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Cobalt-catalyzed aerobic oxidation of (*E*)- and (*Z*)-bishomoallylic alcohols

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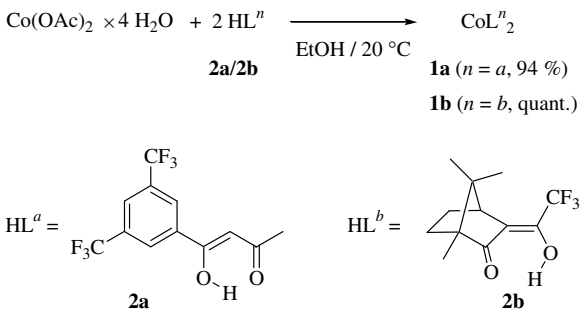
ABSTRACT

Stereoselectivity for (5-phenyltetrahydrofur-2-yl)alkan-1-ol formation (cis:trans < 1:99) from 5-methyl- and 5-phenyl-substituted 1-phenylpent-4-en-1-ols via cobalt-catalyzed aerobic oxidation was independent of the olefinic π-bond configuration of the substrates.

Acceptor-substituted cobalt(II) chelates are valuable reagents for $^3O_2$ activation[1–3] to serve as powerful but selective oxidants for tetrahydrofuran formation from substituted pent-4-en-1-ols (bishomoallylic alcohols).[4–7] The oxidative ring closure occurs with a notable degree of diastereoselection to afford 2,3-trans- (~99% de), 2,4-cis- (~70% de), and 2,5-trans-configured (>99% de) tetrahydrofur-2-yl-methanols in ~70–80% yield.[8–10] If methyl groups are substituted for terminal hydrogen atoms, or tertiary alkenols are used instead of primary or secondary substrates, the cobalt method surprisingly failed to provide a similar degree of product- and diastereoselectivity.[9,11] One of the most striking results in an earlier series of experiments related to this topic originated from an attempt to selectively oxidize an (*E*)-alkenol with O_2 in the presence of a cobalt(II) complex. The stereochemical information originating from the olefinic π-bond was lost in the course of oxidative cyclization although the customary 2,5-trans selectivity for tetrahydrofuran formation was retained.[9] If this selectivity posed a general feature of the cobalt method, it would provide strong mechanistic evidence for stepwise tetrahydrofurylmethanol formation from open chain substrates. The advent of a more reactive cobalt catalyst (vide infra) has enabled us to address the issue of selectivity in oxidative cyclizations of (*E*)- and (*Z*)-alkenols more systematically. The most important results from this investigation showed that the 2,5-trans diastereoselectivity (>99% de) was entirely independent of the π-bond configuration. A consistent ~35/65 distribution of stereoisomers with respect to the newly formed stereocenter in the alkanol side chain pointed in all instances to a symmetric intermediate, and hence to a sequential mechanism for formation of the two new C,O bonds.

4-[3,5-Bis(trifluoromethyl)phenyl]-4-hydroxy-but-3-en-2-one-derived cobalt(II) complex **1a** was discovered in this laboratory in the course of a reactivity survey associated with the search for strong and selective aerobic oxidation catalysts. The compound (yellow crystalline solid)[24,25] was prepared from $Co(OAc)_2 \times 4H_2O$ and 2 equiv of auxiliary **2a** in EtOH, in extension to a method reported for the synthesis of camphor derivative **1b** from **2b** (Scheme 1).[12]

Bishomoallylic alcohols (*E*)/(*Z*)-**3**/**4** were inert toward oxygen [>95% (v/v), 1 bar], if stirred for ~4 h in *i*PrOH at 60 °C. Addition of cobalt(II) reagent **1a** (10 mol %) to a likewise prepared solution of (*E*)-1-phenylhex-4-en-1-ol (*E*)-(**3**)[13] [(*E*):(*Z*) > 99:1; GC, ^{1}H NMR] furnished 63% of trans-2,5-disubstituted tetrahydrofuran



Scheme 1. Preparation of cobalt(II) complexes **1a**–**b**.

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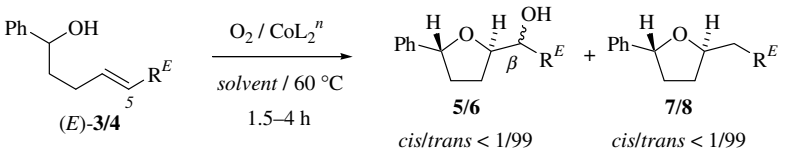
Table 1
Synthesis of 2,5-disubstituted tetrahydrofurans **5**/**6** via aerobic cobalt-catalyzed oxidation of alkenols (*E*)-**3**/**4**



Entry	**3**/**4**	R^E	Solvent	CoL^n/mol %	Convn.	**5**/**6** /% (dr)[a,b]	**7**/**8**/%[a]
1	(*E*)-**3**	CH_3	*i*PrOH	**1a**/10	97	**5**: 63 (33:67)	**7**: 17[c]
2	(*E*)-**3**	CH_3	*i*PrOH	**1b**/20	66	**5**: 34 (56:44)	**7**: — [d]
3	(*E*)-**3**	CH_3	C_6H_6/CHD	**1a**/10	Quant.	**5**: 8 (39:61)	**7**: 86 [e]
4	(*E*)-**4**	C_6H_5	*i*PrOH	**1a**/10	97	**6**: 53 (13:87)	**8**: — [d,f]
5	(*E*)-**4**	C_6H_5	*i*PrOH	**1b**/20	82	**6**: 22 (57:43)	**8**: —[d]
6	(*E*)-**4**	C_6H_5	C_6H_6/CHD	**1a**/10	Quant.	**6**: 37 (38:62)	**8**: 15[g]

[a] *cis*-**5**–**8** were not detected (GC, NMR).
[b] Diastereomeric ratio with respect to configuration at C^β (GC).
[c] Additional products: 2-acetyl-5-phenyltetrahydrofuran (6%), (*E*)-1-phenylhex-4-en-1-one (7%).[15]
[d] Not detected.
[e] Additional product: 2-acetyl-5-phenyltetrahydrofuran (1%).
[f] Additional products: 5-phenyltetrahydrofuran-2-ol (3%),[16] 5-phenyltetrahydrofuran-2-one (3%),[17] 1,5-diphenyl pentane-1,5-diol (7%),[19,20] 1,5-diphenyl-5-hydroxypentane-1-one (4%),[19] 4-phenyl-4-oxobutanal (2%),[18] benzaldehyde (4%).
[g] Additional products: 5-phenyltetrahydrofuran-2-one (2%),[17] benzaldehyde (2%).

5[9] (cis:trans < 1:99; Table 1, entry 1).[26] Reaction parameters (temperature, cobalt concentration, and molar catalyst/substrate ratio) were independently varied (not shown), but finally corresponded to those reported previously for related reactions.[9,11] Oxidation of (*E*)-1,5-diphenylpent-4-en-1-ol (*E*)-(**4**)[13] [(*E*):(*Z*) > 99:1; GC, ^{1}H NMR] under such conditions afforded tetrahydrofuran **6**[14] (cis:-trans < 1:99) as the major product (53%, Table 1, entry 4). A similar efficiency for tetrahydrofuran formation was not attainable, if previously established reagent **1b** served as the catalyst (Table 1, entries 2 and 5). Mass balances were in all instances supplemented in combined GC–MS and NMR investigations using purified samples from larger batches, and data from independently prepared authentic samples[15–20] [e.g., 96% mass balance for the oxidation of (*E*)-**3** and 79% mass balance for transformation of (*E*)-**4**; Table 1, entries 1 and 4).

Diastereoselectivity for construction of the stereocenter at C^β in the alkanol side chain of **5** and **6** ranged from 57/43 to 13/87. It was dependent on the nature of the terminal substituent (i.e., CH_3 or C_6H_5), solvent, and applied cobalt reagent. An assignment of stereoisomers was not attainable on the basis of available spectroscopic data. This issue is subject to ongoing investigations.

A change in solvent from *i*PrOH to a 50/50-mixture of C_6H_6/cyclohexa-1,4-diene (CHD) significantly favored formation of *trans*-2-phenyl-5-ethyltetrahydrofuran *trans*-**7** from (*E*)-**3** (Table 1, entries 1 and 3). No such marked variation in product selectivity was observed in the oxidation of (*E*)-**4** (Table 1, entries 4 and 6).

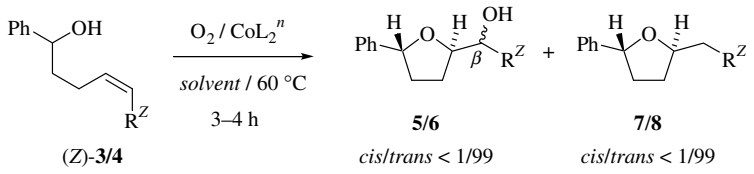
Aerobic oxidations of alkenols (*Z*)-**3**[13] and (*Z*)-**4**[13] [both (*E*):(*Z*) < 1:99; GC, ^{1}H NMR] in *i*PrOH solution of cobalt(II) reagent **1a** (60 °C) afforded 2,5-trans-configured (5-phenyltetrahydrofur-2-yl)alkan-1-ols **5** and **6** as major components, and derivatives **7**/**8** as side products (Table 2, entries 1 and 3).[9,14,16] Configuration at newly formed stereocenters in alkanol side chains of heterocycles **5** and **6** again showed a ~35/65 distribution of stereoisomers, with major components being equivalent to those from aerobic oxidations of substrates (*E*)-**3**/**4** (Table 1). Extended product analysis clarified that autoxidation (formation of 2-acetyl-5-phenyltetrahydrofuran; Table 2, entries 1 and 2), olefin hydration (formation of 1,5-diphenyl pentane-1,5-diol; Table 2, entry 3),[19,20] C,C-bond cleavage (formation of 5-phenyltetrahydrofuran-2-one; Table 2, entry 3),[17] and reduction (formation of 1,5-diphenyl pentan-1-ol, Table 2, entries 3–5)[21] accounted for the fact that combined yields of tetrahydrofurans **5**/**7** and **6**/**8** remained below ~80%. Product diversity in oxidations of (*Z*)-**4** ($R^Z = C_6H_5$) was larger than in transformations of (*Z*)-**3** ($R^Z = CH_3$). The use of CHD/C_6H_6 as the solvent instead of *i*PrOH furnished notable yields of tetrahydrofurans **7**/**8** from alkenols (*Z*)-**3**/**4** (Table 2, entries 2 and 5).

The current investigation on cobalt(II)-catalyzed aerobic oxidations of (*E*)- and (*Z*)-bishomoallylic alcohols provided four distinctive results:

(i) Catalytic activity of bis{4-[3,5-bis(trifluoromethyl)phenyl]-2-(oxo-κ*O*)-but-3-en-4-olatoκ*O*}cobalt(II) (**1a**) for synthesis of (2-phenyltetrahydrofur-2-yl)alkan-1-ols from δ,ε-unsaturated alcohols notably exceeded that of established reagent **1b**.
(ii) Solvent variation from *i*PrOH to CHD/C_6H_6 was associated with a change in product selectivity from oxidative cyclization (formation of substituted tetrahydrofur-2-ylmethanols **5**/**6**) toward alkenol cyclization (synthesis of substituted 2-alkyltetrahydrofurans **7**/**8**). Given mild and pH neutral conditions and the high degree of diastereoselection, the reductive tetrahydrofuran synthesis is expected to offer important prospect for future heterocycle synthesis.[5,22,23]
(iii) The customary 2,5-trans selectivity (cis/trans < 1/99, GC) in aerobic cobalt-catalyzed oxidations of substrates **3**/**4** was retained. It was independent from olefinic π-bond configuration, similar to isomer distribution with respect to the newly formed stereocenter in the alkanol side chain.
(iv) Alkenols having a phenyl substituent attached at terminal position of the olefinic π-bond are prone to undergo C,C-cleavage. The effect was more pronounced for (*E*)-β-alkyl styrene derivative (*E*)-**4** than for its (*Z*)-congener.

The most important implication from the presented data relates to evidence for sequential C,O bond formation in this type of oxidative alkenol ring closure. In combination with the selectivity effect exerted by co-solvent CHD, this finding suggests that the reaction is likely to be terminated via carbon radical trapping. This would imply that groups other than the H-atom should be transferable in the final step of the synthesis, which is being pursued at the moment in this laboratory.

Table 2
Formation of 2,5-disubstituted tetrahydrofurans **5**/**6** via aerobic cobalt-catalyzed oxidation of (*Z*)-configurated bishomoallylic alcohols (*Z*)-**3**/**4**



Entry	**3**/**4**	R^E	Solvent	CoL^n/mol %	Convn.	**5**/**6**/% (dr)[a,b]	**7**/**8**/%[a]
1	(*Z*)-**3**	CH_3	*i*PrOH	**1a**/10	Quant.	**5**: 61 (39:61)	**7**: 8[c]
2	(*Z*)-**3**	CH_3	C_6H_6/CHD	**1a**/10	96	**5**: 9 (38:62)	**7**: 71[d]
3	(*Z*)-**4**	C_6H_5	*i*PrOH	**1a**/10	98	**6**: 17 (35:65)	**8**: 1[e]
4	(*Z*)-**4**	C_6H_5	*i*PrOH	**1b**/20	44	**6**: 9 (67:33)	**8**: –[f,g]
5	(*Z*)-**4**	C_6H_5	C_6H_6/CHD	**1a**/10	89	**6**: 16 (31:69)	**8**: 47[h]

[a] *cis*-**5**–**8** were not detected (GC, NMR).
[b] Diastereomeric ratio with respect to configuration at C^β (GC).
[c] Additional product: 2-acetyl-5-phenyltetrahydrofuran (8%).
[d] Additional product: 2-acetyl-5-phenyltetrahydrofuran (5%).
[e] Additional products: 5-phenyltetrahydrofuran-2-one (3%),[17] 1,5-diphenyl pentan-1-ol (23%),[21] 1,5-diphenyl pentane-1,5-diol (33%),[19,20] (*Z*)-1,5-diphenyl pent-4-en-1-one (3%),[14] 1,5-diphenyl pentan-5-ol-1-one (6%).[18]
[f] Not detected.
[g] Additional product: 1,5-diphenyl pentan-1-ol (19%).[21]
[h] Additional products: 1,5-diphenyl pentan-1-ol (11%),[21] (*Z*)-1,5-diphenyl pent-4-en-1-one (3%) 14.

Acknowledgments

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24. Satisfactory analytical data were obtained for all new compounds prepared in the study.
25. UV/vis (*i*PrOH): λ_{max} ($\lg\varepsilon$/m^2 mol^{-1}) = 231 (3.28), 326 (3.29), 429 nm (qualitative). IR (NaCl) $\tilde{\nu}$3434 cm^{-1}, 2925, 1624, 1590, 1516, 1375, 1280, 1178, 1136, 905, 682. ^{19}F NMR ($CDCl_3$/acetone 565 MHz): δ −55.4. Anal. Calcd for $C_{26}H_{20}O_5F_{12}Co \times$ EtOH: C, 44.65; H, 2.88. Found: C, 44.49; H, 3.07.
26. *trans*-(Tetrahydro-5-phenylfur-2-yl)phenylmethanol *trans*-(**6**): A solution of (*E*)-1,5-diphenylpent-4-en-1-ol (*E*)-(**4**) (0.5 mmol) and cobalt(II) complex **1a** (0.10 equiv) in *i*PrOH (8 mL/mmol) was stirred at 60 °C for 2 h in a stationary oxygen atmosphere. The reaction mixture is allowed to cool to 20 °C afterwards. CH_2Cl_2 (6 mL/mmol) and Et_2O (4 mL/mmol) were added. The solution was washed with satd aq $Na_2S_2O_3$ soln (3 × 5 mL/mmol). Combined $Na_2S_2O_3$ washings were extracted with Et_2O (2 × 4 mL/mmol). (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). *Isomer 1* (minor): R_f = 0.41 [SiO_2, acetone/pentane = 1/5 (v/v)]. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.64–2.35 (m, 4H), 4.47 (m_c, 1H), 5.08 (m, 2H), 7.26–7.49 (m, 10H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 25.4, 35.4, 73.9, 82.0, 83.9, 125.5, 126.0, 127.3, 127.4, 128.3, 128.4, 140.1, 143.1. MS (70 eV, EI): *m*/*z* (%) 236 (M^+-H_2O, 25), 220 (3), 179 (5), 147 (23), 129 (25), 117 (38), 115 (38), 107 (35), 105 (54), 104 (50), 91 (100), 77 (49), 65 (16), 51 (24). *Isomer 2* (major): R_f = 0.27 [SiO_2, acetone/pentane = 1/5 (v/v)]. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.66–2.50 (m, 4H), 3.63–3.69 (m, 1H), 4.25 (d, *J* = 8.9 Hz, 1H), 4.58 (dd, *J* = 10.7, 2.0 Hz, 1H), 7.26–7.50 (m, 10H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 32.2, 33.7, 71.6, 79.8, 85.3, 125.8, 127.4, 127.5, 128.3, 128.4, 128.6, 137.5, 142.3. MS (70 eV, EI): *m*/*z* (%) 236 (M^+-H_2O, 5), 148 (11), 130 (16), 117 (10), 115 (10), 104 (100), 91 (36), 77 (18), 65 (6), 51 (13).