Activation of molecular oxygen and its use in stereoselective tetrahydrofuran-syntheses from δ,ε-unsaturated alcohols†‡

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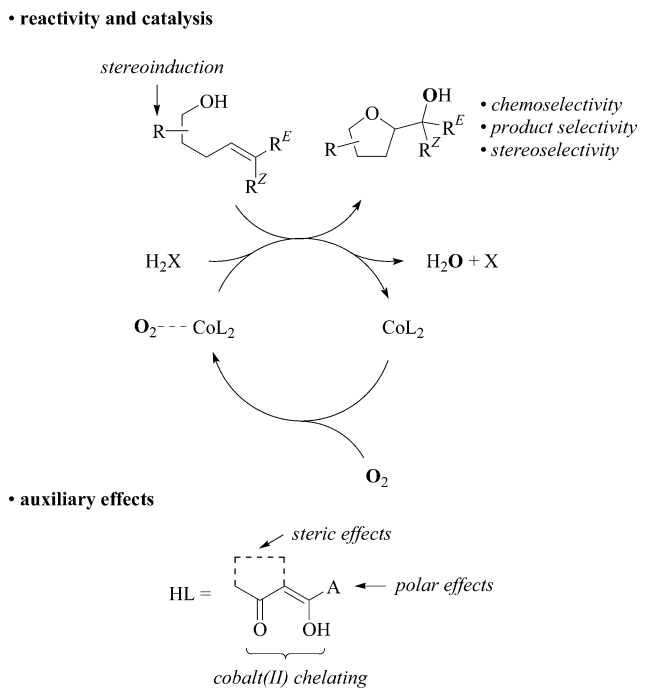
Bishomoallylic alcohols (pent-4-en-1-ols) underwent efficient oxidative cyclizations, if treated with O_2 and bis{2,2,2-trifluoromethyl-1-[(1*R*,4*S*)-1,7,7-trimethyl-2-(oxo-κ*O*)bicyclo[2.2.1]hept-3-yliden]ethanolato-κ*O*}cobalt(II) in solutions of 2-propanol at 60 °C. Ring closures occurred diastereoselectively and afforded 2,3-*trans*- (96% de), 2,4-*cis*- (~60% de), and 2,5-*trans*-substituted (>99% de) (phenyl)tetrahydrofur-2-ylmethanols as major components. Formation of bicyclic compounds and a 2,3,4,5-substituted oxolane was feasible as exemplified by syntheses of oxabicyclo[4.3.0]nonylmethanols and a derivative of natural product magnosalicin in 61–72% (90–99% de). The effectiveness of tetrahydrofuran synthesis was critically dependent on (i) solvent, (ii) reaction temperature, (iii) initial cobalt concentration, (iv) chain length between hydroxyl and vinyl groups, and (v) substitution at reacting entities. A sequence is proposed for rationalizing observed selectivities.

Introduction

In a series of papers it was reported that acceptor-substituted bis{[2-(oxo-κ*O*)prop-1-yliden]methanolato-κ*O*}cobalt(II) complexes, *i.e.* compounds derived from β-diketonate anions and Co(II), were able to induce oxidative cyclization of 1-substituted bishomoallylic alcohols (pent-4-en-1-ols), if heated with a 1–1.5 molar excess of *tert*-butyl hydroperoxide (TBHP) in an atmosphere of molecular oxygen.[1–4] The reaction afforded 5-substituted tetrahydrofur-2-ylmethanols with a notable degree of 2,5-*trans* diastereoselection and has been applied in a number of natural product syntheses.[3–6]

The mechanism of the aerobic tetrahydrofuran synthesis is subject to debate, since cobalt(II) chelates combine affinity for dioxygen binding,[7–13] with a marked propensity for alkyl hydroperoxide decomposition in a Fenton-type manner.[14–17]

Given the fact that functionalized tetrahydrofurans occur widely in nature,[5,18] we became interested in the scope of aerobic alkenol oxidation[19,20] as a tool in stereoselective heterocycle synthesis. Four major achievements were considered necessary for a more profound validation of this reaction. (i) Parameters for conducting tetrahydrofur-2-ylmethanol syntheses using O_2 as terminal oxidant had to be identified and applied to a larger set of 1-, 2-, and 3-substituted pent-4-en-1-ols. (ii) Guidelines for predicting selectivity in aerobic oxidative cyclizations had to be derived. (iii) An extension of the method toward tri- and tetrasubstituted tetrahydrofuran synthesis had to be developed (Scheme 1). The major results of a study performed on the basis of the given key notes showed that acceptor-substituted camphor-derived cobalt(II) chelates were able to catalyze formation of *trans*-2,3-, *cis*-2,4-, and *trans*-2,5-substituted tetrahydrofur-2-ylmethanols from underlying bishomoallylic alcohols and O_2. Addition of TBHP was not required for obtaining yields between 60–80%. The newly developed procedure was furthermore applicable in syntheses of tetrasubstituted and bicyclic oxolanes. Its success,



Scheme 1 Objectives for the development of sustainable tetrahydrofuran syntheses *via* cobalt-catalyzed aerobic alkenol oxidation (A, R = alkyl, aryl; R^E, R^Z = H, CH_3; H_2X = coreductant).

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† The following abbreviations have been used: AIBN = α,α-azobis(isobutyronitrile), CHD = cyclohexa-1,4-diene, DBPO = dibenzoyl peroxide, TBHP = *tert*-butyl hydroperoxide. Products of oxidative ring closure were obtained as racemates. The presented structural formulae of these molecules were drawn by arbitrarily selecting one of the enantiomers.

‡ Electronic supplementary information (ESI) available: Standard instrumentation, protocol for quantitative acetone analysis, procedure for determining enantiomeric purity *via* P NMR, and results from aerobic oxidation in 2-propanol-d_8. See DOI: 10.1039/b804588g

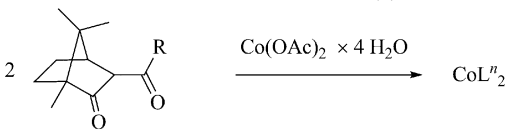
however, was critically dependent on solvent, temperature, cobalt complex concentration, and alkenol constitution.

Results

1. Synthesis and characterization of bis{1-[(1*R*,4*S*)-1,7,7-trimethyl-2-(oxo-κ*O*)bicyclo[2.2.1]hept-3-yliden]methanolato-κ*O*}cobalt(II) complexes

Auxiliaries **1–4** that allowed a swift and efficient survey of parameters that control reactivity and selectivity in oxidative cobalt-catalyzed alkenol ring closure (see also Scheme 1) were prepared *via* α-acylation of (1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, *i.e.* (+)-bornan-2-one, (+)-camphor, in extension to literature procedures.[21,22] Treatment of diketones with $Co(OAc)_2 \cdot 4H_2O$ in EtOH (for **1–3**, Table 1, entries 1–3)[23–25] or in a mixture of aq. EtOH and aq. NaOH (for **4**, Table 1, entry 4)[25] furnished cobalt complexes as red–brown (**5**, **7**[26]), red (**6**),[27] or orange (**8**) crystalline solids. In view of its propensity to liberate diketone **1** upon drying at 20–25 °C under reduced pressure, compound **5** was applied as an *in situ* preparation. Cobalt complexes were characterized *via* MALDI-TOF (**5–8**), UV/Vis- and IR-spectroscopy (**5–8**), and combustion analysis (**6**, **8**). The compounds were readily soluble in polar organic solvents, *e.g.*, EtOH (except for **8**), 2-propanol, THF, Et_2O, acetone, and CH_2Cl_2. They were insoluble in H_2O or aliphatic hydrocarbons. In contrast to complex **8**, cobalt(II) compounds **5–7** showed a marked affinity for solvate formation, as evident from combustion analysis.

Table 1 Conversion of diketones **1–4** into cobalt(II) chelates **5–8**



HL^n : **1–4** **5–8**

Entry	**1–4**	R	Yield of **5–8** [%]
1[a]	**1** (HL^1)	$C(CH_3)_3$	**5**:—[b]
2[a]	**2** (HL^2)	CF_3	**6**: quant.
3[a]	**3** (HL^3)	C_6H_5	**7**: 60
4[c]	**4** (HL^4)	3,5-$(CF_3)_2C_6H_3$	**8**: quant.

[a] Reaction in EtOH at 20 °C. [b] *In situ*-preparation. [c] In EtOH–H_2O, 50 : 50 (*v*/*v*) at 20 °C.

2. Reactivity of bis[β-diketonato(−1)]cobalt(II) complexes toward dioxygen

Cobalt(II) complex **6** served for reasons that are outlined below as a benchmark for probing the reactivity of cobalt(II) compounds in combination with O_2 toward organic substrates. A solution of bis[3-trifluoroacetylcamphorato(−1)]cobalt(II) complex **6** (1.00 mmol, c_o = 0.10 M) in 2-propanol (20 °C) absorbed O_2 with a steadily decreasing rate. Gas uptake was paralleled by a gradual change in color from red (**6**) *via* brown to green. It levelled off after a consumption of 3.21 mmol of the oxidant (~140 h). Product analysis indicated formation of acetone (3.21 mmol) and H_2O (3.20 mmol, see also Table 4). Removal of the volatiles from the solution afforded a green solid. If compared to complex **6**, the IR spectrum of the residue showed apart from two additional new IR-absorptions at 1205 and 1147 cm^{-1} similar bands. UV/Vis absorptions of this material were located at 270 and 600 nm, and a shoulder at 361 nm (*i*PrOH). Chromatographic purification for separating organic components from the residue afforded 3-oxa-1,8,8-trimethylbicyclo[3.2.1]octane-2,4-dione, *i.e.* camphor acid anhydride[28] (0.08 mmol), a 50 : 50 diastereomeric mixture of 4-isopropoxy-1,8,8-trimethylbicyclo[3.2.1]-3-oxaoctan-2-one (0.37 mmol, ESI), and at least one additional camphor-derived product of hitherto unknown constitution.

3. Oxidative cyclizations

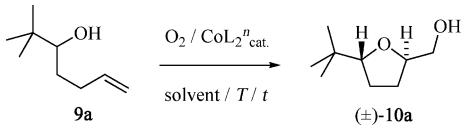
3.1 Establishing parameters for oxidative pent-4-en-1-ol-cyclization. The oxidation of 2,2-dimethylhept-6-en-3-ol (**9a**)[29] was selected as a reporter reaction for establishing parameters for efficient aerobic alkenol ring closures. Type, amount, and initial concentration of cobalt reagents (*i.e.* **5–8**), additive, solvent, and means of thermal activation were varied.

If stirred in a solution of 2-propanol at 60 °C in a stationary O_2 atmosphere (>95%), cobalt(II)-complexes **5–8** induced formation of tetrahydrofuran **10a**[30] with a marked preference for the *trans*-isomer. The yield of product **10a** gradually decreased along the sequence of cobalt(II) complexes **6** (R = CF_3) > **8** [R = 3,5-$(CF_3)_2C_6H_3$] > **7** (R = C_6H_5) ~ **5** [R = $C(CH_3)_3$] (Table 2, entries 1–4). The product was obtained as a racemate, regardless whether the material was isolated at conversions below or above 50%. Its enantiomeric purity was determined by ^{31}P NMR with the aid of a chiral phosphorous-based derivatization reagent.[31] No conversion of **9a** took place, upon substituting $Co(OAc)_2 \cdot 4H_2O$ for, *e.g.*, complex **6** (GC). Purging of O_2 through solutions of **6** and alkenol **9a** in 2-propanol at 60 °C furnished complete turnover of the substrate, however, without providing a satisfactory mass balance (not shown). The use of a monomode microwave instrument§ for inducing thermal activation was associated with shorter reaction times but also with a significant increase in side product formation (*e.g.* Table 2, entry 5).

The yield of product formation was critically dependent on reactant concentration. In a separate study (not shown) it was found that a solution containing 1 mmol of **9a** in 8 mL of solvent afforded the most efficient turnover. A precatalyst concentration of 1.25×10^{-2} M (10 mol%) of **6** posed a reasonable balance between selectivity and time–yield factor. A further investigation showed that initial concentrations of complex **6** below 10^{-2} M provided slower but more chemoselective conversion of substrate **9a** (not shown). Since catalyst deactivation gradually occurred, a complete conversion of alkenol **9a** was not attainable within 15 h, if cobalt concentrations fell below 6.0×10^{-3} M. The UV/Vis spectrum of the spent catalyst pointed to formation of a cobalt(III) residue of unknown constitution. UV/Vis absorptions of the green material [λ/nm = 271, 309sh, 362sh, 607] and strong IR bands at 1203 and 1135 cm^{-1} were similar but not identical to spectral information of a product originating from the reaction between **6** and O_2 (see above).[32] Addition of typical Co(III)→Co(II) reductants,[33] *e.g.* formate, hypophosphite, or L-ascorbate provided a change in color from brown to pink, however,

§ All microwave-assisted experiments were performed using special glassware and microwave equipment.

Table 2 Solvent and catalyst effects in cobalt(II)-catalyzed oxidations of alkenol **9a**



9a (±)-**10a**

Entry	Co(II) [%]	Solvent[a]	T/°C	t/h	Convn. [%][b]	Yield [%] (*cis* : *trans*)[b]
1	**5** [10][c]	*i*PrOH	60	15	24	3 (11 : 89)
2	**6 [10]**	***i*PrOH**	**60**	**2.5**	**91**	**63 (< 1 : 99)**[d]
3	**7** [10]	*i*PrOH	60	3.0	14	4 (< 1 : 99)[d]
4	**8** [10]	*i*PrOH	60	3.0	87	42 (1 : 99)
5	**6** [10]	*i*PrOH	60	1.5[e]	quant.	50 (2 : 98)
6	**6** [20]	EtOH	60	15[f]	quant.	50 (< 1 : 99)[d]
7	**6** [20]	*t*BuOH	60	15[f]	quant.	32 (< 1 : 99)[d]
8	**6** [20]	cC_5H_9OH	60	15[f]	quant.	31 (< 1 : 99)[d]
9	**6** [20]	CF_3CH_2OH	60	15[f]	48	25 (8 : 92)
10	**6** [10]	RR′C=O[g]	60	2.5	70	9[h] (15 : 85)
11	**6** [10]	*t*BuCHO	60	2.5	42	< 1[i] (< 1 : 99)[d]
12	**6** [10]	$EtCH(OEt)_2$	60	2.5	85	42[j] (< 1: 99)[d]
13	**6 [10]**	**CHD–C_6H_6**[k]	**60**	**2.5**	**98**	**8**[l] **(< 1 : 99)**[d]
14	**6** [20]	CH_2Cl_2	20	48[f]	85	28 (6 : 94)

[a] 8 mL of p.a. grade solvent. [b] Quantitative GC measurements; er = 50 : 50 for *trans*-**10a**. [c] *In situ* formation of **5**. [d] *cis*-**10a** not detected (GC). [e] Microwave heating (300 W, monomode instrument). [f] MS 4 Å added. [g] 2-Methylcyclohexanone. [h] Additional product: 2-*tert*-butyl-5-methyltetrahydrofuran **11a** (*cis* : *trans* < 1 : 99, 36%). [i] additional product: 2-*tert*-butyl-5-methyltetrahydrofuran *trans*-**11a** (40%). [j] Additional products: 2-*tert*-butyl-5-methyltetrahydrofuran *trans*-**11a** (13%), 4-*tert*-butyl-δ-valerolactol **14a** (10%). [k] Cyclohexa-1,4-diene : benzene 50 : 50 (*v*/*v*). [l] Additional product: 2-*tert*-butyl-5-methyltetrahydrofuran *trans*-**11a** (90%).

without restoring catalytic activity for oxidative bishomoallylic alcohol cyclization. Addition of NH_4SCN to the 1-pentanol soluble fraction of, *e.g.*, hypophosphite-reduced cobalt residue obtained from aerobic oxidation of **6** in *i*PrOH afforded an UV/Vis absorption at 620 nm, which was indicative of $Co(SCN)_2$. Addition of one of the reductants to an aerated solution of alkenol **9a** and complex **6** in 2-propanol completely inhibited formation of *tert*-butyltetrahydrofurylmethanol **10a**.

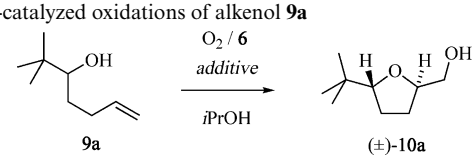
Systematic variation showed a gradual increase in yield of tetrahydrofuran **10a** along the series of applied solvents pivalaldehyde < cyclohexa-1,4-diene (CHD)–C_6H_6 < 2-methylcyclohexanone < CF_3CH_2OH < CH_2Cl_2 < cC_5H_9OH ~ *t*BuOH < 1,1-diethoxypropane < EtOH < *i*PrOH (Table 2, entries 2, 6–14). The use of molecular sieves (4 Å) had no effect (not shown).

2-*tert*-Butyl-5-methyltetrahydrofuran (**11a**)[29] was consistently found as a side product. Its yield generally remained below 15% but became significant (90%), if substrate **9a** was oxidized in a 50 : 50-mixture (*v*/*v*) of 1,4-cyclohexadiene (CHD) and C_6H_6. This observation called for more complete mass balancing, which is summarized in section 3.2.

Addition of *tert*-butyl hydroperoxide (TBHP), either as 70% (*w*/*w*) aqueous solution or as anhydrous 5.5 M solution in nonane did not improve the efficiency of the conversion **9a**→**10a** (Table 3, entries 1–2). Molecular sieves (4 Å) were added in those instances for comparing data to related values from the literature.[1] Addition of typical radical initiators, such as α,α-azobis(isobutyronitrile) (AIBN) or dibenzoyl peroxide (DBPO), were ineffective for improving yields of target compound **10a** (Table 3, entries 3–4).

3.2 Product selectivity and mass balancing. In a second part of the study, mass balancing was performed for obtaining additional information on product- and chemoselectivity of aerobic cobalt-catalyzed oxidation of alkenols **9a–b**.[34,35] Thorough

Table 3 Effect of additives in aerobic cobalt(II)-catalyzed oxidations of alkenol **9a**

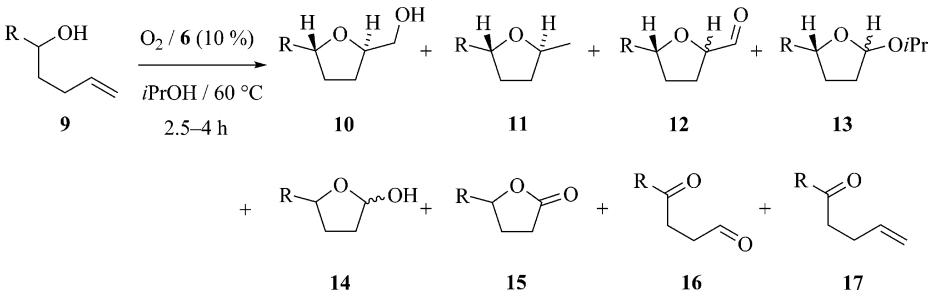


9a (±)-**10a**

Entry	Additive	T/°C	t/h	**6** [mol%]	Convn. of **9a** [%][a]	**10a** [%] (*cis* : *trans*)[a]
1	TBHP–MS 4 Å[b]	50	5	20	82	56 (< 1 : 99)[c]
2	TBHP–MS 4 Å[d]	50	5	20	quant.	62 (< 1 : 99)[c]
3	AIBN[e]	60	2.5	10	94	63 (< 1 : 99)[f]
4	DBPO[e]	60	2.5	10	83	35 (1 : 99)[g]

[a] Quantitative GC measurements. [b] 1.0 equiv. of a 70% (*w*/*w*) aqueous solution. [c] *cis*-**10a** was not detected (GC). [d] 1.0 equiv. of a 5.5 M anhydrous solution in nonane. [e] 1.0 equiv. of α,α-bis(isobutyronitrile) (AIBN) or dibenzoyl peroxide (DBPO). [f] Additional product: 4-*tert*-butyl-δ-valerolactol **14a** (13%). [g] Additional products: 2-*tert*-butyl-5-methyltetrahydrofuran **11a** (15%), 4-*tert*-butyl-δ-valerolactol **14a** (7%).

Table 4 Mass balancing in aerobic cobalt(II)-catalyzed oxidations of 1-substituted pent-4-en-1-ols **9a** and **9b**



					Yield [%][b]							
Entry	**9–17**	R	$[O_2]^a$ [%]	Conv. [%][b]	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
1[c]	**a**	*t*Bu	>95	91	63	—[d]	6	1[e]	11	4	3	—[d]
2[f]	**a**	*t*Bu	>95	98	60	2	5	7[g]	15	6	2	—[d]
3[c]	**b**	Ph	>95	75	49	—[d]	4	—[d]	4	—[d]	13	4
4[c]	**b**	Ph	50	99	63	5	5	—[d]	6	—[d]	13	2
5[f]	**b**	Ph	50	99	59	9	3	—[d]	6	—[d]	17	2
6[c]	**b**	Ph	~21[h]	98	51	20	4	—[d]	4	—[d]	7	1

[a] Gas phase oxygen concentration (*v*/*v*). [b] Quantitative GC measurements. [c] 10 mol% of **6**. [d] Not detected. [e] dr = 62 : 38. [f] Catalyst generated *in situ* from 10 mol% of $Co(OAc)_2 \cdot 4\ H_2O$ and 20 mol% of **2**. [g] dr = 55 : 45. [h] Air.

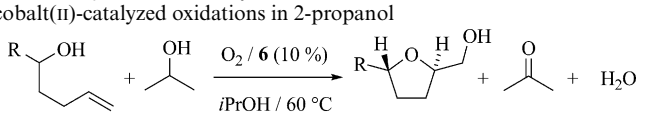
chromatographic separation was supplemented by independent syntheses to furnish the set of compounds **10–17**[36–39] that consistently accounted for 97–99% of products (Table 4, entries 1 and 3). The yields were dependent on initial O_2 concentration in the gas phase. A gradual increase in yield of target compound **10b** was noted along the series of applied O_2 volume percentages ~95% < ~21% < 40% ~ 60% (the latter two not shown) < 50% (Table 4, entries 3–6). *In situ* preparations or independently synthesized cobalt reagent **6** afforded comparable results (Table 4, entries 1–2, 4–5). Treatment of 5-phenylpent-1-ene[40] with O_2 and 10 mol% of catalyst **6** in 2-propanol (60 °C) furnished 91% of recovered olefin and no detectable compounds of oxidative conversion (GC/MS, not shown).

3.3 Probing for secondary products—acetone and H_2O. Reaction mixtures originating from aerobic cobalt-catalyzed oxidation of alkenols **9a** and **9b** in 2-propanol were subjected to quantitative acetone and H_2O analysis using appropriate analytical techniques (Table 5, entries 1–4).[41,42] The yields of both products, were corrected for trace amounts of acetone and water that were present in substrates **9a–b**, analytical grade *i*PrOH, and a solution of cobalt complex **6** that was stirred for 2.5 (**9a**)–3 h (**9b**) in analytical grade 2-propanol at 60 °C in an atmosphere of O_2.

4. Stereoselectivity

4.1 Terminal unsubstituted alkenols. Variation of phenyl substituent positioning furnished the set of substrates **9b–d** for exploring stereoselectivity in aerobic cobalt-catalyzed alkenol ring closures associated with groups attached to position 1, 2, and 3 in pent-4-en-1-ols. If exposed for 15 h to an atmosphere of O_2 in a solution of 2-propanol (60 °C) containing cobalt(II) reagent **6**, alkenols **9b–d** furnished disubstituted tetrahydrofurans **10b–d**[30] as major products (Table 6, entries 1, 4, 8). All oxidations proceeded diastereoselectively and afforded *trans*-**10b** (>99% de), *cis*-**10c** (56% de), and *trans*-**10d** (96% de) as major components.

Table 5 Quantitative analysis of H_2O and acetone formed in aerobic cobalt(II)-catalyzed oxidations in 2-propanol



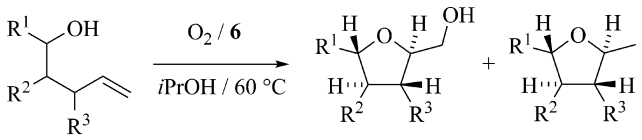
					Yield [%]		
Entry	**9**	R	pO_2/bar	Conv. of **1** [%][a]	**10**[a]	Acetone[b]	H_2O[c]
1	**9a**[d]	*t*Bu	3.0	80 ± 1	**10a**: 50 ± 2	60 ± 6	78 ± 8
2	**9a**	*t*Bu	1.5	82	**10a**: 53	53	71
3	**9b**[d]	Ph	3.0	66 ± 4	**10b**: 25 ± 2	47 ± 5	64 ±10
4	**9b**	Ph	1.5	71	**10b**: 20	46	67

[a] Determined *via* GC. [b] HPLC analysis of derived 2,4-dinitrophenylhydrazone.[41] [c] Karl–Fischer-titration.[42] [d] Mean value ± standard deviation as determined from 5 independent runs.

2-Methyl-substituted tetrahydrofurans, *i.e.* **11b–d**,[34] were identified in all instances as side products. Diastereoselectivity of the latter corresponded to values determined for hydroxyl-substituted derivatives **10b–d**. Enantiomeric purities of alcohols **10b–d** were checked *via* ^{31}P-NMR, after derivatization with a chiral dioxaphospholane.[31] Products **10b–d** were consistently formed as racemates. This result was independent from whether samples from an early phase of the reaction or after complete consumption of substrates **9b–d** were collected for derivatization. In a similar manner, diastereomeric ratios of 2,4-disubstituted tetrahydrofurans **10c** and **11c** were independent from the degree of conversion of **9c**.[43] A decrease in amount of cobalt complex **6** from 20 to 5 mol% generally reduced rates of turnover of **9b–d** but also improved overall selectivity by inhibiting 2-methyltetrahydrofuran formation (Table 6, entries 2–3, 5–7, 9–10).

In a further set of experiments, the effects of an additional substituent attached to position 1 and chain elongation between

Table 6 Product formation in aerobic oxidation of phenyl-substituted bishomoallylic alcohols

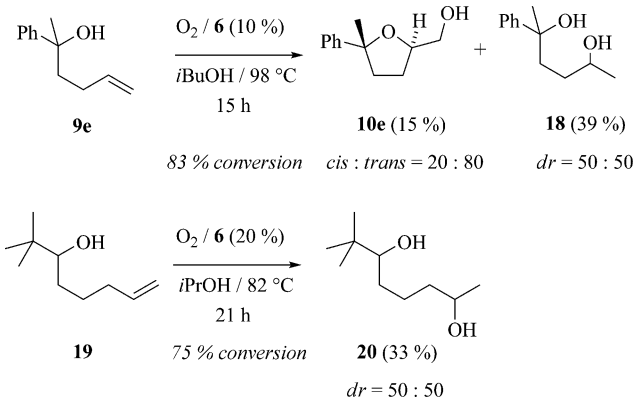


9b–d (±)-**10b–d** **11b–d**

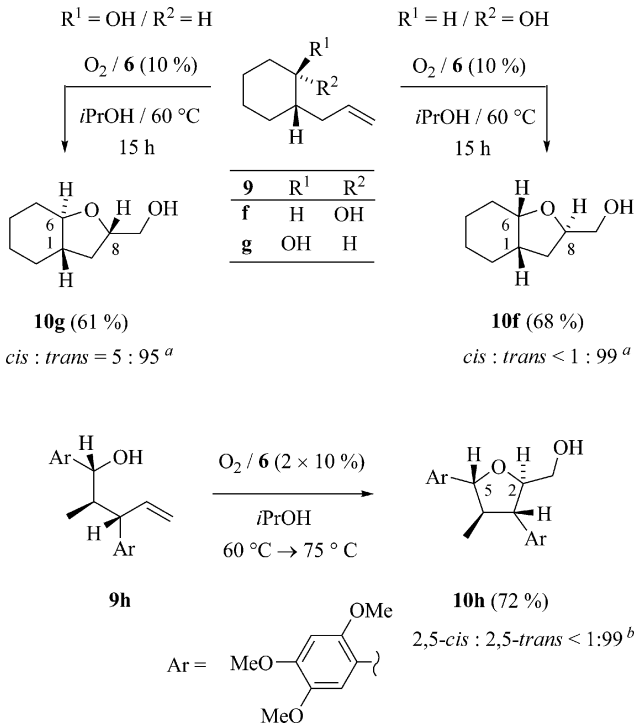
Entry	R^1	R^2	R^3	**6** [mol l^{-1}] (mol%)[a]	**9–11**	Conv. of **9** [%][b]	Yield of **10** [%][b] (*cis* : *trans*)	Yield of **11** [%][b] (*cis* : *trans*)
1	Ph	H	H	0.025 (20)	**b**	quant.	48 (< 1 : 99)[c,d]	24 (< 1 : 99)[c,e]
2	Ph	H	H	0.013 (10)	**b**	99	63 (< 1 : 99)[c,d]	5 (< 1 : 99)[c,e]
3	Ph	H	H	0.008 (6.5)	**b**	86	56 (< 1 : 99)[c,d]	—[f]
4	H	Ph	H	0.025 (20)	**c**	quant.	55 (78 : 22)[d]	31 (66 : 34)[e]
5	H	Ph	H	0.013 (10)	**c**	quant.	61 (78 : 22)[d]	23 (71 : 29)[e]
6	H	Ph	H	0.008 (6.5)	**c**	quant.	76 (78 : 22)[d]	2 (< 1 : 99)[g]
7	H	Ph	H	0.006 (5.0)	**c**	83	72 (80 : 20)[d]	—[f]
8	H	H	Ph	0.025 (20)	**d**	quant.	44 (2 : 98)[d]	16 (< 1 : 99)[c,e]
9	H	H	Ph	0.013 (10)	**d**	98	63 (2 : 98)[d]	5 (< 1 : 99)[c,e]
10	H	H	Ph	0.009 (7.5)	**d**	91	59 (2 : 98)[d]	—[f]

[a] 8 mL of reagent grade *i*PrOH; 15 h reaction time, except for entry 2 (3 h). [b] GC. [c] *cis* Isomer not detected (GC). [d] er for *trans*-**10b**, *cis*/*trans*-**10c**, and *trans*-**10d** = 50 : 50. [e] er not determined. [f] Not detected (GC). [g] *trans*-**11c** not detected (GC).

reacting entities were investigated (Scheme 2). In this case, aerobic oxidation required elevated temperatures in order to occur. Almost no conversion was detected, if 2-phenylhex-5-en-2-ol (**9e**)[44] was aerated for 3 h in a solution of 2-propanol at 60 °C in the presence of complex **6**. In 2-butanol at 98 °C, 83% conversion of **9e** was attainable after a period of 15 h. The reaction afforded 15% of trisubstituted tetrahydrofuran **10e** (*cis* : *trans* = 20 : 80) and 39% of diol **18**[45] (Scheme 2). In a similar way, oxidation of alkenol **19**[46] required elevated temperature for substrate conversion to occur, and extended reaction time to afford a new product in substantial amounts. The material was isolated and identified as diol **20** (Scheme 2).



Scheme 2 Aerobic oxidation of 2-phenylhex-5-en-2-ol (**9e**) and 2,2-dimethyloct-7-en-3-ol (**19**).

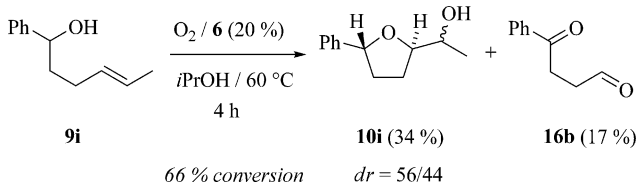


Scheme 3 Stereoselective synthesis of oxabicyclo[4.3.0]nonanes **10f–g** (top), and tetrasubstituted tetrahydrofuran **10h** (bottom). [a] *cis* : *trans*-ratios refer to the relative configuration of substituents attached at positions 6 and 8. [b] ^{1}H NMR.

For investigating whether stereoselectivity in ring closures prevailed in the case of constrained or multiply substituted substrates, appropriate alkenols were prepared and aerated in the presence of complex **6**. Treatment of *cis*- and *trans*-isomers of 2-allylcyclohexanol **9f–g**[47] under established conditions afforded 8-substituted oxabicyclo[4.3.0]nonanes **10f** (68%) and **10g** (61%) in a 6,8-*trans*-selective manner (Scheme 3, top).[48,49] Oxidation of diastereomerically pure alkenol **9h**[50] with O_2 in *i*PrOH (60 °C, 4 h) using cobalt(II) catalyst **6** (10 mol%, $c_0 = 5.0 \times 10^{-3}$ M) and a second batch of cobalt reagent **6** (10 mol%) at 75 °C (15 h) provided diastereomerically pure (^{1}H NMR) tetrasubstituted tetrahydrofuran **10h** (72%, Scheme 3, bottom).

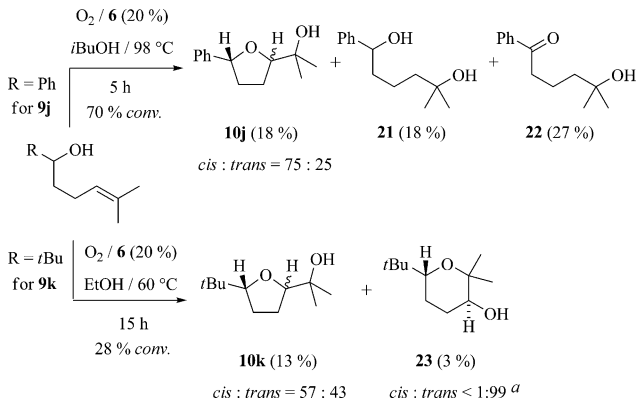
4.2 Oxidation of alkenols having methyl substituents attached at the terminal position of the π-bond. In a final set of oxidations, terminally methyl-substituted alkenols were applied as

substrates. It was the aim to screen for polar and steric substituent effects, since CH_3-substitution is known to control stereoselectivity in other cyclizations, *e.g.* alkenoxyl radical ring closures and peroxide-mediated tetrahydrofuran syntheses.[14,29] Treatment of a solution of (*E*)-1-phenylhex-4-en-1-ol (**9i**)[51] and cobalt reagent **6** for 4 h in *i*PrOH at 60 °C with O_2 furnished 34% of 2,5-*trans*-disubstituted tetrahydrofuran **10i** as a 56 : 44 mixture of diastereomers with respect to the stereogenic center located in the side chain. In addition, 17% of dicarbonyl compound **16b** was detected (GC-MS) (Scheme 4).



Scheme 4 Aerobic oxidation of (*E*)-1-phenylhex-4-en-1-ol (**9i**).

1-Phenyl-5-methylhex-4-en-1-ol (**9j**)[30] underwent almost no conversion if treated with cobalt complex **6** in 2-propanol at 60 °C. A change of solvent to 2-butanol allowed the reaction to be conducted at 98 °C, which led to formation of 2,5-disubstituted tetrahydrofuran **10j** (*cis* : *trans* = 75 : 25),[30] diol **21**,[52] and hydroxyketone **22** (Scheme 5, top). *tert*-Butyl-substituted derivative **9k** was oxidized, if treated with O_2 and catalyst **6** in a solution of EtOH (60 °C), to furnish 13% of tetrahydrofuran **10k** (*cis* : *trans* = 57 : 43) along with 3% of tetrahydropyran **23** (*cis* : *trans* < 1 : 99) (Scheme 5, bottom).



Scheme 5 Aerobic oxidation of terminal dimethyl-substituted alkenols **9j–k**. [a]*cis*-**23** not detected (GC).

Discussion

1. Cobalt complex reactivity toward O_2

Acceptor substituted [*e.g.* CF_3 or 3,5-$(CF_3)_2C_6H_3$] bis[β-diketonato(−1)]cobalt(II) complexes were able to activate O_2 for its application in diastereoselective synthesis of alkyl- and aryl-substituted tetrahydrofurylmethanols *e.g.* **10a–d** from bishomoallylic alcohols **9a–d**. The fact that O_2-pressures above 1 bar decreased rates of alkenol oxidation pointed to competitive substrate and oxidant binding to cobalt (see Table 5). Support for this interpretation originated from an experiment, in which 5-phenylpent-1-ene was applied as substrate. The olefin was inert, whereas 1-phenylpentenol **9b** underwent swift and (stereo)selective 5-*exo*-ring closure under standard conditions (O_2, *i*PrOH, 60 °C, 3 h, 10 mol% of **6**). Oxidative disintegration of cobalt reagent **6** in 2-propanol occurred, if exposed to an atmosphere of O_2. It is supposed that this background reaction accounted for a considerable fraction of catalyst deactivation in the present investigation.

2. Oxidation catalysis

Yields of tetrahydrofur-2-ylmethanols were dependent on solvent, reaction temperature, initial cobalt concentration, and alkenol constitution.

(a) Solvent. Adequate time–yield factors for tetrahydrofur-2-ylmethanol formation were attainable using 2-propanol as solvent. The reaction provided acetone and water as secondary products. Their yields slightly diverged but were clearly correlated with those of tetrahydrofuran formation. Autoxidations that were identified as side reactions, were considered to increase the percentage of reaction water without affecting the acetone balance.

Quantitative alkenol conversion was paralleled by 2-methyltetrahydrofuran formation. An experiment performed in 2-propanol-d_8 at 75 °C (see ESI) provided 18% of 2-phenyl-5-methyltetrahydrofuran **11b** with a 50% degree of deuteration, exclusively at the methyl substituent (^{1}H NMR), which clearly pointed to the solvent as one of the H-atom sources. The role of the solvent in the synthesis of these compounds was furthermore evident from an experiment performed in CHD–C_6H_6, which provided 90% of 2-*tert*-butyl-5-methyltetrahydrofuran **11a**. If bond dissociation energies (381 ± 4 kJ mol^{-1} for 2-C,H in *i*PrOH, and 318 ± 5 kJ mol^{-1} for 3-C,H in CHD)[53] were taken as a guide for interpretation, CHD is expected to serve as H-atom donor in homolytic substitutions. The fact that initiators, such as AIBN and DBPO, failed to significantly alter product selectivities at 60 °C strongly pointed to a radical trapping and thus terminating effect of CHD, and not to an active role in radical generation.

(b) Temperature dependence and initial cobalt(II) concentration. Effects of temperature and initial cobalt(II) complex concentration were correlated in terms of rate and selectivity. Temperatures below 60 °C and initial cobalt(II) concentrations of less than 10^{-2} M reduced rates of oxidative cyclization but improved product selectivity. Conducting oxidations at $T > 60$ °C, regardless of the applied solvent (*e.g.* *i*PrOH or *i*BuOH) and at initial cobalt(II) concentrations of $>10^{-2}$ M increased rates of alkenol oxidation but also provided notable amounts of 2-methyltetrahydrofurans, acyclic alcohols, and products of autoxidation.

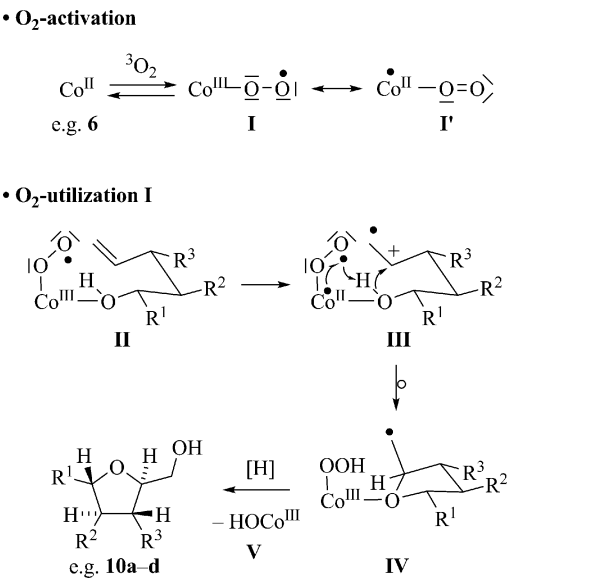
(c) Stereoselectivity. Diastereoselection gradually decreased along substituent positions 1 > 3 > 2. The observed *trans*-2,3- and *trans*-2,5-selectivity of the cobalt method was notable. Explanation on the lack of enantioselectivity in this chemistry, however, has to await profound structural investigations. The cobalt atom in, *e.g.*, complex **6** poses a stereogenic center.[27] The configuration at this site, either in the reagent or in the active oxidant, is entirely unknown. Formation of diastereomerically pure all-*trans*-3,5-diaryl-4-methyl-2-hydroxymethyl-tetrahydrofuran **10h**, a derivative of the natural product magnosalicin,[54,55] indicated that the concept of oxidative ring closure was extendable to the formation

of multiple substituted tetrahydrofurans. Studies associated with the synthesis of 8-substituted oxabicyclo[4.3.0]nonane **10f** revealed that a reversal of from 2,4-*cis* to 2,4-*trans* is feasible, if the former would interfere with an obviously more dominating 2,5-*trans*-stereocontrol.

3. Mechanistic interpretation

Selectivity in cobalt-catalyzed alkenol oxidation was critically dependent on the chain length and substitution pattern at reactive sites. Subtle changes associated with auxiliary, solvent, temperature, and alkenol constitution were reflected in yields and/or product profiles. In combination with available data from the literature dealing with related transformations, a mechanism was proposed (Schemes 6–8) with the aim to address, the origin of the preferred 5-*exo*-ring closure, stereodisintegration associated with oxygenation of (*E*)-configured alkenol **9i**, stereoselection, and product selectivity.

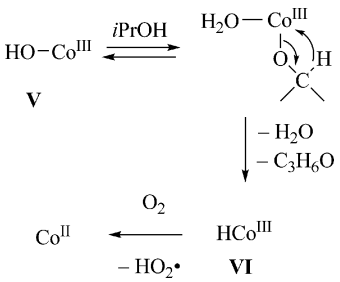
(a) Oxidative 5-*exo*-ring closure. Oxygen activation is considered to occur *via* binding to paramagnetic complex **6**.[43] Due to effects exerted by substituents R in terms of reactivity and selectivity, it is expected that at least one of the auxiliaries remained attached to cobalt in O_2 adduct **I** (Scheme 6). EPR data[56] and computational investigations of dioxygen adducts of cobalt(II) complexes with macrocyclic N_2O_2-donor ligands[57] had been previously interpreted in terms of a doublet ground state.[58,59] If a similar structure and bonding applied for O_2 adducts of (β-diketonato)cobalt complexes, a superoxo-mode of binding is expected to provide a strong Lewis acid *and* a metal based oxidant. In extension to the propensity of bis(trifluoroacetato)cobalt(III) complexes to convert olefins into radical cations,[60] an approach of reacting entities in proposed intermediate **II** is considered to furnish radical cation **III**. A decrease in π-bond order lowers the barrier to rotation toward an almost unhindered torsional movement of entities that were previously connected *via* a double bond. Evidence for this interpretation originated from a ~ 50 : 50 ratio of diastereoisomers with respect to side chain configuration of a product obtained from (*E*)-configured alkenol **9i** (see Scheme 4). A 5-*exo*-mode of hydroxyl O-atom attack onto the oxidized π-bond in this model constitutes the first of two sequential C,O bond forming steps associated with the conversion **9**→**10**.



Scheme 6 Proposed mechanistic scheme for O_2 activation (top) and dioxygen utilization in aerobic cobalt-catalyzed tetrahydrofuran synthesis (bottom).

(b) Stereochemical model. A chair like folding of the alkenol chain in **II** and **III** would direct substituents preferentially into positions that are reminiscent of equatorial sites in cyclohexane. Intramolecular C,O bond formation **III**→**IV** in this model would afford 2,5-*trans*-, 2,4-*cis*-, and 2,3-*trans*-disubstituted products, reflecting experimentally observed diastereoselectivities. Steric encroachment imposed by cobalt coordination (for R^1) and vinyl substitution (for R^3), would not be similarly experienced by R^2.

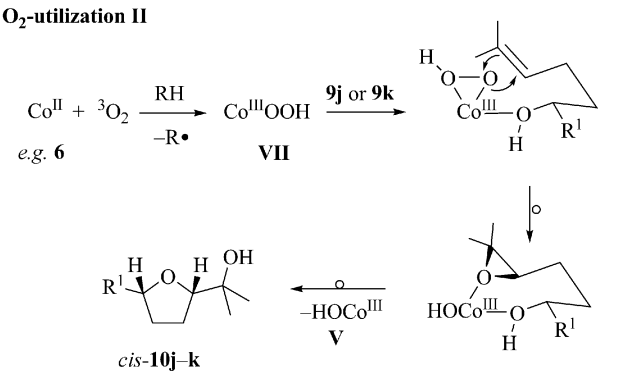
(c) Termination of the sequence and cobalt(II) regeneration. In extension to the well-known driving force of cobalt(II) compounds for alkyl hydroperoxide reduction,[61] intermediate **IV** is expected to furnish tetrahydrofur-2-ylmethanol **10** and hydroxycobalt(III) complex **V** in the presence of a suitable H-atom donor, *e.g.* a solvent molecule.[62] Cobalt(II) regeneration is considered to occur *via* hydride shift from coordinated 2-propanol. This step would yield acetone, H_2O, and hydridocobalt(III) complex **VI** (Scheme 7). This interpretation closely follows the chemistry of hydroxo- and alkanolato[bis(acetylacetonato)]cobalt(III).[63,64]



Scheme 7 Proposed sequence for cobalt(II) regeneration.

(d) Olefin hydration and reversal of diastereoselectivity. Secondary and tertiary alcohols were formed in instances where oxidative cyclization for unknown reasons was slow (see Schemes 2 and 5). The chemistry of olefin hydration using the combination of O_2 and cobalt(II) Schiff base complexes has been extensively investigated.[65] It proceeds *via* alkylperoxy cobalt(III) complex formation and decomposition according to an alkylperoxyl radical pathway (not shown).

Since superoxo cobalt(III) complexes, *e.g.* **I**, have a strong affinity for homolytic H-atom substitution, preferentially from molecules with weak C,H-bonds as present in 2-propanol, hydroperoxy cobalt(III) complex **VII** (Scheme 8) is expected to be formed in instances of slow oxidative cyclization.[17] It is proposed that this intermediate accounts for the reversal of stereoselectivity in tetrahydrofuran formation in going from substrate **9a–b** to dimethyl-substituted derivatives **9j–k**. Alkenol oxygenation in this case is considered to follow a mechanism that has been investigated in *tert*-butylperoxy vanadium(V) chemistry for alkenol **9j** in detail.[30] In extension to this sequence, stereoselective epoxy alcohol formation and isomerization would furnish *cis*-**10j** as major cyclic ether.



Scheme 8 Proposed mechanistic scheme for stereoselective formation of 2,5-*cis*-configured tetrahydrofurans from terminal dimethyl-substituted pent-4-en-1-ols **9j–k** (R^1 = Ph or *t*Bu).

Conclusions

Secondary and primary bishomoallylic alcohols (pent-4-en-1-ols), *e.g.* **9a–d**, underwent efficient oxidative ring closures if treated with molecular oxygen and catalytic amounts (10^{-2} M, 10 mol%) of bis{2,2,2-trifluoromethyl-1-[(1*R*,4*S*)-1,7,7-trimethyl-2-(oxo-κ*O*)bicyclo[2.2.1]hept-3-yliden]ethanolato- κ*O*}cobalt (**6**) in 2-propanol at 60 °C. The reaction proceeded diastereoselectively and was applied for sustainable syntheses of 2,3-*trans*- (96% de), 2,4-*cis*- (56% de), and 2,5-*trans*-di- (>99 de), tri-, and tetrasubstituted tetrahydrofurans. The procedure therefore has the potential to open perspectives for natural product synthesis.

Experimental

1. General remarks

Standard instrumentation and general remarks have been disclosed previously (see also ESI). All solvents and reagents were purified following recommended standard procedures.[66] Petroleum ether refers to the fraction boiling between 30–75 °C.

2. Synthesis of bis[3-acyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-onato(−1)]cobalt(II) complexes

Bis{2,2,2-Trifluoromethyl-1-[(1*R*,4*S*)-1,7,7-trimethyl-2-(oxo-κ*O*)bicyclo[2.2.1]hept-3-yliden]ethanolato-κ*O*}cobalt(II) (6). A solution of (1*R*,4*R*)-3-trifluoroacetyl-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one (**2**) (1.99 g, 8.00 mmol) (ESI) in EtOH (6 mL) was added in an atmosphere of nitrogen to a suspension of $Co(OAc)_2{\cdot}4H_2O$ (996 mg, 4.00 mmol) in EtOH (12 mL). The mixture was stirred for 30 min at 20 °C. The volatiles were removed under reduced pressure to afford complex **6** (2.50 g, quant.) as a red solid, mp > 300 °C (from EtOH), this material was applied in aerobic oxidations. $[\alpha]_D^{20}$ +91.9, (*c* 0.96 in $CHCl_3$). ν_{max} (KBr)/cm^{-1} 2965, 1654, 1560, 1389, 1326, 1270, 1227, 1199, 1132 and 806. δ_F (565 MHz; EtOD) −76.44. MALDI-TOF (DHB) calc for $C_{24}H_{28}O_4F_6Co$: 553.4. Found *m*/*z* 553.3 [M^+]. Calc for $C_{24}H_{28}O_4F_6Co$ (553.41): C, 52.09; H, 5.10. Found: C, 50.40; H, 5.35%. An analytically pure sample was obtained by slowly allowing pentane to diffuse into a solution of **6** in wet THF to furnish hydrated monotetrahydrofuran adduct of **6** as red crystalline solid. λ_{max} (*i*PrOH)/nm 309 (log ε 3.25). Calc. for $C_{28}H_{38}O_6F_6Co$ (643.53): C, 52.26; H, 5.95%. Found: C, 52.36; H, 5.86%.

Bis{2,2-dimethyl-1-[(1*R*,4*S*)-1,7,7-trimethyl-2-(oxo-κ*O*)bicyclo-[2.2.1]hept-3-yliden]propanolato-κ*O*}cobalt(II) (5). Compound **5** was prepared from $Co(OAc)_2{\cdot}4H_2O$ (47.2 mg, 190 μmol) and (1*R*,4*R*)-3-[(2,2-dimethyl-1-oxo)prop-1-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**1**) (89.4 mg, 380 μmol) (ESI) in *i*PrOH in extension to the procedure outlined for cobalt complex **6**. Compound **5** liberated auxiliary **1** upon drying under reduced pressure and was therefore used as obtained in solution (red-colored). $[\alpha]_D^{20}$ +43.5 (*c* 1.00 in MeOH). λ_{max} (MeOH)/nm 281sh and 314 (log ε 2.82). MALDI-TOF (DHB) calc. for $C_{30}H_{46}O_4Co$: 529.6. Found: 529.6 [M^+].

Bis{1-phenyl-1-[(1*R*,4*S*)-1,7,7-trimethyl-2-(oxo-κ*O*)bicyclo-[2.2.1]hept-3-yliden]methanolato-κ*O*}cobalt(II) (7). Compound **7** was obtained from $Co(OAc)_2{\cdot}4H_2O$ (126 mg, μmol) and (1*R*,4*R*)-3-benzoyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**3**) (253 mg, 1.00 mmol) (ESI) as described for derivative **6**. Yield: 175 mg (60%), red–brown crystalline solid, mp 325 °C (EtOH). $[\alpha]_D^{20}$ +95.5 (*c* 0.90 in $CHCl_3$). λ_{max} (EtOH)/nm 233 (log ε 2.76), 327 (2.89). ν_{max} (KBr)/cm^{-1} 2957 and 2870 (CH), 1755 and 1609 (CO), 1575, 1506, 1471, 1374, 1179, 1078, 800, 781 and 700. MALDI-TOF (DHB) calc. for $C_{34}H_{38}O_4Co$: 569.6. Found: 569.3 [M^+] and 591.4 [$(M + Na)^+$].

Bis{1-[3,5-Bis-(trifluoromethyl)benzoyl]-1-[(1*R*,4*S*)-1,7,7-trimethyl-2-(oxo-κ*O*)bicyclo[2.2.1]hept-3-yliden]methanolato-κ*O*}-cobalt(II) (8). Compound **8** was prepared from $Co(OAc)_2{\cdot}4H_2O$ (124 mg, 500 μmol) and (1*R*,4*R*)-3-{1-[3,5-bis-(trifluoromethyl)phenyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**4**) (392 mg, 1.00 mmol) (ESI) in extension to a published procedure.[67] Yield: 419 mg (quant.), orange crystalline solid, mp 173 °C (EtOH–H_2O). $[\alpha]_D^{20}$ +32.4 (*c* 1.00 in $CHCl_3$). λ_{max} (CH_3CN)/nm 228sh, 262sh and 342 (log ε 3.14). ν_{max} (KBr)/cm^{-1} 2964 and 2867 (CH), 1634 (CO), 1523, 1387, 1367, 1278, 1172, 1137, 1107, 1078, 1053, 900, 847 and 680. δ_F (565 MHz; $CDCl_3$) −59.5 and −63.0 (6 : 1). MALDI-TOF (DHB) calc. for $C_{38}H_{34}O_4F_{12}Co$: 841.6. Found: 841.2 [M^+]. Calc. for $C_{38}H_{34}O_4F_{12}Co$ (841.60): C, 54.23; H, 4.07%. Found: C, 54.00; H, 4.10%.

3. Aerobic cobalt-catalyzed oxidations

General procedure. A solution of a substrate (0.40 mmol of **9h**; 0.91 mmol of **9i**; 0.99–1.02 mmol of **9a–d**, **9k**, **19**; 1.55 mmol of **9j**; 2.03 mmol of **9e** and 3.00 mmol of **9f–g**) and a cobalt(II) complex **5–8** (0.05–0.20 equivalents) in a solution of a given solvent (20 mL $mmol^{-1}$ for **9h**; 8 ml/mmol for of **9a–d**, **9i–k**, **19** and 6 mL $mmol^{-1}$ for **9e–g**) was stirred at 20–98 °C for 2–48 h in a stationary oxygen atmosphere. After cooling down to 20 °C, the reaction mixture was diluted with dichloromethane (6 mL $mmol^{-1}$) and Et_2O (4 mL $mmol^{-1}$). The solution was washed with satd. aq. $Na_2S_2O_3$ soln. (3 × 5 mL $mmol^{-1}$). Combined $Na_2S_2O_3$ washings were extracted with Et_2O (2 × 4 mL $mmol^{-1}$). (i) GC Analysis: *n*-decane was added as internal standard to combined organic layers to afford a solution which was quantitatively analyzed by GC *via* independently measured responsivity factors. (ii) Preparative scale experiments: combined organic layers were dried ($MgSO_4$) to afford a solution that was concentrated under reduced pressure.

The remaining residue was purified by column chromatography (SiO_2).

Tetrahydro-5-methyl-5-phenylfur-2-ylmethanol (10e). Yield: 60.0 mg (15%, *cis* : *trans* = 20 : 80) from 357 mg (2.03 mmol) of **9e**. R_f 0.35 [SiO_2, Et_2O–pentane = 2 : 1 (*v*/*v*)], colorless oil. $C_{12}H_{16}O_2$ (192.25). ***trans*-10e**: δ_H (600 MHz; $CDCl_3$) 1.55 (3 H, s, Me), 1.80–1.86 (2 H, m, 3-H, 4-H), 2.02–2.09 (1 H, m, 3-H), 2.24–2.30 (1 H, m, 4-H), 3.58 (1 H, dd, *J* 11.4, 5.5, CH_2OH), 3.77 (1 H, dd, *J* 11.4, 3.3, CH_2OH), 4.17 (1 H, ddd, *J* 12.5, 6.9, 3.3, 2-H), 7.20–7.25 (1 H, m, Ph), 7.31–7.35 (2 H, m, Ph), 7.38–7.41 (2 H, m, Ph). δ_C (150 MHz; $CDCl_3$) 27.3 (C3), 30.4 (Me), 39.4 (C4), 65.4 (CH_2OH), 79.0 (C2), 85.2 (C5), 124.5, 126.4, 128.2, 147.7 (Ph). NOESY (cross peaks) CH_2OH ↔ Me, 2-H ↔ Ph. *m*/*z* (EI, 70 eV) 192 (M^+, 1), 177 (100), 161 (78), 143 (87), 128 (38), 117 (52), 105 (71), 91 (85), 77 (48). ***cis*-10e**: δ_H (600 MHz; $CDCl_3$) 1.52 (3 H, s, Me), 1.80–2.15 (3 H, m, 3-H, 4-H), 2.21–2.31 (1 H, m, 4-H), 3.54 (1 H, dd, *J* 11.6, 6.4, CH_2OH), 3.71 (1 H, dd, *J* 11.5, 3.4, CH_2OH), 4.32 (1 H, ddd, *J* 13.5, 6.9, 3.3, 2-H), 7.20–7.44 (5 H, m, Ph). δ_C (150 MHz; $CDCl_3$) 27.5 (C3), 29.6 (Me), 39.2 (C4), 65.6 (CH_2OH), 79.4 (C5), 85.0 (C2), 124.5, 126.5, 128.2, 148.2 (Ph). *m*/*z* (EI, 70 eV) 177 ($M^+ - CH_3$, 95%), 161 (93), 143 (97), 128 (42), 117 (54), 105 (85), 91 (100), 77 (60).

3-*trans*-4-*cis*-5-*trans*-Tetrahydro-3,5-bis(2,4,5-trimethoxyphenyl)-4-methylfur-2-ylmethanol (10h). Yield: 130 mg (72%, *cis* : *trans* < 1 : 99) from 173 mg (0.40 mmol) of **9h**. R_f 0.42 [SiO_2, acetone–Et_2O = 1 : 3 (*v*/*v*)], colorless solid, mp 46 °C [acetone–Et_2O = 1 : 3 (*v*/*v*)]. $C_{24}H_{32}O_8$ (448.51). δ_H (400 MHz; DMSO-d_6) 0.72 (3 H, d, *J* 6.5, 4-Me), 2.28 (1 H, m_c, 4-H), 3.10 (1 H, dd, *J* 10.6, 9.5, 3-H), 3.27–3.33 (1 H, m, CH_2OH), 3.39 (1 H, ddd, *J* 11.7, 5.6, 2.4, CH_2OH), 3.69 (3 H, s, OMe), 3.73 (3 H, s, OMe), 3.75 (2 × 3 H, s, OMe), 3.76 (3 H, s, OMe), 3.78 (3 H, s, OMe), 4.19 (1 H, ddd, *J* 8.6, 5.9, 2.4, 2-H), 4.62 (1 H, t, *J* 5.7, OH), 4.84 (1 H, d, *J* 9.5, 5-H), 6.66 (1 H, s, Ph), 6.67 (1 H, s, Ph), 6.84 (1 H, s, Ph), 7.06 (1 H, s, Ph). δ_C (100 MHz; $CDCl_3$) 14.1 (4-Me), 48.4, 48.9 (C3 and C4), 56.2, 56.3, 56.6, 56.7, 56.9, 57.0 (6 × OMe), 63.8 (CH_2OH), 81.9 (C5), 84.7 (C2), 98.2, 98.6, 112.0, 113.0, 119.0, 121.5, 143.6, 143.7, 148.7, 149.4, 151.9, 152.6 (Ph). NOESY (cross peaks) 2-H ↔ Ph, 2-H ↔ 4-H, 3-H ↔ 5-H, 3-H ↔ 4-Me, 4-H ↔ Ph, 5-H ↔ 4-Me; *m*/*z* (EI, 70 eV) 448 (M^+, 45%), 388 (15), 357 (6), 221 (16), 209 (100), 181 (64), 151 (19).

***trans*-1-(5-Phenyltetrahydrofur-2-yl)ethanol *trans*-(10i).**

Isomer 1. Yield: 33.0 mg (19%) from 160 mg (0.91 mmol) of **9i**, R_f 0.38 [SiO_2, acetone–pentane = 1 : 5 (*v*/*v*)], colourless oil. δ_H(400 MHz; $CDCl_3$) 1.18 (3 H, d, *J* 6.4, 2′-H), 1.68–1.77 (1 H, m, 3-H), 1.89 (1 H, m_c, 4-H), 2.11 (1 H, m_c, 3-H), 2.37 (1 H, m_c, 4-H), 2.61 (1 H, s, OH), 3.68 (1 H, dq, J_d 6.7, J_q 6.4, 1′-H), 4.00 (1 H, ddd, *J* 7.3, 2-H), 4.96 (1 H, dd, *J* 8.8, 5.9, 5-H), 7.26–7.29 (1 H, m, Ph-H) and 7.34–7.35 (4 H, m, Ph-H); δ_C (150 MHz; $CDCl_3$) 18.5 (C2′), 28.7 (C3), 35.8 (C4), 70.7 (C1′), 80.7 (C5), 84.5 (C2), 125.6, 127.4, 128.3 and 142.7 (Ph); NOESY (cross peaks) 2-H ↔ Ph, 1-H′ ↔ 5-H, 2-H ↔ OH. *m*/*z* (EI, 70 eV) 192 (M^+, 8%), 174 (12), 147 (85), 129 (51), 117 (24), 104 (99), 91 (100), 77 (31) and 51 (16).

Isomer 2. Yield: 25.9 mg (15%) from 160 mg of **9i**, R_f 0.29 [SiO_2, acetone–pentane = 1 : 5 (*v*/*v*)], colourless oil. δ_H (600 MHz; $CDCl_3$) 1.18 (3 H, d, *J* 6.4, 2′-H), 1.86–1.94 (1 H, m, 3-H), 1.94–1.99 (1 H, m, 4-H), 2.01–2.07 (1 H, m, 3-H), 2.39 (1 H, m_c, 4-H), 4.06–4.10 (1 H, m, 1′-H), 4.14 (1 H, m_c, 2-H), 5.02 (1 H, dd, *J* 8.7, 6.1, 5-H), 7.27–7.30 (1 H, m, Ph-H) and 7.33–7.34 (4 H, m, Ph-H); δ_C (150 MHz; $CDCl_3$) 17.9 (C2′), 25.5 (C3), 35.6 (C4), 68.1 (C1′), 81.6 (C5), 83.7 (C2), 125.5, 127.3, 128.4 and 143.3 (Ph); NOESY (cross peaks) 2-H ↔ Ph. *m*/*z* (EI, 70 eV) 192 (M^+, 10%), 174 (10), 147 (91), 129 (45), 117 (22), 104 (100), 91 (99), 77 (27) and 51 (15).

7,7-Dimethyloctane-2,6-diol (20). Yield: 55.6 mg (31%, dr = 50 : 50) from 160 mg (1.02 mmol) of **19**, R_f 0.28 [SiO_2, acetone–petroleum ether = 2 : 5 (*v*/*v*)], colorless oil. δ_H (400 MHz; $CDCl_3$) 0.89 (2 × 9 H, s, 7-Me), 1.19 (2 × 3 H, d, *J* 6.2, 1-H), 1.23–1.68 (2 × 6 H, m, 3-H, 4-H, 5-H), 1.72 (2 × 2 H, s, OH), 3.20 (2 × 1 H, d, *J* 10.4, 6-H), 3.83 (2 × 1 H, m_c, 2-H). δ_C (100 MHz; $CDCl_3$) 23.1 and 23.2 (C4), 23.5 and 23.6 (C1), 25.7 (C8), 31.2 and 31.4 (C5), 34.9 (C7), 39.2 and 39.3 (C3), 68.0 and 68.2 (C2), 79.9 (C6). *m*/*z* (EI, 70 eV) 141 ($M^+ - CHO$, 1%), 117 (8), 99 (63), 87 (16), 81 (100), 71 (18), 57 (58), 43 (36), 29 (9). Calc. for $C_{10}H_{22}O_2$ (174.28): C, 68.92; H, 12.72. Found: C, 68.60; H, 12.63%.

5-Hydroxy-5-methyl-1-phenylhexan-1-one (22). Yield: 86.8 mg (27%) from 295 mg (1.55 mmol) of **9j**, R_f 0.43 [SiO_2, acetone–pentane = 1 : 3 (*v*/*v*)], colorless oil. $C_{13}H_{18}O_2$ (206.28). δ_H (400 MHz; DMSO-d_6) 1.07 (2 × 3 H, s, Me), 1.35–1.42 (2 H, m, 3-H), 1.64 (2 H, m_c, 4-H), 2.98 (2 H, t, *J* 7.3, 2-H), 4.13 (1 H, s, OH), 7.47–7.54 (2 H, m, Ph), 7.58–7.64 (1 H, m, Ph), 7.92–7.97 (2 H, m, Ph). δ_C (150 MHz; DMSO-d_6) 19.0 (C3), 29.3 (Me), 38.5, 43.0 (C2 and C4), 68.7 (C5), 127.8, 128.7, 133.0, 136.7 (Ph), 200.2 (C1). *m*/*z* (EI, 70 eV) 192 ($M^+ - CH_2$, 2%), 188 (14), 170 (5), 147 (4), 133 (27), 120 (55), 105 (100), 77 (56), 59 (29), 55 (21).

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