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Functionalized Tetrahydrofurans from Alkenols and Olefins/Alkynes via Aerobic Oxidation−Radical Addition Cascades

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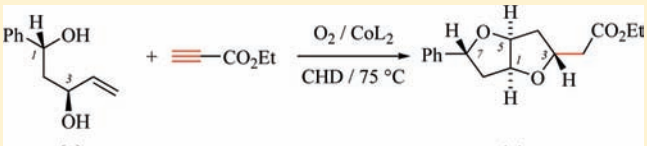
S Supporting Information

ABSTRACT: Aerobic oxidation of alkyl- and phenyl-substituted 4-pentenols (bishomoallyl alcohols), catalyzed by cobalt(II) complexes in solutions of γ-terpinene or cyclohexa-1,4-diene, stereoselectively gave tetrahydrofurylmethyl radicals. Cyclized radicals were trapped with monosubstituted olefins (e.g., acrylonitrile, methyl acrylate), (*E*)- and (*Z*)-1,2-diacceptor-substituted olefins (e.g., dimethyl fumarate, fumarodinitrile, *N*-phenyl maleic imide), and ester-substituted alkynes (e.g., ethyl propynoate). Oxidation−addition cascades thus furnished side-chain-substituted (CN, CO_2R, COR, or SO_2R) di- and trisubstituted tetrahydrofurans in stereoselective reactions (2,3-trans, 2,4-cis, and 2,5-trans). A diastereomerically pure bistetrahydrofuran was prepared in a cascade consisting of two aerobic oxidations, one alkyne addition, and one final H-atom transfer.



CHD = cyclohexa-1,4-diene

HL = e.g. 1-phenyl-4,4,4-trifluorobutane-1,3-dione

1. INTRODUCTION

Carbon radical addition to alkenes has become a cornerstone of organic synthesis from the time methods to selectively generate radicals and principles to control reactivity and selectivity became available.[1−5] Useful carbon radical additions in synthesis are fast and exothermic processes that proceed via early transition states. In early transition states, according to frontier molecular orbital theory, favorable interactions arise between the singly occupied molecular orbital (SOMO) of the radical and a suitable orbital of the alkene. Nucleophilic alkyl radicals (primary, secondary, or tertiary) have high SOMO energies and therefore interact with the lowest unoccupied molecular orbital (LUMO) of an electrophilic, that is an acceptor-substituted, alkene. Addition of the nucleophilic radical thereby occurs at the terminal alkene position.[6,7]

Radicals in synthesis must be generated from progenitors, such as alkyl halides, xanthates, mixed anhydrides, chalcogenides, or carbonyl compounds, to mention the most important product classes.[1,3] The dominating mechanism to transform a precursor for synthetic applications into a radical is the chain reaction. In a chain reaction, radical concentrations are kept low to prevent unproductive radical/radical reactions, such as combination or disproportionation, in order to favor productive reactions, such as trapping with an olefin or a heteroatom donor (cf. Scheme 1).[8,9] Conducting a chain reaction requires a mediator. A mediator is a reagent formally composed of a transferable group and a chain-propagating radical. A typical mediator is Bu_3SnH, consisting of $Bu_3Sn^•$, which is the chain-propagating radical, and $H^•$, the reducing equivalent. By this approach, stoichiometric amounts of radical progenitor and mediator are consumed. Catalytic sustainable methods for radical generation are surprisingly rare,[10−12] in spite of the growing significance of radical reactions in synthesis.[13−15]

To combine advantages of catalysis, stereoselective synthesis, and radical chemistry for synthesis of tetrahydrofuran-derived natural products,[16−18] we chose to functionalize the alkenol double bond in a sequence of polar and free radical reactions.[14,19,20] This sequence of transformation steps is not available from oxidation catalysis or radical chemistry alone. For our strategy, we selected oxidation catalysis to construct the tetrahydrofuran ring. The oxidation leaves a cyclized radical, which must be trapped by the alkene. Termination of the sequence requires a reductant. To maintain the catalytic cycle, the same reductant must convert the oxidized form of the catalyst into the reduced form, which is the active reagent (Scheme 1).

The results of our study show that substituted 4-pentenols undergo stereoselective tetrahydrofuran ring closures if oxidized with molecular oxygen in solutions containing cyclohexa-1,4-diene (CHD). The oxidation, which is catalyzed by cobalt(II) diketonate complexes, generates tetrahydrofurylmethyl radicals which add to acceptor-substituted alkenes. By this approach, tetrahydrofurans were stereoselectively prepared (2,3-trans, 2,4-cis, and 2,5-trans) in up to 66% yield. The products were side-chain substituted with CN, CO_2R, COR, and SO_2R groups, originating from the alkene/alkyne (R = alkyl). We applied the method to prepare a diastereomerically pure bistetrahydrofuran in a cascade, consisting of two aerobic oxidations, one alkyne addition, and one final H-atom transfer.

2. RESULTS AND DISCUSSION

2.1. Cobalt(II) Complexes. In earlier studies it was discovered that complexes of cobalt(II), derived from trifluoromethyl-substituted

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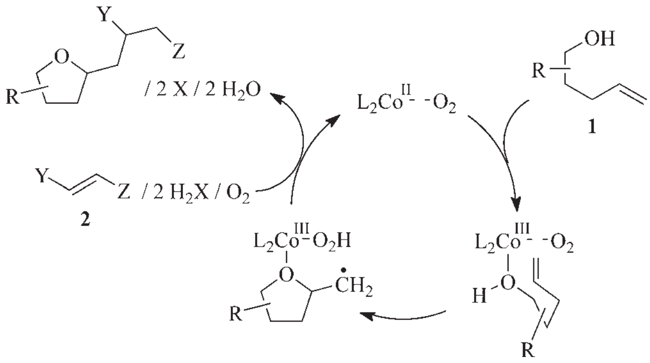
Scheme 1. Mechanistic Concept for Heterobisfunctionalization of Alkenols via Aerobic Oxidation−Radical Addition Cascades[a]



[a] H_2X = e.g., 1,4-cyclohexadiene (CHD) or γ-terpinene (γ-Ter), R = e.g., alkyl or aryl; Z = e.g., CO_2CH_3 or CN; Y = e.g., H or Z; HL = 1,3-diketone; for reactions with alkynes, refer to section 2.4.

1,3-diketones, are able to activate molecular oxygen for oxidative cyclization of 4-pentenols.[19−22] From benchmark reactivity tests using donor- and acceptor-substituted diketonates as auxiliaries for cobalt(II), we selected cobalt(II) complex **3**,[23] an established reagent that was available from a previous study, and derivative **4**,[24] for performing oxidation−addition cascades. The improved stability and reactivity of cobalt(II) complex **4** was discovered in a late phase of the project. It was applied for the most important substrate permutations but not for all (vide infra). Analytical data showed that the monoethanol adduct of bis{4-[3,5-bis(trifluoromethyl)phenyl]-(2-oxo-κO)-but-3-en-(4-olato-κO}cobalt(II) (**3**) and the dihydrate of bis-[1,1,1-trifluoro-2-(oxo-κO)-4-phenylbut-3-en-4-olato-κO]cobalt(II) (**4**) are formed from the synthesis. We used both complexes, the way they were obtained from the synthesis, as oxidation catalysts (see Table 1.

2.2. Cascades with Terminal Olefins. *2.2.1. Parameters for Selective Alkylative Trapping.* Acrylonitrile **2a** served as a reporter substrate for elucidating principles of aerobic oxidation−olefin addition cascades because rate constants,[25] regioselectivity,[26] and theoretical details[27] of carbon radical addition to the alkene are known in detail from Bu_3SnH- and alkylmercury hydride-mediated reactions.[8] From the results of mechanistic studies, we derived that (i) alkenol, olefin, and cobalt concentrations, (ii) reaction temperature, (iii) the concentration and chemical nature of the reductant H_2X, (iv) the cobalt(II) reagent, and (v) olefin reactivity are important parameters to adjust for conducting oxidation−addition cascades.

(i). Alkenol, Olefin, and Cobalt Concentrations. We considered 24 h as a reasonable time limit to achieve quantitative conversion of substrate **1a**. To meet this prerequisite, a solution of 1-phenyl-4-pentenol **1a** (0.33 M) in cyclohexa-1,4-diene (CHD; 3.3 M)/toluene containing cobalt(II) complex **3** (5 mol %) has to be stirred at a reaction temperature of 60 °C in an open flask equipped with a reflux condenser. This set up provides 85% of *trans*-5-methyl-2-phenyltetrahydrofuran **5a**.[14] In an atmosphere of argon under otherwise similar conditions, substrate **1a** is virtually inert.

Alkenol and cobalt(II) concentrations are a critical parameter for the oxidative part of the cascade. Their concentrations were therefore kept constant in reactions performed in the presence of acrylonitrile **2a**. We found that 1.7 M acrylonitrile **2a** is required to prepare 59% of addition products **6** (44%) and **10** (15%), besides 16% of byproduct **5a**[28] (Table 2, entry 4). Yields of addition products and the fraction of **6** versus **10** from cobalt-catalyzed reactions are similar to references from radical additions to acrylonitrile, mediated by Bu_3SnH or substituted cyclohexa-1,4-dienes.[1,29] Higher acrylonitrile concentrations increase the yield of 2-fold addition product **10**, whereas lower concentrations of the alkene favored formation of reduction product **5a**. Concentrations of 1.5−1.7 M (i.e., ~5 equiv with respect to **1a**), depending on the solubility of the alkene in toluene/CHD mixtures, were therefore used as standard to compare the alkene reactivity (cf. section 2.2).

(ii). Temperature Effects. The onset of cobalt-catalyzed oxidative ring closure occurs at temperatures above 30 °C (Figure 1). Quantitative alkenol turnover is attainable within 24 h at 60 °C. An increase of the reaction temperature from 60 to 90 °C leads to a plateau for monoaddition product formation at 75 °C and for dinitrile formation at 60 °C (Figure 1). The yield of 5-methyl-2-phenyltetrahydrofuran **5a** gradually increases as the reaction temperature rises from 30 to 90 °C. We therefore performed aerobic oxidations catalyzed by cobalt complex **3** in the following sections at 60 °C, whereas phenyl-trifluoromethyl-butanedione derivative **4** was more active at 75 °C.

(iii). Concentration and Chemical Nature of Reductant H_2X. Turnover in cobalt-catalyzed aerobic alkenol oxidation requires a chemoselective reductant. We used CHD and γ-terpinene as reductants for the oxidation−addition cascade. Cyclohexa-1,3-diene was surprisingly less effective than CHD (cyclohexa-1,4-diene). A likewise performed oxidation of **1a** catalyzed by **3** provided 22% of **5a** in the absence of acrylonitrile **2a**. If acrylonitrile **2a** is added, turnover entirely stops. Assumed Diels−Alder adducts between acrylonitrile and cyclohexa-1,3-diene were not found (GC-MS).

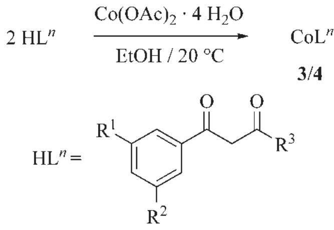
γ-Terpinene (γ-Ter), a naturally occurring compound,[30] is a very effective alternative to CHD. In aerobic oxidations catalyzed by cobalt(II) compounds, γ-terpinene is oxidized to isopropyl-4-methylbenzene (>200%). From results of Karl Fischer titrations[19] we concluded that notable amounts of water form in aerobic alkenol oxidations in 1,4-dihydroarene solution. The amount of water, however, was not systematically quantified.

A gradual increase of CHD concentration improved the yield of tetrahydrofuryl butyronitrile **6**. This trend leveled off at c_0^{CHD} = 3−4 M (Figure 2). The same trend is observed for dinitrile formation (product **10**), although at lower yields. The yield of 2-phenyl-5-methyltetrahydrofuran **5a** correlates with CHD concentration. We therefore concluded that CHD is involved in formation of product **5a** (vide infra). To achieve maximum selectivity for monoaddition product formation, we chose a value ~3.3 M as the standard CHD concentration in oxidation−addition cascades.

(iv). Cobalt(II) Reagents. Aerobic oxidative cyclization of 1-phenyl-4-pentenol **1a** is catalytic in cobalt(II) complexes **3** and **4**. No oxidative transformation of **1a** occurs if catalysts **3** and **4** are replaced by $Co(OAc)_2$ (as the tetrahydrate or in anhydrous form). Cobalt(II) complex **4** in combination with γ-terpinene at a temperature of 75 °C was more reactive than **3** (Supporting Information), thus allowing us to reduce the amount of catalyst by 40% and shorten reaction times by ~70%. Catalyst **4**, however, did not necessarily lead to the highest yields, so that both catalysts, that is **3** and **4**, were checked. The best yields obtained are given in the tables and schemes.

(v). Olefin Reactivity. Alkenes substituted by a CO_2CH_3 (**2b**), $COCH_3$ (**2c**), and SO_2CH_3 group (**2d**) give monoaddition

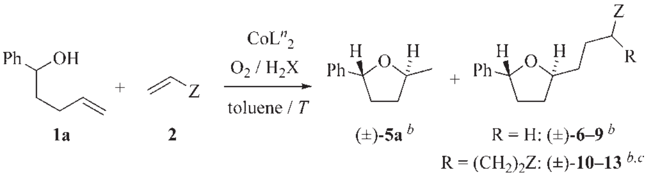
Table 1. Preparation of Cobalt(II) Chelates from CF_3-Substituted 1,3-Diketones



entry	HL^n	R^1 = R^2	R^3	3/4/%	δ^{19}F/ppm^a	$\nu_{C=O}$/cm^{-1b}	λ_{max}/nm (lg $\varepsilon/\varepsilon^*$)^c
1	HL^1	CF_3	CH_3	3: 94^e	−55.4	1624	231 (3.28), 305 (2.67), 429 sh
2	HL^2	H	CF_3	4: 99^d	6.1	1609	252 (3.33), 319 (3.55)

[a] In acetone/$CDCl_3$ [50:50 (v/v)]. [b] Pelletized in KBr. ε in $m^2\ mol^{-1}$. [c] $\varepsilon^* = 1\ m^2\ mol^{-1}$. [d] Formed as EtOH adduct (combustion analysis). [e] Formed as dihydrate (combustion analysis) that quantitatively loses H_2O upon drying (IR).

Table 2. Selectivity in Aerobic Alkenol Oxidation−Olefin Addition Cascades[a]



entry	2	Z	CoL$''_2$^{d}	H_2X	T/°C	5a/%	6−9/%	10−13/%
1	**2a**	CN	3	CHD	60	29	**6**: 34	**10**: 11
2	**2a**	CN	3	γ-Ter	60	16	**6**: 40	**10**: 18
3	**2a**	CN	4	CHD	75	23	**6**: 35	**10**: 12
4	**2a**	CN	4	γ-Ter	60	15	**6**: 41	**10**: 16
5	**2a**	CN	4	γ-Ter	75	16	**6**: 44	**10**: 15
6	**2b**	CO_2CH_3	3	CHD	60	28	**7**: 27	**11**: 13
7	**2b**	CO_2CH_3	3	γ-Ter	75	30	**7**: 32	**11**: 13
8	**2c**	$C(O)CH_3$	3	CHD	60	19	**8**: 21	**12**: 20
9	**2c**	$C(O)CH_3$	4	γ-Ter	75	27	**8**: 31	**12**: 13
10	**2d**	SO_2CH_3	4	CHD	60	20	**9**: 43	**13**: −^{e}

[a] Quantitative alkenol conversion within 24 (for **3**) or 8 h (for **4**). [b] Cis:trans < 1:99 (GC and ^{1}H NMR). [c] 50/50 ratio of diastereomers with respect to the stereocenter in the α-position to CN. [d] 5 mol % of **3** and 3 mol % of **4** with respect to alkenol **1a**. [e] Not detected (^{1}H NMR, GC).

products **7**−**9** besides 2-fold-addition products **10**−**12** if treated under standard conditions (Table 2, entries 6−10). Surprisingly, no 2-fold addition product was found in reactions starting from methyl vinyl sulfone (**2d**). The oxidative ring closure of 1-phenyl-4-pentenol **1a** occurs in all instances 2,5-trans selectively (^{1}H NMR, GC). For stereoassignment, we used NOESY spectra and chemical shift correlations (^{1}H, ^{13}C) obtained from a combined NMR/X-ray diffraction study.[31] The stereocenter 2′, which is in proximity to the cyano group in dinitrile **10**, is formed without diastereoselectivity (dr =50:50). Despite considerable efforts, we were not able to obtain useful yields for reactions between **1a** and crotononitrile (13% of monoaddition product; 58% of **5a**) or cinnamoyl nitrile [44% of **5a**; traces of addition product (GC-MS); not shown] using the available catalysts.

2.2.2. Mechanistic Considerations. To verify the radical nature of oxidatively cyclized 4-pentenol **1a**, we chose, in extension to the existing mechanistic and stereochemical analysis, a kinetic approach.[14]

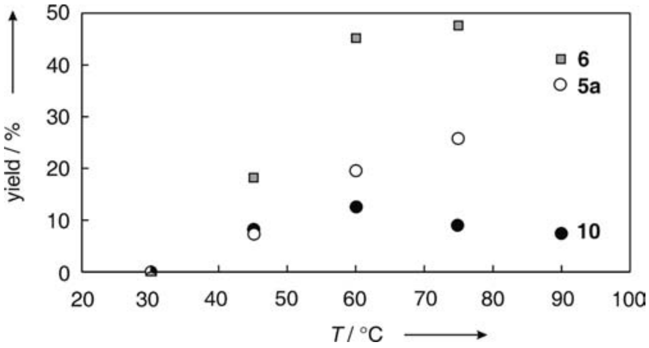


Figure 1. Temperature profile of product selectivity in aerobic oxidation of alkenol **1a** in the presence of acrylonitrile **2a** and CHD catalyzed by **3** (c_0^{2a} = 1.5 M; 5.0 equiv; c_0^{CHD} = 3.5 M in toluene; c_0^{1a} = 0.30 M, c_0^{3} = 0.02 M).

Structure effects on rate constants of primary alkyl radicals in additions or H-atom abstractions are small within the experimental error. Therefore, we used the rate constants of the ethyl radical (H-atom abstraction from CHD) and the 5-hexen-1-yl radical (addition to acrylonitrile **2a** and methyl acrylate **2b**) for describing the reactivity of assumed primary radical **14**. To apply reference data for ambient temperature reactions for comparison with experimental values obtained at 60−75 °C, temperature effects on homolytic substitution (from CHD) and addition (to **2a**−**c**) were assumed to be similar.

Since H-atom abstractions from CHD and primary alkyl radical additions to acrylonitrile are irreversible, the ratio of **5a** versus the combined yield of addition products **6** and **10** directly leads to an experimental partial rate factor (f_2^{exp}; Table 3, eq 1). The physical organic meaning of the partial rate factor is similar to a relative rate constant. A relative rate constant, however, is determined from a series of experiments, whereas the partial rate factor is an approximation from only one data point.

By inserting absolute rate constants from the literature and considering respective concentrations from our experiments (3.0 M for CHD and 1.5 M for alkenes **2a**−**c**; Table 2), partial rate factors were calculated according to eq 1 (f_2^{calcd}). Values f_2^{exp} and f_2^{calcd} for olefins **2a**−**c** nearly match. We therefore conclude that the reactivity of **14** and of primary alkyl radicals used to reference

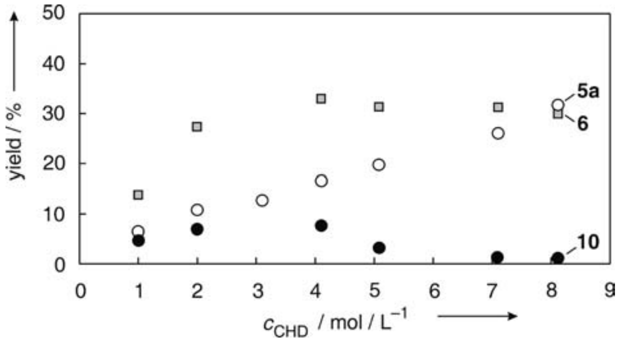


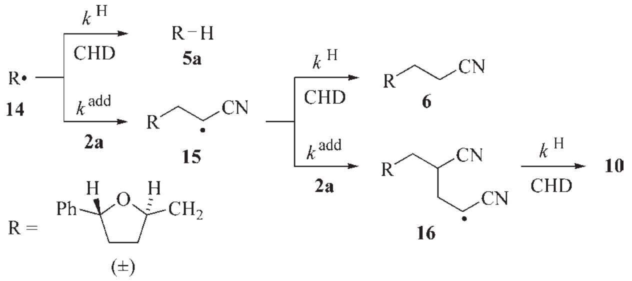
Figure 2. Correlation of product selectivity and CHD concentration in aerobic alkenol oxidations in the presence of acrylonitrile **2a** (toluene as cosolvent; $c_0^{\mathbf{2a}}$ = 1.5 M; $c_0^{\mathbf{1a}}$ = 0.30 M; $c_0^{\mathbf{3}}$ = 0.02 M; T = 60 °C).

Table 3. Correlation of Calculated Rate Factors f_2^{calcd} versus Experimental Data from Aerobic Alkenol Oxidation in the CHD/2 Competition System (cf. Scheme 2)

entry	**2**	Z	f_2^{calcd} [a]	f_2^{exp} [b]
1	**2a**	CN	4.7[c]	1.7
2	**2b**	CO_2CH_3	1.4[c]	1.4
3	**2c**	$C(O)CH_3$	(2.2)[d]	2.2

[a] For 3.0 M CHD and 1.5 M olefin concentration according to eq 1; $k^{\text{H}} = 5.8 \times 10^4$ M^{-1} s^{-1} ($^{\bullet}C_2H_5$ + CHD; 27 °C).[32] [b] For 60 °C (cf. Table 2, entries 1, 6, and 8). [c] $k^{\text{add}} = 5.4 \times 10^5$ M^{-1} s^{-1} [$H_2C{=}CH(CH_2)_3CH_2^{\bullet}$ + **2a**] and 1.6×10^5 M^{-1} s^{-1} [$H_2C{=}CH(CH_2)_3CH_2^{\bullet}$ + **2b**] for 20 °C in CH_2Cl_2. [d] Estimated on the basis of relative rate constants for 5-hexen-1-yl radical addition to methyl acrylate and methyl vinyl ketone ($k_{\mathbf{2c}}^{\text{add}}/k_{\mathbf{2b}}^{\text{add}}$ = 1.6 at 69 °C).[33−35]

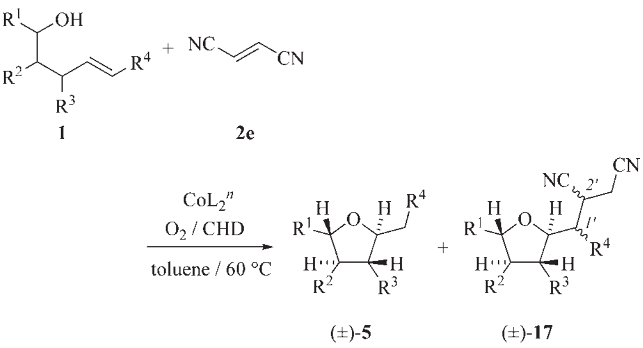
Scheme 2. Elementary Reactions for Rate Factor (f_{2a}) Analysis in Aerobic Oxidation Olefin Addition Cascades (see text and Table 3)



partial rate factor analysis is similar (Table 3).

$$\frac{([\mathbf{6}] + [\mathbf{10}])}{[\mathbf{5a}]} = f_{2a} = \frac{k^{\text{add}}[\mathbf{2a}]}{k^{\text{H}}[\text{CHD}]} \qquad (1)$$

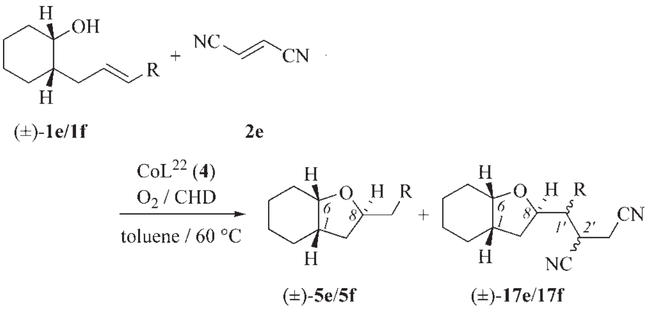
Table 4. Oxidation−Radical Addition Cascades Starting from Phenylpent-4-en-1-ols 1a−d and Fumarodinitrile 2e[a]



entry	**1**	R^1	R^1	R^3	R^4	CoL^n_2 [b]	**5**/% (cis:trans)[c]	**17**/% (cis:trans)[c]
1	**1a**	Ph	H	H	H	**3**	**5a**: 2 (<1:99)	**17a**: 66 (<1:99)
2	**1a**	Ph	H	H	H	**4**	**5a**: 1 (<1:99)	**17a**: 66 (<1:99)
3	**1b**	Ph	H	H	CH_3	**3**	**5b**: −[c]	**17b**: 58 (<1:99)
4	**1c**	H	Ph	H	H	**3**	**5c**: −[c]	**17c**: 58 (74:26)
5	**1d**	H	H	Ph	H	**3**	**5d**: 8 (3:97)	**17d**: 53 (3:97)

[a] For reactant concentrations refer to the text and the Experimental Section; quantitative conversion of **1a−d**. [b] 5 mol % of **3** and 3 mol % of **4** with respect to alkenol **1a**. [c] Not detected (GC-MS). [d] 50/50 mixture of diastereomers with respect to the configuration of the substituents at the 1′ and 2′ positions.

Table 5. Oxabicyclo[4.3.0]nonylmethylbutyrodinitrile Synthesis from *cis*-Allylcyclohexanols 1e and 1f and Fumarodinitrile 2e



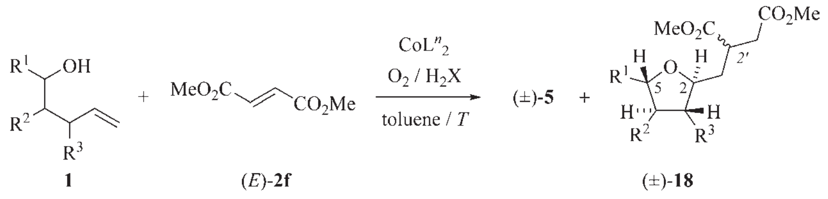
entry	**1**	R	**5**/% (cis:trans)[a]	**17**/% (cis:trans)[a]
1	**1e**	H	**5e**: 5 (<1:99)	**17e**: 67 (<1:99)
2	**1f**[b]	CO_2CH_3	**5f**: 24 (17:87)	**17f**: 19 (25:75)

[a] Refers to positions 6 and 8. [b] Control in the absence of **2e**:**5f**: 73% (8:92).

2.3. Terminating Sequential Reactions with 1,2-Substituted Alkenes. We chose fumarodinitrile **2e** (c_0 = 1.7 M) to improve the selectivity of monoaddition product formation. Alkyl radicals (nucleophilic) add faster to the olefin **2e** than to acrylonitrile **2a**.[6] The set of substrates was extended to 1-, 2-, or 3-phenyl-substituted 4-pentenols **1a−d** and to *cis*-2-allyl cyclohexanol **1e** to broaden the scope of the method. We performed all experiments under standard conditions, leading to butyrodinitriles **17a−b** (2,5-trans), **17d** (2,3-trans), and **17e** (6,8-trans; Tables 4 and 5). Cis selectivity is found for oxidations starting from 2-phenyl-4-pentenol **1c** (2,4-cis), which is in agreement with the stereochemical guidelines of the cobalt method.[14] The use of catalysts **3** and **4** provided a similar yield for **17a** but different values for **17e** (67% for catalyst **4** and 47% for catalyst **3**). Compared to the acrylonitrile reactions, yields of reduction products **5a−d**[14,28,32] remained low (<1−8%). No 2-fold alkene addition products to cyclized radicals were found (GC-MS).

To probe an oxidation−cyclization cascade starting from an acceptor-substituted alkenol, we subjected substrate **1f** (R = CO_2CH_3) and fumarodinitrile **2e** to standard conditions. From

Table 6. CoL_2-Catalyzed Oxidation of Phenylpent-4-en-1-ols **1a**−**c** in the Presence of Dimethyl Fumarate (*E*)-**2f**[a]



entry	1	R^1	R^1	R^3	CoL''_2[b]	*T*/°C	H_2X	**5**/% (cis:trans)	**18**/% (cis:trans)[c,d]
1	**1a**	Ph	H	H	**3**	60	CHD	**5a**: 15 (1:99)	**18a**: 51 (<1:99)
2	**1a**	Ph	H	H	**4**	75	γ-Ter	**5a**: 28 (<1:99)	**18a**: 60 (<1:99)
3	**1c**	H	Ph	H	**3**	60	CHD	**5c**: —[e]	**18c**: 57 (73:27)
4	**1d**	H	H	Ph	**3**	60	CHD	**5d**: 27 (5:95)	**18d**: 47 (5:95)

[a] For reactant concentrations refer to the text and the Experimental Section; quantitative conversion of **3**. [b] 5 mol % of **3** and 3 mol % of **4** with respect to alkenol **1a**. [c] Cis/trans ratios refer to the relative configuration of the substituents at tetrahydrofuran. [d] 50/50 mixture of diastereomers with respect to the configuration at position 2′. [e] Not detected (GC).

Scheme 3. Alkenol Oxidation−Alkylation Sequences Starting from (*Z*)-1,2-Diacceptor-Substituted Olefins

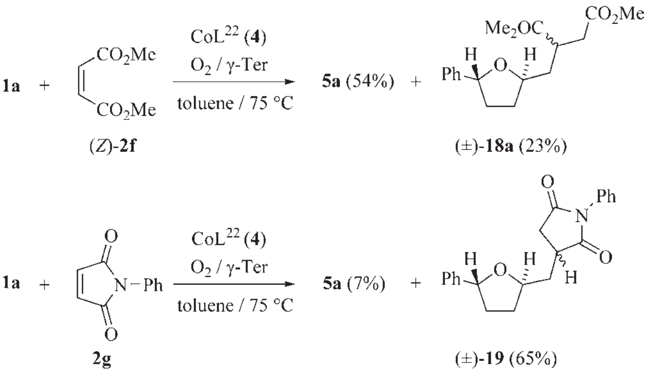
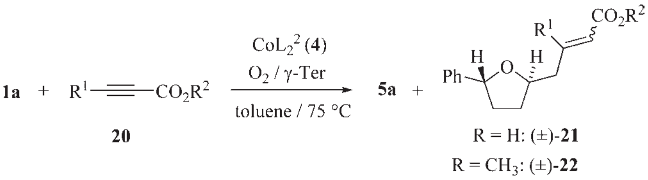


Table 7. Substituent Effects in Oxidative Cyclization−Alkyne Addition Cascades[a]



entry	R^1	R^2	**20**	**5a**/%[a]	**21**/**22**/% (*E*:*Z*)[a]
1	H	Et	**20a**	41	**21**: 47 (53:47)
2	CO_2CH_3	Me	**20b**	28	**22**: 50 (62:38)

[a] Quantitative conversion of **1a**; cis:trans < 2:98 for **5a**, **21**, and **22** (^1H NMR); 3 mol % of **4**.

this experiment, reduction product **5f** and butyrodinitrile **17f** were obtained in low-yields (Table 5, entry 2). This observation is in line with the reduced nucleophilicity of the radical that is formed from oxidative cyclization of **1f** and thus the lower rate for addition to alkene **2e**. From previous studies on acceptor-substituted substrates,[14] we were prepared to find lower trans selectivity for oxidative cyclization of **1f** (66% for **5f**) compared to **1e** (>99% for **5e**). Treatment of alkenol **1f** with a potassium *tert*-butoxide in toluene on the other hand provides a 55/45 mixture of **5f** (81%, not shown), whereas Lewis-acidic cobalt(II) complex **4** did not induce cyclization of the substrate.

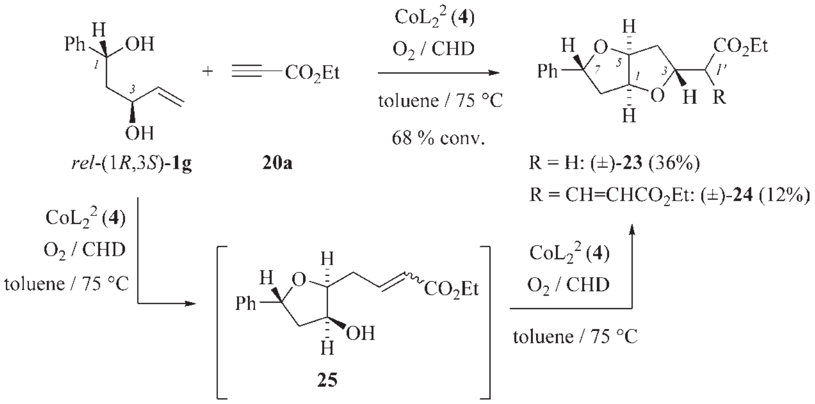
Starting from alkenols **1a** and **1c**−**d** and dimethyl fumarate (*E*)-**2f**, we prepared tetrahydrofurans **18a** and **18c**−**d** in yields between 47% and 60% (Table 6). Product and stereoselectivity thereby follow the same trends as outlined for fumarodinitrile reactions (cf. Table 4). The use of dimethyl maleate (*Z*)-**2f** provided only 23% dimethyl [2-(2-phenyltetrahydrofuryl-5-methyl)] succinate **18a** but 54% of reduction product **5a** (Scheme 3, top). The data and a rate factor analysis [$f_{(E)\text{-}\mathbf{2f}}/f_{(Z)\text{-}\mathbf{2f}} = 5.1$ for 75 °C] show that different performances of (*E*)-**2f** and (*Z*)-**2f** in the cobalt method correlate with the relative reactivity of cyclohexyl radical addition to the alkenes ($k^{\text{rel}} = k_{(E)\text{-}\mathbf{2f}}/k_{(Z)\text{-}\mathbf{2f}} = 10$, 20 °C).[6]

Attempts to apply maleic acid anhydride to conduct oxidation−cyclization cascades lead to an irreversible deactivation of catalysts **3** and **4**. *N*-Phenyl maleic imide, on the other hand, provided 65% of addition product **19** if subjected to standard conditions (Scheme 3, bottom).

2.4. Trapping with Alkynes. Mono- and 2-fold ester-substituted alkynes gave α,β-unsaturated esters **21** and **22** under standard conditions (Table 7). We transformed the yields into relative reactivity and thereby used methyl acrylate (**2b**) as a reference. The value $f_{\mathbf{2b}}/f_{\mathbf{20a}} = 1.4$ (75 °C) compares reasonably well with the relative rate constant for cyclohexyl radical addition to methyl acrylate **2b** and methyl propynoate ($k^{\text{rel}} = 3.0$, 20 °C).[6] We therefore explain the chemistry of alkyne trapping in oxidation−radical addition cascades in extension to the mechanism outlined for reactions with alkenes (Schemes 1 and 2). Support for this interpretation comes from stereochemical analysis of fumarate formation from **20b**.[33] Syn-selective H-atom transfer onto vinyl radicals having small substituents attached in the β position to the radical center generally is favored, thus providing an explanation for the (*E*)-selectivity in the synthesis of fumarate **22** (Table 7, entry 2).

Aerobic oxidation of alkenol *rel*-(1*R*,3*S*)-**1f** and ethyl propiolate **20a** in CHD/toluene catalyzed by cobalt(II) complex **4** furnished bistetrahydrofuran **23** as the single diastereomer

Scheme 4. Bistetrahydrofuran Formation in Oxidation−Alkyne Addition−Oxidation Cascade



without the necessity to apply a hydroxyl protecting group (Scheme 5). The total yield of **1f**-derived products added to 48% at a conversion of 68%. Substrate turnover stopped in a reproducible manner at this point and could not be taken to completion, even upon addition of further aliquots of catalyst **4** and CHD.

To explain this chemistry, we assumed that alkyne trapping by the intermediate vinyl radical and subsequent reduction leads to alkenol **25**. In a second aerobic alkenol cyclization, alkenol **25** is transformed into product **23**. For two reasons, we consider the second cyclization to occur via a cobalt-catalyzed reaction as well. First, the fused tetrahydrofuran ring is formed with the trans selectivity that is characteristic for the cobalt method (see text associated with Table 5).[19] Second, at one stage of the reaction a carbon nucleophile must have existed, which added to ethyl propynoate (**20a**) to give after H-atom abstraction from CHD product **24** [12%; mixture of (*E*)/(*Z*)-isomers in favor of (*E*)-**24**] (Scheme 4).

3. CONCLUDING REMARKS

The synthesis of side-chain-extended tetrahydrofurans from alkenols and acceptor-substituted alkenes combines aspects of aerobic oxidation catalysis and reductive alkyl radical chemistry. The combination of a polar and a radical reaction for adding chemically different entities at the two carbons of a π bond is not available from oxidation catalysis or free radical chemistry alone. The method is furthermore one of the few catalytic procedures for radical generation in synthesis.

From a synthetic point of view, the cobalt method is expected to offer a quite general solution for radical generation from 4-pentenols. Also, other acceptor-substituted olefins that are applied for carbon−carbon bond formation via radical addition to alkenes, such as aryl vinyl sulfones or 1,1-dichloroalkenes, shall be considered as candidates for broadening the scope of the homologization step. In terms of efficiency, the cobalt method compares well with values from Bu_3SnH-mediated reactions that uses stoichiometric amounts of the progenitor (such as an alkyl halide, xanthate, or carboxylic acid) and an acceptor-substituted olefin.

The major challenge for further improving selectivity in oxidation−addition cascades certainly lies in the quest for a smarter reductant, which is able to maintain the catalytic cycle but also to more delicately respond to polarity differences between cyclized radicals and more electrophilic carbon radicals that result from addition to an acceptor-substituted alkene. By this approach formation of 2-fold addition and reduction products will be minimized to improve the yield of 1/1 addition products (e.g., **6**). Although this selectivity is not perfect for Bu_3SnH and CHD chemistry as well,[6,8,34] the cobalt(II) method could add another dimension to this issue.

4. EXPERIMENTAL SECTION

4.1. General. For general laboratory practice and instrumentation see ref 14 and the Supporting Information.

4.2. Reaction of 1-Phenylpent-4-enol (1a) with Fumarodinitrile 2e. A suspension of alcohol **1a** (164 mg, 1.01 mmol), fumarodinitrile **2e** (396 mg, 5.07 mmol), CHD (1.0 mL, 10.2 mmol), and cobalt(II) reagent **3** (33.2 mg, 50.8 μmol) in toluene (1.6 mL) was stirred for 21 h at 60 °C while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C. Unspent fumarodinitrile was removed by filtration. The filtrate was purified by column chromatography [SiO_2, acetone/pentane = 1:5−1:3 (v/v)].

*trans-2-Methyl-5-phenyltetrahydrofuran (**5a**)*[28]. Yield: 3.1 mg (19.1 μmol, 2%).

*2-[(trans-5-Phenyltetrahydrofur-2-yl)-methyl] Butanedinitrile (**17a**).* Yield: 161 mg (66%); colorless oil [cis:trans < 1:99, 50/50 mixture of diastereoisomers with respect to C_α]. $R_f = 0.22$ for acetone/pentane =1:5 (*v*/*v*). δ_H ($CDCl_3$, 400 MHz) 1.69−1.78 (1 H, m), 1.86−2.11 (3 H, m), 2.24−2.30 (1 H, m), 2.37−2.42 (1 H, m), 2.80 (2 H, d, *J* 6.5), 2.83−2.95 (2 H, m), 3.21 (1 H, quint, *J* 6.5), 3.26−3.31 (1 H, m), 4.38−4.43 (1 H, m), 4.99−5.04 (1 H, m), 7.27−7.36 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 20.3/21.2, 25.8/26.5, 32.36/32.39, 34.7/35.0, 36.2/37.9, 75.7/76.6, 80.5/80.7, 115.7/116.0, 118.9/119.1, 125.4, 127.4, 128.3, 142.5/142.6. Anal. Calcd for $C_{15}H_{16}N_2O$ (240.30): C, 74.97; H, 6.71; N, 11.66. Found: C, 74.63; H, 6.50; N, 11.62. MS (EI) *m*/*z* (%) 240 (31, M^+), 223 (6), 183 (12), 146 (14), 129 (9), 117 (32), 105 (100), 91 (44), 77 (37).

4.3. Reaction of Alkenol 1a with Dimethyl Butynedioate (20b). A solution of alcohol **1a** (164 mg, 1.01 mmol), alkyne **20b** (727 mg, 5.01 mmol), γ-terpinene (1.9 mL, 98% pure, 11.5 mmol), and $[CoL^2_2\ (\mathbf{4})]\cdot 2H_2O$ (15.8 mg, 30.0 μmol) in toluene (0.4 mL) was stirred for 7 h at 75 °C while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and directly poured onto a column (SiO_2) for chromatographic purification [acetone/pentane =1:10−1:5 (v/v)].

*trans-2-Methyl-5-phenyltetrahydrofuran (**5a**)*[28]. Yield: 45.1 mg (278 μmol, 28%).

*Dimethyl 2-[(trans-5-phenyltetrahydrofur-2-yl)methyl] (Z)-Butenedioate ((Z)-**22**).* Yield: 59.6 mg (19%), colorless oil. $R_f = 0.42$ for acetone/pentane = 1:5 (v/v). δ_H ($CDCl_3$, 400 MHz) 1.72−1.85 (2 H, m), 2.11−2.20 (1 H, m), 2.38−2.43 (1 H, m), 3.02 (1 H, dd, *J* 12.4, 4.8), 3.29 (1 H, dd, *J* 12.4, 8.4), 3.72 (3 H, s), 3.79 (3 H, s), 4.46 (1 H, quint, *J* 6.3), 4.96 (1 H, t, *J* 6.6), 6.84 (1 H, s), 7.20−7.32 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 31.4, 33.5, 34.6, 51.6 (CH_3), 52.5 (CH_3), 78.4, 79.9, 125.6, 127.0, 127.7, 128.2, 143.4, 144.7, 166.2, 167.4. MS (EI) *m*/*z* (%) 304 (4, M^+), 272 (4), 244 (3), 185 (12), 147 (100), 129 (45), 120 (24), 105 (22), 91 (72), 77 (16).

*Dimethyl 2-[(trans-5-Phenyltetrahydrofur-2-yl)methyl] (E)-Butenedioate ((E-**22**).* Yield: 96.1 mg (31%), colorless oil. R_f = 0.21 acetone/pentane = 1:5 (v/v). δ_H ($CDCl_3$, 400 MHz) 1.68−1.77 (1 H, m), 1.82−1.91 (1 H, m), 2.14−2.21 (1 H, m), 2.35−2.42 (1 H, m), 2.59−2.76 (2 H, m), 3.73 (3 H, s), 3.82 (3 H, s), 4.39 (1 H, quint, *J* 6.6), 5.01 (1 H, t, *J* 7.3), 6.00 (1 H, s), 7.22−7.35 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 31.9, 34.9, 40.6, 51.8 (CH_3), 52.3 (CH_3), 77.1, 80.5, 121.8, 125.4, 127.1, 128.3, 143.2, 146.8, 165.3, 169.0. MS (EI) *m*/*z* (%) 304 (3, M^+), 272 (6), 244 (4), 185 (9), 147 (97), 129 (54), 120 (21), 105 (31), 91 (100), 77 (24).

4.4. Reaction of *rel*-(1*R*,3*S*)-1-Phenylpent-4-en-1,3-diol (1f) with Ethyl Propynoate (20a). A solution of alkenol **1f** (193 mg, 1.08 mmol), alkyne **20a** (1.09 g, 10.8 mmol), CHD (1.5 mL, 15.3 mmol), and $[CoL^2_2\ (\mathbf{4})]\cdot 2H_2O$ (28.9 mg, 55.0 μmol) in toluene (1.5 mL) was stirred at 60 °C for 16 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and directly poured onto a column (SiO_2) for chromatographic purification [acetone/petroleum ether =1:5 (v/v)].

*Ethyl 2-{rel-(2R,3aS,5R,6aS)-Hexahydro-2-phenylfuro[3,2-b]fur-5-yl} Acetate (**23**).* Yield: 108 mg (36%), colorless oil. R_f = 0.37 for acetone/pentane =1:5 (v/v). δ_H ($CDCl_3$, 600 MHz) 1.28 (3 H, t, *J* 7.2), 1.81 (1 H, ddd, *J* 13.6, 9.4, 5.1), 1.90 (1H, ddd, *J* 13.6, 10.4, 4.6), 2.38 (1 H, dd, *J* 13.6, 5.1), 2.48−2.65 (3 H, m), 4.18 (2 H, q, *J* 7.2), 4.55−4.60 (1 H, m), 4.82 (1 H, t, *J* 4.6), 4.92 (1 H, t, *J* 4.6), 5.08 (1 H, dd, *J* 10.4, 5.1), 7.29−7.36 (5 H, m). δ_C ($CDCl_3$, 150 MHz) 14.2, 40.6, 40.9, 43.9, 60.6, 76.4, 81.3, 84.1, 84.2, 125.7, 127.5, 128.4, 141.7, 171.0. MS (EI) *m*/*z* (%) 276 (4, M^+), 258 (6), 189 (22), 117 (25), 105 (100), 91 (15), 77 (25).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures and spectral and analytical data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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