_3N (1.5 equiv), then catechol (1.2 equiv), THF, 0−5 °C then rt, 2.5 h; (iii) O_2, rt, 12 h. [b] In this experiment catechol was omitted.

the *trans* compound was identical (Table 1, Entry 3). It is worth noting that the hydrolysis of the intermediate boronate ester occurred spontaneously in the aqueous workup. By using Method B, 1-phenylcyclohexene (**2**) afforded **5**, as a mixture of *trans*/*cis* diastereomers in a 9:1 ratio (Table 1, Entry 4). The hydroboration of enol ether **3** (Method B) produced, after oxidation and aqueous workup, the corresponding 1,2-diol **6** in modest yield (46%) and selectivity (*trans*/*cis* = 4:1) (Table 1, Entry 5). Only a small amount of the desired product was obtained when triethylamine was omitted.

(b) Oxidation of Terminal Olefins. Although regiochemistry of the free-radical hydroxylation reaction is controlled during the hydroboration step the ratio of the regioisomers may be influenced by the relative stability of the primary versus secondary radical intermediate and the relative propensity toward overoxidation of the alcohols under the reaction conditions. The regioselectivity of the hydroxylation reaction was studied by using substrates **7**−**10** (Table 2). The free-radical hydroxylation of styrene **7** by using Method B followed similar trends as classical hydroboration reactions. The hydroxylated products **11a** and **11b** were isolated directly after aqueous workup, and without alcaline treatment (Table 2, Entry 1). The yield in alcohols **a** + **b** (69%) decreased when triethylamine was omitted (47%). Hydroboration of **7** with catecholborane and $RhCl(PPh_3)_3$ Wilkinson's catalyst (Method C) followed by oxidation in the presence of triethylamine afforded selectively the most substituted alcohol **11b** as a single product (76%; Table 2, Entry 2). This result shows that the oxidation of trialkylboronic esters with molecular oxygen is compatible with the presence of a metal catalyst such as rhodium. When triethylamine was omitted the yield of the desired alcohol decreased to 55%. When the hydroboration was performed under Fu's conditions[23] (Method D) by using a catalytic amount of *N*,*N*-dimethylacetamide (10%) followed by oxidation with molecular oxygen, the less substituted alcohol **11a** was isolated as the major regioisomer (**11a**:**11b** = 12:1) (Table 2, Entry 3). Once again, the overall yield (80%) of the transformation decreased

TABLE 2. Free-Radical Hydroxylation of Terminal Olefins 7−10



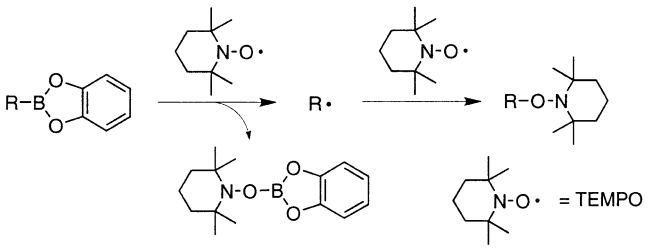
Entry	Alkene	Products	Method[a]	Yield (%) selectivity (**a** : **b**) with Et_3N	Yield (%) selectivity (**a** : **b**) without Et_3N
1		**11a+11b**	B	69% (9 : 1)	47% (9.5 : 1)
2	 **7**	**11b**	C	76%	55%
3		**11a+11b**	D	80% (12 : 1)	59% (12 : 1)
4	 **8**	**12a+12b**	B	71% (11 : 1)	54% (10 : 1)
5		**12a+12b**	D	87% (8 : 1)	56% (9 : 1)
6	 **9**	**13a+13b**	B	81% (2 : 1)	64% (5 : 1)
7		**13a+13b**	D	65% (5 : 2)	68% (5 : 2)
8	 **10**	**14a**	B	62%	44%

[a] Key: Method B: (i) BH_3·SMe_2 in THF (1.2 equiv), 0−5 °C, then rt, 4 h; (ii) Et_3N (1.5 equiv), then catechol (1.2 equiv), THF, 0−5 °C then rt, 2.5 h; (iii) O_2, rt, 12 h. Method C: (i) $RhCl(PPh_3)_3$ (5%), catecholborane (2 equiv), THF, 0−5 °C, then rt, 1 h; (ii) Et_3N (2.5 equiv), 0−5 °C then rt; (iii) O_2, rt, 12 h. Method D: (i) $CH_3CON(Me)_2$ (10%), catecholborane (2 equiv), THF, 0−5 °C, then rt, 2.5 h, then MeOH (1.1 equiv); (ii) Et_3N (2.5 equiv), 0−5 °C then rt; (iii) O_2, rt, 12 h.

when triethylamine was omitted (59%). In each reaction, and independently of the conditions used, a small amount of acetophenone (3−5%) was formed along with the desired alcohols. The hydroxylation reaction was generalized to terminal olefins **8**−**10** (Table 2, Entries 4−8). When compounds **8** and **9** were treated under conditions B a mixture of regioisomers was obtained with a marked preference for the less substituted alcohols **12a** and **13a** (Table 2, Entries 4 and 6). Also, hydroboration under Fu's conditions (Method D) followed by oxidation with molecular oxygen afforded the less substituted alcohols **12a** and **13a** as the major products (Table 2, Entries 5 and 7). Likewise, hydroxylation of quinine **10** with 5 molar equiv of BH_3·SMe_2 (Method B) followed by oxidation with O_2 and decomplexation of the aminoborane in refluxing ethanol afforded only alcohol **14a** as single product in 62% yield. In general, lower yields were obtained when triethylamine was omitted (Table 2, Entry 8).

Hydroxylation with TEMPO. Nitroxides such as TEMPO are known to react with carbon-centered radicals to give alkoxyamines with well-characterized rate constants and thus they have been used as kinetic and mechanistic probes for radical processes. This radical coupling reaction has also found some interesting synthetic applications.[26,27] For instance, a broad range of alkyl radicals, generated from organocobalt,[28] organosa-

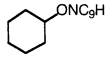
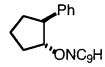
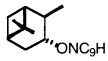
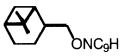
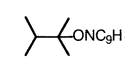
SCHEME 3



marium[29] and organomercury,[30] organotellurides,[31] as well as from halides with tin hydride, ditin, and silanes or dimanganese decacarbonyl,[32] from hydrazine by treatment with lead dioxide,[33] have been shown to react efficiently with nitroxides. However, the reaction of persistent nitroxyl radicals with organoboranes has not been reported so far. An early attempt by Braslau has shown that the direct oxidation of trialkylboranes by TEMPO does not occur without using a stoichiometric amount of di-*tert*-butylhyponitrite as a source of *tert*-butoxyl radicals.[34] In this reaction, the nitroxide does only trap the final alkyl radical that is generated by the reaction of the trialkylborane with a *tert*-butoxyl radical. Interestingly, we discovered that *B*-alkylcatecholboranes are much more reactive than trialkylboranes and that they react readily with persistent nitroxyl radicals.

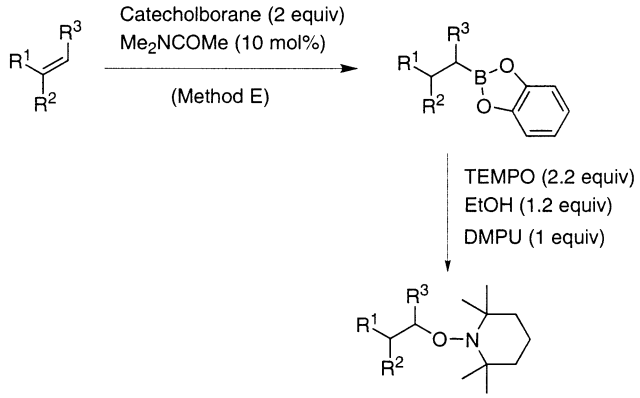
(a) Direct Hydroxylation of *B*-Alkylcatecholboranes. *B*-Alkylcatecholboranes were prepared by hydroboration of the corresponding alkenes **15**−**19** with catecholborane (2 equiv) in the presence of a catalytic amount of *N*,*N*-dimethylacetamide in dichloromethane. The excess of catecholborane was solvolyzed with ethanol (1.2 equiv) and DMPU (1 equiv) was then added followed by the addition of TEMPO (2.2 equiv) (Method E). This one-pot procedure furnished the alkoxyamines **20**−**24** in moderate to good yields (Table 3). In the absence of DMPU, a decrease of the yields was observed. For instance, the yield in **20** was decreased from 87% to 63% yield. A similar but more pronounced effect was already observed in the oxygen-initiated conjugate addition of *B*-alkylcatechoboranes to enones.[35]The best yields have been obtained with secondary alkyl radicals generated from cyclohexene, 1-phenylcyclopentene, and α-pinene (Table 3, Entries 1−3). Primary and tertiary alkylcatecholboranes generated from *β*-pinene and 2,3-dimethyl-2-butene afforded the corresponding alkoxyamines with slightly lower yields (<65% yield) than secondary alkylcatecholboranes (Table 3, Entries 4 and 5). The stereochemical outcome of these reactions corresponds very well to expectations for radical processes.[36] Indeed, reaction of phenylcyclopentene **16** afforded the *trans* alkoxyamine **21** (71% yield) with good diastereoselectivity (*trans*/*cis*

TABLE 3. Hydroboration of Alkenes 15−19 Followed by Reaction with TEMPO According to Scheme 4

Entry	Alkene		Alkoxyamine,[a] yield (diastereoselectivity)	
1		**15**		**20**, 87%
2		**16**		**21**, 71% (dr 89:11)[b]
3		**17**		**22**, 82% (dr 97:3)[b]
4		**18**		**23**, 57% (dr 91:9)[b]
5		**19**		**24**, 64%

[a] Key: Method E: (i) catecholborane (2 equiv) and $MeCONMe_2$ (10 mol %) in refluxing CH_2Cl_2, then EtOH (1.2 equiv); (ii) DMPU (1 equiv) and TEMPO (2.2 equiv) at room temperature. [b] Only the major diastereomer is drawn. [c] NC_9H_{18} = 2,2,6,6-tetramethylpiperidin-1-yl.

SCHEME 4



DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (= *N*,*N*′-dimethylpropyleneurea)

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(32) (a) Kinney, R. J.; Jones, W. D.; Bergman, R. G. *J. Am. Chem. Soc.* **1974**, *96*, 870−876. (b) Barrett, A. G. M.; Bezuidenhoudt, B. C. B.; Melcher, L. M. *J. Org. Chem.* **1990**, *55*, 5196. (c) Barrett, A. G. M.; Rys, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 837. (d) Boger, D. L.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 1271. (e) Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E. *Tetrahedron Lett.* **1999**, *40*, 6095−6098.

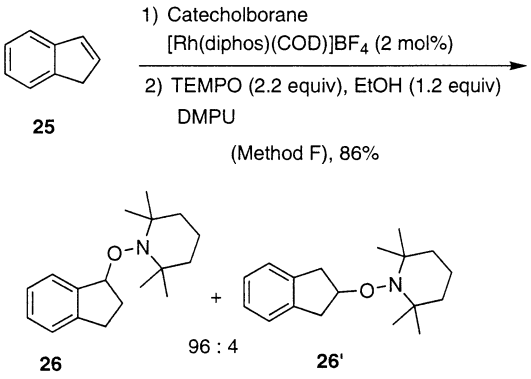
(33) Braslau, R.; Naik, N.; Zipse, H. *J. Am. Chem. Soc.* **2000**, *122*, 8421−8434.

(34) Braslau, R.; Anderson, M. O. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, p 129.

(35) Ollivier, C.; Renaud, P. *Chem. Eur. J.* **1999**, *5*, 1468−1473.

(36) For a discussion of the stereoselectivity of radical reactions in cyclic systems, see: (a) Renaud, P. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, pp 400−415. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; Wiley-VCH: Weinheim, Germany, 1995.

SCHEME 5



89:11, Entry 2).[36] In turn, α-pinene **17** was hydroborated with complete stereoselectivity from the less hindered face, and the subsequent radical reaction occurred with complete stereocontrol, *anti* to the neighboring methyl group and to the *gem*-dimethyl moiety.[37] The case of *β*-pinene **18** (Table 3, Entry 4) is simpler since the newly formed stereogenic center is controlled during the hydroboration step. A major drawback of the catecholborane hydroboration under Fu's conditions is its lack of regioselectivity with olefins conjugated to an aromatic ring such as indene. Therefore, it was of interest to test if the TEMPO-mediated oxidation conditions were compatible with transition metal catalyzed reaction. Indeed, it is well established that transition metal catalyzed hydroboration of arylethene derivatives give predominantly the benzylic boronates. Excellent results have been obtained with the commercially available cationic rhodium complex [Rh(diphos)COD)]BF_4.[38] Starting from indene **25**, the hydroboration was performed with 2 mol % of [Rh(diphos)-COD)]BF_4 (Method F) followed by TEMPO radical-mediated oxidation. The benzylic alkoxyamine **26** and 2-substituted regioisomer **26′** were isolated in 86% yield (Scheme 5).

(b) Tandem Conjugate Addition−Hydroxylation Process. Alkyl radicals generated for *B*-alkylcatecholboranes have been used for conjugate additions.[35,41] We were interested in developing a tandem process where the radical issued from the conjugate addition is trapped with TEMPO. The radical addition of cyclohexyl radicals generated from cyclohexene **15** to different olefins was examined (Scheme 6). After hydroboration with Fu's conditions, activated olefins (5 equiv) were added followed by a slow addition of TEMPO (2.2 equiv) (Method G). The results are presented in Table 4 and show clearly that this tandem process is efficient with highly reactive olefins such as *N*-phenylmaleimide. In this case, the *trans* isomer of **27** is isolated in 70% yield (Table 4, Entry 1). With dimethyl fumarate, the direct reaction of the

SCHEME 6

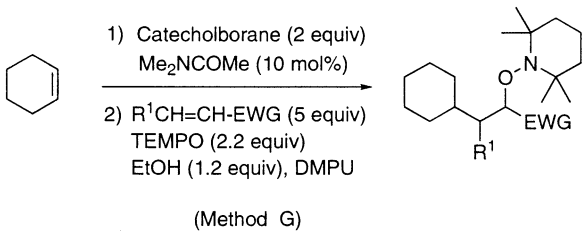
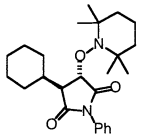
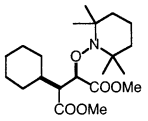
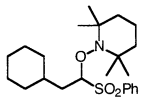


TABLE 4. Tandem Conjugate Addition−Aminoxylation According to Scheme 6

Entry	Alkene	Addition product,[a] yield (yield of 20) diastereoselectivity
1	*N*-phenylmaleimide	 **27**, 70%[b] (<2%) dr > 98:2
2	dimethyl fumarate	 **28**, 31%[b] (27%) dr >98:2
3	phenyl vinyl sulfone	 **29**, 18% (57%)

[a] Key: Method G: (i) catecholborane (2 equiv) and $MeCONMe_2$ (10 mol %) in refluxing CH_2Cl_2, then EtOH (1.2 equiv); (ii) DMPU (1 equiv), alkene (5 equiv), and TEMPO (2.2 equiv) over 2 h at room temperature. [b] Yield of isolated product.

cyclohexyl radical with TEMPO is becoming an important side reaction and the product of the tandem reaction, **28**, is isolated in only 31% yield as a single diastereomer together with 27% of **20**, the product of direct trapping of the cyclohexyl radical with TEMPO (Entry 2). The very high level of stereocontrol in **27** and **28** (Table 4, Entries 1 and 2) may be due to the decomposition by *β*-fragmentation of the minor diastereoisomer (in both cases, the minor isomer should be more prone to *β*-fragmentation according to an *anti* elimination mechanism). With phenyl vinyl sulfone, the product **20** of direct trapping is the major product (57% yield) and only 18% of the desired product **29** is obtained (Table 4, Entry 3). It is worth noting that no elimination product was isolated in this experiment.

Discussion

The radical nature of the reaction for both the oxygen- and the TEMPO-mediated hydroxylation reaction was demonstrated by the reaction of (+)-2-carene **30** (Scheme 7). According to this radical-clock experiment, the intermediate cyclopropylmethyl radical undergoes a ring opening to a homoallyl radical, which is trapped by an excess of oxyl radical. No fragmentation occurs in turn when the transformation proceeds via a polar mechanism or resulted from a concerted process.[39]

Hydroxylation of (+)-2-carene **30** under Fu's conditions (Method D) followed by oxidation with molecular oxygen afforded a 2:1 mixture of alcohols **31** and **32**. The separation of the two isomers was tedious and was finally

(37) The diastereoselectivity of the reaction was measured by ^1H NMR.

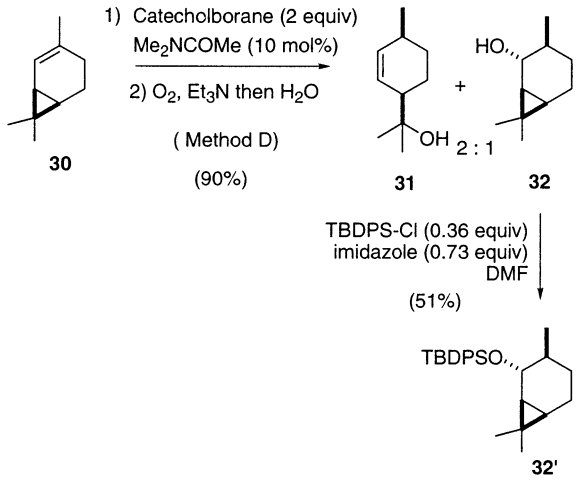
(38) (a) Hayashi, T.; Matsumoto, Y.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 601−612. (b) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957−5026. (c) Burgess, K.; Ohlmeyer, M. *J. Chem. Rev.* **1991**, *91*, 1179−1191.

(39) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176.

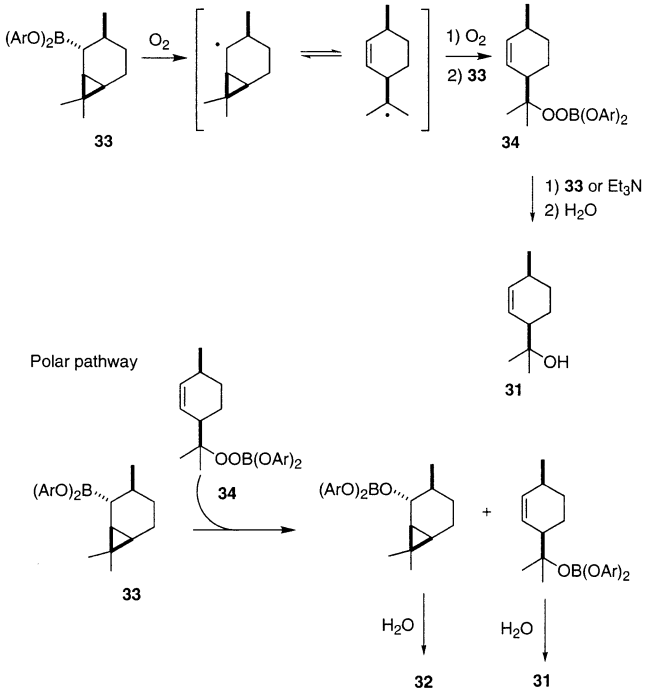
(40) (a) Davies, A. G.; Roberts, P. B. *J. Chem. Soc. B* **1969**, 311−321. (b) Wilke, G.; Heimbach, P. *Liebigs Ann. Chem.* **1962**, *652*, 7−21.

(41) (a) Cadot, C.; Cossy, J.; Dalko P. I. *Chem. Commun.* **2000**, 1017−1018. (b) Ollivier, C.; Renaud, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 925−928.

SCHEME 7



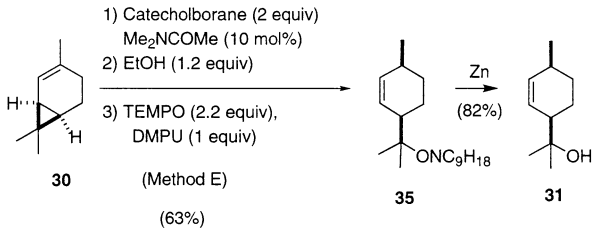
SCHEME 8



overcome by selective silylation of **32**. The presence of the two structural isomers is in favor of parallel radical and polar paths in the oxidation step. A such polar versus free-radical dichotomy was earlier established in analogous transformations.[19,20,40] According to the general consensus, the initial free-radical oxidation−fragmentation reaction followed by recombination produces a perborate **34.** This perborate intermediate **34** is also a good oxidizing agent of the starting material. This second oxidation step gives rise the corresponding borate esters by intermolecular redox reaction via a polar path leaving the cyclopropyl ring unaffected. Thus the formed borate esters may evolve to the corresponding alcohols **31** and **32** respectively, by hydrolysis (Scheme 8).[19,20,24]

Although the parallel mechanisms match with the classical free-radical fragmentation and intermolecular redox reaction established earlier, it does not explain the effect of the additive. The role of trialkylamine is probably double. On one hand, the aminoborane intermediate

SCHEME 9



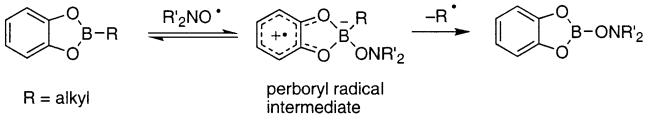
formed from alkyl boronates in the presence of triethylamine may facilitate the homolytic fragmentation of the C−B bond. This marked effect of the additive was shown earlier in the radical alkylation of alkylboronic esters.[41] On the other hand, the triethylamine may serve to quench the intermediate perborate esters and leads to the corresponding alkyl borates and amine *N*-oxides.[4] This mild decomposition depletes the ketone-forming and polycondensation free-radical paths thus increasing the yield of the hydroxylation products. Furthermore, the amine oxide formed may oxidize the starting material alkylboronic esters via a polar path and can produce **32** according to the earlier proposed mechanism.[4]

The radical nature of the TEMPO-mediated hydroxylation reaction was probed similarly by a radical-clock experiment with (+)-2-carene **30**. The rate constants for the reaction of carbon-centered radicals with TEMPO at room temperature are lying between 10^8 and 10^9 M^{-1} s^{-1}.[42] The cyclopropylcarbinyl radical derived from 2-carene **30** is expected to rearrange with a rate constant higher than 10^9 s^{-1}.[43] Therefore, the reaction of **30** with TEMPO is expected to deliver the ring-opening product if a radical mechanism is involved. Experimentally, the radical nature of the mechanism was confirmed since hydroboration of **30** under Fu's conditions (Method D) followed by oxidation of the intermediate alkylboronate with TEMPO (2.2 equiv) afforded exclusively the rearranged alkoxyamine **35**. The cyclopropane-opened adduct was reduced with Zn/AcOH to afford the corresponding alcohol **31** in excellent yield (Scheme 9).[44]

It is also important to point out that these reactions work efficiently with *B*-alkylcatecholboranes but not with trialkylboranes. For instance, under similar reaction conditions (with and without DMPU), triethylborane gave no trace of 1-ethoxy-2,2,6,6-tetramethylpiperidine. It is well-known that electronic and steric effects influence considerably the reactivity of organoboranes toward peroxyl radicals.[45] Due to π bonding between boron and oxygen, boronic esters are less reactive than trialkylboranes toward alkoxyl radicals. On the basis of this simple consideration, *B*-alkylcatecholboranes should be more reactive than the corresponding dialkyl boronates since the lone pair of the oxygen is partially delocalized onto the aromatic ring. More important, it was clearly demonstrated by ESR that a delocalized perboryl radical intermediate (a radical ate complex) is involved in the

(42) Sobeck, J.; Martschke, R.; Fischer, H. *J. Am. Chem. Soc.* **2001**, *123*, 2489−2857.
(43) Newcomb, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, pp 317−336.
(44) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876−2883.
(45) Davies, A. G.; Roberts, B. P. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, p 547.

SCHEME 10



substitution reaction at boron.[46] The stabilization of this intermediate certainly accounts for the high reactivity of *B*-alkylcatecholboranes in radical reactions. A similar mechanism involving a stabilized perboryl radical is also presumably involved for the reaction with TEMPO (Scheme 10).

The role of DMPU is not understood at the moment but a plausible hypothesis would be that it helps the fragmentation of the intermediate perboryl radical (radical ate complex) by complexing the final borate.

Conclusions

Alkylboronic ester derivatives afford, in the presence of persistent oxyl radicals such as molecular oxygen and 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), the corresponding oxygenated products. The reaction is based on the exceptional reactivity of *B*-alkylcatecholborane derivatives toward these persistent radicals and the efficient trapping of the generated carbon-centered radicals by the reagents. Despite the radical−radical recombination nature of these processes, a fair level of stereoselectivity and yield were reached. The positive role of nitrogen-containing Lewis bases such as amides and tertiary amides was also demonstrated. Due to the very mild reaction conditions and the experimental simplicity of the transformations, the reactions presented here constitute a valuable alternative to the classical oxidative treatment for the conversion of *B*-alkylcatecholboranes to alcohols. Furthermore, possible extension of this chemistry to cascade reactions involving cyclization reactions followed by hydroxylation processes is under investigation and should become an attractive procedure for the preparation of highly fonctionalized polycyclic systems.

Experimental Section

General. Reactions were performed under inert atmosphere. CH_2Cl_2 was freshly distilled from CaH_2 under N_2. Reagents were obtained from commercial sources and used as received. Also, pure O_2 from a cylinder was used, and was introduced either directly or by using balloons. Flash column chromatography: silica gel (0.063−0.200 and 0.04−0.063 mm). Thin-layer chromatography (TLC): silica gel 60 F_{254} analytical glass or aluminum sheet plates. Mp: not corrected. ^{1}H NMR (200, 300, 360, and 500.13 MHz) and ^{13}C NMR (50.3, 75.5, 90.5, and 125.8 MHz); chemical shift δ in ppm relative to tetramethylsilane (δ 0 ppm) or $CHCl_3$ for ^{1}H, (δ 7.26 ppm) and $CDCl_3$ for ^{13}C (δ 77.0 ppm). MS *m*/*z* (%): EI (70 eV), CI (CH_4), and FAB (2-nitrobenzyl alcohol with Ar at 8 kV). Elementary analysis: Ecole d'Ingénieurs de Fribourg, CH-1705 Fribourg, Switzerland, Ilse Beetz, Microanalytisches Laboratorium, D-8640 Kronach, Germany, and Service Régional de Microanalyses de l'Université P. et M. Curie, Paris, France.

Reaction with Oxygen. Method A: To a solution of BH_3·THF complex (1.2 mmol, 1.2 mL, 1.0 M in THF) was added olefin (1.0 mmol) in one portion at 0−5 °C. The mixture was stirred for 4 h then Et_3N (210 μL, 1.5 mmol) was added in one portion at 0−5 °C. After 5 min of stirring at 0−5 °C a solution of catechol (132 mg, 1.2 mmol) in THF (400 μL) was introduced. After 2.5 h at room temperature, a gentle stream of dry oxygen was bubbled through the reaction mixture for 1 h. The mixture was stirred vigorously for an additional 11 h, maintaining the oxygen atmosphere over the reaction mixture. The solution was diluted with CH_2Cl_2, washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

Method B: To a solution of BH_3·Me_2S complex (1.2 mmol, 600 μL, 2.0 M in THF) was added olefin (1.0 mmol) in one portion at 0−5 °C. The mixture was stirred for 4 h then Et_3N (210 μL, 1.5 mmol) was added in one portion at 0−5 °C. After 5 min of stirring at 0−5 °C a solution of catechol (132 mg, 1.2 mmol) in THF (400 μL) was introduced. After 2.5 h at room temperature, a gentle stream of dry oxygen was bubbled through the reaction mixture for 1 h. The mixture was stirred vigorously for an additional 11 h, maintaining the oxygen atmosphere over the reaction mixture. The solution was diluted with CH_2Cl_2, washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

Method C: To a solution of $RhCl(PPh_3)_3$ (46 mg, 5%) and olefin (1.0 mmol) in THF (1 mL) was added catecholborane (213 μL, 2 mmol) dropwise at 0−5 °C. The mixture was stirred for 1 h then Et_3N (350 μL, 2.5 mmol) was slowly introduced at 0−5 °C. After 15 min of stirring at 0−5 °C a gentle stream of dry oxygen was bubbled through the reaction mixture for 1 h. The mixture was stirred vigorously for an additional 11 h, maintaining the oxygen atmosphere over the reaction mixture. The solution was diluted with CH_2Cl_2, washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

Method D: To a solution of *N*,*N*-dimethylacetamide (9 μL, 0.1 mmol) and olefin (1.0 mmol) in THF (1 mL) was added catecholborane (213 μL, 2 mmol) dropwise at 0−5 °C. The mixture was stirred for 2.5 h at room temperature then methanol (44 μL, 1.1 mmol) was introduced at 0−5 °C. After 15 min of stirring Et_3N (110 μL**,** 1.5 mmol) was added at 0−5 °C. After 15 min of stirring at this temperature a gentle stream of dry oxygen was bubbled through the reaction mixture for 1 h. The mixture was stirred vigorously for an additional 11 h at room temperature, maintaining the oxygen atmosphere over the reaction mixture. The solution was diluted with CH_2Cl_2, washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

(1*R,2*S**)-2-Methylindanol (*trans*-4) and (1*S**,2*S**)-2-Methylindanol (*cis*-4).**[47] (a) Prepared according to method B from **1** (402 μL, 3 mmol). Purification by flash chromatography (petroleum ether/ethyl acetate 80:20) afforded **4** (377 mg, 85%) as a 10:1 mixture of two isomers (^{1}H NMR). Waxy white solid. Mp 86−88 °C. *trans*-**4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, J = 7.0 Hz, 3H), 2.22 (br s, 1H), 2.26 (m, 1H), 2.48 (dd, J = 15.8 and 8.1 Hz, 1H), 3.13 (dd, J = 15.8 and 7.7 Hz, 1H), 4.72 (apparent t, J = 6.2 Hz, 1H), 7.24 (m, 3H), 7.38 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 37.8, 45.2, 82.7, 123.8, 124.7, 126.5, 127.9, 142.0, 144.9. *cis*-**4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, J = 7.0 Hz, 3H), 2.22 (br s, 1H), 2.58 (m, 1H), 2.70 (dd, J = 16.0 and 7.1 Hz, 1H), 2.98 (dd, J = 16.0 and 7.1 Hz, 1H), 5.01 (apparent t, J = 6.3 Hz, 1H), 7.38 (m, 1H), 7.24 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 37.8, 39.2, 77.5, 124.8 (2C), 126.5, 128.3, 143.2, 144.7. IR (mixture of two diastereomers) (KBr) 3380, 1460, 1330, 1290, 1210, 1090, 1050,

(46) Baban, J. A.; Goodchild, N. J.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1986**, 157−161.

(47) Bowers, N. I.; Boyd, D. R.; Sharma, N. D.; Goodrich, P. A.; Groocock, M. R.; Blacker, A. J.; Goode, P.; Dalton, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1453−1462.

1010 cm^{-1}. MS (EI, 70 eV) *m*/*z* 148 (M$^+$, 78), 147 (100), 133 (25), 115 (27), 91 (34), 77 (11), 51 (7).

(b) Prepared according to method A from **1** (402 μL, 3 mmol). Purification by flash chromatography (petroleum ether/ethyl acetate 80:20) afforded **4** (315 mg, 71%) as a 10:1 mixture of two isomers (^{1}H NMR).

(c) Prepared according to method A without catechol from **1** (402 μL, 3 mmol). Purification by flash chromatography (petroleum ether/ethyl acetate 80:20) afforded **4** (288 mg, 65%) as a 10:1 mixture of two isomers (^{1}H NMR).

(1*R,2*S**)-2-Phenylcyclohexanol (*trans*-5) and (1*S**,2*S**)-2-Phenylcyclohexan-1-ol (*cis*-5).**[48] Prepared according to method B from **2** (477 μL, 3 mmol). Purification by flash chromatography (petroleum ether/ethyl acetate 80:20) afforded **5** (338 mg, 64%) as a 9:1 mixture of two isomers. *trans*-**5**: Waxy white solid. Mp 54−55 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 4H), 1.68 (br s, 1H), 1.78 (m, 1H), 1.88 (m, 2H), 2.12 (m, 1H), 2.44 (td, J = 12.9 and 3.7 Hz, 1H), 3.65 (td, J = 10.0 and 4.0 Hz, 1H), 7.27−7.36 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.9, 33.2, 34.3, 53.1, 74.2, 126.6, 127.8 (2C), 128.6 (2C), 143.3. IR (KBr) 3300, 1490, 1445, 1335, 1305, 1280, 1230, 1200, 1050 cm^{-1}. MS (EI, 70 eV) *m*/*z* 176 (M$^+$, 93), 158 (14), 130 (64), 104 (49), 91 (100), 77 (16), 57 (11). *cis*-**5**: Waxy white solid. Mp 46−48 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (m, 2H), 1.64 (m, 4H), 1.97 (m, 3H), 2.72 (td, J = 12.9 and 2.9 Hz, 1H), 4.00 (m, 1H), 7.25 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 24.3, 26.2, 32.9, 47.9, 70.5, 123.4, 127.7 (2C), 128.4 (2C), 143.9. IR (KBr) 3430, 1600, 1495, 1450, 1380, 1330, 1280, 1260, 1225, 1180, 1120, 1050 cm^{-1}. MS (EI, 70 eV) *m*/*z* 176 (M$^+$, 80), 158 (12), 117 (42), 104 (46), 91 (100), 78 (14), 57 (12).

(1*R,2*R**)-Cyclohexane-1,2-diol (*trans*-6) and (1*R**,2*S**)-Cyclohexane-1,2-diol (*cis*-6).** Prepared according to method B from **3** (583 μL, 3 mmol). Purification by flash chromatography (petroleum ether/ethyl acetate 20:80) afforded **6** (160 mg, 46%) as a 4:1 mixture of two isomers. *trans*-**6**: Waxy white solid. Mp 105−107 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (m, 4H), 1.89 (m, 2H), 2.15 (m, 2H), 3.48 (m, 2H), 5.06 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5 (2C), 34.3 (2C), 84.1 (2C). IR (KBr) 3380, 1445, 1360, 1350, 1290, 1235, 1195, 1065, 1040 cm^{-1}. MS (EI, 70 eV) *m*/*z* 116 (M$^+$, 12), 98 (38), 83 (37), 70 (100), 57 (53). *cis*-**6**: Waxy white solid. Mp 98−99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (m, 2H), 1.78 (m, 4H), 1.95 (m, 2H), 3.88 (m, 2H), 5.00 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0 (2C), 31.1 (2C), 72.0 (2C). IR (KBr) 3395, 3275, 2516, 2430, 1440, 1365, 1260, 1130, 1075 cm^{-1}. MS (EI, 70 eV) *m*/*z* 116 (M$^+$, 16), 98 (40), 83 (39), 70 (100), 57 (53).

2-Phenylethanol (11a) and 1-Phenylethanol (11b).[49] Prepared according to method B from **7** (344 μL, 3 mmol). Purification by flash chromatography (petroleum ether/ethyl acetate 80:20) gave **11** (252 mg, 69%) as a 9:1 mixture of two isomers. Colorless oil. **11a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (br s, 1H), 2.88 (t, J = 6.6 Hz, 2H), 3.85 (t, J = 6.2 Hz, 2H), 7.22−7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.9, 63.3, 126.2, 128.3 (2C), 128.8 (2C), 138.5. IR (neat) 3440, 1600, 1490, 1450, 1180, 1045 cm^{-1}. MS (EI, 70 eV) *m*/*z* 122 (M$^+$, 35), 103 (4), 91 (100), 77 (5), 65 (15), 51 (5). **11b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, J = 6.6 Hz, 3H), 2.90 (br s, 1H), 4.85 (q, J = 6.6 Hz, 1H), 7.31 (m, 1H), 7.38 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 70.0, 125.3 (2C), 127.2, 128.2 (2C), 145.7. IR (neat) 3350, 1600, 1490, 1450, 1370, 1200, 1075, 1030, 1010 cm^{-1}. MS (EI, 70 eV) *m*/*z* 122 (M$^+$, 39), 107 (100), 79 (84), 51 (15).

4-(Benzyloxy)butanol (12a)[50] **and 3-(Benzyloxy)butanol (12b).**[51] Prepared according to method B from **8** (486 μL, 3 mmol). Purification by flash chromatography (petroleum ether/ethyl acetate 80:20) afforded **12** (383 mg, 71%) as a 11:1 mixture of two isomers. Colorless oil. **12a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (m, 4H), 3.34 (br s, 1H), 3.50 (t, J = 5.9 Hz, 2H), 3.58 (t, J = 6.1 Hz, 2H), 4.50 (s, 2H), 7.20−7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 29.5, 62.0, 70.0, 72.6, 127.3, 127.4 (2C), 128.1 (2C), 137.9. IR (neat) 3380, 1450, 1365, 1210, 1100, 1060 cm^{-1}. MS (EI, 70 eV) *m*/*z* 180 (MH$^+$, 2), 161 (3), 107 (70), 91 (100), 79 (14), 55 (5). Anal. Calcd for $C_{11}H_{16}O_2$ (180.25): C, 73.30; H, 8.95. Found: C, 73.22; H, 9.09. **12b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, J = 6.2 Hz, 3H), 1.76 (m, 2H), 2.90 (br s, 1H), 3.69 (m, 2H), 4.02 (m, 1H), 4.55 (s, 2H), 7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ 23.3, 38.1, 67.6, 69.1, 73.3, 127.6 (2C), 127.7, 128.4 (2C), 137.9. IR (neat) 3400, 1495, 1450, 1370, 1205, 1100, 1025 cm^{-1}. MS (EI, 70 eV) *m*/*z* 180 (M$^+$, 1), 161 (18), 120 (17), 107 (52), 91 (100), 79 (14), 56 (14). Anal. Calcd for $C_{11}H_{16}O_2$ (180.25): C, 73.30; H, 8.95. Found: C, 73.13; H, 9.07.

1-[Methyl(*p*-toluenesulfonyl)amino]propanol (13a) and 1-[Methyl(*p*-toluenesulfonyl)amino]propan-2-ol (13b). Prepared according to method B from **9** (675 μL, 3 mmol). Flash chromatography (petroleum ether/ethyl acetate 20:80) gave **13** (590 mg, 81%) as a 2:1 mixture of two isomers. Colorless oil. **13a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (m, 2H), 2.39 (s, 3H), 2.69 (br s, 1H), 2.71 (s, 3H), 3.08 (t, J = 6.6 Hz, 2H), 3.71 (t, J = 5.7 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 29.9, 34.8, 46.6, 58.7, 127.1 (2C), 129.6 (2C), 134.1, 143.4. IR (neat) 3460, 1600, 1460, 1335, 1165, 1085, 1050 cm^{-1}. MS (EI, 70 eV) *m*/*z* 243 (M$^+$, 1), 198 (97), 155 (100), 91 (93), 65 (15); Anal. Calcd for $C_{11}H_{17}NSO_3$ (243.33): C, 54.30; H, 7.04; N, 5.75. Found: C, 54.17; H, 7.24; N, 5.63. **13b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, J = 6.6 Hz, 3H), 2.39 (s, 3H), 2.78 (s, 3H), 2.79 (m, 2H), 3.00 (dd, J = 13.8 and 8.3 Hz, 1H), 3.96 (m, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 21.3, 36.5, 57.5, 63.4, 127.2 (2C), 129.6 (2C), 133.9, 143.5. IR (neat) 3450, 1460, 1340, 1160, 1085 cm^{-1}. MS (EI, 70 eV) *m*/*z* 243 (M$^+$, 1), 198 (82), 155 (100), 91 (80), 65 (15). Anal. Calcd for $C_{11}H_{17}NSO_3$ (243.33): C, 54.30; H, 7.04; N, 5.75. Found: C, 54.56; H, 7.46; N, 5.61.

α-[3-(2-Hydroxyethyl)-1-azabicyclo[2.2.2]oct-6-yl]-6-methoxyquinoleine-4-methanol (14a). Prepared according to method B from **10** (972 mg, 3 mmol). Purification by flash chromatography (CH_2Cl_2/methanol 80:20; CH_2Cl_2/methanol 50:50) gave **14a** (636 mg, 62%) as a single isomer. Waxy white solid. Mp 201−202 °C; $[\alpha]_D$ −150° (*c* 1, MeOH). ^{1}H NMR (300 MHz, CD_3OD) δ 1.64 (m, 4H), 1.91 (m, 2H), 2.11 (m, 2H), 2.64 (m, 1H), 2.89 (m, 1H), 3.30 (m, 2H), 3.67 (t, J = 6.6 Hz, 2H), 3.89 (m, 1H), 4.16 (s, 3H), 5.10 (br s, 2H), 5.80 (d, J = 2.6 Hz, 1H), 7.58 (m, 2H), 7.89 (d, J = 4.8 Hz, 1H), 8.11 (d, J = 10.3 Hz, 1H), 8.87 (d, J = 4.8 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 21.5, 27.3, 28.7, 33.1, 38.6, 44.1, 56.4, 59.3, 60.9, 61.0, 72.3, 102.5, 120.0, 123.3, 128.1, 131.4, 144.7, 148.1, 150.6, 159.7. IR (KBr) 3450, 1600, 1580, 1520, 1445, 1355, 1245, 1190, 1105, 1050 cm^{-1}. Anal. Calcd for $C_{20}H_{26}O_3N_2$ (342.43): C, 70.15; H, 7.65; N, 8.18. Found: C, 69.08; H, 7.99; N, 7.66. HRMS (CI, CH_4) calcd for $C_{20}H_{27}O_3N_2$ [MH$^+$] 343.2022, found 343.2024.

Reactions with TEMPO. Method E: Catecholborane (0.64 mL, 6.0 mmol) was added dropwise at 0 °C under N_2 to a solution of the olefin (3.0 mmol) and *N*,*N*-dimethylacetamide (28.0 μL, 0.3 mmol) in CH_2Cl_2 (2 mL), and the reaction mixture was heated under reflux for 3 h. EtOH (0.21 mL, 3.6 mmol) was added at 0−5 °C and the solution was stirred for 15 min at room temperature. To this solution were successively added TEMPO (1.03 g, 6.6 mmol) in CH_2Cl_2 (4 mL) and DMPU (0.36 mL, 3.0 mmol). The reaction was stirred overnight at room temperature. The resulting mixture was treated with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography (hexane, hexane/diethyl ether).

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Method F: Catecholborane (0.43 mL, 4.0 mmol) was added dropwise at 0−5 °C to a solution of the olefin (2.0 mmol) and [Rh(diphos)(COD)]BF_4 (29 mg, 0.04 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was stirred overnight at 20 °C, EtOH (0.14 mL, 2.4 mmol) was added at 0−5 °C, and the solution was stirred for 15 min at room temperature. To this solution were successively added TEMPO (687 mg, 4.4 mmol) in CH_2Cl_2 (1 mL) and DMPU (0.24 mL, 2.0 mmol). The reaction was stirred overnight at room temperature. The resulting mixture was treated with a saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography (hexane, hexane/diethyl ether).

Method G: Catecholborane (0.64 mL, 6.0 mmol) was added dropwise at 0−5 °C under N_2 to a solution of the olefin (3.0 mmol) and *N*,*N*-dimethylacetamide (28.0 μL, 0.3 mmol) in CH_2Cl_2 (2.0 mL). The reaction mixture was heated under reflux for 3 h and EtOH (0.21 mL, 3.6 mmol) was added at 0−5 °C and the solution was stirred for 15 min at room temperature. The activated alkene (15.0 mmol) in CH_2Cl_2 (13 mL) and DMPU (0.36 mL, 3.0 mmol) were successively added followed by TEMPO (1.03 g, 6.6 mmol) in CH_2Cl_2 (6 mL) via syringe-pump over 2 h at room temperature. The reaction mixture was stirred for 3 h at room temperature. The resulting solution was treated with a saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography (hexane, hexane/ethyl acetate).

1-(Cyclohexyloxy)-2,2,6,6-tetramethylpiperidine (20). Prepared according to method E from **15** (305 μL, 3.0 mmol). Flash chromatography (hexane, hexane/diethyl ether 95:5) gave **20** (621 mg, 87%). Colorless oil. ^{1}H NMR (500.13 MHz, $CDCl_3$, 50 °C) δ 1.12 (s, 12H), 1.10−1.28 (m, 6H), 3.57−3.63 (m, 1H), 1.44 (br s, 4H), 1.49−1.55 (m, 2H), 1.71−1.75 (m, 2H), 2.02−2.08 (m, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.3, 20.3, 25.1, 25.9, 32.9, 34.4, 40.2, 59.6, 81.7. IR (neat) 1452, 1375, 1257, 1132, 1043 cm^{-1}. MS (EI, 70 eV) *m*/*z* 240 ([MH]$^+$, 24), 239 (M$^+$, 10), 157 (14), 142 (100), 110 (4), 84 (10), 70 (12), 56 (36). Anal. Calcd for $C_{15}H_{29}NO$ (239.40): C, 75.26; H, 12.21. Found: C, 75.27; H, 12.30.

2,2,6,6-Tetramethyl-1-[(2-phenylcyclopentyl)oxy]piperidine (21). Prepared according to method E from **16** (432 mg, 3.0 mmol). Flash chromatography (hexane, hexane/diethyl ether 95:5) gave **21** (641 mg, 71%) as a 89:11 mixture of two isomers (^{1}H NMR). Colorless oil. *trans*-**21** (major): ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 0.60−1.81 (m, 18H), 1.90−2.22 (m, 4H), 2.09−2.19 (m, 2H), 3.13 (ddd, *J* = 9.8, 7.2, and 6.3 Hz, 1H), 4.32 (dt, *J* = 6.1 and 6.0 Hz, 1H), 7.14−7.18 (m, 2H), 7.23−7.32 (m, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.2, 23.3, 32.2, 33.3, 40.3, 51.1, 92.2, 125.7, 127.8, 128.1, 145.6. 4 CH_3 and 2 C signals from the oxy-2,2,6,6-tetramethylpiperidin-1-yl moiety were not observed but are present as large signals. *cis*-**21** (minor): ^{1}H NMR (500.13 MHz, $CDCl_3$) characteristic signals: δ 3.22 (ddd, *J* = 9.8, 7.2, and 6.3 Hz, 1H), 4.44 (dt, *J* = 6.4 and 5.7 Hz, 1H). *trans*- and *cis*-**21**: IR (neat) 1603, 1493, 1469, 1452, 1375, 1360, 1260, 1242, 1134, 1032 cm^{-1}. MS (CI, CH_4) *m*/*z* 302 (MH$^+$, 100), 157 (35), 140 (80), 117 (5), 91 (7). Anal. Calcd for $C_{20}H_{31}NO$ (301.47): C, 79.68; H, 10.36. Found: C, 79.62; H, 10.43.

2,2,6,6-Tetramethyl-1-[(2,2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)oxy]piperidine (22). Prepared according to method E from **17** (476 μL, 3.0 mmol). Flash chromatography (hexane, hexane/diethyl ether 95:5) gave **22** (724 mg, 82%) as a 97:3 mixture of two isomers (^{1}H NMR). Waxy white solid. **22** (major): ^{1}H NMR (500.13 MHz, $CDCl_3$, 50 °C) δ 0.88 (s, 3H), 1.14−1.21 (m, 18H), 1.43−1.47 (m, 7H), 1.73 (td, *J* = 5.8, 2.3 and 1H), 1.88 (sept, *J* = 3.3 Hz, 1H), 2.11 (ddd, *J* = 14.4, 4.3, and 3.1 Hz, 1H), 2.19−2.37 (m, 3H), 4.22 (ddd, *J* = 9.5, 9.4, and 4.6 Hz, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$, 50 °C) δ 17.3, 21.7, 23.6, 27.5, 32.9, 34.5, 38.4, 40.6, 41.6, 44.3, 48.1, 59.7, 82.3. The 4 CH_3 signals of the oxy-2,2,6,6-tetramethylpiperidin-1-yl moiety were observed neither at room temperature nor at 50 °C. **22** (minor): ^{1}H NMR (500.13 MHz, $CDCl_3$) characteristic signal: δ 3.96−3.90 (m, 1H). **22** (mixture of isomers): IR (neat) 1471, 1373, 1257, 1180, 1132 cm^{-1}. MS (EI, 70 eV) *m*/*z* 294 (MH$^+$, 10), 158 (29), 142 (100), 138 (8), 96 (15), 82 (46), 55 (26). HRMS (ESI in CH_3CN) calcd for $C_{19}H_{35}NO$ [MH]$^+$ 294.2796, found 294.2792.

1-{[(6,6-Dimethylbicyclo[3.1.1]hept-2-yl)methyl]oxy}-2,2,6,6-tetramethylpiperidine (23). Prepared according to method E from **18** (476 μL, 3.0 mmol). Flash chromatography (hexane, hexane/diethyl ether 95:5) gave **23** (506 mg, 57%) as a 91:9 mixture of two isomers (^{1}H NMR). Waxy white solid. **23** (major): ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.09 (br s, 6H), 1.14 (br s, 3H), 1.16 (br s, 3H), 1.17 (s, 3H), 1.27−1.61 (m, 8H), 1.83−1.96 (m, 4H), 2.05−2.08 (m, 1H), 2.28−2.38 (m, 2H), 3.66 (dd, *J* = 8.2 and 6.9 Hz, 1H), 3.73 (t, *J* = 8.2 Hz, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.1, 19.1, 20.2, 23.2, 26.2, 28.0, 33.2, 33.1, 33.4, 38.5, 39.6, 40.6, 41.4, 43.5, 59.7, 81.3. **23** (minor): ^{1}H NMR (500.13 MHz, $CDCl_3$) characteristic signals: δ 3.60−3.54 (m, 2H). **23** (mixture of diastereomers): IR (neat) 1469, 1372, 1360, 1261, 1244, 1132, 1049 cm^{-1}. MS (CI, CH_4) *m*/*z* 294 (MH$^+$, 95), 293 (M$^+$, 40), 278 (32), 157 (27), 141 (100), 126 (21), 96 (6), 81 (17), 70 (7). Anal. Calcd for $C_{19}H_{35}NO$ (293.49): C, 77.76; H, 12.02. Found: C, 77.86; H, 12.01.

2,2,6,6-Tetramethyl-1-[(1,1,2-trimethylpropyl)oxy]piperidine (24). Prepared according to method E from **19** (352 μL, 3.0 mmol). Flash chromatography (hexane, hexane/diethyl ether 95:5) gave **24** (461 mg, 64%). Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.89 (s, 3H), 0.91 (s, 3H), 1.08 (s, 6H), 1.11 (s, 6H), 1.15 (s, 6H), 1.24−1.31 (m, 1H), 1.39−1.62 (m, 5H), 2.05 (sept, *J* = 6.7 Hz, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.2, 18.3, 20.7, 22.6, 35.0, 38.3, 41.0, 59.2, 81.2. IR (neat) 2974, 2934, 1468, 1373, 1255, 1140, 1095 cm^{-1}. MS (EI, 70 eV) *m*/*z* 242 (MH$^+$, 6), 158 (12), 142 (100), 84 (8), 70 (10), 55 (17). Anal. Calcd for $C_{15}H_{31}NO$ (241.42): C, 74.63; H, 12.94. Found: C, 74.25; H, 12.90.

1-(2,3-Dihydro-1*H*-inden-1-yloxy)-2,2,6,6-tetramethylpiperidine (26). Prepared according to method F from indene (235 μL, 2.0 mmol). Flash chromatography (hexane, hexane/diethyl ether 95:5) gave **26** and **26′** (473 mg, 86%) as a 96:4 mixture of two isomers (^{1}H NMR). Colorless oil. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.11 (br s, 3H), 1.15 (br s, 3H), 1.26 (br s, 6H), 1.30−1.68 (m, 6H), 2.12−2.03 (m, 1H), 2.48 (dddd, *J* = 12.2, 7.2, and 6.3, 3.1 Hz, 1H), 2.66−2.73 (m, 1H), 2.92 (ddd, *J* = 15.5, 8.3, and 3.1 Hz, 1H), 5.36 (dd, *J* = 7.4 and 6.8 Hz, 1H), 7.19−7.23 (m, 3H), 7.56−7.60 (m, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.2, 20.4, 29.8, 34.7, 35.8, 40.4, 88.4, 125.0, 124.6, 125.8, 127.6, 143.3, 143.9. The two quaternary carbon atoms from the oxy-2,2,6,6-tetramethylpiperidin-1-yl group are missing. IR (neat) 1462, 1375, 1360, 1336, 1257, 1132, 1061 cm^{-1}. MS (EI, 70 eV) *m*/*z* 274 (MH$^+$, 15), 158 (37), 142 (100), 117 (89), 91 (7), 70 (11), 55 (13). Anal. Calcd for $C_{18}H_{27}NO$ (273.42): C, 79.07; H, 9.95. Found: C, 79.03; H, 10.01.

3-Cyclohexyl-1-phenyl-4-[(2,2,6,6-tetramethyl-1-piperidinyl)oxy]-2,5-pyrrolidinedione (27). Prepared according to method G from **15** (305 μL, 3.0 mmol) and *N*-phenylmaleimide (2.60 g, 15.0 mmol). Flash chromatography (hexane/ethyl acetate 90:10) gave **27** (868 mg, 70%). For analytical purposes, a sample was recrystallized from hexane at −18 °C. White solid. Mp 73−76 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.14 (s, 3H), 1.24 (s, 6H), 1.09−1.63 (m, 11H), 1.66−1.89 (m, 5H), 1.92−2.02 (m, 1H), 3.03 (ddd, *J* = 3.8 and 1.7 Hz, 1H), 4.64 (d, *J* = 1.8 Hz, 1H), 7.27−7.30 (m, 2H), 7.32−7.39 (m, 1H), 7.43−7.48 (m, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 176.7, 173.6, 131.7, 129.1, 128.5, 126.3, 82.2, 60.7, 60.3, 52.9, 40.1, 39.9, 34.3, 33.4, 31.4, 30.0, 29.7, 26.4, 26.2, 25.9, 20.4, 17.1. IR (KBr) 1780, 1711, 1599, 1500, 1454, 1379, 1186, 1134 cm^{-1}. FAB-MS *m*/*z* 413.3 [MH$^+$] (calcd average for $C_{25}H_{37}N_2O_3$ 413.6). Anal. Calcd for $C_{25}H_{36}N_2O_3$ (412.57): C, 72.78; H, 8.80. Found: C, 72.82; H, 8.74.

Dimethyl 2-Cyclohexyl-3-[(2,2,6,6-tetramethyl-1-piperidinyl)oxy]butanedioate (28). Prepared according to method G from **15** (305 μL, 3.0 mmol) and dimethyl fumarate (2.16 g, 15.0 mmol). Flash chromatography (hexane/ethyl acetate 94:6 then 90:10) gave **28** (352 mg, 31%) and **20** (194 mg, 27%). For analytical purposes, a sample was recrystallized from hexane at −18 °C. White solid. Mp 83−85 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.03 (s, 3H), 1.04 (s, 3H), 1.31 (s, 3H), 0.91−1.73 (m, 17H), 2.89 (dd, J = 9.7 and 6.3 Hz, 1H), 3.70 (s, 6H), 4.72 (d, J = 9.7 Hz, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.0, 20.0, 20.1, 26.1, 26.3, 26.5, 29.2, 31.4, 33.0, 33.7, 37.6, 40.3, 40.8, 51.3, 51.5, 53.3, 59.5, 61.3, 82.4, 171.2, 172.6. IR (KBr) 1740, 1726, 1468, 1437, 1361, 1348, 1279, 1259, 1155, 1026 cm^{-1}. MS (CI, CH_4) m/z 384 (MH^+, 18), 368 (6), 156 (100), 140 (73), 126 (12), 83 (5), 55 (6). Anal. Calcd for $C_{21}H_{37}NO_5$ (383.53): C, 65.77; H, 9.72. Found: C, 65.72; H, 9.72.

1-{[2-Cyclohexyl-1-(phenylsulfonyl)ethyl]oxy}-2,2,6,6-tetramethylpiperidine (29). Prepared according to method G from **15** (305 μL, 3 mmol) and phenyl vinyl sulfone (2.52 g, 15 mmol). Flash chromatography (hexane/AcOEt 94:6 then 90:10) gave **29** (216 mg, 18%) and **20** (410 mg, 57%). For analytical purposes, a sample was recrystallized from hexane at −18 °C. White solid. Mp 85−88 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 0.67 (s, 3H), 0.93 (s, 3H), 1.00 (s, 6H), 0.86−1.07 (m, 2H), 1.13−1.57 (m, 9H), 1.64−1.75 (m, 3H), 1.84 (ddd, J = 14.7, 9.4, and 4.4 Hz, 1H), 1.76−2.01 (m, 3H), 2.22 (ddd, J = 14.8, 9.5, and 3.3 Hz, 1H), 4.99 (dd, J = 9.4 and 3.3 Hz, 1H), 7.54−7.58 (m, 2H), 7.61−7.66 (m, 1H), 7.95−7.97 (m, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 17.0, 20.3, 20.9, 25.9, 26.1, 26.5, 32.5, 33.4, 33.9, 34.0, 34.4, 34.5, 40.1, 40.4, 59.8, 61.4, 94.3, 128.7, 129.4, 133.4, 138.1. IR (KBr) 1446, 1361, 1321, 1305, 1286, 1147, 1086 cm^{-1}. FAB-MS m/z 408.3 [MH^+] (calcd average for $C_{23}H_{38}NO_3S$ (408.6)). Anal. Calcd for $C_{23}H_{37}NO_3S$ (407.61): C, 67.77; H, 9.15. Found: C, 67.72; H, 9.20.

2-(1*R*,4*S*)-4-(Methylcyclohexen-2-yl)-2-propanol (31)[42] **and (1*R*,2*S*,3*R*,6*S*)-2-*tert*-Butyldiphenylsilyloxy-3,7,7-trimethylbicyclo[4.1.0]heptane (32′).** Prepared according to method D from **30** (315 μL, 3 mmol). Purification by flash chromatography (petroleum ether/AcOEt 70:30) gave **31** and **32** (277 mg, 90%) in a 2:1 ratio (^{1}H NMR). To separate **31** and **32**, compound **32** was converted selectively to the corresponding *tert*-butyldiphenylsilyl ether **32′**. This transformation was realized as follows: To a mixture of alcohols **31** and **32** (116 mg, 0,75 mmol) in DMF (1 mL) were added successively imidazole (40 mg, 0.55 mmol,) and TBDPSCl (70 μL, 0.27 mmol), and the mixture was stirred for 4 h at room temperature. The mixture was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (petroleum ether/AcOEt 90:10) afforded the desired silyl ether **32′** (39 mg, 51%) and the unreacted tertiary alcohol **31**. **32′**: Colorless oil. $[\alpha]_D$ +22.2° (*c* 0.8, petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.55 (m, 1H), 0.62 (s, 3H), 0.67 (s, 3H), 0.77 (dd, J = 9.6 and 2.9 Hz, 1H), 0.85 (d, J = 6.6 Hz, 3H), 1.15 (s, 9H), 1.45 (m, 4H), 1.75 (m, 1H), 3.19 (dd, J = 9.9 and 2.9 Hz, 1H), 7.42 (m, 6H), 7.75 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 16.6, 19.0, 19.1, 19.6, 20.6, 27.1 (3C), 28.4, 30.6, 30.8, 37.8, 74.7 127.3 (4C), 129.2, 129.3, 134.7, 135.0, 136.1 (4C). IR (neat) 1590, 1470, 1460, 1425, 1390, 1375, 1360, 1190, 1110, 1090, 1070 cm^{-1}. MS (EI, 70 eV) m/z 392 (M^+, 0.1), 335 (32), 257 (1), 199 (100), 183 (7), 135 (9), 77 (2). Anal. Calcd for $C_{26}H_{36}OSi$ (392.65): C, 79.53; H, 9.24. Found: C, 79.73; H, 9.43.

2-[(1*R*,4*S*)-4-Methyl-2-cyclohexen-1-yl]-2-propanol (31).[42] To a stirred solution of the alkoxyamine **35** (147 mg, 0.50 mmol) in 3:1:1 AcOH/:THF/H_2O (7 mL) at room temperature was added Zn dust (375 mg, 5.90 mmol) in small portions. The stirred mixture was heated for 4 h at 60 °C. The cooled mixture was filtered through a pad of silica gel. The filtrate was concentrated in vacuo. The residue was neutralized with 15% aq Na_2CO_3 and extracted with CH_2Cl_2. The extract was washed with brine and dried ($MgSO_4$) and concentrated. Purification by flash chromatography afforded the alcohol **31** (63 mg, 82%) as a colorless liquid. $[\alpha]_D^{21}$ −74° (*c* 0.75, C_6H_6) (lit.[52] $[\alpha]_D^{21}$ −47.3° (*c* 0.54, C_6H_6)). ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.98 (d, J = 7.3 Hz, 3H), 1.18 (s, 3H), 1.22 (s, 3H), 1.42−1.53 (m, 2H), 1.57 (br s, 1H), 1.60−1.75 (m, 2H), 2.06−2.14 (m, 1H), 2.15−2.25 (m, 1H), 5.65−5.71 (m, 1H), 5.74−5.79 (m, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 20.3, 20.9, 26.3, 27.8, 28.7, 28.8, 46.6, 72.7, 126.3, 135.5. IR (neat) 3384, 3020, 2955, 2967, 1651, 1456, 1365, 1213, 1146, 1118, 1035 cm^{-1}. MS (CI, CH_4) m/z 154 (M, 3), 153 (8), 137 (100), 109 (6), 95 (29), 81 (70), 59 (31). Anal. Calcd for $C_{10}H_{18}O$ (154.25): C, 77.87; H, 11.76. Found: C, 77.39; H, 11.60. HRMS (CI, isobutane) calcd for $C_{10}H_{17}$ $[MH]^+ - H_2O$ 137.1330, found 137.1325.

2,2,6,6-Tetramethyl-1-{1-methyl-1-[(1*R*,4*S*)-4-methyl-2-cyclohexen-1-yl]ethoxy}piperidine (35). Prepared according to the general procedure E from (+)-2-carene **30** (474 μL, 3.0 mmol). Flash chromatography (hexane, hexane/diethyl ether 95:5) gave **35** (552 mg, 63%). $[\alpha]_D^{21}$ −49.8° (*c* 0.54, C_6H_6). Colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.98 (d, J = 7.0 Hz, 3H), 1.09 (s, 3H), 1.10 (s, 3H), 1.19 (s, 3H), 1.12 (s, 6H), 1.21 (s, 3H), 1.25−1.31 (m, 2H), 1.43−1.59 (m, 6H), 1.61−1.75 (m, 2H), 2.14−2.20 (m, 1H), 2.50−2.56 (m, 1H), 5.65−5.70 (m, 1H), 5.75−5.79 (m, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 17.2, 20.5, 20.8, 21.0, 23.6, 23.8, 28.8, 29.2, 34.9, 35.2, 41.0, 47.0, 59.3, 80.9, 128.6, 133.7. IR (neat) 2932, 1457, 1375, 1363, 1208, 1178, 1132 cm^{-1}. MS (CI, CH_4) m/z 294 (MH^+, 41), 158 (69), 140 (100), 95 (10), 81 (13). Anal. Calcd for $C_{19}H_{35}NO$ (293.49): C, 77.76; H, 12.02; N, 4.77. Found: C, 77.95; H, 12.12; N, 4.66.

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