Kaskaden aus Aerober Oxidation und Radikalischer Funktionalisierung zum Aufbau Cyclischer Ether

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Was die Philosophen über die Realität sagen, ist oft so enttäuschend wie ein Schild in einem Laden, auf dem steht „Hier wird gebügelt“.
Bringt man dann seine Kleider zum Bügeln hin, kommt man sich dumm vor, denn nur das Schild wird verkauft.

Søren Kierkegaard

Die vorliegende Arbeit wurde in der Zeit von Dezember 2008 bis Juli 2013 in der Fachrichtung Organische Chemie des Fachbereichs Chemie der Technischen Universität Kaiserslautern unter der Leitung von Herrn Prof. Dr. Jens Hartung angefertigt.

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Darüber hinaus wurden die Promotionsergebnisse als Posterbeiträge und als Vortrag auf folgenden Tagungen präsentiert:

(V) Posterbeitrag: *Functionalized Tetrahydrofurans from Alkenols and Olefins/Alkynes via Aerobic Oxidation – Radical Addition Cascades*: P. Fries, J. Hartung, *GDCh Wissenschaftforum*, Bremen **2011**.

(VI) Vortrag: *Von aktiviertem Sauerstoff zu funktionalisierten Tetrahydrofuranen*, P. Fries, J. Hartung, *Cobalt-Workshop*, Kaiserslautern **2012**.

(VII) Posterbeitrag: *Catalytic Aerobic Oxidation / Radical Functionalization Cascades For Stereoselective Synthesis of Tetrahydrofurans*: P. Fries, M. K. Müller, A. Heyer, J. Hartung, *Nachhaltigkeit in der Chemischen Synthese*, Kaiserslautern **2012**.

Eidesstattliche Erklärung

Hiermit erkläre ich ehrenwörtlich, dass ich die vorliegende Arbeit selbständig angefertigt und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt habe.

Ich erkläre außerdem, dass diese Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat und ich, außer den mit dem Zulassungsgesuch urkundlich vorgelegten Graden, keine weiteren akademischen Grade erworben habe oder zu erwerben versucht habe.

Kaiserslautern, den 07.08.13 _____

Erläuterungen

Die vorliegende Arbeit ist in eine Zusammenfassung, eine Einleitung (Kapitel 1), einen Kenntnisstand mit Aufgabenstellung (Kapitel 2), drei unabhängige Ergebnisteile (Kapitel 3, 4 und 5) sowie in einen allgemeinen Anhang (Kapitel 6) untergliedert. Dabei sind Abbildungen, Schemata und Tabellen für jedes Kapitel neu nummeriert. Strukturformeln sind aus Gründen der Eindeutigkeit für die gesamte Arbeit durchgehend nummeriert.

Für jedes Kapitel ist ein separates Literaturverzeichnis mit Literaturangaben angegeben, wobei Literaturstellen, die mehrfach zitiert werden, jeweils für jedes Kapitel neu berücksichtigt werden.

Experimentelle Daten, allgemeine Methoden sowie die verwendeten Messgeräte sind im Anhang bei der dem Kapitel zugehörigen Publikation aufgeführt.

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Zusammenfassung

Die aerobe Cobalt-katalysierte Oxidation von Alkenolen ist eine Reaktionssequenz, die zum stereoselektiven Aufbau funktionalisierter Tetrahydrofurane genutzt werden kann. Im ersten, katalytisch verlaufenden Teil der Reaktion werden mit hoher Diastereoselektivität nucleophile Tetrahydrofurylmethyl-Radikale gebildet, welche im zweiten Teil mit einer Reihe von Reagenzien abgefangen werden können. Neben der H-Atom- oder Br-Atom-Übertragung beschäftigt sich die vorliegende Arbeit mit der alkylierenden Terminierung durch Addition an Alkene und Alkine sowie mit der Übertragung von Alkylsulfanyl-Gruppen zur Synthese Thioether-funktionalisierter Tetrahydrofurane. Durch die Entschlüsselung des zugrunde liegenden Reaktionsprinzips konnte die Methode für die stereoselektive Synthese von Tetrahydropyranen und nicht-cyclischen Ethern nutzbar gemacht werden.

Akzeptor-substituierte Olefine sind geeignete Reaktionspartner für die im Verlauf der Cobalt-katalysierten aeroben Oxidation gebildeten nucleophilen Tetrahydrofurylmethyl-Radikale. Durch radikalische Addition und anschließenden H-Atom-Transfer können Seitenketten-funktionalisierte Tetrahydrofurane in Ausbeuten bis 67% erhalten werden, wobei die durch direkte H-Atom-Übertragung gebildteten reduktiv terminierten Tetrahydrofurane als Nebenprodukte gebildet werden. Die bei alkylierender Terminierung auftretenden Diastereoselektivitäten stimmen mit denen überein, die für reduktive oder bromierende Terminierung beobachtet worden sind. Anhand der Produktverhältnisse konnten relative Geschwindigkeitsfaktoren bestimmt werden, die den Radikal-Charakter der Zwischenstufe bestätigen. Im Gegensatz zu klassischen Radikalreaktionen verläuft auch die Addition an Alkine mit ausreichend hoher Geschwindigkeit um Tetrahydrofurane mit ungesättigter Seitenkette in synthetisch sinnvollen Ausbeuten darzustellen. Diese Eigenschaft konnte zum Aufbau eines diastereomerenreinen Bistetrahydrofurans in einer Kaskade von zwei Cyclisierungen genutzt werden.

Durch radikalische Substitution an Disulfiden können in Cobalt-katalysierten Oxidationen Alkylsufanyl-funktionalisierte Tetrahydrofurane aufgebaut werden, ohne dass die so gebildeten Thioether selbst zu Sulfoxiden und Sulfonen oxidiert werden. Die Einführung der Methylsulfanyl-Gruppe konkurriert dabei mit der direkten H-Atom-Übertragung und eröffnete so die Möglichkeit aus einer Reihe konkurrenzkinetischer Experimente die Geschwindigkeitskonstante für die Übertragung der Methylsulfanyl-Gruppe zu ermitteln. Die Methode ermöglichte die Vereinfachung und Verbesserung der Synthese eines Wirkstoff-Derivats sowie die Darstellung eines 2,6-*trans*-konfigurierten Tetrahydropyrans.

Darauf aufbauend wurde eine vollständige Methode zum Aufbau von Tetrahydropyranen ausgehend von Hexenolen entwickelt, die die hohe Diastereoselektivität, die bei der Cyclisierung von Pentenolen beaobachtet wird, beibehält. Das Prinzip der radikalischen Funktionalisierung, z.B. durch bromierende oder alkylierende Terminierung ist auch in Tetrahydropyransynthesen anwendbar. Aus den beobachteten Selektivitäten konnte ein stereochemisches Modell für die Cyclisierung abgeleitet werden: Die durch sterische Faktoren des Liganden erzwungene pseudoaxiale Orientierung des Substituenten in Position 1 führen zu 2,6-*trans*- und 2,5-*trans*-selektiv verlaufenden Cyclisierungen. 1,2-*like*- und 1,3-*like*-konfigurierte Alkenole begünstigen den Ringschluss und steigern das *cis*:*trans*-Verhältnis auf $<$1:99.

Mit der Synthese von nicht-cyclischen Ethern ausgehend von Alkoholen und Alkenen konnte gezeigt werden, dass der Mechanismus der aeroben Cobalt-katalysierten Oxidation über die Synthese von Tetrahydrofuranen und Tetrahydropyranen hinaus anwendbar ist und für die Erforschung weiterer Transformationen unter veränderten Reaktionsbedingungen bereit steht.

1 Einleitung

Cyclische Ether sind ein in der Natur weit verbreitetes Strukturmotiv[1], welches sich biosynthetisch ausgehend von Terpenen,[2, 3] Acetogeninen[4] und Polyketiden[5] aufbauen lässt. Tetrahydrofurane und Tetrahydropyrane sind die häufigsten Vertreter dieser Klasse, was auf die thermodynamische Stabilität[6, 7] von Fünfring- und Sechsringsystemen sowie die natürliche Verfügbarkeit der entsprechenden Vorstufen zurückzuführen ist. Das hohe Vorkommen pharmakologisch interessanter Eigenschaften macht diese Verbindungsklasse zum Gegenstand intensiver wissenschaftlicher Untersuchungen und hat dazu beigetragen, dass neuartige Wirkstoffe auf Grundlage des Tetrahydrofuran- und Tetrahydropyran-Strukturmotivs entworfen werden (Abb. 1.1).

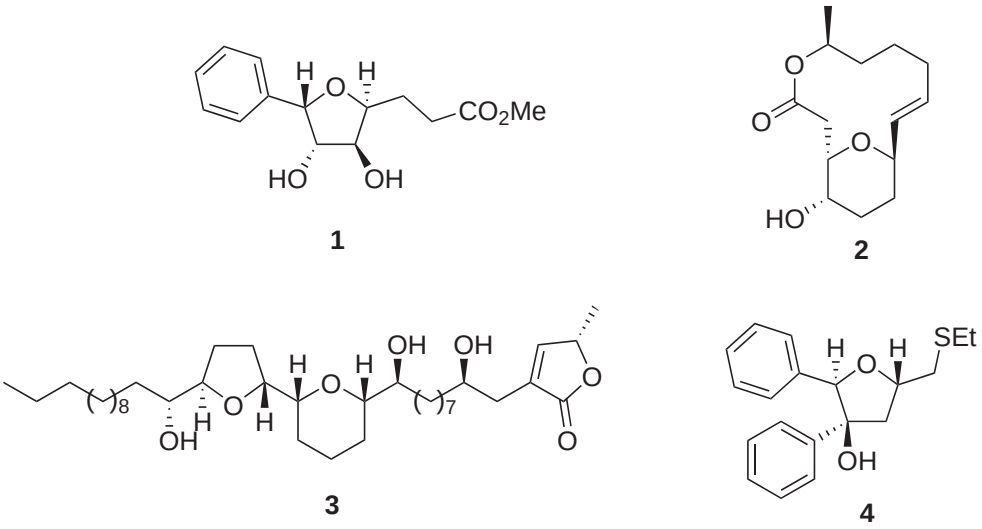
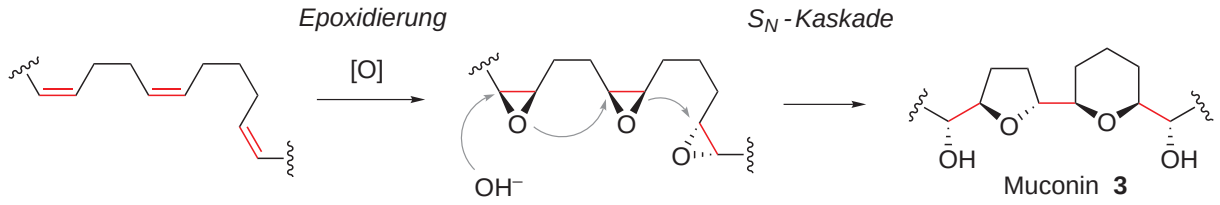


Abbildung 1.1: Natur- und Wirkstoffe auf Basis cyclischer Ether.

Beispiele für cytotoxisch wirkende Tetrahydrofurane und Tetrahydropyrane sind das in der Rinde von *Goniothalamus borneensis* enthaltene Goniothalesdiol **1**,[8] sowie das Aspergillid A **2**,[9] welches aus dem Meerespilz *Aspergillus ostianus* gewonnen werden konnte. Bei diesen beiden Naturstoffen handelt es sich um 2,5-*trans*- bzw. 2,6-*trans*-konfigurierte cyclische Ether, die eine Carboxylat-Funktionalisierung in der Seitenkette aufweisen. Unter den zahlreichen acetogeninen Polyether-Verbindungen aus Annonen-Gewächsen ist Muconin **3**[10] ein Vertreter mit benachbarten Tetrahydrofuran- und Tetrahydropyraneinheiten. Diese aus den Blättern von *Rollinia mucosa* gewonnene Verbindung zeigt eine starke Cytotoxizität gegenüber menschlichen Tumorzellen.[11] Die Wirkung solcher Polyether-Verbindungen aus Annonen-Gewächsen beruht unter anderem auf einer Inhibierung der NADH:Ubichinon-Oxidoreduktase (Komplex I der Atmungskette). Der entzündungshemmende Wirkstoff **4**,[12] der eine selektive Inhibierung der Cyclooxygenase II bewirkt ohne dabei die negativen

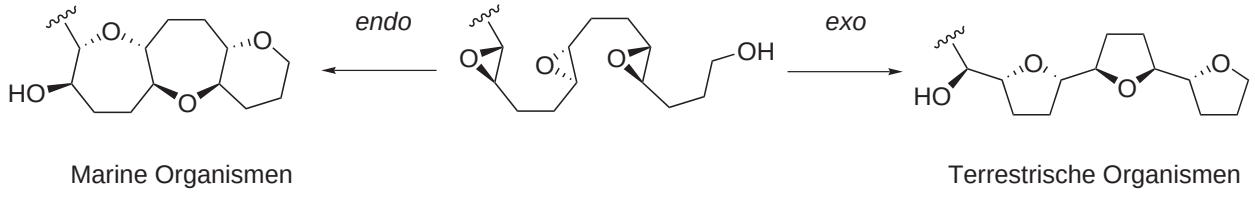
Nebenwirkungen vergleichbarer Vorgängerprodukte zu verursachen,[13] wurde ebenfalls ausgehend von einer Tetrahydrofuran-Grundstruktur entwickelt und zeichnet sich durch eine Thioether-Seitenkette aus.

Trotz der großen Diversität innerhalb der Gruppe der natürlich vorkommenden cyclischen Ether ist die Substitution an den beiden endocyclischen Positionen ein gemeinsames Merkmal fast aller Vertreter dieser Gruppe. Biosynthese-Modelle erklären diese Eigenschaft über die Bildungsweise cyclischer Ether: Ausgehend von Polyenen werden C,C-Doppelbindungen erst enzymatisch epoxidiert, worauf der Angriff eines O-Nucleophils in einer Kaskade von einem oder mehreren Ringschlüssen die Tetrahydrofuran- und Tetrahydropyran-Strukturen hoch stereoselektiv aufbaut (Schema 1.1).[14, 15, 16]



Schema 1.1: Modell der Biosynthese typischer Tetrahydrofuran- und Tetrahydropyranstrukturen am Beispiel von Muconin **3**.[10, 15]

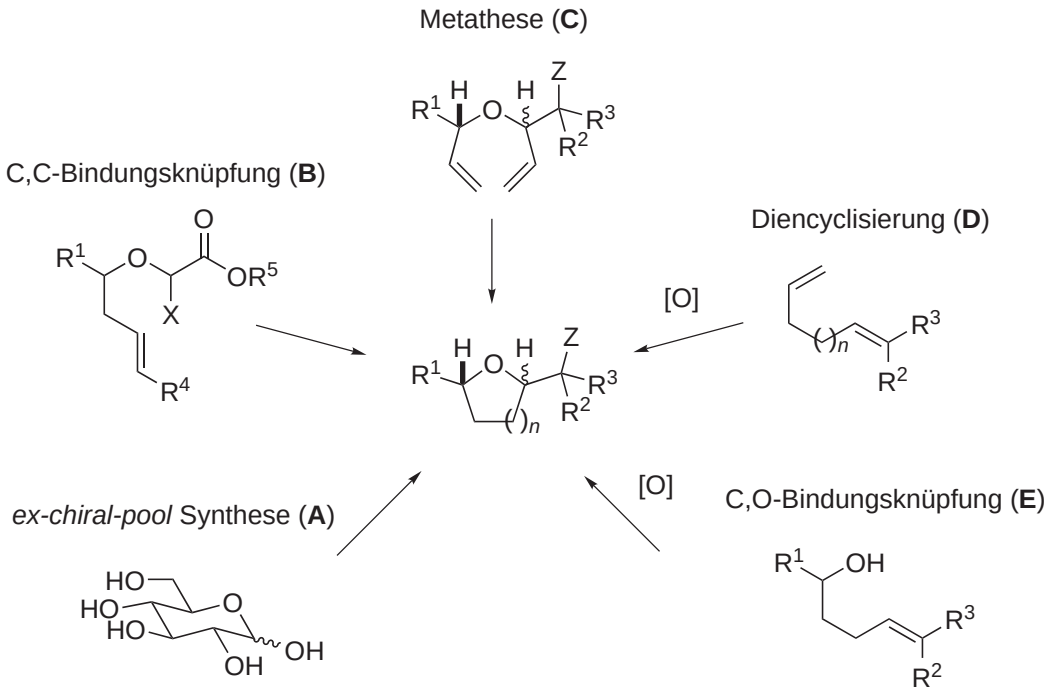
Der Ringschluss erfolgt bei Landlebewesen den Baldwin-Regeln[17] gemäß *exo*-selektiv, was zu kleineren Ringgrößen (Tetrahydrofuranen) und benachbarten Ringen führt, während in Meeresorganismen Polyepoxide durch *endo*-selektiv verlaufende Kaskaden in annelierte Polyetherringe (Tetrahydropyrane, Oxepane) überführt werden (Schema 1.2).



Schema 1.2: Die Cyclisierung eines Polyepoxids kann nach *exo*-selektiven (terrestrische Organismen) oder *endo*-selektiven Kaskaden (marine Organsimen) erfolgen.[18]

Da die natürlichen Resourcen, aus denen solche pharmakologisch aktive Verbindungen gewonnen werden können, begrenzt sind, ist es die Aufgabe der organischen Chemie, synthetische Zugänge zu verschieden substituierten cyclischen Ethern zu erschließen. Die pharmakologische Wirksamkeit der genannten Verbindungen ist neben anderen Faktoren oftmals stark abhängig von ihrer räumlichen Struktur, d.h. von der Konfiguration der Stereozentren

eines Moleküls. Um dieser ausgeprägten Struktur-Wirkungs-Beziehung gerecht zu werden, wurden Methoden entwickelt, die eine selektive Synthese β-funktionalisierter O-Heterocyclen ermöglichen (Schema 1.3).[19]

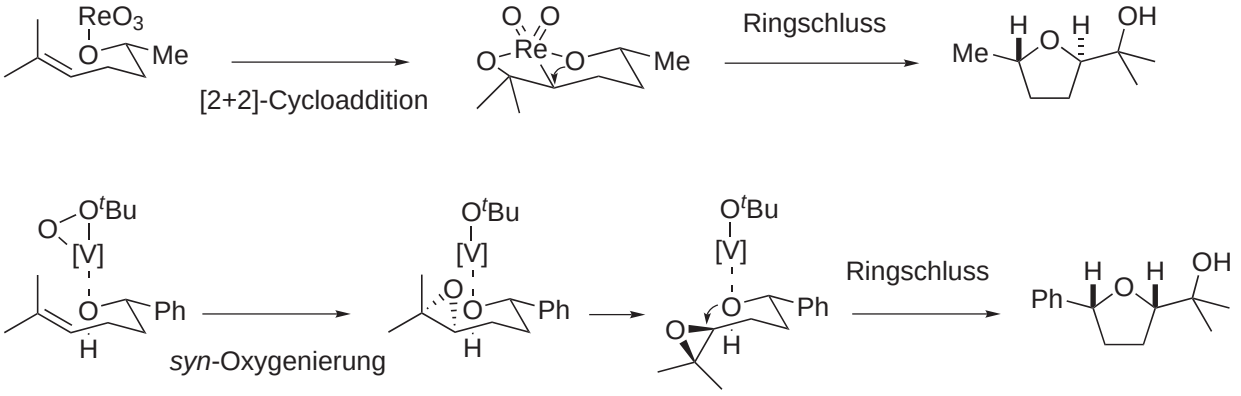


Schema 1.3: Synthetischer Zugang zu β-funktionalisierten Tetrahydrofuranen und Tetrahydropyranen; [O] = aktive Sauerstoff-Verbindung; R^{1-5} = Aryl, Alkyl; X, Z = funktionelle Gruppe; n = 1, 2.

In *ex-chiral-pool*-Synthesen (**A**) kann die in Kohlenhydraten enthaltene Stereoinformation genutzt werden.[20, 21] Die Modifikation solcher Primärmetabolite bietet einen einfachen Zugang zu enantiomerenreinen Produkten, allerdings ohne die Flexibilität eine bestimmte Konfiguration einstellen zu können. Zu den C,C-verknüpfenden Reaktionen zählen intramolekulare Michael-analoge Additionen[23] (**B**) sowie Ruthenium-katalysierte Ringschlussmetathesen[22] (**C**). Auch in diesen Fällen muss die Konfiguration an den beiden Positionen in Nachbarschaft zum Sauerstoffatom bereits vor dem Ringschluss festgelegt sein. Unter Aufbau neuer Stereozentren können 1,5-Diene durch $KMnO_4$ oder OsO_4 zu 2,5-*cis*-konfigurierten Tetrahydrofuranen oxidiert werden (**D**).[24, 25] Analog hierzu erfolgt der Aufbau von 2,6-*trans*-konfigurierten Tetrahydropyranen aus 1,6-Dienen.[26] In beiden Fällen wird die Stereoselektivität der Reaktion durch zwei *syn*-selektive [3+2]-Cycloadditionen des hochvalenten Metalloxids an die olefinischen Doppelbindungen bestimmt.[27] Eine Schwäche der Methode ist jedoch die Beschränkung auf symmetrische, doppelt hydroxylierte Heterocyclen. Aus einfachen, offenkettigen Vorstufen lassen sich Tetrahydrofurane unter Generierung eines neuen Stereozentrums in C,O-verknüpfenden Reaktionen aufbauen (**E**). Vorteilhaft ist

hierbei die Möglichkeit, durch die Wahl der Methode die Konfiguration des aufzubauenden Rings steuern zu können.

In Übergangsmetall-vermittelten Oxidationen können 1-Pentenole mit hoher Stereokontrolle in β-funktionalisierte Tetrahydrofurane überführt werden. Als terminale Oxidantien kommen hierbei formale O-Atom-Donoren wie Peroxide (H_2O_2, *tert*-Butylhydroperoxid [TBHP]) oder molekularer Sauerstoff in Frage. Späte Übergangsmetalle, wie etwa Rhenium(V) werden durch Peroxide selbst zu hochvalenten Metall-Oxo-Komplexen oxidiert und sind so in der Lage olefinische Doppelbindungen zu oxidieren (Metall-Oxo-Route).[29] Eine Umlagerung aus einem intermediär gebildeten Metallaoxetan führt selektiv zu 2,5-*trans*-konfigurierten Tetrahydrofuranen (Schema 1.4). Diese Methode erfordert allerding den Einsatz stöchiometrischer Mengen an Rhenium-Reagenz. Atomökonomischer sind katalytisch ablaufende Prozesse wie die Oxidation mit Vanadium(V)-Komplexen. Frühe Übergangsmetalle wie Vanadium(V) sind in der Lage, Peroxide durch Bildung eines Peroxy-Komplexes zu aktivieren, ohne dass sich die Oxidationsstufe des Metalls dabei ändert (Metall-Peroxy-Route).[30] In einer *syn*-Oxygenierung kann ein Sauerstoffatom auf die C,C-Doppelbindung übertragen werden, worauf durch intramolekularen Angriff des O-Nucleophils der Ringschluss zu 2,5-*cis*-konfigurierten Tetrahydrofuranen erfolgt (Schema1.4).

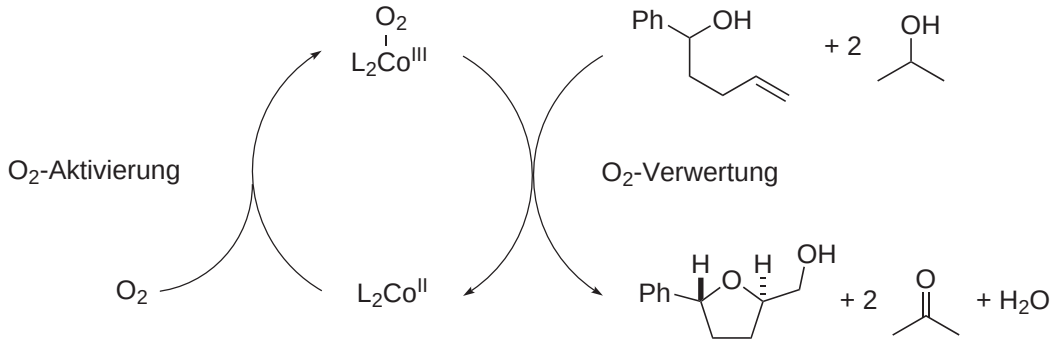


Schema 1.4: Stereochemische Modelle der Rhenium(VII)-vermittelten Oxidation[29] (oben) und der Vanadium(V)-katalysierten Oxidation[30] (unten).

Allerdings verlaufen Vanadium(V)-katalysierte Oxidationen nur mit unzureichender Regiokontrolle, da neben Tetrahydrofuranen, die aus einer 5-*exo*-Cyclisierung hervorgehen, immer auch Tetrahydropyrane, die aus 6-*endo*-Cyclisierungen stammen, gebildet werden.[30]

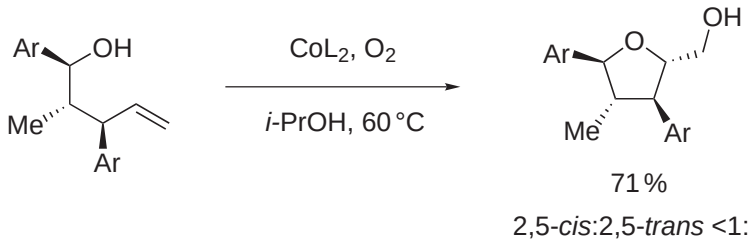
Neben Rhenium und Vanadium haben in den vergangenen Jahren besonders Cobalt(II)-katalysierte oxidative Alkenol-Cyclisierungen großes Interesse erfahren. Dieser Reaktionstyp erlaubt die stereoselektive Synthese *trans*-konfigurierter Tetrahydrofurane unter Verwendung katalytischer Mengen geeigneter Cobalt-Komplexe und ist seit

seiner erstmaligen Erwähnung im Jahr 1990 durch Mukaiyama[31] mehrfach erfolgreich in Naturstoffsynthesen[32, 33, 34] zur Anwendung gekommen. Sie ist die nachhaltigste unter den genannten Methoden, da molekularer Sauerstoff (O_2) in diesem Falle das terminale Oxidans ist.[35] Ermöglicht wird dies durch die Fähigkeit der verwendeten Cobalt-Komplexe, den günstigen und einfach zugänglichen, aber inhärent reaktionsträgen Sauerstoff zu aktivieren und für die Verwendung als Oxidationsmitel nutzbar zu machen (Schema 1.5).



Schema 1.5: Aktivierung und Verwertung von molekularem Sauerstoff durch Cobalt(II); HL = z.B. Trifluoracetylcampher.[35]

Mit ihrer hohen Chemo-, Regio- und Diastereoselektivität ist die aerobe Cobalt(II)-katalysierte Oxidation für die stereoselektive Synthese ideal geeignet und kam als Schlüsselschritt der Synthese eines Magnosalicin-Derivates zum Einsatz. Der Ringschluss verläuft dabei ausschließlich 5-*exo*- und 2,5-*trans*-selektiv (Schema 1.6).[35]



Schema 1.6: Synthese eines Magnosalicin-Derivates über aerobe Cobalt(II)-katalysierte Oxidation; HL = Trifluoracetylcampher, Ar = 2,4,5-Trimethoxyphenyl.[35]

Der Transformation von offenkettigem Alkenol zu mehrfach substituiertem Tetrahydrofuran liegt eine Reaktionssequenz zugrunde, die sich aufteilt in eine katalytische aerobe Oxidation durch Cobalt(II) und eine radikalische Funktionalisierung unter neutralen, reduktiven Bedingungen. Die Untersuchung dieser Kaskade und ihre Anwendung zum Aufbau cyclischer Ether als wertvolle Synthesebausteine in der Naturstoffsynthese soll Thema und Inhalt der vorliegenden Arbeit sein.

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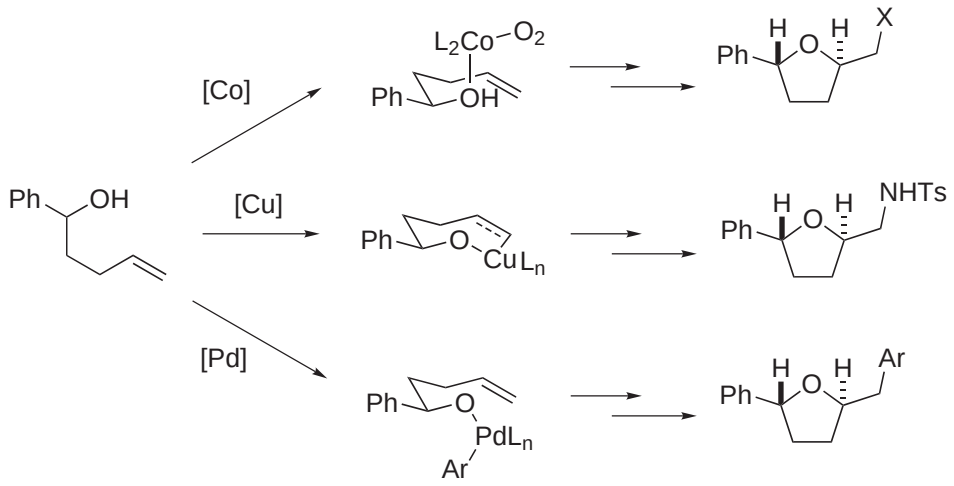
2 Hintergrund und Aufgabenstellung

2.1 Darstellung cyclischer Ether in Kaskaden-Reaktionen

Unter Kaskadenreaktionen[1], zum Teil auch als Tandem-[2] oder Dominoreaktionen[3] bekannt, versteht man eine Abfolge von mindestens zwei Reaktionsschritten, die ausgehend von einem Satz an Startmaterialien definiert nacheinander ablaufen, ohne dass weitere Reagenzien zugegeben oder Zwischenstufen isoliert werden müssen. Der Einsatz solcher sequentieller Reaktionen ist für die stereoselektive Heterocyclensynthese besonders interessant, da so in einer Stufe sowohl der Ringschluss unter Aufbau eines neuen Stereozentrums wie auch die Einführung einer neuen funktionellen Gruppe erfolgen kann. Unter den Übergangsmetall-vermittelten Methoden, die auf diese Weise Tetrahydrofurane ausgehend von Alkenolen aufbauen, zählen neben der Cobalt-Methode Kupfer- und Palladium-vermittelte Reaktionen (Schema 2.1):[4, 5, 6]



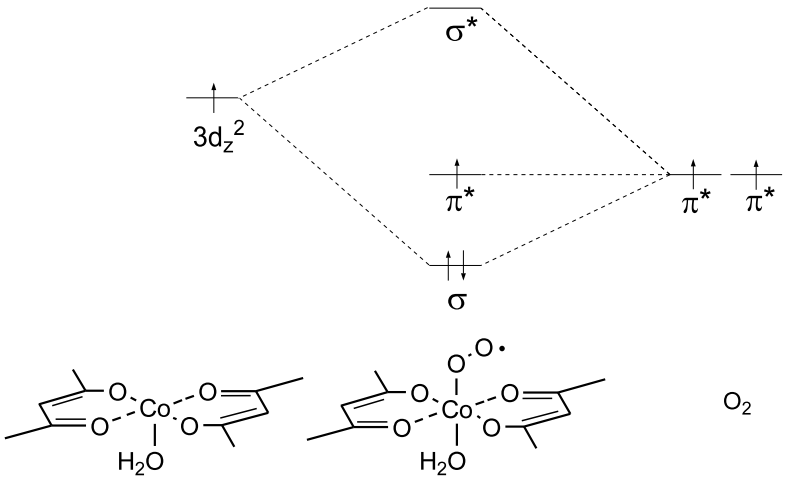
Schema 2.1: Kaskadenreaktionen zum Aufbau funktionalisierter Tetrahydrofurane; Ar = Aryl,[5] Alkinyl;[6] [Co], [Cu], [Pd] = Übergangsmetallkomplexe; X = OH, Br.

Alle drei Methoden erlauben es, Tetrahydrofurane in hoher *trans*-Stereoselektivität aufzubauen. Die Kupfer-Methode bietet in Anwesenheit von Aminen Zugang zu synthetisch interessanten N-funktionalisierten Tetrahydrofuranen, verlangt aber den stöchiometrischen Einsatz von Kupferkomplexen. Die Funktionalisierung durch Einführung von Aromaten nach der Palladium-Methode ist vom Standpunkt der Natur- und Wirkstoffsynthese weniger nützlich als eine durch die Cobalt-Methode erreichbare Funktionalisierung durch -OH oder -Br, die Ansatzpunkte für nachfolgende Reaktionsschritte bietet. Weiterhin erfolgen sowohl die Kupfer- als auch die Palladium-vermittelte Reaktion unter Zusatz starker Basen, während die Cobalt-katalysierte Oxidation unter milden, pH-neutralen Bedingungen abläuft.

2.2 Die aerobe Cobalt-katalysierte Oxidation im Focus: Stand der Forschung

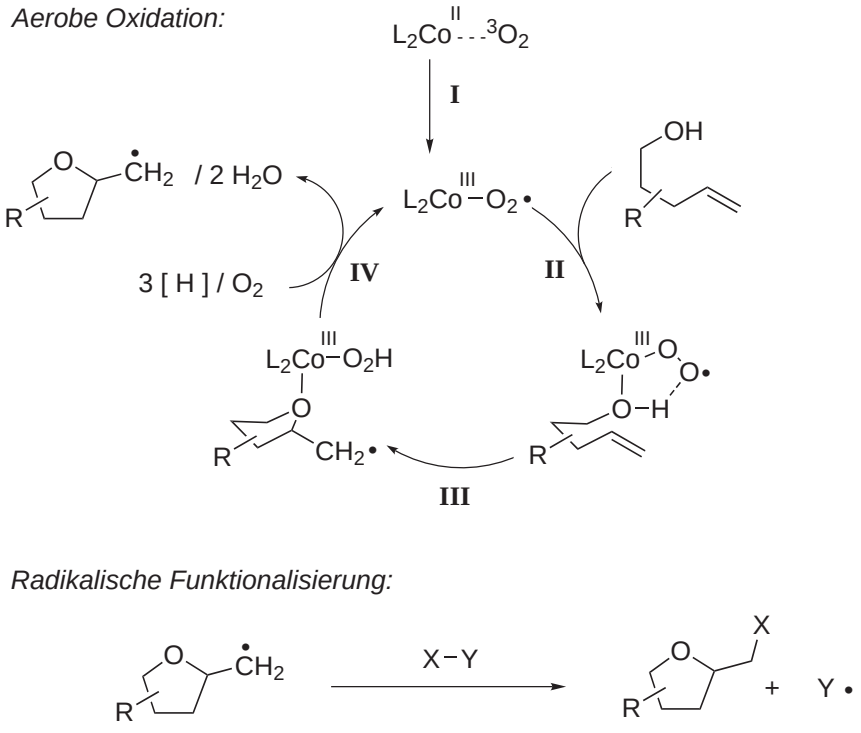
Die Cobalt(II)-katalysierte Oxidation von Alkenolen, wie sie von Mukaiyama beschrieben worden war,[7] verlief unter Zusatz von 1.5 Äquivalenten TBHP und Molsieb in einer Atmosphäre von reinem Sauerstoff. In unserem Arbeitskreis wurde die Methode dahingehend verbessert, dass auf den Zusatz von Additiven verzichtet und die Reaktion in einer Atmosphäre mit 20 % O_2, d.h. an Luft durchgeführt werden kann.[8] Dieser Fortschritt wurde durch eine neue Generation von Cobalt-Komplexen ermöglicht, die zu einer effizienteren Sauerstoff-Aktivierung in der Lage sind.

Der elektronische Grundzustand von molekularem Sauerstoff ist ein Triplett-Zustand ($^3\Sigma_g^-$). Reaktionen mit organischen Substraten, die im Singulett-Zustand vorliegen, sind daher nicht ohne weiteres möglich.[9] Allerdings kann Disauerstoff durch Bindung an geeignete Übergangsmetalle, zu denen auch Cobalt gehört, aktiviert werden,[10] um in Oxidationen eingesetzt zu werden.[11, 12] Diese Aktivierung, die in einem Kooperationsprojekt mit der Universität Karlsruhe näher untersucht wurde, ist der erste Teilschritt der Cobalt-katalysierten Oxidation: Durch die Annährung des O_2-Moleküls an das Cobalt-Zentralatom eines low-spin[13] Cobalt(II)-Diketonat-Komplexes[14, 15] kann das einfach besetzte $3d_{z^2}$-Orbital des Cobalts mit einem der beiden π^*-Orbitale des molekularen Sauerstoffs wechselwirken und schließlich eine neue σ-Bindung ausbilden.[16, 17, 18] Das so gebildete Cobalt-Sauerstoff-Addukt liegt im Dublett-Zustand vor, mit einem ungepaarten Elektron, welches am nicht gebundenen Ende des Disauerstoffs lokalisiert ist (Schema 2.2).[18]



Schema 2.2: Bildung der Cobalt-Sauerstoff-Bindung an einem Cobalt-Diketonat-Komplex durch Annäherung des Sauerstoff-Moleküls an das Cobalt-Zentralatom.

Die Bindung von molekularem Sauerstoff unter Ausbildung eines Cobalt-Superoxo-Komplexes ist eine reversible Reaktion[19] und zugleich der erste Schritt (**I**) im ersten Teil der Reaktionssequenz, der *aeroben Oxidation* (Schema 2.3):

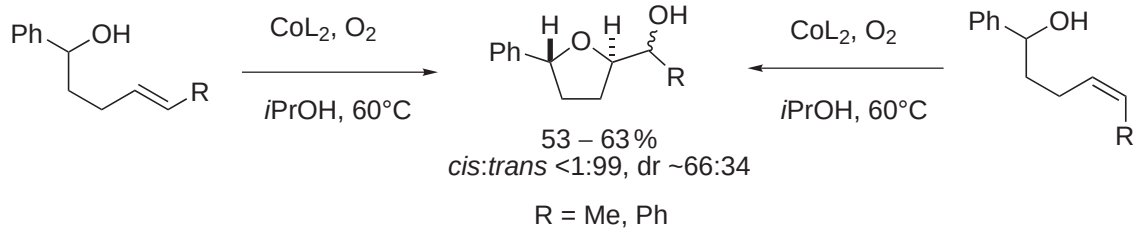


Schema 2.3: Postulierter Katalysecyclus für die Oxidation von Pentenolen und anschließende radikalische Funktionalisierung; HL = z.B. 3',5'-Bis(trifluormethyl)benzoylaceton; X-Y = z.B. 1,4-Cyclohexadien (H-C_6H_7).

Im nächsten Schritt (**II**) wird ein Alkenol an das Cobalt-Zentralatom koordiniert. Dabei ist es für den weiteren Verlauf der Reaktion notwendig und aus thermodynamischer Sicht aufgrund der Möglichkeit der Wasserstoffbrückenbindung zwischen der OH-Gruppe des Alkenols und dem *end-on* gebundenen Disauerstoff auch günstig, wenn Alkenol und Disauerstoff sich in räumlicher Nähe zueinander befinden, d.h. im Komplex *cis* zueinander angeordnet sind.[18] Schließlich kann in Schritt **III** eine H-Atom-Übertragung auf den Disauerstoff sowie ein Elektronentransfer aus der C,C-Doppelbindung stattfinden. Durch intramolekulare C,O-Bindungsknüpfung wird das Tetrahydrofurylalkyl-Radikal gebildet und freigesetzt. Der verbleibende Cobalt-Hydroperoxido-Komplex wird in Schritt **IV** durch ein Reduktans zu H_2O und dem freien Cobalt(II)-Komplex abgebaut, welcher durch Aufnahme von molekularem Sauerstoff wieder in den Katalysecyclus eintritt.

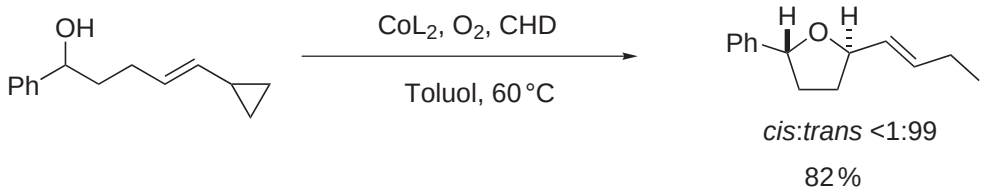
Dass es sich bei dem aus dem Katalysecyclus hervorgehenden Intermediat um eine radikalische Spezies handeln könnte, zeigte sich in einer Reihe diagnostischer Versuche: Eine

stereochemische Studie[20] zeigte, dass terminal (*E*)- und (*Z*)-substituierte Pentenole unter Verlust der stereochemischen Information oxidiert werden. Aus diesem Ergebnis konnte das Auftreten reaktiver konfigurativ labiler Intermediate abgeleitet werden (Schema 2.4).



Schema 2.4: Die Oxidation (*E*)- und (*Z*)-konfigurierter Alkenole führt zu identischen Produkten; HL = 3',5'-Bis(trifluormethyl)benzoylaceton.

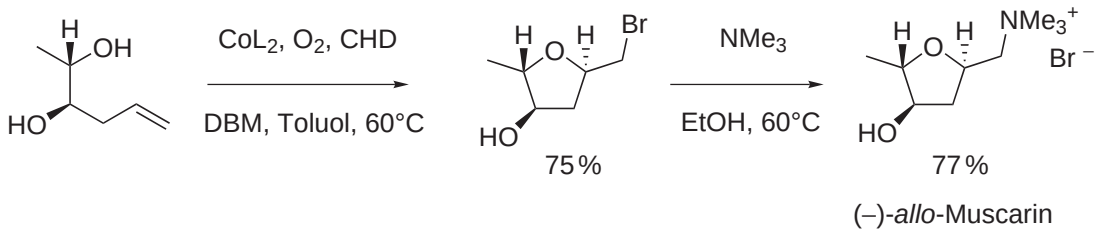
Die Übertragung der Hydroxylgruppe im zweiten Teil der Reaktionssequenz, der *radikalischen Funktionalisierung*, erfolgt nach dem bisher beschriebenen Mechanismus durch Angriff des Tetrahydrofurylmethylradikals am Hydroperoxocobalt-Komplex in einer radikalischen Substitution. Dieser Weg konnte durch Austausch des Reduktionsmittels von Isopropanol zu 1,4-Cyclohexadien (CHD) praktisch vollständig unterdrückt werden. In Anwesenheit von CHD erfolgt ein Abfang des Intermediats durch H-Atom-Übertragung unter Bildung reduktiv terminierter Methyltetrahydrofurane. Einen weiteren Hinweis darauf, dass es sich bei den Intermediaten um radikalische Zwischenstufen handeln könnte, lieferte die Oxidation eines terminal Cyclopropyl-substituierten Alkenols: Die Öffnung der Cyclopropyleinheit im Verlauf der Reaktion deutet auf das intermediäre Auftreten eines Tetrahydrofurylmethyl-Radikals hin (Schema 2.5).[21, 22]



Schema 2.5: Beobachtete Umlagerung bei der Oxidation eines Cyclopropyl-substituierten Alkenols; HL = 3',5'-Bis(trifluormethyl)benzoylaceton.[21]

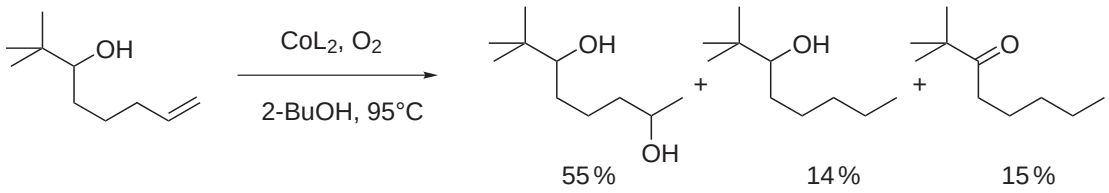
Werden der Reaktionsmischung Brom-Atom-Donoren wie Bromtrichlormethan oder Diethyldibrommalonat (DBM) zugesetzt, kann die Reaktion durch Übertragung eines Bromatoms terminiert werden. Diese Art der Reaktionsführung ermöglicht die stereoselektive Synthese von Brommethyl-Tetrahydrofuranen, die dazu geeignet sind, in nachfolgenden Reaktio-

nen weiter modifiziert zu werden. Eine solche Cobalt-katalysierte Oxidation mit bromierender Terminierung kam bei der Synthese von (–)-*allo*-Muscarin zum Einsatz (Schema 2.6).[21]



Schema 2.6: Synthese von (–)-*allo*-Muscarin über aerobe Cobalt(II)-katalysierte Oxidation; HL = 3',5'-Bis(trifluormethyl)benzoylaceton.[21]

Eine der Grenzen der Methode war zu Beginn der vorliegenden Arbeit die Anwendbarkeit auf Alkenole anderer Kettenlänge: Eine oxidative Cyclisierung von 1-Hexenolen ganz analog der Reaktion der entsprechenden 1-Pentenole war offensichtlich nicht möglich. Statt der oben beschriebenen Cyclisierung traten verschiedene Nebenreaktionen ein, unter denen die Hydratisierung der C,C-Doppelbindung den größten Anteil hatte (Schema 2.7).[23, 24]



Schema 2.7: Hydratisierung, Hydrierung und Autoxidation treten bei der Oxidation von 2,2-Dimethyloct-7-en-3-ol auf; HL = 3',5'-Bis(trifluormethyl)benzoylaceton.[23, 24]

Vor diesem Hintergrund und aufbauend auf den beschriebenen Vorarbeiten ergab sich die folgende Aufgabenstellung für die vorliegende Arbeit:

- Konkurrenzkinetische Studien zur Bestätigung des Radikal-Charakters der Zwischenstufe in Kaskadenreaktionen aus Alkenol-Oxidation und Addition an Alkene und Alkine.
- Entwicklung einer Methode zur stereoselektiven Synthese Thioether-funktionalisierter Tetrahydrofurane unter aerob oxidativen Bedingungen.
- Entschlüsselung des allgemeinen Reaktionsprinzips, das es ermöglicht, die Methode auf die Synthese von Tetrahydropyranen sowie nicht-cyclischer Ether zu erweitern.

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3 Alkylierende Terminierung durch radikalische Addition

3.1 Zusammenfassung

Durch Zusatz von Akzeptor-substituierten Olefinen in Cobalt-katalysierten aeroben Oxidationen können Seitenketten-funktionalisierte Tetrahydrofurane in synthetisch sinnvollen Ausbeuten (34 – 67%) erhalten werden. Die dabei auftretenden Diastereoselektivitäten stimmen mit denen überein, die für reduktive oder bromierende Terminierung beobachtet worden sind. Der Radikal-Charakter der Zwischenstufen wurde anhand der aus den Produktverhältnissen ermittelten relativen Geschwindigkeitsfaktoren bestätigt. Eine Methode zur Addition an Alkine konnte erfolgreich entwickelt und zum Aufbau eines diastereomerenreinen Bistetrahydrofurans genutzt werden.

3.2 Hintergrund, Zielsetzung und Strategie

Bis auf wenige Ausnahmen[1, 2, 3] ist bis heute die Erzeugung von Radikalen und darauf aufbauende Reaktionen an stöchiometrische Mengen an Radikalvorläufern und die Verwendung von Bu_3SnH gebunden. Mit der aeroben Cobalt-katalysierten Oxidation von Alkenolen war jedoch nicht nur eine Vorschrift zur Synthese von Tetrahydrofuranen, sondern effektiv auch eine Methode zur katalytischen Radikalerzeugung entwickelt worden. Eine nähere Untersuchung bezüglich des Charakters des radikalischen Intermediates sollte anhand der radikalischen Addition an Olefine die Frage klären, ob und wie die bekannten Prinzipien der Radikalchemie auf eine Cobalt-katalysierte Reaktion übertragen werden können. Die radikalische Addition an Olefine ist eine Reaktion, die in Konkurrenz zur direkten H-Atom-Übertragung steht und daher für konkurrenzkinetische Untersuchungen geeignet ist.[4, 5] Vor diesem Hintergrund leitete sich ein Projekt mit den folgenden Zielsetzungen ab:

- Entwicklung einer Methode, die es erlaubt, die radikalische Addition an Olefine für die Cobalt-katalysierte Oxidation von Alkenolen nutzbar zu machen. Aus den so erhaltenen Produktmischungen sollten Geschwindigkeitsfaktoren ermittelt werden, die den freien Radikal-Charakter der Zwischenstufe bestätigen und den postulierten Reaktionsmechanismus untermauern sollten.

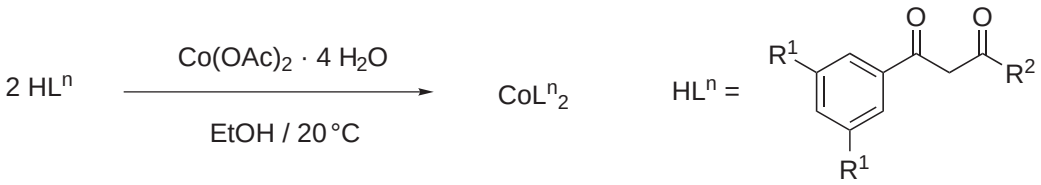
- Untersuchung der Möglichkeit einer Addition an Alkine. Dieser Reaktionstyp, der mit der klassischen Radikalchemie nicht leicht zu verwirklichen ist, bietet synthetisch interessante Perspektiven zur weiteren Funktionalisierung der so gebildeten Tetrahydrofurane.

3.3 Ergebnisse und Diskussion

3.3.1 Cobalt-Komplexe – im Zentrum des Geschehens

In einer vorangegangen Studie[7] hatte sich gezeigt, dass der Wechsel von Campher-abgeleiteten Liganden hin zu Auxiliaren mit Benzoylaceton-Grundstruktur mit einer verbesserten Reaktivität und Stabilität des Komplexes im Reaktionsverlauf einherging. Der ausgehend von 3',5'-Bis(trifluormethyl)benzoylaceton gebildete Cobalt-Komplex **5** sowie der strukturell ähnliche, aus Benzoyltrifluoraceton hergestellte Komplex **6** wurden in einem Screening verschiedener Cobalt-Diketonat-Komplexe als katalytisch aktivste Verbindungen identifiziert (Tabelle 3.1).

Tabelle 3.1. Übersicht über die verwendeten Komplexe und Liganden



Eintrag	HL^n	$CoL^n{}_2$ / %	R^1	R^2	$\delta\,^{19}F$ / ppm	$\tilde{\nu}_{C=O}$ / cm^{-1}
1	HL^1	**5** / 94	CF_3	CH_3	−55.4	1624
2	HL^2	**6** / 99	H	CF_3	+6.1	1609

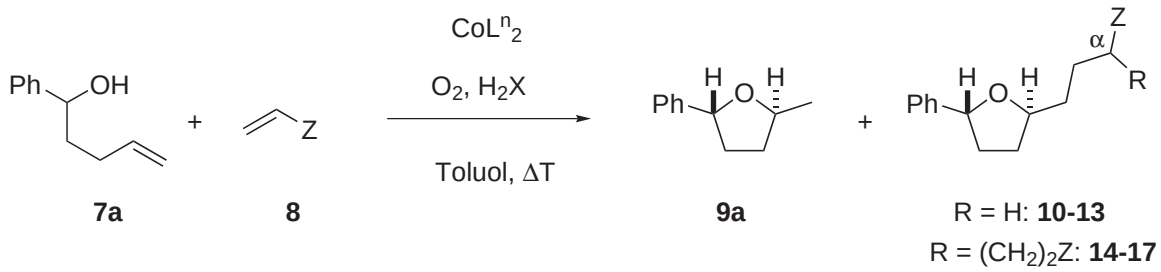
Die Darstellung dieser Komplexe erfolgt durch Zugabe einer ethanolischen Lösung des Liganden zu einer wässrigen Lösung von Cobaltacetat, wobei z.B. Komplex **6** als gelber Feststoff in Form des Dihydrates ausfällt und als solches direkt in der Katalyse eingesetzt werden kann. Die wasserfreie Form kann durch Trocknung im Vakuum erhalten werden und zeigt im Vergleich zur hydrathaltigen Form eine identische katalytische Aktivität. Katalytisch absolut inaktiv hingegen sind einfache Cobaltsalze wie Cobaltacetat sowohl als Hydrate wie auch in wasserfreier Form.

3.3.2 Grundlagen der Reaktivität

Aus einer Reaktion von 1-Phenylpent-4-en-1-ol (**7a**), einem einfach Akzeptor-substituierten Olefin **8** und 1,4-Cyclohexadien (CHD) können grundsätzlich drei verschiedene Produkte gewonnen werden: Neben dem aus einem einfachen H-Einfang hervorgehenden Reduktionsprodukt **9a** werden zwei weitere Verbindungen gebildet, die durch Addition des nucleophilen

Radikals an das Olefin gebildet werden. Die als Einfachadditionsprodukt bezeichneten Verbindungen **10–13** stammen aus einer einfachen Addition an das Olefin, während Verbindungen **14–16** zwei Additionsschritte vor dem finalen H-Atom-Transfer durchlaufen sind (Tabelle 3.2). Das Verhältnis dieser Produkte zueinander spiegelt die relativen Geschwindigkeitskonstanten der einzelnen Reaktionen wider (Addition vs. H-Abstraktion) und ist abhängig von den gewählten Bedingungen: Für eine Olefin-Konzentration von 1.7 mol·L^{-1}, die die Löslichkeit aller verwendeten Alkene gewährleistet, wurde der Bereich von 3–4 mol·L^{-1} als optimale CHD-Konzentration ermittelt. Anstelle von CHD lässt sich grundsätzlich immer auch das natürlich vorkommende und gesundheitlich weniger bedenkliche γ-Terpinen (γ-Ter) verwenden, das in einigen Fällen die Bildung des Einfachadditionsproduktes begünstigt (Tabelle 3.2, Eintrag 1 und 2). Reaktionstemperaturen von 60–75 °C führen zu höchsten Ausbeuten an Einfachadditionsprodukt. Höhere Temperaturen hingegen führen zu einer bevorzugten Bildung des Reduktionsprodukts **9a**, während bei Raumtemperatur praktisch keine Reaktion mehr stattfindet.

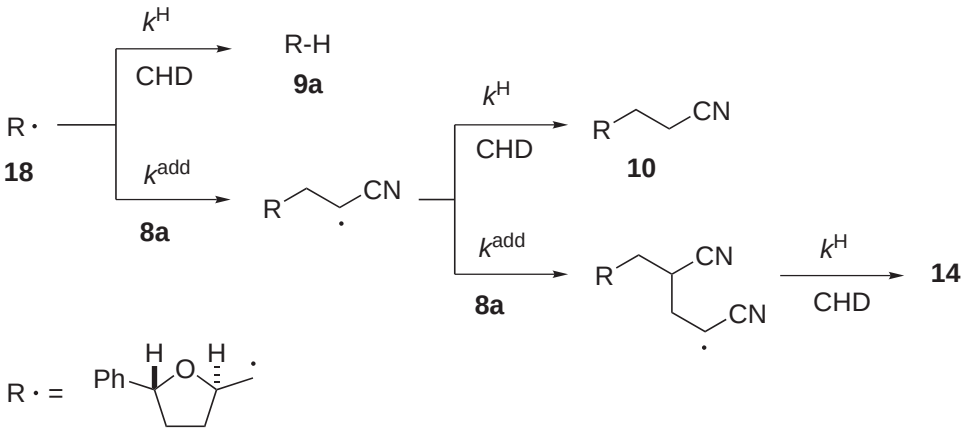
Tabelle 3.2. Alkenol-Oxidation und Addition an verschiedene Olefine



Eintrag	**8**	Z	CoL$^n{}_2$ [a]	H_2X	T / °C	**9a** / %	**10–13** / %	**14–17**[b] / %
1	**8a**	CN	**5**	CHD	60	29	**10**: 34	**14**: 11
2	**8a**	CN	**6**	γ-Ter	75	16	**10**: 44	**14**: 15
3	**8b**	CO_2CH_3	**5**	γ-Ter	75	30	**11**: 32	**15**: 13
4	**8c**	$COCH_3$	**6**	γ-Ter	75	27	**12**: 31	**16**: 13
5	**8d**	SO_2CH_3	**6**	CHD	60	20	**13**: 43	**17**: –[c]

a: 5mol% für **5**, 3mol% für **6**. *b*: 50/50-Mischung der Diastereomeren bezogen auf C-α. *c*: nicht nachweisbar (GC, ^{1}H-NMR)

3.3.3 Mechanistische Betrachtungen



Schema 3.1: Elementarschritte der radikalischen Addition zur Bestimmung der Geschwindigkeitsfaktoren.

Die Abstraktion eines H-Atoms durch das Tetrahydrofurylmethyl-Radikal **18** ist, ebenso wie die Addition an ein Olefin, eine kinetisch kontrollierte und daher irreversible Reaktion. Aus dem Verhältnis von Reduktionsprodukt **9a** zu der Summe der beiden durch Addition an Acrylnitril entstandenen Produkte **10** und **14** lässt sich somit ein experimenteller Geschwindigkeitsfaktor f^{exp} bestimmen. Ein solcher Geschwindigkeitsfaktor entspricht in seiner Aussage einer relativen Geschwindigkeitskonstante, wird aber im Gegensatz zu Geschwindigkeitskonstanten nicht aus einer Reihe konkurrenzkinetischer Experimente ermittelt, sondern stellt nur eine Annäherung aus einer Ein-Punkt-Korrelation dar. Ein berechnter Faktor f^{calc}, der aus literaturbekannten Geschwindigkeitskonstanten ermittelt werden kann, dient zur Überprüfung der Qualität dieser Näherung. Ergeben sich für f^{exp} und f^{calc} ähnliche Werte, so deutet dies auf Intermediate mit vergleichbarer Reaktivität hin. Für die gut untersuchten Ethyl- und Hexenyl-Radikale existieren bereits Geschwindigkeitskonstanten für die H-Abstraktion von CHD (k^H) sowie für die Addition an Acrylnitril und Methylacrylat (k^{add}). Ein aus den Geschwindigkeitskonstanten k^{add} und k^H berechneter Faktor f^{calc} sollte mit f^{exp} übereinstimmen, falls die Reaktivität des Radikals **18** der eines freien Radikals entspricht (Schema 3.1, Gleichung 3.1).

$$\frac{[\mathbf{10}] + [\mathbf{14}]}{[\mathbf{9a}]} = f = \frac{k^{add} \cdot [\mathbf{8a}]}{k^H \cdot [\mathrm{CHD}]} \tag{3.1}$$

Setzt man in Gleichung 3.1 die aus der Literatur entnehmbaren Werte für k^{add}[8, 9, 10] und k^H[11], sowie die Ausgangskonzentrationen für Olefin und CHD ein, so erhält man

Werte für f^{calc}, die mit den aus den Produktausbeuten ermittelten Werten f^{exp} im Rahmen der Toleranzgrenze übereinstimmen. Während die Übereinstimmung im Falle von Methylacrylat **8b** und Methylvinylketon **8c** tatsächlich sehr gut ist (Tabelle 3.3, Eintrag 2 und 3), gibt es im Falle von Acrylnitril **8a** eine leichte Abweichung (Tabelle 3.3, Eintrag 1).

Tabelle 3.3. Vergleich berechneter und experimenteller Geschwindigkeitsfaktoren.

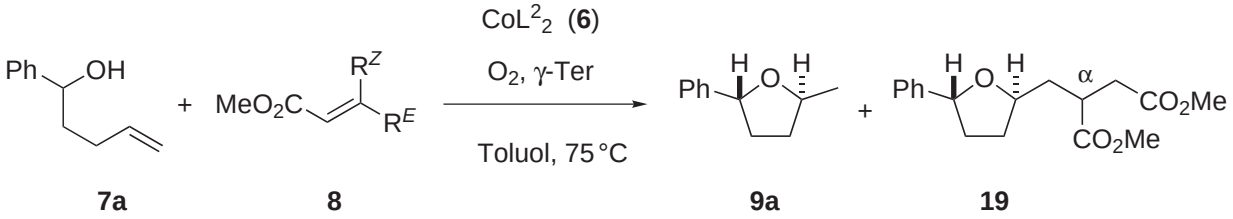
Eintrag	**8**	Z	$f^{calc\ a}$	$f^{exp\ b}$
1	**8a**	CN	4.7[c]	1.7
2	**8b**	CO_2CH_3	1.4[c]	1.4
3	**8c**	$COCH_3$	2.2[d]	2.2

a: [CHD] = 3.0 mol·L^{-1}, [**8**] = 1.5 mol·L^{-1}, $k^H = 5.8 \cdot 10^4$ M^{-1}s^{-1} ($\cdot C_2H_5$ + CHD; 27 °C). *b*: Werte für Reaktionen bei 60 °C. *c*: k^{add}(**8a**) $= 5.4 \cdot 10^5$ M^{-1}s^{-1} ($\cdot C_6H_{11}$ + **8a**), k^{add}(**8b**) $= 1.6 \cdot 10^5$ M^{-1}s^{-1} ($\cdot C_6H_{11}$ + **8b**), beide für 20 °C. *d*: abgeschätzt ausgehend von den relativen Geschwindigkeitskonstanten für die Addition des Hexenyl-Radikals an Methylacrylat und Methylvinylketon (k^{add}(**8c**)/k^{add}(**8b**) = 1.6; 69 °C)

Anhand dieser Übereinstimmung kann man erkennen, dass sich das im Reaktionsverlauf auftretende Intermediat **18** verhält wie ein freies Radikal und sich im Wesentlichen nicht von anderen primären C-Radikalen unterscheidet. Dieses Ergebnis unterstreicht den postulierten Mechanismus (Schema 2.3) und macht weitere radikalische Funktionalisierungen mit Hilfe der in der Literatur bereits beschriebenen Geschwindigkeitskonstanten planbar.

Generell erfolgt die Addition von C-Radikalen an (*E*)- und (*Z*)-konfigurierte Olefine unterschiedlich schnell.[5] Dieses Prinzip schlägt sich auch in den Produktverhältnissen in Cobalt(II)-katalysierten Oxidationen nieder, wie das Beispiel Dimethylfumarat/Dimethylmaleat zeigt (Tabelle 3.4): Im Falle von (*E*)-konfiguriertem Dimethylfumarat **8e** wird die Bildung des Additionsproduktes gegenüber dem direkten H-Abfang durch CHD bevorzugt, während (*Z*)-konfiguriertes Dimethylmaleat die Bildung des Reduktionsproduktes begünstigt. Das Verhältnis der Geschwindigkeitsfaktoren für beide Reaktionen (f(**8e**)/f(**8f**) = 5.1, 75 °C) spiegelt dabei die generelle Selektivität freier Radikale, wie z.B. des Cyclohexyl-Radikals gegenüber diesen Olefinen wider ($k^{rel} = k$(**8e**)/k(**8f**) = 10, 20 °C).[5] Der Vergleich zeigt aber auch, dass der Unterschied in der Reaktivität zwischen Fumarat und Maleat in der Cobalt-Methode weniger stark ausgeprägt ist, was auf zusätzliche Effekte in diesem Falle hindeutet.

Tabelle 3.4. (*E*)- und (*Z*)-Olefine führen zu verschiedenen Produktverhältnissen.

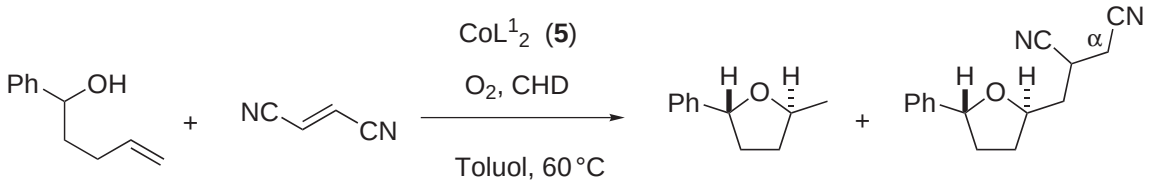


7a **8** **9a** **19**

Eintrag	**8**	R^Z	R^E	**9a** / %	**19**^{a} / %
1	**8e**	H	CO_2Me	28	60
2	**8f**	CO_2Me	H	54	23

a: 50/50-Mischung der Diastereomeren bezogen auf Cα.

Die Addition nucleophiler Alkyl-Radikale an (*E*)-konfigurierte, zweifach Akzeptor-substituierte Olefine wie Dimethylfumarat **8e** oder Fumarodinitril **8g** verläuft schneller als die Addition an die entsprechenden einfach Akzeptor-substituierten Olefine wie Methylacrylat **8b** oder Acrylnitril **8a**.[5] Die Bildung der Einfachadditionsprodukte ist daher gegenüber der Bildung des Reduktionsproduktes begünstigt. Mehrfachadditionen werden mit diesen Olefinen nicht beobachtet (Schema 3.2).



7a **8g** **9a** **20**

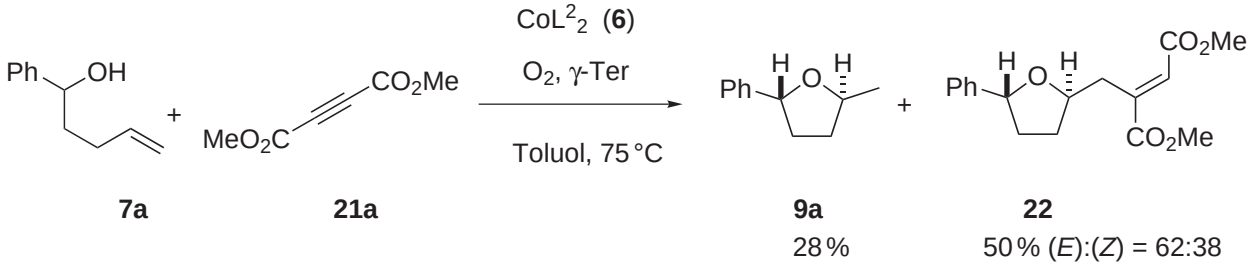
2 % 66 %

Schema 3.2: Der Einsatz zweifach Akzeptor-substituierte Olefine, wie z.B. Fumarodinitril, führt zu höherer Chemoselektivität.

Um die Anwendungsbreite der Reaktion zu verdeutlichen, wurde die Reihe der verwendeten Alkenole auf 2- und 3-Phenyl-substituierte 4-Pentenole erweitert. Die dabei auftretenden *cis*:*trans*-Selektivitäten sind charakteristisch für die Cobalt-Methode und stehen im Einklang mit denen, die für reduktive oder bromierende Terminierung beobachtet worden sind:[12] In Kaskadenreaktionen dieser Art bleibt also die Stereoselektivität des Ringschlusses unbeeinflusst von der Art der darauf folgenden Funktionalisierung.

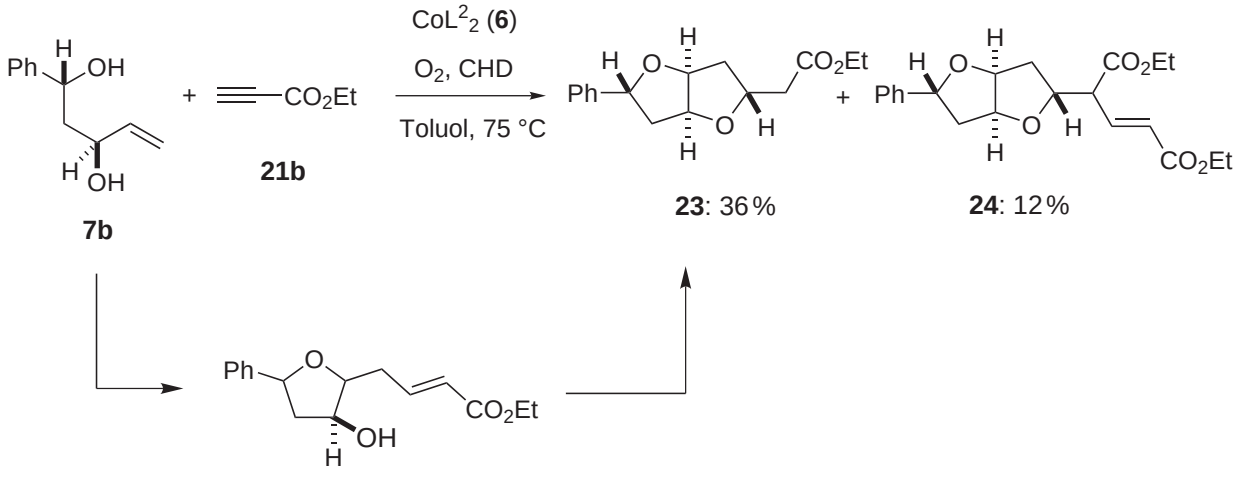
3.3.4 Ein Schritt weiter: Addition an Alkine

Zur Gruppe verwendbarer Substrate gehören auch einfach und zweifach Akzeptor-substituierte Alkine, da auch diese bei Standard-Reaktionsbedingungen unter C,C-Bindungsknüpfung an den Tetrahydrofurylmethyl-Rest addiert werden können (Schema 3.3). Bemerkenswert ist dabei die Leichtigkeit, mit der sich diese Reaktion vollzieht, besonders im Hinblick darauf, dass radikalische Additionen an Alkine in der klassischen Radikalchemie im Vergleich zur Addition an Alkene langsam verlaufen.[13] Ausgehend von den bekannten Geschwindigkeitskonstanten sollte also der Anteil an Additionsprodukten deutlich geringer sein. Vorstellbar ist eine Koordination des Alkins an das Cobalt-Zentrum, welche die Reaktion mit dem ebenfalls am Cobalt-Zentrum gebildeten Radikal gegenüber einem Abfang durch den H-Atom-Donor begünstigen könnte.



Schema 3.3: Die Verwendung von Dimethylacetylendicarboxylat erlaubt die Darstellung Fumarat-abgeleiteter Tetrahydrofurane.

Für Anwendungen in der Synthese ist die Addition an Alkine besonders interessant, da die daraus hervorgehenden Produkte eine C,C-Doppelbindung enthalten, die für weitere Transformationen zur Verfügung steht (Schema 3.4).



Schema 3.4: Synthese eines Bistetrahydrofurans ausgehend von Diol **7b**.

Eine Kaskade aus Alkenol-Oxidation, Addition an ein Alkin und einer zweiten Alkenol-Oxidation mit finalem H-Atom-Transfer konnte mit *rel*-(1*R*,3*S*)-1-Phenylpent-4-en-1,3-diol (**7b**) erfolgreich durchgeführt werden: Im Zuge der Reaktion wird hochselektiv nur ein Stereoisomer gebildet, beide Tetrahydrofuraneinheiten weisen die für die Cobalt-Methode charakteristische *trans*-Konfiguration auf. Neben dem durch H-Atom-Einfang gebildeten Produkt **23** findet man auch in geringerer Menge das Bistetrahydrofuran **24**, das durch Addition an Alkin **21b** nach dem zweiten Ringschluss entstanden ist.

3.4 Ausblick

Die Terminierung einer Cobalt-katalysierten Oxidation durch Addition an Alkene und Alkine macht deutlich, dass es sich dabei um eine Methode handelt, die den stereoselektiven Aufbau eines Tetrahydrofurans mit der nachfolgenden Verlängerung der Seitenkette in einem Schritt vereinigen kann. Die Ergebnisse dieses Projektes zeigen außerdem, dass die Methode Zugang zu Produkten bietet, die auf anderen Wegen nicht oder nur schwer zu erhalten sind. Davon ausgehend erschien es plausibel, kettenverlängernde Terminierungen auch durch radikalische Substitution durchführen zu können und so z.B. Tetrahydofurane darzustellen, deren Seitenkette durch Thioether funktionalisiert sind. Diese Herausforderung, potentiell oxidationslabile Thioether unter den aerob oxidativen Bedingungen der Cobalt-Methode darzustellen, wurde im darauf folgenden Projekt angegangen.

3.5 Forschungsartikel

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

Patrick Fries, Daniel Halter, Alexander Kleinschek, Jens Hartung, *J. Am. Chem. Soc.* **2011**, *133*, 3906–3912.

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

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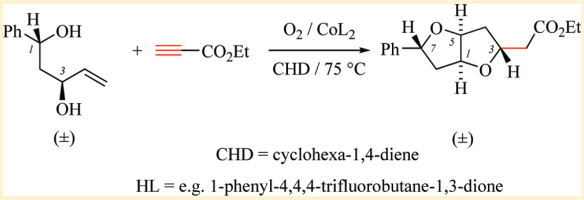
Supporting Information

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.



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 $Bu_3Sn^{\bullet}$, which is the chain-propagating radical, and $H^{\bullet}$, 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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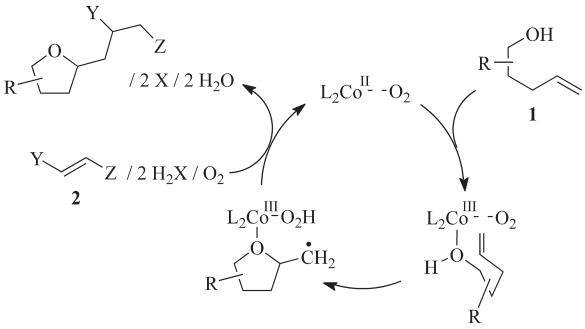
Scheme 1. Mechanistic Concept for Heterobisfunctionalization of Alkenols via Aerobic Oxidation−Radical Addition Cascades[a]



[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.

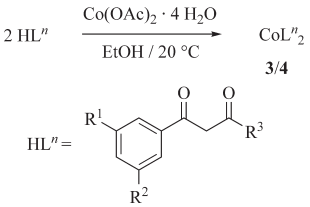
A gradual increase of CHD concentration improved the yield of tetrahydrofuryl butyronitrile **6**. This trend leveled off at c_0^{CHD} = 3−4 M (Figure 2). The same trend is observed for dinitrile formation (product **10**), although at lower yields. The yield of 2-phenyl-5-methyltetrahydrofuran **5a** 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

dx.doi.org/10.1021/ja108403s |J. Am. Chem. Soc. 2011, 133, 3906–3912

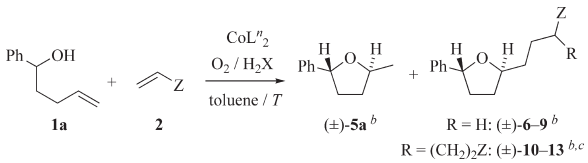
Table 1. Preparation of Cobalt(II) Chelates from CF_3-Substituted 1,3-Diketones



entry	HL^n	$R^1 = R^2$	R^3	3/4/%	$\delta^{19}F$/ppm[a]	$\nu_{C=O}/cm^{-1}$[b]	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^n_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 ^1H 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 (^1H 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 (^1H NMR, GC). For stereoassignment, we used NOESY spectra and chemical shift correlations (^1H, ^{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

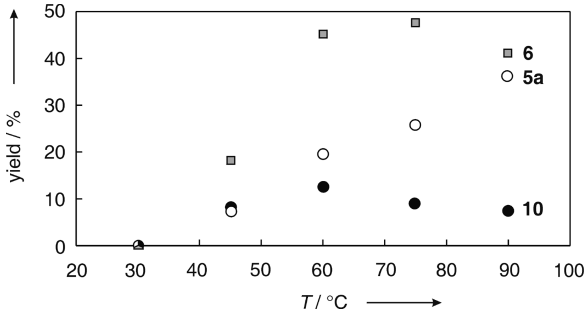


Figure 1. Temperature profile of product selectivity in aerobic oxidation of alkenol **1a** in the presence of acrylonitrile **2a** and CHD catalyzed by **3** (c_0^{2a} = 1.5 M; 5.0 equiv; c_0^{CHD} = 3.5 M in toluene; c_0^{1a} = 0.30 M, c_0^{3} = 0.02 M).

to the existing mechanistic and stereochemical analysis, a kinetic approach.[14]

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

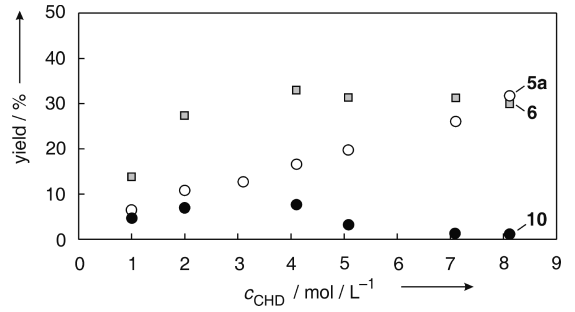


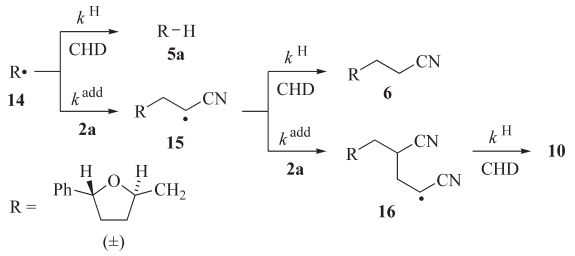
Figure 2. Correlation of product selectivity and CHD concentration in aerobic alkenol oxidations in the presence of acrylonitrile **2a** (toluene as cosolvent; c_0^{2a} = 1.5 M; c_0^{1a} = 0.30 M; c_0^{3} = 0.02 M; T = 60 °C).

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^H = 5.8 × 10^4 M^{-1} s^{-1} ($^•C_2H_5$ + CHD; 27 °C).[32] [b] For 60 °C (cf. Table 2, entries 1, 6, and 8). [c] k^{add} = 5.4 × 10^5 M^{-1} s^{-1} [H_2C=$CH(CH_2)_3CH_2^•$ + **2a**] and 1.6 × 10^5 M^{-1} s^{-1} [H_2C=$CH(CH_2)_3CH_2^•$ + **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 ($k_{2c}^{add}/k_{2b}^{add}$ = 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)



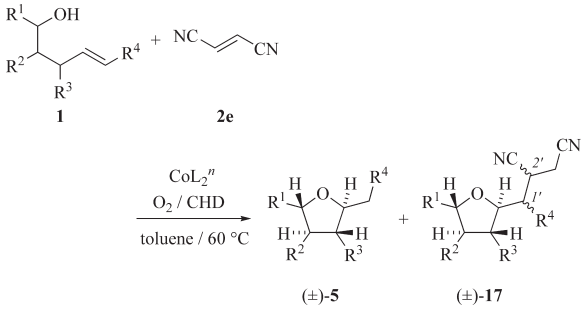
partial rate factor analysis is similar (Table 3).

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

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

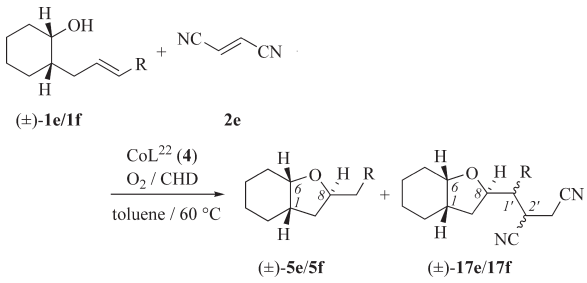
Table 4. Oxidation−Radical Addition Cascades Starting from Phenylpent-4-en-1-ols 1a−d and Fumarodinitrile 2e[a]



entry	1	R^1	R^1	R^3	R^4	$CoL_2^{n\,b}$	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).

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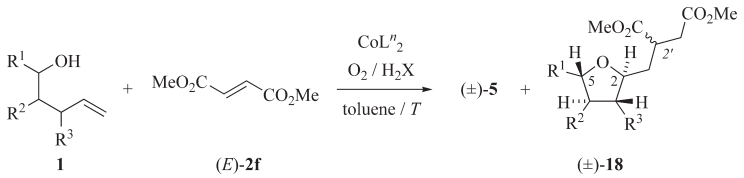
Table 6. CoL_2-Catalyzed Oxidation of Phenylpent-4-en-1-ols 1a−c in the Presence of Dimethyl Fumarate (*E*)-2f[a]

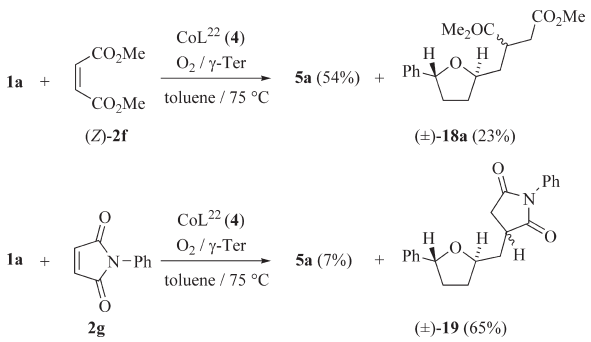


1 (*E*)-2f

entry	1	R^1	R^1	R^3	CoL^n_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).

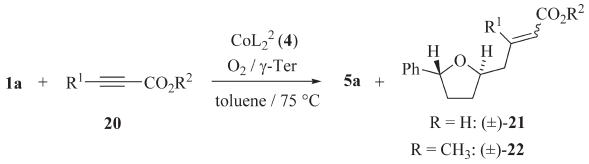
Scheme 3. Alkenol Oxidation−Alkylation Sequences Starting from (*Z*)-1,2-Diacceptor-Substituted Olefins



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 ($k^{rel} = k_{(E)\text{-}\mathbf{2f}}/k_{(Z)\text{-}\mathbf{2f}} = 10$, 20 °C).[6]

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** (^{1}H NMR); 3 mol % of **4**.

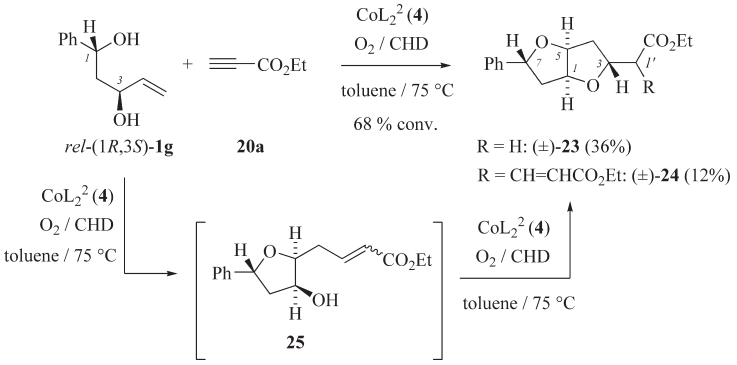
Attempts to apply maleic acid anhydride to conduct oxidation−cyclization cascades lead to an irreversible deactivation of catalysts **3** and **4**. *N*-Phenyl maleic imide, on the other hand, provided 65% of addition product **19** if subjected to standard conditions (Scheme 3, bottom).

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 ($k^{rel} = 3.0$, 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

dx.doi.org/10.1021/ja108403s |*J. Am. Chem. Soc.* 2011, 133, 3906–3912

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 $[CoL^2_2$ (**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,

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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 $[CoL^2_2$ (**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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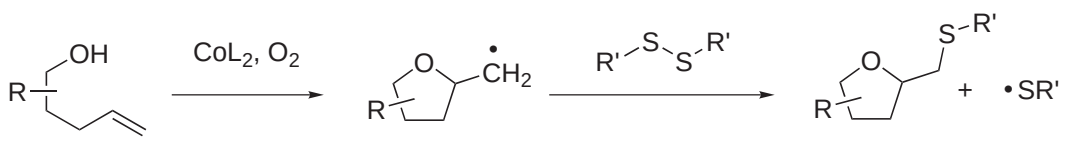
4 Methylsulfanyl-Cyclisierungen mit Disulfiden

4.1 Zusammenfassung

Durch Zusatz von Dimethyldisulfid können 4-Pentenole in Cobalt-katalysierten Oxidationen in Methylsufanyl-substituierte Tetrahydrofurane überführt werden, ohne dass die so gebildeten Thioether selbst zu Sulfoxiden und Sulfonen oxidiert werden. Die Einführung der Methylsulfanyl-Gruppe erfolgt durch radikalische Substitution am Disulfid und konkurriert somit mit der direkten H-Atom-Übertragung durch CHD. Aus einer Reihe konkurrenzkinetischer Experimente konnte die Geschwindigkonstante für die Übertragung der Methylsulfanyl-Gruppe ermittelt werden. ($k^{SMe} = 3 \cdot 10^4$ $\mathrm{M^{-1}s^{-1}}$). Die Methode ermöglichte die Vereinfachung und Verbesserung der Synthese eines Wirkstoff-Derivats sowie die Darstellung eines 2,6-*trans*-konfigurierten Tetrahydropyrans.

4.2 Hintergrund, Zielsetzung und Strategie

Der übliche Weg zur Darstellung von Thioethern in der präparativen organischen Chemie ist die nucleophile Substitution durch Thiole.[1, 2] Diese sind allerdings bekannt für ihren äußerst unangenehmen Geruch, der auch noch in geringster Verdünnung gut wahrnehmbar ist.[3, 4] Methyl-substituierte Thioether, die in der Natur-[5] und Wirkstoffsynthese[6] von besonderer Bedeutung sind, müssen nach dieser Methode mit Methanthiol aufgebaut werden – eine Verbindung, die durch üblen Geruch und hohe Toxizität abschreckt und zudem schlecht handhabbar ist, da sie unter Normalbedingungen als Gas vorliegt. Eine alternative Möglichkeit zur Darstellung von Thioethern ohne den Einsatz von Thiolen ist die radikalisch verlaufende homolytische Substition an Disulfiden,[7, 8, 9] die Mitte des 20. Jahrhunderts in der klassischen, Zinn-basierten Radikalchemie bereits intensiv untersucht worden ist.[10] Für die Cobalt-katalysierte Oxidation von Alkenolen bedeutet dies, dass Aryl- oder Alkylsulfanyl-Gruppen auf das im Katalysecyclus gebildete Tetrahydrofurylmethyl-Radikal gemäß Schema 4.1 übertragen werden können:



Schema 4.1: Cobalt-katalysierte Oxidation: Terminierung durch radikalische Substitution an Disulfiden; R, R' = Aryl, Alkyl.

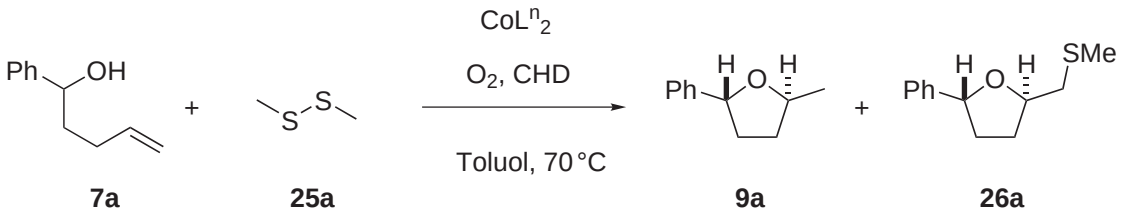
Aufgrund des stereoselektiven Ringschlusses im ersten Teilschritt der Reaktion sind Verbindungen wie der in Kapitel 1 erwähnte Wirkstoff **4** (Abb. 1.1) attraktive Zielverbindungen für die Anwendung einer solchen Methode. Vor diesem Hintergrund leitete sich ein Projekt mit der folgender Aufgabenstellung ab:

- Entwicklung einer Methode zur Darstellung Thioether-funktionalisierter Tetrahydrofurane auf der Grundlage der Cobalt-katalysierten Oxidation von Alkenolen.
- Bestimmung der Geschwindigkeitskonstanten für die Übertragung der Methylsulfanyl-Gruppe durch konkurrenzkinetische Studien.
- Anwendung der Methylsulfanyl-Cyclisierung in der Synthese eines potentiellen Wirkstoffs aus der Familie der Cyclooxygenase II-Inhibitoren.

4.3 Ergebnisse und Diskussion

4.3.1 Rahmenbedingungen für Thioether-Funktionalisierungen

Überträgt man das allgemeine, in Schema 4.1 illustrierte Prinzip des Alkylsulfanyl-Transfers auf die Oxidation von 1-Phenylpent-4-en-1-ol, so erhält man folgende Reaktionsgleichung (Schema 4.2):



Schema 4.2: Reaktionsgleichung für die Darstellung Alkylsulfanyl-funktionalisierter Tetrahydrofurane, am Beispiel von Alkenol **7a** und Dimethyldisulfid (**25a**)

Das Verhältnis der beiden Produkte **26a** und **9a** ist dabei abhängig von der Konzentration der beiden miteinander konkurrierenden Radikalabfangreagenzien CHD und Dimethyldisulfid (DMDS). Bei konstanter CHD-Konzentration (1.4 mol·L^{-1}) geht eine Erhöhung der DMDS-Konzentration mit steigenden Ausbeuten an **26a** einher (Abb. 4.1).

Präparativ interessante Ausbeuten an Thioether-funktionalisierten Tetrahydrofuranen **26** sind also durch hohe Konzentrationen and Disulfid und möglichst geringe Konzentrationen an CHD möglich. Wegen des dadurch anfallenden großen Volumens an Disulfid kann auf den Zusatz von Toluol als Cosolvens verzichtet werden. Ein vollkommener Verzicht auf CHD sollte

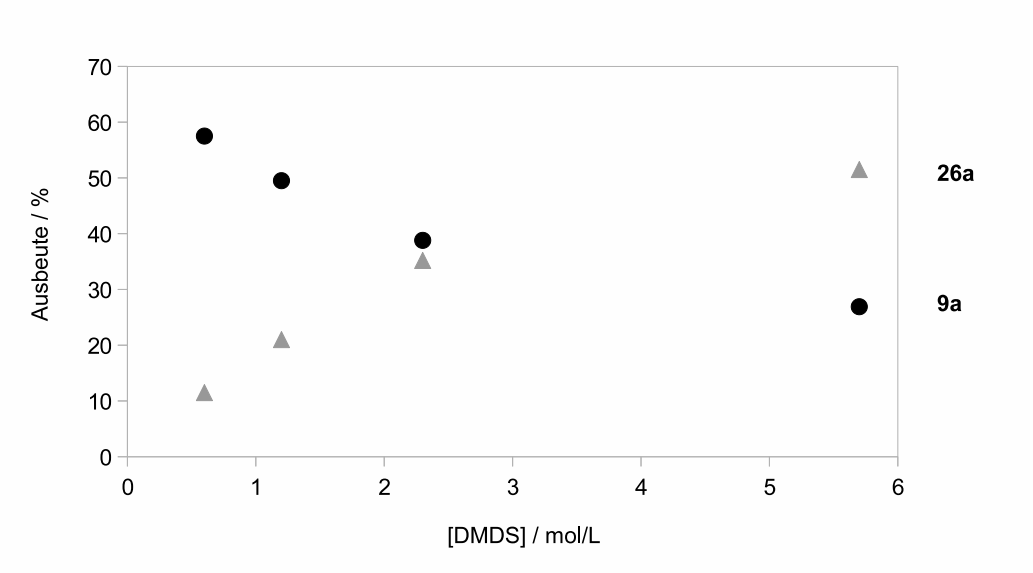
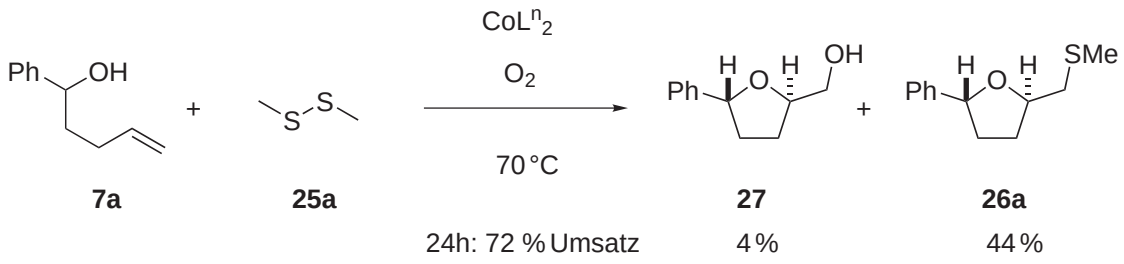


Abbildung 4.1: Produktverteilung in Abhängigkeit von der DMDS-Konzentration.

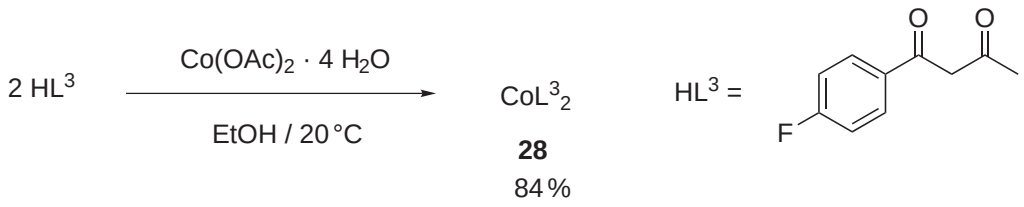
dazu führen, dass die Reaktion in Ermangelung eines Reduktionsäquivalents zum Erliegen kommt. Es hat sich jedoch in Kontrollexperimenten gezeigt, dass auch ohne Zusatz von CHD eine Reaktion stattfindet und das gewünschten Produkt **26a** gebildet wird (Schema 4.3). In diesem Fall scheint das im großen Überschuss vorhandene Disulfid als Reduktionsmittel zu wirken.



Schema 4.3: Kontrollversuch: Reaktion ohne 1,4-Cyclohexadien.

Gemäß der mechanistischen Modellvorstellung kann unter solchen Bedingungen kein Reduktionsprodukt **9** gebildet werden. Allerdings bietet diese Art der Reaktionsführung keine interessante präparative Perspektive. Die Reaktion wird mit Dimethyldisulfid als alleiniges Reduktionsmittel sehr langsam: Während in CHD-haltigen Reaktionsmischungen das Edukt nach sechs Stunden meist vollständig umgesetzt ist, beobachtet man im CHD-freien Fall auch nach 24h keinen vollständigen Umsatz. Weiterhin wird 5-Phenyltetrahydrofur-2-ylmethanol (**27**), das aus der intramolekularen Übertragung einer OH-Gruppe hervorgeht, als neues Nebenprodukt gebildet.

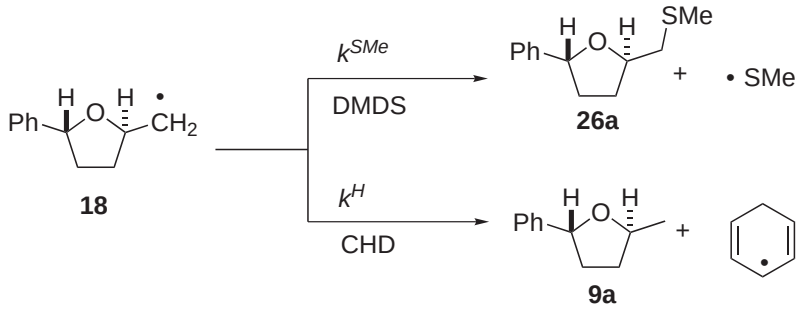
Schwefelhaltige Verbindungen im Allgemeinen und auch Disulfide im Speziellen wirken gegenüber vielen Metallen als Katalysatorgifte,[11] die den katalytisch ablaufenden Teil der Reaktion inhibieren. Projektbegleitende Untersuchungen zum Einfluss der verwendeten Cobalt-Komplexe ergaben, dass Liganden, die im Vergleich zu Benzoyltrifluoraceton (HL^2) weniger stark akzeptor-substituiert sind, geringere Inhibierung und somit höhere Umsatzraten bei gleichbleibender Selektivität liefern. Cobalt-Komplex **28**, der sich von *p*-Fluorbenzoylaceton (HL^3) ableitet, wurde daher standardmäßig als Katalysator in Alkylsulfanyl-Cyclisierungen eingesetzt (Schema 4.4).[12]



Schema 4.4: Darstellung von Cobalt-Komplex **28**.[12]

4.3.2 Konkurrenzkinetische Studien

Zur Bestimmung der Geschwindigkeitskonstanten für die Methylsulfanyl-Übertagung wurden konkurrenzkinetische Studien mit Dimethyldisulfid und CHD unter Bedingungen pseudo-erster Ordnung durchgeführt. Die Geschwindigkeitsfaktoren f für Methylsulfanyl-Übertragung gegenüber H-Atom-Übertragung wurden gemäß Gleichung 4.1 aus den Produktverhältnissen von **26a** und **9a** in Abhängigkeit der DMDS-Konzentration (0.6–5.7 mol·L^{-1}) für CHD-Konzentrationen von 1.4 mol·L^{-1}, 3.2 mol·L^{-1} und 5.1 mol·L^{-1} ermittelt (Schema 4.5, Abb. 4.2).



Schema 4.5: Elementarschritte der Reaktion von *trans*-2-Phenyltetrahydrofurylmethyl-Radikal **18** mit DMDS und CHD.

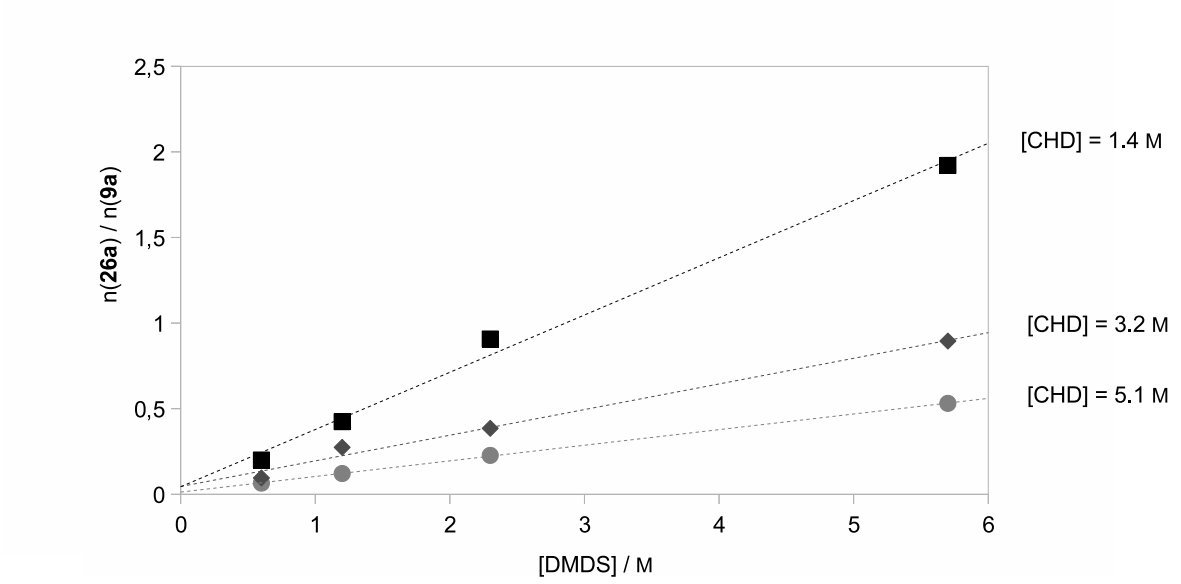


Abbildung 4.2: Auftragung der Produktverhältnisse **26a**/**9a** in Abhängigkeit der DMDS-Konzentration für CHD-Konzentrationen von 1.4, 3.2 und 5.1 mol·L^{-1}.

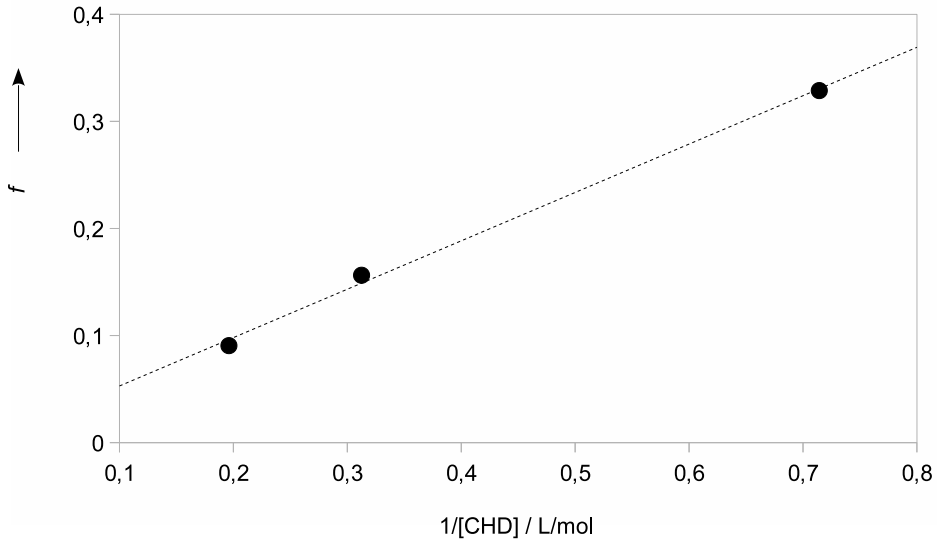


Abbildung 4.3: Die Auftragung von f gegen die reziproke CHD-Konzentration liefert die relative Geschwindigkeitskonstante für die Methylsulfanyl-Übertragung.

$$\frac{[\mathbf{26a}]}{[\mathbf{9a}]} = f \cdot [\mathrm{DMDS}] \tag{4.1}$$

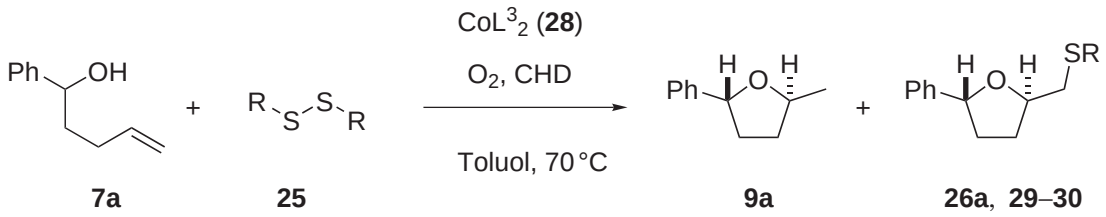
$$f = \frac{k^{SMe}}{k^{H}} \cdot \frac{1}{[\mathrm{CHD}]} \tag{4.2}$$

Eine Auftragung der so ermittelten Geschwindigkeitsfaktoren f gegen die reziproke CHD-Konzentration zeigt einen linearen Verlauf. Die Steigung dieser Ursprungsgeraden entspricht gemäß Gleichung 4.2 der relativen Geschwindigkeitskonstanten $k^{rel} = k^{SMe}/k^{H} = 0.5$ bei 70 °C. Für eine Geschwindigkeitskonstante $k^{H} = 6 \cdot 10^4$ $\mathrm{M^{-1}s^{-1}}$ (für $\cdot C_2H_5$ bei 27 °C)[13] ergibt sich somit ein Wert für k^{SMe} von $3 \cdot 10^4$ $\mathrm{M^{-1}s^{-1}}$.

4.3.3 Variation der Disulfide

Die Verwendung anderer Disulfide führt zu geringerer Chemoselektivität, d.h. geringeren Anteilen an thioalkylierten Tetrahydrofuranen (Tabelle 4.1). Dies ist zum einen darauf zuückzuführen, dass mit diesen Reagenzien die erforderlichen hohen Disulfid-Konzentrationen nicht mehr zu erreichen sind, zum anderen scheint bei Di-*tert*-butyldisulfid die sterische Abschirmung der beiden Schwefel-Zentren einen radikalischen Angriff effektiv zu verhindern.[14]

Tabelle 4.1. Alkylsulfanyl-Cyclisierungen mit verschiedenen Disulfiden.

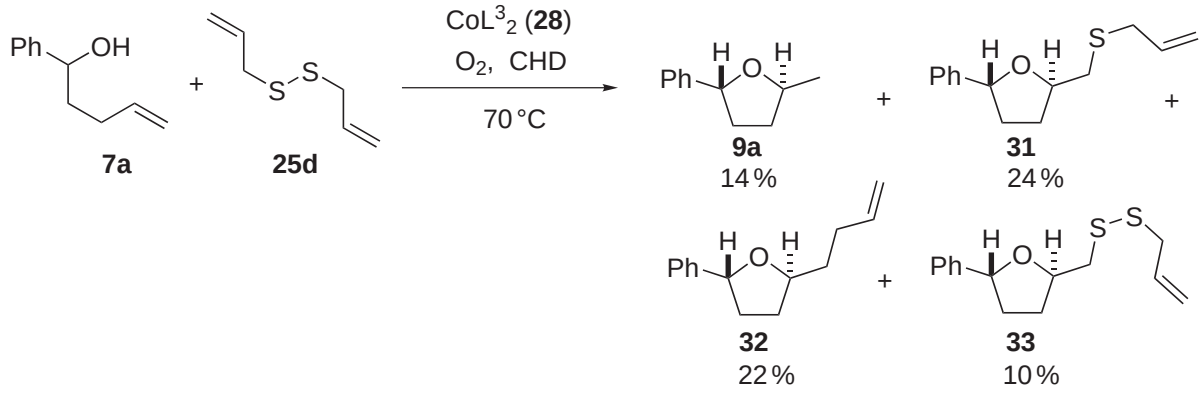


7a **25** **9a** **26a**, **29**–**30**

Eintrag	**25**	R	[**25**] / mol·L^{-1}	[CHD] / mol·L^{-1}	**9a**/%	**26a**, **29**–**30**/%
1	**25a**	Me	9.5	1.0	10	**26a**: 72
2	**25b**	Et	6.7	1.7	39	**29**: 36
3	**25c**	*t*-Bu	4.7	0.9	70	**30**: –[a]

a: nicht nachweisbar (GC, ^{1}H-NMR)

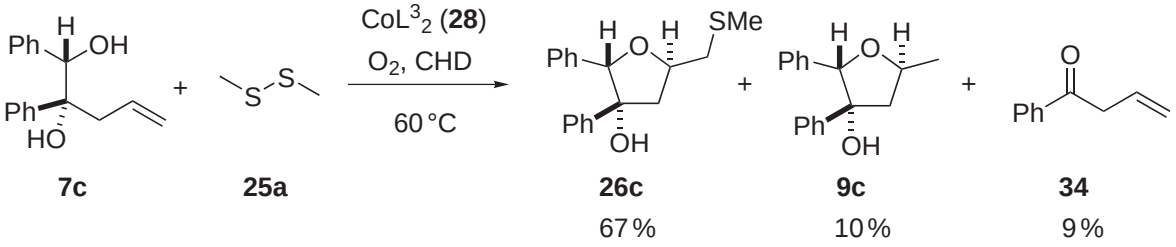
Der Einsatz von Diallyldisulfid führt hingegen zur Bildung zweier neuer Produkte: Zum einen wird das Butenyl-substituierte Tetrahydrofuran **32** durch eine Allylgruppenübertragung nach Keck[15] gebildet, zum anderen scheint das aus diesem Vorgang zurückbleibende Allyldithiyl-Radikal in Rekombination mit dem Tetrahydrofurylmethyl-Radikal **18** Disulfid **33** zu bilden (Schema 4.6).



Schema 4.6: Die Verwendung von Diallyldisulfid (**25d**) führt zu Bildung von Produkten, die durch Übertragung von Allyl- bzw. Allyldithiyl-Gruppen hervorgehen.

4.3.4 Anwendung in der Wirkstoffsynthese

Als Zielverbindung für Methylsulfanyl-Cyclisierungen bot sich das Methyl-Analogon **26c** des eingangs erwähnten Cyclooxygenase II-Inhibitors **4** an (Abb. 1.1).[16] Unter leicht modifizierten Standardbedingungen konnte **26c** erfolgreich dargestellt werden (Schema 4.7):

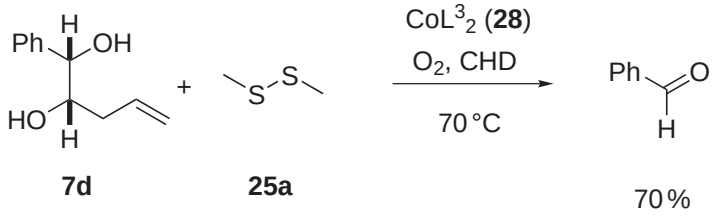


Schema 4.7: Synthese von Wirkstoff-Ananlogon **26c**.

Mit Hilfe der Cobalt-Methode konnte somit gegenüber dem in der Literatur beschriebenen Verfahren[16] eine zweistufige Synthese (Iodcyclisierung und nucleophile Substitution) auf eine einstufige Reaktion verkürzt werden, wobei gleichzeitig die Selektivität des Ringschlusses von *cis*:*trans* = 20:80 auf *cis*:*trans* <1:99 verbessert und so die Effizienz der Reaktion gesteigert werden konnte.

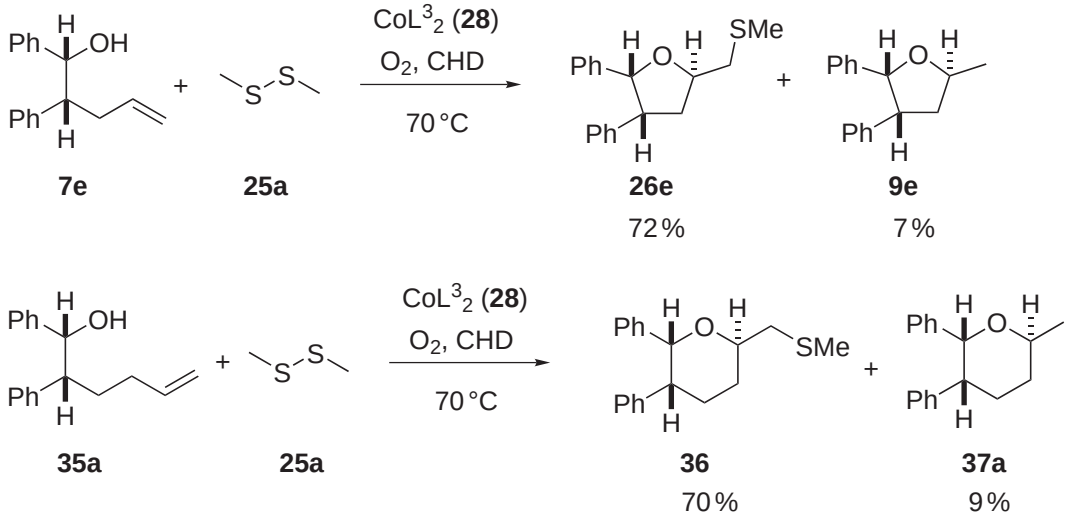
Die Reaktion verläuft bei 60 °C unter teilweiser Fragmentierung des eingesetzten Alkendiols, was sich in der Bildung von Benzaldehyd (GC, nicht quantifiziert) und Keton **34** niederschlägt. Bei einer Reaktionstemperatur von 70 °C steigt der Anteil der Fragmentierung und damit die Bildung von **34** auf 40 %, während die Ausbeute an **26c** auf 22 % sinkt. Die Ursache für dieses bis dahin noch nicht beobachtete Verhalten war auf die zweite OH-Funktion in Position 2 des Alkendiols zurückzuführen: Alkendiol **7d** wird unter Standard-Reaktionsbedingungen praktisch vollständig fragmentiert und bildet cyclisierte Produkte nur

in Spuren (GC) (Schema 4.8).



Schema 4.8: Alkendiol **7d** erleidet Fragmentierung unter Standard-Reaktionsbedingungen.

Eine zweite Phenyl-Gruppe in Position 2 des Alkenols erwies sich indes nicht als nachteilhaft. Ohne Fagmentierung oder Bildung anderer Nebenprodukte verlief die Umsetzung von *like*-1,2-Diphenylpent-4-en-1-ol (**7e**). Überraschend und unerwartet war die Tatsache, dass auch ein derartig konfiguriertes Hexenol einer Methylsulfanyl-Cyclisierung unterzogen werden konnte: Das zu **7e** homologe *like*-1,2-Diphenylhex-5-en-1-ol (**35a**) lieferte mit der gleichen Diastereoselektivität (2,6-*cis*:2,6-*trans* <1:99) ein vergleichbares Produktverhältnis (Schema 4.9):



Schema 4.9: Methylsulfanyl-Cyclisierung mit 1,2-*like*-konfigurierten Pentenol **7e** und dem homologen Hexenol **35a**.

4.4 Ausblick

Mit den Ergebnissen dieses Projekts stehen nun Wege offen, Methylsulfanyl-substituierte Tetrahydrofurane effizient in hoher Stereoselektivität und ohne die Verwendung von Methanthiol darzustellen. Die Übertragung der Allylgruppe in Reaktionen mit Diallyldisulfid ist eine synthetisch interessante Nebenreaktion und verdient weitere Beachtung, um mit möglichen anderen Allylgruppen-übertragenden Reagenzien als eigenständige Methode der Funktionalisierung ausgebaut zu werden. Die im Zuge dieses Projekts beobachtete erste erfolgreiche Synthese von Tetrahydropyranen war erfreulich, besonders im Hinblick auf die Mühen, die in vergangenen Arbeiten aufgewendet worden waren dieses Ziel zu erreichen.[17, 18] Daher war es naheliegend, zu überprüfen, welche Voraussetzungen allgemein gelten müssen, um Tetrahydropyrane mit Hilfe der Cobalt-Methode darstellen zu können und warum die charakteristische *trans*-Selektivität beim Wechsel von Pentenolen zu Hexenolen erhalten bleibt. Die Entschlüsselung des zugrunde liegenden stereochemischen Prinips sollte daher gezielt in einem neuen Projekt angegangen und bearbeitet werden.

4.5 Forschungsartikel

An aerobic oxidation/homolytic substitution-cascade for stereoselective methylsulfanyl-cyclization of 4-pentenols

Patrick Fries, Melanie Kim Müller, Jens Hartung, *Org. Biomol. Chem.* **2013**, *11* , 2630–2637.

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An aerobic oxidation/homolytic substitution-cascade for stereoselective methylsulfanyl-cyclization of 4-pentenols†

Patrick Fries, Melanie Kim Müller and Jens Hartung*

4-Pentenols (dihomoallylic alcohols) are oxidized by cobalt(II)-activated dioxygen in solutions of dimethyl disulfide and cyclohexa-1,4-diene to afford methylsulfanyl (CH_3S)-functionalized tetrahydrofurans in up to 74% yield. The reaction is a cascade, composed of oxidative alkenol cyclization providing tetrahydrofuryl-2-methyl radicals, which are trapped in dimethyl disulfide. Homolytic methylsulfanyl substitution by carbon radicals is a slow reaction, as exemplified by the rate constant of $k^{SCH_3} = 3 \times 10^4$ M^{-1} s^{-1} (70 °C) derived from competition kinetics for the reaction between dimethyl disulfide and the *trans*-2-phenyl-tetrahydrofuryl-5-methyl radical. Methylsulfanyl-cyclizations therefore are experimentally performed in neat dimethyl disulfide, containing the minimum amount of cyclohexa-1,4-diene necessary for attaining almost quantitative alkenol conversion. The oxidative tetrahydrofuran synthesis occurs with noteworthy (>99%) 2,5-*trans*-stereoselectivity, as shown by the synthesis of diastereomerically pure 2,3- and 2,3,3-substituted 5-(methylsulfanyl)methyltetrahydrofurans from stereodefined 1,2-di- and 1,2,2-trisubstituted 4-pentenols. Changing the chemical nature of the disulfide reagent or the alkenol extends the scope of alkylsulfanyl-cyclization to ethylsulfanyl-cyclization, allylsulfanyl-transfer, or tetrahydropyran synthesis.

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Introduction

The methylsulfanyl group (SCH_3) is a soft and strongly nucleophilic group, which enhances the response to receptor binding of bioactive compounds[1,2] and opens in sulfoxidized form pathways for selective functional group interconversion or carbon-skeleton rearrangement.[3,4]

Standard approaches to synthesis of methyl thioethers are nucleophilic substitution and addition.[5,6] In substitutions, methylthioethers are formed in a Williamson-type approach from organic thiols and methyl electrophiles, or alternatively from carbon electrophiles and methanethiol. The standard reagent for introducing the methylsulfanyl group by addition is methanethiol, which adds to Michael-type acceptors in polar or in homolytic reactions.

Methanethiol is at room temperature a toxic malodorous gas that for many is unpleasant to use.[7] An alternative reagent to methanethiol in thioether-synthesis is dimethyl disulfide. Dimethyl disulfide is a liquid, which boils under standard conditions at 112 °C. The compound has a cabbage-like smell that many experience as significantly less disturbing than the offensive odor of methanethiol.[8]

The use of dialkyl- and diaryl disulfides for sulfur functionalization, particularly of carbon radicals, was mechanistically explored by the end of the 20th century.[9–11] The kinetic data summarized from this era show that thiyl radicals rapidly add to alkenes, or homolytically abstract hydrogens from aliphatic C,H-bonds.[12] Thiyl radicals, on the other hand, react comparatively slowly with monovalent heteroatom functional groups, such as halogens, arylthioethers or selenoethers, which are customarily used for carbon radical generation in chain reactions.[13,14] With the advent of thiohydroxamate-based carbon radical progenitors, researchers started to make use of the potential of this method for developing homolytic phenylsulfanylations,[11,15,16] however, leaving the field of methylsulfanylation and the use of more atom-economic radical progenitors largely unexplored.

In a project on atom-economic tetrahydrofuran synthesis we recently found that 4-pentenols furnish tetrahydrofuryl-2-methyl radicals, if oxidized by cobalt-activated molecular oxygen.[17–20] The convincing selectivity of this method prompted us to address the question of sulfur functionalization of carbon radicals again, with the aim to combine stereoselective 4-pentenol ring closure[21] and homolytic alkylsulfanyl-transfer to a new cascade (Scheme 1).

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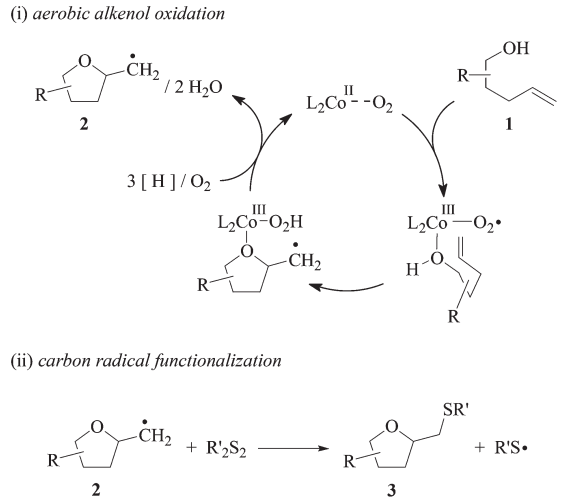
†Electronic supplementary information (ESI) available: Standard instrumentation, carbon-13 NMR-spectra of selected compounds, and protocols for synthesis of alkenols, cobalt(II) complexes, products of sulfoxidation, See DOI: 10.1039/c3ob26590k



Scheme 1 Mechanistic model of an aerobic oxidation/homolytic substitution-cascade for alkylsulfanyl-cyclization of 4-pentenol **1** {[H] = hydrogen atom from *e.g.* cyclohexa-1,4-diene (CHD); R = *e.g.* phenyl or alkyl; R′ = *e.g.* methyl, ethyl, or allyl, L^- = 1-arylbutane-1,3-dione monoanion (*cf.* Table 1)}.

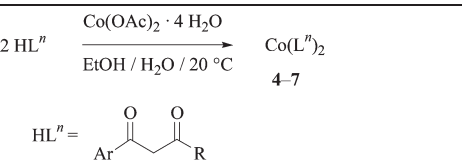
The major results from the study show that 4-pentenols undergo rapid and chemoselective methylsulfanyl-cyclizations, if oxidized by molecular oxygen in solutions of dimethyl disulfide and cyclohexa-1,4-diene (CHD). The 4-pentenol ring closure proceeds with noteworthy 5-*exo*- and 2,5-*trans*-selectivity, allowing to prepare diastereomerically pure 2,3- and 2,3,3-substituted 5-(methylsulfanyl)methyltetrahydrofurans. Replacing dimethyl disulfide by other disulfides, or the 4-pentenol by a 5-hexenol, extends the scope of alkylsulfanyl-cyclization to ethylsulfanyl-cyclization, allylsulfanyl-transfer, and to tetrahydropyran synthesis.

Results and discussion

1 Cobalt(II) complexes

From a screening of catalysts for mediating oxidative alkenol ring closure by molecular oxygen, we selected fluoro-substituted cobalt(II)-bis(β-diketonate)-complexes **4–7** of the general formula $Co(L^n)_2$ (Table 1) for the pursuit of the alkylsulfanyl-cyclization project.[22] One of the candidates, 4,4,4-trifluoro-1-phenylbutane-1,3-dione-derived complex $Co(L^1)_2$ (**4**), was available from a previous project,[23] whereas compounds **5–7** were newly prepared by mixing cobalt(II)-acetate tetrahydrate and two aliquots of the underlying 1-arylbutane-1,3-dione HL^n (n = 2–4) in aqueous solutions of ethanol. Cobalt(II) bis-(β-diketonate) complexes **4–7** were characterized on a routine basis by infrared-spectroscopy, combustion analysis, and ESI-mass spectrometry. In fluorine-19 NMR spectra,[24,25] we noticed a strong deshielding of alkyl-bound fluorines in $Co(L^1)_2$ (**4**) (δ = 6.4), if referenced to fluorine-NMR chemical shifts of the enol HL^1 (−77.5 ppm) and the lithium enolate $Li(L^1)$ (−76.9 ppm). For aryl-bound fluorine in HL^2 (−108.3 ppm), cobalt(II)-binding induces a slight shielding (−112.0 ppm for **5**; Table 1). Although the quantum chemical origin of these shift dispersions remained unclear, this information offered on a qualitative basis a guideline for characterizing cobalt(II) compounds **4–7**.

Table 1 Preparation of cobalt(II) chelates from fluorinated 1,3-diketones



Entry	HL^n	Ar	R	**4–7**/%	δ $^{19}F^a$/ppm	$\nu_{C=O}$ ^{b}/cm^{-1}
1	HL^1	Ph	CF_3	**4**: 99[c]	+6.4	1609
2	HL^2	*p*-FC_6H_4	CH_3	**5**: 84[c]	−112.0	1603
3	HL^3	*p*-FC_6H_4	CF_3	**6**: 89[d]	−110.3/+7.6	1616
4	HL^4	*p*-FC_6H_4	*p*-FC_6H_4	**7**: 70[d]	−110.9	1600

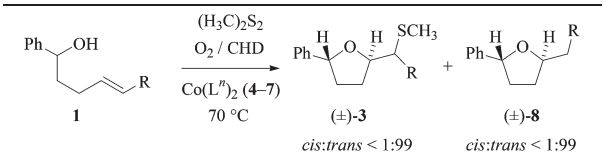
[a] In acetone–$CDCl_3$ [50 : 50 (v/v)], *versus* α,α,α-trifluorotoluene as the internal standard. [b] Pelletized in KBr. [c] Dihydrate. [d] Bisethanol-adduct.

Cobalt complexes prepared according to the general method (Table 1) contain water- (**4** and **5**) or ethanol molecules (**6** and **7**). Solvate-free cobalt complexes can be obtained by drying, for example, compounds **6** and **7** at 90 °C under reduced pressure (2×10^{-1} mbar). If tested for catalytic reactivity and selectivity in aerobic alkenol oxidations, solvated and solvate-free complexes performed similarly. For practical reasons, we used the solvate complexes as oxidation catalysts.

2 Alkylsulfanyl-cyclization of 4-pentenols

2.1 Parameters for selective methylsulfanyl-cyclization. By systematically adapting the reaction temperature, dimethyl disulfide concentration, chemical nature and concentration of the reducing agent (see Scheme 1), and the catalyst/substrate-ratio, we found that 2-phenyl-5-[(methylsulfanyl)methyl]tetrahydrofuran **3a** is available in up to 59% yield from a solution of 1-phenyl-4-penten-1-ol (**1a**), containing 8.5 molar concentration of dimethyl disulfide, 2.0 molar concentration of cyclohexa-1,4-diene (CHD), and 5 mol% of cobalt(II) complex **5**. This solution is kept for three hours at 70 °C in a flask connected to a reflux condenser left open at the top for saturating the reaction mixture with air. The alkenol conversion under such conditions varied from catalyst to catalyst, leading to values of 66–94%, with the highest degree of conversion consistently found for oxidations catalyzed by *p*-fluorophenylbutanedionato-derived cobalt complex **5**. Oxidation of **1a** under such conditions furnishes 2-phenyl-5-methyltetrahydrofuran **8a** as a by-product, supplementing the mass balance for alkenol-derived compounds to 88% (Table 2, entry 2). According to proton-NMR-, NOESY-, and GC-MS data, tetrahydrofurans **3a** and **8a** are formed exclusively as 2,5-*trans*-stereoisomers.[26] A control conducted in an atmosphere of dry nitrogen under otherwise identical conditions (*cf.* Table 2, entry 2) did not provide tetrahydrofurans **3a** and **8a** (GC). From

Table 2 Reactivity and selectivity in aerobic methylsulfanyl-cyclization of alkenols **1a–c**



Entry	$Co(L^n)_2$	**1**/R	Conv.[a]/%	**3**[b,c]/%	**8**[b]/%
1	**4**	**1a**/H	75	**3a**/47	**8a**/22
2	**5**	**1a**/H	94	**3a**/59	**8a**/29
3	**6**	**1a**/H	66	**3a**/41	**8a**/20
4	**7**	**1a**/H	75	**3a**/46	**8a**/22
5	**4**	**1b**/CO_2CH_3	55	**3b**/15	**8b**/38
6	**5**	**1b**/CO_2CH_3	78	**3b**/18	**8b**/50
7	**4**	**1c**/CH_3	74	**3c**/44	**8c**/23
8	**5**	**1c**/CH_3	82	**3c**/50	**8c**/24

[a] 3 h reaction time, 5 mol% of $Co(L^n)_2$ (see text), c_{CHD} = 2.0 M, c_{DMDS} = 8.5 M. [b] Yields determined *via* GC. [c] 50/50-mixture of stereoisomers with respect to the stereocenter in the tetrahydrofurylmethyl side chain for **3b** and **3c**.

this information we concluded that molecular oxygen is a key reagent for the oxidative alkenol conversion into cyclic ethers **3a** and **8a**.

The second important reagent for attaining catalytic oxidative alkenol turnover is cyclohexa-1,4-diene (CHD). The diene delivers reducing equivalents for converting dioxygen into water and for reducing cobalt(III) to cobalt(II), which is the active form of the catalyst for dioxygen activation (Scheme 1).[17] In some applications, we tested γ-terpinene as the substitute for CHD. Some of the γ-terpinene-derived oxidation products were difficult to separate from methylsulfanyl-cyclized products, which let us to adhere to CHD as the reductant. In controls we noticed that methylsulfanyl-cyclization also occurs in the absence of CHD, although at a slower rate and less selectively. If stirred, for example, for twenty four hours at 70 °C in a solution of dimethyl disulfide, a fraction of 28% of phenylpentenol **1a** remains unchanged. The rest of the alkenol is converted into products, from which we were only able to separate and to characterize thioether **3a** (44%), being formed exclusively as 2,5-*trans*-isomer, and *trans*-5-phenyltetrahydrofuryl-2-methanol (4%), which is not produced in solutions containing CHD.[23,27]

As we raised the dimethyl disulfide concentration from 0.6 to 5.7 M at a fixed CHD-concentration of 1.4 M, the yield of thioether **3a** gradually increases, whereas the fraction of reduction product **8a** becomes smaller (Fig. 1). From this responsivity we concluded that dimethyl disulfide and CHD compete for the same reactive intermediate, which, according to the mechanistic model outlined in Scheme 1, is the *trans*-2-phenyltetrahydrofuryl-5-methyl radical (**2a**).[17] The unknown rate constant for methylsulfanyl-transfer from dimethyl disulfide to primary carbon radical **2a** became available from competition kinetics performed under pseudo-first order conditions (Scheme 2). From a primary plot of product ratios

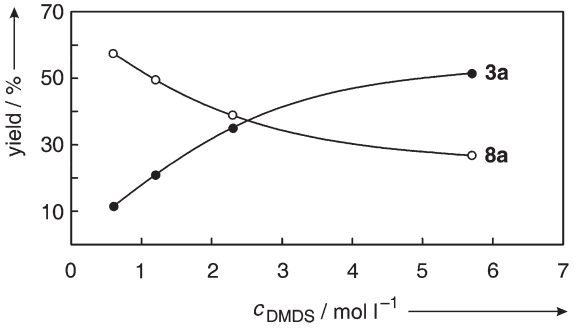
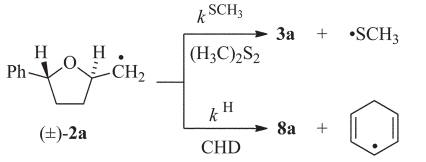


Fig. 1 Relationship between product selectivity in methylsulfanyl-cyclization of phenylpentenol **1a** and dimethyl disulfide (DMDS)-concentration (c_0^{CHD} = 1.4 M, c_0^{1a} = 0.11 M, c_0^{4} = 5.7 μM, T = 70 °C).



$$\frac{[\,\mathbf{3a}\,]}{[\,\mathbf{8a}\,]} = \frac{k^{SCH_3}}{k^{H}} \frac{[(H_3C)_2S_2]}{[CHD]} \qquad \text{eqn (1)}$$

$$f = \frac{k^{SCH_3}}{k^{H}} \cdot \frac{1}{[CHD]} \qquad \text{eqn (2)}$$

Scheme 2 Elementary reactions (top) and equations for numeric analysis of the rate constant (bottom) of homolytic SCH_3-substitution (k^{SCH_3}) from dimethyl disulfide (DMDS) by the *trans*-2-phenyltetrahydrofuryl-2-methyl radical (**2a**).

3a/**8a** *versus* the dimethyl disulfide concentration in the range of 0.6–5.7 M, we calculated according to eqn (1) partial rate factors f for thiomethyl substitution *versus* hydrogen atom abstraction by primary radical **2a**, at fixed CHD-concentrations of 1.4 M, 3.2 M and 5.1 M (Fig. 2). The slope of a linear correlation of f *versus* reciprocal cyclohexa-1,4-diene concentrations, in a secondary plot according to eqn (2), provides the relative rate constant $k^{rel} = k^{SCH_3}/k^{H}$, having a value of 0.5 at a temperature of 70 °C (Fig. 3). If referenced toward k^{H} for H-atom transfer from CHD to the ethyl radical at 27 °C, and assuming a similar temperature dependence of the two homolytic substitutions, the rate of homolytic methylsulfanyl-radical substitution translates into $k^{SCH_3} = 3 \times 10^4\ M^{-1}\ s^{-1}$ (70 °C).

The information gained from competition kinetics suggests that the largest split for thioether synthesis is attainable in solutions containing the maximum concentration of dimethyl disulfide and the minimum amount of CHD, necessary for maintaining a reasonable rate of oxidative alkenol turnover. In synthesis, we used a 9.5 molar concentration of dimethyl disulfide and 0.95 molar concentration of CHD. For turning over alkenols of unknown reactivity, such as substrates **1b–c**, we almost doubled the concentration of CHD to obtain

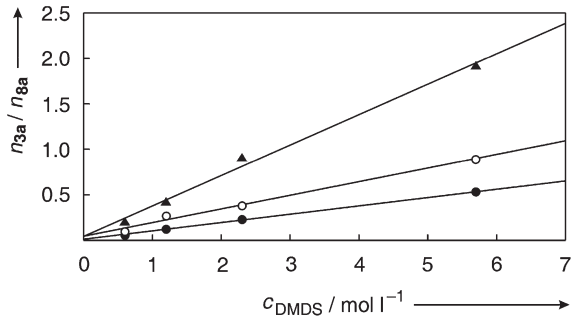


Fig. 2 Primary plot – correlation of product ratios **3a**/**8a** *versus* reactant concentration for oxidation of alkenol **1a** at fixed CHD-concentrations (▲ = 1.4 M, ○ = 3.2 M, ● = 5.1 M) for determining the partial rate factors *f*, according to eqn (1) (*cf.* Scheme 2; c_0^{1a} = 0.12 M, c_0^{4} = 5.9 μM, *T* = 70 °C).

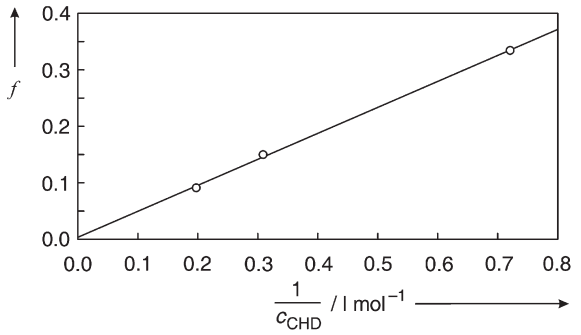
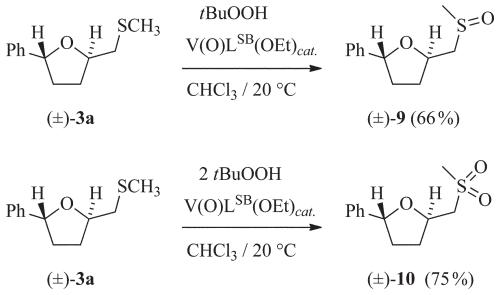
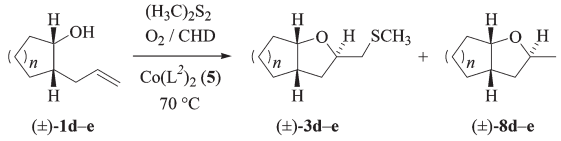


Fig. 3 Secondary plot – correlation of partial rate factor *f* *versus* reciprocal CHD-concentration for determining the relative rate constant k^{SCH_3} according to eqn (2).



Scheme 3 Sulfoxidation of thioether **3a** by *tert*-butyl hydroperoxide [V(O)-L^{SB}(OEt) = 2-[(2-oxidophenyl)iminomethyl](ethanolato)oxidovanadium(v), used as an EtOH-solvate].

Table 3 Oxidative cyclization of *cis*-2-allylcycloalkanols



Entry	**1**/**3**/**8**	*n*	**3**[a]/% (*cis* : *trans*)	**8**[a]/% (*cis* : *trans*)
1	**d**	1	71 (<1 : 99)	11 (<1 : 99)
2	**e**	2	74 (<1 : 99)	10 (<1 : 99)

[a] Relative configuration refers to substituents next to the endocyclic oxygen atom.

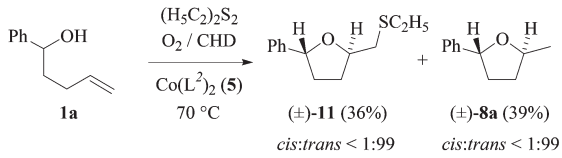
reasonable yields of products, particularly from reactions catalyzed by less reactive cobalt complexes. Oxidations of alkenol **1b** having an acrylate type double bond, for example, furnish more reduced than methylsufanyl-cyclized product (Table 2, entries 5 and 6). From the yields of thioether **3b** and methyltetrahydrofuran **8b**, and the concentration of the trapping reagents dimethyl disulfide and CHD, we estimated a relative rate constant for methylsulfanyl *versus* hydrogen atom transfer leading to a value of $k^{SCH_3}/k^{H} \approx 0.1$ for an ester-substituted tetrahydrofuryl-2-methyl radical, derived from **1b** (Table 2, entry 6). The same analysis applied for alkenol **1c**, having an internal dialkyl-substituted π-bond, furnishes a value of $k^{SCH_3}/k^{H} \approx 0.5$ for trapping of a methyl-substituted tetrahydrofuryl-2-methyl radical (Table 2, entry 8). Selectivity and yields of products **3c** and **8c** are identical to data obtained for oxidative conversion of alkenol **1a** under identical conditions.

In GC-mass spectra recorded from reaction mixtures, after having separated cobalt-residues by adsorptive filtration, we never found experimental evidence for sulfoxide- or sulfone-formation. We independently prepared sulfoxide **9** and sulfone **10** (Scheme 3), to use information on their retention times (GC), chemical shifts (proton- and carbon-13 NMR), and resonance fine structures to clarify this aspect in a more systematic manner. These efforts, in summary, confirmed that sulfoxidation products are not notably formed in this new method for thioether synthesis.

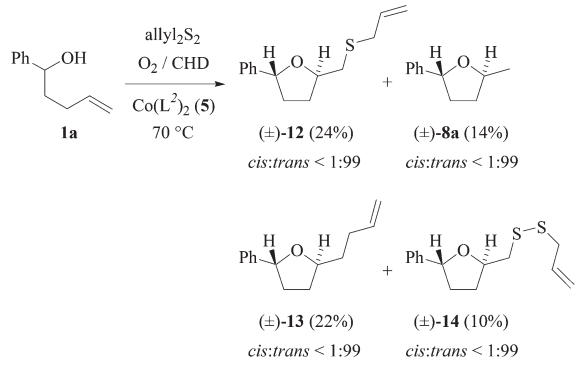
From *cis*-2-allylcyclopentanol **1d** and *cis*-2-allylcyclohexanol **1e** we prepared methylsulfanyl-functionalized oxabicycloalkanes **3d–e** in 71–74% yield along with 10–11% of reduction products **8d–e** (Table 3, entries 1 and 2). The analytical data show that all bicyclic products are formed as single diastereomers, having substituents next to the endocyclic oxygen bound in relative *trans*-configuration to the heterocyclic core.

2.2 Aerobic cobalt-catalyzed oxidation in the presence of disulfides other than dimethyl disulfide. For extending the scope of the new thioether synthesis, we replaced dimethyl disulfide by diethyl disulfide and diallyl disulfide. Oxidation of 1-phenylpentenol **1a** in a 6.7 M solution of diethyl disulfide, containing 1.7 M concentration of CHD and 5 mol% of cobalt complex **5**, provided 36% of ethyl thioether **11** and about the same amount of reduction product **8a** (39%) (Scheme 4).

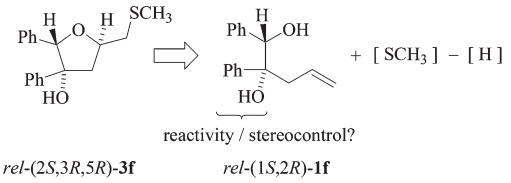
From cobalt-catalyzed oxidation of phenylpentenol **1a** in a solution of diallyl disulfide (4.6 M) and CHD (1.7 M), we isolated allyl thioether **12** (24%), methyl-substituted tetrahydrofuran **8a** (14%), 2-phenyl-5-butenyltetrahydrofuran **13** (22%), and disulfide **14** (10%) (Scheme 5). Butenyl-substituted tetrahydrofuran **13** possibly originates from a sequence of carbon



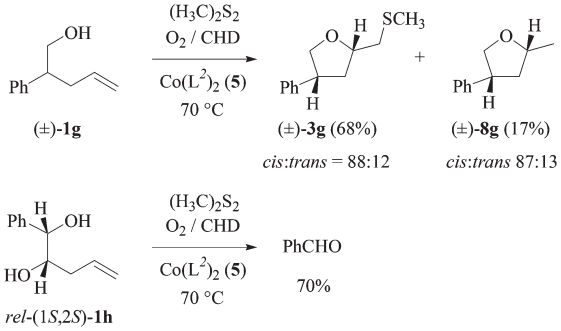
Scheme 4 Termination of cobalt-catalyzed oxidative alkenol cyclization by diethyl disulfide.



Scheme 5 Products of aerobic cobalt-catalyzed alkenol oxidation in the presence of diallyl disulfide.



Scheme 6 Approach to synthesis of a methylsulfanyl-derivative of a potent cyclooxygenase 2-inhibitor[30] *via* stereoselective methylsulfanyl-cyclization of trisubstituted alkenol **1f**.



Scheme 7 Study of the effect of an alkenol substituent in position 2 on the reactivity and selectivity of cobalt-catalyzed oxidation.

radical addition to the terminal alkene carbon in diallyl disulfide, followed by allyldisulfanyl radical elimination. This sequence is mechanistically similar to the pathway reported for carbon radical allylation by allylphenylsulfide,[28,29] and furthermore explains the origin of mixed disulfide **14** as the putative combination product of the allyldisulfanyl radical and the phenyltetrahydrofurylmethyl radical **2a**.

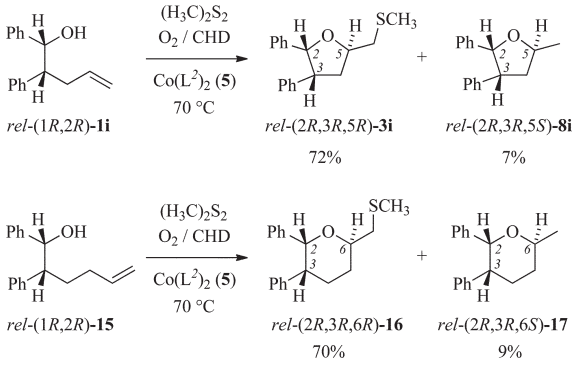
Attempts to prepare the *tert*-butylsulfanyl derivative of **3a** from phenylpentenol **1a**, cobalt-catalyst **5**, di-(*tert*-butyl) disulfide (4.7 M), and cyclohexa-1,4-diene (0.9 M) exclusively provided *trans*-2-phenyl-5-methyltetrahydrofuran (**8a**), and therefore was not further pursued. Considering the underlying mechanism of competitive carbon radical-trapping by CHD and a dialkyl disulfide, we think that homolytic substitution at di-(*tert*-butyl) disulfide is too slow to notably compete with hydrogen atom trapping from CHD.

3 Application in synthesis

To use the potential of the new oxidation/homolytic substitution-cascade in synthesis, we chose 2,3,3,5-tetrasubstituted tetrahydrofuran **3f** as the target. The ethylsulfanyl derivative of this product is a potent cyclooxygenase 2-inhibitor,[30] which was prepared in three steps from the underlying alkenol *via* iodocyclization, separation of the 20/80-mixture of *cis*/*trans*-diastereomers, and substitution of ethylthiolate for iodide. Our objective in synthesis of compound **3f** was to (i) apply the outstanding 2,5-*trans*-stereoselectivity for tetrahydrofuran formation of the cobalt-catalyzed alkenol cyclization, (ii) avoid the iodocyclization step, and (iii) prepare the methylsulfanyl-functionalized derivative (Scheme 6), which for uncommented reasons had not been included in the cyclooxygenase structure–activity survey.[30]

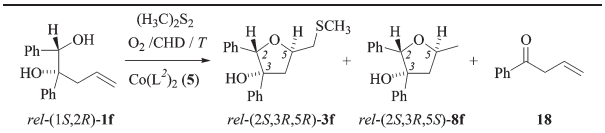
To approach target molecule **3f**, we addressed at first the effects of a phenyl and a hydroxyl group in position 2 in oxidative 4-pentenol ring closures, conducted in dimethyl disulfide. 2-Phenylpent-4-en-1-ol (**1g**) provides under such conditions 2-phenyl-4-(methylsulfanyl)methyltetrahydrofuran (**3g**) as the major product, along with a minor fraction of reduction product **8g** (Scheme 7, top). Both products were obtained as an 88/12-mixture of *cis*/*trans*-stereoisomers, which is in line with previous findings and a general stereochemical guideline for this chemistry.[17] Attempts to oxidize *rel*-(1*S*,2*S*)-1-phenyl-4-pentene-1,2-diol *rel*-(1*S*,2*S*)-(**1h**) under standard conditions furnished exclusively benzaldehyde (Scheme 7, bottom). From this information we concluded that aerobic oxidation catalyzed by cobalt complexes is able to selectively break the central carbon–carbon bond of a glycol. This phenomenon is currently under investigation in our laboratory.

To explore the effects of cumulative phenyl substitution on selectivity in methylsulfanyl-cyclization, we oxidized *rel*-(1*R*,2*R*)-1,2-diphenylpentenol *rel*-(1*R*,2*R*)-**1i** and the higher homologue, *rel*-(1*R*,2*R*)-1,2-diphenylhexenol *rel*-(1*R*,2*R*)-**15** in solutions of dimethyl disulfide and CHD. From both reactions, we isolated substantial yields (70–72%) of diastereomerically pure methylsulfanyl-cyclized products **3i** and **16**, and minor amounts of reduced products **8i** and **17**. All the cyclic ethers have substituents next to endocyclic oxygen attached in relative *trans*-configuration to the heterocyclic core (Scheme 8).



Scheme 8 Oxidations of 1,2-*like*-configured alkenols catalyzed by cobalt(II)-complexes.

Table 4 Products of aerobic alkenediol-oxidation in solutions of CHD and dimethyl disulfide



Entry	*T*/°C	**2f**/%	**7f**/%	**18**/%
1	70	22	11	40
2	60	67	10	9

With an extension of the cobalt method to tetrahydropyran synthesis we encountered an interesting stereochemical question. In tetrahydrofuran, 2,5-*trans*-configuration of substituents is thermochemically favored.[23] In tetrahydropyran, 2,6-*trans*-configuration places one of the carbon substituents into axial position, which is thermochemically disfavored.[31] Since tetrahydropyrans **16** and **17** are the only examples of 6-*exo*-alkenol cyclization from cobalt-catalyzed aerobic oxidation so far, we have no explanation of the origin of this selectivity.

With the necessary information at hand to finalize the project, we oxidized *rel*-(1*S*,2*R*)-1,2-diphenylpenten-1,2-diol *rel*-(1*S*,2*R*)-(**1f**) in a solution of dimethyl disulfide/CHD at lower temperature for preventing glycol cleavage as effectively as possible. From an oxidation performed at 60 °C, we isolated by chromatography 67% of stereochemically pure 2,3,3,5-tetrasubstituted tetrahydrofuran **3f** and 10% of reduction product **8f**, both showing 2,5-*trans*-configuration (Table 4, entry 2). From the reaction mixture, we further isolated 9% of phenylpropenyl ketone **18**, which is the major product from an oxidation conducted at 70 °C (Table 4, entry 1).

Concluding remarks

Methylsulfanyl-cyclization is a new approach to stereoselective synthesis of tetrahydrofurans bearing a methylthioether functional group in the side chain next to the endocyclic oxygen. The mechanism follows the scheme put forward to explain other oxidative alkenol cyclizations mediated by cobalt-activated dioxygen, and uses homolytic methylsulfanyl transfer to tetrahydrofuryl-2-methyl radicals as a new conclusive step.

The oxidation/homolytic substitution-cascade is particularly useful in constructing 2,5-*trans*-configured tetrahydrofurans, as exemplified by synthesis of diastereomerically pure 2,5-di-, 2,3,5-tri-, and 2,3,3,5-tetrasubstituted cyclic ethers. In view of the ease, intermediates and products along the sequence can be oxidized, it is worth to emphasize that we never found alkyl hydroperoxides, sulfoxides, or sulfones as side products. We relate this noteworthy chemoselectivity to the reductant cyclohexa-1,4-diene, originally added to maintain reactivity and selectivity in the catalytic cycle by *in situ* reducing cobalt(III) to cobalt(II).

Cyclohexa-1,4-diene, combined with a fluoro-substituted cobalt(II)-catalyst of the type **5**, furthermore opens new aspects in this chemistry, as shown by the synthesis of a trisubstituted tetrahydropyran from a 5-hexenol. We have attempted the oxidative 6-*exo*-cyclization many times before and always failed. The success described in this article possibly arises from the ability of cyclohexa-1,4-diene to balance selectivity in oxidative and reductive steps in a more appropriate manner than previously used reductants.

The tetrahydropyran synthesis described in this article suggests that the concept of oxidation/homolytic substitution-cascade possibly extends to the synthesis of larger heterocycles, or intermolecular carbon–oxygen bond formation. Both questions are being addressed at the moment in our laboratory.

Experimental

1 General

For general laboratory practice and instrumentation see ref. 18 and the ESI.†

2 Cobalt complexes

A solution of 4-fluorobenzoylacetone (367 mg, 2.04 mmol) in EtOH (5 mL) was poured into an aqueous solution (15 mL) of cobalt acetate tetrahydrate (250 mg, 1.00 mmol). The yellow precipitate was filtrated and dried. Bis-[1-(4-fluorophenyl)-3-(oxo-κ*O*)-but-1-en-1(olato-κ*O*)]cobalt(II)dihydrate (**5**): Yield: 381 mg (841 mmol, 84%), yellow solid. ν_{max} (KBr)/cm^{-1} 3391 (OH), 1603 (CO), 1572, 1523, 1499, 1417, 1388, 1297, 1233, 1157, 1163, 1110, 1011; δ_F ($CDCl_3$–acetone, 377 MHz) −112.0. Found C, 53.33; H, 4.92. $C_{20}H_{20}CoF_2O_6$ (453.30) requires C, 52.99; H, 4.45%. ESI-MS: Found: 439.99 [$CoL^2{}_2$ + Na^+], $C_{20}H_{16}CoF_2NaO_4$ requires 440.02.

3 Aerobic oxidation reactions

3.1 Oxidation of 1-phenylpent-4-en-1-ol (1a). A solution of alcohol **1a** (163 mg, 1.01 mmol) and cobalt catalyst **5** (22.9 mg, 50.5 μmol) in dimethyl disulfide (9.5 mL) and CHD (1.0 mL) was stirred at 70 °C for 6 h while being exposed to the

laboratory atmosphere. The reaction mixture was cooled to 20 °C and concentrated under reduced pressure to afford a residue that was purified by column chromatography [SiO_2, Et_2O–pentane = 1 : 10 (v/v)]. *trans*-2-Methyl-5-phenyltetrahydrofuran (**8a**). Yield: 16.2 mg (100 μmol, 10%). Analytical data agree with published values.[32] *trans*-2-(Methylsulfanyl)-methyl-5-phenyltetrahydrofuran (**3a**). Yield: 151 mg (726 μmol, 72%), R_f 0.50 [SiO_2, acetone–pentane = 1 : 5 (v/v)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.84–1.94 (2 H, m), 2.20–2.25 (1 H, m), 2.22 (3 H, s, Me), 2.39–2.43 (1 H, m), 2.70 (1 H, dd, *J* 13.3, 6.7), 2.82 (1 H, dd, *J* 13.3, 5.4), 4.45 (1 H, quin, *J* 6.4), 5.07 (1 H, t, *J* 6.9), 7.25–7.27 (1 H, m), 7.33–7.36 (4 H, m). NOESY 2-H || 5-H. δ_C (100 MHz, $CDCl_3$) 16.5 (CH_3), 31.7, 35.2, 39.6, 79.2, 80.8, 125.5, 127.1, 128.3, 143.3. GC-MS (EI, 70 eV) *m*/*z* (%) 208 (39, M^+), 147 (100), 129 (63), 117 (20), 105 (31), 91 (94), 77 (25). HRMS (EI^+) *m*/*z* 208.0921 (M^+); calculated mass for $C_{12}H_{16}OS^+$: 208.0922.

3.2 Oxidation of *rel*-(1*S*,2*R*)-1,2-diphenylpent-4-en-1,2-diol (1f). A solution of alcohol **1f** (127 mg, 500 μmol) and cobalt catalyst **5** (11.5 mg, 25.4 μmol) in dimethyl disulfide (5.0 mL) and CHD (0.5 mL) was stirred at 60 °C for 5 h while being exposed to the laboratory atmosphere. The reaction mixture was cooled to 20 °C and concentrated under reduced pressure to afford an oily residue that was purified by column chromatography [SiO_2, Et_2O–pentane = 1 : 10 (v/v)]. *rel*-(2*S*,3*R*,5*S*)-5-Methyl-2,3-diphenyltetrahydrofuran-3-ol (**8f**). Yield: 12.9 mg (50.7 μmol, 10%), R_f 0.42 [SiO_2, acetone–pentane = 1 : 5 (v/v)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.49 (3 H, d, *J* 6.1), 1.74 (1 H, d, *J* 1.8, OH), 2.21–2.27 (1 H, m), 2.52 (1 H, dd, *J* 12.9, 5.5), 4.76–4.83 (1 H, m), 5.40 (1 H, s), 7.03–7.07 (2 H, m), 7.24–7.26 (3 H, m), 7.28–7.31 (1 H, m), 7.37 (2 H, t, *J* 7.7), 7.40–7.44 (2 H, m). δ_C (100 MHz, $CDCl_3$) 21.5, 50.9, 75.2, 83.5, 90.0, 125.3, 126.6, 127.1, 128.1, 128.26, 128.29, 136.0, 142.1. GC-MS (EI, 70 eV) *m*/*z* (%) 254 (<1, M^+), 236 (13), 193 (10), 178 (6), 165 (8), 148 (88), 133 (65), 115 (23), 105 (100), 91 (8), 77 (65). HRMS (EI^+) *m*/*z* 254.1312 (M^+); calculated mass for $C_{17}H_{18}O_2^+$: 254.1307. *rel*-(2*S*,3*R*,5*R*)-5-(Methylsulfanyl)-methyl-2,3-diphenyltetrahydrofuran-3-ol (**3f**). Yield: 100 mg (334 μmol, 67%), R_f 0.37 [SiO_2, acetone–pentane = 1 : 5 (v/v)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.78 (1 H, s, OH), 2.26 (3 H, s, CH_3), 2.56 (1 H, d, *J* 7.4), 2.88–2.99 (1 H, m), 4.86–4.94 (1 H, m), 5.45 (1 H, s), 7.05 (2 H, dd, *J* 6.3, 2.7), 7.23–7.32 (4 H, m), 7.38 (2 H, t, *J* 7.4), 7.42–7.46 (2 H, m). NOESY 2-H || 5-H. δ_C (150 MHz, $CDCl_3$) 16.9 (Me), 39.7, 47.9, 78.4, 83.2, 89.5, 125.3, 126.6, 127.2, 128.27, 128.34, 135.5, 141.7. GC-MS (EI, 70 eV) *m*/*z* (%) 300 (<1, M^+), 234 (3), 221 (8), 192 (8), 147 (17), 115 (10), 105 (100), 91 (8), 77 (33). HRMS (EI^+) *m*/*z* 282.1090 ($M^+ - H_2O$); calculated mass for $C_{18}H_{18}OS^+$: 282.1078.

3.3 Oxidation of *rel*-(1*R*,2*R*)-1,2-diphenylhex-5-en-1-ol (15). A solution of alcohol **15** (169 mg, 669 μmol) and cobalt catalyst **5** (15.1 mg, 33.3 μmol) in dimethyl disulfide (6.6 mL) and CHD (0.65 mL) was stirred at 70 °C for 16 h while being exposed to the laboratory atmosphere. Another batch of cobalt catalyst **5** (15.2 mg, 33.5) and CHD (0.65 mL) were added and the reaction mixture was stirred for another 6 h at 70 °C. The reaction mixture was cooled to 20 °C and concentrated under reduced pressure to afford a residue that was purified by column chromatography [SiO_2, Et_2O–pentane = 1 : 10 (v/v)]. *rel*-(2*R*,3*R*,6*S*)-6-Methyl-2,3-diphenyltetrahydropyran (**17**). Yield: 15.4 mg (61.0 μmol, 9%), R_f 0.56 [SiO_2, acetone–pentane = 1 : 5 (v/v)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.21 (3 H, d, *J* 6.1), 1.39–1.49 (1 H, m), 1.58–1.68 (1 H, m), 1.85–2.00 (1 H, m), 3.92 (1 H, d, *J* 8.4), 4.09 (1 H, quind, *J*(quin) 7.9, J_d 6.1), 4.76 (td, J_t 8.4, J_d 6.2), 7.14–7.19 (2 H, m), 7.23–7.29 (6 H, m), 7.33–7.37 (1 H, m). δ_C (100 MHz, $CDCl_3$) 21.4, 31.6, 33.6, 57.0, 75.3, 80.4, 126.1, 126.3, 128.2, 128.4, 128.6, 128.7, 142.8, 143.1. GC-MS (EI, 70 eV) *m*/*z* (%) 252 (<1, M^+), 178 (3), 165 (17), 152 (7), 115 (5), 85 (100), 77 (3). HRMS (EI^+) *m*/*z* 252.1515 (M^+); calculated mass for $C_{18}H_{20}O$: 252.1514. *rel*-(2*R*,3*R*,6*R*)-6-(Methylsulfanyl)-methyl-2,3-diphenyltetrahydropyran (**16**). Yield: 134 mg (450 μmol, 67%), R_f 0.51 [SiO_2, acetone–pentane = 1 : 5 (v/v)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.57–1.72 (2 H, m), 1.84–1.93 (1 H, m), 1.95–2.04 (1 H, m), 2.09 (3 H, s, CH_3), 2.55 (1 H, dd, *J* 13.3, 7.2), 2.69 (1 H, dd, *J* 13.3, 5.1), 3.92 (1 H, d, *J* 8.1), 4.16 (1 H, quin, *J* 6.6), 4.75 (1 H, td, J_t 8.1, J_d 6.0), 7.13–7.19 (2 H, m), 7.21–7.28 (6 H, m), 7.32–7.36 (2 H, m). NOESY 2–H ↔ 3-H, 2-H || 6-H, 3-H || 6-H. δ_C (100 MHz, $CDCl_3$) 16.4 (Me), 31.2, 31.3, 39.3, 56.8, 79.1, 81.1, 126.1, 126.3, 128.1, 128.3, 128.5, 128.7, 142.4, 142.9. GC-MS (EI, 70 eV) *m*/*z* (%) 298 (<1, M^+), 237 (1), 193 (5), 178 (5), 165 (21), 152 (12), 131 (100), 115 (8), 103 (20), 87 (20). HRMS (EI^+) *m*/*z* 298.1384 (M^+); calculated mass for $C_{19}H_{22}OS$: 298.1391.

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5 Tetrahydropyrane und intermolekulare Kupplungen

5.1 Zusammenfassung

Mit Hilfe des Benzoyltrifluoraceton-abgeleiteten Cobalt-Komplexes und unter Verwendung von CHD als H-Atom-Donor konnten verschiedene einfach und zweifach substituierte Tetrahydropyrane aus den entsprechenden 1-Hexenolen dargestellt werden. Das Prinzip der radikalischen Funktionalisierung, z.B. durch bromierende oder alkylierende Terminierung ist auch in Tetrahydropyransynthesen anwendbar. Die Cyclisierungen verlaufen 2,6-*trans*- und 2,5-*trans*-selektiv. 1,2-*like*- und 1,3-*like*-konfigurierte Alkenole begünstigen den Ringschluss und steigern das *cis*:*trans*-Verhältnis auf <1:99. Aus den beobachteten Selektivitäten konnte ein stereochemisches Modell für die Cyclisierung abgeleitet werden. Das der Methode zugrunde liegende allgemeinen Reaktionsprinzip konnte für die Synthese offenkettiger Ether in intermolekularen Kupplungen von Alkoholen mit Alkenen genutzt werden.

5.2 Hintergrund, Zielsetzung und Strategie

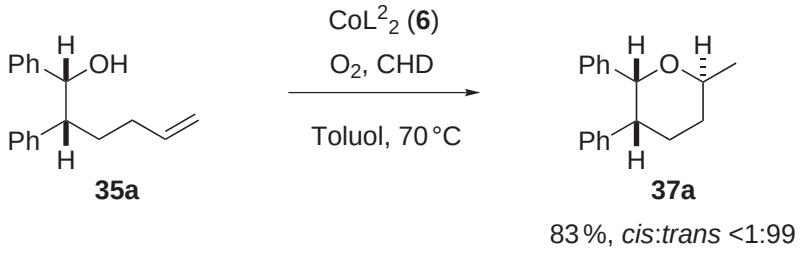
Tetrahydropyrane sind, ähnlich wie Tetrahydrofurane, wichtige Strukturmotive in zahlreichen Naturstoffen. Den einfachsten Zugang zu dieser Stoffklasse bietet die Cyclisierung von 5-Hexenolen. Durch Oxidation der C,C-Doppelbindung mit Hilfe von Lewis-Säuren[1], Halogenen[2], Metall-Oxo[3] und Metall-Peroxo-Verbindungen[4] kann der Angriff des nucleophilen Sauerstoff und somit die Bildung des Tetrahydropyran-Gerüstes ermöglicht werden. Der Ringschluss wird hierbei mit mäßigerer facialer Selektivität vollzogen. Diese ist auf eine sesselförmige Konformation der Kette beim Ringschluss zurückzuführen, bei der eine äquatoriale Anordnung der Substituenten entlang der Kette zur bevorzugten Bildung von 2,3-*trans*, 2,4-*cis*, 2,5-*trans* und 2,6-*cis*-konfigurierten Molekülen führt. Beim Blick auf die verfügbaren Methoden, Tetrahydropyrane mit höherer Stereoselektivität aufzubauen,[5, 6, 7] fällt auf, dass bis auf die Diencyclisierung[8] kaum ein Verfahren der bekannten Tetrahydrofuransynthesen in der Lage ist, höhere Homologe der Ausgangsverbindungen zu den entsprechenden Tetrahydropyranen umzusetzen. Frühere Versuche deuteten darauf hin, dass auch die Cobalt-Methode in diese Gruppe einzuordnen sei.[9] In der Studie zur Synthese Methylsulfanyl-substituierter Tetrahydrofurane hatte sich jedoch gezeigt, dass die Bildung von Tetrahydropyranen ausgehend von Hexenolen unter bestimmten Bedingungen doch möglich ist. Diese Entdeckung gab den Anstoß für ein darauf aufbauendes Projekt mit den folgenden Zielsetzungen:

- Entwicklung eines stereochemischen Modells, das auf Basis beobachteter Selektivitäten bei der Cobalt-katalysierten Oxidation von Hexenolen Voraussagen für zukünftige Cyclisierungen erlaubt und erklärt, unter welchen Bedingungen Tetrahydropyransynthesen möglich sind.
- Erschließung des für die Cobalt-Methode bisher unbekannten Bereichs der intermolekularen Reaktionen durch die Synthese nicht-cyclischer Ether ausgehend von Alkoholen und Alkenen.

5.3 Ergebnisse und Diskussion

5.3.1 Der Selektivität auf der Spur

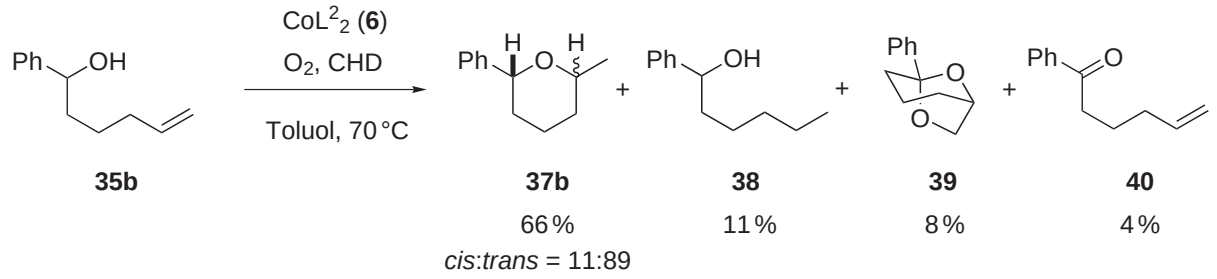
Das aus dem vorangegangenen Projekt bekannte *like*-1,2-Diphenylhex-5-en-1-ol (**35a**) ist in der Lage, in einer aeroben Cobalt-katalysierten Reaktion hoch stereoselektiv zu *rel*-(2*R*,3*R*,6*S*)-6-Methyl-2,3-diphenyltetrahydropyran (**37a**) umgesetzt zu werden. Die Reaktion verläuft schnell und ohne Bildung nachweisbarer Nebenprodukte (Schema 5.1).



Schema 5.1: 1,2-*like*-konfigurierte Hexenole werden *trans*-selektiv zu den entsprechenden Tetrahydropyranen umgesetzt.

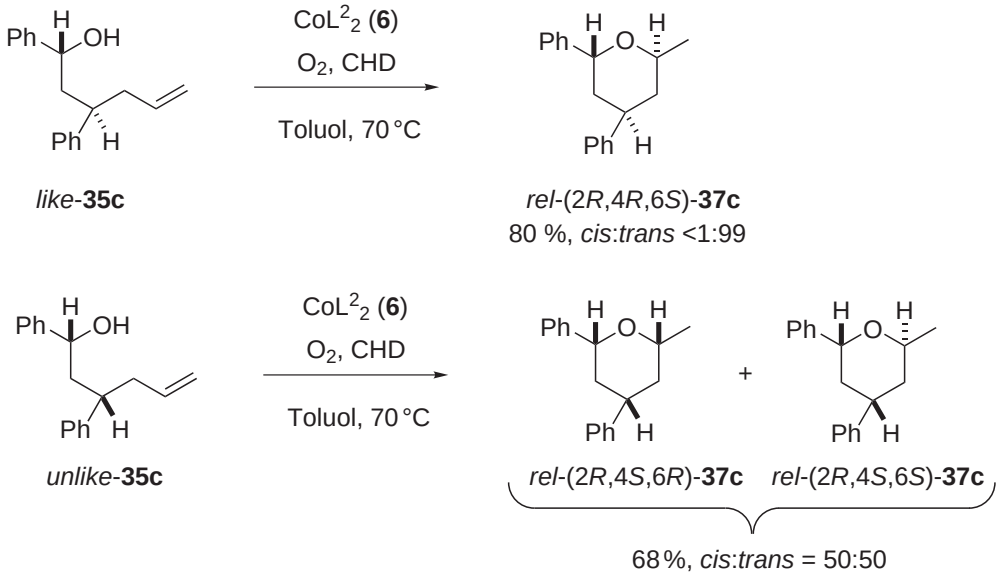
In einer von Müller durchgeführten Studie[10] zur Oxidation einfach substituierter Hexenole konnte gezeigt werden, dass Substituenten in Position 1 und 2 einen *trans*-selektiven Ringschluss begünstigen. Der im Vergleich zum 5-*exo*-Ringschluss entsprechend substituierter Pentenole langsame 6-*exo*-Ringschluss[11] wird von der Bildung verschiedener Nebenprodukte begleitet, die aus bekannten, durch Cobalt(II) katalysierte Prozessen, z.B. Hydrierung der Doppelbindung (Alkanol **38**) oder Autoxidation (Alkenon **40**) hervorgehen (Schema 5.2).[12, 13]

Wie an der unterschiedlichne Reaktivität der Alkenole **35a** und **35b** abzulesen ist, unterstützt ein zweiter Substituent die Cyclisierung. Durch die offensichtlich höhere Reaktionsgeschwindigkeit wird die Bildung von Nebenprodukten vollständig unterdrückt. Eine nähere



Schema 5.2: Die Oxidation von 1-Phenylhex-5-en-1-ol (**35b**) erfolgt unter Bildung von Nebenprodukten.[10]

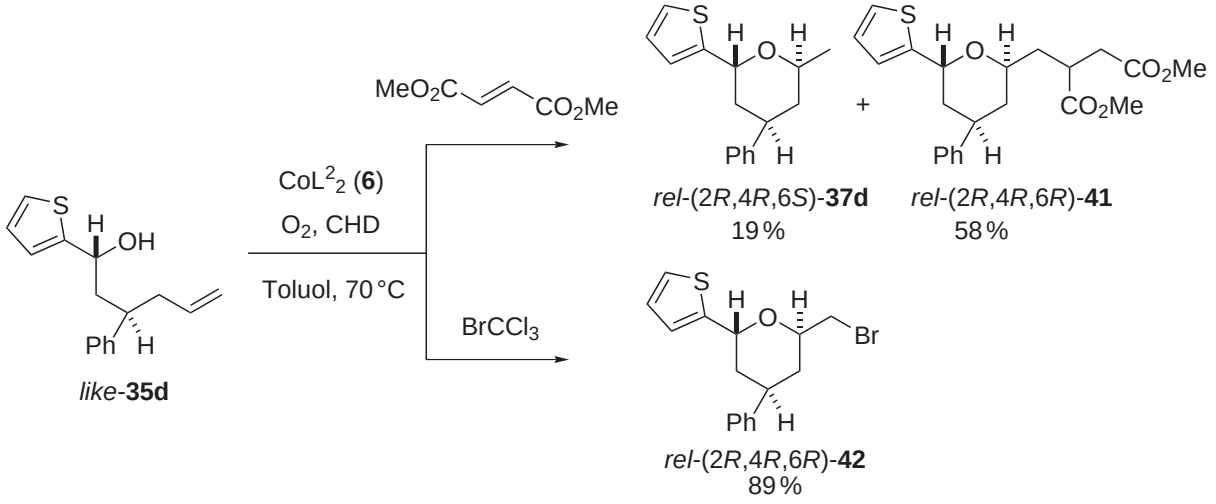
Untersuchung der Effekte, die ein zweiter Substituent ausübt, wurde an der synthetisch leicht zugänglichen Gruppe der 1,3-disubstituierten Hexenole durchgeführt. Diese Reihe von Alkenolen zeigte in aeroben Cobalt-katalysierten Oxidationen ein auffälliges Verhalten: Während 1,3-*like*-konfigurierte Alkenole selektiv nur ein isomerenreines Produkt (2,6-*trans*, 4,6-*cis*) lieferten, wurden im Falle von 1,3-*unlike*-konfigurierten Alkenolen stets 1:1-Mischungen von 2,6-*cis* und 2,6-*trans*-Tetrahydropyranen erhalten (Schema 5.3). Die beobachtete Selektivität ist dabei von polaren Effekten des Substituenten in Position 1 unabhängig und gilt gleichermaßen für Thienyl-, Phenyl-, Difluorphenyl und Pentafluorphenyl-substituierte Hexenole.



Schema 5.3: Die Selektivität des Ringschlusses ist bei 1,3-disubstituierten Hexenolen abhängig von ihrer relativen Konfiguration.

Neben der reduktiven Terminierung durch H-Atom-Einfang kann die Oxidation von Hexenolen zur Darstellung synthetisch interessanter Verbindungen auch bromierend[14] oder alkylierend[15] terminiert werden. Diese, in vorangegangenen Projekten für die Pentenol-Oxidation entwickelten Methoden der Terminierung, können auch in der Synthese von Te-

trahydropyranen angwendet werden und verlaufen im Vergleich zu reduktiver Terminierung mit identischer facialer Selektivität. Auch die aus der Produktverteilung ablesbare Chemoselektivität im Falle der Reaktion mit Dimethylfumarat entspricht der für die Oxidation von Pentenolen (Schema 5.4).



Schema 5.4: Die Möglichkeit der Darstellung funktionalisierter Tetrahydropyrane konnte am Beispiel der bromierenden und der alkylierenden Terminierung gezeigt werden.

Diese Ergebnisse zeigen, dass der Teilschritt der radikalischen Funktionalisierung für die Umsetzung von Pentenolen und Hexenolen identisch verläuft. Bestimmend ist also nur die Reaktivität des freien Radikals: In diesem Stadium spielen Konfiguration und Zusammensetzung des ursprünglichen Alkenols sowie die Art des verwendeten Cobalt-Komplexes keine Rolle mehr. Das Ergebnis zeigt auch, dass der Mechanismus, nach dem Pentenole und Hexenole umgesetzt werden, der gleiche sein muss und gegebenenfalls auf alle Reagenzkombinationen von Alkoholen und Alkenen anwendbar ist.

5.3.2 Entwicklung eines Stereochemischen Modells

Auf Basis der erhaltenen Daten aus Pentenol- und Hexenol-Cyclisierungen war es nun möglich, ein allgemein gültiges stereochemisches Modell für die aerobe Cobalt-katalysierte Oxidationen abzuleiten. Diesem Modell nach zufolge verläuft die Cyclisierung von Hexenolen über einen sesselförmigen Übergangszustand. Die terminale Vinylgruppe weist dabei in Richtung des Cobalt-Zentrums, während ein Substituent in Position 1 des Alkenols in pseudoaxialer Orientierung vorliegt. Diese Ausrichtung ist die Grundlage für einen raschen und *trans*-selektiven Ringschluss. Substituenten in Position 2 und 3 unterstützen diese Ausrichtung, wenn sie pseudoäquatorial orientiert sind: Dies ist bei 1,2-*like*- und 1,3-*like*-konfigurierten Hexenolen der Fall (Abb. 5.1).

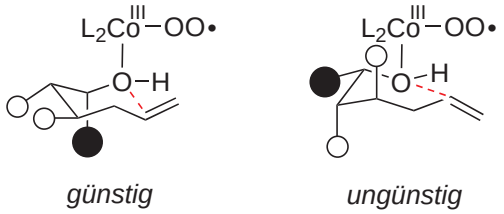


Abbildung 5.1: Stereochemisches Modell für die Cyclisierung von Hexenolen.

Eine für die Cyclisierung ungünstige Situation liegt hingegen im Falle von 1,3-*unlike*-konfigurierten Hexenolen vor: Sind beide Substituenten pseudoäquatorial orientiert, wird der Ringschluss *cis*-selektiv vollzogen. Trotz der thermodynamischen Begünstigung durch die äquatoriale Anordnung beider Substituenten ist diese Ausrichtung ungeeignet für den Ringschluss: Der Substituent in Position 1 weist dann in den Raum, der gegebenenfalls von den Liganden am Cobalt-Zentrum eingenommen wird, während die terminale Vinylgruppe vom Cobalt-Zentrum weg weist. Die umgekehrte Anordnung der Alkenol-Kette begünstigt den Ringschluss, der dann *trans*-selektiv verläuft. Die pseudoaxiale Orientierung beider Substituenten ist jedoch thermodynamisch ungünstig. Sind beide Substituenten Phenyl-Reste, halten sich die genannten Effekte die Waage und eine 1:1-Mischung von 2,6-*cis*- und 2,6-*trans*-Tetrahydropyran wird gebildet.

Ebenso können mit diesem Modell die beobachteten Selektivitäten bei der Oxidation von Pentenolen erklärt werden: Eine pseudoäquatoriale Anordnung der möglichen Substituenten entlang der Kette führt zu den bekannten 2,5-*trans*, 2,4-*cis*- und 2,3-*trans*-Selektivitäten[9, 14](Abb 5.2). Aufgrund der geringeren Kettenlänge scheint in diesem Falle die pseudoäquatoriale Orientierung des Substituenten in Position 1 nicht zu einer sterischen Hinderung durch die Liganden zu führen.

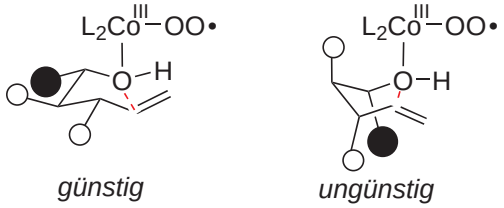
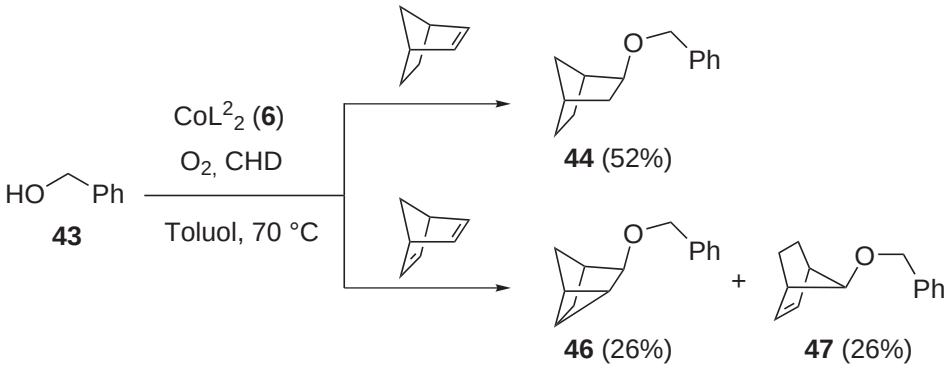


Abbildung 5.2: Stereochemisches Modell für die Cyclisierung von Pentenolen.

5.3.3 Intermolekulare Reaktionen

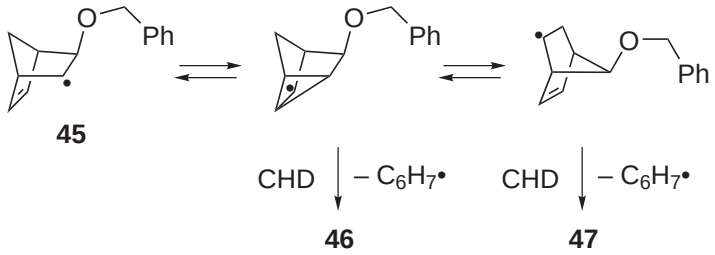
Die Umsetzung von Hexenolen in aeroben Cobalt-katalysierten Oxidationen hatte gezeigt, dass unter den richtigen Voraussetzungen auch die im Vergleich zur Fünfringbildung langsame 6-*exo*-Cyclisierung in der Cobalt-Methode genutzt werden kann. Mit diesem Ergebnis

war es erstmals möglich, den Mechanismus der Reaktion auf ein einfaches, allgemeingültiges Prinzip zurückzuführen: Wenn ein Alkohol an das Cobalt-Zentrum koordiniert wird und eine C,C-Doppelbindung in räumliche Nähe gebracht werden kann, können beide Einheiten unter Ausbildung einer neuen C,O-Bindung und Bildung eines C-Radikals in α-Position zur neu geküpften Bindung modifiziert werden. Die Gültigkeit dieses Prinzips ließ sich mit der intermolekularen Kupplung von Alkoholen und Alkenen verdeutlichen: Die Reaktion von Benzylalkohol **43** mit Norbornen liefert *exo*-2-Benzyloxynorbornan (**44**) in 52% Ausbeute (Schema 5.5).



Schema 5.5: Intermolekulare Kupplung von Benzylalkohol mit den Alkenen Norbornen und Norbornadien.

Ersetzt man Norbornen durch Norbornadien, werden statt des erwarteten *exo*-2-benzyloxy-5-norbornen das Tricylan-Derivat **46** und die zum erwarteten Produkt regioisomere Verbindung **47** zu gleichen Anteilen gebildet. Dieses Produktbild ist nur dann erklärbar, wenn man ein intermediär vorliegendes Radikal **45** annimmt. Dieses befindet sich in einem Gleichgewicht von Umlagerungen,[16] aus dem die Produkte **46** und **47** durch reduktive Terminierung hervorgehen können (Schema 5.6).



Schema 5.6: Ein Gleichgewicht von Umlagerungen führt zu den boebachteten Produkten **46** und **47**.

An diesem Beispiel lässt sich erkennen, dass auch die intermolekulare Kupplung über radikalische Zwischenstufen und somit nach dem grundsätzlich gleichen Mechanismus

wie die Cyclisierung von Pentenolen und Hexenolen verläuft. Das Auftreten von Nebenprodukten bei solchen Reaktionen (im Falle von Kupplungen mit Benzylalkohol ist es vor allem die Oxidation zu Benzaldehyd) macht aber deutlich, dass der Reaktionspfad der C,O-Bindungsknüpfung nur einer von mehreren möglichen ist, und gibt Anlass zu weitergehender Forschung auf diesem Gebiet.

5.4 Ausblick

Die kontinuierliche und erfolgreiche Weiterentwicklung der Cobalt-Methode von der Oxidation von Pentenolen hin zur Oxidation von Hexenolen und schließlich der intermolekularen Kupplung von Alkenen und Alkoholen verdeutlicht, dass der Methode ein Prinzip zugrunde liegt, das auch Anwendungsmöglichkeiten jenseits der Heterocyclensynthese bietet. Die Frage, ob die intermolekulare Kupplung stereoselektiv verlaufen kann und wie die Selektivität in diesen Fällen gesteuert werden kann, werden zukünftige Untersuchungen an geeigneten Substraten zeigen. Aber auch andere Reaktionspfade, wie die Bildung der Nebenprodukte **38**–**40**, die bei der Oxidation einfach substitierter Hexenole auftreten, oder die Fragmentierung der Alkendiole **7c** und **7d**, sind Gegenstand weiterer Untersuchungen, die zu einem besseren Verständnis der Abläufe in Cobalt-katalysierten Oxidation beitragen werden.

5.5 Forschungsartikel

Stereoselective Synthesis of Sidechain-Functionalized Tetrahydropyrans from 5-Hexenols

Patrick Fries, Melanie Kim Müller, Jens Hartung, *Tetrahedron (zur Veröffentlichung eingereicht).*

Stereoselective Synthesis of Sidechain-Functionalized Tetrahydropyrans from 5-Hexenols

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Keywords: Addition; Aerobic oxidation; Alkenol; Alkene; Bromocyclization; Catalysis; Dioxygen; Cobalt(II) complexes; Michael acceptor; Radical; Stereoselective synthesis, Tetrahydropyran.

Abstract: Trihomoallylic alcohols (5-hexenols) furnish constitutionally dissymmetric α-methyltetrahydropyrans, when treated with air in solutions of cyclohexa-1,4-diene (CHD) and a cobalt(II) bis(β-diketonate)-catalyst. The reaction is a two-step cascade providing tetrahydropyranyl-2-methyl radicals from oxidative 6-exo-trig cyclizations and subsequently products of selective carbon radical trapping. In solutions of bromotrichloromethane, 5-hexenols according to this sequence are converted into 6-bromomethyltetrahydropyrans in up to 89% yield. Three component reactions between dimethyl fumarate, CHD, and a 5-hexenol furnish under similar conditions α-tetrahydropyranyl-2-methyl succinates as major (57–58%) and substituted α-methyltetrahydropyrans as minor products (19–21%). Cobalt-catalyzed tetrahydropyran syntheses from 5-hexenols occur 2,6-trans-, 2,5-trans-, and 2,4-cis-selectively, as exemplified by synthesis of diastereomerically pure 2,3,6- and 2,4,6-substituted tetrahydropyrans from 1,2- and 1,3-*like*-disubstituted 5-hexenols.

1. Introduction

Constitutionally dissymmetric tetrahydropyrans occur widely in nature. The ether nucleus thereby in secondary metabolites arises from oxidative cyclization of terpenols,[1,2] acetogenins,[3] and polyketides.[4,5] Terminal oxidants to bringing about the alkenol cyclization are dioxygen and hydrogen peroxide, activated by metal co-factors of oxidative enzymes.[6,7] The protein serves as auxiliary for the metal co-factor and as template for folding the alkenol and controlling facial selectivity for oxygen atom transfer to the carbon-carbon double bond.[8,9]

In organic synthesis, as in nature, the standard approach for preparing constitutionally dissymmetric tetrahydropyrans is the 5-hexenol cyclization.[10,11] In order to add the hydroxyl

oxygen to a non-Michael-type carbon-carbon double bond following to the common nucleophile/electrophile concept, polarity at one of the reacting entities needs to be reverted.

An Umpolung of polarity at oxygen is feasible by converting a hydroxyl oxygen into a radical oxygen.[12] 5-Hexen-1-oxyl radicals, for example, intramolecularly add to non-activated terminal double bonds, providing sidechain functionalized tetrahydropyrans, when trapped with a suitable heteroatom donor. Mechanistically, tetrahydropyran synthesis via oxygen radical cyclization proceeds via chain reactions starting from a suitable alkenoxyl radical progenitor, other than the 5-hexenol.[13]

In the more general synthetic approach to stereoselective synthesis of tetrahydropyrans 5-hexenols are oxidized at the carbon-carbon π-bond, for example, by Lewis acids,[14] molecular halogens,[15,16,17] high-valent transition metal oxo compounds,[18,19] or transition metal peroxido complexes.[20] Such reactions customarily furnish side-chain functionalized tetrahydropyrans as ~70/30-mixtures of stereoisomers, containing the 2,3-trans-, 2,4-cis-, 2,5-trans-, and 2,6-cis-stereoisomer in excess. Diastereomeric ratios of this kind and the degree of diastereoselection arise from conformational interplay between substituents and a chair-like folded alkenol chain, as the hydroxyl oxygen and the activated carbon-carbon double bond approach for building the tetrahydropyran nucleus.[21]

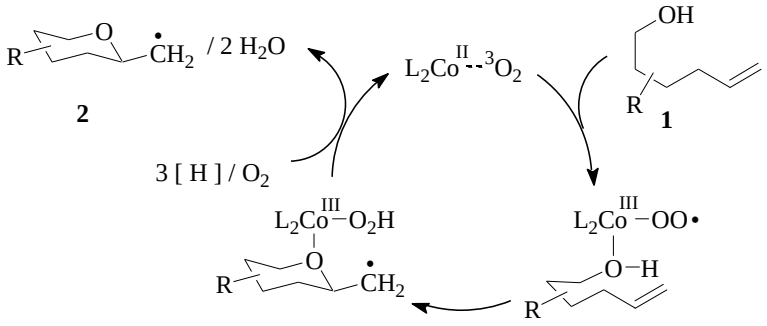
Improving or reverting stereoselectivity in electrophile-induced C,O-cyclizations is feasible by modifying the mechanism from substrate- to auxiliary- or reagent-controlled.[20] In dichloroacetylperrhenate/dichloroacetic anhydride-mediated 5-hexenol cyclizations,[22] or oxidations of 1,6-dienes[23,24] and hept-6-ene-1,2-diols by high-valent transition metal oxo compounds,[25,26] the oxygen atom is transferred in a syn-specific manner from the oxidant to

the π-bond of the twofold coordinated alkenol.[18] This approach furnishes derivatives of *trans*-2,6-bis(hydroxymethyl)-tetrahydropyrans in considerable diastereomeric excess. If used in synthesis of secondary metabolites, this approach evokes additional transform steps for converting a chiral constitutionally symmetric product into a constitutionally dissymmetric bioactive tetrahydropyran.

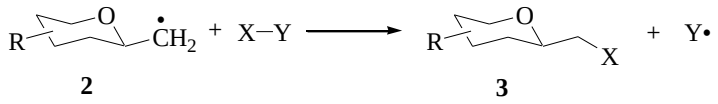
To stereoselectively prepare constitutionally dissymmetric tetrahydropyrans in a new approach, we chose to oxidize 5-hexenols by molecular oxygen in a cobalt-catalyzed reaction.[27,28,29] In the course of a preceding study we unexpectedly observed an instance of 2,6-*trans*-specific 6-*exo*-alkenol cyclization, providing a 2,3,6-substituted sidechain functionalized tetrahydropyran.[30] This finding motivated us to investigate effects exerted by one and two substituents on yields and stereoselectivity of aerobic 5-hexenol cyclizations. Furthermore, we were interested in finding methods for introducing synthetically useful functional groups in the final step of the reaction cascade.

The major results from the study show that 5-hexenols chemoselectively cyclize when treated in solutions of cyclohexa-1,4-diene, toluene, and a cobalt bis-(β-diketonate) complex exposed to air at 70 °C, leading to 2,6-trans-, 2,5-trans-, and 2,4-cis-substituted tetrahydropyrans as major products. Oxidations conducted in solutions of bromotrichloromethane provide 6-bromomethyltetrahydropyrans, as exemplified by synthesis of diastereomerically pure 2,4,6-substituted six-membered ethers from 1,3-*like*-disubstituted 5-hexenols. Three-component reactions between a 5-hexenol, dimethyl fumarate, and cyclohexa-1,4-diene (CHD) furnish side chain extended functionalized tetrahydropyrans in up to 58% yield.

(i) *aerobic 5-hexenol oxidation*



(ii) *tetrahydropyryl-2-methyl radical functionalization*



Scheme 1. Proposed mechanism for tetrahydropyran formation from 5-hexenol **1** in a cascade of aerobic oxidation (step i) and radical functionalization (step ii); [H] = hydrogen atom from, e.g., cyclohexa-1,4-diene (CHD); R = aryl or alkyl; L^- = 1-arylbutane-1,3-dione monoanion (cf. Table 1); X–Y = e.g. CHD or $BrCCl_3$; the dashed line denotes coordinate triplet dioxygen binding to a cobalt(II) bis-(β-diketonate) complex CoL_2 (for structure formulas of CoL_2, refer to section 2.1)

2. Results and Discussion

2.1. Cobalt complexes

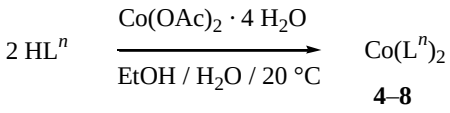
From a screening of catalysts, we selected fluoro-substituted cobalt(II)-bis(β-

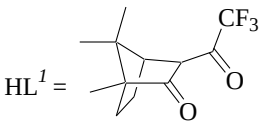
diketonate)-complexes **4**–**8** of the general formula $Co(L^n)_2$ (Table 1) for pursuing the tetrahydropyran project. Compounds **4**, **5**, and **6** were available from a previous study.[28,31] *p*-Fluorophenylbutane-1,3-dione-derived cobalt complexes **7** and **8** were newly prepared by mixing two aliquots of diketones[32] $HL^{4–5}$, and one equivalent of cobalt(II)-acetate tetrahydrate in aqueous ethanol (Table 1, entries 3 and 5). All cobalt compounds were characterized by infrared-spectroscopy, electron spectroscopy (UV/Vis), combustion analysis, ESI-mass spectrometry, and fluorine-19 NMR spectroscopy (Table 1 and Supplementary data).

Cobalt complexes **7** and **8** precipitate as yellow (**7**) to orange (**8**) dihydrates, which were used as such for activating dioxygen in oxidation catalysis. Crystal ethanol or water can be removed by drying, for example, complex **6** at 90 °C under reduced pressure (0.2 mbar), as experimentally verified by disappearance of the OH-stretching mode at ~3400 reciprocal wavenumbers. The anhydrous formulation of **6** is a brown powder, which is similarly active for catalyzing oxidative 5-hexenol cyclization, as the hydrated material.

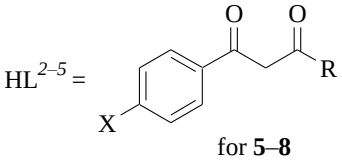
Fluorinated bis-[butane-1,3-dionato(–1)]cobalt(II) complexes **4**–**8** are sparingly soluble at room temperature in cyclohexa-1,4-diene/toluene-mixtures. At temperatures of ~40 °C and above the solutions turn yellow, indicating that cobalt complexes start to dissolve under such conditions. The yellow color changes to green upon contact with air at elevated temperatures. The green color prevails until the reaction is terminated by filtering the solution through a short pad of sodium thiosulfate and magnesium sulfate, for removing cobalt residues and water before analyzing product mixtures by gas chromatography in combination with mass spectrometry.

Table 1. Preparation and spectroscopic characteristics of fluorinated bis-[butane-1,3-dionato(–1)]-cobalt(II) complexes





for **4**



for **5**–**8**

entry	HL^n	X	R	**4**–**8** [a] / %	λ_{max} (lg $\varepsilon/\varepsilon^*$) [b] / nm	$\nu_{C=O}$ / cm^{-1} [c]
1	HL^1	–	–	**4**: 89	309 (3.25)	1560, 1654
2	HL^2	H	CF_3	**5**: 99	319 (3.55)	1576, 1609
3	HL^3	F	CH_3	**6**: 84	316 (3.01)	1575, 1603
4	HL^4	F	CF_3	**7**: 89	319 (3.04)	1586, 1616
5	HL^5	F	C_7F_{15}	**8**: 96	323 (2.93)	1593, 1617

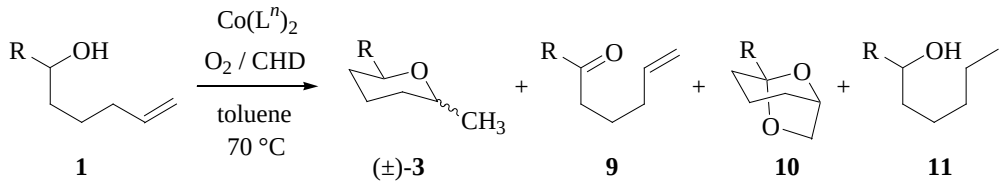
[a] Dihydrate. [b] ε in $m^2\ mol^{-1}$; $\varepsilon^* = 1\ m^2\ mol^{-1}$. [c] From samples pelletized in potassium bromide.

2.2 Synthesis of tetrahydropyrans

2.2.1 From monosubstituted 5-hexenols

From systematic variation of reaction parameters, we identified conditions to prepare 2-phenyl-6-methyltetrahydropyran **3a** from 1-phenyl-5-hexen-1-ol (**1a**) in up to 69% yield. For attaining this selectivity, a solution of alkenol **1a**, CHD, and cobalt(II) catalyst **5** in toluene has to be heated for 22 hours hours at 70 °C, while allowing air to diffuse into the reaction mixture through a reflux condenser. No tetrahydropyran **3a** forms, if a similarly prepared solution is kept in an atmosphere of nitrogen.

Table 2. Products of aerobic oxidation from 1-substituted 5-hexenols **1a**–**c**



1 (±)-**3** **9** **10** **11**

entry	R / index [a]	$Co(L^n)_2$	conv. **1** / % [b]	**3** / % (*cis*:*trans*)	**9** / %	**10** / %	**11** / %
1	Ph / **a**	**4** (*n* = 1)	64	23 (7:93)	14	2	– [c]
2	Ph / **a**	**5** (*n* = 2)	> 99	66 (11:89)	4	8	11
3	Ph / **a**	**6** (*n* = 3)	37	7 (8:92)	20	– [c]	– [c]
4	Ph / **a**	**7** (*n* = 4)	98	59 (12:88)	6	6	11
5	Ph / **a**	**8** (*n* = 5)	96	69 (16:84)	6	6	9
6	CH_3 / **b**	**5** (*n* = 2)	> 99	60 (17:83)	– [c]	– [c]	– [c]
7	*c*-C_6H_{11} / **c**	**5** (*n* = 2)	87	40 (7:93)	1	5	– [c]

[a] For compounds **1**, **3**, **9**–**11**; $c^0_{\mathbf{1}}$ = 0.5 M, c^0_{CHD} = 5.0 M, [b] Refers to 22 h reaction time and 5 mol% $Co(L^n)_2$ (c^0 = 25 mM). [c] Not detected.

The degree of oxidative alkenol conversion in the standard timeframe of twenty-two hours changes from moderate to quantitative, depending on the nature of the cobalt catalyst. The structure of cobalt compounds **4**–**8** seems to have no significant effect on cis/trans-ratio of phenylmethyltetrahydropyran **3a** obtained from aerobic oxidation (Table 2, entries 1–5). Five mole percent of 4,4,4-trifluoro-1-phenylbutane-1,3-dione-derived cobalt complex **5** suffice to quantitatively convert alkenol **1a** into products of selective oxidation within the chosen standard reaction time, while other cobalt catalysts required extended reaction times to drive oxidative alkenol conversion to completion. Given the reactivity, we selected cobalt(II) complex **5** as oxidation catalyst for continuing the study. Perfluoroheptyl-substituted cobalt

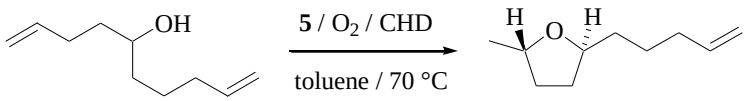
derivative **8**, on the other hand, is not able to quantitatively turn over substrate **1a** within twenty-four hours at 70 °C in a solution having half the volume of toluene replaced by bromoperfluoroheptane. Since fluorinated solvents dissolve higher concentrations of dioxygen than non-fluorinated hydrocarbons,[33] we concluded from this experiment that the dioxygen concentration in standard toluene/CHD-solutions is not rate limiting for oxidizing 5-hexenols catalyzed by cobalt(II) bis-(β-diketonate) complexes.

Products other than tetrahydropyran **3a** formed from substrate **1a** and dioxygen are hexenophenone **9a**, bicyclic acetal **10a**, and phenylhexanol **11a** supplementing the mass balance for 5-hexenol-derived products to ~ 90% (Table 2, entry 2). Ketones are familiar by-products in aerobic cobalt-catalyzed oxidation of secondary alcohols, if alternative oxidative transformations are slow. Phenylhexanol **11a**, on the other hand, arises form π-bond reduction in alkenol **1a** by CHD in combination with cobalt catalyst **5**.[34,35] The sequence leading from phenylhexenol **1a** to bicyclic acetal **10a** is new but was not further addressed in this study, given the low yield of this product.

Oxidations of 1-substituted 5-hexenols other than phenylhexenol **1a**, provide 2,6-dimethyltetrahydropyran **3b** and 2-cyclohexyl-6-methyltetrahydropyran **3c** predominantly as 2,6-trans-stereoisomer, starting from 1-methyl-5-hexenol **1b** or 1-cyclohexyl-substituted alkenol **1c** in solutions of cobalt catalyst **5** in CHD/toluene exposed to air (Table 2, entries 6–7). Oxidizing 1-cyclohexyl-5-hexenol **1c** under such conditions furnishes ketone **9c** (1%) and bicyclic acetal **10c** (5%) as by-products (Table 2, entry 7), whereas no additional compounds were isolated from aerobic oxidation of 1-methyl-5-hexenol **1b**.

For calibrating relative rate of aerobic 5-hexenol oxidation for tetrahydropyran synthesis

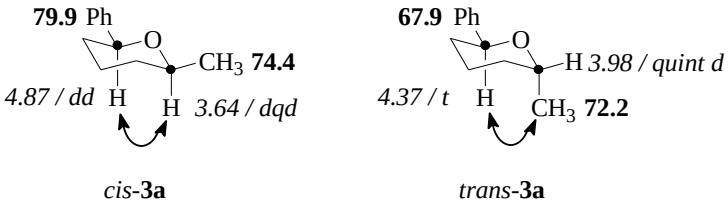
compared to tetrahydrofuran formation from 4-pentenols, we treated dienol **1d** with cobalt(II) complex **5** and air in a solution of toluene and CHD. The experiment furnishes exclusively 2,5-trans-disubstituted tetrahydrofuran *trans*-**12**, as judged by NMR-spectroscopy (Scheme 2). Considering the precision of routine NMR-analysis, we estimated that aerobic 5-*exo*-cyclization is by a factor of at least 24 faster than the 6-*exo*-ring closure in dienol **1d**.



1d (±)-*trans*-**12** 62%

Scheme 2. Experiment for comparing relative rate of aerobic 5-*exo*- to 6-*exo*-alkenol cyclization.

For stereochemical analysis of tetrahydropyrans **3a**–**c** we used in all instances NMR spectroscopy. Fine structures of proton-NMR resonances provide information on axial and equatorial orientation of substituents at tetrahydropyran. Systematic absence and presence of NOESY-cross signals indicate close contacts between protons in relative 1,3-*cis*-position (for **3a** see Figure 1). Shift dispersion between endocyclic carbons of cis- and trans-stereoisomers allow to deduce sites of axially bound substituents at tetrahydropyran by high field-shifts of carbon resonances in α- and in γ-position.[36]

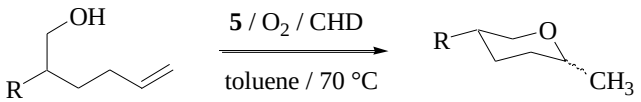


cis-**3a** *trans*-**3a**

Figure 1. NMR-spectroscopic information relevant for stereochemical analysis of 2-phenyl-6-methyltetrahydropyran (**3a**) (double headed arrows symbolize NOESY-interactions; numbers in bold refer to carbon-13 chemical shifts in deuterochloroform of endocyclic positions marked a black bullet; numbers and multiplicities printed in italics refer to proton-NMR-shifts and fine structures in deuterochloroform).

For elucidating stereodirecting effect exerted by a substituent at position 2, we exposed 2-phenyl- and 2-isopropyl-substituted substrates **1e** and **1f** in solutions of CHD/toluene and catalytic amounts of cobalt complex **5** to air. Both alkenols are quantitatively oxidized under such conditions, providing tetrahydropyrans **3e**–**f** as ~12/88-mixtures of 2,5-cis/trans-stereoisomers.

Table 3. Formation of 2,5-disubstituted tetrahydropyrans from 2-substituted 5-hexenols



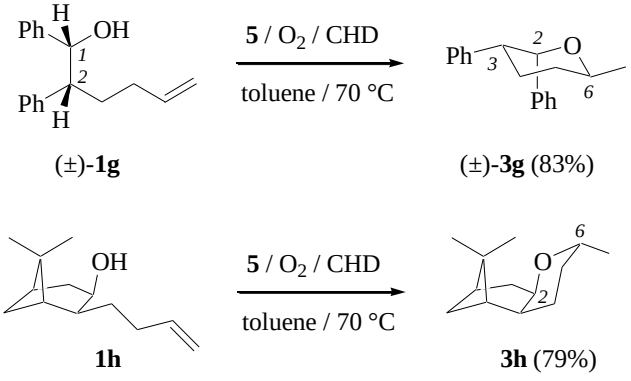
1 (±)-**3**

entry	R	**1** and **3**	**3** / % (*cis*:*trans*)
1	Ph	**e**	66 (12:88)
2	$CH(CH_3)_2$	**f**	57 (11:89)

2.2.2 From disubstituted 5-hexenols

Disubstituted 5-hexenols having substituents bound to asymmetrically substituted carbons at positions 1 *and* 2, or 1 *and* 3 exist as pair of *like*- and *unlike*-diastereomers, depending on whether configuration at the stereocenters is the same (*R*,*R* or *S*,*S* for *like*) or not the same (*R*,*S* or *R*,*S* for *unlike*). For synthetic reasons, we used 1,2-*like*-, 1,3-*like*- and 1,3-*unlike*-diastereoisomers as substrates for elucidating stereochemical principles of aerobic 5-hexenol 6-*exo*-ring closures.

In the series of 1,2-*like*-configured substrates, 1,2-diphenyl-5-hexenol **1g** furnishes diastereomerically pure 2,3,6-substituted tetrahydropyran **3g**, heated in a solution containing cobalt catalyst **5** exposed to air (Scheme 3, top). The *cis*-isomer of 2-butenyl-6,6-dimethylbicyclo[3.1.1]heptan-3-ol **1h**, under such conditions, affords bicylohexyl-fused tetrahydropyran **3h** as only product (Scheme 3, bottom). From the time required to achieve quantitative oxidative conversion of substrates **3g** and **3h** we concluded that 1,2-*like*-configured 5-hexenols are by a factor ~2 more reactive than monosubstituted congeners.



(±)-**1g** (±)-**3g** (83%)

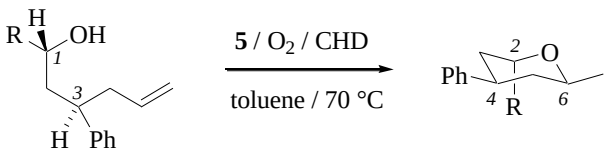
1h **3h** (79%)

Scheme 3. Stereoselective tetrahydropyran formation from *rel*-(1*R*,2*R*)-1,2-diphenylhexenol **1g** and *rel*-(1*S*,2*S*,3*R*,5*R*)-2-(buten-4-yl)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (**1h**).

From NOESY-spectra and vicinal coupling constants in combination with the Karplus-relationship for predicting dihedral angles from ^{3}J-coupling constants we assigned trans-arrangement of the methyl group with respect to substituents attached to carbons 2 and 3. By comparing diastereomeric ratio for tetrahydropyran synthesis from 1- and 2-substituted 5-hexenols **1a**–**c**, **1e**–**f** to values obtained from **1g** and **1h** we concluded that 1,2-*like* is a matching configuration of substituents for stereocontrol in cobalt-catalyzed aerobic 5-hexenol oxidation.

1,3-*like*-disubstituted 5-hexenols *rel*-(1*R*,3*R*)-**1i**–**k** are quantitatively oxidized with four hours when heated at 70 °C in a solution containing cobalt complex **5** and air, providing diastereomerically pure tetrahydropyrans **3i**–**k** in ~80% yield (Table 4, entries 1–3). From the doublet of triplet fine structure (J_t = 13 Hz) of the axial proton at carbon 5, high-field shift to ~2.9 ppm for the proton bound to carbon 4, and a ~5 Hz doublet coupling for 2-H, we deduced that substituents in products formed from *like*-**1i**–**k** are bound axially at carbon 2 and equatorially at carbons 4 and 6 (Table 4).

Table 4. Synthesis of 2,4,6-trisubstituted tetrahydropyrans from 1,3-*like*-5-hexenols

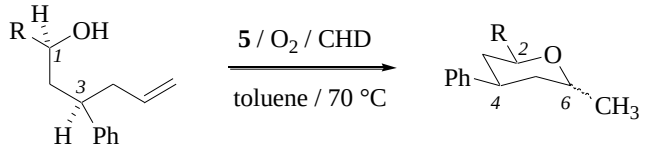


1 **3**

entry	R	*rel*-(1*R*,3*R*)-**1** / *like*-**1**	*rel*-(2*R*,4*R*,6*S*)-**3** / %
1	Ph	**i**	80
2	2-thienyl	**j**	79
3	2,4-difluorophenyl	**k**	79

Cobalt-catalyzed aerobic oxidation of 1,3-*unlike*-diastereomers of 5-hexenols **1i**–**k** afford ~50/50-mixtures of cis/trans-stereoisomers with respect to relative position of the 6-methyl group with respect to substituents bound to carbons 2 and 4 (Table 5, entries 1–3).

Table 5. Stereoselective synthesis of 2,4,6-trisubstituted tetrahydropyrans from 1,3-*unlike* configured 5-hexenols



1 **3**

entry	R	*rel*-(1*S*,3*R*)-**1**	*rel*-(2*S*,4*R*)-**3** / % (*cis*:*trans*) [a]
1	Ph	**i**	68 (50:50)
2	2-thienyl	**j**	74 (43:57)
3	2,4-difluorophenyl	**k**	70 (51:49)

[a] Relative configuration of 2 and 6.

From diastereomeric ratios obtained by oxidizing 1,3-disbustituted 5-hexenols **1i**–**k** compared to values obtained for oxidation of 1-substituted derivatives **1a**–**c** we concluded that 1,3-*like* is a stereochemically matching configuration, whereas 1,3-*unlike* poses a mismatched arrangement.

2.2.3 A transition state model for aerobic oxidative 5-hexenol cyclization

To rationalize mechanistic aspects leading from triplet dioxygen and 5-hexenols to tetrahydropyran, and for correlating orientation and position of alkenol substituents to relative configuration of tetrahydropyrans obtained from cobalt-catalyzed oxidative cyclizations, we developed a reaction model for explaining some of the steps.

In the stereochemical model, dioxygen binds to the cobalt(II) bis-(β-diketonate) complex leading to a low-spin cobalt(III) superoxo complex,[37] similar to dioxygen binding in cobalt(II) complexes bearing four nitrogen donor atoms,[38] or a combination of two nitrogen- and two oxygen donor atoms.[39] Intramolecular hydrogen bonding between dioxygen and the alkenol hydroxyl group favors cis-orientation of the two substituents (Figure 2).

Electron-deficient cobalt bis-(β-diketonate) complexes are strong Lewis acids, as shown in previous studies, and in supplementary extended X-ray absorption fine structure (EXAFS)-spectra conducted on cyclohexa-1,4-diene-binding to **5**.[31, 40] In a molecular orbital model, binding of an alkene to a cobalt(III) superoxo complex is feasible via overlap between the π-type orbital from carbon-carbon double and the σ*-orbital of one of the cobalt diketonate-oxygen bonds (Figure 2).[37]

Once dioxygen and the substrate are bound to cobalt, electron transfer from the π-bond to cobalt-coordinated dioxygen may occur converting the carbon-carbon double bond into a radical cation for accepting the hydroxyl oxygen. Cobalt-bound superoxide is subsequently reduced to water, as identified a previous study using γ-terpinene instead of CHD as reductant.[27] In this picture, CHD also reduces cobalt(III) to cobalt(II), presumably via an intermediate hydridocobalt complex, explaining the ability of the reactants to reduce a carbon-carbon double bond (cf. Table 2).

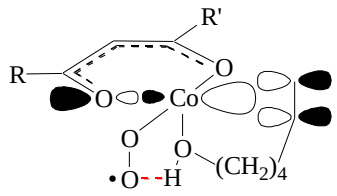


Figure 2. Model for visualizing hydrogen bonding between the alkenol- and the superoxo ligand (dashed red line), and bonding interaction between the carbon-carbon double bond and a virtual molecular orbital associated with a cobalt-oxygen bond (R, R' = CF_3, CH_3, or aryl; cf. Table 1; for the sake of clarity, the second diketonate auxiliary is omitted).

The lowest in energy conformer adopted by the alkenol ligand, as the oxidized π-bond and the hydroxyl oxygen approach, is a C,O-stretched chair conformer of tetrahydropyran (Figure 3). Substituents attached to the aliphatic chain in this conformer favor for reasons of torsional strain equatorial positions, explaining the preference for 2,4-cis- and 2,5-trans-6-*exo*-cyclization. A substituent at carbon 3 in this model favors 2,3-trans-selective tetrahydropyran ring closure, which has not yet been experimentally pursued.

Explaining in this model the origin of 2,6-trans-stereocontrol requires to position the alkyl or the phenyl substituent at the hydroxyl carbon in the transition state for C,O-cyclization axially. If approximated by the *A*-value, axial orientation of the phenyl group raises the Gibbs free energy of 2-phenyltetrahydropyran by 15 kJ mol^{-1} at 298 K of (Supplementary data).[41] Momentarily we have no other explanation for this unexpected conformational behavior than steric repulsion between the cobalt complex and the substituent at carbon 1 (Figure 3).[42,43]

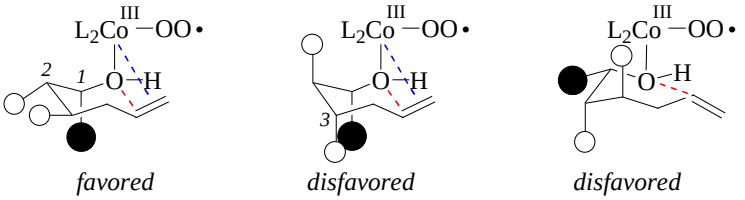


Figure 3. Stereochemical model for predicting selectivity in aerobic cobalt-catalyzed 5-hexenol cyclization (black circles mark the stereochemical leading substituent in position 1 of the alkenol; dashed red lines describe trajectory of C,O-bond formation, blue dashed line marks proposed interactions between cobalt and the alkenol π-bond).

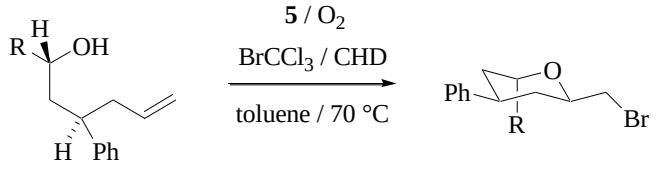
2.3 Functionalized tetrahydropyrans

Following principles of diastereocontrol by 5-hexenol substituents we focused in the second part of the study on method development for introducing heteroatom substituents or adding functionalized C_2-building at the exocyclic carbon after 6-*exo*-trig-C,O-cyclization. In the following sections, we summarize the most representative examples developed for this purpose.

2.3.1 Bromocyclization

If heated in solutions of toluene containing bromotrichloromethane, CHD, cobalt(II) complex **5** and air, 5-hexenols furnish 6-bromomethyltetrahydropyrans. For attaining reasonable time/yield-factors of oxidative conversion of the *like*-stereoisomers of 1,3-disubstituted 5-hexenols **1i**–**j**, three portions of five mole percent cobalt(II) reagent **5** have to be added in regular intervals within twenty-four hours, providing 2,4-aryl-6-bromomethyltetrahydropyrans **13i**–**j** in up to 89% yield (Tables 6 and 7).

Table 6. Stereoselective 6-*exo*-bromocyclization of 1,3-*like*-configured 5-hexenols

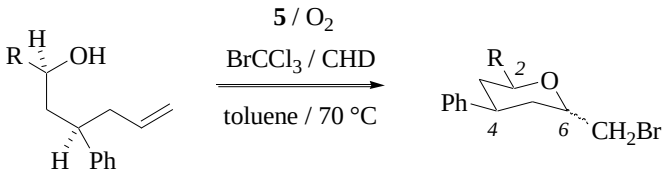


1 **13**

entry	R	*rel*-(1*R*,3*R*)-**1**	*rel*-(2*R*,4*R*,6*R*)-**13** / %
1	Ph	**i**	76
2	2-thienyl	**j**	89

In 6-*exo*-bromocyclization configuration associated with stereocenters of the alkenol copies into relative configuration of substituents at tetrahydropyran, as predicted by the stereochemical model. 1,3-*like*-stereoisomers of substrates **1i**–**j** furnish stereochemically pure bromomethyltetrahydropyrans *rel*-(2*R*,4*R*,6*R*)-**13i**–**j** (Table 6), whereas the 1,3-*unlike*-isomers of **1i**–**j** afford 50/50-mixture of 2,6-*cis*/*trans*-stereoisomers of *rel*-(2*S*,4*R*)-**13i**–**j** (Table 7). Bromotrichloromethane has no effect on stereoselectivity of the tetrahydropyran ring closure, but gradually transforms cobalt β-diketonate complex **5** into cobalt(II) bromide. Cobalt(II) bromide is not able to activate dioxygen for oxidative 5-hexenol cyclization, explaining the need for larger quantity of cobalt(II) chelate complex **5** for achieving quantitative alkenol turnover in timeframes that compare to oxidative cyclization in toluene/CHD.

Table 7. Synthesis of bromomethyltetrahydropyrans from 1,3-*like*-configured 5-hexenols



1 **13**

entry	R	*rel*-(1*S*,3*R*)-**1**	*rel*-(2*S*,4*R*)-**13** / % (*cis*:*trans*) [a]
1	Ph	**i**	77 (50:50)
2	2-thienyl	**j**	75 (41:59)

[a] Relative configurations refer to substituents at C2 and C6.

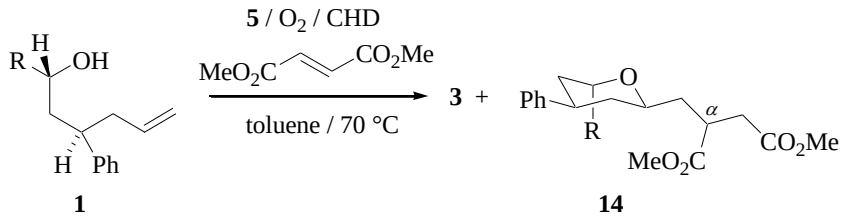
2.3.2 α-(Tetrahydropyranyl-2-methyl) succinates from three-component reactions

Side chain-extended tetrahydropyrans, such as α-(tetrahydropyranyl-2-methyl) succinates **14i**–**j** are available in ~58% yield from three-component reactions between dimethyl fumarate, CHD, and 5-hexenols *like*-**1i**–**j** in solutions containing 5 mole percent of catalyst **5** and air (Table 8). Methyltetrahydropyrans **3i**–**j** are formed under such conditions as by-products in 19–21% yield.

The tetrahydropyranylmethyl succinate/methyltetrahydropyran-ratio reflects differences in rate constants for tetrahydropyranyl-2-methyl radical-trapping by CHD and by the alkene (Scheme 4). Improving the yield of **14**, in principle, is feasible by raising dimethyl fumarate-concentration, or reducing concentration of the reductant CHD. Dimethyl fumarate, however, is a solid, used for synthesis of succinates **14i**–**j** as saturated solution in toluene/CHD at 70 °C. The strategy to circumvent unwanted reduction of carbon radicals **2i**–**j** is to lower CHD-concentration, which also slows rates of cobalt(III)-to-cobalt(II) reduction and hydrogen atom transfer to adduct radicals **15i**–**j** for terminating the oxidation/radical trapping cascade. Since

yields of the succinates **14i**–**j** compare to yields obtained from tributyltinhydride-mediated carbon radical addition to dimethyl fumarate,[44] we did not further adapt CHD-concentration in this series of experiments.

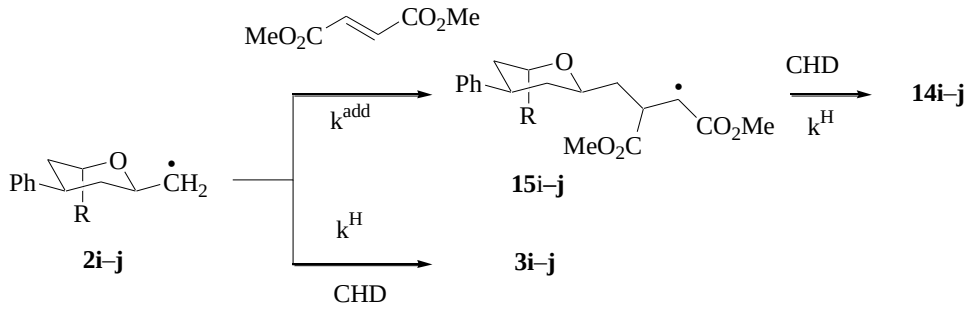
Table 8. Products of aerobic oxidation/alkene-trapping cascades



1 **14**

entry	R	*rel*-(1*R*,3*R*)-**1**	*rel*-(2*R*,4*R*,6*S*)-**3** / %	*rel*-(2*R*,4*R*,6*R*)-**14** / % [a]
1	Ph	**i**	21	57
2	2-thienyl	**j**	19	58

[a] 50/50-ratio of stereoisomers at C_α

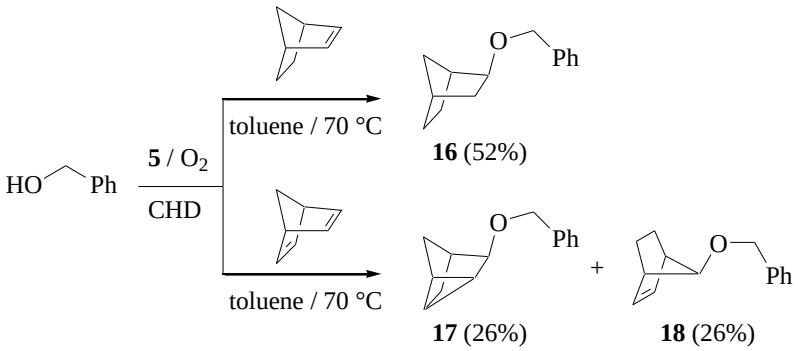


Scheme 4. Competing elementary reactions in three-component reactions α-(tetrahydropyranyl-2-methyl) succinates (k^H = rate constant for H-atom transfer; k^{add} = rate constant for addition).

2.4 Alkanol/Alkene-cross coupling

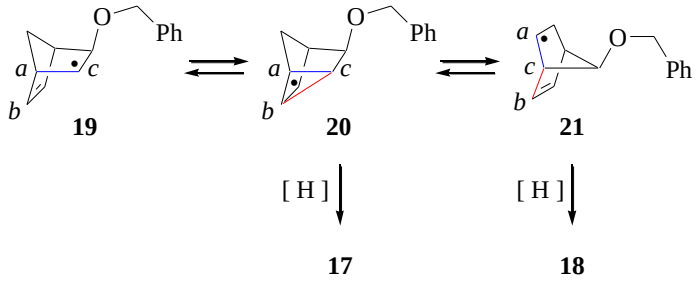
The reaction model outlined in Figure 2 implies that bis-(β-diketonate)(superoxo)cobalt(III) complexes, bind alkenols via the π-bond and the hydroxyl oxygen. Cross coupling of an alkanol and an alkene under non acidic conditions so far is not attainable in synthesis and therefore was pursued in this study with the aim to test the reaction model.

Benzyl alcohol, a 2.5-fold excess of norbornene, and 2.5 mole percent of cobalt catalyst **5**, when heated in a solution of CHD/toluene exposed to air, furnish 2-*exo*-benzyloxynorbornane **16** in 52% yield (Scheme 5). In an atmosphere of nitrogen or in the absence of cobalt catalyst **5**, no alkanol/alkene-cross coupling occurs. A second experiment starting from benzyl alcohol and norbornadiene afforded a ~50/50-mixture of *O*-benzyl ethers **17** and **18** in 52% total yield (Scheme 5).



Scheme 5. Products of intermolecular carbon-oxygen bond formation from aerobic cobalt-catalyzed oxidation.

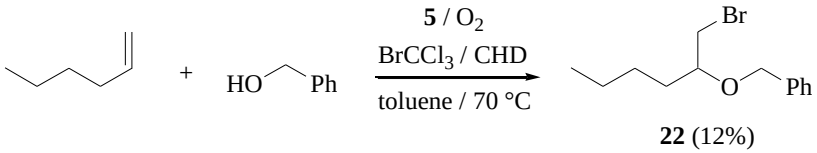
From proton-NMR shift values and fine structures, NOESY-spectra, and carbon-13 NMR shift dispersions we concluded that the benzyloxy substituent is bound in *exo*-position to bicyclic ether **16** and tricyclic derivative **17**, and anti with respect to the π-bond in norbornene derivative **18**. Adding benzyl alcohol from the *exo*-face to norbornene, according to the general mechanistic model (Scheme 1),[27,28] furnishes α-benzyloxynorbornenyl radical **19** (Scheme 6).[45] Intermediates of this type cyclize in a 3-*exo*-trig manner and subsequently ring open by breaking the β-carbon-carbon bond to afford carbon radicals **20** and **21**.[46] Trapping of rearranged radicals **20** and **21** by CHD furnishes *O*-benzyl ethers **17** and **18**, explaining structures of major products by the existing reaction model, validating its predicting power.



Scheme 6. Proposed intermediates and pathway for product formation from aerobic benzyl alcohol addition to norbornadiene (cf. Scheme 5; [H] = CHD).

Attempts to prepare vicinal bromohydrin ethers from norbornene, benzyl alcohol, and bromotrichloromethane afforded a mixture of 2-trichloromethyl-3-bromobicyclo[2.2.1]-heptane, unidentified products, and traces of 2-benzyloxy-3-bromobicyclo[2.2.1]heptane. We have so far no explanation for this unusual product diversity and repeated the experiment by replacing 1-hexene for norbornene (Scheme 7). From this reaction, we isolated 12%

bromohydrin ether **22**, along with benzaldehyde (9%), dibenzyl ether (12%), and benzyl benzoate (26%). The major product obtained from this experiment is 1,1,1-trichloro-2-bromoheptane, the addition product of bromotrichloromethane across the double bond of 1-hexene.



22 (12%)

Scheme 7. β-Bromohydrin formation in a three-component reaction.

3. Concluding Remarks

Molecular oxygen activated by fluoro-substituted cobalt(II) bis-(β-diketonate) complexes is able to oxidize substituted 5-hexenols into derivatives of tetrahydropyran. The reaction is a cascade providing substituted tetrahydrofuryl-2-methyl radicals, which are trapped by homolytic substitution or addition to an electron-deficient alkene to afford snythetically useful building blocks.

Concerning stereoselectivity for the tetrahydropyran ring closure, the cobalt-catalyzed alkenol oxidation shows an unusual preference for 2,6-trans-cyclization, complementing the existing methods for 2,6-cis-cyclization in tetrahydropyran synthesis. The true value of the cobalt method, as far as we see, arises from a unique cross-over in reactivity from oxidative for generating carbon radicals to reductive for chemoselectively trapping carbon radicals without providing alkyl hydroperoxides and typical successor products,[47] such as carbonyl

compounds or alcohols. Carbon radical trapping offers more perspectives for diversifying syntheses than polar reactions.[48] Selectivity in radical substitutions and additions is not significantly affected by solvent effects or additives such as Lewis-acids or other polar components. In radical chemistry, selectivity is guided by rates, which often are straightforward to control by concentration of the trapping reagent. Replacing a reagent, for example a heteroatom donor by an alkene, generally does not change the underlying chemistry, which is distinctively different compared to selectivity in polar transformations.

In order to further develop the field of aerobic cobalt-catalyzed oxidation, we developed in this study a mechanistic model for explaining selectivity in tetrahydropyran synthesis. The aspects summarized in this device allowed us to predict new reactions such as the intermolecular alkanol/alkene cross-coupling. For uncovering the principles of this chemistry in more detail, it is essential to uncover the mechanism of carbon-oxygen bond formation by addressing the chemical nature of the reactive intermediates. We think that this challenge has the potential to clarify whether the concept of cascades composed of a polar primary reaction and a secondary radical reaction for chemically diversifying primary products poses a more general concept in synthesis of ethers.

4. Experimental

4.1. General Remarks

Standard instrumentation and general remarks have been disclosed previously (see also the Supplementary data). All solvents and reagents were purified following recommended standard procedures.[49]

4.2 Reductive termination

*4.2.1 Oxidation of 1-phenylhex-5-en-1-ol (**1a**)*: A solution of alcohol **1a** (712 mg, 4.04 mmol) and cobalt complex **5** (108 mg, 206 µmol) in toluene (4.0 mL) and CHD (4.0 mL) was stirred at 70 °C for 14.5 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***cis*-6-Methyl-2-phenyltetrahydropyran *cis*-(3a)**.[50] Yield: 47.7 mg (271 µmol, 7 %), R_f 0.88 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.26 (3 H, d, *J* 6.2), 1.28–1.36 (1 H, m), 1.44–1.58 (1 H, m), 1.61–1.75 (2 H, m), 1.77–1.86 (1 H, m), 1.88–1.98 (1 H, m), 3.64 (1 H, dqd, J_d 11.2, J_q 6.5, J_d 2.4), 4.37 (1 H, dd, *J* 11.2, 2.0), 7.21–7.42 (5 H, m). δ_C (150 MHz, $CDCl_3$) 22.3, 24.1, 33.1, 33.5, 74.4, 79.9, 126.0, 127.2, 128.3, 143.5. NOESY (cross peaks) 2-H ↔ 6-H. MS (EI) *m*/*z* 176 (56) [M^+], 158 (5), 147 (2), 132 (9), 129 (8), 117 (14), 105 (98), 104 (100), 98 (5), 91 (27), 79 (34), 77 (48), 70 (9), 65 (9), 55 (17), 51 (17). ***trans*-6-Methyl-2-phenyltetrahydropyran *trans*-(3a)**.[51] Yield: 417 mg (2.36 mmol, 59 %), R_f 0.80 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.27 (3 H, d, *J* 6.2), 1.39–1.46 (1 H, m), 1.62–1.82 (3 H, m), 1.92 (2 H, q, *J* 5.5), 3.98 (1 H, quind, J_{quin} 6.5, J_d 3.8), 4.87 (1 H, t, *J* 5.3), 7.21–7.27 (1 H, m), 7.32–7.37 (2 H, m), 7.37–7.42 (2 H, m). δ_C (150 MHz, $CDCl_3$) 18.8, 19.4, 30.3, 31.3, 67.9, 72.2, 126.4, 126.8, 128.3, 142.4. MS (EI) *m*/*z* 176 (40) [M^+], 158 (5), 147 (2), 132 (8), 117 (16), 107 (84), 105 (84), 104 (100), 91 (30), 79 (31), 77 (39), 70 (8), 65 (7), 55 (16), 51 (15). **1-Phenylhex-5-en-1-one (9a)**.[52] Yield: 31.4 mg (180 µmol, 4 %), R_f 0.80 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.61–1.82 (2 H, m), 2.17 (2 H, q, *J* 7. 3), 2.96–3.01 (2 H, m), 4.99–5.05 (2 H, m), 5.83 (1 H, ddt, J_d 17.0, 10.2, J_t 6.7), 7.37–7.42 (1 H, m), 7.43–7.50 (2 H, m), 7.52–7.60 (1

H, m), 7.92–7.99 (2 H, m). MS (EI) *m*/*z* 174 (7) [M^+], 145 (1), 133 (1), 120 (55), 105 (100), 91 (4), 77 (55). **5-Phenyl-6,8-dioxabicyclo[3.2.1]octane (10a)**. Yield: 58.5 mg (309 µmol, 8 %), R_f 0.60 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.20–1.35 (1 H, m), 1.54–1.63 (1 H, m), 1.74–1.82 (1 H, m), 1.88–2.11 (3 H, m), 4.00 (1 H, ddd, *J* 6.7, 5.3, 1.2), 4.10 (1 H, d, *J* 6.4), 4.71 (1 H, s). δ_C (150 MHz, $CDCl_3$) 17.3, 28.1, 36.1, 69.2, 75.4, 108.0, 125.1, 128.1, 128.2, 141.3. MS (EI) *m*/*z* 190 (4) [M^+], 160 (1), 133 (1), 117 (4), 105 (100), 91 (5) 77 (25). ν_{max} (KBr) / cm^{-1} 3058, 3029, 2937, 2888, 1718 (CO), 1684 (CO), 1598 (CO), 1492, 1449, 1348, 1286, 1119, 1024, 1011. **1-Phenylhexan-1-ol (11a)**.[53] Yield: 79.5 mg (446 µmol, 11 %), R_f 0.53 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 0.78–0.92 (3 H, m), 1.20–1.50 (6 H, m), 1.66–1.88 (3 H, m), 4.66 (1 H, t, *J* 6.6), 7.26–7.31 (1 H, m), 7.32–7.37 (4 H, m). δ_C (150 MHz, $CDCl_3$) 14.0, 22.6, 25.5, 31.7, 39.1, 74.7, 125.9, 127.5, 128.4, 144.9. MS (EI) *m*/*z* 178 (4) [M^+], 160 (15), 128 (3), 117 (50), 107 (100), 91 (20), 79 (40). Analytic data agree with published values.

*4.2.2 Oxidation of hept-6-en-2-ol (**1b**)*: A solution of alcohol **1b** (108 mg, 946 µmol) and cobalt complex **5** (28.7 mg, 54.6 µmol) in toluene (1.0 mL) and CHD (1.0 mL) was stirred at 70 °C for 16 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***cis*-2,6-Dimethyltetrahydropyran *cis*-(3b)**.[54] Yield: 10.5 mg (93.2 µmol, 10 %), R_f 0.88 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.17 (6 H, d, *J* 6.1), 1.07–1.38 (6 H, m), 3.82–3.97 (2 H, m). δ_C (100 MHz, $CDCl_3$) 18.2, 21.8, 33.1, 73.7. MS (EI) *m*/*z* 114 (13) [M^+], 99 (100), 81 (51), 70 (36), 55 (62). ***trans*-2,6-Dimethyltetrahydropyran *trans*-(3b)**.[54] Yield: 52.9 mg (463 µmol, 50 %), R_f 0.78 [SiO_2,

acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.18 (6 H, d, *J* 6.6), 1.20–1.36 (6 H, m), 3.95–4.01 (2 H, m). δ_C (100 MHz, $CDCl_3$) 18.2, 19.6, 31.5, 66.8. MS (70 eV, EI): *m*/z (%) = 114 (13, M^+), 99 (100), 81 (51), 70 (36), 55 (62).

*4.2.3 Oxidation of 1-cyclohexylhex-5-en-1-ol (**1c**)*: A solution of alcohol **1c** (182 mg, 1.00 mmol) and cobalt complex **5** (28.7 mg, 54.6 µmol) in toluene (1.0 mL) and CHD (1.0 mL) was stirred at 70 °C for 18 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. Starting material **1c** was recovered in 13 % (23.6 mg, 129 µmol). **Cyclohexyl-6-methyltetrahydropyran (3c)**. Yield: 71.3 mg (392 µmol, 40 %) as 7/93-mixture of cis/trans-isomers, R_f 0.83 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. ***cis*-2-Cyclohexyl-6-methyltetrahydropyran *cis*-(3c)**. δ_H (400 MHz, $CDCl_3$) 0.81–0.96 (2 H, m), 1.15 (3 H, d, *J* 6.4), 1.17–1.33 (3 H, m), 1.39–1.51 (1 H, m), 1.51–1.68 (7 H, m), 1.69–1.79 (2 H, m), 1.86–1.95 (2 H, m), 3.61 (1 H, td, J_t 7.9, J_d 6.2), 3.79–3.84 (1 H, m). MS (EI) *m*/*z* 135 (18), 99 (100), 81 (80), 67 (17), 55 (46). ***trans*-2-Cyclohexyl-6-methyltetrahydropyran *trans*-(3c)**. δ_H (400 MHz, $CDCl_3$) 0.81−0.96 (2 H, m), 1.15 (3 H, d, *J* 6.4), 1.17–1.33 (3 H, m), 1.39–1.51 (1 H, m), 1.51–1.68 (7 H, m), 1.69–1.79 (2 H, m), 1.86–1.95 (2 H, m), 3.30–3.37 (1 H, m), 3.85 (1 H, quind, J_{quin} 6.5, J_d 3.5). δ_C (100 MHz, $CDCl_3$) 18.6, 19.7, 26.1, 26.2, 26.6, 26.8, 29.3, 31.7, 38.9, 66.9, 75.6. MS (EI) *m*/*z* 181 (1), 149 (1), 135 (1), 99 (100), 83 (12), 81 (73), 67 (13), 55 (36). **1-Cyclohexylhex-5-en-1-one (9c)**.[55] Yield: 2.00 mg (10.9 µmol, 1 %), R_f 0.71 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.18−1.40 (5 H, m), 1.51−1.85 (7 H, m), 1.98−2.10 (2 H, m), 2.43 (2 H, t, *J* 7.4), 4.92–5.05 (2 H, m), 5.76 (1 H, ddt, J_d 17.1, 10.2, J_t 6.7). **5-Cyclohexyl-6,8-**

dioxabicyclo[3.2.1]octane (10c). Yield: 10.2 mg (52.0 μmol, 5 %), R_f 0.61 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.02−1.31 (6 H, m), 1.39–1.94 (11 H, m), 3.77 (1 H, ddd, *J* 6.7, 5.3, 1.2), 3.91 (1 H, d, *J* 6.8), 4.49 (1 H, m). δ_C (100 MHz, $CDCl_3$) 16.9, 26.29, 26.32, 26.4, 27.0, 27.1, 28.7, 30.8, 45.2, 68.9, 74.8, 110.5. MS (EI) *m*/*z* 196 (6) [M^+], 168 (1), 127 (2), 122 (2), 111 (55), 95 (3), 83 (100), 67 (14).

*4.2.4 Oxidation of deca-1,9-dien-5-ol (**1d**)*: A solution of alcohol **1d** (137 mg, 890 μmol) and cobalt complex **5** (26.7 mg, 50.8 μmol) in toluene (1.0 mL) and CHD (1.0 mL) was stirred at 70 °C for 13.5 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***trans*-5-Methyl-2-(pent-4-enyl)-tetrahydrofuran (12)**. Yield: 85.0 mg (55.1 mmol, 62 %), R_f 0.74 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.21 (3 H, d, *J* 6.0), 1.32–1.66 (6 H, m), 1.96–2.12 (4 H, m), 3.92–4.02 (1 H, m), 4.03–4.16 (1 H, m), 4.89–5.04 (2 H, m), 5.80 (1 H, ddt, J_d 17.0, 10.3, J_t 6.6). δ_C (100 MHz, $CDCl_3$) 21.4, 25.5, 32.3, 33.8, 34.0, 35.7, 74.4, 78.6, 114.4, 138.8. NOESY (cross peaks) 2-H ↔ CH_3, 5-H ↔ 1'-H. MS (EI) *m*/*z* 136 (1), 125 (3), 111 (15), 98 (10), 95 (4), 85 (100), 81 (5), 67 (29), 57 (16), 55 (18). HRMS (EI^+) *m*/*z* 154.1343 [M^+)] calculated mass for $C_{10}H_{18}O^+$: 154.1358.

*4.2.5 Oxidation of 2-phenylhex-5-en-1-ol (**1e**)*: A solution of alcohol **1e** (177 mg, 1.00 mmol) and cobalt complex **5** (27.1 mg, 51.6 μmol) in toluene (1.0 mL) and CHD (1.0 mL) was stirred at 70 °C for 15 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20

(*v*/*v*)]. **3-Phenyl-6-methyltetrahydropyran (3e)**. Yield: 117 mg (664 µmol, 66 %) as 12/88-mixture of cis/trans-isomers, R_f 0.80 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. ***cis*-3-Phenyl-6-methyltetrahydropyran *cis*-(3e)**. δ_H (400 MHz, $CDCl_3$) 1.28 (3 H, d, *J* 6.2), 1.34–2.10 (4 H, m), 2.72−2.87 (1 H, m), 3.67 (1 H, dqd J_d 9.2, J_q 6.2, J_d 3.1), 3.89 (1 H, dd, *J* 11.7, 3.5), 4.19 (1 H, dq, J_d 12.1, J_q 1.8), 7.15–7.25 (3 H, m), 7.42–7.49 (2 H, m). δ_C (100 MHz, $CDCl_3$) 20.9, 28.8, 29.2, 38.9, 69.6, 72.7, 125.9, 128.1, 128.3, 144.8. MS (EI) *m*/*z* 176 (18) [M^+], 161 (2), 154 (3), 117 (14), 104 (100), 91 (16), 78 (8). HRMS (EI^+) *m/z* 176.1197 [M^+]; calculated mass for $C_{12}H_{16}O^+$: 176.1201. ***trans*-3-Phenyl-6-methyltetrahydropyran *trans*-(3e)**. δ_H (400 MHz, $CDCl_3$) 1.28 (3 H, d *J* 6.2), 1.46 (1 H, qd, J_q 12.4, J_d 5.2), 1.80 (1 H, qd, J_q 12.8, J_d 4.0), 1.77–1.87 (1 H, m) 2.04–2.11 (1 H), 2.86 (1 H, tt, *J* 11.6, 4.0), 3.43 (1 H, t, *J* 11.3), 3.50 (1 H, dqd, J_d 11.7, J_q 6.0, J_d 3.0), 4.01 (1 H, dq, J_d 11.2, J_q 2.2), 7.18–7.25 (3 H, m), 7.28–7.34 (2 H, m). δ_C (100 MHz, $CDCl_3$) 21.9, 30.6, 33.6, 42.6, 73.7, 73.8, 126.6, 127.3, 128.5, 142.4. MS (EI) *m*/*z* 176 (4) [M^+], 161 (1), 143 (1), 129 (4), 117 (16), 104 (100), 98 (7), 91 (22), 85 (29), 78 (10). HRMS (EI^+) *m/z* 176.1208 [M^+]; calculated mass for $C_{12}H_{16}O^+$: 176.1201.

*4.2.6 Oxidation of 2-isopropylhex-5-en-1-ol (**1f**)*: A solution of alcohol **1f** (125 mg, 881 µmol) and cobalt complex **5** (27.0 mg, 51.4 µmol) in toluene (1.0 mL) and CHD (1.0 mL) was stirred at 70 °C for 23 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. **3-Isopropyl-6-methyltetrahydropyran (3f)**. Yield: 70.8 mg (498 µmol, 57 %) as 11/89-mixture of cis/trans-isomers, R_f 0.85 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. ***cis*-3-Isopropyl-6-methyltetrahydropyran *cis*-(3f)**. δ_H (400 MHz, $CDCl_3$) 0.87 (6 H, dd *J*

6.5, 2.6), 0.90–0.98 (1 H, m), 1.16 (3 H, d *J* 6.1), 1.17–1.38 (3 H, m), 1.53–1.60 (1 H, m), 1.88–1.96 (1 H, m), 3.47–3.55 (2 H, m), 3.93 (1 H, dt, J_d 11.7, J_t 2.6) δ_C (100 MHz, $CDCl_3$) 20.8, 21.2, 21.3, 25.2, 25.7, 29.3, 40.8, 69.0, 73.4. MS (EI) *m*/*z* 142 (9) [M^+], 128 (8), 127 (100), 109 (40), 83 (27), 70 (47), 55 (51). HRMS (EI^+) *m/z* 142.1359 [M^+]; calculated mass for $C_9H_{18}O^+$: 142.1358. ***trans*-3-Isopropyl-6-methyltetrahydropyran *trans*-(3f)**. δ_H (400 MHz, $CDCl_3$) 0.87 (6 H, dd *J* 6.5, 2.6), 0.90–0.98 (1 H, m), 1.16 (3 H, d *J* 6.1), 1.17–1.38 (3 H, m), 1.60–1.67 (1 H, m), 1.82–1.89 (1 H, m), 3.13 (1 H, t, *J* 10.9), 3.31 (1 H, dqd, J_d 11.2, J_q 6.0, J_d 2.4), 3.98 (1 H, dq, J_d 11.3, J_q 2.1). δ_C (100 MHz, $CDCl_3$) 19.8, 20.2, 21.9, 27.4, 29.9, 33.7, 41.9, 71.9, 73.7. MS (EI) *m*/*z* 142 (19) [M^+], 128 (10), 127 (1), 129 (100), 109 (54), 99 (3), 97 (4), 95 (6), 83 (23), 70 (41), 55 (59). HRMS (EI^+) *m/z* 142.1362 [M^+]; calculated mass for $C_9H_{18}O^+$: 142.1358.

4.2.7 Oxidation of like-*1,2-diphenylhex-5-en-1-ol (**1g**)*: A solution of alcohol **1g** (127 mg, 504 µmol) and cobalt complex **5** (11.2 mg, 24.7 µmol) in toluene (2.0 mL) and CHD (1.0 mL) was stirred at 70 °C for 5 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*R*,3*R*,6*S*)-6-Methyl-2,3-diphenyltetrahydropyran (3g)**. Yield: 106 mg (419 µmol, 83 %), R_f 0.56 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.21 (3 H, d, *J* 6.1), 1.39–1.49 (1 H, m), 1.58–1.68 (1 H, m), 1.85–2.00 (1 H, m), 3.92 (1 H, d, *J* 8.4), 4.09 (1 H, quind, J_{quin} 7.9, J_d 6.1), 4.76 (1 H, dt, J_d 8.4, J_t 6.2), 7.14–7.19 (2 H, m), 7.23–7.29 (6 H, m), 7.33–7.37 (1 H, m). δ_C (100 MHz, $CDCl_3$) 21.4, 31.6, 33.6, 57.0, 75.3, 80.4, 126.1, 126.3, 128.2, 128.4, 128.6, 128.7, 142.8, 143.1. MS (EI) *m/z* 252 (1) [M^+], 178

(3), 165 (17), 152 (7), 115 (5), 85 (100), 77 (3). Anal. Calcd. for $C_{18}H_{20}O$ (252.35): C 85.67; H 7.99. Found: C 85.46; H 7.73.

*4.2.8 Oxidation of (1S,2S,3R,5R)-2-(but-3-enyl)-6,6-dimethylbicyclo[3.1.1]-heptan-3-ol (**1h**)*: A solution of alcohol **1h** (98.0 mg, 504 µmol) and cobalt complex **5** (13.2 mg, 25.1 µmol) in toluene (2.0 mL) and CHD (1.0 mL) was stirred at 70 °C for 2 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. (**1*R*,3*R*,5*R*,8*S*,9*S*)-5,10,10-Trimethyl-4-oxatricyclo[7.1.0^{3,8}]undecane (3h).** Yield: 77.5 mg (399 µmol, 79 %), R_f 0.76 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 0.89 (1 H, d, *J* 9.7), 1.04 (1 H, tdd, J_t 13.5, J_d 10.1, 2.9), 1.16 (3 H, s), 1.18 (3 H, s), 1.18 (3 H, d, *J* 6.2), 1.37 (1 H, ddt, J_d 12.7, 6.4, J_t 3.2), 1.62 (1 H, qd, J_q 13.2, J_d 3.0), 1.79 (1 H, q, *J* 2.4), 1.81–1.91 (4 H, m), 2.08 (1 H, dddd, *J* 13.0, 9.0, 6.2, 2.4), 2.28–2.41 (2 H, m), 4.02 (1 H, dquin, J_d 9.8, J_{quin} 6.7), 4.14 (1 H, td, J_t 9.3, J_d 3.1). δ_C (100 MHz, $CDCl_3$) 20.3, 21.8, 24.3, 28.1, 31.7, 32.6, 35.7, 38.5, 40.9, 45.9, 46.0, 61.8, 69.0. MS (EI) *m/z* 194 (1) [M^+], 176 (2), 153 (9), 136 (7), 125 (100), 107 (9), 91 (23), 82 (46), 69 (44). HRMS (EI^+) *m/z* 194.1675 [M^+]; calculated mass for $C_{13}H_{22}O^+$: 194.1671.

4.2.9 Oxidation of like*-1,3-diphenylhex-5-en-1-ol rel-(1R,3R)-(**1i**)*: A solution of alcohol *rel*-(1*R*,3*R*)-**1i** (126 mg, 501 µmol) and cobalt complex **5** (13.4 mg, 25.5 µmol) in toluene (2.0 mL) and CHD (0.5 mL) was stirred at 70 °C for 5 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column

chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*R*,4*R*,6*S*)-6-methyl-2,4-diphenyltetrahydropyran *rel*-(2*R*,4*R*,6*S*)-(3i)**. Yield: 102 mg (403 µmol, 80 %), R_f 0.60 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.24 (3 H, d, *J* 6.2), 1.54 (1 H, td, J_t 12.8, J_d 11.1), 1.73 (1 H, dddd, *J* 12.8, 3.4, 2.1), 2.18 (1 H, ddd, *J* 13.9, 12.8, 5.6), 2.52 (1 H, dddd, *J* 13.9, 3.4, 1.6), 2.88 (1 H, tt, *J* 12.5, 3.5), 3.71 (1 H, dqd, J_d 11.1, J_q 6.2, J_d 2.1), 5.25 (1 H, d, *J* 5.3), 7.20–7.25 (3 H, m), 7.26–7.30 (1 H, m), 7.30–7.34 (2 H, m), 7.41 (2 H, t, *J* 7.8), 7.48 (2 H, d, *J* 8.2). δ_C (150 MHz, $CDCl_3$) 21.9, 33.7, 36.5, 41.2, 66.5, 73.5, 126.3, 126.6, 126.7, 128.6, 140.7, 145.8. MS (EI) *m/z* 252 (13) [M^+], 209 (6), 174 (46), 147 (6), 131 (13), 117 (18), 104 (100), 91 (21), 77 (18). HRMS (EI^+) *m/z* 252.1505 [M^+]; calculated mass for $C_{18}H_{20}O^+$: 252.1514.

4.2.10 Oxidation of unlike-*1,3-diphenylhex-5-en-1-ol rel-(1S,3R)-(**1i**)*: A solution of alcohol *rel*-(1*S*,3*R*)-**1i** (137 mg, 544 µmol) and cobalt complex **5** (28.5 mg, 54.3 µmol) in toluene (1.2 mL) and CHD (0.5 mL) was stirred at 70 °C for 15 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*S*,4*R*,6*S*)-6-methyl-2,4-diphenyltetrahydropyran *rel*-(2*S*,4*R*,6*S*)-(3i)**. Yield: 47.6 mg (189 µmol, 35 %), R_f 0.57 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.33 (3 H, d, *J* 6.2), 1.51 (1 H, td, J_t 12.7, J_d 11.1), 1.69 (1 H, td, J_t 12.7, J_d 11.3), 1.89 (1 H, ddt, J_d 13.2, 3.8, J_t 2.0), 2.05 (1 H, ddt, J_d 13.2, 3.7, J_t 2.0), 2.97 (1 H, tt, *J* 12.3, 3.7), 3.80 (1 H, dqd, J_d 11.0, J_q 6.2, J_d 2.0), 4.53 (1 H, dd, *J* 11.2, 2.0), 7.17–7.26 (4 H, m), 7.27–7.35 (4 H, m), 7.38–7.42 (2 H, m). δ_C (150 MHz, $CDCl_3$) 22.1, 40.7, 40.9, 42.1, 74.1, 79.5, 125.9, 126.3, 126.7, 127.3, 128.3, 128.5, 142.9, 145.5. MS (EI) *m/z* 252 (8) [M^+], 209 (8), 174 (27), 147 (3), 131 (8), 117

(17), 104 (100), 91 (22), 77 (21). HRMS (EI^+) *m/z* 252.1509 [M^+]; calculated mass for $C_{18}H_{20}O^+$: 252.1514. ***rel*-(2*S*,4*R*,6*R*)-6-methyl-2,4-diphenyltetrahydropyran *rel*-(2*S*,4*R*,6*R*)-(3i)**. Yield: 46.0 mg (182 µmol, 34 %), R_f 0.55 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.48 (3 H, d, *J* 6.8), 1.69–1.78 (2 H, m), 2.00–2.10 (2 H, m), 3.19 (1 H, tt, *J* 12.6, 3.7), 4.54 (1 H, quin, *J* 6.5), 4.82 (1 H, dd, *J* 11.5, 2.1), 7.17–7.35 (8 H, m), 7.37–7.42 (2 H, m). δ_C (150 MHz, $CDCl_3$) 17.2, 36.2, 37.1, 41.5, 69.7, 71.4, 125.9, 126.3, 126.8, 127.3, 128.3, 128.5, 143.1, 145.6. MS (EI) *m/z* 252 (3) [M^+], 234 (3), 194 (10), 174 (19), 147 (15), 131 (10), 117 (18), 104 (100), 91 (24), 77 (24). HRMS (EI^+) *m/z* 252.1512 [M^+]; calculated mass for $C_{18}H_{20}O^+$: 252.1514.

*4.2.11 Oxidation of like-1-(thien-2-yl)-3-phenyl-hex-5-en-1-ol rel-(1R,3R)-(**1j**)*: A solution of alcohol *rel*-(1*R*,3*R*)-**1j** (158 mg, 610 µmol) and cobalt complex **5** (14.8 mg, 28.2 µmol) in toluene (2.0 mL) and CHD (1.0 mL) was stirred at 70 °C for 4 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*R*,4*R*,6*S*)-6-methyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*R*,4*R*,6*S*)-(3j)**. Yield: 124 mg (479 µmol, 79 %), R_f 0.58 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.14 (3 H, d, *J* 6.1), 1.44 (1 H, td, *J* 12.5, 11.5), 1.67 (1 H, ddt, J_d 12.9, 3.5, J_t 1.8), 2.09 (1 H, ddd, *J* 14.2, 12.5, 5.7), 2.28 (1 H, ddt, J_d 13.9, 3.5, J_t 1.7), 2.98 (1 H, tt, *J* 12.5, 3.5), 3.82 (1 H, dqd, J_d 11.5, J_q 6.1, J_d 1.7), 5.32 (1 H, d, *J* 5.5), 6.88–6.91 (1 H, m), 6.94 (dd, *J* 4.9, 3.5), 7.11–7.18 (3 H, m), 7.21–7.27 (3 H, m). δ_C (100 MHz, $CDCl_3$) 21.8, 35.5, 36.8, 40.7, 67.0, 71.8, 124.5, 125.1, 126.4, 126.8, 127.0, 128.6, 145.5, 146.2. MS (EI) *m/z* 258 (55) (M^+), 215 (4), 200 (4), 180 (21), 131 (22), 118 (25), 111 (32), 104 (100), 91 (28), 77 (23). Anal. Calcd. for $C_{16}H_{18}OS$

(258.38): C 74.38; H 7.02; S 12.41. Found: C 74.31; H 7.02; S 12.19. HRMS (EI^+) *m/z* 258.1086 [M^+]; calculated mass for $C_{16}H_{18}OS^+$: 258.1078.

4.2.12 Oxidation of unlike-*1-(thien-2-yl)-3-phenyl-hex-5-en-1-ol rel-(1S,3R)-(**1j**)*: A solution of alcohol *rel*-(1*S*,3*R*)-**1j** (145 mg, 560 µmol) and cobalt complex **5** (14.7 mg, 28.0 µmol) in toluene (2.0 mL) and CHD (1.0 mL) was stirred at 70 °C for 15 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*S*,4*R*,6*S*)-6-Methyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*S*,4*R*,6*S*)-(3j)**. Yield: 61.4 mg (238 µmol, 42 %), R_f 0.58 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.32 (3 H, d, *J* 6.1), 1.53 (1 H, td, J_t 12.7, J_d 11.1), 1.79–1.92 (2 H, m), 2.19 (1 H, ddt, J_d 13.1, 3.8, J_t 1.9), 2.96 (1 H, tt, *J* 12.3, 3.7), 3.82 (1 H, dqd, J_d 11.2, J_q 6.1, J_d 1.7), 4.79 (1 H, dd, *J* 11.1, 1.7), 6.94–6.97 (1 H, m), 7.00 (1 H, dd, *J* 3.4, 1.0), 7.20–7.27 (4 H, m), 7.30–7.35 (2 H, m). δ_C (100 MHz, $CDCl_3$) 22.0, 40.4, 40.6, 41.9, 74.3, 75.4, 123.4, 124.4, 126.4, 126.8, 128.6, 145.2, 146.0. MS (EI) *m/z* 258 (26) [M^+], 215 (3), 200 (5), 180 (19), 131 (19), 118 (24), 111 (30), 104 (100), 91 (27), 77 (20). Anal. Calcd. for $C_{16}H_{18}OS$ (258.38): C 74.38; H 7.02; S 12.41. Found: C 74.33; H 7.01; S 12.19. HRMS (EI^+) *m/z* 258.1077 (M^+); calculated mass for $C_{16}H_{18}OS^+$: 258.1078. ***rel*-(2*S*,4*R*,6*R*)-6-Methyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*S*,4*R*,6*R*)-(3j)**. Yield: 46.4 mg (180 µmol, 32 %), R_f 0.56 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.47 (3 H, d, *J* 6.8), 1.72 (1 H, ddt, J_d 13.2, 3.7, J_t 1.7), 1.85 (1 H, td, J_t 12.6, J_d 11.5), 2.07 (1 H, td, J_t 13.1, J_d 5.7), 2.17 (1 H, dt, J_d 12.6, J_t 3.7), 3.16 (1 H, tt, *J* 12.6, 3.7), 4.54 (1 H, quin, *J* 6.5), 5.08 (1 H, dd, *J* 11.5, 2.2), 6.93–6.98 (2 H, m), 7.19–7.27 (4 H, m), 7.29–7.34 (4 H, m). δ_C (100 MHz, $CDCl_3$) 17.2, 36.0, 36.8, 41.6, 67.7,

70.0, 123.2, 124.3, 126.4, 126.8, 128.6, 145.2, 146.7. MS (EI) *m/z* 258 (44) [M^+], 215 (3), 200 (3), 180 (13), 131 (17), 118 (22), 111 (24), 104 (100), 91 (25), 77 (12). Anal. Calcd. for $C_{16}H_{18}OS$ (258.38): C 74.38; H 7.02; S 12.41. Found: C 74.12; H 6.85; S 12.46. HRMS (EI^+) *m/z* 258.1077 [M^+]; calculated mass for $C_{16}H_{18}OS^+$: 258.1078.

*4.2.13 Oxidation of like-1-(2,4-difluorophenyl)-3-phenylhex-5-en-1-ol rel-(1R,3R)-(**1k**)*: A solution of alcohol *rel*-(1*R*,3*R*)-**1k** (146 mg, 507 µmol) and cobalt complex **5** (13.0 mg, 24.7 µmol) in toluene (2.0 mL) and CHD (1.0 mL) was stirred at 70 °C for 4 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*R*,4*R*,6*S*)-6-Methyl-4-phenyl-2-(2,4-difluorophenyl)tetrahydropyran *rel*-(2*R*,4*R*,6*S*)-(3k)**. Yield: 116 mg (402 µmol, 79 %), R_f 0.60 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.25 (3 H, d, *J* 6.2), 1.59 (1 H, td, J_t 13.0, J_d 10.7), 1.80–1.87 (1 H, m), 2.17 (1 H, td, J_t 13.3, J_d 6.0), 2.50–2.57 (1 H, m), 2.94 (1 H, tt, *J* 12.4, 3.6), 3.76 (1 H, dqd, J_d 11.0, J_q 6.2, J_d 1.9), 5.32 (1 H, d, *J* 5.9), 6.83 (1 H, ddd, *J* 11.3, 8.8, 2.5), 6.92 (1 H, td, J_t 8.3, J_d 2.6), 7.22–7.27 (3 H, m), 7.52 (1 H, td, J_t 8.9, J_d 6.4). δ_C (100 MHz, $CDCl_3$) 22.0, 34.9, 37.2 (d, *J* 4.5), 37.2, 40.6, 67.4, 70.4, 104.5 (dd, *J* 27.2, 25.3), 110.9 (dd, *J* 20.7, 3.6), 123.9 (dd, *J* 12.7, 3.6), 126.4, 126.7, 130.1 (dd, *J* 9.1, 6.4), 145.5, 160.3 (dd, *J* 134, 11.8), 162.7 (dd, 131, 12.7). MS (EI) *m/z* 288 (2) [M^+], 270 (2), 210 (41), 141 (19), 127 (10), 117 (18), 104 (100), 91 (19), 78 (15). HRMS (EI^+) *m/z* 288.1328 [M^+]; calculated mass for $C_{18}H_{18}OF_2^+$: 288.1328.

4.2.14 Oxidation of unlike-*1-(2,4-difluorophenyl)-3-phenylhex-5-en-1-ol rel-(1S,3R)-(**1k**)*: A solution of alcohol *rel*-(1*S*,3*R*)-**1k** (147 mg, 509 µmol) and cobalt complex **5** (13.1 mg, 24.9 µmol) in toluene (2.0 mL) and CHD (1.0 mL) was stirred at 70 °C for 15 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v* ***rel*-(2*S*,4*R*,6*S*)-6-Methyl-4-phenyl-2-(2,4-difluorophenyl)-tetrahydropyran *rel*-(2*S*,4*R*,6*S*)-(3k)**. Yield: 50.2 mg (174 µmol, 34 %), R_f 0.58 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless crystalline solid. δ_H (400 MHz, $CDCl_3$) 1.35 (3 H, d, *J* 6.2), 1.54 (1 H, td, J_t 12.7, J_d 11.1), 1.93 (1 H, ddt, J_d 13.1, 3.8, J_t 1.9), 2.06–2.10 (1 H, m), 3.02 (1 H, tt, *J* 12.3, 3.7), 3.84 (1 H, dqd, J_d 10.9, J_q 6.2, J_d 2.0), 4.84 (1 H, dd, *J* 11.1, 1.3), 6.78 (1 H, ddd, *J* 10.5, 9.0, 2.5), 6.90 (1 H, tdd, J_t 8.4, J_d 2.5, 1.2), 7.20–7.27 (3 H, m), 7.30–7.36 (2 H, m), 7.57 (1 H, td, J_t 8.6, J_d 6.4). δ_C (100 MHz, $CDCl_3$) 22.0, 40.0, 40.5, 41.9, 72.8, 74.3, 103.4 (t, *J* 25.4), 111.3 (dd, *J* 19.7, 3.6), 126.2 (dd, *J* 13.6, 3.6), 126.4, 126.7, 128.3 (dd, *J* 9.2, 6.4), 128.5, 145.2, 159.4 (dd, *J* 248, 11.8), 162.0 (dd, *J* 248, 11.8). MS (EI) *m/z* 288 (5) [M^+], 270 (2), 210 (20), 140 (14), 127 (9), 117 (16), 104 (100), 91 (16), 78 (13). HRMS (EI^+) *m/z* 288.1333 [M^+]; calculated mass for $C_{18}H_{18}OF_2^+$: 288.1326. ***rel*-(2*S*,4*R*,6*R*)-6-methyl-4-phenyl-2-(2,4-difluorophenyl)-tetrahydropyran *rel*-(2*S*,4*R*,6*R*)-(3k)**. Yield: 52.7 mg (183 µmol, 36 %), R_f 0.56 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.50 (3 H, d, *J* 6.8), 1.64 (1 H, td, J_t 12.7, J_d 11.4), 1.76 (1 H, ddt, J_d 13.2, 3.6, J_t 1.8), 2.02–2.12 (2 H, m), 3.22 (1 H, tt, *J* 12.6, 3.6), 4.55 (1 H, quin, *J* 6.5), 5.13 (1 H, dd, *J* 11.3, 1.9), 6.77 (1 H, ddd, *J* 10.5, 8.8, 2.5), 6.89 (1 H, tdd, J_t 8.4, J_d 2.6, 1.3), 7.21–7.28 (3 H, m), 7.29–7.35 (2 H, m), 7.54 (1 H, td J_t 8.5, J_d 6.5). δ_C (100 MHz, $CDCl_3$) 17.0, 36.0, 37.0, 40.6, 64.7, 69.9, 103.4 (t, *J* 25.4), 111.3 (dd, *J* 21.1, 3.6), 126.4, 126.8, 128.2 (dd, *J* 9.9, 6.5) 128.5, 145.3, 159.2 (dd, *J* 248, 11.8), 162.0 (dd, 248, 11.8). MS (EI) *m/z* 288 (1)

[M^+], 270 (3), 210 (21), 147 (16), 140 (10), 127 (8), 117 (19), 104 (100), 91 (20), 78 (14). HRMS (EI^+) *m/z* 288.1316 [M^+]; calculated mass for $C_{18}H_{18}OF_2^+$: 288.1326.

*4.2.15 Oxidation of norbornene and benzyl alcohol (**15**)*: A solution of benzyl alcohol (**15**) (221 mg, 2.02 mmol) and cobalt complex **5** (26.2 mg, 50.6 µmol) in toluene (2.0 mL), CHD (1.0 mL) and norbornene (487 mg, 5.12 mmol) was stirred at 70 °C for 19 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/pentane = 1:10 (*v*/*v*)]. **2-*exo*-Benzyloxynorbornane (16)**.[56] Yield: 213 mg (1.05 mmol, 52 %), colorless oil.

*4.2.16 Oxidation of norbornadiene and benzyl alcohol (**15**)*: A solution of benzyl alcohol (**15**) (113 mg, 1.04 mmol) and cobalt complex **5** (13.3 mg, 25.3 µmol) in toluene (2.0 mL), CHD (0.5 mL) and norbornadiene (235 mg, 2.53 mmol) was stirred at 70 °C for 24 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/pentane = 1:10 (*v*/*v*)]. **7-*anti*-Benzyloxy-bicylo[2.2.1]hept-2-ene (18)**. Yield: 53.1 mg (265 µmol, 26 %), R_f 0.59 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 0.98–1.02 (2 H, m), 1.83–1.87 (2 H, m), 2.70 (2 H, dq, J_d 3.7, J_q 2.1), 3.33 (1 H, s), 4.44 (2 H, s), 5.98 (2 H, t, *J* 2.1), 4.49 (2 H, dd, *J* 24.5, 11.7), 7.27–7.38 (5 H, m). δ_C (100 MHz, $CDCl_3$) 21.9, 43.4, 70.2, 88.9, 127.4, 127.5, 128.3, 134.2, 138.5. MS (EI) *m/z* 200 (1) [M^+], 120 (9), 91 (100), 79 (33). HRMS (EI^+) *m/z* 200.1204 [M^+] calculated mass for $C_{14}H_{16}O^+$: 200.1201. **3-*exo*-Benzyloxynortricyclene (17)** Yield: 52.3 mg (261 µmol, 26 %), R_f 0.55 [SiO_2,

acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.15–1.20 (2 H, m), 1.23–1.29 (3 H, m), 1.35 (1 H, d, *J* 10.6), 1.89 (1 H, d, *J* 9.7), 2.02 (1 H, s), 3.63 (1 H, t, *J* 1.2), 4.49 (2 H, dd, *J* 24.5, 11.7), 7.26–7.29 (1 H, m), 7.32–7.37 (4 H, m). δ_C (100 MHz, $CDCl_3$) 11.0, 12.8, 14.1, 29.7, 30.4, 32.5, 71.0, 84.3, 127.4, 127.7, 128.3, 138.8. MS (EI) *m/z* 200 (1) [M^+], 109 (29), 91 (100), 79 (43). HRMS (EI^+) *m/z* 200.1213 [M^+]; calculated mass for $C_{14}H_{16}O^+$: 200.1201.

4.3 Brominative termination

4.3.1 Oxidation of like-*1,3-diphenylhex-5-en-1-ol rel-(1R,3R)-(**1i**)*: A solution of alcohol *rel*-(1*R*,3*R*)-**1i** (127 mg, 504 µmol) and cobalt complex **5** (13.5 mg, 25.7 µmol) in toluene (2.0 mL), bromotrichloromethane (0.5 mL) and CHD (0.5 mL) was stirred at 70 °C for 24 h while being exposed to laboratory atmosphere. A second (13.4 mg) and third (13.2 mg) batch of cobalt catalyst were added after 2 and 5 h. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*R*,4*R*,6*R*)-6-bromomethyl-2,4-diphenyltetrahydropyran *rel*-(2*R*,4*R*,6*R*)-(13i)**. Yield: 126 mg (381 µmol, 76 %), R_f 0.55 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.67 (1 H, td, J_t 12.4, J_d 11.3), 1.88 (1 H, ddt, J_d 12.7, 3.9, J_t 2.1), 2.26 (1 H, ddd, *J* 14.0, 13.0, 5.6), 2.58 (1 H, ddt, J_d 13.9, 3.5, J_t 1.8), 2.97 (1 H, tt, *J* 12.5, 3.7), 3.43–3.51 (2 H, m), 3.87 (1 H, dddd, *J* 11.2, 6.6, 4.3, 2.2), 5.39 (1 H, d, *J* 5.6), 7.26–7.30 (3 H, m), 7.33–7.40 (3 H, m), 7.47 (2 H, t, *J* 7.8), 7.58 (2 H, d, *J* 8.2). δ_C (150 MHz, $CDCl_3$) 33.4, 36.0, 36.1, 37.7, 69.7, 73.9, 126.56, 126.63, 127.0, 128.7, 139.6, 144.9. MS (EI) *m/z* 330/332 (6/6) [M^+], 252/254 (25/25), 193 (24), 173 (13), 145 (9), 131 (36), 115/117 (18/18), 104 (100), 91 (42), 77

(29). Anal. Calcd. for $C_{18}H_{19}BrO$ (331.25): C 65.27; H 5.78. Found: C 65.36; H 5.88. HRMS (EI^+) *m/z* 330.0644, 323.0627 [M^+]; calculated mass for $C_{18}H_{19}OBr^+$: 330.0619, 332.0599.

4.3.2 Oxidation of unlike-*1,3-diphenylhex-5-en-1-ol rel-(1S,3R)-(**1i**):* A solution of alcohol *rel*-(1*S*,3*R*)-**1i** (127 mg, 503 µmol) and cobalt complex **5** (13.2 mg, 25.1 µmol) in toluene (2.0 mL), bromotrichloromethane (0.5 mL) and CHD (0.5 mL) was stirred at 70 °C for 24 h while being exposed to laboratory atmosphere. A second (13.4 mg) and third (13.5 mg) batch of cobalt catalyst were added after 2 and 5 h. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*S*,4*R*,6*R*)-6-bromomethyl-2,4-diphenyltetrahydropyran *rel*-(2*S*,4*R*,6*R*)-(13i) and *rel*-(2*S*,4*R*,6*S*)-6-bromomethyl-2,4-diphenyltetrahydropyran *rel*-(2*S*,4*R*,6*S*)-(13i)**. Yield: 129 mg (389 µmol, 77 %) as 50/50-mixture of 2,6-*cis*/*trans*-isomers, R_f 0.59 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.51 (1 H, td, J_t 12.8, J_d 10.9), 1.63 (1 H, td, J_t 12.5, J_d 11.9), 1.70 (1 H, td, J_t 12.8, J_d 11.6), 1.92–2.13 (5 H, m), 2.93 (1 H, tt, *J* 12.0, 3.4), 2.99 (1 H, tt, *J* 12.3, 3.7), 3.39 (1 H, dd, *J* 10.4, 5.6), 3.46 (1 H, dd, *J* 10.4, 5.4), 3.65 (1 H, dd, *J* 10.3, 7.8), 3.77 (1 H, dd, *J* 10.4, 7.3), 3.81 (1 H, dtd, J_d 10.8, J_t 5.5, J_d 2.1), 4.39 (1 H, q, *J* 7.2), 4.51 (1 H, dd, *J* 11.3, 2.1), 4.63 (1 H, dd, *J* 11.5, 2.5), 7.10–7.34 (20 H, m). δ_C (150 MHz, $CDCl_3$) 31.5, 33.2, 35.5, 36.3, 37.0, 40.5, 40.6, 41.6, 72.4, 73.5, 76.96 79.5, 125.7, 125.9, 126.68, 126.71, 127.6, 128.3, 128.4, 128.56, 128.61, 142.1, 142.2, 144.6, 144.7. MS (EI) *m/z* 330/332 (9/9) [M^+], 252/254 (23/23), 193 (24), 173 (10), 145 (8), 131 (27), 117 (15), 104 (100), 91 (38), 77 (25). HRMS (EI^+) *m/z* 330.0622, 330.0604, 332.0608, 332.0594 [M^+]; calculated mass for $C_{18}H_{19}OBr^+$: 330.0619, 332.0599.

4.3.3 Oxidation of like-*1-(thien-2-yl)-3-phenyl-hex-5-en-1-ol rel-(1R,3R)-**(1j)**:* A solution of alcohol *rel*-(1*R*,3*R*)-**1j** (107 mg, 416 µmol) and cobalt complex **5** (11.4 mg, 21.7 µmol) in toluene (2.0 mL), bromotrichloromethane (0.5 mL) and CHD (0.5 mL) was stirred at 70 °C for 24 h while being exposed to laboratory atmosphere. A second (11.2 mg) and third (11.5 mg) batch of cobalt catalyst were added after 2 and 5 h. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*R*,4*R*,6*R*)-6-bromomethyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*R*,4*R*,6*R*)-(13j)**. Yield: 125 mg (370 µmol, 89 %), R_f 0.54 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.64 (1 H, td, J_t 12.6, J_d 11.1), 1.89 (1 H, ddt, J_d 12.8, 3.9, J_t 2.0), 2.22 (1 H, ddd, *J* 13.8, 12.8, 5.9), 2.35–2.41 (1 H, m), 3.11 (1 H, tt, *J* 12.6, 3.6), 3.43–3.46 (2 H, m), 4.02 (1 H, dqd, J_d 5.9, J_q 5.4, J_d 2.1), 5.50 (1 H, d, *J* 5.7), 7.02–7.06 (2 H, m), 7.24–7.37 (6 H, m). δ_C (100 MHz, $CDCl_3$) 35.4, 36.0, 36.4, 37.2, 70.1, 72.2, 125.0, 125.4, 126.7, 127.1, 128.7, 144.7, 144.8. MS (EI) *m/z* 336/338 (68/68) [M^+], 258/260 (21/21), 199 (15), 179 (15), 145 (11), 131 (76), 110 (72), 104 (100), 91 (53), 77 (25). HRMS (EI^+) *m/z* 336.0171, 338.0168 [M^+]; calculated mass for $C_{16}H_{17}OSBr^+$: 336.0183, 338.0163.

*4.3.4 Oxidation of unlike-1-(thien-2-yl)-3-phenyl-hex-5-en-1-ol (rel-(1S,3R)-**(1j)***: A solution of alcohol *rel*-(1*S*,3*R*)-**1j** (105 mg, 408 µmol) and cobalt complex **5** (11.5 mg, 21.9 µmol) in toluene (2.0 mL), bromotrichloromethane (0.5 mL) and CHD (0.5 mL) was stirred at 70 °C for 24 h while being exposed to laboratory atmosphere. A second (11.5 mg) and third (11.2 mg) batch of cobalt catalyst were added after 2 and 5 h. The reaction mixture was cooled to 20 °C

and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*S*,4*R*,6*R*)-6-bromomethyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*S*,4*R*,6*R*)-(13j) and *rel*-(2*S*,4*R*,6*S*)-6-bromomethyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*S*,4*R*,6*S*)-(13j)**. Yield: 103 mg (305 µmol, 75 %) as 49/51-mixture of 2,6-*cis*/*trans*-isomers, R_f 0.50 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.57–1.64 (1 H, m), 1.87–1.98 (2 H, m), 2.10 (1 H, ddd, *J* 14.3, 12.9, 5.7), 2.17 (2 H, tdt, J_t 14.4, J_d 3.3, J_t 1.8), 2.24 (1 H, d, *J* 12.9), 3.02 (1 H, tt, *J* 12.3, 3.7), 3.08 (1 H, tt, *J* 12.6, 3.7), 3.45 (1 H, dd, *J* 10.3, 5.7), 3.56 (1 H, dd, *J* 10.3, 5.6), 3.74 (1 H, dd, *J* 10.4, 8.1), 3.87 (1 H, dd, *J* 10.4, 7.5), 3.93 (1 H, dtd, J_d 10.9, J_t 5.8, J_d 2.1), 4.47 (1 H, q, *J* 6.8), 4.86 (1 H, dd, *J* 11.2, 1.5), 5.01 (1 H, dd, *J* 11.4, 1.8), 6.97–7.01 (2 H, m), 7.02–7.05 (2 H, m), 7.24–7.39 (12 H, m). δ_C (150 MHz, $CDCl_3$) 31.3, 32.9, 35.0, 36.1, 36.8, 40.2, 40.5, 41.3, 68.6, 73.6, 75.7, 77.3, 123.6, 123.8, 124.8, 126.5, 126.71, 126.74, 128.6, 128.7, 144.2, 144.4, 145.1, 145.3. ***rel*-(2*S*,4*R*,6*R*)-(13j)**. MS (EI) *m/z* 336/338 (48/48) [M^+], 258/260 (11/11), 199 (11), 131 (57), 111 (53), 104 (100), 91 (49), 69 (25). HRMS (EI^+) *m/z* 336.0190,338.0173 [M^+]; calculated mass for $C_{16}H_{17}OSBr^+$: 336.0183, 338.0163. ***rel*-(2*S*,4*R*,6*S*)-13j**. MS (EI) *m/z* 336/338 (26/26) [M^+], 258/260 (14/14), 199 (21), 131 (63), 111 (68), 104 (100), 91 (51), 69 (30). HRMS (EI^+) *m/z* 336.0189, 338.0177 [M^+]; calculated mass for $C_{16}H_{17}OSBr^+$: 336.0183, 338.0163.

*4.3.5 Oxidation of 1-hexene and benzyl alcohol (**15**):* A solution of benzyl alcohol (**15**) (217 mg, 2.01 mmol) and cobalt complex **5** (26.8 mg, 51.0 µmol) in bromotrichloromethane (1.0 mL), CHD (1.0 mL) and 1-hexene (3.0 mL) was stirred at 70 °C for 72 h while being exposed to laboratory atmosphere. A second (26.7 mg) and third (27.1 mg) batch of cobalt catalyst were added after 24 and 48 h. The reaction mixture was cooled to 20 °C and purified by

column chromatography [SiO_2, Et_2O/pentane = 1:20 (*v*/*v*)]. 2-Benzyloxy-1-bromohexane and dibenzyl ether appeared to be inseparable and were obtained as a combined fraction. **2-Benzyloxy-1-bromohexane (22)**. Yield: 66.7 mg (246 µmol, 12 %), R_f 0.74 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 0.91 (3 H, t, *J* 7.0), 1.26–1.50 (4 H, m), 1.63–1.71 (2 H, m), 3.47 (2 H, d, *J* 5.1), 3.59 (1 H, ddt, J_d 7.0, 5.9, J_t 5.1), 4.55 (1 H, d, *J* 11.5), 4.67 (1 H, d, *J* 11.5), 7.28–7.42 (5 H, m). δ_C (100 MHz, $CDCl_3$) 14.0, 22.6, 27.3, 32.9, 35.0, 71.7, 78.2, 127.7, 128.4, 129.3, 133.3, 150.6. MS (EI) *m/z* 177 (9), 105 (3), 91 (100), 77 (3). HRMS (EI^+) *m/z* 270.0634, 272.0627 [M^+]; calculated mass for $C_{13}H_{19}OBr^+$: 270.0619, 272.0599.

4.4 Alkylative termination

4.4.1 Oxidation of like-*1,3-diphenylhex-5-en-1-ol rel-(1R,3R)-(**1i**):* A solution of alcohol *rel*-(1*R*,3*R*)-**1i** (107 mg, 423 µmol), dimethyl fumarate (355 mg, 2.46 mmol) and cobalt complex **5** (11.4 mg, 21.7 µmol) in toluene (2.0 mL) and CHD (0.5 mL) was stirred at 70 °C for 24 h while being exposed to laboratory atmosphere. A second (11.6 mg) and third (11.3 mg) batch of cobalt catalyst were added after 2 and 5 h. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*R*,4*R*,6*S*)-6-methyl-2,4-diphenyltetrahydropyran *rel*-(2*R*,4*R*,6*S*)-(3i)**. Yield: 22.1 mg (87.6 µmol, 21 %), colorless oil. **Dimethyl 2-[*rel*-(2*R*,4*R*,6*R*)-2,4-diphenyltetrahydropyranyl-6-yl]-methyl) succinate *rel*-(2*R*,4*R*,6*R*)-(14i)**. Yield: 95.1 mg (240 µmol, 57 %, 50/50-mixture of diastereoisomers with respect to the carbon in α-position to the succinate ester group, R_f 0.34 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400

MHz, $CDCl_3$) 1.39–1.53 (3 H, m), 1.58–1.77 (2 H, m), 1.97 (1 H, ddd, *J* 14.4, 9.2, 5.1), 2.04–2.16 (2 H, m), 2.40–2.84 (6 H, m), 2.79–2.91 (2 H, m), 3.10–3.23 (2 H, m), 3.38–3.54 (2 H, m), 3.58 (3 H, s), 3.61 (3 H, s), 3.62 (6 H, s), 3.59 (2 H, t, *J* 5.0), 7.12–7.27 (12 H, m), 7.31 (4 H, td, J_t 7.7, J_d 3.7), 7.37–7.43 (4 H, m). δ_C (100 MHz, $CDCl_3$) 33.3, 35.3, 36.1, 36.3, 36.9, 37.8, 37.9, 38.0, 38.8, 39.6, 39.8, 51.7, 51.8, 51.9, 67.5, 68.0, 73.3, 73.4, 126.37, 126.41, 126.78, 126.83, 126.9, 128.53, 128.55, 140.1, 140.2, 145.36 145.44, 172.1, 172.2, 175.2, 175.5. MS (EI) *m/z* 396 (1) [M^+], 346 (3), 291 (27), 259 (32), 209 (49), 193 (35), 146 (18), 115 (25), 104 (100), 91 (36), 77 (16). HRMS (EI^+) *m/z* 396.1949 [M^+]; calculated mass for $C_{24}H_{28}O_5^+$: 396.1937.

*4.4.2 Oxidation of like-1-(thien-2-yl)-3-phenyl-hex-5-en-1-ol rel-(1R,3R)-(**1j**)*: A solution of alcohol *rel*-(1*R*,3*R*)-**1j** (118 mg, 457 µmol), dimethyl fumarate (398 mg, 2.76 mmol) and cobalt complex **5** (12.1 mg, 23.0 µmol) in toluene (2.0 mL) and CHD (0.5 mL) was stirred at 70 °C for 24 h while being exposed to laboratory atmosphere. A second (11.7 mg) and third (12.2 mg) batch of cobalt catalyst were added after 2 and 5 h. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/acetone/pentane = 1:1:20 (*v*/*v*)]. ***rel*-(2*R*,4*R*,6*S*)-6-methyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*R*,4*R*,6*S*)-(3j)**. Yield: 22.2 mg (85.9 µmol, 19 %), colorless oil. **Dimethyl 2-[*rel*-(2*R*,4*R*,6*R*)-4-phenyl-2-(thien-2-yl)-tetrahydropyr-6-yl]-methyl succinate *rel*-(2*R*,4*R*,6*R*)-(14j)**. Yield: 107 mg (266 µmol, 58 %, 50/50-mixture of diastereoisomers with respect to the carbon in α-position to the succinate ester group, R_f 0.28 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.47–1.78 (6 H, m), 1.87 (1 H, ddd, *J* 14.3, 8.3, 2.8), 2.05 (1 H, ddd, *J* 14.3, 9.4, 4.8), 2.13–2.24 (2 H, m), 2.33–2.41 (2 H, m), 2.56–2.81 (4 H, m), 3.09 (2 H, app. tdt, J_t 12.4,

J_d 3.3, J_t 3.1), 3.16–3.24 (2 H, m), 3.67 (3 H, s), 3.691 (3 H, s), 3.694 (3 H, s), 3.71 (3 H, s), 5.40 (2 H, t, *J* 5.3), 3.74–3.88 (2 H, m), 6.98–7.05 (4 H, m), 7.21–7.27 (6 H, m), 7.29–7.37 (6 H, m). δ_C (100 MHz, $CDCl_3$) 35.3, 35.4, 36.5, 36.6, 36.7, 37.7, 38.0, 39.2, 39.4, 51.7, 51.8, 51.9, 68.1, 68.9, 71.6, 71.7, 124.8, 124.9, 125.1, 125.3, 126.5, 126.7, 126.97, 127.01, 128.6, 145.1, 145.2, 145.4, 145.6, 172.3, 175.2, 175.6. MS (EI) *m/z* (%) = 402 (23) [M^+], 257 (13), 215 (87), 200 (27), 146 (22), 110 (56), 104 (100), 91 (30), 77 (12). HRMS (EI^+) *m/z* 402.1510 [M^+]; calculated mass for $C_{22}H_{26}O_5S^+$: 402.1501.

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Supplementary data. Instrumentation, reagent specification, preparation of alkenols, carbon-13 NMR-spectra of selected compounds, and *A*-value analysis of 2-phenyltetrahydropyran. Supplementary data associated with this article can be found in the online version at doi: ....

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6 Anhang

6.1 Allgemeine experimentelle Methoden

6.1.1 Verwendete Messgeräte

Kernresonanzspektren (^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR): Die ^{1}H-, ^{13}C- und ^{19}F-NMR-Spektren wurden bei Raumtemperatur an den FT-NMR-Geräten DPX 200, DPX 400 und DMX 600 der Fa. Bruker aufgenommen. Die chemischen Verschiebungen der Signale sind in Einheiten der δ-Skala angegeben [ppm]. Als interner Standard dienten bei ^{1}H-NMR-Spektren die Resonanzsignale der Restprotonen des verwendeten deuterierten Lösungsmittels [7.26 ($CDCl_3$)] bzw. die entsprechenden Resonanzsignale bei ^{13}C-NMR-Spektren [77.0 ($CDCl_3$)]. Als interner Standard bei ^{19}F-NMR-Spektren diente α,α,α-Trifluortoluol (–63.72).[2] Die Multiplizität der Signale wird durch folgende Abkürzungen wiedergegeben:
s = Singulett, d = Dublett, t = Triplett, q = Quartett, quin = Quintett und m = Multiplett. Die Kopplungskonstanten J sind in Hertz (Hz) angegeben.

Probenvorbereitung für NOE-Experimente: Die NOE-Proben (in $CDCl_3$ bzw. CD_3OD) wurden durch 10-minütiges Einleiten von Argon im Ultraschallbad gespült und sorgsam verschlossen. Die Spektren wurden an einem DMX 600 Spektrometer der Fa. Bruker aufgenommen.

6.1.2 Chromatographische Methoden

Dünnschichtchromatographie (DC): Es wurden Kieselgel-Aluminiumfolien 60 F254 der Fa. Merck verwendet. Zur Detektion der Substanzen wurden die Fluoreszenzlöschungen bei 254 nm, die Anregung der Eigenfluoreszenzen bei 366 nm sowie das Färbeverhalten gegenüber Schwefelsäure-Anisaldehyd-Reagenz (Ekkerts-Reagenz) genutzt. Die angegeben R_f-Werte beziehen sich auf die oben genannten Kieselgel-Aluminiumfolien.

Säulenchromatographie (SC): Als Säulenfüllmaterial diente Kieselgel der Fa. Merck mit einer Korngröße von 0.063–0.200 mm. Die Säulen wurden nass befüllt.

Gaschromatogramme/Massenspektren(GC/MS): Für die GC/MS-Analysen wurde der Auto-Sampler 7683 Series, der Gaschromatograph 6890N und das Massenspektrometer 5973 der Fa. Agilent Technologies verwendet. Die Auswertung wurde mit Hilfe der Software MSD Chemstation D01.02.16 durchgeführt. Als Trägergas diente Helium mit einer Flussrate von 1 ml/min (59.7 kPa). Die Injektor- und Detektortemperaturen betrugen 250 °C. Zur Trennung wurde eine HP-5-MS-Säule (30 m × 0.25 mm, 0.25 μm Filmdicke) der Fa. Agilent (Model No. 19091S-433) verwendet. Dabei lag das Splitverhältnis bei 1:10 bzw. 1:100.

Temperaturprogramm: Anfangstemperatur 40 °C (3 min), linearer Temperaturanstieg (10 °C/min) bis 280 °C, Endtemperatur 280 °C (10 min).
MS/SIM Scan Parameters: solvent delay 4 min, Scan-Modus mit Scanbereich von 50-800 u, Ionisierungsenergie 70 eV.

6.1.3 Vorbereitung der Versuche

Lösungsmittel und Inertgas: Die verwendeten Lösungsmittel wurden nach Standardmethoden gereinigt und getrocknet.[1] Als Inertgas wurde Stickstoff verwendet.

6.2 Ergänzende Experimentelle Daten zu Kapitel 3

Supporting Information for

Synthesis of Functionalized Tetrahydrofurans from Alkenols and Olefins/Alkynes via Aerobic Oxidation – Radical Addition Cascades

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2 Instrumentation and Reagent Specification S2
3 Cobalt Complexes S3
4 Oxidation – Radical Addition Cascades S3
5 NMR Spectra of Selected Compounds S17
6 References S25

1 General Remarks

(i) The compound numbering in the Supporting information is consistent with that of the accompanying publication. (ii) References refer exclusively to the Supporting Information.

2 Instrumentation and Reagent Specification

^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded with FT-NMR DPX 400 and DMX 600 instruments (*Bruker*). Chemical shifts refer to the δ-scale (coupling constants J are given in Hz). The resonances of residual protons and the corresponding carbons of deuterated solvents ($CDCl_3$: δ_H 7.26, δ_C 77.0) were used as internal standards for ^{1}H-, and ^{13}C-NMR. ^{19}F-NMR chemical shifts were referenced versus α,α,α-Trifluorotoluene (δ_F −63.72) as internal standard.

Mass spectra (EI, 70 eV) were recorded with a Mass Selective Detector HP 6890 (*Hewlett Packard*).

Combustion analyses were performed with a vario Micro cube CHNS (*Elementar Analysentechnik / Hanau*).

Reaction progress was monitored via thin layer chromatography (TLC) on aluminium sheets coated with silica gel (60 F_{254}, *Machery-Nagel*). Compounds were detected by UV-light (254 nm) or by staining of developed TLC sheets with Ekkert's reagent.

IR spectra were recorded from pelletized samples in KBr using a FT-IR 1000 spectrometer (*Perkin Elmer*).

UV/Vis-spectra were recorded in 1 cm-quartz cuvettes with a Cary 100 spectrometer (*Varian*) at 20 °C using analytical grade solvents. Molar extinction coefficients (ε) are reported in m^2mol^{-1}.

GC/MS Analysis was performed with a HP 6890 Series (*Hewlett Packard*) with a ZB5 column (*Phenomenex*, 30 m × 0.25 mm, 0.25 µm). Temperature program: 40 °C (3 min), linear temperature rise (10 °C min^{-1}) to 280 °C, final temperature 280 °C (10 min).

All solvents were purified according to standard procedures.[1]

1-Phenylpent-4-en-1-ol (**1a**),[2,3] 1-phenylhex-4-en-1-ol (**1b**),[2] 2-phenylpent-4-en-1-ol (**1c**),[4] 3-phenylpent-4-en-1-ol (**1d**)[2,5] *cis*-2-allylcyclohexanol (**1e**)[6] , methyl 3-(2-hydroxy-cyclohex-1-yl)-prop-2-enoate (**1f**)[6,7], 1-phenylpent-4-en-1,3-diol (**1g**)[8] and bis-{4-[3,5-bis-(trifluoromethyl)-phenyl]-(2-oxo-κ*O*)-but-3-en-(4-olato-κ*O*)}-cobalt(II) (**3**)[7] were prepared according to published procedures.

3 Cobalt Complexes

Bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (4): A solution of benzoyltrifluoroacetone (2.01 g, 9.27 mmol) in EtOH (6.0 mL) was added to an aqueous solution of cobalt(II) acetate tetrahydrate (1.11 g, 4.46 mmol in 20 mL H_2O) and stirred at 20 °C for 1 h. The yellow precipitate was filtered and dried in vacuo. Yield: 2.32 g, 4.42 mmol, 99%; λ_{max} (EtOH) / nm (lg $\varepsilon/\varepsilon^*$) 252 (3.33), 319 (3.55); ν_{max} (KBr) / cm^{-1} 3383 (OH), 1608 (CO), 1574, 1535, 1490, 1460, 1433, 1288, 1252, 1186, 1163, 1132, 1077, 1026; δ_F ($CDCl_3$/acetone, 377 MHz) 6.1; Anal. calcd for $C_{20}H_{16}CoF_6O_6$ (525.26): C 45.73; H 3.07. Found: C 45.97; H 3.16.

4 Oxidation – Radical Addition Cascades

4.1 Comparing reactivity of cobalt(II) complexes in aerobic alkenol turnover

Cobalt complex **3** () or **4** () (15 µmol) was added to a solution of alcohol **1a** (0.5 mmol) in acrylonitrile (0.2 mL), CHD (0.8 mL) and toluene (1.0 mL). The reaction mixture was stirred at 60 °C while being exposed to laboratory atmosphere. Turnover of substrate **1a** was measured via GC in time intervals (Figure S1).

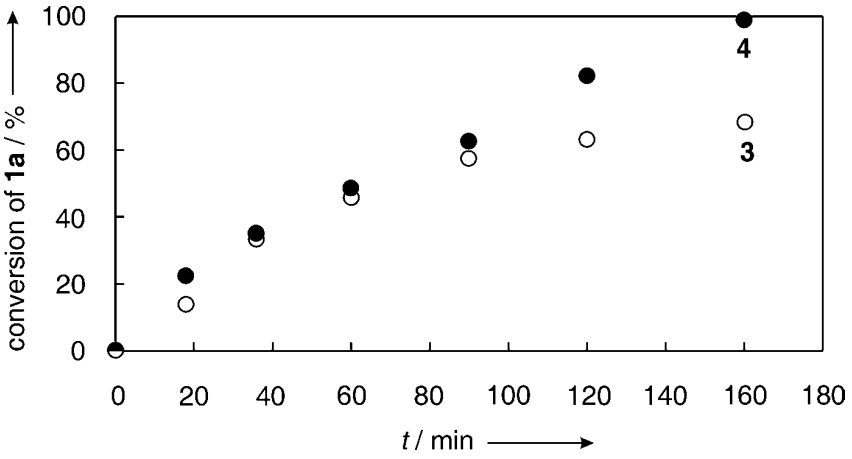

Figure S1. Time-dependency of 1-phenyl-4-penten-1-ol turnover using cobalt complexes **3**(○) and 4 (●) (60 °C, 3 mol % catalyst).

4.2 Oxidation of 1-phenylpent-4-en-1-ol (1a)

4.2.1 Reaction with acrylonitrile: A solution of alcohol **1a** (123 mg, 755 µmol) and Bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (**4**) (11.8 mg, 22.5 µmol) in γ-terpinene (1.4 mL, 98%, 8.5 mmol), toluene (0.65 mL) and acrylonitrile (**2a**) (201 mg, 3.79 mmol) was stirred at 75 °C for 6 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified without further concentration by column chromatography [SiO_2, acetone/pentane = 1:10 → 1:5 (*v*/*v*)]. ***trans*-2-methyl-5-phenyltetrahydrofuran (5a)**. Yield: 20.0 mg (123 µmol, 16 %). Analytical data agree with published values.[2] **4-(*trans*-5-phenyltetrahydrofur-2-yl)-butyronitrile (6).** Yield: 71.0 mg (330 µmol, 44 %, *cis*:*trans* <1:99), R_f 0.36 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.65–1.94 (6 H, m), 2.15–2.20 (1 H, m), 2.35–2.40 (1 H, m), 2.45 (2 H, td, J_t 7.0, J_d 2.0), 4.22 (1 H, quint, *J* 6.6), 4.99 (1 H, dd, *J* 8.2, 6.4), 7.24–7.31 (5 H, m). δ_C (150 MHz, $CDCl_3$) 17.2, 22.6, 32.5, 34.9, 35.1, 78.9, 80.3, 119.7 (CN), 125.5, 127.2, 128.3, 143.5. GC-MS (EI, 70 eV) *m/z* (%) 215 (52, M^+), 157 (17), 147 (61), 130 (42), 120 (93), 105 (100), 91 (98), 77 (52), 65 (17), 51 (30). Anal. calcd for $C_{14}H_{17}NO$ (215.29): C 78.10; H 7.96; N 6.51. Found: C 78.05; H 8.00; N 6.80. **[2-(*trans*-5-phenyltetrahydrofur-2-yl)-eth-1yl]-glutarodinitrile (10).** Yield: 29.7 mg (111 µmol, 15 %, *cis*:*trans* <1:99, 50/50-mixture of *rel*-2*S*/2*R*-diastereoisomers), R_f 0.24 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 600 MHz) 1.66–1.94 (6 H, m), 1.99 (2 H, dt, J_d 14.6, J_t 6.5), 2.16–2.22 (1 H, m), 2.35–2.40 (3 H, m), 2.52–2.65 (2 H, m), 2.83–2.90 (1 H, m), 4.19–4.25 (1 H, m), 4.97–5.01 (1 H, m), 7.24–7.35 (5 H, m). δ_C ($CDCl_3$, 150 MHz) 15.4, 28.2 / 28.4, 28.6 / 29.5, 30.6 / 31.2, 32.5 / 32.6, 33.2 / 33.7, 35.1 / 35.2, 78.5 / 79.3, 80.4, 118.0 (CN), 120.3 / 120.4 (CN), 125.6, 127.3, 128.4, 143.3.

4.2.2 Reaction with methyl acrylate: A solution of alcohol **1a** (122 mg, 751 µmol) and Bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (**4**) (11.8 mg, 22.5 µmol) in γ-terpinene (1.4 mL, 98%, 8.5 mmol), toluene (0.5 mL) and methyl acrylate (**2b**) (330 mg, 3.79 mmol) was stirred at 75 °C for 6 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified without further concentration by column chromatography [SiO_2, acetone/pentane = 1:10 → 1:5

(*v*/*v*)]. ***trans*-2-methyl-5-phenyltetrahydrofuran (5a)**. Yield: 36.4 mg (224 µmol, 30 %). Analytical data agree with published values.[2]

Methyl 4-(*trans*-5-phenyltetrahydrofur-2-yl)-butyrate (7). Yield: 60.4 mg (243 µmol, 32 %, *cis*:*trans* <1:99), R_f 0.58 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 400 MHz) 1.53–1.90 (6 H, m), 2.11–2.19 (1 H, m), 2.31–2.39 (3 H, m), 3.67 (3 H, s), 4.20 (1 H, quint, *J* 6.3), 4.98 (1 H, t, *J* 7.3), 7.22–7.34 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 21.7, 32.3, 34.0, 35.3, 35.4, 51.4 (Me), 79.5, 80.1, 125.5, 127.0, 128.2, 143.8, 174.0. GC-MS (70 eV, EI) *m/z* (%) 248 (2, M^+), 147 (53), 144 (56), 129 (44), 120 (100), 112 (50), 105 (48), 91 (89), 77 (30). **Dimethyl [2-(*trans*-5-phenyltetrahydrofur-2-yl)-eth-1-yl]-glutarate (11).** Yield: 33.7 mg (101 µmol, 13 %, *cis*:*trans* <1:99, 50/50-mixture of *rel*-2*S*/2*R*-diastereoisomers), R_f 0.32 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 400 MHz) 1.47–1.73 (5 H, m), 1.77–1.96 (3 H, m), 2.10–2.17 (1 H, m), 2.29–2.40 (3 H, m), 2.43–2.49 (1 H, m), 3.67 (3 H, s), 3.68 (3 H, s), 4.11–4.20 (1 H, m), 4.97 (1 H, t, *J* 7.3), 7.21–7.37 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 27.0 / 27.2, 28.6 / 28.9, 31.7, 32.2 / 32.3, 33.5 / 33.8, 35.21 / 35.25, 44.5 / 44.7, 51.6 (Me), 79.4 / 79.6, 80.11 / 80.14, 125.5, 127.0, 128.2, 143.68 / 143.70, 173.35 / 173.38, 175.8 / 175.9. GC-MS (70 eV, EI) *m/z* (%) 334 (<1, M^+), 274 (10), 253 (13), 230 (20), 215 (40), 183 (22), 166 (34), 147 (86), 129 (53), 120 (66), 105 (75), 91 (100), 77 (30).

4.2.3 Reaction with methyl vinyl ketone: A solution of alcohol **1a** (163 mg, 1.00 mmol) and bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (**4**) (15.8 mg, 30.1 µmol) in γ-terpinene (1.9 mL, 98%, 11.5 mmol), toluene (0.8 mL) and methyl vinyl ketone (**2c**) (355 mg, 5.06 mmol) was stirred at 75 °C for 7 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified without further concentration by column chromatography [SiO_2, acetone/pentane = 1:10 → 1:5 (*v*/*v*)]. ***trans*-2-methyl-5-phenyltetrahydrofuran (5a)**. Yield: 44.5 mg (274 µmol, 27 %). Analytical data agree with published values.[2] **5-(*trans*-2-phenyltetrahydrofur-5-yl)-pentan-2-one (8).** Yield: 73.0 mg (314 µmol, 31 %, *cis*:*trans* <1:99), R_f 0.40 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 400 MHz) 1.49–1.76 (5 H, m), 1.79–1.89 (1 H, m), 2.09–2.18 (1 H, m), 2.13 (3 H, s), 2.32–2.39 (1 H, m), 2.49 (2 H, t, *J* 6.6), 4.18 (1 H, quint, *J* 6.5), 4.97 (1 H, dd, *J* 8.0, 6.6), 7.21–7.32 (5 H, m). δ_C ($CDCl_3$, 100

MHz) 20.5, 29.9 (Me), 32.4, 35.3, 35.4, 43.7, 79.6, 80.2, 125.5, 127.0, 128.3, 143.8, 209.1. GC-MS (70 eV, EI) *m/z* (%) 232 (3, M^+), 214 (4), 147 (44), 128 (57), 120 (64), 117 (38), 105 (45), 91 (100), 77 (34). **[3-(*trans*-2-phenyltetrahydrofur-5-yl)-eth-1-yl]-heptane-2,6-dione (12).** Yield: 38.7 mg (128 µmol, 13 %, *cis*:*trans* <1:99, 50/50-mixture of *rel*-3*S*/3*R*-diastereoisomers), R_f 0.20 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 600 MHz) 1.45–1.89 (8 H, m), 2.10–2.19 (7 H, m), 2.32–2.46 (3 H, m), 2.48–2.55 (1 H, m), 4.10–4.15 (1 H, m), 4.93–4.98 (1 H, m), 7.23–7.35 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 24.5 / 24.7, 27.8 / 28.0, 28.6 / 29.0, 30.0 (Me), 32.3 / 32.4 (Me), 33.5 / 33.6, 35.2, 40.77 / 40.82, 51.8 / 51.9, 79.5 / 79.7, 80.2, 125.5, 127.1, 128.3, 143.7, 208.1, 212.1 / 212.2. GC-MS (70 eV, EI) *m/z* (%) 302 (<1, M^+), 284 (12), 226 (4), 183 (30), 147 (57), 129 (46), 120 (35), 117 (32), 105 (46), 91 (100), 77 (30).

4.2.4 Reaction with methyl vinyl sulfone: A solution of alcohol **1a** (123 mg, 755 µmol) and bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (**4**) (11.8 mg, 22.5 µmol) in cyclohexa-1,4-diene (0.9 mL, 9.2 mmol), toluene (0.9 mL) and methyl vinyl sulfone (**2d**) (459 mg, 4.24 mmol) was stirred at 75 °C for 16 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified without further concentration by column chromatography [SiO_2, acetone/pentane = 1:5 (*v*/*v*)]. ***trans*-2-methyl-5-phenyltetrahydrofuran (5a).** Yield: 24.3 mg (150 µmol, 20 %). Analytical data agree with published values.[2] **3-(*trans*-5-phenyltetrahydrofur-2-yl)-prop-1-yl methyl sulfone (9).** Yield: 87.1 mg (325 µmol, 43 %, *cis*:*trans* = <1:99), R_f 0.12 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 600 MHz) 1.65–1.71 (1 H, m), 1.75 (2 H, q, *J* 7.2), 1.83–1.90 (1 H, m), 1.96–2.10 (2 H, m), 2.14–2.19 (3 H, m), 2.34–2.39 (1 H, m), 2.90 (3 H, s), 3.06–3.17 (2 H, m), 4.22 (1 H, dt, J_d 14.1, J_t 6.1), 4.98 (1 H, dd, *J* 8.3, 6.7), 7.23–7.34 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 19.8, 32.4, 34.4, 35.2, 40.4 (Me), 54.8, 79.1, 80.3, 125.5, 127.2, 128.3, 143.4. GC-MS (70 eV, EI) *m/z* (%) 268 (2, M^+), 250 (2), 164 (8), 147 (20), 129 (20), 120 (100), 105 (31), 91 (42), 77 (16).

4.2.5 Reaction with fumaronitrile: A suspension of alcohol **1a** (164 mg, 1.01 mmol) and bis-{4-[3,5-bis-(trifluoromethyl)-phenyl]-(2-oxo-κ*O*)-but-3-en-(4-olato-κ*O*)}-cobalt(II) (**3**) (33.2 mg, 50.8 µmol) in cyclohexa-1,4-diene (1.0 mL, 10.2 mmol), toluene (1.6 mL) and

fumaronitrile (**2e**) (396 mg, 5.07 mmol) was stirred at 60 °C for 21 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C. Unspent fumaronitrile was removed by filtration and the filtrate was purified by column chromatography [SiO_2, acetone/pentane = 1:5 → 1:3 (*v*/*v*)]. ***trans*-2-methyl-5-phenyltetrahydrofuran (5a)**. Yield: 3.1 mg (19.1 µmol, 2 %). Analytical data agree with published values.[2] **2-[(*trans*-5-phenyltetrahydrofur-2-yl)-methyl]-succinodinitrile (17a).** Yield: 161 mg (670 µmol, 66 %, *cis*:*trans* <1:99, 50/50-mixture of *rel*-2*S*/2*R*-diastereoisomers), R_f 0.22 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. 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, 3*-H), 2.83–2.95 (2 H, m, 3**-H), 3.21 (1 H, quint, *J* 6.5, 2*-H), 3.26–3.31 (1 H, m, 2**-H), 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, 142.56 / 142.59. 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. GC-MS (70 eV, EI) *m/z* (%) 240 (31, M^+), 223 (6), 183 (12), 146 (14), 129 (9), 117 (32), 105 (100), 91 (44), 77 (37).

4.2.6 Reaction with dimethyl fumarate: A suspension of alcohol **1a** (168 mg, 1.04 mmol) and bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (**4**) (15.8 mg, 30.0 µmol) in γ-terpinene (1.5 mL, 98%, 9.1 mmol), toluene (1.0 mL) and dimethylfumarate ((*E*)-**2f**) (720 mg, 5.00 mmol) was stirred at 60 °C for 20 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C. Unspent dimethylfumarate was removed by filtration and the filtrate was purified by column chromatography [SiO_2, acetone/PE = 1:5 (*v*/*v*)]. ***trans*-2-methyl-5-phenyltetrahydrofuran (5a)**. Yield: 48.0 mg (296 µmol, 28 %). Analytical data agree with published values.[2] **dimethyl 2-[(*trans*-5-phenyltetrahydrofur-2-yl)-methyl]-succinate (18a).** Yield: 192 mg (625 µmol, 60 %, *cis*:*trans* <1:99, 50/50-mixture of *rel*-2*S*/2*R*-diastereoisomers), R_f 0.21 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 400 MHz) 1.60–1.87 (3 H, m), 1.91–2.08 (1 H, m), 2.11–2.22 (1 H, m), 2.32– 2.40 (1 H, m), 2.58–2.82 (2 H, m), 3.01–3.13 (1 H, m), 3.66 / 3.70 (3 H, s), 3.67 (3 H, s), 4.20– 4.27 (1 H, m), 4.96 (1 H, t, *J* 7.3), 7.23–7.36 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 32.6, 35.0, 35.7 / 36.2, 37.8 / 38.0, 38.9 / 39.1, 51.7 (Me), 51.9 (Me), 77.1 / 77.7, 80.0, 125.4 / 125.5 , 127.0, 128.3, 143.5 / 143.6, 172.3, 175.2 / 175.3. Anal. calcd for $C_{17}H_{22}O_5$ (306.35): C 66.65; H 7.24. Found: C 66.21; H 7.13.

GC-MS (70 eV, EI) *m/z* (%) 306 (1, M^+), 274 (3), 246 (4), 225 (26), 202 (31), 187 (46), 170 (37), 155 (41), 147 (30), 129 (36), 120 (67), 105 (73), 91 (100), 77 (34).

4.2.7 Reaction with dimethyl maleate :A solution of alcohol **1a** (163 mg, 1.01 mmol) and bis-{4-[3,5-bis-(trifluoromethyl)-phenyl]-(2-oxo-κ*O*)-but-3-en-(4-olato-κ*O*)}-cobalt(II) (**3**) (32.9 mg, 50.4 µmol) in 1,4-cyclohexadiene (1.0 mL, 97% 10.2 mmol), toluene (1.3 mL) and dimethyl maleate ((*Z*)-**2f**) (755 mg, 5.24 mmol) was stirred at 60 °C for 6 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified without further concentration by column chromatography [SiO_2, acetone/pentane = 1:10 → 1:5 (*v*/*v*)]. ***trans*-2-methyl-5-phenyltetrahydrofuran (5a)**. Yield: 84.1 mg (518 µmol, 52 %). Analytical data agree with published values.[2] **dimethyl 2-[(*trans*-5-phenyltetrahydrofur-2-yl)-methyl]-succinate (18a).** Yield: 73.9 mg (241 µmol, 24 %, *cis*:*trans* <1:99, 50/50-mixture of *rel*-2*S*/2*R*-diastereoisomers), colorless oil.

4.2.8 Reaction with *N*-phenylmaleimide: A solution of alcohol **1a** (126 mg, 774 µmol) and bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (**4**) (11.8 mg, 22.5 µmol) in γ-terpinene (1.4 mL, 98%, 8.5 mmol), toluene (0.2 mL) and *N*-phenylmaleimide (**2g**) (665 mg, 3.76 mmol) was stirred at 75 °C for 6 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified without further concentration by column chromatography [SiO_2, acetone/pentane = 1:10 → 1:5 → 1:3 (*v*/*v*)]. ***trans*-2-methyl-5-phenyltetrahydrofuran (5a)**. Yield: 8.3 mg (51.2 µmol, 7 %). Analytical data agree with published values.[2] **2-[(*trans*-5-phenyltetrahydrofur-2-yl)-methyl]-*N*-phenylsuccinimide (19).** Yield: 170 mg (505 µmol, 65 %, *cis*:*trans* <1:99, 50/50-mixture of *rel*-2*S*/2*R*-diastereoisomers), **Isomer 1:** R_f 0.16 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 400 MHz) 1.71–1.80 (1 H, m), 1.85–1.95 (2 H, m), 2.20–2.33 (1 H, m), 2.37–2.45 (1 H, m), 2.85 (1 H, dd, *J* 18.3, 5.2), 3.09 (1 H, dd, *J* 18.3, 9.3), 3.30–3.36 (1 H, m), 4.30–4.36 (1 H, m), 5.04 (1 H, t, *J* 7.2), 7.24–7.41 (8 H, m), 7.47 (2 H, t, *J* 7.6). δ_C ($CDCl_3$, 100 MHz) 32.6, 34.7, 34.8, 36.9, 37.8, 76.6, 80.3, 125.5, 126.4, 127.2, 128.4, 128.5, 129.1, 132.0, 143.1, 175.7 (CO), 179.0 (CO). **Isomer 2:** R_f 0.13 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless crystalline solid. δ_H ($CDCl_3$, 400 MHz) 1.70–1.78 (1 H, m), 1.84–1.93 (1 H, m), 2.32–2.46 (3 H, m), 2.07–2.18

(2 H, m), 2.19–2.29 (1 H, m), 2.36–2.43 (1 H, m), 2.89–3.16 (3 H, m), 4.44–4.51 (1 H, m), 4.95 (1 H, t, *J* 7.2), 7.14 (2 H, d, *J* 8.1), 7.28–7.35 (8 H, m). δ_C ($CDCl_3$, 100 MHz) 32.4, 33.7, 34.8, 36.5, 38.5, 77.1, 80.1, 125.6, 126.5, 127.2, 128.2, 128.3, 128.9, 132.1, 142.9, 175.9 (CO), 179.2 (CO). Anal. calcd for $C_{21}H_{21}NO_3$ (335.40): C 75.20; H 6.31; N 4.18. Found: C 74.83; H 6.19; N 4.10. GC-MS (70 eV, EI): *m/z* (%) = 335 (18, M^+), 231 (80), 216 (100), 188 (73), 175 (65), 161 (52), 147 (25), 120 (74), 105 (62), 91 (98), 77 (55).

4.2.9 Reaction with ethyl propiolate: A solution of alcohol **1a** (164 mg, 1.01 mmol) and bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (**4**) (15.8 mg, 30.0 μmol) in γ-terpinene (1.9 mL, 98%, 11.5 mmol), toluene (0.6 mL) and ethyl propiolate (**20a**) (505 mg, 5.04 mmol) was stirred at 75 °C for 7 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified without further concentration by column chromatography [SiO_2, acetone/pentane = 1:10 → 1:5 (*v*/*v*)]. ***trans*-2-methyl-5-phenyltetrahydrofuran (5a)**. Yield: 68.0 mg (419 μmol, 41 %). Analytical data agree with published values.[2] **Ethyl (*Z*)-4-(5-Phenyltetrahydrofur-2-yl)-but-2-en-oate (*Z*)-(21).** Yield: 56.7 mg (218 μmol, 22 %, *cis*:*trans* <1:99), R_f 0.46 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 400 MHz) 1.29 (1 H, t, *J* 7.1), 1.70–1.79 (1 H, m), 1.82–1.91 (1 H, m), 2.12–2.19 (1 H, m), 2.34–2.42 (1 H, m), 2.93–3.08 (2 H, m), 4.18 (2 H, q, *J* 7.1), 4.36 (1 H, quint, *J* 6.6), 5.02 (1 H, t, *J* 7.2), 5.89 (1 H, d, *J* 11.6), 6.41 (1 H, dt, J_d 11.6, J_t 7.3), 7.22–7.33 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 14.2, 31.9, 35.17, 35.21, 59.8, 78.9, 80.5, 121.2, 125.6, 127.1, 128.3, 143.5, 146.3, 166.4. GC-MS (70 eV, EI) *m/z* (%) 260 (<1, M^+), 215 (5), 169 (5), 156 (5), 147 (100), 129 (57), 117 (20), 105 (25), 91 (95), 77 (21). **Ethyl (*E*)-4-(5-Phenyltetrahydrofur-2-yl)-but-2-en-oate (*E*)-(21).** Yield: 65.1 mg (250 μmol, 25 %, *cis*:*trans* <1:99), R_f 0.37 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 400 MHz) 1.28 (1 H, t, *J* 7.1), 1.66–1.75 (1 H, m), 1.82–1.92 (1 H, m), 2.12–2.19 (1 H, m), 2.33–2.40 (1 H, m), 2.44–2.61 (2 H, m), 4.19 (2 H, q, *J* 7.1), 4.35 (1 H, quint, *J* 6.6), 5.02 (1 H, t, *J* 7.2), 5.93 (1 H, d, *J* 15.3), 7.00 (1 H, dt, J_d 15.3, J_t 7.6), 7.22–7.34 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 14.2, 31.9, 35.1, 38.7, 60.2, 78.1, 80.6, 123.5, 125.5, 127.1, 128.3, 143.3, 145.0, 166.4. GC-MS (70 eV, EI) *m/z* (%) 260 (6, M^+), 214 (1), 147 (100), 129 (45), 117 (12), 105 (20), 91 (64), 77 (8).

4.2.10 Reaction with dimethyl acetylenedicarboxylate: A solution of alcohol **1a** (164 mg, 1.01 mmol) and bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (**4**) (15.8 mg, 30.0 μmol) in γ-terpinene (1.9 mL, 98%, 11.5 mmol), toluene (0.4 mL) and dimethyl acetylenedicarboxylate (**20b**) (727 mg, 5.01 mmol) was stirred at 75 °C for 7 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified without further concentration by column chromatography [SiO_2, acetone/pentane = 1:10 → 1:5 (*v*/*v*)]. ***trans*-2-methyl-5-phenyltetrahydrofuran (5a)**. Yield: 45.1 mg (278 μmol, 28 %). Analytical data agree with published values.[2] **Dimethyl 2-[(*trans*-5-phenyltetrahydrofuran-2-yl)methyl]-maleate (*Z*)-(22).** Yield: 59.6 mg (196 μmol, 19 %, *cis*:*trans* = <1:99), R_f 0.42 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. 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 (Me), 52.5 (Me), 78.4, 79.9, 125.6, 127.0, 127.7, 128.2, 143.4, 144.7, 166.2, 167.4. GC-MS (70 eV, 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-phenyltetrahydrofuran-2-yl)methyl]-fumarate (*E*)-(22).** Yield: 96.1 mg (316 μmol, 31 %, *cis*:*trans* = <1:99), R_f 0.21 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. 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, 35.0, 40.6, 51.8 (Me), 52.4 (Me), 77.1, 80.5, 121.8, 125.4, 127.1, 128.3, 143.2, 146.9, 165.3, 169.0. GC-MS (70 eV, EI) *m/z* (%) 304 (3, M^+), 272 (6), 244 (4), 185 (9), 147 (97), 129 (54), 120 (21), 105 (31), 91 (100), 77 (24).

4.3 Oxidation of 1-phenylhex-4-en-1-ol (1b)

4.3.1 Reaction with fumaronitrile: A solution of alcohol **1b** (181 mg, 1.03 mmol) and bis-{4-[3,5-bis-(trifluoromethyl)-phenyl]-(2-oxo-κ*O*)-but-3-en-(4-olato-κ*O*)}-cobalt(II) (**3**) (66.2 mg, 101 μmol)) in 1,4-cyclohexadiene (1.0 mL, 98%, 10.2 mmol), toluene (1.6 mL) and fumaronitrile (**2e**) (400 mg, 5.02 mmol), was stirred at 60 °C for 21 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C. Unspent

fumaronitrile was removed by filtration and the filtrate was purified by column chromatography [SiO_2, acetone/pentane = 1:5 → 1:3 (*v*/*v*)]. **2-[1-(*trans*-5-phenyltetrahydrofur-2-yl)-eth-1-yl]-succinodinitrile (17b).** Yield: 150 mg (58 %, *cis*:*trans* <1:99, 50/50-mixture of *rel*-2*S*/2*R*- and *rel*-1'*S*/1'*R*-diastereoisomers), colorless oil. δ_H ($CDCl_3$, 400 MHz) (1 isomer) 1.13 (3 H, d, *J* 6.8), 1.71–1.91 (2 H, m), 2.08–2.15 (1 H, m), 2.23–2.29 (1 H, m), 2.36–2.42 (1 H, m), 2.85–2.93 (1 H, m), 3.11–3.20 (2 H, m), 4.13–4.19 (1 H, m), 5.03 (1 H, dd, *J* 8.4, 6.3), 7.28–7.37 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 15.1, 19.4, 32.3, 33.8, 35.0, 39.9, 81.2, 81.3, 116.8 (CN), 118.1 (CN), 125.3, 127.4, 128.4, 142.7. GC-MS (70 eV, EI) *m/z* (%) 254 (24, M^+), 197 (14), 171 (11), 147 (62), 129 (42), 117 (35), 105 (35), 91 (100), 77 (38).

4.4 Oxidation of 2-phenylpent-4-en-1-ol (1c)

4.4.1 Reaction with fumaronitrile: A solution of alcohol **1c** (174 mg, 1.07 mmol) and bis-{4-[3,5-bis-(trifluoromethyl)-phenyl]-(2-oxo-κ*O*)-but-3-en-(4-olato-κ*O*)}-cobalt(II) (**3**) (32.8 mg, 50.2 μmol)) in 1,4-cyclohexadiene (1.0 mL, 98%, 10.2 mmol), toluene (1.6 mL) and fumaronitrile (**2e**) (401 mg, 5.03 mmol), was stirred at 60 °C for 21 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C. Unspent fumaronitrile was removed by filtration and the filtrate was purified by column chromatography [SiO_2, acetone/pentane = 1:5 → 1:3 (*v*/*v*)]. **2-[(4-phenyltetrahydrofur-2-yl)-methyl]-succinodinitrile (17c).** Yield: 149 mg (620 μmol, 58 %, *cis*:*trans* = 74:26, 50/50-mixture of *rel*-2*S*/2*R*-diastereoisomers), colorless oil. δ_H ($CDCl_3$, 600 MHz) 1.69–1.77 (1 H, m, *cis*), 1.94 (2 H, ddd, *J* 13.8, 10.2, 5.1, *trans*), 2.03–2.15 (3 H, m, *trans*, *cis*), 2.27 (1 H, dq, J_d 7.3, J_q 7.3, *trans*), 2.56 (1H, dq, J_d 7.3, J_q 6.5, *cis*), 2.82–2.97 (4 H, m, *cis*, *trans*), 3.21 (1 H, quint, *J* 6.5, *cis*/*trans*-2*-H), 3.29–3.29 (1 H, m, *cis*/*trans*-2**-H), 3.45–3.54 (2 H, m, *cis*, *trans*), 3.76 (1 H, td, J_t 8.3, J_d 3.2, *trans*), 3.83 (1 H, dt, J_d 14.9, J_t 8.5, *cis*), 4.17 (1 H, t, *J* 8.2, *cis*-THF-5*-H), 4.20–4.27 (2 H, m, *cis*-THF-5**-H, *trans*-THF-5*-H), 4.33–4.39 (1 H, m, *trans*-THF-5**-H) 7.23–7.34 (10 H, m, *cis*, *trans*). δ_C ($CDCl_3$, 100 MHz) 20.3 / 21.3 (*trans*), 20.4 / 21.1 (*cis*), 25.7 / 26.2 (*trans*), 26.1 / 26.6 (*cis*), 35.9 / 37.6 (*cis*), 36.4 / 38.0 (*trans*), 39.8 (*trans*), 40.8 / 41.0 (*cis*), 44.2 / 44.4 (*trans*), 45.1 / 45.2 (*cis*), 74.2 / 74.4 (*cis*), 74.7 / 74.8 (*trans*), 75.3 / 76.0 (*trans*), 76.2 / 76.9 (*cis*), 115.6 / 115.9 (CN), 118.7 / 118.9 (CN), 126.80 / 126.82, 127.1 / 127.2, 128.68 / 128.70, 141.3 / 141.4. Anal. calcd for $C_{15}H_{16}N_2O$ (240.30): C 74.97; H 6.71; N 11.66. Found: C 74.64; H 6.84; N

11.54. GC-MS (70 eV, EI) *m/z* (%) 240 (17, M^+), 209 (8), 156 (30), 147 (18), 129 (27), 117 (100), 108 (24), 91 (83), 77 (21).

4.4.2 Reaction with dimethyl fumarate: A solution of alcohol **1c** (151 mg, 929 µmol) and bis-{4-[3,5-bis-(trifluoromethyl)-phenyl]-(2-oxo-κ*O*)-but-3-en-(4-olato-κ*O*)}-cobalt(II) (**3**) (32.8 mg, 50.2 µmol)) in 1,4-cyclohexadiene (1.0 mL, 98%, 10.2 mmol), toluene (1.3 mL) and dimethyl fumarate (**2f**) (727 mg, 5.04 mmol), was stirred at 60 °C for 6 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C. Unspent dimethyl fumarate was removed by filtration and the filtrate was purified by column chromatography [SiO_2, acetone/pentane = 1:5 (*v*/*v*)]. **Dimethyl 2-[(4-phenyltetrahydrofur-2-yl)-methyl]-succinate (18c).** Yield: 162 mg (530 µmol, 57 %, *cis*:*trans* = 73:27, 50/50-mixture of *rel*-2*S*/2*R*-diastereoisomers), R_f 0.28 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 400 MHz) 1.60–2.18 (3 H, m), 2.41–2.52 (1 H, m), 2.57–2.81 (2 H, m), 3.00–3.11 (1 H, m), 3.38– 3.48 (1 H, m), 3.67–3.71 (6 H, m), 3.73–3.79 (1 H, m), 4.01–4.22 (2 H, m), 7.19–7.32 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 35.4 / 36.2 (*trans*), 35.5 / 36.3 (*cis*), 37.3 / 37.7 (*cis*), 37.6 / 37.9 (*trans*), 38.6 / 38.8 (*trans*), 38.8 / 39.1 (*cis*), 39.8 / 40.0 (*trans*), 41.1 (*cis*), 51.7 / 51.9 (Me), 51.8 / 51.9 (Me), 73.99 / 74.05 (*cis*), 74.48 / 74.53 (*trans*), 77.3 (*trans*), 77.5 / 78.1 (*cis*), 126.47 / 126.51, 127.1 / 127.2, 128.5, 142.0 / 142.3, 172.2 / 172.7, 175.1 / 175.2. Anal. calcd for $C_{17}H_{22}O_5$ (306.35): C 66.65; H 7.24. Found: C 66.44; H 7.38. GC-MS (70 eV, EI) *m/z* (%) 306 (1, M^+), 225 (13), 189 (9), 161 (31), 146 (88), 129 (45), 114 (58), 104 (22), 91 (100), 77 (16).

4.5 Oxidation of 3-phenylpent-4-en-1-ol (1d)

4.5.1 Reaction with fumaronitrile: A solution of alcohol **1d** (166 mg, 1.03 mmol) and bis-{4-[3,5-bis-(trifluoromethyl)-phenyl]-(2-oxo-κ*O*)-but-3-en-(4-olato-κ*O*)}-cobalt(II) (**3**) (32.6 mg, 49.9 µmol)) in 1,4-cyclohexadiene (1.0 mL, 98%, 10.2 mmol), toluene (1.6 mL) and fumaronitrile (**2e**) (400 mg, 5.02 mmol), was stirred at 60 °C for 24 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C. Unspent fumaronitrile was removed by filtration and the filtrate was purified by column chromatography [SiO_2, acetone/pentane = 1:5 → 1:3 (*v*/*v*)].***trans*-2-methyl-3-phenyltetrahydrofuran (5d)**. Yield: 14.0 mg (86.3 µmol, 8 %, *cis*:*trans* = 3:97). Analytical data agree with published values.[9] **2-[(*trans*-3-phenyltetrahydrofur-2-yl)-**

methyl]-succinodinitrile (17d). Yield: 132 mg (548 µmol, 53 %, *cis*:*trans* = 3:97, 50/50-mixture of *rel*-2*S*/2*R*-diastereoisomers), colorless oil. δ_H ($CDCl_3$, 600 MHz) 1.81–2.03 (2 H, m), 2.12–2.20 (1 H, m), 2.39–2.44 (1 H, m), 2.73–2.99 (3 H, m), 3.12 (1 H, quint, *J* 6.5, 2*-H), 3.15–3.20 (1 H, m, 2**-H), 3.92–3.97 (1 H, m), 3.99–4.10 (1 H, m), 7.23–7.36 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 20.5 / 21.2, 25.9 / 26.6, 34.3 / 35.1, 35.2 / 35.8, 51.5 / 51.6, 67.9 / 68.0, 82.0 / 82.8, 115.6 / 115.9 (CN), 118.6 / 118.9 (CN), 127.2, 127.4, 128.9, 139.78 / 139.84. Anal. calcd for $C_{15}H_{16}N_2O$ (240.30): C 74.97; H 6.71; N 11.66. Found: C 74.75; H 6.81; N 11.78. GC-MS (70 eV, EI): *m/z* (%) = 240 (1, M^+), 147 (4), 128 (4), 117 (100), 115 (26), 91 (35), 77 (11).

4.5.2 Reaction with dimethyl fumarate: A solution of alcohol **1d** (168 mg, 1.03 mmol) and bis-{4-[3,5-bis-(trifluoromethyl)-phenyl]-(2-oxo-κ*O*)-but-3-en-(4-olato-κ*O*)}-cobalt(II) (**3**) (33.1 mg, 50.7 µmol)) in 1,4-cyclohexadiene (1.0 mL, 98%, 10.2 mmol), toluene (1.3 mL) and dimethyl fumarate (**2f**) (731 mg, 5.07 mmol), was stirred at 60 °C for 6 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C. Unspent dimethyl fumarate was removed by filtration and the filtrate was purified by column chromatography [SiO_2, acetone/pentane = 1:5 (*v*/*v*)]. ***trans*-2-methyl-3-phenyltetrahydrofuran (5d)**. Yield: 45.9 mg (283 µmol, 27 %, *cis*:*trans* = 5:95). Analytical data agree with published values.[9] **Dimethyl 2-[(3-phenyltetrahydrofur-2-yl)-methyl]-succinate (18d).** Yield: 148 mg (484 µmol, 47 %, *cis*:*trans* = 5:95, 50/50-mixture of *rel*-2*S*/2*R*-diastereoisomers), R_f 0.25 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 400 MHz) 1.64–1.74 (1 H, m), 1.88–1.95 (1 H, m), 2.03–2.11 (1 H, m), 2.33–2.40 (1 H, m), 2.50– 2.59 (1 H, m), 2.63–2.73 (1 H, m), 2.89 (1 H, q, *J* 8.5), 2.80–3.04 (1 H, m), 3.60–3.66 (6 H, m), 3.79 (1 H, td, J_t 8.7, J_d 2.6, THF-2*-H), 3.85 (1 H, td, J_t 8.7, J_d 2.6, THF-2**-H), 3.93–4.03 (2 H, m), 7.21–7.30 (5 H, m). δ_C ($CDCl_3$, 100 MHz) 35.2 / 35.3, 35.4 / 35.6, 35.8 / 36.1, 38.8 / 39.0, 51.4 / 51.5, 51.7 (Me), 51.9 (Me), 67.56 / 67.60, 83.4 / 83.8, 126.8, 127.5, 128.7, 141.3, 172.2, 175.0, 175.3. Anal. calcd for $C_{17}H_{22}O_5$ (306.35): C 66.65; H 7.24. Found: C 66.25; H 7.30. GC-MS (70 eV, EI) *m/z* (%) 306 (1, M^+), 275 (6), 161 (12), 146 (20), 129 (5), 118 (100), 115 (21), 91 (45), 77 (8).

4.6 Oxidation of *cis*-2-allylcyclohexan-1-ol (1e)

4.6.1 Reaction with fumaronitrile: A suspension of alcohol **1e** (141 mg, 1.01 mmol) and bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (**4**) (16.0 mg, 30.5 μmol) in cyclohexa-1,4-diene (1.5 mL, 15.3 mmol), toluene (1.0 mL) and fumaronitrile (**2e**) (391 mg, 4.92 mmol) was stirred at 60 °C for 20 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C. Unspent fumaronitrile was removed by filtration and the filtrate was purified by column chromatography [SiO_2, acetone/pentane = 1:5 (*v*/*v*)]. ***rel*-(1*S*,6*S*,8*R*)-8-methyl-7-oxabicyclo[4.3.0]nonan (5e).** Yield: 4.0 mg (24.7 μmol, 22 %). Analytical data agree with published values.[7b] **2-({*rel*-(1*S*,6*S*,8*R*)-7-oxabicyclo[4.3.0]non-8-yl}-methyl)-succinodinitrile (17e).** Yield: 145 mg (666 μmol, 67 %, *cis*:*trans* = <1:99, 50/50-mixture of *rel*-2*S*/2*R*-diastereoisomers), R_f 0.26 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H ($CDCl_3$, 600 MHz) 1.17–1.25 (2 H, m), 1.35–1.41 (2 H, m), 1.48–1.54 (1 H, m), 1.55–1.61 (2 H, m), 1.61–1.66 (1 H, m), 1.75–2.00 (4 H, m), 2.01–2.06 (1 H, m), 2.80–2.94 (2 H, m), 3.14–3.23 (1 H, m), 3.90–3.94 (1 H, m), 4.25–4.30 (1 H, m). δ_C ($CDCl_3$, 150 MHz) 20.2 / 21.3, 20.4, 23.84 / 23.86, 25.9 / 26.7, 27.3, 28.0, 37.1 / 37.9, 38.7, 38.8, 73.0 / 74.1, 76.7 / 76.8, 115.7 / 115.9 (CN), 119.0 / 119.2 (CN). GC-MS (70 eV, EI) *m/z* (%) 218 (3, M^+), 201 (14), 175 (67), 161 (18), 125 (29), 107 (35), 95 (20), 81 (100), 67 (39).

4.7 Oxidation of Methyl 3-(2-hydroxycyclohex-1-yl)-prop-2-enoate (1f)

4.7.1 Reaction with fumaronitrile: A suspension of alcohol **1f** (100 mg, 505 μmol) and bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (**4**) (8.0 mg, 15.2 μmol) in cyclohexa-1,4-diene (0.5 mL, 5 mmol), toluene (1.0 mL) and fumaronitrile (**2e**) (202 mg, 2.53 mmol) was stirred at 60 °C for 20 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C. Unspent fumaronitrile was removed by filtration and the filtrate was purified by column chromatography [SiO_2, acetone/pentane = 1:5 (*v*/*v*)]. **Methyl 2-({ *rel*-(1*S*,6*S*,8*R*)-7-oxabicyclo[4.3.0]non-8-yl}-methyl)-acetate (5f).** Yield: 24.4 mg (123 μmol, 24 %, *cis*:*trans* = 17:83). δ_H ($CDCl_3$, 400 MHz) 1.10–1.61 (6 H, m), 1.62–1.72 (1 H, m), 1.81–1.94 (2 H, m), 1.62–1.72 (1 H, m), 1.61–1.66 (1 H, m), 2.43 (1 H, dd *J* 15.1, 6.3), 2.62 (1 H, dd, *J* 15.1, 7.2), 3.67 (3 H, s), 3.95 (1 H, q, *J* 4.8), 4.53 (1 H, quin, *J* 7.1). δ_C ($CDCl_3$, 100 MHz) 20.5, 23.9, 27.3, 28.1,

38.1, 38.3, 41.6, 51.6, 73.4, 76.7, 171.8. **Methyl 2-({ *rel*-(1*S*,6*S*,8*R*)-7-oxabicyclo[4.3.0]non-8-yl}-methyl)-3,4-dicyanobutanoate (17f).** Yield: 25.9 mg (93,7 µmol, 19 %, *cis*:*trans* = 25:75, 50/50-mixtures of *rel*-2*S*/2*R* and *rel*-3*S*/3*R* diastereoisomers), R_f 0.18 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless crystalline solid. δ_H ($CDCl_3$, 600 MHz) 1.14–1.96 (20 H, m, *cis/trans*), 2.04–2.10 (1 H, m, *trans*), 2.16–2.14 (1 H, m, *cis*), 2.75 (1 H, dd, *J* 9.7, 5.1, *trans*, *), 2.87–3.19 (5 H, m, *cis/trans*), 3.49 (1 H, ddd, *J* 8.1, 7.0, 4.4, *trans*, #), 3.59 (1 H, dt, *J* 7.2, 5.1, trans, ##), 3.68–3.72 (1 H, m, *cis*, #/##), 3.77 / 3.78 (3 H, s, Me, *trans*), 3.78 / 3.80 (3 H, s, Me, *cis*), 3.84–3.87 (1 H, m, *cis*), 3.95 (1 H, q, *J* 3.8, *trans*), 4.11–4.22 (1 H, m, *cis*, */**), 4.36 (1H, dt, *J* 9.7, 7.3, *trans*, *), 4.41 (1H, dt, *J* 9.2, 7.3, trans, **). δ_C ($CDCl_3$, 150 MHz) 19.0 / 19.7 (*trans*), 19.2 / 19.7 (*cis*), 20.0 (*trans*), 21.1 (*cis*), 23.4 / 23.5 (*cis*), 23.7 / 23.8 (*trans*), 27.2 (*trans*), 27.8 / 27.9 (*trans*), 28.5 / 28.7 (*cis*), 29.0 / 29.3 (*trans*), 29.1 / 29.4 (*cis*), 36.8 / 36.9 (*cis*), 37.2 / 37.3 (*cis*), 37.7 / 37.8 (*trans*), 37.8 / 37.9 (*trans*), 50.0 / 51.5 (*cis*), 50.9 / 52.3 (*trans*), 52.6 / 52.7 (*trans*), 52.7 / 53.1 (*cis*), 75.0 / 75.5 (*trans*), 75.8 / 76.3 (*cis*), 77.4 / 77.6 (*trans*), 78.1 / 78.2 (*cis*), 115.1 / 115.4 (*cis*), 115.6 / 116.0 (*trans*), 117.0 / 117.2 (*cis*), 117. / 117.4 (*trans*), 127.2 / 129.1 (*trans*), 128.1 / 129.5 (*cis*), 129.2 / 129.7 (*trans*), 130.1 / 130.4 (*cis*), 169.5 / 170.0 (*trans*), 169.6 / 169.9 (*cis*). GC-MS (70 eV, EI) *m/z* (%) 276 (<1, M^+), 236 (3), 222 (3), 203 (24), 197 (100), 165 (12), 95 (14), 74 (34), 67 (16).

4.8 Oxidation of *rel*-(1*R*,3*S*)-1-phenylpent-4-en-1,3-diol (1g)

4.8.1 Reaction with ethyl propiolate: A solution of *rel*-(1*R*,3*S*)-1-phenylpent-4-en-1,3-diol (**1g**) (193 mg, 1.08 mmol) and bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4-(olato-κ*O*)]cobalt(II) dihydrate (**4**) (28.9 mg, 55.0 µmol) in cyclohexa-1,4-diene (1.5 mL, 15.3 mmol), toluene (1.5 mL) and ethyl propiolate (1.09 g, 10.8 mmol) was stirred at 60 °C for 16 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified without further concentration by column chromatography [SiO_2, acetone/PE = 1:5 (*v*/*v*)]. **Ethyl 2-{*rel*-(2*R*,3a*S*,5*R*,6a*S*)-hexahydro-2-phenylfuro[3,2-b]fur-5-yl}-acetate (23).** Yield: 108 mg (390 µmol, 36 %, *cis*:*trans* = <1:99), R_f 0.37 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. 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. GC-MS (70 eV, EI) *m/z* (%) 276 (4, M^+), 258 (6), 189 (22), 117 (25), 105 (100), 91 (15), 77 (25).

5 NMR Spectra of Selected Compounds

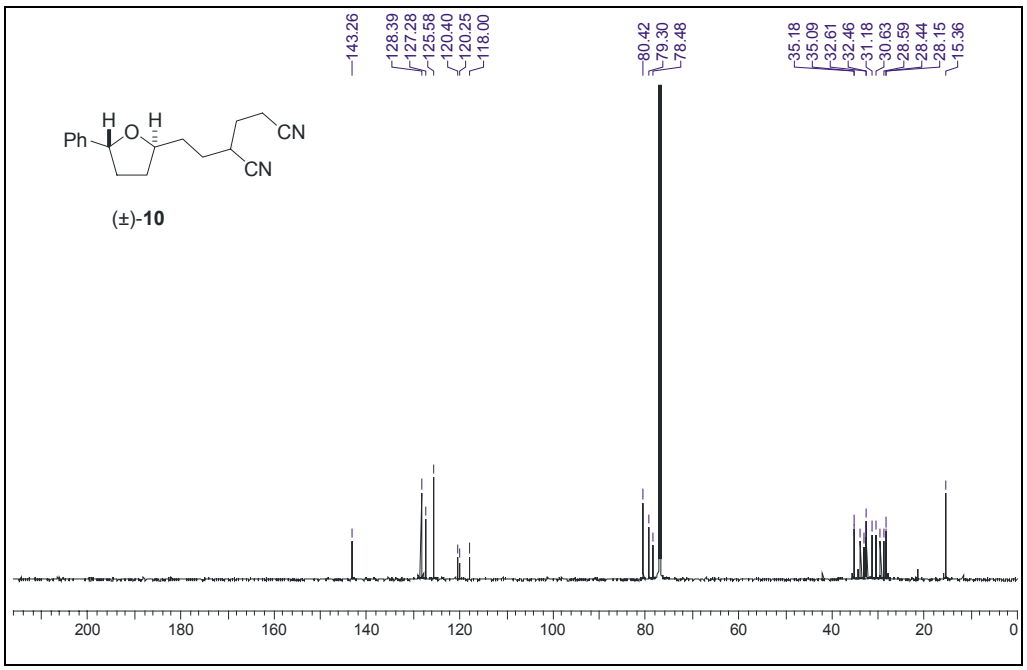

Figure S2. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$) of [2-(*trans*-5-phenyltetrahydrofur-2-yl)-eth-1yl]-glutarodinitrile (**10**).

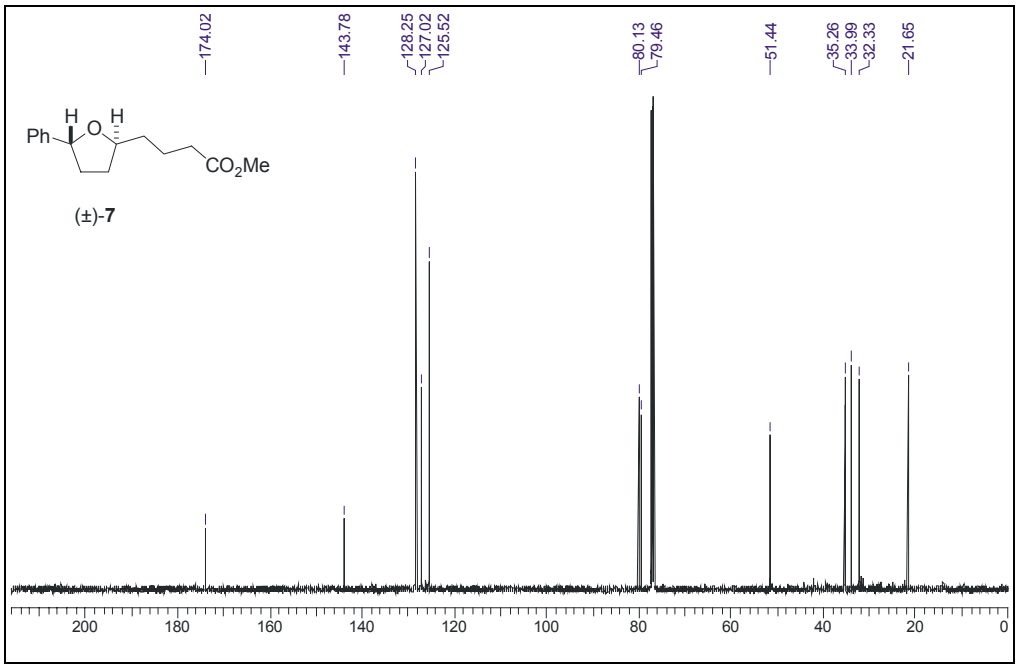

Figure S3. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of Methyl 4-(*trans*-5-phenyltetrahydrofur-2-yl)-butyrate (**7**).

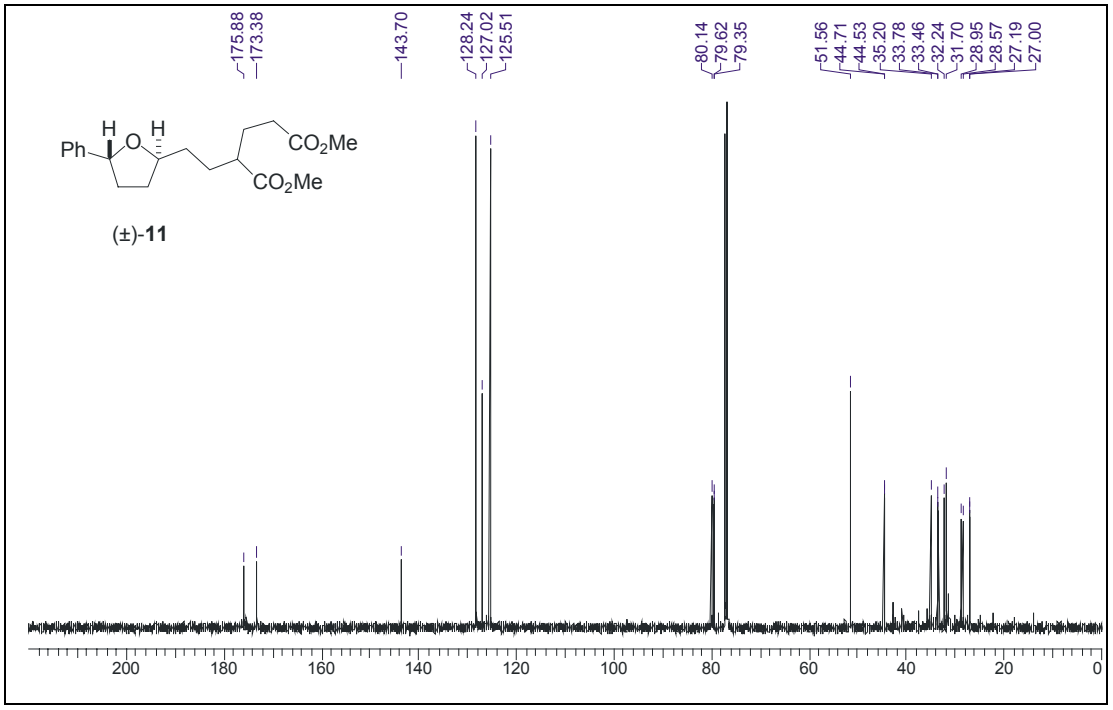

Figure S4. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of Dimethyl [2-(*trans*-5-phenyltetrahydrofur-2-yl)-eth-1-yl]-glutarate (**11**).

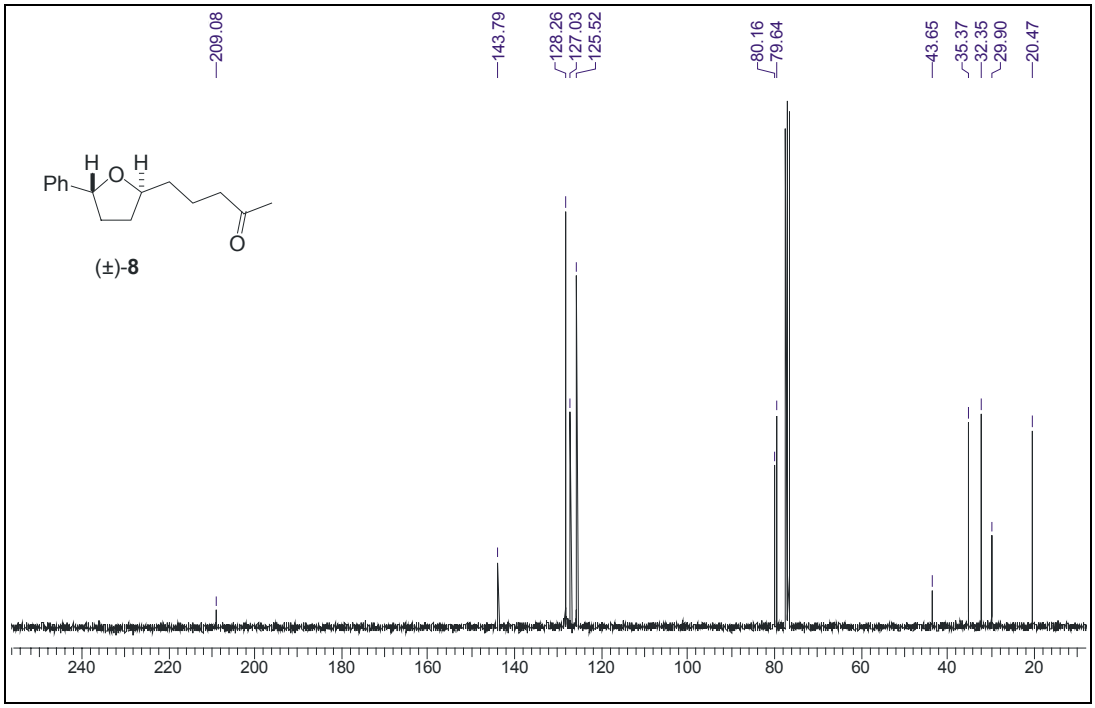

Figure S5. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of 5-(*trans*-2-phenyltetrahydrofur-5-yl)-pentan-2-one (**8**).

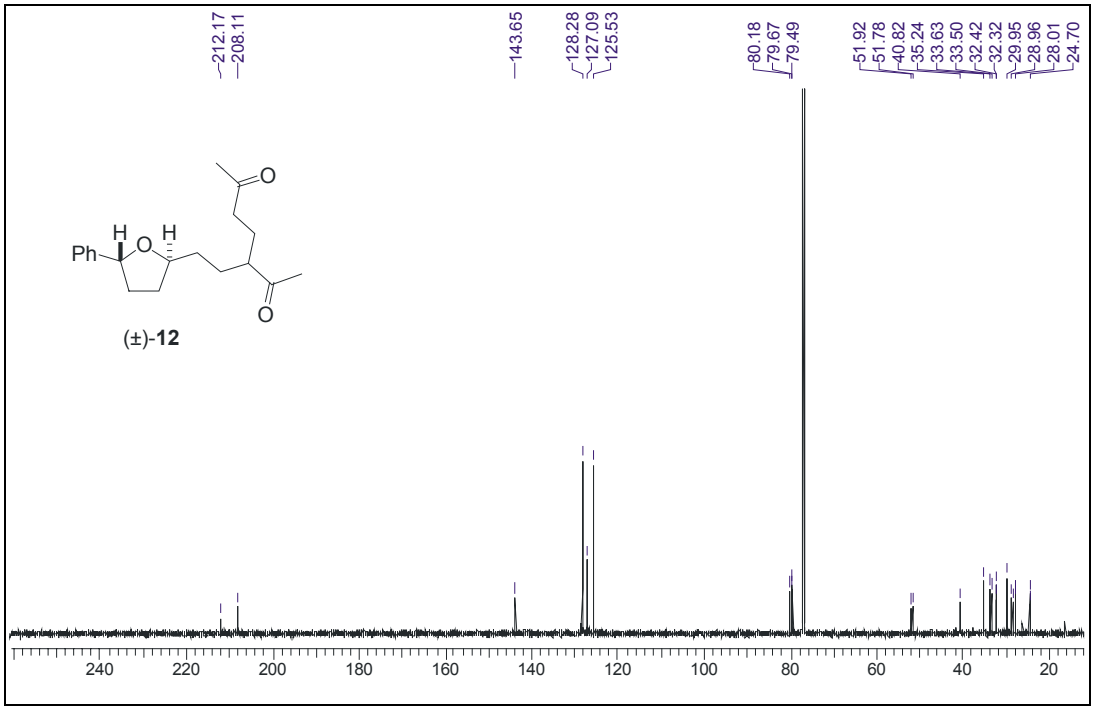

Figure S6. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of [3-(*trans*-2-phenyltetrahydrofur-5-yl)-eth-1-yl]-heptane-2,6-dione (**12**).

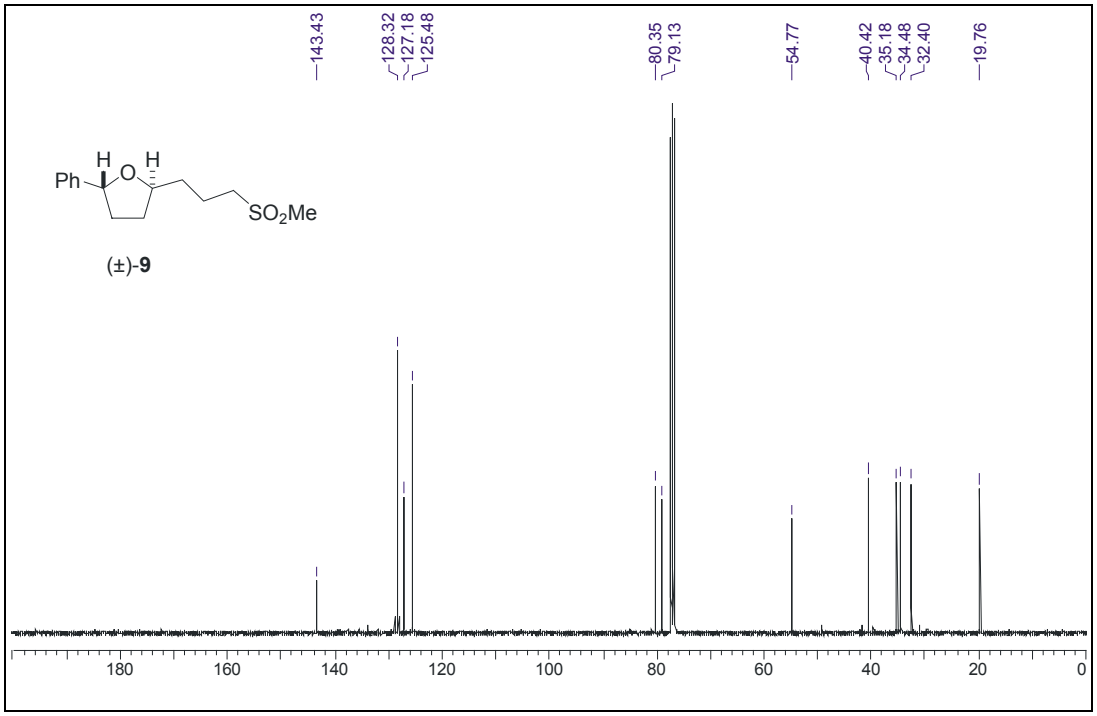

Figure S7. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of 3-(*trans*-5-phenyltetrahydrofur-2-yl)-prop-1-yl methyl sulfone (**9**).

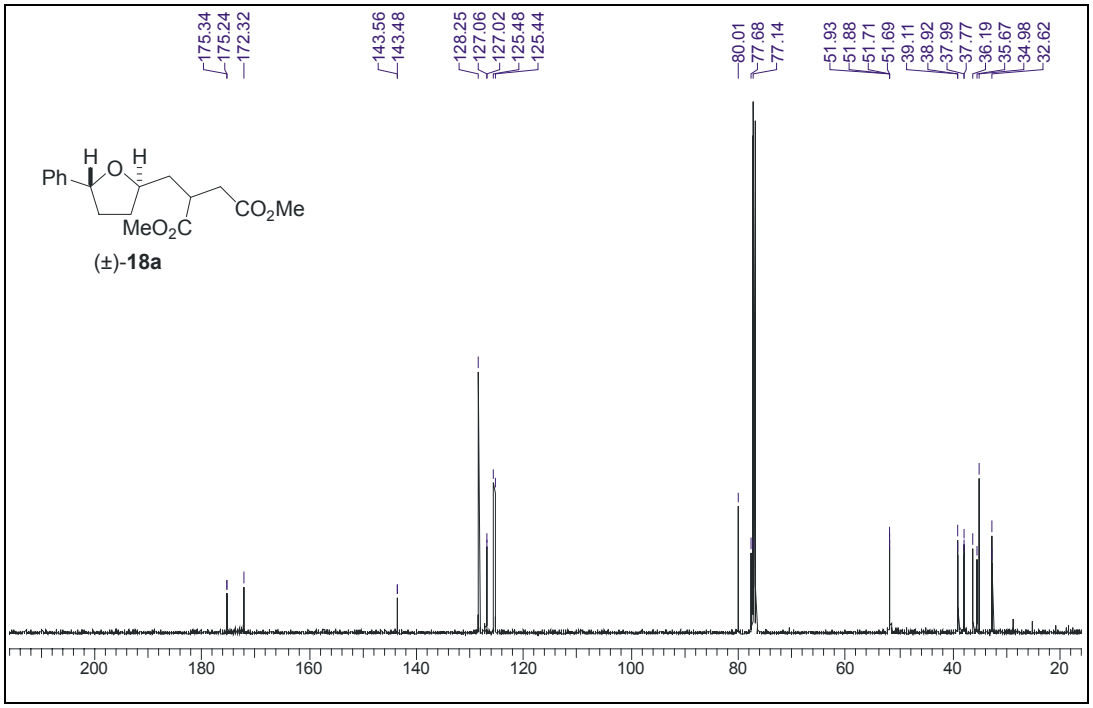

Figure S8. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of dimethyl 2-[(*trans*-5-phenyltetrahydrofur-2-yl)-methyl]-succinate (**18a**).

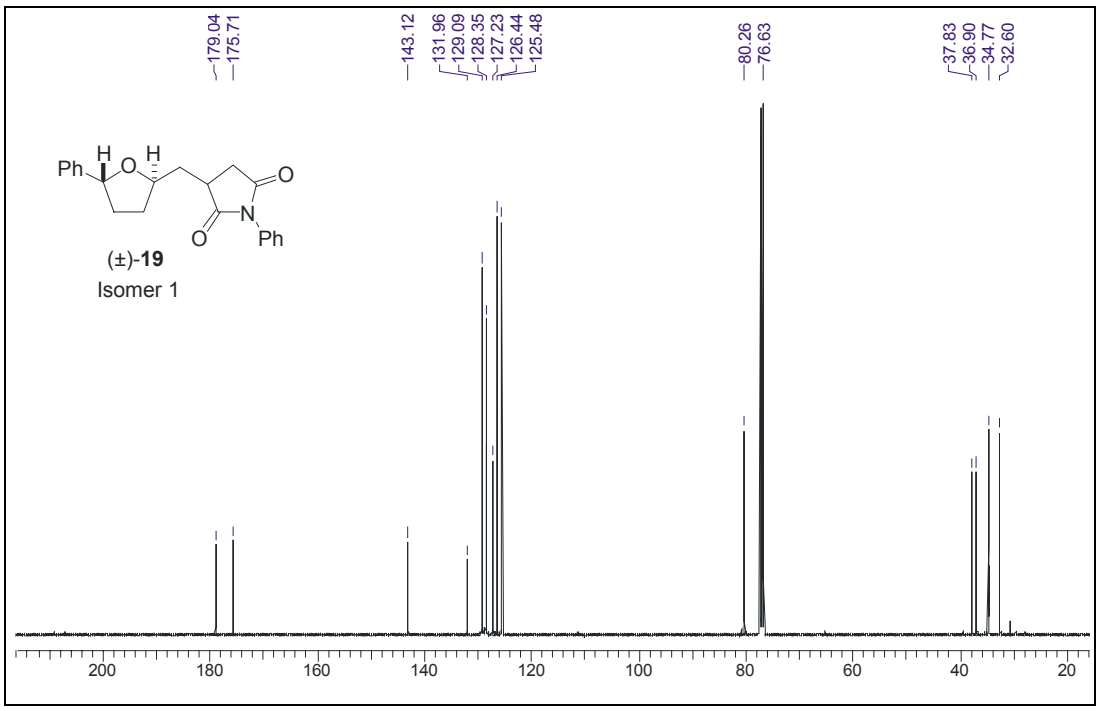

Figure S9. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of 2-[(*trans*-5-phenyltetrahydrofur-2-yl)-methyl]-*N*-phenylsuccinimide (**19**) (Isomer 1).

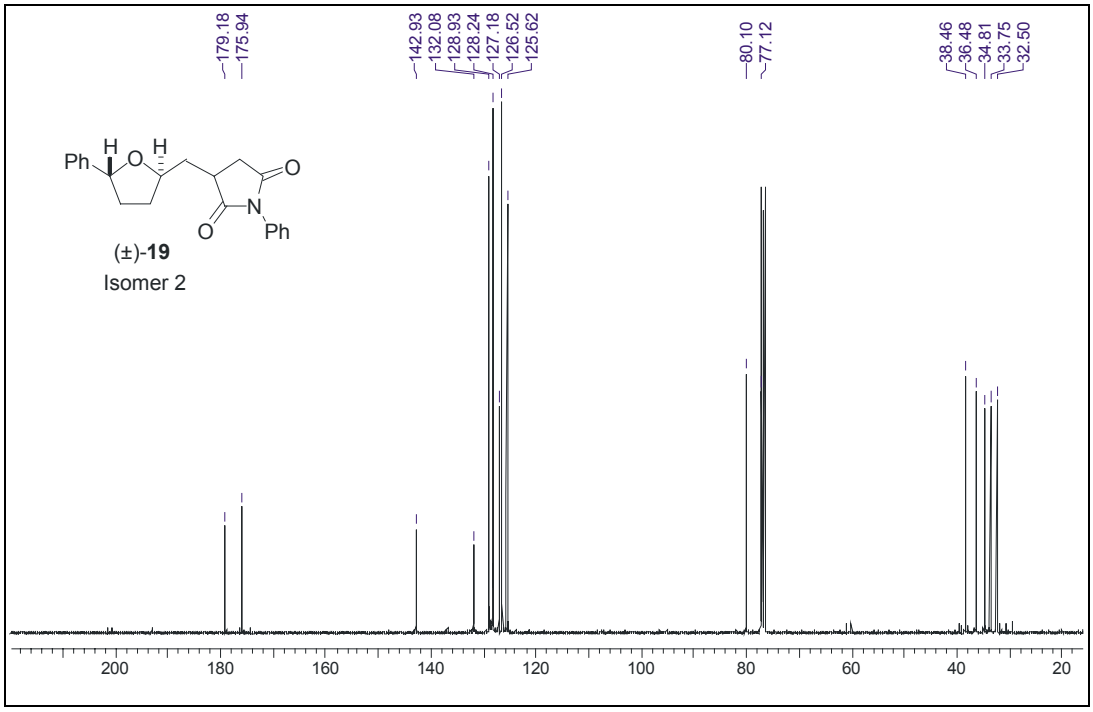

Figure S10. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of 2-[(*trans*-5-phenyltetrahydrofur-2-yl)-methyl]-*N*-phenylsuccinimide (**19**) (Isomer 2).

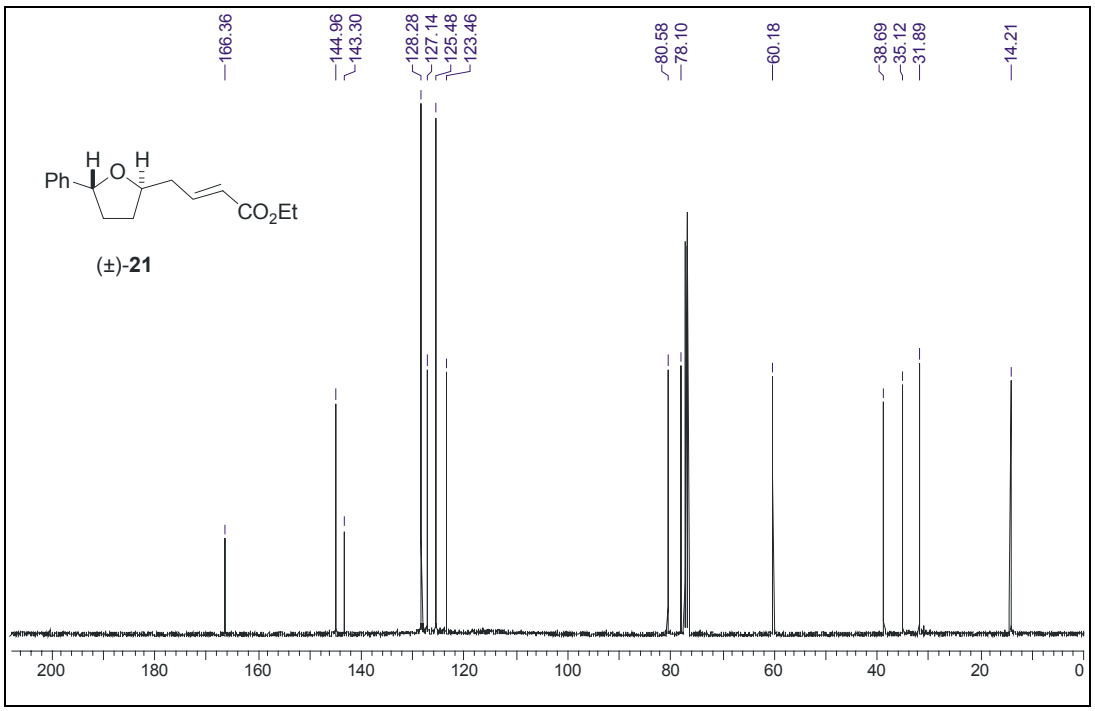

Figure S11. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of ethyl (*E*)-4-(5-Phenyltetrahydrofur-2-yl)-but-2-en-oate (**21**).

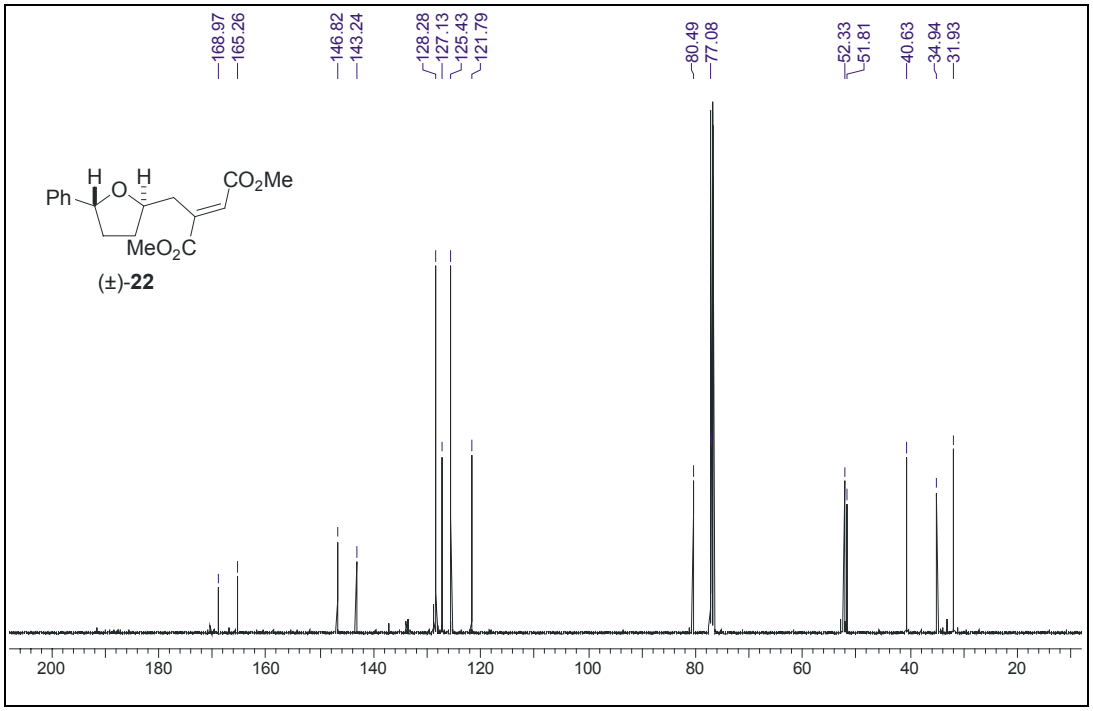

Figure S12. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of Dimethyl 2-[(*trans*-5-phenyltetrahydrofuran-2-yl)methyl]-fumarate (**22**).

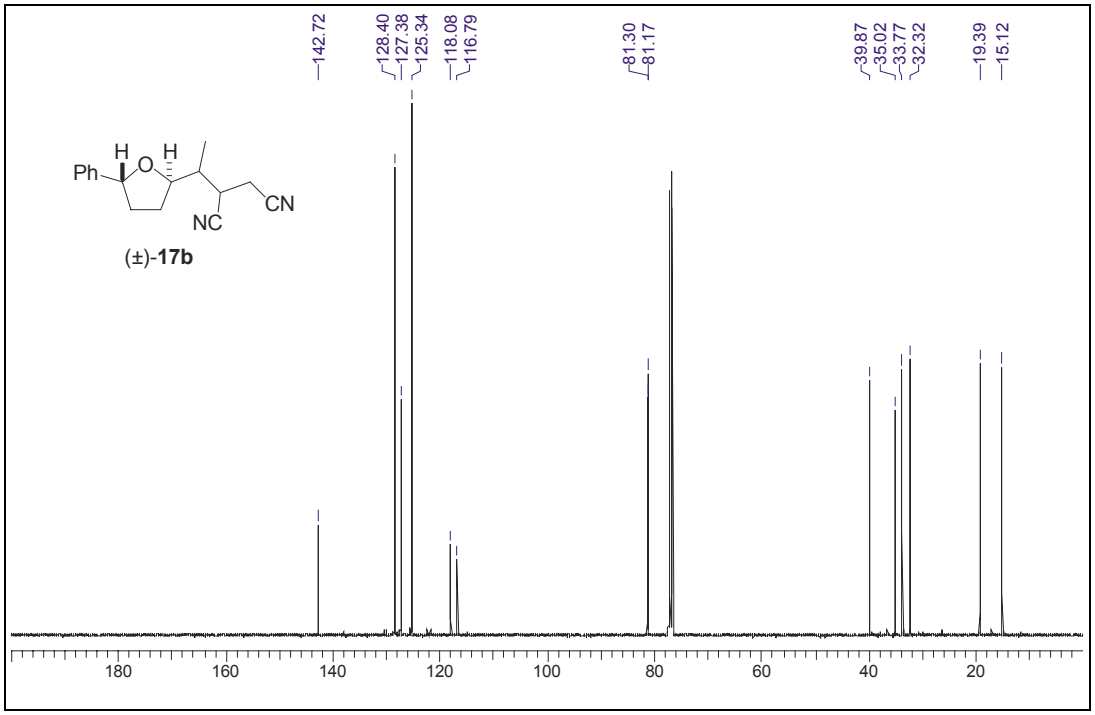

Figure S13. ^{13}C-NMR spectrum (100 MHz) of 2-[1-(*trans*-5-phenyltetrahydrofur-2-yl)-eth-1-yl]-succinodinitrile (**17b**) (1 isomer).

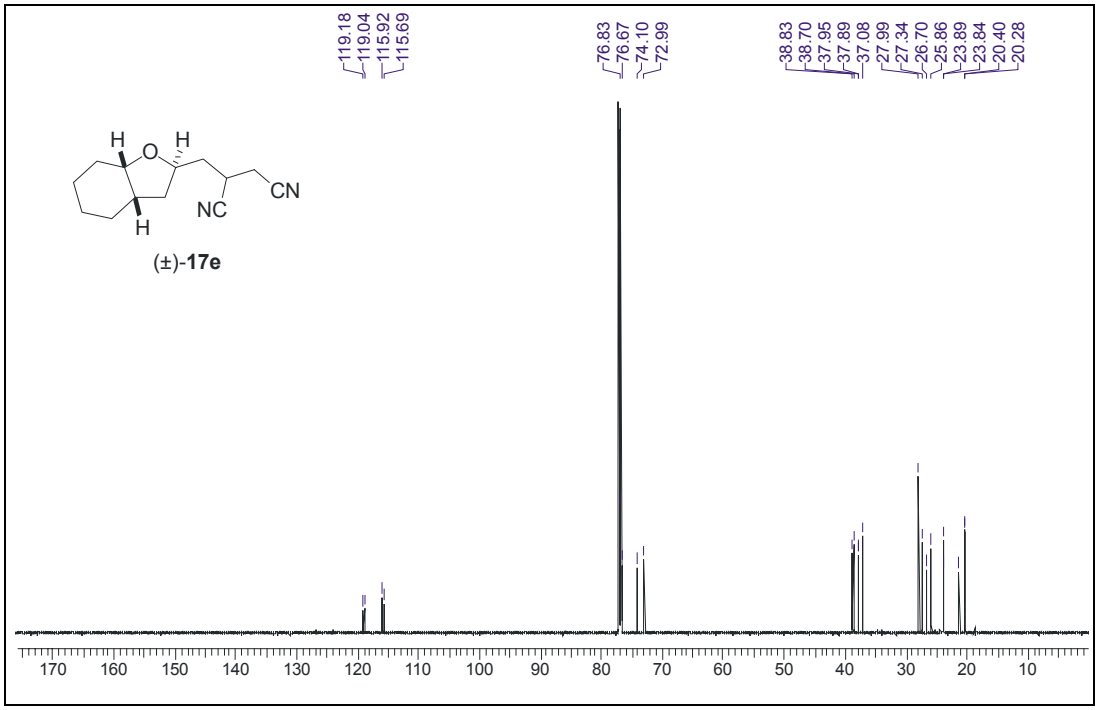

Figure S14. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$) of 2-({rel-(1*S*,6*S*,8*R*)-7-oxabicyclo[4.3.0]non-8-yl}-methyl)-succinodinitrile (**17e**).

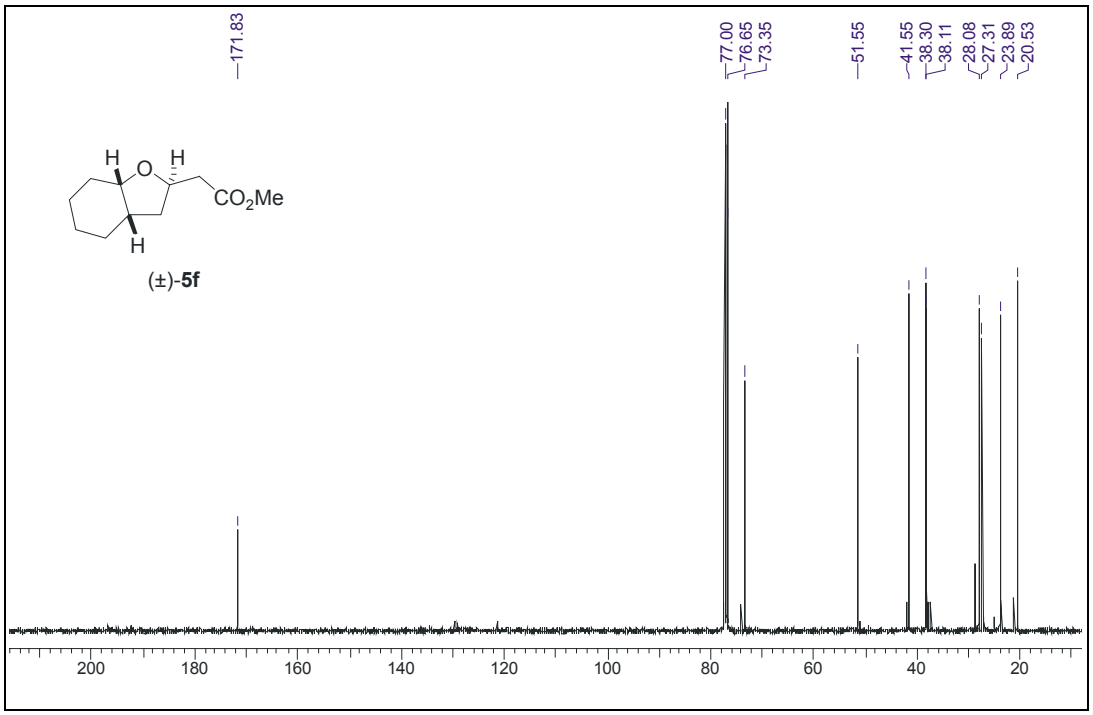

Figure S15. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of Methyl 2-({ *rel*-(1*S*,6*S*,8*R*)-7-oxabicyclo[4.3.0]non-8-yl}-methyl)-acetate (**5f**).

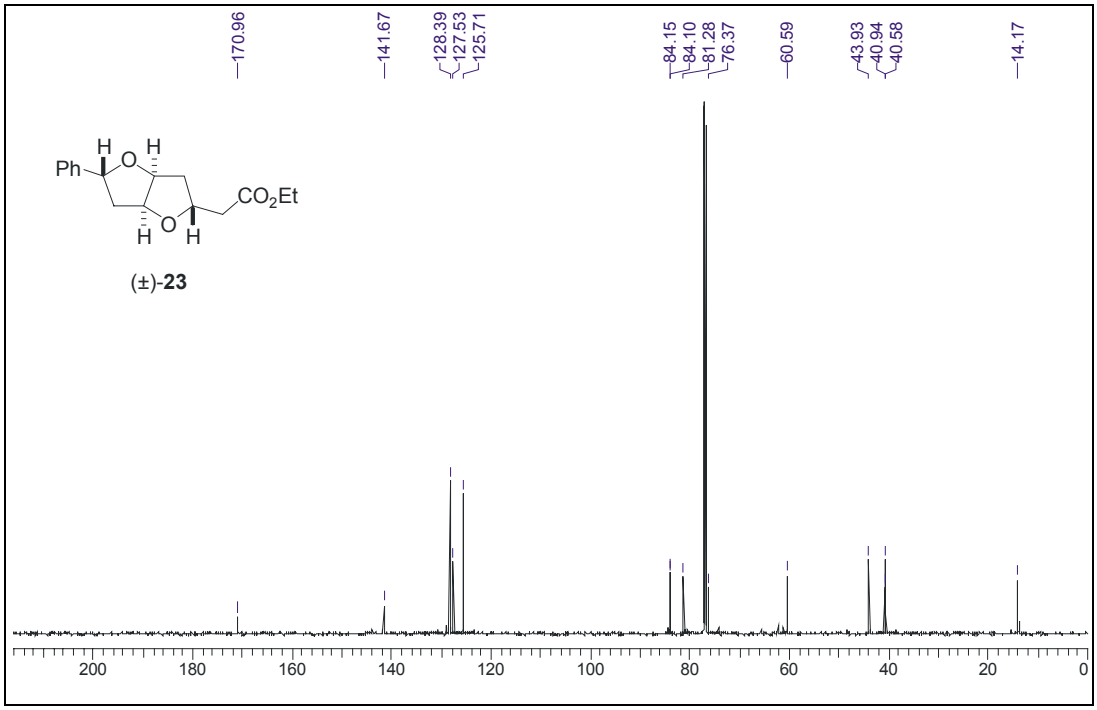

Figure S16. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$) of ethyl 2-(*rel*-(2*R*,3a*S*,5*R*,6a*S*)-hexahydro-2-phenylfuro[3,2-b]furan-5-yl)acetate (**23**).

6 References

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6.3 Ergänzende Experimentelle Daten zu Kapitel 4

Electronic Supporting Information for

An aerobic oxidation/homolytic substitution-cascade for stereoselective methylsulfanyl-cyclization of 4-pentenols

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8. References S23

1 General Remarks

(i) The compound numbering in the Electronic Supporting information is consistent with the accompanying publication. (ii) References refer exclusively to the Electronic Supporting Information.

2 Instrumentation and Reagent Specification

^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded with FT-NMR DPX 400 and DMX 600 instruments (*Bruker*). Chemical shifts refer to the δ-scale (coupling constants J are given in Hz). The resonances of residual protons and the corresponding carbons of deuterated solvents ($CDCl_3$: δ_H 7.26, δ_C 77.0) were used as internal standards for ^{1}H-, and ^{13}C-NMR. ^{19}F-NMR chemical shifts were referenced versus α,α,α-Trifluorotoluene (δ_F –63.72) as internal standard.

GC/MS Analysis were performed with a HP 6890 Series (*Hewlett Packard*) with a ZB5 column (*Phenomenex*, 30 m × 0.25 mm, 0.25 µm). Temperature program: 40 °C (3 min), linear temperature rise (10 °C min^{-1}) to 280 °C, final temperature 280 °C (10 min). Mass spectra (EI, 70 eV) were recorded with a Mass Selective Detector HP 6890 (*Hewlett Packard*).

Electrospray ionization mass spectrometry (ESI-MS) was performed with a *Bruker amazonX ion trap instrument*. The ion source was used in positive and negative electrospray ionization mode. Scan speed was 32500 m/z s^{-1} in ultra scan mode (0.3 FWHM / m/z), 4650 m/z s^{-1} in maximum resolution (<0.1 FWHM / m/z) scan range was 70 to 2200 m/z. Sample solutions in acetonitrile at concentrations of approx. 0.4 µM were continuously infused into the ESI chamber at a flow rate of 2 µL/min using a syringe pump. Nitrogen was used as drying gas with flow rate of 3.0 L/min at 220 °C. The solutions were sprayed at a nebulizer pressure of 4 psi (275.8 mbar) and the electrospray needle was typically held at 4.5 kV. The instrument was controlled by *Bruker Trap Control 7.0 software*. Data analysis was performed using *Bruker Data Analysis 4.0 software*.

Combustion analyses were performed with a vario Micro cube CHNS (*Elementar Analysentechnik / Hanau*).

Reaction progress was monitored via thin layer chromatography (TLC) on aluminium sheets coated with silica gel (60 F_{254}, *Machery-Nagel*). Compounds were detected by UV-light (254 nm) or by staining of developed TLC sheets with Ekkert's reagent.

IR spectra were recorded from pelletized samples in KBr using a FT-IR 1000 spectrometer (*Perkin Elmer*).

All solvents were purified according to standard procedures.[1]

1-Phenylpent-4-en-1-ol (**1a**),[2,3] (*E*)-Methyl 6-hydroxy-6-phenylhex-2-enoate (**1b**),[4] 1-phenylhex-4-en-1-ol (**1c**),[5] *cis*-2-allylcyclopentanol (**1d**),[6] *cis*-2-allylcyclohexanol (**1e**),[7] *rel*-(1*S*,2*R*)-1,2-diphenylpent-4-en-1,2-diol (**1f**),[8] 2-phenylpent-4-en-1-ol (**1g**),[9] *rel*-(1*S*,2*S*)-1-phenylpent-4-en-1,2-diol (**1h**)[10], and *rel*-(1*R*,2*R*)-1,2-diphenylpent-4-en-1-ol (**1i**)[11] were prepared according to published procedures.

3 Cobalt Complexes and Alkenols

All cobalt complexes were prepared as reported previously.[12]

3.1.1 Bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κ*O*)-but-3-en-4(olato-κ*O*)]cobalt(II) dihydrate (4). Yellow solid (99 %), ν_{max} (KBr) / cm^{-1} 3383 (OH), 1608 (CO), 1574, 1535, 1490, 1460, 1433, 1288, 1252, 1186, 1163, 1132, 1077, 1026; δ_F ($CDCl_3$/acetone, 377 MHz) +6.1. Found C, 45.97; H, 3.16. $C_{20}H_{16}CoF_6O_6$ (525.26) requires C, 45.73; H, 3.07 %. ESI-MS: Found: 511.94 [$CoL^1{}_2$+Na^+], $C_{20}H_{12}CoF_6NaO_4$ requires 511.99.

3.1.2 Bis-[1-(4-fluorophenyl)-3-(oxo-κ*O*)-but-1-en-1(olato-κ*O*)]cobalt(II) dihydrate (5). Yellow solid (84 %), ν_{max} (KBr) / cm^{-1} 3391 (OH), 1603 (CO), 1572, 1523, 1499, 1417, 1388, 1297, 1233, 1157, 1163, 1110, 1011; δ_F ($CDCl_3$/acetone, 377 MHz) –112.0. Found C, 53.33; H, 4.92. $C_{20}H_{20}CoF_2O_6$ (453.30) requires C, 52.99; H, 4.45 %. ESI-MS: Found: 439.99 [$CoL^2{}_2$+Na^+], $C_{20}H_{16}CoF_2NaO_4$ requires 440.02.

3.1.3 Bis-[1,1,1-trifluoro-4-(4-fluorophenyl)-2-(oxo-κ*O*)-but-3-en-4(olato-κ*O*)]-cobalt(II) × 2 EtOH (6). Orange solid (89 %), ν_{max} (KBr) / cm^{-1} 3399 (OH), 1616 (CO), 1584, 1535, 1546, 1504, 1458, 1312, 1288, 1239, 1184, 1137, 1061, 1013; δ_F ($CDCl_3$/acetone, 377 MHz) +6.7, –107.0. Found C, 46.68; H, 3.78. $C_{24}H_{22}CoF_8O_6$ (617.35) requires C, 46.69; H, 3.59 %. ESI-MS: Found: 547.93 [$CoL^3{}_2$+Na^+], $C_{20}H_{10}CoF_8NaO_4$ requires 547.97.

3.1.4 Bis-[1,3-di(4-fluorophenyl)-3-(oxo-κ*O*)-prop-1-en-1(olato-κ*O*)]cobalt(II) × 2 EtOH (7). Yellow solid (76 %), ν_{max} (KBr) / cm^{-1} 3367 (OH), 1600 (CO), 1574, 1553, 1527, 1491, 1433, 1387, 1300, 1218, 1157, 1096, 1051, 1012; δ_F ($CDCl_3$/acetone, 377 MHz) –110.9. Found C, 61.23; H, 4.60. $C_{34}H_{30}CoF_4O_6$ (669.53) requires C, 60.99; H, 4.52 %. ESI-MS: Found: 600.13 [$CoL^4{}_2$+Na^+], $C_{30}H_{18}CoF_4NaO_4$ requires 600.04.

3.2.1 rel-(1*R*,2*R*)-1,2-Diphenylhex-5-en-1-ol (15)

A solution of *trans* stilbene oxide (1.01 g, 5.10 mmol) in dry Et_2O (15 mL) was added in an atmophere of nitrogen in a dropwise manner to a solution of but-4-en-1-yl magnesium bromide prepared from 4-bromo-1-butene (1.43 g [97 %], 10.3 mmol) and

magnesium (339 mg, 14.0 mmol) in dry Et_2O (15 mL). The reaction mixture was stirred for 17 h at 22 °C and successively treated with satd. aqueous NH_4Cl (20 mL) and aqueous 1 M HCl (10 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 15 mL). Combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was purified by column chromatography [SiO_2, acetone/pentane = 1/10, (*v*/*v*)]. Yield: 522 mg (2.07 mmol, 41 %), R_f 0.41 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.46–1.53 (1 H, m), 1.57–1.65 (2 H, m), 2.13–2.21 (1 H, m), 2.26–2.33 (1 H, m), 3.89 (1 H, d, *J* 8.6), 4.37 (1 H, td, J_t 8.6, J_d 2.6), 4.95 (1 H, d, *J* 10.3), 5.01 (1 H, dd, *J* 17.0, 1.8), 5.78 (1 H, ddt, J_d 17.0, 10.3, J_t 6.8), 7.18–7.25 (3 H, m), 7.27–7.34 (5 H, m) 7.37–7.41 (2 H, m). δ_C (100 MHz, $CDCl_3$) 30.1, 34.1, 58.9, 73.1, 114.8 , 126.5, 126.9, 128.2, 128.6, 128.7, 128.8, 129.0, 129.1, 138.4, 141.3, 142.2.

4 Oxidation – Radical Substitution Cascades

4.1 Oxidation of 1-phenylpent-4-en-1-ol (1a)

4.1.1 Trapping with methyl disulfide

A solution of alcohol **1a** (163 mg, 1.01 mmol) and cobalt catalyst **5** (22.9 mg, 50.5 µmol) in methyl disulfide (9.5 mL) and CHD (1.0 mL) was stirred at 70 °C for 6 h, while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and concentrated under reduced pressure to afford a residue that was purified by column chromatography [SiO_2, Et_2O/pentane = 1:10 (*v*/*v*)].

***trans*-2-(methylsulfanyl)methyl-5-phenyltetrahydrofuran (3a)**. Yield: 151 mg (726 µmol, 72 %), R_f 0.50 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.84–1.94 (2 H, m), 2.20–2.25 (1 H, m), 2.22 (3 H, s, CH_3), 2.39–2.43 (1 H, m), 2.70 (1 H, dd, *J* 13.3, 6.7), 2.82 (1 H, dd, *J* 13.3, 5.4), 4.45 (1 H, quin, *J* 6.4), 5.07 (1 H, t, *J* 6.9), 7.25–7.27 (1 H, m), 7.33–7.36 (4 H, m). NOESY 2-H || 5-H. δ_C (100 MHz, $CDCl_3$) 16.5 (CH_3), 31.7, 35.2, 39.6, 79.2 , 80.8, 125.5, 127.1, 128.3, 143.3. GC-MS (EI, 70 eV) *m/z* (%) 208 (39, M^+), 147 (100), 129 (63), 117 (20), 105 (31), 91 (94), 77 (25). HRMS (EI^+) *m/z* 208.0921 (M^+); calculated mass for $C_{12}H_{16}OS^+$: 208.0922.

***trans*-2-methyl-5-phenyltetrahydrofuran (8a)**. Yield: 16.2 mg (100 µmol, 10 %). Analytical data agree with published values.[2]

4.1.2 Trapping with ethyl disulfide

A solution of alcohol **1a** (163 mg, 1.00 mmol) and cobalt catalyst **5** (22.7 mg, 50.1 µmol) in diethyl disulfide (2.49 g, 20.2 mmol) and CHD (0.5 mL) was stirred at 70 °C for 16 h, while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/pentane = 1:10 (*v*/*v*)].

***trans*-2-(ethylsulfanyl)methyl-5-phenyltetrahydrofuran (11)**. Yield: 80.6 mg (363 µmol, 36 %), R_f 0.50 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.28 (3 H, t, *J* 7.4), 1.79–1.93 (2 H, m), 2.17–2.26 (1 H, m), 2.35–2.43 (1 H, m), 2.64 (2 H, q, *J* 7.4), 2.70 (1 H, dd, *J* 13.3, 7.0), 2.84 (1 H, dd, *J* 13.3, 5.3),

4.41 (1 H, quin, *J* 6.4), 5.05 (1 H, t, *J* 7.0), 7.21–7.28 (1 H, m), 7.31–7.38 (4 H, m). δ_C (100 MHz, $CDCl_3$) 14.9, 26.8, 31.8, 35.2, 37.1, 79.4 , 80.8, 125.5, 127.1, 128.3, 143.3. GC-MS (EI, 70 eV) *m/z* (%) 222 (17, M^+), 161 (5), 147 (100), 129 (53), 117 (24), 105 (41), 91 (87), 77 (40). HRMS (EI^+) *m/z* 222.1080 (M^+); calculated mass for $C_{13}H_{18}OS^+$: 222.1078.

***trans*-2-methyl-5-phenyltetrahydrofuran (8a)**. Yield: 63.8 mg (393 µmol, 39 %). Analytical data agree with published values.[2]

4.1.3 Trapping with allyl disulfide

A solution of alcohol **1a** (163 mg, 1.00 mmol) and cobalt catalyst **5** (22.8 mg, 50.1 µmol) in diallyl disulfide (2.50 mL [80 %], 13.7 mmol) and CHD (0.5 mL) was stirred at 70 °C for 16 h, while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and purified by column chromatography [SiO_2, Et_2O/pentane = 1:10 (*v*/*v*)].

***trans*-2-(but-1'-en-4'-yl)-5-phenyltetrahydrofuran (13).** Yield: 43.7 mg (216 µmol, 22 %), R_f 0.64 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.58–1.71 (2 H, m), 1.75–1.91 (2 H, m), 2.10–2.19 (2 H,m), 2.33–2.41 (1 H, m), 4.21 (1 H, ddt J_d 7.5, 6.8, J_t 6.2), 4.95–5.02 (2 H, m), 5.06 (1 H, dq, J_d 17.1, J_q 1.7), 5.87 (1 H, ddt, J_d 17.1, 10.3, J_t 6.6), 7.21–7.35 (5 H, m). δ_C (100 MHz, $CDCl_3$) 30.4, 32.3, 35.3, 35.4, 79.4, 80.1, 114.5, 125.5, 127.0, 128.3, 138.5, 143.9. GC-MS (EI, 70 eV) *m/z* (%) 202 (19, M^+), 187 (6), 173 (8), 160 (11), 147 (65), 129 (42), 117 (40), 105 (100), 91 (89), 77 (33). HRMS (EI^+) *m/z* 202.1358 (M^+); calculated mass for $C_{14}H_{18}O^+$: 202.1358.

Another fraction of a colorless oil was obtained (106 mg) R_f 0.52 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], which consisted of ***trans*-2-methyl-5-phenyltetrahydrofuran** (**8a**) (145 µmol, 14 %)**, *trans*-2-(allylsulfanyl)-methyl-5-phenyltetrahydrofuran** (**12**) (241 µmol, 24 %), [δ_H (400 MHz, $CDCl_3$) 2.64 (1 H, dd, *J* 13.4, 6.6), 2.77 (1 H, dd, *J* 13.4, 5.7), 3.18–3.28 (2 H, m), 4.40 (1 H, quin, *J* 6.4), 5.04 (1 H, t, *J* 7.0), 5.09–5.16 (1 H, m), 5.87 (1 H, ddt, J_d 17.0, 9.9, J_t 7.3), 5.82 (1 H, ddt, J_d 17.0, 9.9, J_t 7.2); GC-MS (EI, 70 eV) *m/z* (%) 234 (3, M^+), 193 (18), 160 (15), 147 (96), 129 (56), 117 (21), 105 (52), 91 (100), 77 (27). HRMS (EI^+) *m/z* 234.1083 (M^+); calculated mass for $C_{14}H_{18}OS^+$: 234.1078.] and ***trans*-(5'-phenyltetra-hydrofuryl)-methyl allyl disulfide** (**14**) (96.4 µmol, 10 %), [δ_H (400 MHz, $CDCl_3$) 2.86 (1 H, dd, *J* 13.3, 6.8), 3.06 (1 H, dd, *J* 13.3, 5.7), 3.38 (2 H, d, *J* 7.4), 4.49 (1 H, quin, *J* 6.5), 5.12–5.18 (1 H,

m), 5.22 (1 H, dq, J_d 17.0, J_q 1.3), 5.87 (1 H, ddt, J_d 17.0, 9.9, J_t 7.3); GC-MS (EI, 70 eV) *m/z* (%) 266 (3, M^+), 193 (21), 160 (9), 147 (77), 129 (54), 117 (29), 105 (85), 91 (100), 77 (39). HRMS (EI^+) *m/z* 266.0797 (M^+); calculated mass for $C_{14}H_{18}OS_2^+$: 266.0799.]. Due to overlap in the high field area of the ^{1}H-NMR spectrum (1.5–2.5 ppm), signals of 3-H and 4-H of the tetrahydrofuran rings could not be assigned unequivocally to either of the three compounds (**8a**, **12**, **14**).

4.2 Oxidation of *cis*-2-(prop-2-en-1-yl)cyclopentan-1-ol (1d)

A solution of alcohol **1d** (84.5 mg, 669 µmol) and cobalt catalyst **5** (15.0 mg, 33.1 µmol) in dimethyl disulfide (6.35 mL [99%], 70.9 mmol) and CHD (0.65 mL) was stirred at 70 °C for 6 h, while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and concentrated under reduced pressure to afford a residue that was purified by column chromatography [SiO_2, methyl *tert*-butyl ether/pentane = 1:10 → 1:5 (*v*/*v*)].

***rel*-(1*S*,3*R*,5*S*)-3-(methylsulfanyl)methyl-2-oxabicyclo[3.3.0]octane (3d)**. Yield: 81.9 mg (475 µmol, 71 %), R_f 0.60 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.36–1.44 (1 H, m), 1.46–1.80 (7 H, m), 1.85 (1 H, dd, *J* 8.2, 7.6), 2.13 (3 H, s, CH_3), 2.47–2.55 (1 H, m), 2.60–2.71 (2 H, m), 4.14 (1 H, quin, *J* 6.5), 4.51–4.56 (1 H, m). δ_C (100 MHz, $CDCl_3$) 16.3 (CH_3), 24.7, 32.8, 34.7, 38.8, 39.1, 42.7, 78.5, 84.8. GC-MS (EI, 70 eV) *m/z* (%) 172 (6), 124 (1), 111 (51), 93 (7), 81 (6), 67 (100). HRMS (EI^+) *m/z* 172.0912 (M^+); calculated mass for $C_9H_{16}OS^+$: 172.0922.

***rel*-(1*S*,3*S*,5*S*)-3-methyl-2-oxabicyclo[3.3.0]octane (8d)**. Yield: 926 µg (7.35 µmol, 11 %), R_f 0.53 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.17 (1 H, d, *J* 6.1), 1.33–1.42 (1 H, m), 1.44–1.54 (1 H, m), 1.57–1.78 (6 H, m), 2.61–2.71 (1 H, m), 4.03–4.10 (1 H, m), 4.51–4.58 (1 H, m). δ_C (100 MHz, $CDCl_3$) 20.6, 25.1, 34.8, 41.5, 43.1, 74.8, 84.4. GC-MS (EI, 70 eV) *m/z* (%) 126 (8, M^+), 111 (80), 97 (42), 83 (7), 67 (100). HRMS (EI^+) *m/z* 126.1033 (M^+); calculated mass for $C_8H_{14}O^+$: 126.1045.

4.3 Oxidation of *cis*-2-(prop-2-en-1-yl)cyclohexan-1-ol (1e)

A solution of alcohol **1e** (140.7 mg, 1.00 mmol) and cobalt catalyst **5** (23.3 mg, 51.4 µmol) in dimethyl disulfide (9.5 mL [99%], 106 mmol) and CHD (1.0 mL) was

stirred at 70 °C for 8 h, while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and concentrated under reduced pressure to afford a residue that was purified by column chromatography [SiO_2, Et_2O/pentane = 1:10 (*v*/*v*)].

***rel*-(1*S*,3*R*,5*S*)-3-(methylsulfanyl)-methyl-2-oxabicyclo[4.3.0]nonane (3e)**. Yield: 138.3 mg (742 µmol, 74 %), R_f 0.69 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.12–1.26 (2 H, m), 1.32–1.59 (5 H, m), 1.71–1.77 (1 H, m), 1.81–1.88 (2 H, m), 2.00–2.06 (1 H, m), 2.13 (3 H, s, Me), 2.56 (1 H, dd, *J* 13.2, 6.5), 2.67 (1 H, dd, *J* 13.2, 5.6), 3.97 (1 H, q, *J* 3.7), 4.30 (1 H, quin, *J* 6.7). δ_C (100 MHz, $CDCl_3$) 16.3 (CH_3), 20.5, 23.9, 27.5, 28.2, 38.1, 38.3, 40.5, 76.2, 76.8. GC-MS (EI, 70 eV) *m/z* (%) 186 (7, M^+), 168 (3), 125 (40), 107 (31), 81 (100). HRMS (EI^+) *m/z* 186.1073 (M^+); calculated mass for $C_{10}H_{18}OS^+$: 186.1078.

***rel*-(1*S*,3*S*,5*S*)-3-methyl-2-oxabicyclo[4.3.0]nonane (8e)**. Yield: 13.9 mg (99.1 µmol, 10 %). Analytical data agree with published values.[7a]

4.4 Oxidation of *rel*-(1*S*,2*R*)-1,2-diphenylpent-4-en-1,2-diol (1f)

A solution of alcohol **1f** (127 mg, 500 µmol) and cobalt catalyst **5** (11.5 mg, 25.4 µmol) in methyl disulfide (5.0 mL) and CHD (0.5 mL) was stirred at 60 °C for 5 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and concentrated under reduced pressure to afford an oily residue that was purified by column chromatography [SiO_2, Et_2O/pentane = 1:10 (*v*/*v*)].

***rel*-(2*S*,3*R*,5*R*)-5-(methylsulfanyl)methyl-2,3-diphenyltetrahydrofuran-3-ol (3f).** Yield: 100 mg (334 µmol, 67 %), R_f 0.37 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.78 (1 H, s, OH), 2.26 (3 H, s, CH_3), 2.56 (1 H, d, *J* 7.4), 2.88–2.99 (1 H, m), 4.86–4.94 (1 H, m), 5.45 (1 H, s), 7.05 (2 H, dd, *J* 6.3, 2.7), 7.23–7.32 (4 H, m), 7.38 (2 H, t, *J* 7.4), 7.42–7.46 (2 H, m). NOESY 2-H || 5-H. δ_C (150 MHz, $CDCl_3$) 16.9 (CH_3), 39.7, 47.9, 78.4, 83.2, 89.5, 125.3, 126.6, 127.2, 128.27, 128.34, 135.5, 141.7. GC-MS (EI, 70 eV) *m/z* (%) 300 (<1, M^+), 234 (3), 221 (8), 192 (8), 147 (17), 115 (10), 105 (100), 91 (8), 77 (33). HRMS (EI^+) *m/z* 282.1090 (M^+–H_2O); calculated mass for $C_{18}H_{18}OS^+$: 282.1078.

***rel*-(2*S*,3*R*,5*S*)-5-methyl-2,3-diphenyltetrahydrofuran-3-ol (8f)**. Yield: 12.9 mg (50.7 µmol, 10 %), R_f 0.42 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 1.49 (3 H, d, *J* 6.1), 1.74 (1 H, d, *J* 1.8, OH), 2.21–2.27 (1 H, m), 2.52 (1 H, dd, *J* 12.9, 5.5), 4.76–4.83 (1 H, m), 5.40 (1 H, s), 7.03–7.07 (2 H, m), 7.24–

7.26 (3 H, m), 7.28–7.31 (1 H, m), 7.37 (2 H, t, *J* 7.7), 7.40–7.44 (2 H, m). δ_C (100 MHz, $CDCl_3$) 21.5, 50.9, 75.2, 83.5, 90.0, 125.3, 126.6, 127.1, 128.1, 128.26, 128.29, 136.0, 142.1. GC-MS (EI, 70 eV) *m/z* (%) 254 (<1, M^+), 236 (13), 193 (10), 178 (6), 165 (8), 148 (88), 133 (65), 115 (23), 105 (100), 91 (8), 77 (65). HRMS (EI^+) *m/z* 254.1312 (M^+); calculated mass for $C_{17}H_{18}O_2^+$: 254.1307.

4.5 Oxidation of 2-phenylpent-4-en-1-ol (1g)

A solution of alcohol **1g** (164 mg, 1.01 mmol) and cobalt catalyst **5** (22.9 mg, 50.5 µmol) in dimethyl disulfide (9.5 mL [99%], 106 mmol) and CHD (1.0 mL) was stirred at 70 °C for 6 h, while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and concentrated under reduced pressure to afford a residue that was purified by column chromatography [SiO_2, Et_2O/pentane = 1:10 (*v*/*v*)].

***cis*-2-(methylsulfanyl)methyl-4-phenyltetrahydrofuran (3g)**. Yield: 144 mg (692 µmol, 68 %, *cis*:*trans* 88:12), R_f 0.48 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.84 (1 H, dt, J_d 12.3, J_t 10.0), 2.20 (3 H, s, CH_3), 2.53 (1 H, ddd, *J* 12.3, 7.2, 5.8), 2.71–2.77 (1 H, m), 2.78–2.85 (1 H, m), 3.44–3.55 (1 H, m), 3.84 (1 H, t, *J* 8.3), 4.19 (1 H, t, *J* 8.3), 4.23–4.31 (1H, m), 7.19–7.36 (5 H, m). NOESY 2-H ↔ 4-H. δ_C (100 MHz, $CDCl_3$) 16.4 (CH_3, *trans*), 16.5 (CH_3, *cis*), 39.1 (*trans*), 39.4 (*cis*), 39.7 (*trans*), 40.3 (*cis*), 44.5 (*trans*), 45.6 (*cis*), 74.5 (*cis*), 74.8 (*trans*), 78.5 (*trans*), 79.6 (*cis*), 126.6, 127.2, 128.6, 141.8 (*cis*), 142.1 (*trans*). GC-MS (EI, 70 eV) *m/z* (%) 208 (15, M^+), 190 (4), 147 (52), 129 (39), 115 (14), 103 (10), 91 (100), 77 (14). HRMS (EI^+) *m/z* 208.0928 (M^+); calculated mass for $C_{12}H_{16}OS^+$: 208.0922.

***cis*-2-methyl-4-phenyltetrahydrofuran (8g)**. Yield: 27.3 mg (168 µmol, 17 %). Analytical data agree with published values.[2,9]

4.6 Oxidation of *rel*-(1*S*,2*S*)-1-phenylpent-4-en-1,2-diol (1h)

A solution of alcohol **1h** (89.2 mg, 500 µmol) and cobalt catalyst **5** (11.6 mg, 25.6 µmol) in dimethyl disulfide (5.0 mL [99%], 55.8 mmol) and CHD (0.5 mL) was stirred at 70 °C for 6 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C. A GC-MS-spectrum revealed that Benzaldehyde (70 %) was the major product.

4.7 Oxidation of *rel*-(1*R*,2*R*)-1,2-diphenylpent-4-en-1-ol (1i)

A solution of alcohol **1i** (120 mg, 504 µmol) and cobalt catalyst **5** (11.6 mg, 25.6 µmol) in dimethyl disulfide (5.0 mL [99%], 55.8 mmol) and CHD (0.5 mL) was stirred at 70 °C for 8 h while being exposed to laboratory atmosphere. The reaction mixture was cooled to 20 °C and concentrated under reduced pressure to afford a residue that was purified by column chromatography [SiO_2, Et_2O/pentane = 1:10 (*v*/*v*)].

***rel*-(2*R*,4*R*,5*R*)-2-(methylsulfanyl)methyl-4,5-diphenyltetrahydrofuran (3i)**. Yield: 103 mg (360 µmol, 72 %), R_f 0.42 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 2.26 (3 H, s, CH_3), 2.30–2.39 (1 H, m), 2.47–2.57 (1 H, m), 2.78–2.85 (1 H, m), 2.74–2.83 (1 H, m), 2.87–2.95 (1 H, m), 3.78 (1 H, q, *J* 6.7), 4.83 (1 H, quin, *J* 6.3), 5.37 (1 H, d, *J* 6.3), 6.85–6.97 (4 H, m), 7.02–7.12 (6 H, m). NOESY 2-H ↔ 3-H, 2-H || 5-H, 3-H || 5-H. δ_C (100 MHz, $CDCl_3$) 16.5 (CH_3), 37.2, 40.3, 50.2, 78.4, 84.1, 126.3, 126.6, 127.4, 127.7, 128.5, 139.3, 139.6. HRMS (EI^+) *m/z* 284.1209 (M^+); calculated mass for $C_{18}H_{20}OS^+$: 284.1235.

***rel*-(2*R*,3*R*,5*S*)-5-methyl-2,3-diphenyltetrahydrofuran (8i).** Yield: 8.72 mg (36.6 µmol, 7 %), R_f 0.45 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.44 (3 H, d, *J* 6.3), 2.09 (1 H, ddd, *J* 12.7, 7.4, 5.3), 2.51 (1 H, ddd, *J* 13.0, 7.4, 6.3), 3.78 (1 H, q, *J* 6.6), 4.78–4.88 (1 H, m), 5.36 (1 H, d, *J* 6.3), 6.85–6.98 (4 H, m), 7.03–7.13 (6 H, m). δ_C (100 MHz, $CDCl_3$) 22.9, 39.3, 50.3, 74.9, 83.5, 126.1, 126.3, 126.5, 127.4, 127.7, 128.5, 139.7, 139.9. HRMS (EI^+) *m/z* 238.1364 (M^+); calculated mass for $C_{17}H_{18}O^+$: 238.1358.

4.8 Oxidation of rel-(1*R*,2*R*)-1,2-diphenylhex-5-en-1-ol (15)

A solution of alcohol **15** (169 mg, 669 µmol) and cobalt catalyst **5** (15.1 mg, 33.3 µmol) in methyl disulfide (6.6 mL) and CHD (0.65 mL) was stirred at 70 °C for 16 h while being exposed to laboratory atmosphere. Another batch of cobalt catalyst **5** (15.2 mg, 33.5 µmol) and CHD (0.65 mL) were added and the reaction mixture was stirred another 6 h at 70 °C. The reaction mixture was cooled to 20 °C and concentrated under reduced pressure to afford a residue that was purified by column chromatography [SiO_2, Et_2O/pentane = 1:10 (*v*/*v*)].

***rel*-(2*R*,3*R*,6*R*)-6-(methylsulfanyl)-methyl-2,3-diphenyltetrahydropyran (16).** Yield: 134 mg (450 µmol, 67 %), R_f 0.51 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.57–1.72 (2 H, m), 1.84–1.93 (1 H, m), 1.95–2.04 (1 H, m), 2.09

(3 H, s, CH_3), 2.55 (1 H, dd, *J* 13.3, 7.2), 2.69 (1 H, dd, *J* 13.3, 5.1), 3.92 (1 H, d, *J* 8.1), 4.16 (1 H, quin, *J* 6.6), 4.75 (1 H, dt, J_d 8.1, J_t 6.0), 7.13–7.19 (2 H, m), 7.21–7.28 (6 H, m), 7.32–7.36 (2 H, m). NOESY 2-H ↔ 3-H, 2-H || 6-H, 3-H || 6-H. δ_C (100 MHz, $CDCl_3$) 16.4 (CH_3), 31.2, 31.3, 39.3, 56.8, 79.1, 81.1, 126.1, 126.3, 128.1, 128.3, 128.5, 128.7, 142.4, 142.9. GC-MS (EI, 70 eV) *m/z* (%) 298 (<1, M^+), 237 (1), 193 (5), 178 (5), 165 (21), 152 (12), 131 (100), 115 (8), 103 (20), 87 (20). HRMS (EI^+) *m/z* 298.1384 (M^+); calculated mass for $C_{19}H_{22}OS$: 298.1391.

***rel*-(2*R*,3*R*,6*S*)-6-methyl-2,3-diphenyltetrahydropyran (17)**. Yield: 15.4 mg (61.0 µmol, 9 %), R_f 0.56 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.21 (3 H, d, *J* 6.1), 1.39–1.49 (1 H, m), 1.58–1.68 (1 H, m), 1.85–2.00 (1 H, m), 3.92 (1 H, d, *J* 8.4), 4.09 (1 H, quind, J_{quin} 7.9, J_d 6.1), 4.76 (1 H, dt, J_d 8.4, J_t 6.2), 7.14–7.19 (2 H, m), 7.23–7.29 (6 H, m), 7.33–7.37 (1 H, m). δ_C (100 MHz, $CDCl_3$) 21.4, 31.6, 33.6, 57.0, 75.3, 80.4, 126.1, 126.3, 128.2, 128.4, 128.6, 128.7, 142.8, 143.1. GC-MS (EI, 70 eV) *m/z* (%) 252 (<1, M^+), 178 (3), 165 (17), 152 (7), 115 (5), 85 (100), 77 (3). HRMS (EI^+) *m/z* 252.1515 (M^+); calculated mass for $C_{18}H_{20}O$: 252.1514.

5 5-Phenyltetrahydrofuryl-2-methyl methyl sulfoxide (9)

A solution of *tert*-butyl hydroperoxide (0.25 mL, 0.5–0.6 M, in nonane/$CHCl_3$) was added under nitrogen atmosphere to a solution of 2-[(2-oxidophenyl)-iminomethyl](ethanolato)oxidovanadium(V)[14] (10.7 mg, 29.0 µmol) in $CHCl_3$ (2.0 mL). The mixture was briefly refluxed (5 min), a solution of *trans*-2-(methylsulfanyl)methyl-5-phenyltetrahydrofuran (**3a**) (59.7 mg, 289 µmol) in $CHCl_3$ (2.0 mL) was added to the warm solution and the reaction mixture was stirred at 22 °C for 48 h. The dark brown solution was filtrated through a short pad of neutral Al_2O_3 for removing the vanadium residues. The filtrate was concentrated under reduced pressure to leave an oil, which was purified by flash chromatography (SiO_2, acetone). Yield: 42.4 mg, 189 µmol, 66 %, R_f 0.12 [SiO_2, acetone], colorless oil, 50/50 mixture of diastereomers with respect to configuration at sulfur. δ_H (400 MHz, $CDCl_3$) 1.76–2.03 (4 H, m), 2.26–2.35 (2 H, m), 2.37–2.46 (2 H, m), 2.66 (3 H, s, CH_3), 2.70 (3 H, s, CH_3), 2.92–3.09 (4 H, m), 4.61–4.74 (2 H, m), 5.06 (2 H, dt, J_d 8.1, J_t 6.1), 7.21–7.27 (2 H, m), 7.28–7.35 (8 H, m). δ_C (100 MHz, $CDCl_3$) 32.3, 32.7, 35.0, 38.9, 39.8, 58.8, 61.6, 73.2, 73.4, 80.8, 81.1, 125.4, 127.3, 128.31, 128.33, 142.6, 142.7. HRMS (EI^+) *m/z* 224.0834 (M^+) respectively 224.0821 (M^+); calculated mass for $C_{12}H_{16}O_2S^+$: 224.0871. The intensity of the molecular ion in HRMS spectra of the two diastereomeric sulfoxides was very weak. Since the retention times (GC) of the sulfoxide diastereomers differ from derived thioether *trans*-**3a**, the fragments at *m/z* 208.0919 (diastereomer 1) and *m/z* 208.0916 (diastereomer 2), originating from a formal loss of oxygen (calculated mass for $C_{12}H_{16}OS^+$: 208.0922) was used to characterize the sulfoxide stereoisomers of **9**.

6 5-Phenyltetrahydrofuryl-2-methyl methyl sulfone (10)

A solution of *tert*-butyl hydroperoxide (0.1 mL, 5–6 M, in nonane) was added under nitrogen atmosphere to a solution of 2-[(2-oxidophenyl)iminomethyl]-(ethanolato)oxidovanadium(V)[14] (18.2 mg, 49.3 µmol) in $CHCl_3$ (2.5 mL). The mixture was briefly refluxed (5 min), a solution of *trans*-2-(methylsulfanyl)methyl-5-phenyltetrahydrofuran (**3a**) (104 mg, 497 µmol) in $CHCl_3$ (2.5 mL) was added to the warm solution and the reaction mixture was stirred at 22 °C for 48 h. The dark brown solution was filtrated through a short pad of neutral Al_2O_3 for removing the vanadium residues. The filtrate was concentrated under reduced pressure to leave an oil, which was purified by flash chromatography [SiO_2, acetone/CH_2Cl_2 = 1/40 (*v*/*v*)]. Yield: 89.5 mg, 372 µmol, 75 %, R_f 0.43 [SiO_2, acetone/CH_2Cl_2 = 1:40 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.79–1.96 (2 H, m), 2.29–2.36 (1 H, m), 2.39–2.47 (1 H, m), 3.06 (3 H, s, CH_3), 3.33 (1 H, dd, *J* 14.7, 9.1), 4.73 (1 H, tdd, J_t 8.6, J_d 6.0, 2.5), 5.08 (1 H, dd, *J* 8.5, 6.1), 7.25–7.37 (5 H, m). δ_C (100 MHz, $CDCl_3$) 32.5, 34.9, 42.6, 60.3, 74.0, 81.2, 125.2, 127.4, 128.5, 142.5. HRMS (EI^+) *m/z* 240.0814 (M^+); calculated mass for $C_{12}H_{16}O_3S^+$: 240.0820.

7. Library of carbon-13 NMR spectra of selected compounds

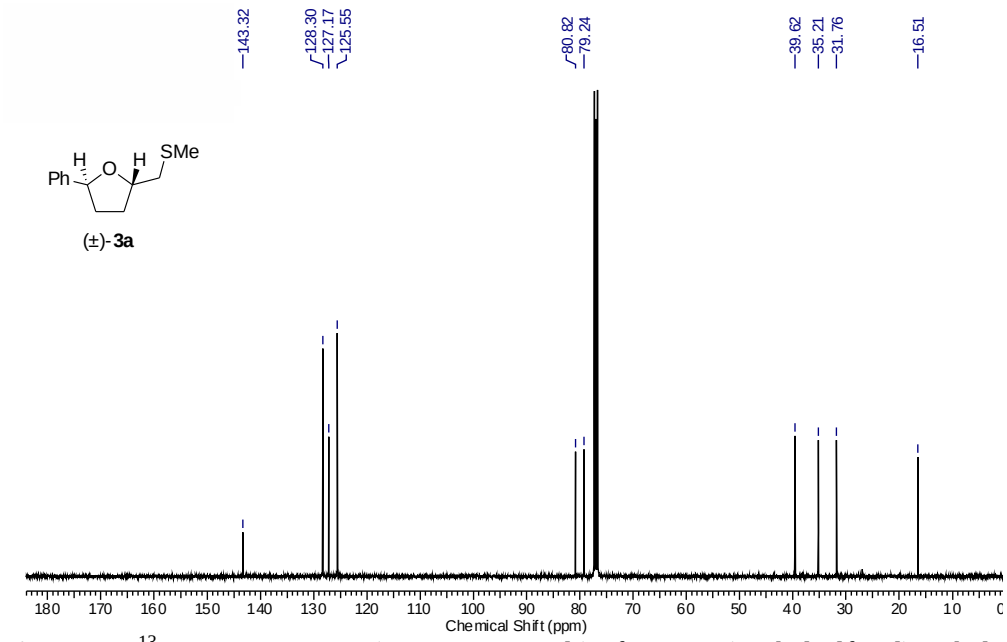

Figure S1: ^{13}C-NMR spectrum (150 MHz, $CDCl_3$) of *trans*-2-(methylsulfanyl)methyl-5-phenyltetrahydrofuran (**3a**).

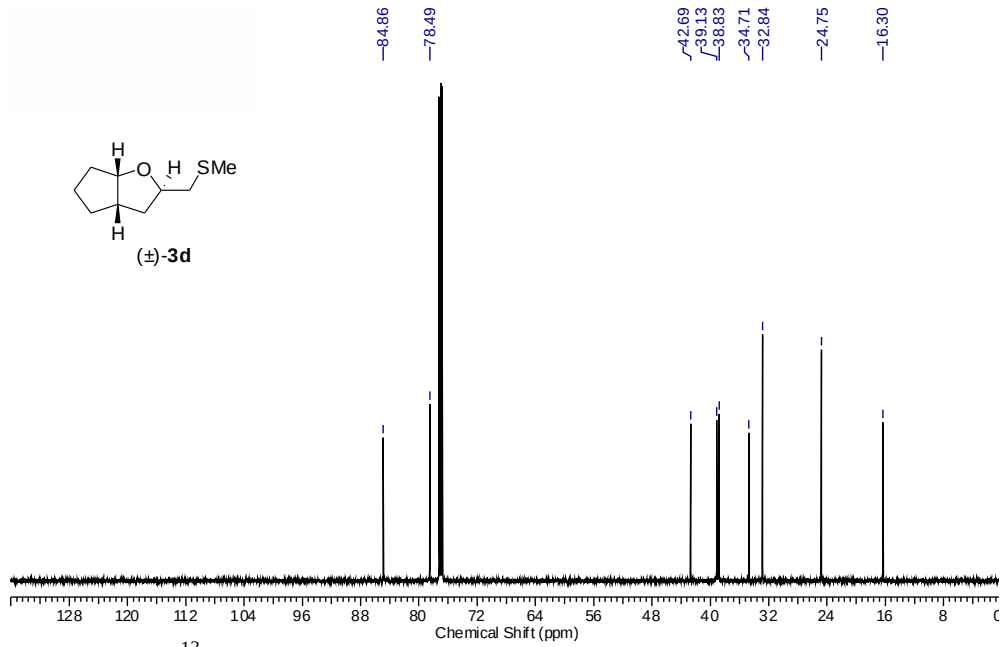

Figure S2: ^{13}C-NMR spectrum (150 MHz, $CDCl_3$) of *rel*-(1*S*,3*R*,5*S*)-3-(methylsulfanyl)methyl-2-oxabicyclo[3.3.0]octane (**3d**).

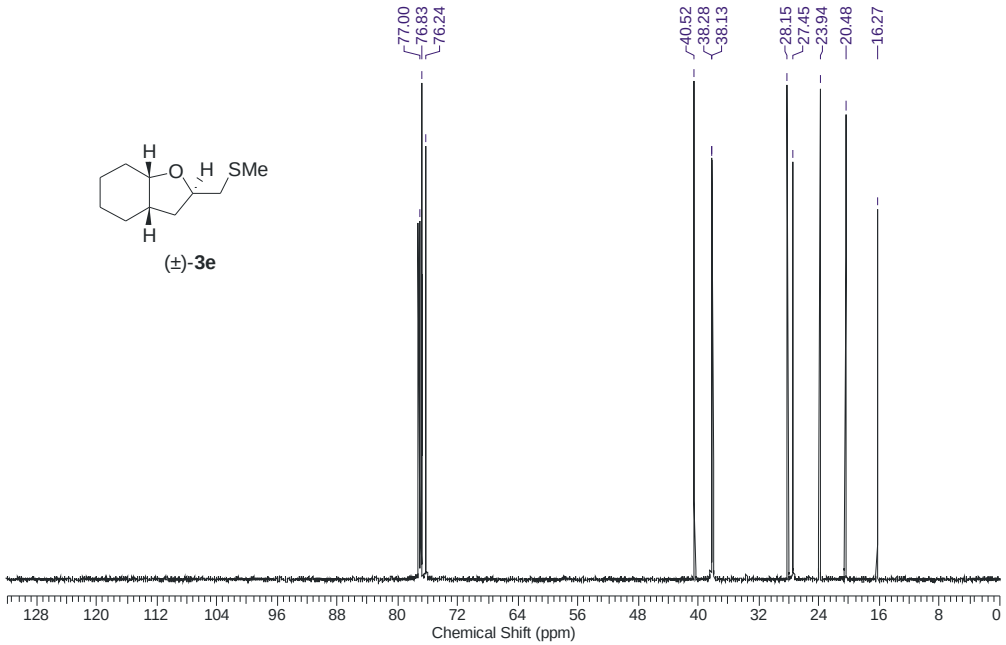

Figure S3. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$) of *rel*-(1*S*,3*R*,5*S*)-3-(methylsulfanyl)methyl-2-oxabicyclo[4.3.0]nonane (**3e**).

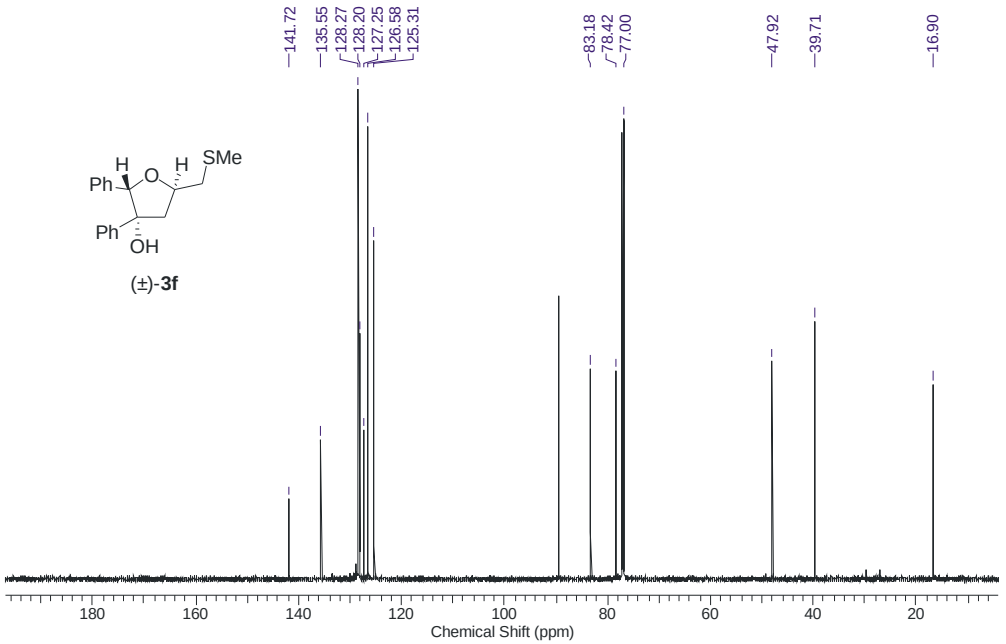

Figure S4. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$) of *rel*-(2*S*,3*R*,5*R*)-5-(methylsulfanyl)methyl-2,3-diphenyltetrahydrofuran-3-ol (**3f**).

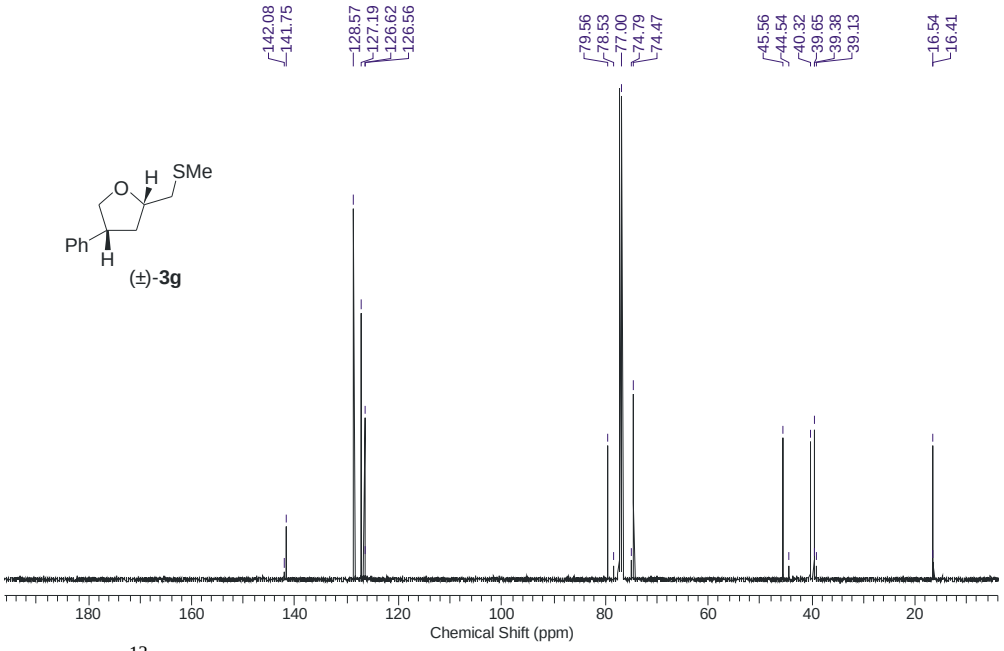

Figure S5. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of *cis*-2-(methylsulfanyl)methyl-4-phenyltetrahydrofuran (**3g**).

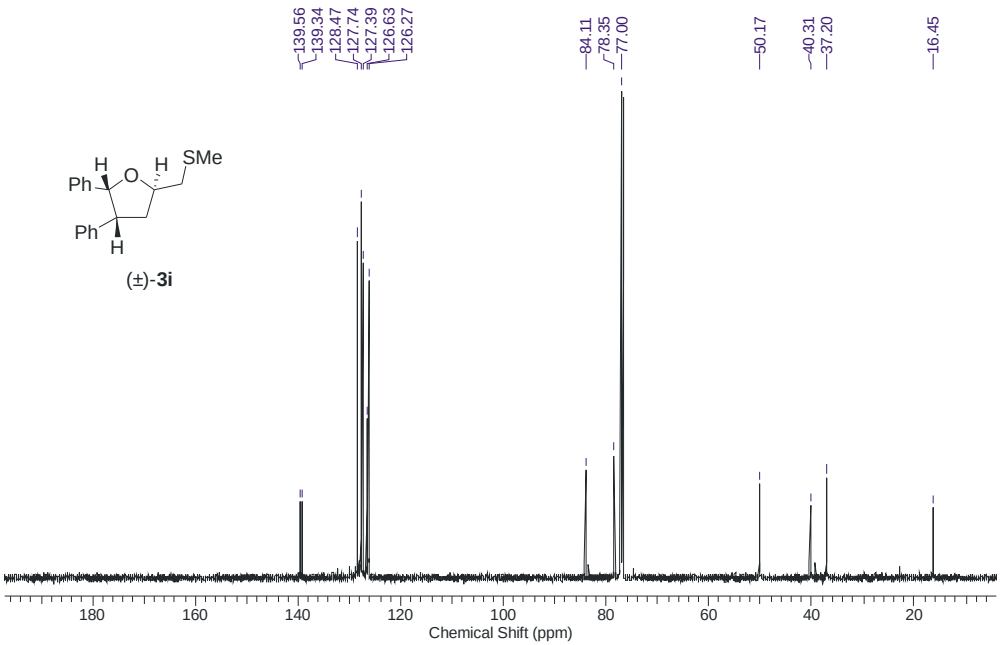

Figure S6. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$) of *rel*-(2*R*,4*R*,5*R*)-2-(methylsulfanyl)methyl-4,5-diphenyltetrahydrofuran (**3i**).

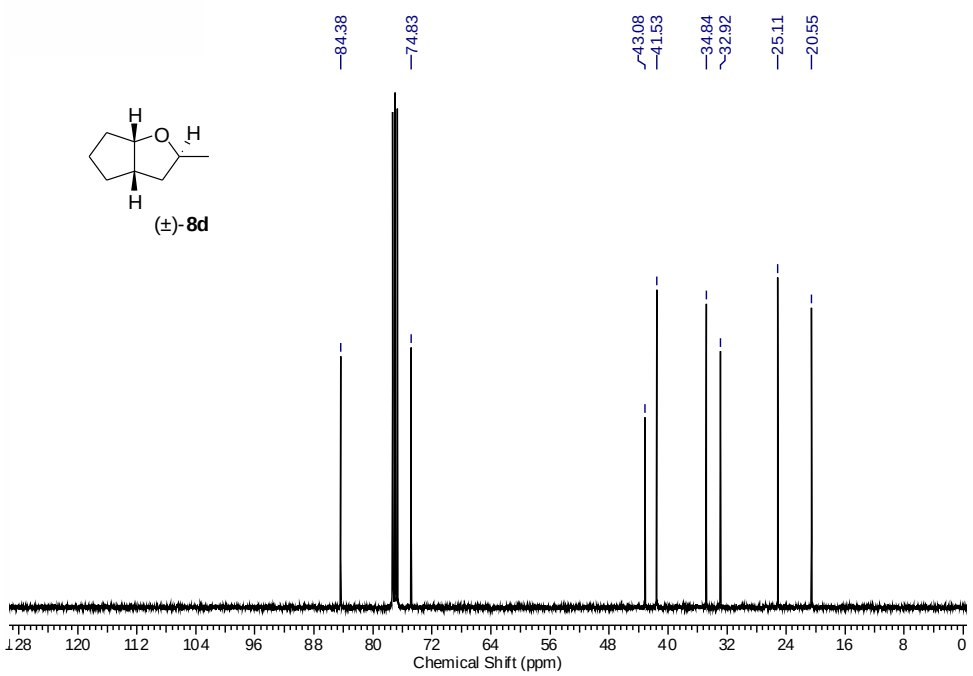

Figure S7. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of *rel*-(1*S*,3*S*,5*S*)-3-Methyl-2-oxabicyclo[3.3.0]octane (**8d**) .

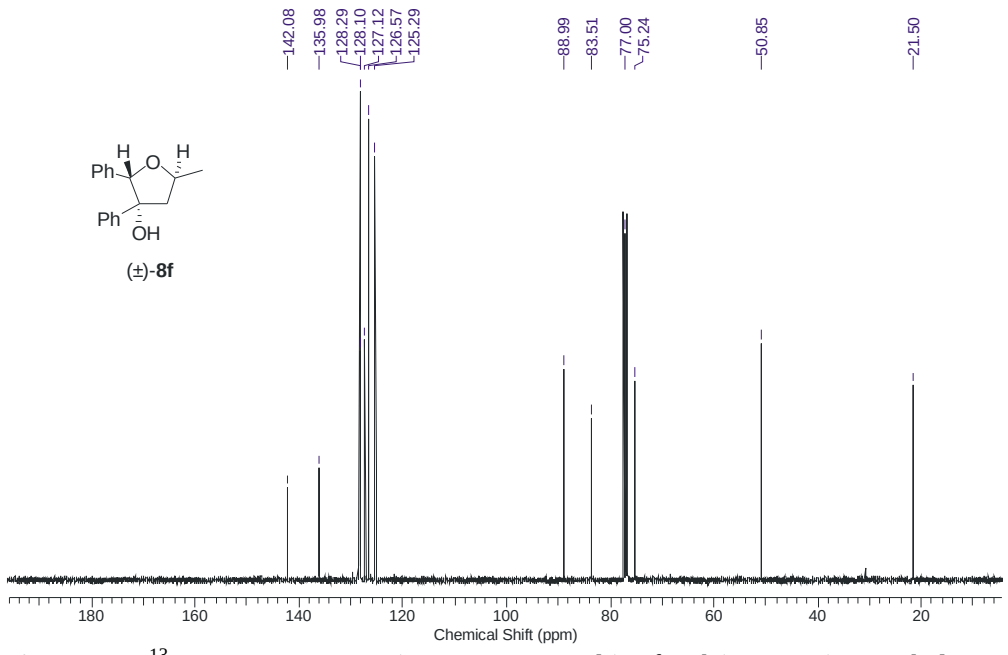

Figure S8. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of *rel*-(2*S*,3*R*,5*S*)-5-methyl-2,3-diphenyltetrahydrofuran-3-ol (**8f**).

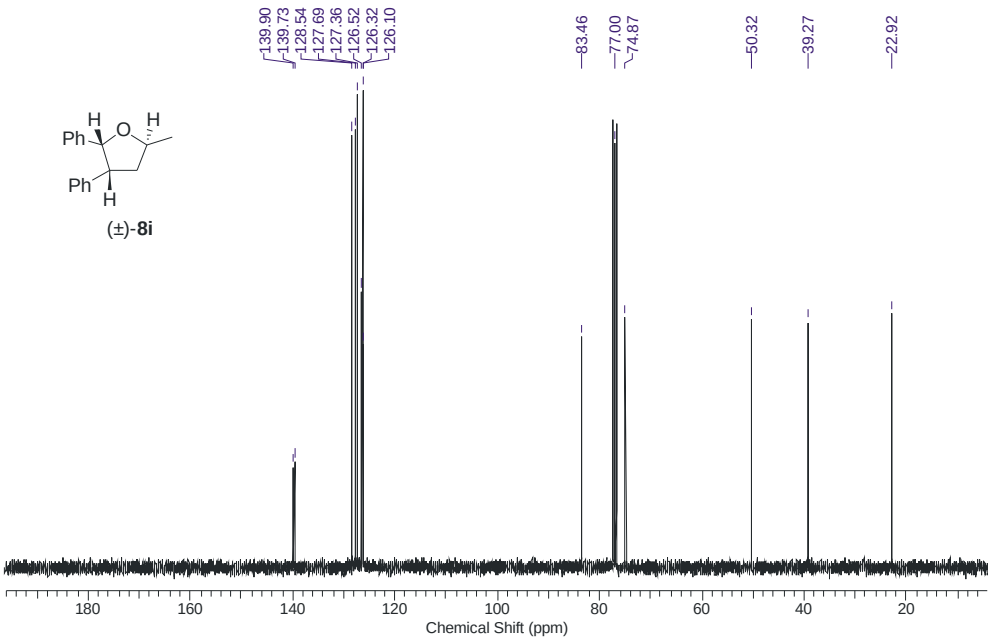

Figure S9. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of *rel*-(2*R*,3*R*,5*S*)-5-methyl-2,3-diphenyltetrahydrofuran (**8i**).

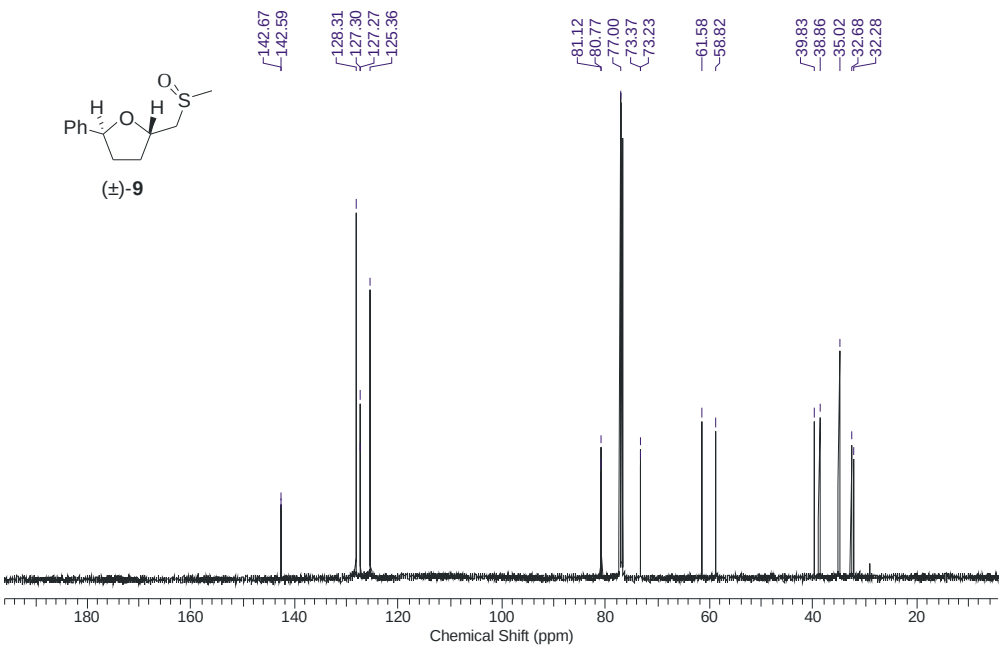

Figure S10. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of (5-Phenyltetrahydrofuryl)-2-methyl methyl sulfoxide (**9**) (50/50-mixture of stereoisomers at sulfur).

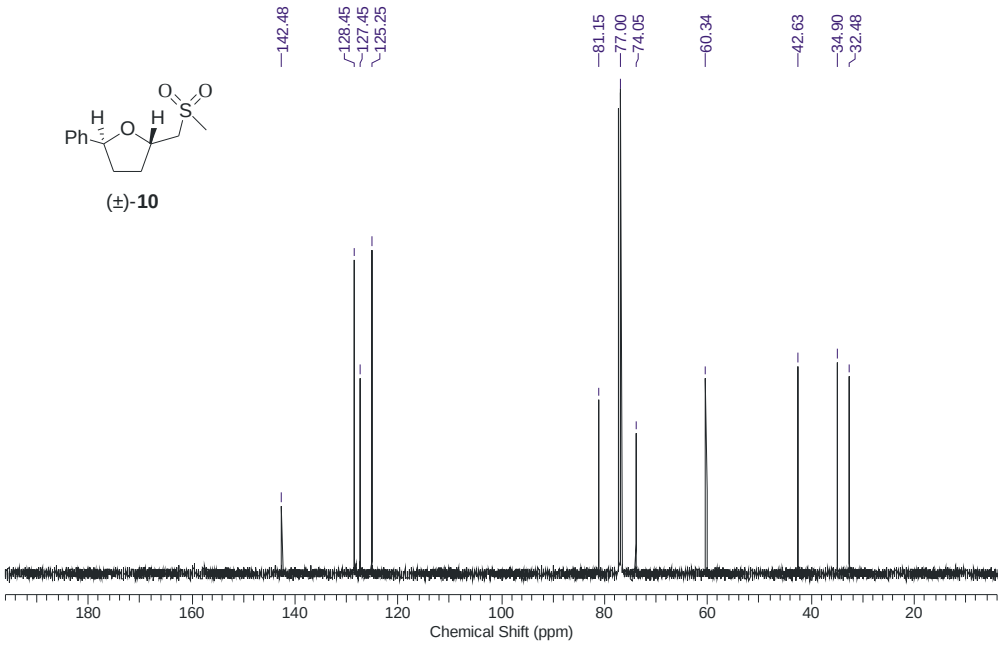

Figure S11: ^{13}C-NMR spectrum (150 MHz, $CDCl_3$) of (5-phenyltetrahydrofuryl)-2-methyl methyl sulfone (**10**).

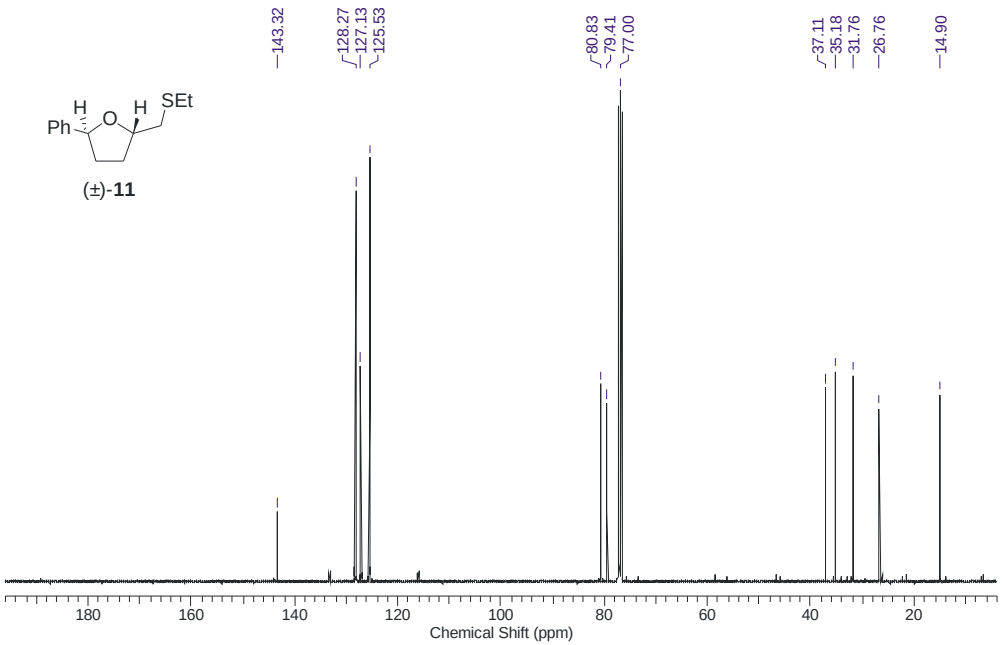

Figure S12. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of *trans*-2-(ethylsulfanyl)methyl-5-phenyltetrahydrofuran (**11**).

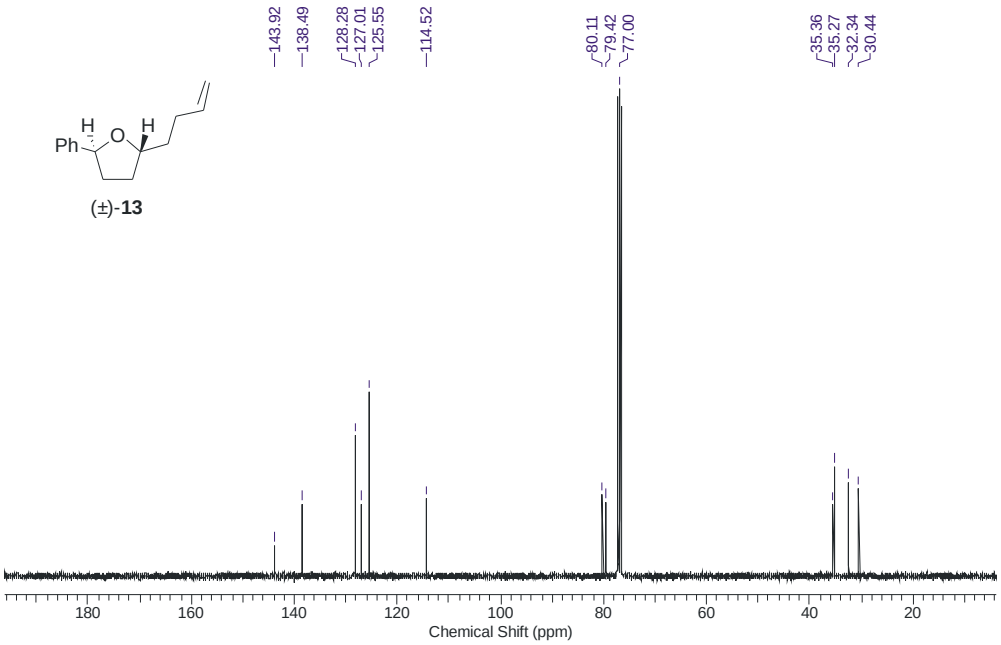

Figure S13. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of *trans*-2-(but-1-en-4-yl)-5-phenyltetrahydrofuran (**13**).

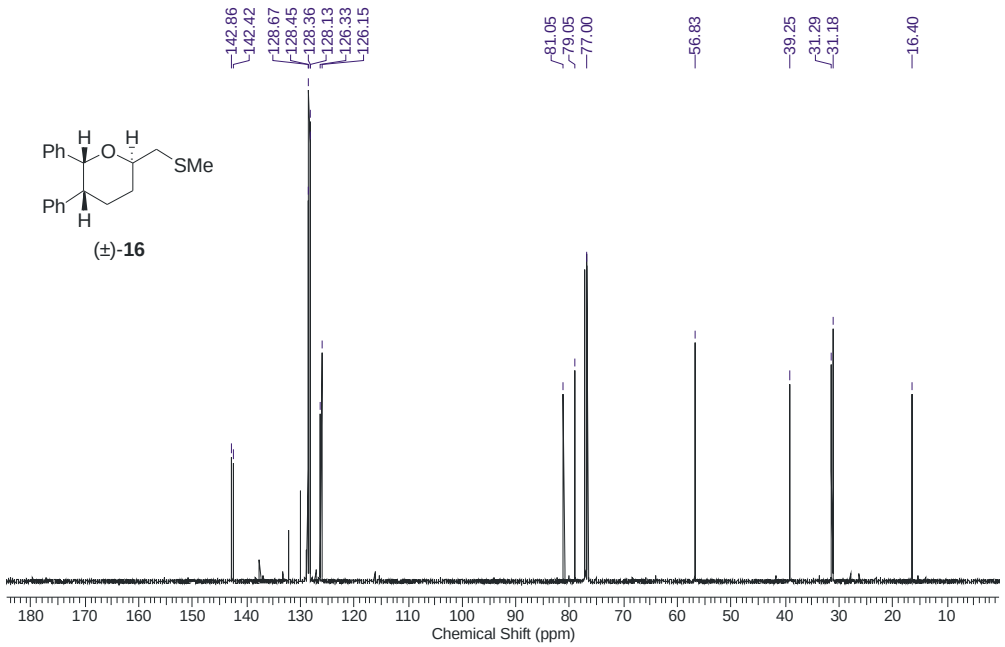

Figure S14. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$) of *rel*-(2*R*,3*R*,6*R*)-6-(methylsulfanyl)-methyl-2,3-diphenyltetrahydropyran (**16**).

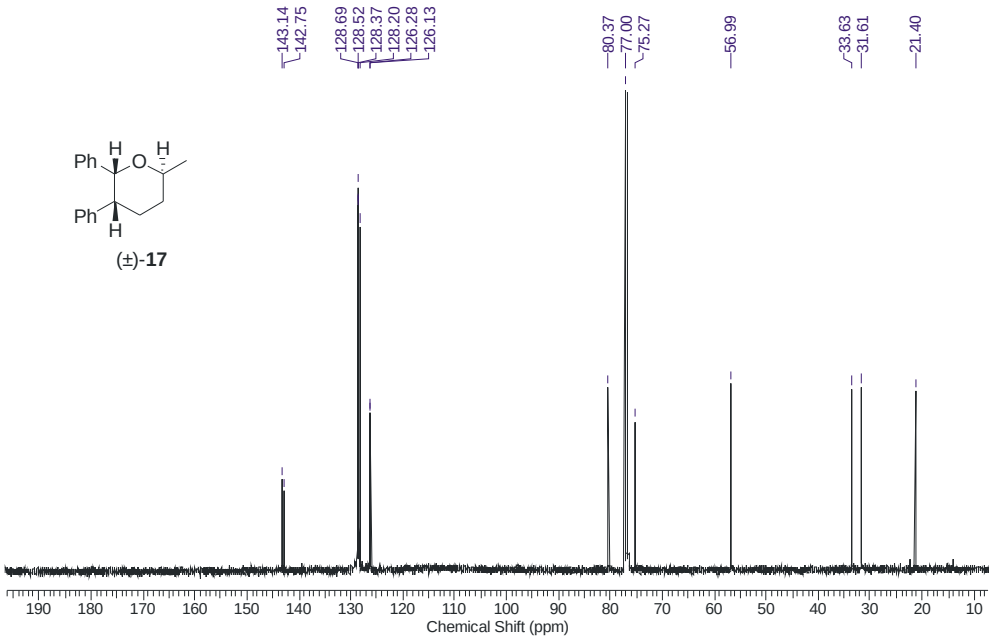

Figure S15. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of *rel*-(2*R*,3*R*,6*S*)-6-methyl-2,3-diphenyltetrahydropyran (**17**).

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6.4 Ergänzende Experimentelle Daten zu Kapitel 5

Supporting Information for

Stereoselective Synthesis of Sidechain-Functionalized Tetrahydropyrans from 5-Hexenols

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3 Alkenols S3
4 Computational Chemistry S10
5 Proton- and Carbon-13 NMR-Spectra of Selected Compounds S14
6 References S28

1 General Remarks

(i) The compound numbering in the Supporting information is consistent with that of the accompanying publication. (ii) References refer exclusively to the Supporting Information. (iii) Oxygen atoms in B3LYP/6-31+G**-calculated structures (section 4) are depicted in red, carbons in gray and hydrogens in white.

2 Instrumentation and Reagent Preparation

2.1 NMR

^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded with FT-NMR DPX 400 and DMX 600 instruments (*Bruker*). Chemical shifts refer to the δ-scale (coupling constants *J* are given in Hz). The resonances of residual $CHCl_3$ and of the carbon in $CDCl_3$ (δ_H 7.26, δ_C 77.0) were used as internal standards. ^{19}F-NMR chemical shifts were referenced versus α,α,α-Trifluorotoluene (δ_F –63.72) as internal standard.

2.2 Mass spectrometry

Mass spectra (EI, 70 eV) were recorded with a Mass Selective Detector HP 6890 (*Hewlett Packard*).

2.3 Combustion analysis

Combustion analyses were performed with a vario Micro cube CHNS (*Elementar Analysentechnik / Hanau*).

2.4 Thin layer chromatography

Reaction progress was monitored via thin layer chromatography (tlc) on aluminium sheets coated with silica gel (60 F_{254}, *Merck*). Compounds on developed tlc-sheets were detected with the aid of the UV-VIS indicator commercially disposed on the sheets becoming apparent by hand lamps emitting 254-nm light. As alternative method for detecting compounds, tlc-sheets were developed by staining with Ekkert´s reagent and subsequent heating.

2.5 Infrared spectroscopy

IR spectra were recorded from pelletized samples in KBr using a FT-IR 1000 spectrometer (*Perkin Elmer*).

2.6 Gas chromatography coupled to mass spectrometry

GC/MS Analysis was performed with a HP 6890 Series (*Hewlett Packard*) with a ZB5 column (*Phenomenex*, 30 m × 0.25 mm, 0.25 μm). Temperature program: 40 °C (3 min), linear temperature rise (10 °C min^{-1}) to 280 °C, final temperature 280 °C (10 min).

2.7 High resolution mass spectrometry

Mass spectroscopy (EI, 70 eV), GCT Premier Micromass (*Waters*).

2.8 Purification of solvents

All solvents were purified according to standard procedures.[1]

2.9 References for synthesis of starting materials

1-Phenylhex-5-en-1-ol (**1a**),[2] hept-6-en-2-ol (**1b**),[3] 1-cyclohexylhex-5-en-1-ol (**1c**),[4] deca-1,9-dien-5-ol (**1d**),[5] 2-phenylhex-5-en-1ol (**1e**),[6] 2-isopropylhex-5-en-1-ol (**1f**),[7] and *like*-1,2-piphenylhex-5-en-1-ol (**1g**)[8] were prepared according to published procedures.

3 Alkenols

3.1 1,3-Diphenylhex-5-en-1-ol

3.1.1 1,3-Diphenylhex-5-en-1-one

1,3-Diphenylhex-5-en-1-one was prepared from chalcone (655 mg [97 %], 3.05 mmol) and allyl trimethyl silane in a Hosomi-Sakurai-reaction.[9,10] Yield: 559 mg (2.23 mmol, 73 %), R_f 0.52 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 2.40–2.52 (2 H, m), 3.29 (2 H, dd, *J* 7.1, 1.4), 3.48 (1 H, quin, *J* 7.1), 4.93–5.04 (2 H, m), 5.69 (1 H, ddt, J_d 17.1, 10.1, J_t 7.1), 7.15–7.31 (5 H, m), 7.40–7.45 (2 H, m), 7.50–7.56 (1 H, m), 7.87–7.93 (2 H, m). Analytical data agree with published values.[10]

3.1.2 1,3-Diphenylhex-5-en-1-ol (1i)

A solution of 1,3-diphenylhex-5-en-1-one (1.53 g, 6.11 mmol) in dry diethyl ether (20 mL) was added in a dropwise manner to a suspension of $LiAlH_4$ (149 mg, 3.93 mmol) in dry diethyl ether (20 mL). The reaction mixture was refluxed for 3 hours, cooled, to 0 °C. An aqueous saturated solution of NH_4Cl (40 mL) was added slowly. The phases were separated. The aqueous layer was extracted with diethyl ether (3 × 20 mL). Combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to leave an oil, which was purified by column chromatography [SiO_2, acetone/diethyl ether/pentane = 1/1/20, (*v*/*v*)]. **1,3-*unlike*-1,3-Diphenylhex-5-en-1-ol *rel*-(1*S*,3*R*)-(1i)**. Yield: 594 mg (2.36 mmol, 39 %), R_f 0.39 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.71 (1 H, d, *J* 3.7, OH), 1.88 (1 H, dddd, *J*, 14.2, 11.2, 3.2, 1.2), 2.12 (1 H, ddd, *J* 14.2, 10.3, 4.1), 2.32–2.45 (2 H, m), 3.05 (1 H, dtd, J_d 11.2, J_t 7.3, J_d 4.1), 4.37 (1 H, dt, J_d 10.3, J_t 3.2), 4.91–5.00 (2 H, m), 5.68 (1 H, ddt, J_d 17.1, 10.1, J_t 7.1), 7.21–7.37 (10 H, m). δ_C (100 MHz, $CDCl_3$) 41.7, 42.3, 45.4, 71.7, 116.2, 125.5, 126.3, 127.3, 127.8, 128.5, 136.7, 144.3, 145.3. MS (EI) *m*/*z* 252 (1) [M^+], 234 (12), 209 (7), 193 (33), 178 (9), 130 (30), 115 (51), 107 (100), 91 (34), 79 (42), 77 (30). Anal. Calcd. for $C_{18}H_{20}O$ (252.35): C 85.67; H 7.99. Found: C 85.46; H 7.89. **1,3-*like*-1,3-Diphenylhex-5-en-1-ol *rel*-(1*R*,3*R*)-(1i)**. Yield: 647 mg, (2.56 mmol, 42 %), R_f 0.34 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.68 (1 H, d, *J*

2.3, OH), 2.08–2.24 (2 H, m), 2.27–2.43 (2 H, m), 2.48–2.57 (1 H, m), 4.51 (1 H, t, *J* 6.3), 4.87–4.96 (2 H, m), 5.56 (1 H, ddt, J_d 17.1, 10.1, J_t 7.0), 7.13–7.38 (10 H, m). δ_C (100 MHz, $CDCl_3$) 41.5, 42.3, 44.6, 73.0, 116.2, 125.5, 126.3, 127.7, 128.5, 136.4, 144.1, 144.5. MS (EI) *m*/*z* 252 (1) [M^+], 234 (16), 209 (7), 193 (49), 178 (8), 130 (46), 115 (78), 107 (100), 91 (46), 79 (42), 77 (44). Anal. Calcd. for $C_{18}H_{20}O$ (252.35): C 85.67; H 7.99. Found: C 85.51; H 7.92.

3.2 1-(Thien-2-yl)-3-phenylhex-5-en-1-ol

3.2.1 1-(Thien-2-yl)-3-phenylhex-5-en-1-one

1-(Thien-2-yl)-3-phenylhex-5-en-1-on was prepared from 3-phenyl-1-(2-thienyl)-2-propen-1-one (2.22 g [97 %], 10.0 mmol) and allyltrimethylsilane in a Hosomi-Sakurai-reaction.[9,10] Yield: 732 mg (2.86 mmol, 29 %), R_f 0.50 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)]. δ_H (400 MHz, $CDCl_3$) 2.37–2.49 (2 H, m), 3.11–3.23 (2 H, m), 3.42 (1 H, quin, *J* 7.1), 4.90–5.00 (2 H, m), 5.64 (1 H, ddt, J_d 17.1, 10.1, J_t 7.1), 7.05 (1 H, dd, *J* 5.0, 3.8), 7.12–7.17 (1 H, m), 7.18–7.27 (5 H, m), 7.56 (1 H, dd, *J* 4.9, 1.1), 7.61 (1 H, dd, *J* 3.8, 1.1). Analytical data agree with published values.[10]

3.2.2 1-(Thien-2-yl)-3-phenylhex-5-en-1-ol (1j)

A solution of 1-(thiophen-2'-yl)-3-phenylhex-5-en-1-one (717 mg, 2.80 mmol) in dry diethyl ether (14 mL) was added in a dropwise manner to a suspension of $LiAlH_4$ (65.0 mg, 1.71 mmol) in dry diethyl ether (7 mL). The reaction mixture was refluxed for 3 hours and cooled to 0 °C. An aqueous solution of saturated aqueous NH_4Cl (20 mL) was added slowly. The phases were separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). Combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to leave an oil, which was purified by column chromatography [SiO_2, acetone/diethyl ether/pentane = 1/1/20, (*v*/*v*)]. **1,3-*unlike*-1-(Thien-2-yl)-3-phenylhex-5-en-1-ol *rel*-(1*S*,3*R*-(1j)**. Yield: 312 mg (1.21 mmol, 43%), R_f 0.34 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 2.04 (1

H, ddd, *J* 13.8, 11.2, 2.9), 2.24 (1 H, ddd, *J* 14.2, 10.2, 4.1), 2.37–2.45 (2 H, m), 3.03–3.09 (1 H, m), 4.59–4.64 (1 H, m), 4.93–5.01 (2 H, m), 5.69 (1 H, ddt, J_d 17.0, 10.0, J_t 7.0), 6.87 (1 H, d, *J* 3.2), 6.92 (1 H, dd, *J* 5.0, 3.5), 7.19–7.25 (4 H, m), 7.30–7.35 (2 H, m). δ_C (100 MHz, $CDCl_3$) 41.6, 42.1, 45.3, 67.6, 116.3, 123.3, 124.4, 126.4, 126.6, 127.8, 128.5, 136.6, 144.0, 149.2. Anal. Calcd. for $C_{16}H_{18}OS$ (258.38): C 74.38; H 7.02; S 12.41. Found: C 74.37; H 7.12; S 12.46. **1,3-*like*-1-(Thien-2-yl)-3-phenylhex-5-en-1-ol (*rel*-(1*R*,3*R*)-1j)**. Yield: 328 mg (1.27 mmol, 45%), R_f 0.32 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (600 MHz, $CDCl_3$) 2.18–2.27 (2 H, m), 2.32–2.41 (2 H, m), 2.56–2.61 (1 H, m), 4.71–4.75 (1 H, m), 4.91–4.98 (2 H, m), 5.60 (1 H, ddt, J_d 17.1, 10.1, J_t 6.9), 6.89 (1 H, dd, *J* 3.7, 1.0), 6.97 (1 H, dd, *J* 5.0, 3.5), 7.15 (2 H, d, *J* 7.0), 7.20–7.24 (1 H, m), 7.28 (1 H, dd, *J* 5.0, 1.0), 7.30–7.33 (2 H, m). δ_C (100 MHz, $CDCl_3$) 41.4, 42.3, 44.9, 68.5, 116.3, 124.5, 124.9, 126.4, 126.5, 127.7, 128.5, 136.3, 144.2, 148.0. Anal. Calcd. for $C_{16}H_{18}OS$ (258.38): C 74.38; H 7.02; S 12.41. Found: C 74.41; H 7.04; S 12.45.

3.3 1-(2,4-Difluorophenyl)-3-phenylhex-5-en-1-ol

3.3.1 1-(2,4-Difluorophenyl)-3-phenylprop-2-en-1-one

1-(2',4'-Difluorophenyl)-3-phenylprop-2-en-1-one was prepared from benzaldehyde and 2,4-difluoroacetophenone (3.99 g, 25.0 mmol) according to Verma et al.[11] Yield: 4.30 g (17.6 mmol, 70 %). δ_H (400 MHz, $CDCl_3$) 6.91 (1 H, ddd, *J* 10.9, 8.7, 2.4), 6.96–7.03 (1 H, m), 7.36–7.44 (4 H, m), 7.60–7.65 (2 H, m), 7.78 (1 H, dd, *J* 15.7, 1.9), 7.90 (1 H, td, J_t 8.5, J_d 6.6). Analytical data agree with published values.[11]

3.3.2 1-(2,4-Difluorophenyl)-3-phenylhex-5-en-1-one

1-(2,4-Difluorophenyl)-3-phenylhex-5-en-1-one was prepared from 1-(2,4-difluorophenyl)-3-phenylprop-2-en-1-one (1.95 g, 7.98 mmol) and allyltrimethylsilane in a Hosomi-Sakurai reaction.[8,9] Yield: 1.94 g (6.79 mmol, 85 %), R_f 0.51 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 2.40 (2 H, tt, *J* 7.1,

1.1), 3.18–3.32 (2 H, m), 3.40 (1 H, dtd, J_d 13.3, J_t 7.6, J_d 1.4), 4.90–5.00 (2 H, m), 5.64 (1 H, ddt, J_d 17.2, 10.1, J_t 7.0), 6.77–6.90 (2 H, m), 7.11–7.26 (5 H, m), 7.74 (1 H, td, J_t 8.6, J_d 6.6). δ_C (100 MHz, $CDCl_3$) 40.6, 40.8, 49.3 (d, *J* 7.3), 104.6 (dd, *J* 28.1, 24.5). 112.1 (dd, *J* 21.5, 3.6), 116.8, 122.5 (dd, *J* 13.4, 3.6), 126.4, 127.5, 128.4, 132.6 (dd, *J* 10.6, 4.5), 144.1, 162.4 (dd, *J* 257, 12.7), 165.6 (dd, *J* 257, 11.8), 195.8 (d, *J* 4.5). δ_F (376 MHz, $CDCl_3$) –102.2, –104.6. HRMS (EI^+) *m/z* 286.1180 [M^+]; calculated mass for $C_{18}H_{16}OF_2^+$: 286.1169.

3.3.3 1-(2,4-Difluorophenyl)-3-phenylhex-5-en-1-ol (1k)

A solution of 1-(2,4-difluorophenyl)-3-phenylhex-5-en-1-one (1.92 g, 6.71 mmol) in dry diethyl ether (20 mL) was added in a dropwise manner to a suspension of $LiAlH_4$ (173 mg, 4.56 mmol) in dry diethyl ether (10 mL). The reaction mixture was refluxed for 3 hours and cooled to 0 °C. An aqueous solution of saturated aqueous NH_4Cl (30 mL) was added slowly. The phases were separated and the aqueous phase extracted with diethyl ether (3 × 15 mL). Combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to leave an oil, which was purified by column chromatography [SiO_2, acetone/diethyl ether/pentane = 1/1/20, (*v*/*v*)]. **1,3-*unlike*-1-(2,4-Difluorophenyl)-3-phenylhex-5-en-1-ol *rel*-(1*S*,3*R*)-(1k)**. Yield: 675 mg (2.34 mmol, 35%), R_f 0.37 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.74 (1 H, d, *J* 4.9, OH), 1.90–1.98 (1 H, m), 2.08 (1 H, ddd, *J* 14.5, 9.6, 4.3), 2.31–2.44 (2 H, m), 2.97–3.06 (1 H, m), 4.62–4.68 (1 H, m), 4.91–5.00 (2 H, m), 5.67 (1 H, ddt, J_d 17.1, 10.0, J_t 7.1), 6.71 (1 H, ddd, *J* 10.7, 8.6, 2.5), 6.84 (1 H, dddd, *J* 8.9, 8.0, 2.5, 1.2), 7.20–7.25 (3 H, m), 7.30–7.35 (2 H, m), 7.39 (1 H, td, J_t 8.6, J_d 6.3). δ_C (100 MHz, $CDCl_3$) 41.9, 42.2, 43.7, 65.7, 103.6 (t, *J* 25.6), 111.2 (dd, *J* 20.7, 4.1), 116.3, 126.4, 127.8, 128.1 (dd, *J* 14.1, 3.2), 128.5, 136.5, 143.8, 149.4 (dd, *J* 248, 11.8), 162.0 (dd, *J* 248, 11.8). δ_F (376 MHz, $CDCl_3$) –116.6 (1 F, dt, J_d 10.3, J_t 8.0), –113.3 (1 F, quin, *J* 8.0). MS (EI) *m/z* 288 (1) [M^+], 270 (14), 229 (46), 214 (8), 166 (10), 151 (25), 143 (100), 127 (28), 115 (43), 105 (25), 91 (28), 77 (11). HRMS (EI^+) *m/z* 288.1334 (M^+); calculated mass for $C_{18}H_{18}OF_2^+$: 288.1326. **1,3-*like*-1-(2,4-Difluorophenyl)-3-phenylhex-5-en-1-ol *rel*-(1*R*,3*R*)-(1k)**. Yield: 1.00 g (3.47 mmol, 52%), R_f 0.34 [SiO_2,

acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.73–1.85 (1 H, br.s, OH), 2.07–2.21 (2 H, m), 2.31–2.47 (2 H, m), 2.65 (1 H, tt, *J* 8.4, 6.1), 4.86 (1 H, td, J_t 6.9, J_d 4.4), 4.90–5.00 (2 H, m), 5.60 (1 H, ddt, J_d 17.1, 10.1, J_t 7.0), 6.78 (1 H, ddd, *J* 10.7, 8.6, 2.5), 6.86 (1 H, tdd, J_t 8.4, J_d 2.5, 1.2), 7.13–7.18 (2 H, m), 7.19–7.24 (1 H, m), 7.28–7.35 (3 H, m). δ_C (100 MHz, $CDCl_3$) 41.1, 42.7, 43.9, 67.0, 103.8 (t, *J* 25.4), 111.4 (dd, *J* 22.7, 3.6), 116.5, 126.5, 127.1 (dd, *J* 13.6, 3.6), 127.6, 128.7 (dd, *J* 10.0, 6.4), 136.2, 144.4, 159.9 (dd, *J* 228, 11.8), 162.3 (dd, *J* 227, 13.6). δ_F (376 MHz, $CDCl_3$) –116.2 (1 F, dt, J_d 10.3, J_t 8.0), –112.6 (1 F, dt, J_d 15.7, J_t 7.6). MS (EI) *m*/*z*) 288 (1) [M^+], 270 (19), 229 (63), 214 (11), 166 (13), 151 (31), 143 (100), 127 (41), 115 (54), 105 (28), 91 (39), 77 (15). HRMS (EI^+) *m/z* 288.1334 [M^+]; calculated mass for $C_{18}H_{18}OF_2^+$: 288.1326.

3.4 (1*S*,2*S*,3*R*,5*R*)-2-(But-3-enyl)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (1h)

3.4.1 (1*R*,5*R*)-2-Methylen-6,6-dimethylbicyclo[3.1.1]heptan-3-one (pinocarvone)

Pinocarvone was synthesized from (1*S*)-β-pinene, selenium dioxide, and TBHP according to Höld et al.[12] δ_H (400 MHz, $CDCl_3$) 0.81 (3 H, s), 1.20–1.26 (1 H, m), 1.30 (1 H, d, *J* 10.1), 1.36 (3 H, s), 2.20 (1 H, tt, *J* 6.2, 3.1), 2.53 (1 H, dd, *J* 19.5, 2.9), 2.63–2.73 (2 H, m), 2.77 (1 H, t, *J* 6.1), 5.02 (1 H, d, *J* 1.7), 5.97 (1 H, d, *J* 1.7). Analytical data agree with published values.[12]

3.4.2 (1*S*,2*S*,5*R*)-2-(But-3-enyl-6,6-dimethylbicyclo[3.1.1]heptan-3-one [2-(But-3-enyl)-isonopinone]

2-(But-3-enyl)-isonopinone was prepared from pinocarvone (1.72 g, 11.5 mmol) and allyltrimethylsilane in a Hosomi-Sakurai-reaction.[10] Yield: 1.06 g (5.53 mmol, 48 %, 95/5-mixture of 1,2-*cis*/*trans*-isomers), R_f 0.66 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)]. δ_H (400 MHz, $CDCl_3$) 0.85 (3 H, s), 1.16 (1 H, d, *J* 10.3), 1.31 (3 H, s), 2.05–2.21 (5 H, m), 2.25–2.31 (1 H, m), 2.47–2.54 (1 H, m), 2.58–2.67 (2 H, m), 4.94–5.06 (2 H, m), 5.78 (1 H, ddt, J_d 17.0, 10.5, J_t 6.4). δ_C (100 MHz, $CDCl_3$) 19.9 (*trans*), 22.0 (*cis*), 26.5

(*trans*), 27.0 (*cis*), 28.6 (*trans*), 29.1 (*trans*), 30.4 (*cis*), 31.3 (*trans*), 32.3 (*cis*), 34.0 (*cis*), 38.0 (*trans*), 38.7 (*cis*), 39.1 (*cis*), 39.2 (*trans*), 41.3 (*trans*), 42.0 (*cis*), 44.5 (*trans*), 44.8 (*cis*), 51.2 (*trans*), 56.0 (*cis*), 115.0 (*trans*), 115.1 (*cis*), 138.1 (*trans*), 138.2 (*cis*), 214.4 (*cis*), 214.9 (*trans*). HRMS (EI^+) *m/z* 192.1511 [M^+]; calculated mass for $C_{13}H_{20}O^+$: 192.1514.

3.4.3 (1*S*,2*S*,3*R*,5*R*)-2-(But-3-enyl)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (1h)

A solution of 2-(but-3-enyl)-isonopinone (1.00 g, 5.20 mmol) in dry diethyl ether (20 mL) was added in a dropwise manner to a suspension of $LiAlH_4$ (198 mg, 5.22 mmol) in dry diethyl ether (10 mL). The reaction mixture was refluxed for 3 hours and cooled to 0 °C. Water (5 mL) was carefully added (evolution of gas) to hydrolyze unspent $LiAlH_4$ at 0 °C providing a colorless precipitate, which was fitrated off. The organic phase was separated and concentrated under reduced pressure to leave an oil, which was purified by column chromatography [SiO_2, acetone/diethyl ether/pentane = 1/1/20, (*v*/*v*)]. Yield: 515 mg (2.65 mmol, 51 %), R_f 0.51 [SiO_2, acetone/pentane = 1:5 (*v*/*v*)], colorless oil. δ_H (400 MHz, $CDCl_3$) 1.02 (3 H, s), 1.04 (1 H, d, *J* 10.0), 1.17 (3 H, s), 1.40–1.50 (1 H, m), 1.78 (1 H, ddt, J_d 13.9, 5.5, J_t 2.0), 1.83–1.93 (2 H, m), 1.98–2.14 (3 H, m), 2.20 (1 H, dtd, J_d 10.0, J_t 6.1, J_d 2.0), 2.30 (1 H, dtd, J_d 10.0, J_t 7.1, J_d 3.2), 2.47 (1 H, ddd, *J* 13.9, 9.6, 4.3), 4.39–4.49 (1 H, m), 4.94 (1 H, ddt, J_d 10.1, 2.2, J_t 1.2), 5.02 (1 H, dq, J_d 17.1, J_q 1.8), 5.02 (1 H, ddt, J_d 17.1, 10.1, J_t 6.6). δ_C (100 MHz, $CDCl_3$) 22.2, 27.6, 28.5, 29.6, 33.8, 37.7, 38.7, 40.4, 45.4, 45.5, 63.9, 114.5, 139.3. MS (EI) *m/z* 194 (1) [M^+], 176 (3), 161 (8), 135 (37), 109 (25), 95 (32), 91 (63), 81 (82), 70 (100), 67 (62). HRMS (EI^+) *m/z* 194.1659 [M^+]; calculated mass for $C_{13}H_{22}O^+$: 194.1671.

A second fraction of a colorless crystalline solid obtained from column chromatragphy (199 mg, 1.02 mmol, 20 %), which consisted predominantly of (1*S*,2*S*,3*S*,5*R*)-2-but-3-enyl-6,6-dimethyl-bicyclo[3.1.1]heptan-3-ol, being contaminated with a minor fraction of (1*S*,2*R*,3*R*,5*R*)-2-but-3-enyl-6,6-dimethylbicyclo[3.1.1]heptan-3-ol.

4 Computational Chemistry – Conformers of 2-Phenyltetrahydropyran

All calculations were carried out with Gaussian03[13], using the density functional/Hartree-Fock hybrid model B3LYP and split valence tripple-ζ basis set 6-31+G(d,p). No symmetry or internal coordinate constraints were applied during energy function minimization. The ultrafine grid in combination with the tight option for energy function minimization was used. The absence of imaginary modes of vibration characterized computed structures as minima. Approximate Gibbs free energies ($G_{298.15}$) were obtained through thermochemical analysis for 298.15 K by unscaled frequency calculation from the thermal correction reported by Gaussian03. Likewise obtained Gibbs free energies took into account zero-point correction, thermal correction, and entropy.

4.1 Axial orientation of the phenyl group

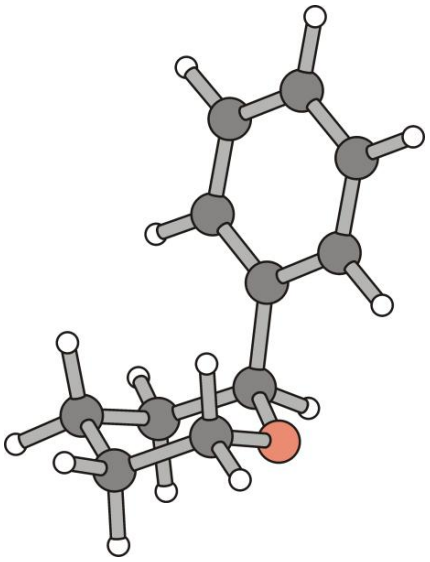

Figure S1. Equilibrium geometry of the conformer having the 2-phenyl group in 2-phenyltetrahydropyran oriented axially.

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.317032	1.232802	0.136261
2	6	0	-0.681049	0.029035	0.470306
3	6	0	-1.399519	-1.166845	0.306949
4	6	0	-2.706489	-1.160638	-0.182394
5	6	0	-3.328267	0.046773	-0.515557
6	6	0	-2.628148	1.242951	-0.352467
7	6	0	0.724864	-0.033138	1.082160
8	8	0	1.405679	-1.242960	0.707293
9	6	0	1.844406	-1.274105	-0.656169
10	6	0	2.806292	-0.128330	-0.970990
11	6	0	2.155069	1.217951	-0.619997
12	6	0	1.635752	1.180975	0.825668
13	1	0	2.325401	-2.248659	-0.779372
14	1	0	0.975269	-1.234913	-1.330903
15	1	0	3.085314	-0.166476	-2.031551
16	1	0	3.725748	-0.260694	-0.385698
17	1	0	1.326035	1.414632	-1.312391
18	1	0	2.871640	2.038669	-0.742098
19	1	0	1.123723	2.111768	1.091211
20	1	0	2.488406	1.090262	1.509875
21	1	0	0.598778	-0.142985	2.166496
22	1	0	-0.918052	-2.105086	0.564220
23	1	0	-3.240850	-2.099263	-0.301374
24	1	0	-4.345579	0.054074	-0.896217
25	1	0	-3.098145	2.189051	-0.606620
26	1	0	-0.798392	2.178699	0.253451

Zero-point correction=	0.227286 (Hartree/Particle)
Thermal correction to Energy=	0.237162
Thermal correction to Enthalpy=	0.238107
Thermal correction to Gibbs Free Energy=	0.191392
Sum of electronic and zero-point Energies=	-502.628659
Sum of electronic and thermal Energies=	-502.618783
Sum of electronic and thermal Enthalpies=	-502.617839
Sum of electronic and thermal Free Energies=	-502.664554

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4.2 Equatorial orientation of the phenyl group

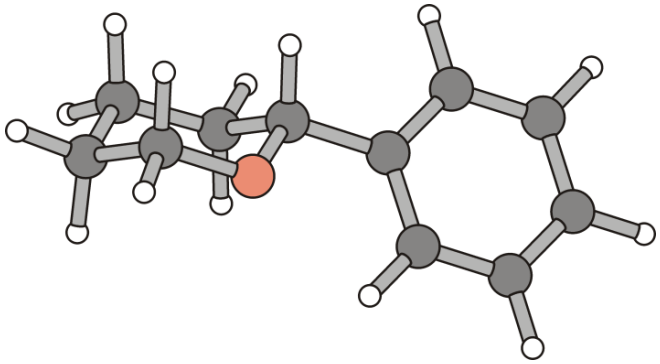

Figure S2. Equilibrium geometry of the conformer having the 2-phenyl group in 2-phenyltetrahydropyran oriented equatorially.

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.207075	-1.047987	-0.509224
2	6	0	2.607515	-0.992024	-0.779134
3	6	0	3.372653	-0.269597	0.330439
4	6	0	2.782965	1.130756	0.553467
5	6	0	1.260878	1.044270	0.745360
6	6	0	0.606745	0.245668	-0.400445
7	1	0	2.930157	-2.031966	-0.882260
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9	1	0	4.436024	-0.211601	0.065743
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Zero-point correction=                           0.226727 (Hartree/Particle)
Thermal correction to Energy=                    0.236776
Thermal correction to Enthalpy=                  0.237720
Thermal correction to Gibbs Free Energy=         0.190275
Sum of electronic and zero-point Energies=           -502.634395
Sum of electronic and thermal Energies=              -502.624346
Sum of electronic and thermal Enthalpies=            -502.623402
Sum of electronic and thermal Free Energies=         -502.670847

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5 Proton- and Carbon-13 NMR-Spectra of Selected Compounds

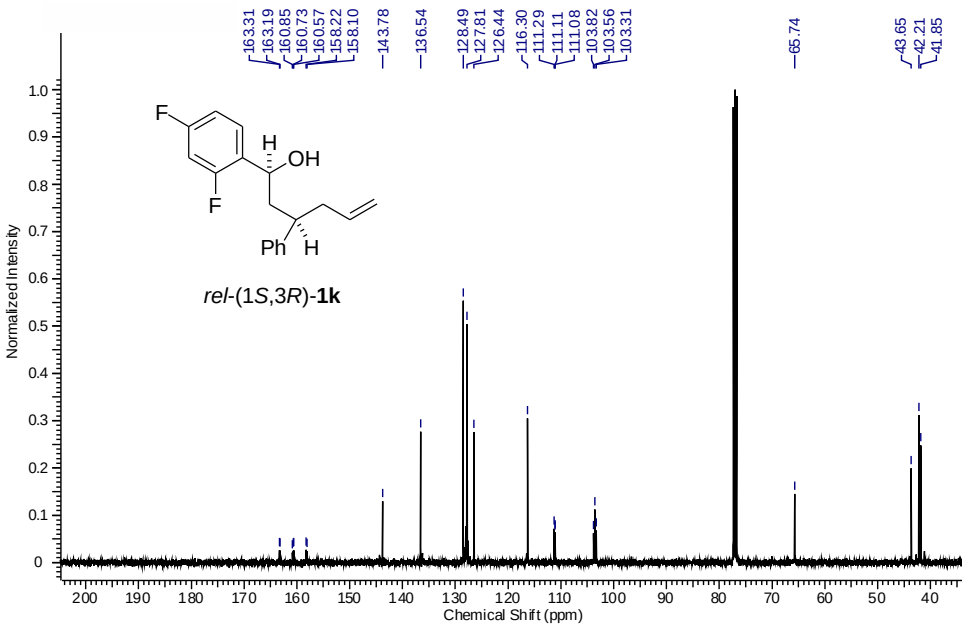

Figure S3. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of 1,3-*unlike*-1-(2,4-difluorophenyl)-3-phenylhex-5-en-1-ol *rel*-(1*S*,3*R*)-(**1k**).

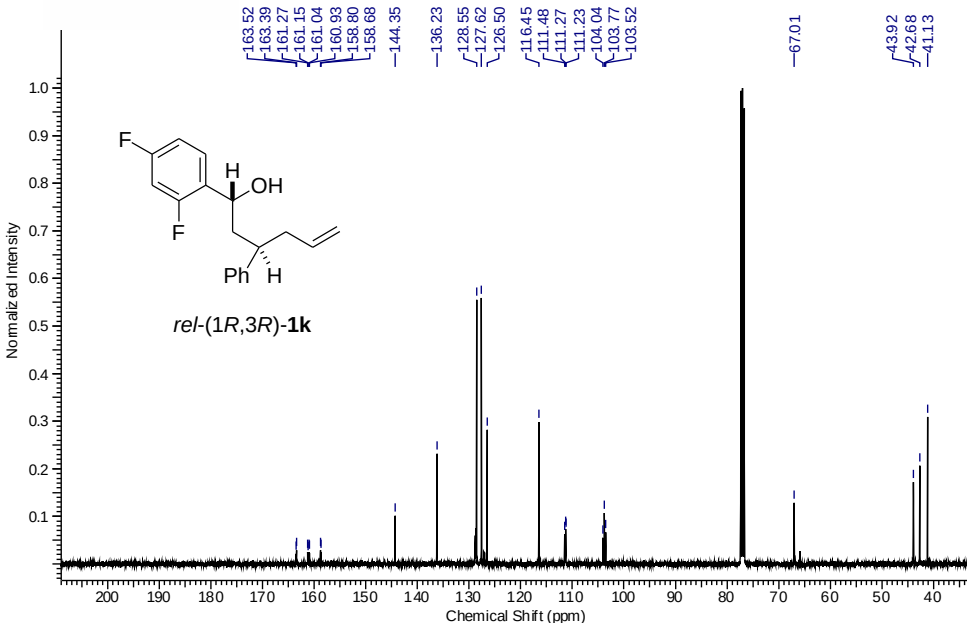

Figure S4. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of 1,3-*like*-1-(2,4-difluorophenyl)-3-phenylhex-5-en-1-ol *rel*-(1*R*,3*R*)-(**1k**).

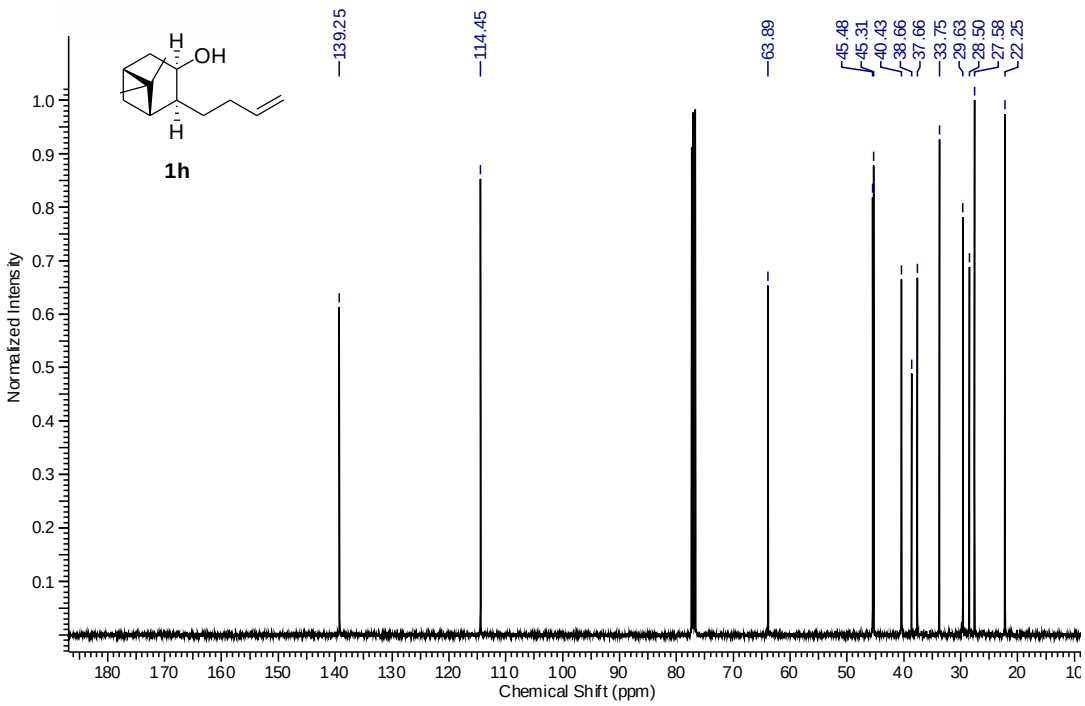

Figure S5. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of (1*S*,2*S*,3*R*,5*R*)-2-(but-3-enyl)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (**1h**).

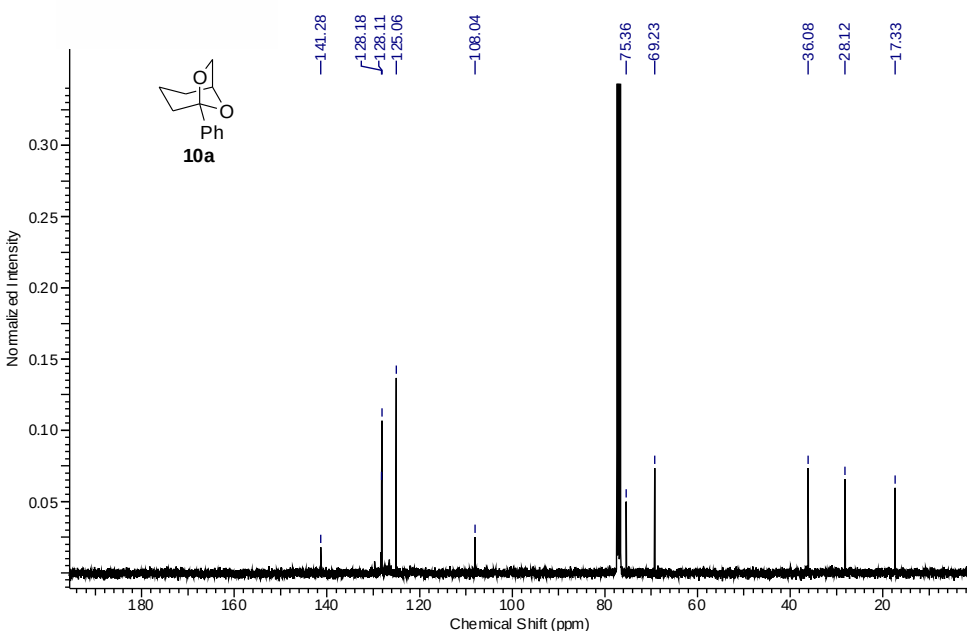

Figure S6: ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of 5-phenyl-6,8-dioxabicyclo-[3.2.1]octane (**10a**).

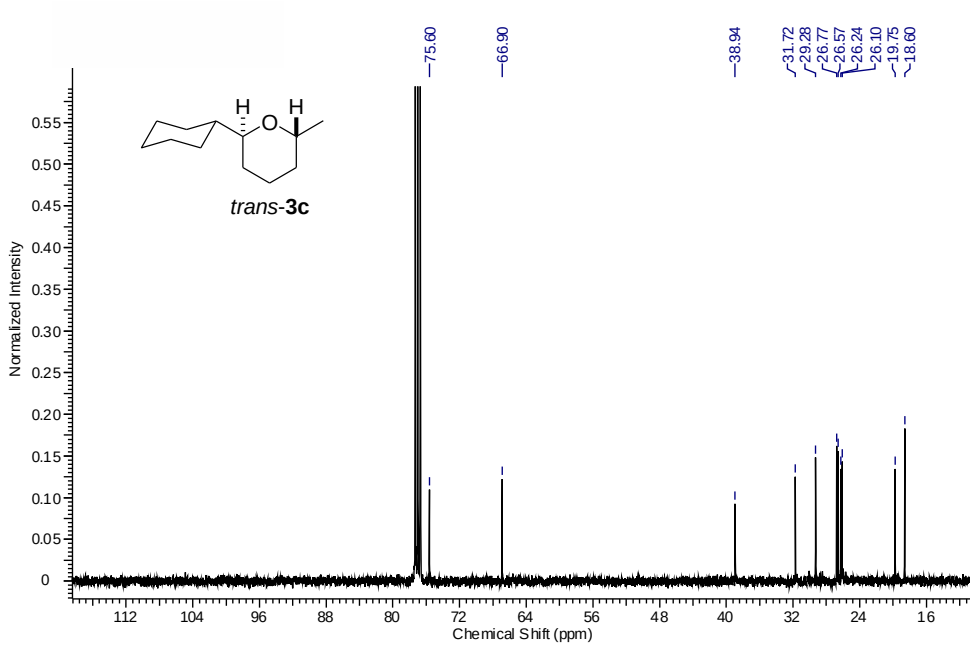

Figure S7. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *trans*-2-cyclohexyl-6-methyltetrahydropyran *trans*-(**3c**).

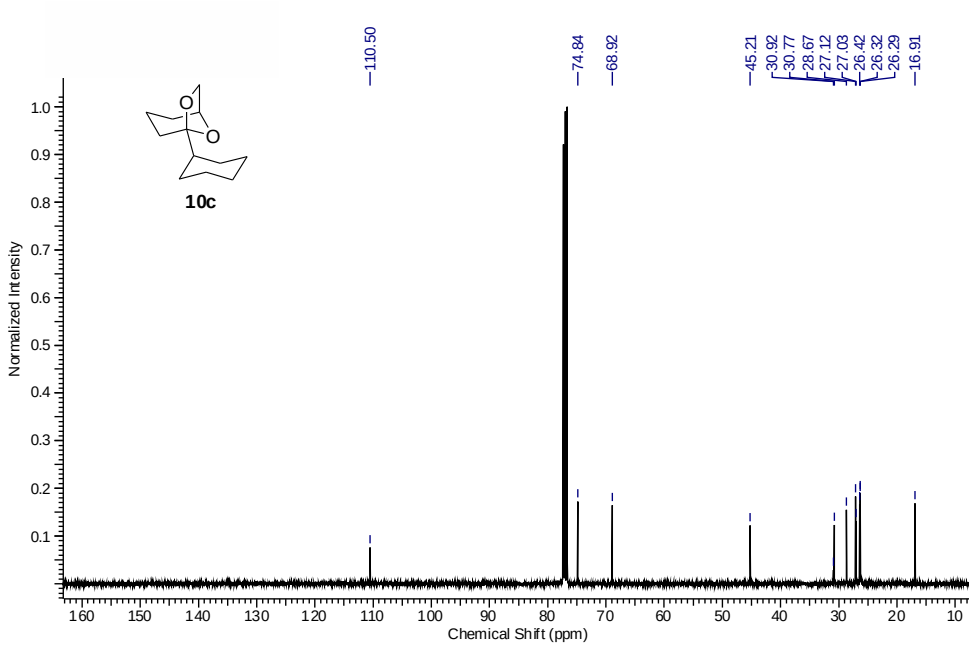

Figure S8. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of 5-cyclohexyl-6,8-dioxabicyclo[3.2.1]octane (**10c**).

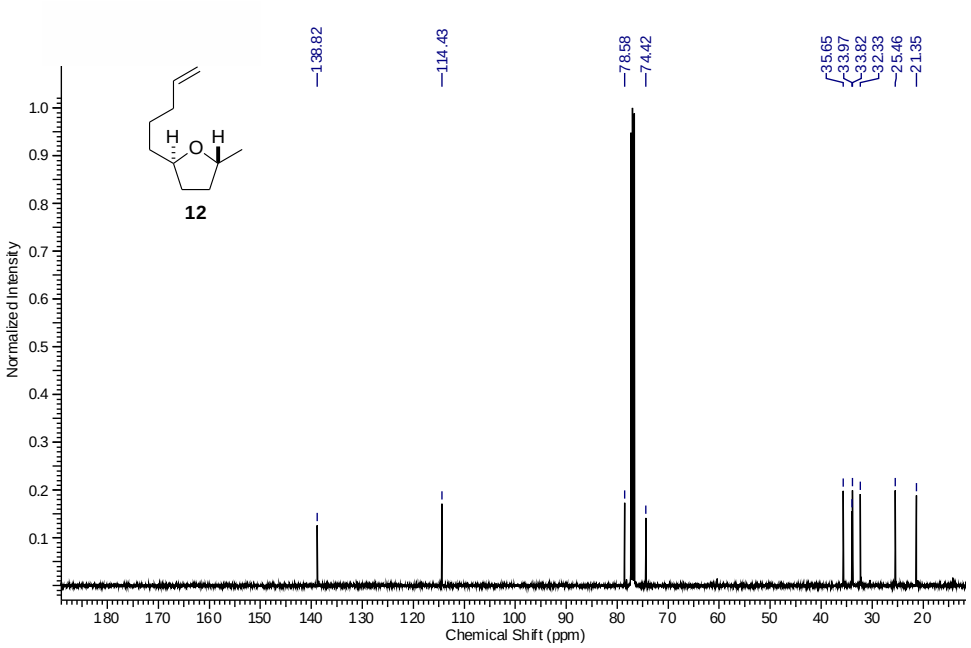

Figure S9. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *trans*-5-methyl-2-(pent-4-enyl)-tetrahydrofuran (**12**).

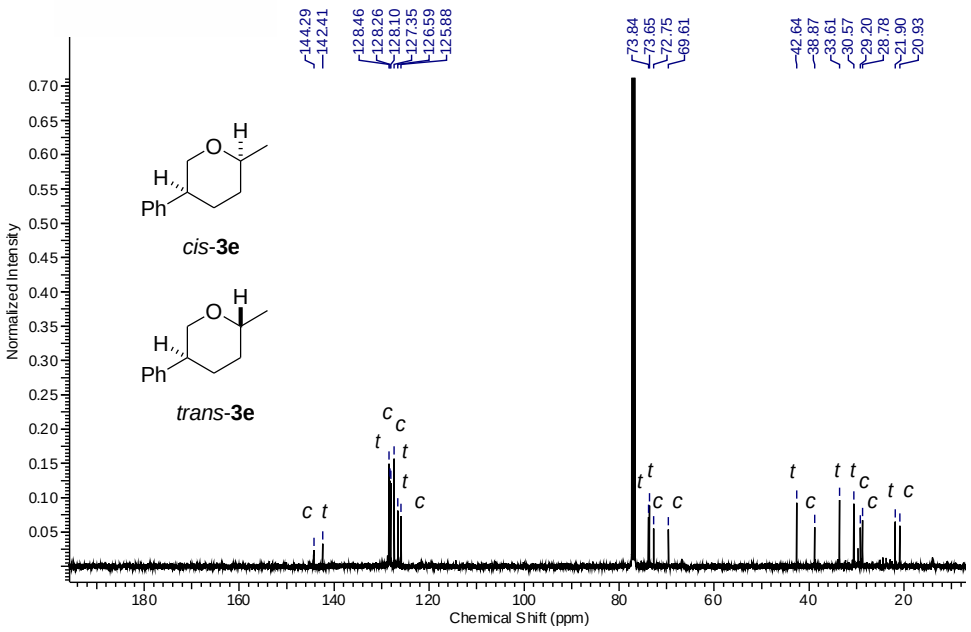

Figure S10. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *cis*- and *trans*-3-phenyl-6-methyltetrahydropyran *cis*- and *trans*-(**3e**).

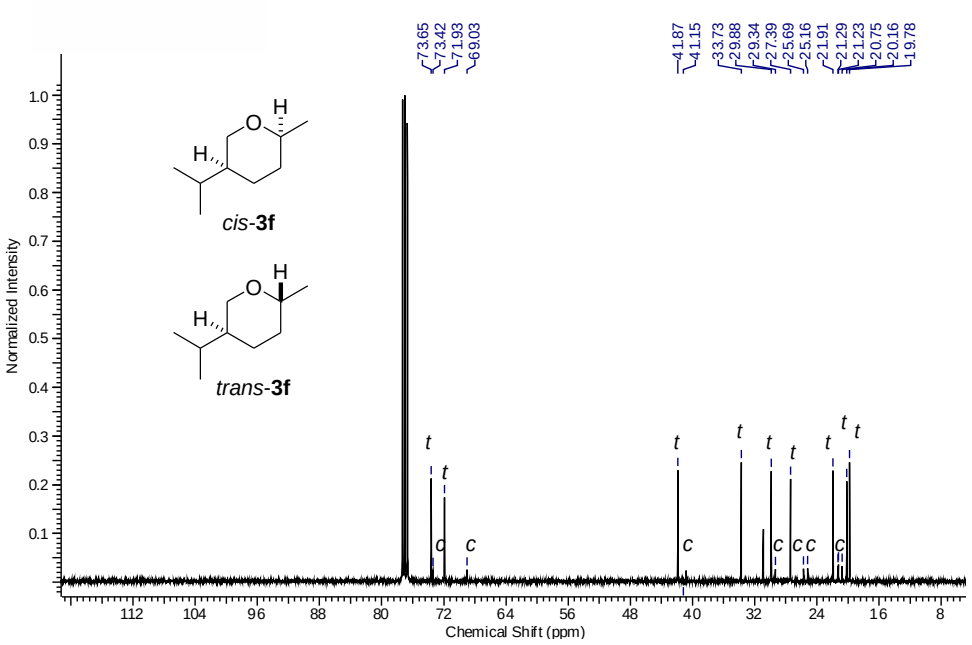

Figure S11. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *cis*- and *trans*-3-isopropyl-6-methyltetrahydropyran *cis*- and *trans*-(**3f**).

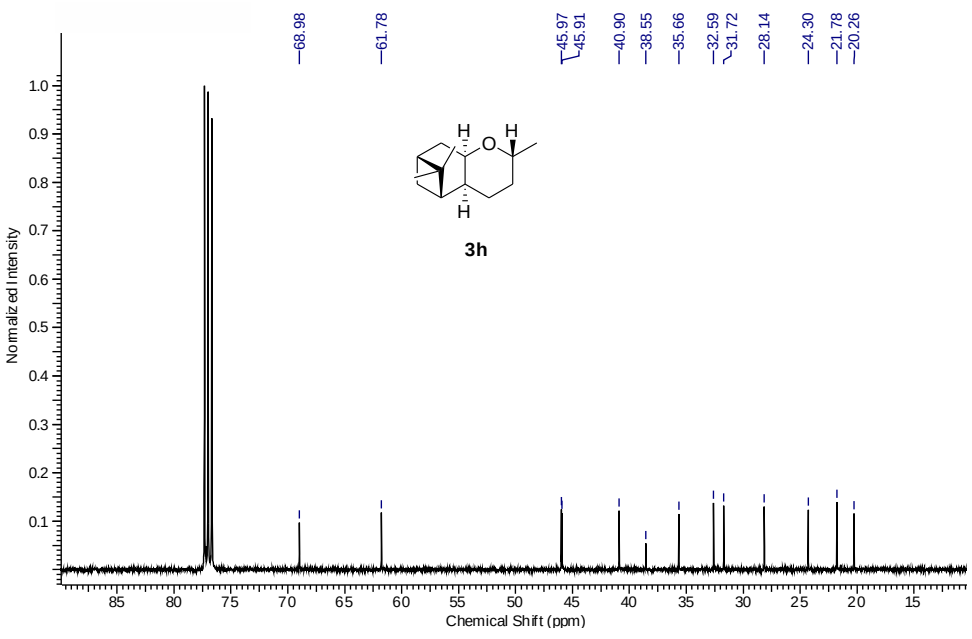

Figure S12. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of (1*S*,2*S*,4*R*,6*R*,8*R*)-3,3,8-trimethyl-7-oxatricyclo[4.4.0.1^{2,4}]undecane (**3h**).

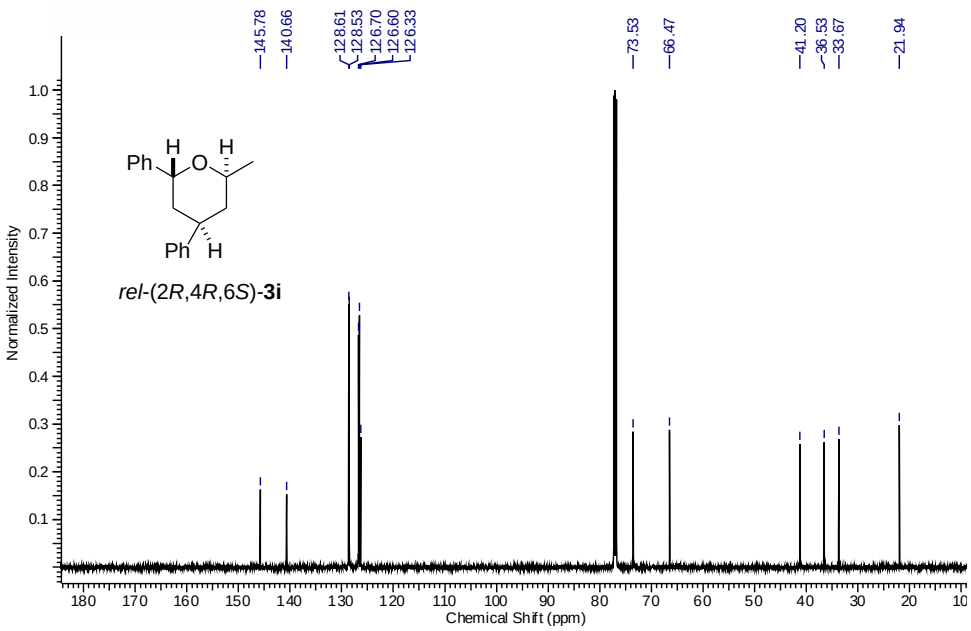

Figure S13. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$, room temperature) of *rel*-(2*R*,4*R*,6*S*)-6-methyl-2,4-diphenyltetrahydropyran *rel*-(2*R*,4*R*,6*S*)-(**3i**).

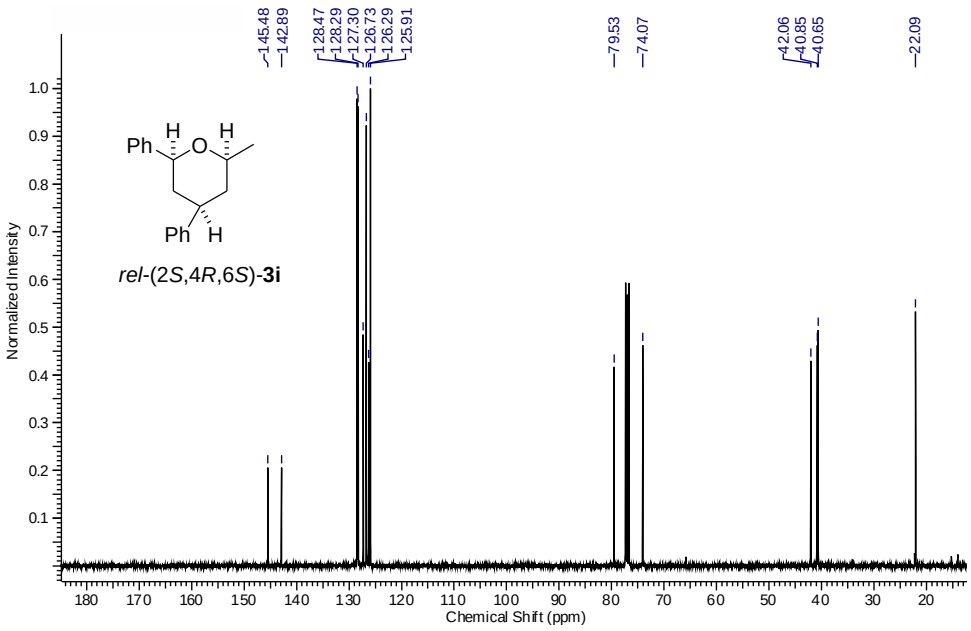

Figure S14. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *rel*-(2*S*,4*R*,6*S*)-6-methyl-2,4-diphenyltetrahydropyran *rel*-(2*S*,4*R*,6*S*)-(**3i**).

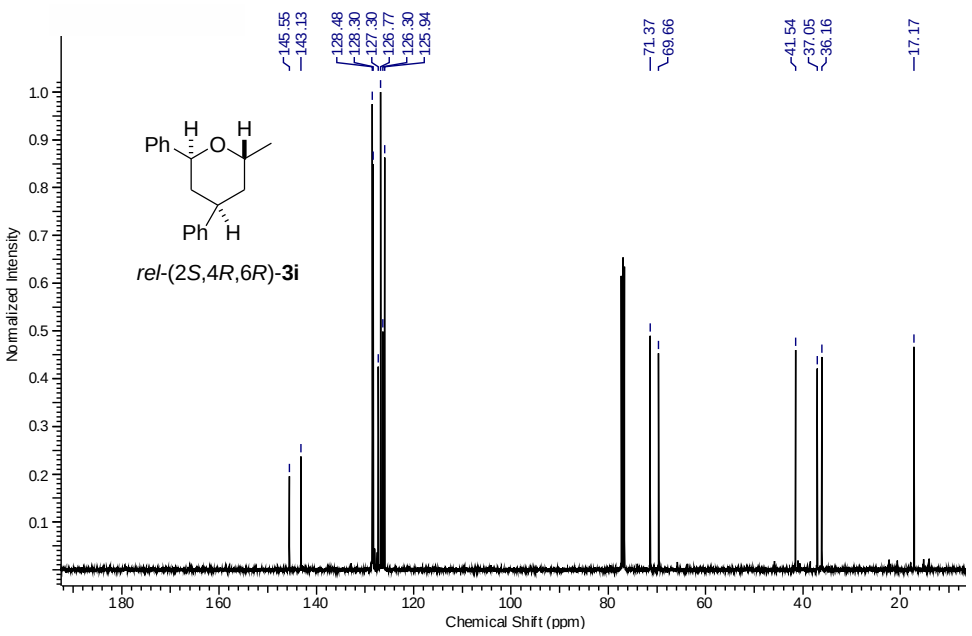

Figure S15. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *rel*-(2*S*,4*R*,6*R*)-6-methyl-2,4-diphenyltetrahydropyran *rel*-(2*S*,4*R*,6*R*)-(**3i**).

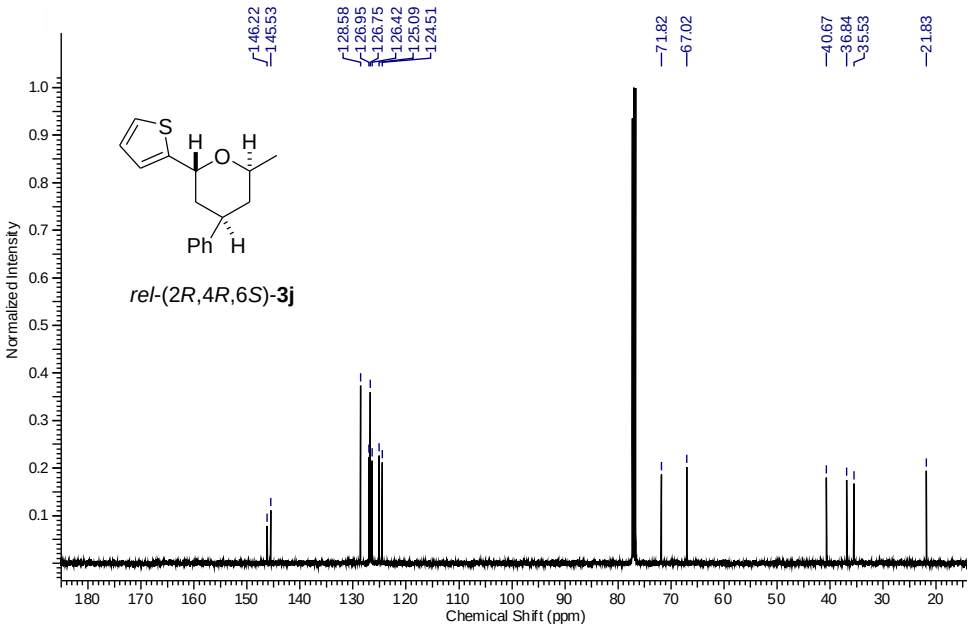

Figure S16. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *rel*-(2*R*,4*R*,6*S*)-6-methyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*R*,4*R*,6*S*)-(**3j**).

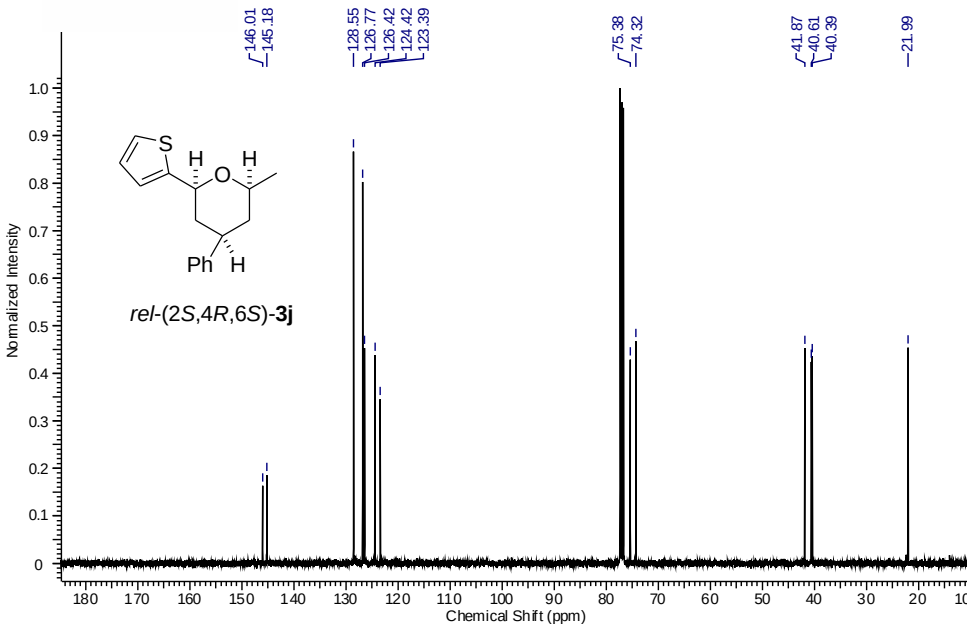

Figure S17. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *rel*-(2*S*,4*R*,6*S*)-6-methyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*S*,4*R*,6*S*)-(**3j**).

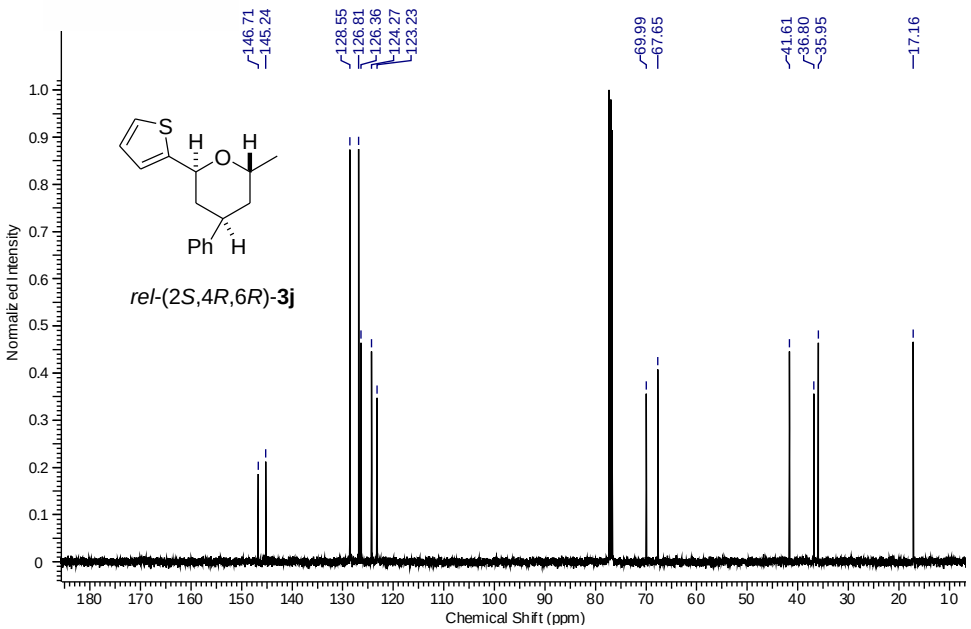

Figure S18. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *rel*-(2*S*,4*R*,6*R*)-6-methyl-4-phenyl-2-(thien-2-yl)tetrahydropyran *rel*-(2*S*,4*R*,6*R*)-(**3j**).

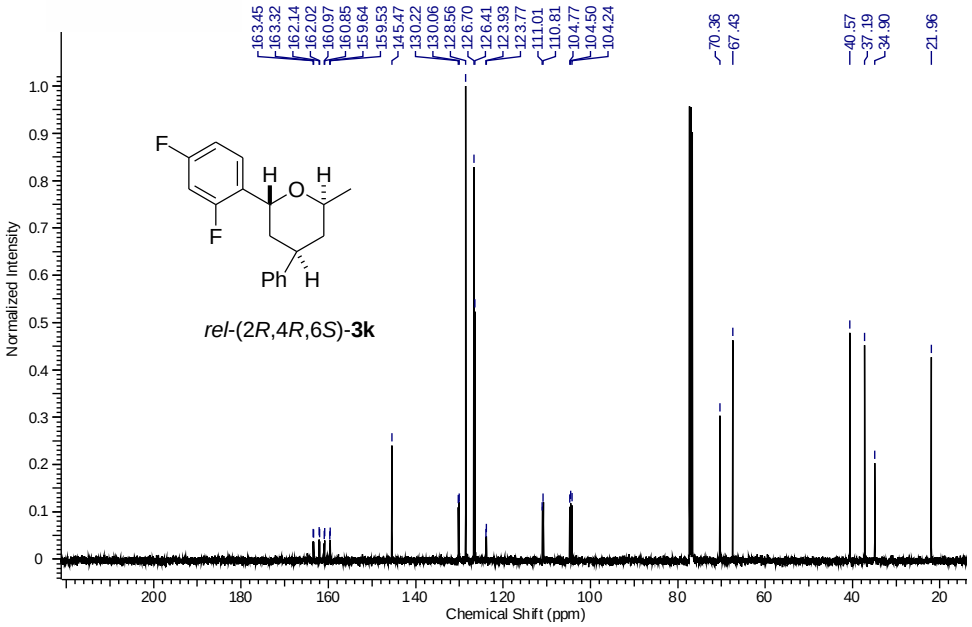

Figure S19. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *rel*-(2*R*,4*R*,6*S*)-6-methyl-4-phenyl-2-(2,4-difluorophenyl)-tetrahydropyran *rel*-(2*R*,4*R*,6*S*)-(**3k**).

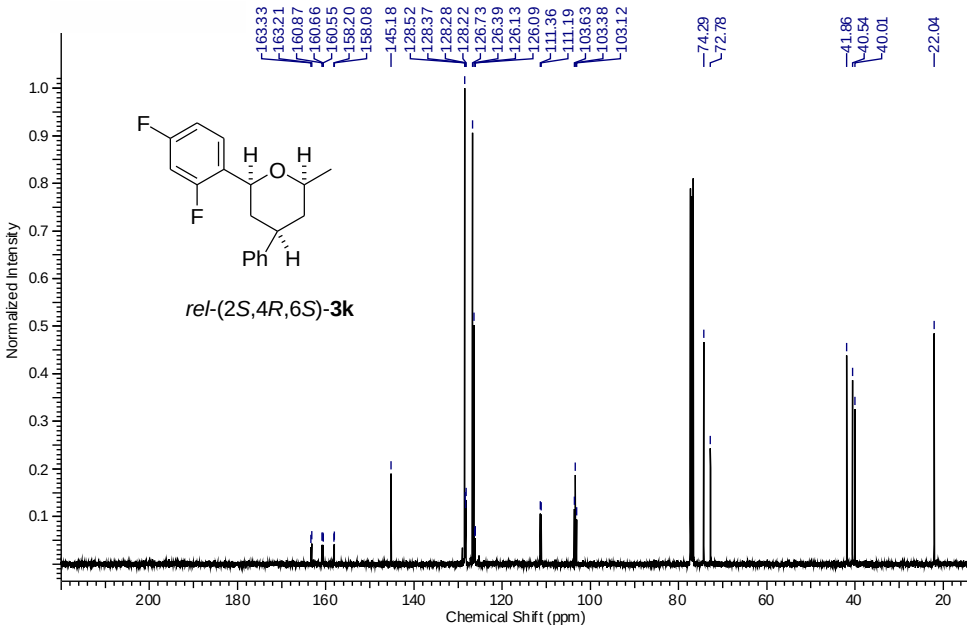

Figure S20. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *rel*-(2*S*,4*R*,6*S*)-methyl-4-phenyl-2-(2,4-difluorophenyl)-tetrahydropyran *rel*-(2*S*,4*R*,6*S*)-(**3k**).

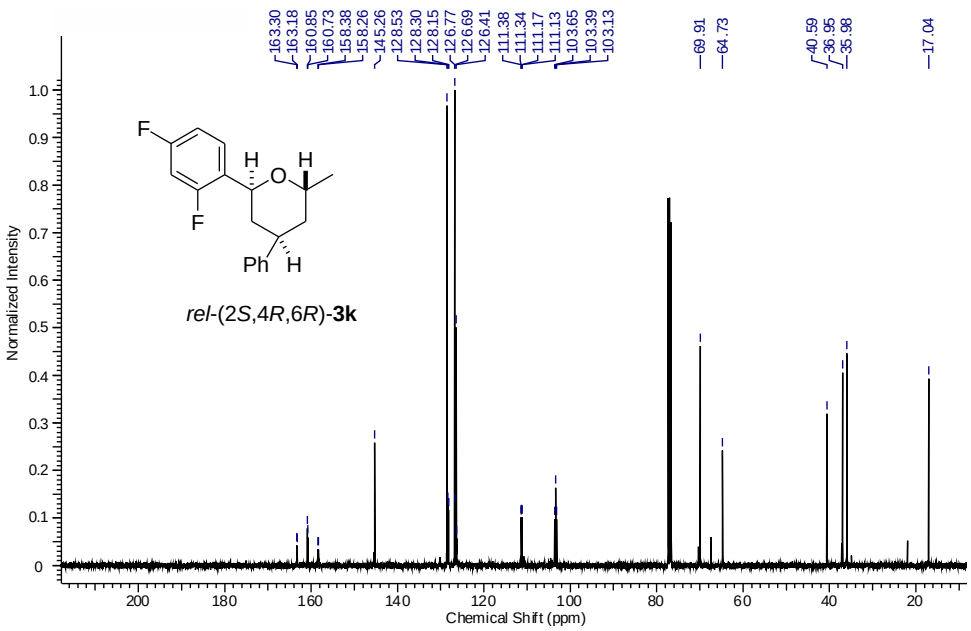

Figure S21. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *rel*-(2*S*,4*R*,6*R*)-methyl-4-phenyl-2-(2,4-difluorophenyl)-tetrahydropyran *rel*-(2*S*,4*R*,6*R*)-(**3k**).

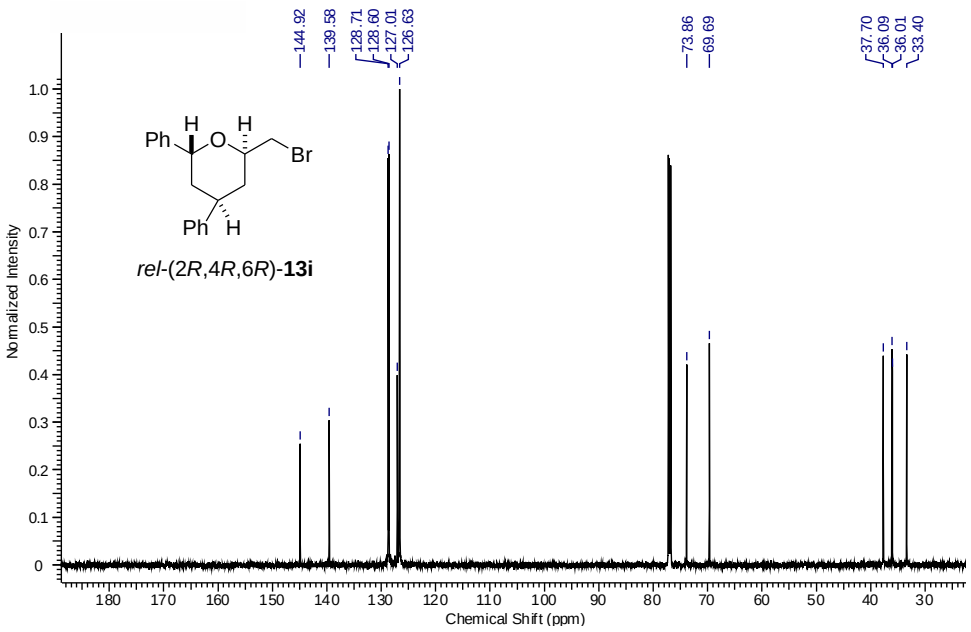

Figure S22. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$, room temperature) of *rel*-(2*R*,4*R*,6*R*)-6-bromomethyl-2,4-diphenyltetrahydropyran *rel*-(2*R*,4*R*,6*R*)-(**13i**).

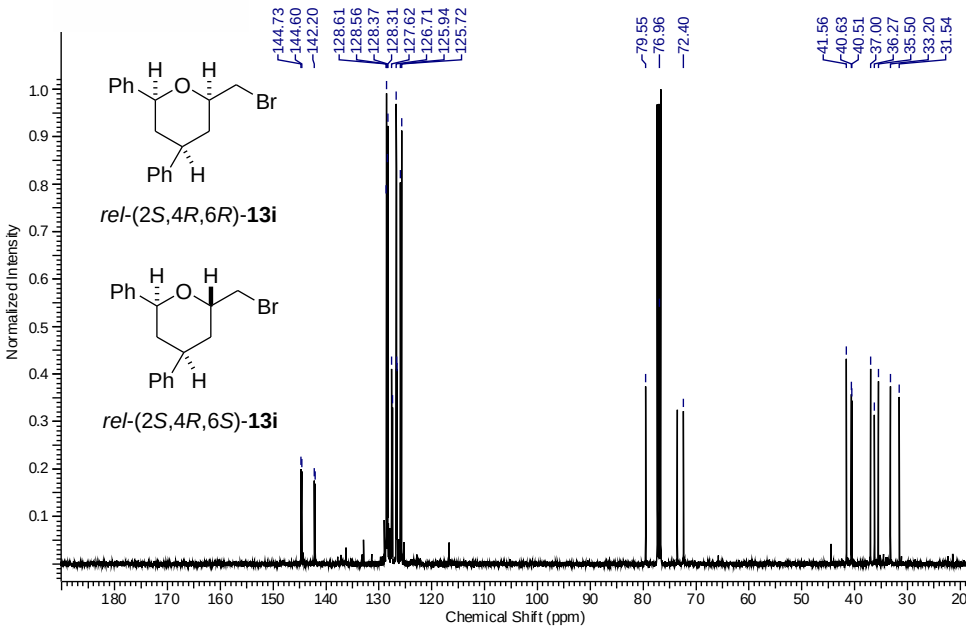

Figure S23. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of *rel*-(2*S*,4*R*,6*R*)-6-bromomethyl-2,4-diphenyltetrahydropyran *rel*-(2*S*,4*R*,6*R*)-(**13i**) and *rel*-(2*S*,4*R*,6*S*)-6-bromomethyl-2,4-diphenyltetrahydropyran *rel*-(2*S*,4*R*,6*S*)-(**13i**).

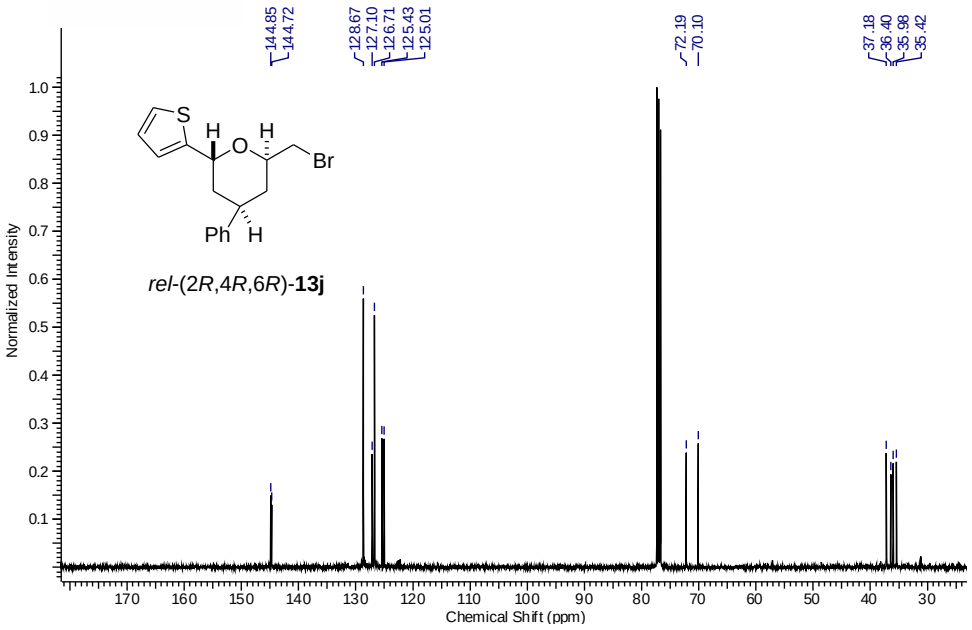

Figure S24. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temp.) of *rel*-(2*R*,4*R*,6*R*)-6-bromomethyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*R*,4*R*,6*R*)-(**13j**).

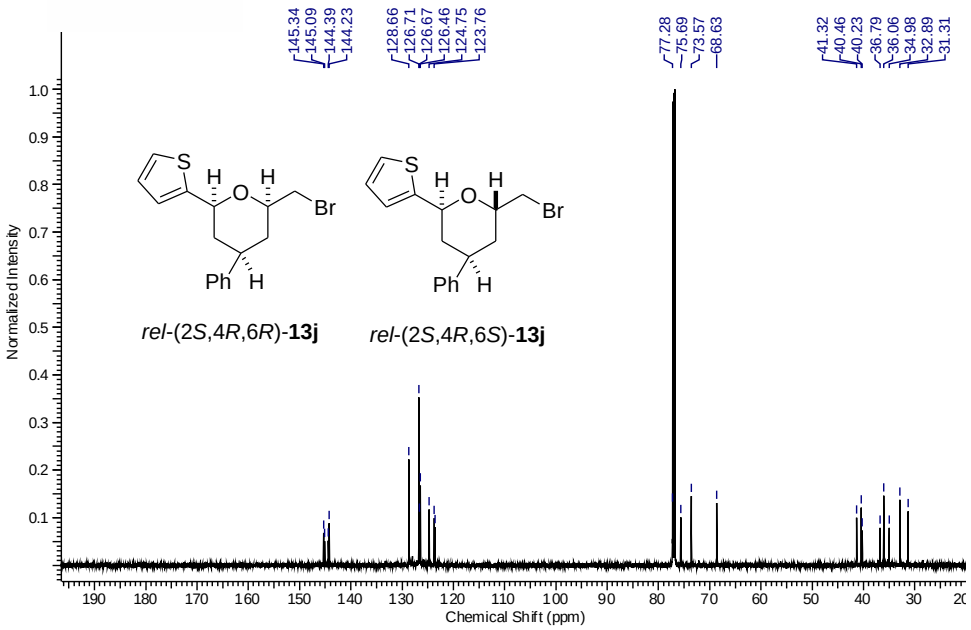

Figure S25. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$, room temperature) of *rel*-(2*S*,4*R*,6*R*)-6-bromomethyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*S*,4*R*,6*R*)-(**13j**) and *rel*-(2*S*,4*R*,6*S*)-6-bromomethyl-4-phenyl-2-(thien-2-yl)-tetrahydropyran *rel*-(2*S*,4*R*,6*S*)-(**13j**).

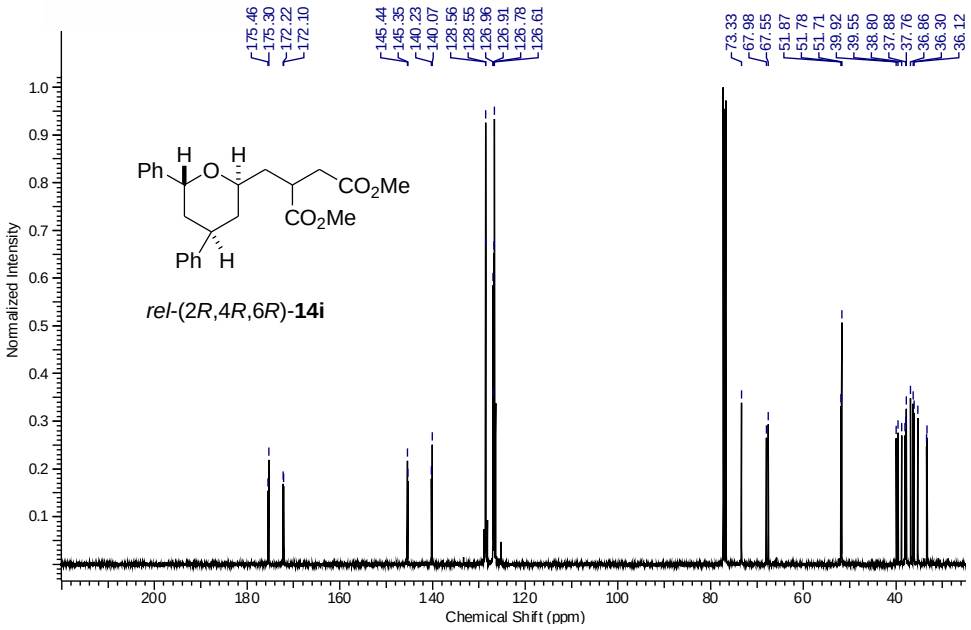

Figure S26. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of dimethyl 2-[(2*R*,4*R*,6*R*)-2,4-diphenyltetrahydropyran-6-yl]-methyl succinate *rel*-(2*R*,4*R*,6*R*)-(**14i**).

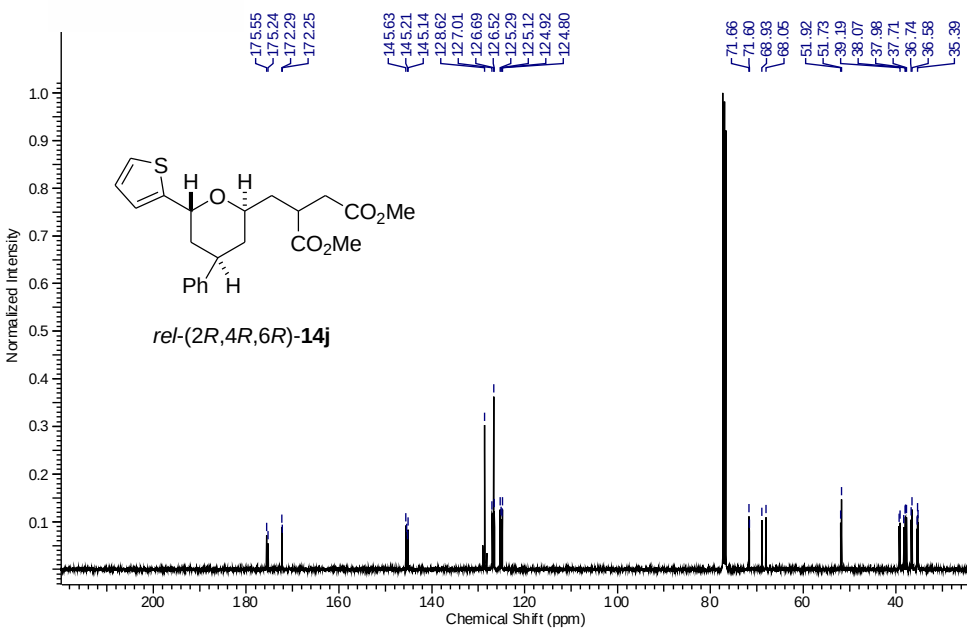

Figure S27. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of dimethyl 2-[*rel*-(2*R*,4*R*,6*R*)-4-phenyl-2-(thien-2-yl)-tetrahydropyran-6-yl]-methyl succinate *rel*-(2*R*,4*R*,6*R*)-(**14j**).

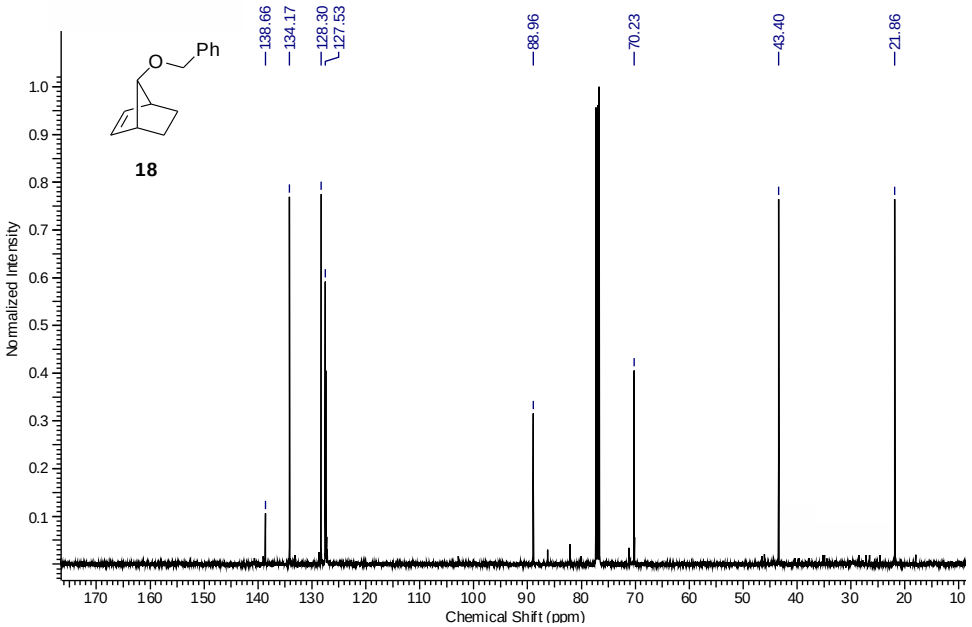

Figure S28. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$, room temperature) of 7-*anti*-benzyloxybicylo[2.2.1]hept-2-ene (**18**).

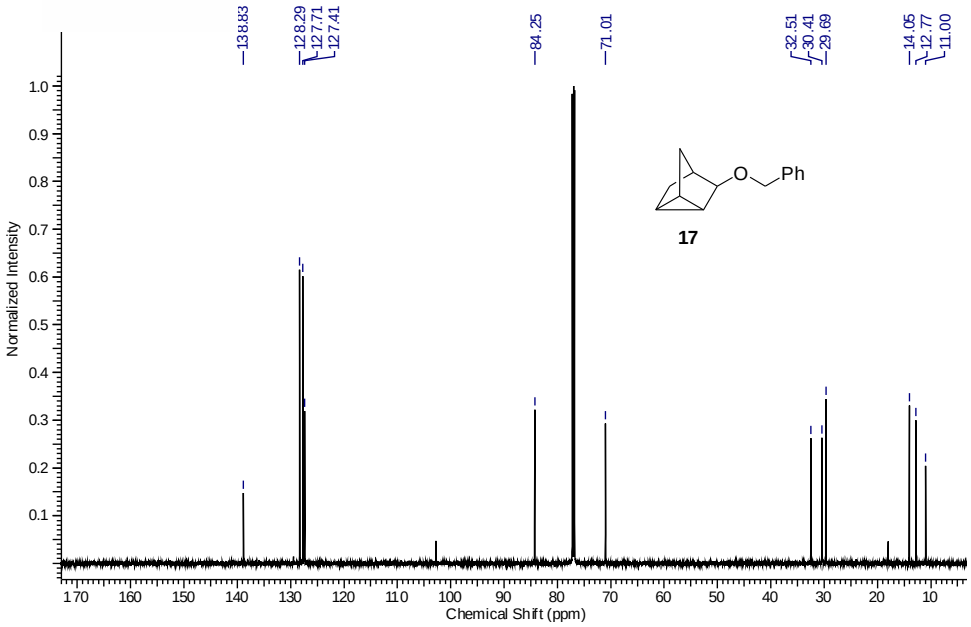

Figure S29. ^{13}C-NMR spectrum (150 MHz, $CDCl_3$, room temperature) of 3-*exo*-benzyloxynortricyclene (**17**).

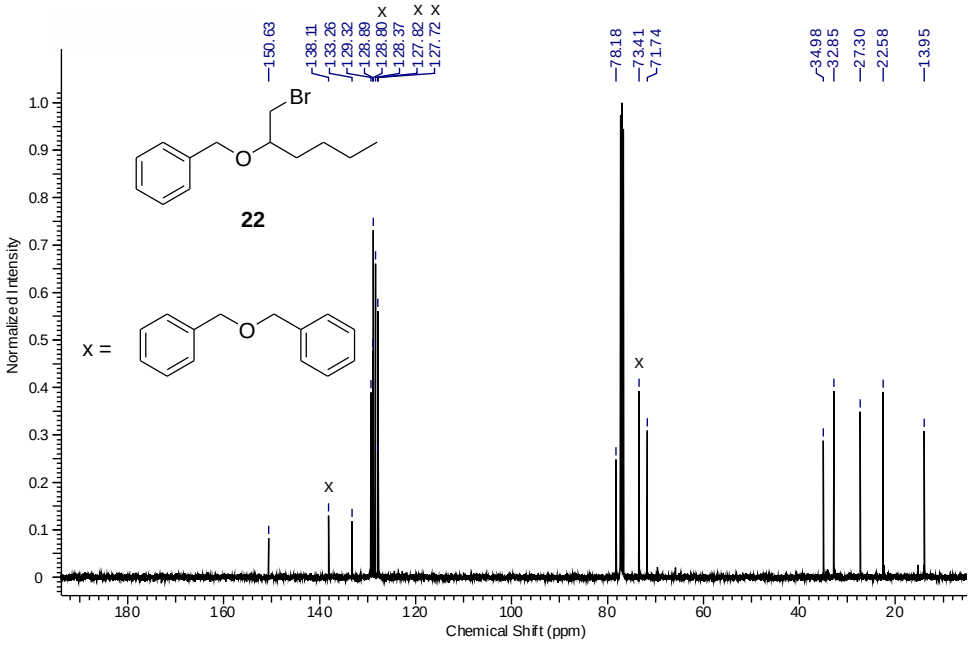

Figure S30. ^{13}C-NMR spectrum (100 MHz, $CDCl_3$, room temperature) of 2-benzyloxy-1-bromohexane (**22**)

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6.5 Kurzmitteilung

Reductive and Brominative Termination of Alkenol Cyclization in Aerobic Cobalt-Catalyzed Reactions

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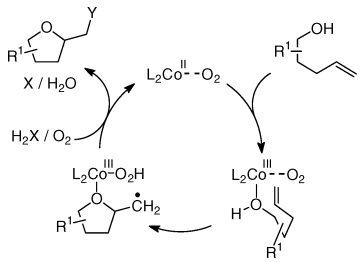
Aerobic oxidations of substituted pent-4-en-1-ols (bishomoallylic alcohols) occur with notable rates and diastereoselectivity, if catalyzed with appropriate cobalt(II) chelates.[1,2] The ring closure furnishes substituted tetrahydrofuryl-2-methanols (Scheme 1, Y = OH), which constitute valuable building blocks for natural product synthesis.[3,4] In an attempt to oxidize (*E*)- and (*Z*)-configured substrates under such conditions, however, a loss of stereochemical information associated with the olefinic π-bond was observed. This finding was explained with the appearance of configurationaly labile reactive intermediates.[5] In the present report we provide evidence that these intermediates are free carbon radicals that can be converted with a variety of reagents into synthetically useful functional groups. Since oxidative catalytic methods in carbon radical chemistry so far were restricted to hydrocarbon oxyfunctionalization,[6] it was our aim in the present study to develop methods for reductive, brominative, and alkylative termination of aerobic cobalt catalyzed alkenol cyclizations.[7]

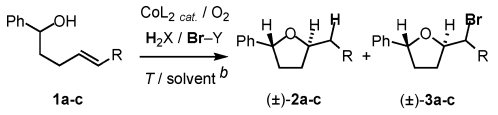
Scheme 1. Proposed Catalytic Cycle for Aerobic Alkenol Oxidation[a]



[a] (H_2X = coreductant, R^1 = e.g. alkyl or aryl; Y = OH, H; for Y = Br, and alkyl and for CoL_2, see text).

Reductive ring closures of chosen reporter substrates, i.e. 1-phenylpent-4-en-1-ols **1a**−**c**, required heating (60−75 °C) in solutions of cyclohexa-1,4-diene (CHD, 20 equiv) containing 1−4 mol % of {4-[3,5-bis(trifluoromethyl)-phenyl]-4-oxybut-3-en-2-one}-cobalt(II) (CoL_2). The reactions were run in an open flask that was connected to a reflux condenser, to allow extensive contact with air. This setup gave 2,5-*trans*-substituted tetrahydrofurans **2a**−**c** (94 ≤ de <99%) in 80−88% yields (Table 1, entries 1, 5, and 8). No substrate turnover occurred in the absence of O_2, CHD, and CoL_2 or by substituting cobalt(II) acetate or donor-substituted cobalt(II)-diketonate complexes for CoL_2. Tetrahydrofuryl-2-methanols (Scheme 1, Y = OH) were not formed in these runs as evident from GC analysis in combination with a highly sensitive color test, i.e. the absence of bluish staining with Ekkert's reagent of developed SiO_2-coated tlc sheets at R_f = 0.13 [petroleum ether/acetone, 5:1 (v/v)]. Formation of suspected alcohols became evident as CHD concentrations fell below ∼3 M. Replacement of CHD with its naturally occurring derivative γ-terpinene (isopropyl-4-methylcyclohexa-1,4-diene) was effective without a change in selectivity (Table 1, entries 2, 6, and 9). Such reactions provided isopropyl-4-methylbenzene and H_2O as secondary products. This finding pointed to an active role of applied dihydroarenes in H-atom transfer reactions, for instance, Co(III)/Co(II) reduction for maintaining the catalytic cycle, or completion of O_2 conversion into H_2O. The stoichiometry of this redox chemistry is under current investigation.

Table 1. Reagent Guided Selectivity in Cobalt-Catalyzed Alkenol Cyclizations[a]



1a-c (±)-**2a-c** (±)-**3a-c**

a: R = H; **b**: R = Me; **c**: R = CO_2Me

entry	1−3	CoL_2[c]/ mol %	H_2X[d]/ equiv	Br−Y/ equiv	T/ °C	(±)-2[e]/ %	(±)-3[e]/ %
1	**a**	1	CHD/20	−	60	85	−
2	**a**	1.5	γ-Ter/12	−	80	82	−
3	**a**	4 × 5	CHD/30	$BrCCl_3$/10	60	−[g]	85
4	**a**	2 × 5	CHD/30	DBM[f]/6	60	4	82
5	**b**	2 × 2	CHD/20	−	75	80	−
6	**b**	2 × 2	γ-Ter/12	−	80	70	−
7	**b**	4 × 10	CHD/30	$BrCCl_3$/10	75	−[g]	87[h]
8	**c**	2 + 1	CHD/20	−	75	88	−
9	**c**	3 + 2	γ-Ter/12	−	80	81	−
10	**c**	3 × 10	CHD/30	$BrCCl_3$/10	75	76	13[h]

[a] Quantitative conversion of **1a**−**c** (tlc). [b] Toluene for brominations; no additional solvent for reductions. [c] Portions of CoL_2 were added in 3 h intervals. [d] CHD = cyclohexa-1,4-diene, γ-Ter = γ-terpinene (isopropyl-4-methylcyclohexa-1,4-diene). [e] *cis*/*trans* < 1/99 for **2a**−**b**, **3a**−**c**, *cis*/*trans* = 3/97 for **2c** (GC). [f] DBM = diethyl dibromomalonate. [g] Not detected (GC−MS and ^{1}H NMR). [h] Two isomers isolated (additional stereogenic center in side chain); dr = 65:35 for **3b** and 54:46 for **3c** (determined by GC).

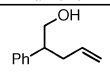
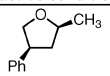
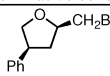
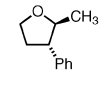
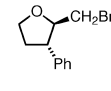
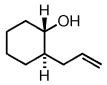
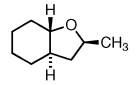
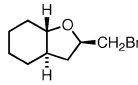
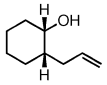
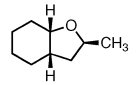
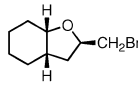
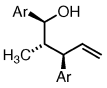
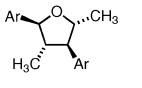
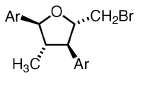
A change in selectivity from reductive termination to bromocyclization was attainable upon addition of $BrCCl_3$ or diethyl dibromomalonate (DBM) to standard reaction mixtures (Table 1, entries 3, 4, 7).[8,9] Toluene was added as cosolvent for improving selectivity of the system. Diastereoselectivities of brominated heterocycles **3a**−**b** corresponded to values reported for tetrahydrofurans **2a**−**b** in the absence of $BrCCl_3$. Acceptor-substituted alkenol **1c** was the only substrate that resisted effective bromocyclization under such conditions (Table 1, entry 10), possibly for reasons suggested in the mechanistic discussion below. The rates of bromocyclizations were smaller than those of the reductions (i.e., formation of **2**) and required larger amounts of CoL_2.

To further explore the scope of the cobalt-method, additional mono-, di-, and trisubstituted alkenols **1d**−**h** were transformed with O_2/CoL_2 in CHD into products of reductive ring closure (formation

10.1021/ja904577c CCC: $40.75

of **2d**−**h**). Conversion of the given substrates using O_2/CoL_2 as oxidant in solutions of CHD, toluene, *and* $BrCCl_3$ consistently provided bromocyclized compounds **3d**−**h**. Derived tetrahydrofur-2-ylmethanols were not detected in any of these runs. Observed *cis*/*trans* ratios of products **2d**−**h**/**3d**−**h** (Table 2) agreed with stereoselectivity reported for oxidative cyclizations of the reactants in *i*PrOH in the same temperature range. The latter solvent is particularly useful for tetrahydrofurylmethanol synthesis from pent-4-en-1-ols in aerobic cobalt-catalyzed oxidations.[2]

Table 2. Products of Reductive and Brominative Alkenol Cyclization in Aerobic Cobalt-Catalyzed Reactions (See the Supporting Information)

alkenol	reductive conditions[a]	brominative conditions[b]
 (±)-**1d**	 (±)-**2d** (79 % / 75:25)	 (±)-**3d**(89 % / 73:27)
 (±)-**1e**	 (±)-**2e** (84 % / 2:98)	 (±)-**3e** (84 % / <1:99)
 (±)-**1f**	 (±)-**2f** (78 % / 12:88)	 (±)-**3f** (85 % / 9:91)
 (±)-**1g**	 (±)-**2g** (83 % / <1:99)	 (±)-**3g** (96 % / <1:99)
 (±)-**1h**	 (±)-**2h** (84 % / <1:99)	 (±)-**3h** (22 % / <1:99) [c]

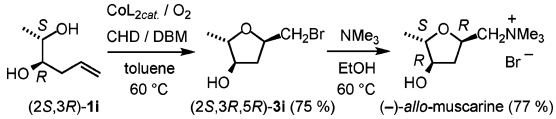
[a] 1−5 mol % CoL_2, 60−75 °C, 7−24 h, 20 equiv of CHD. [b] 15−40 mol % CoL_2, 60−75 °C, 8−22 h, 30 equiv of CHD, 10 equiv of $BrCCl_3$. [c] Additional product: ∼36% of (2,4,5-trimethoxyphenyl)prop-1-ene. Numbers in parentheses refer to yields and *cis*/*trans* ratios.

Reductive cyclization of diastereomerically pure (1*S**,2*S**,3*R**)-1,3-bis[2,4,5-(trimethoxy)phenyl]-2-methylpent-4-en-1-ol (±)-**1h**[10] provided target compound (±)-**2h**, i.e. the 5-epimer of naturally occurring antiallergic lignane magnosalicine, in 84% yield.[11] The origin of a surprisingly low yield of 22% of bromocyclization product (±)-**3h**, in combination with an unsatisfactory mass balance, even by taking formation of 36% of (2,4,5-trimethoxy)-phenylprop-1-ene into account, certainly requires future attention.

The outstanding 2,5-*trans* diastereoselectivity of cobalt-catalyzed bromocyclizations was applied in a concise synthesis of enantiomerically pure (−)-*allo*-muscarine,[12,13] one of the physiologically active constituents of the fly agaric *Amanita muscaria*[14] (Scheme 2). For practical reasons, bromocyclization of (2*S*,3*R*)-hex-5-en-2,3-diol, (2*S*,3*R*)-(**1i**), was conducted in the presence of DBM as a trapping reagent. This variation improved the yield from 65% ($BrCCl_3$) to 75%. It furthermore prevented consumption of substrate (2*S*,3*R*)-**1i** by side reactions, such as $BrCCl_3$ addition across the olefinic double bond, and thus allowed more convenient purification of product (2*S*,3*R*,5*R*)-**3i** from the reaction mixture.

If compared to other electrophile-induced ring closures, it is worth noting that polar bromocyclizations of substrate (2*S*,3*R*)-**1i** (nucleophilic oxygen), e.g., with Br_2, affords a 40/60 mixture (20 °C) of (2*S*,3*R*,5*R*)-**3i** versus the undesired (2*S*,3*R*,5*S*)-isomer.[15] The (2*R*,3*S*)-3-hydroxy-hex-5-en-2-oxyl radical in turn (electrophilic

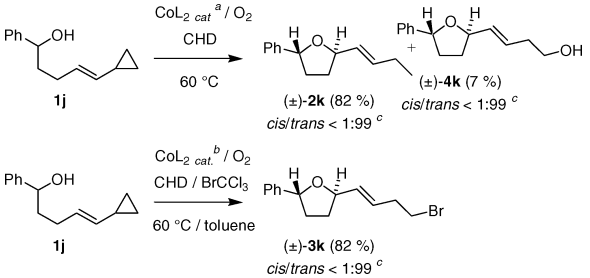
Scheme 2. Synthesis of (−)-*allo*-Muscarine



oxygen, not shown) requires an adequate hydroxyl protecting group[13] to undergo 5-*exo*-trig cyclization and not a very effective β-fragmentation. No 3-hydroxyl-protecting group was necessary in the case of the cobalt-catalyzed bromocyclization.

The chemical nature of the reactive intermediate relevant for explaining selectivity in the terminating step was scrutinized in aerobic cobalt-catalyzed oxidations of cyclopropyl-substituted phenylpentenol **1j**. If conducted in CHD, the reaction furnished exclusively butenyl-substituted, diastereomerically pure tetrahydrofurans **2k** and **4k** but no cyclopropyl-substituted derivatives (^{1}H NMR and GC-MS; Scheme 3). Formation of alcohol (±)-**4k** under such conditions was unexpected in view of the observations summarized above (Tables 1−2). This product was not found in reaction mixtures obtained from aerobic oxidations of **1j** in the presence of $BrCCl_3$ (Scheme 3).

Scheme 3. Formation of Butenyl-Substituted Tetrahydrofurans



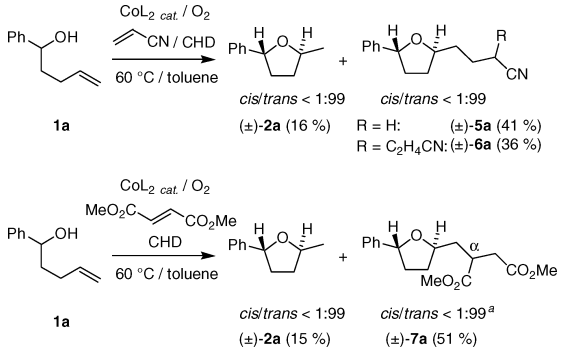
[a] 10 mol % of CoL_2 [b] 4 × 5 mol % of CoL_2. [c] GC and ^{1}H NMR.

The third objective, i.e., alkylative trapping of cyclized alkenols, was feasible starting from substrate **1a** in solutions of toluene (60 °C) that contained a 3−5 M concentration of CHD and 2−4 M levels of preferentially an electron-deficient alkene. The use of acrylonitrile provided 41% of 1,1-adduct (±)-**5a**, 36% of 1,2-addition product (±)-**6a**, and 16% of reduction product **2a** (Scheme 4 and Supporting Information). Equimolar $BrCCl_3$/acrylonitrile mixtures afforded under otherwise identical conditions exclusively bromocyclization product **3a** (GC−MS; not shown). The use of dimethyl fumarate and CHD gave 51% of 1,1-adduct (±)-**7a** and 15% of *trans*-5-methyl-2-phenyltetrahydrofuran **2a** (Scheme 4). Formation of 1,2-addition products from alkenol **1a** and dimethyl fumarate was not observed.

From a mechanistic point of view, the results collected in the current study provide strong evidence for an alkenol conversion that occurs in two consecutive steps. The combination of CoL_2/O_2 thereby is assumed to serve as a one-electron oxidant for transformation of the olefin into a radical cation and subsequently into an intermediate that is for the following reasons proposed to be a free carbon radical (see also Scheme 1).[2,16]

(i) Formation of ω-bromobutenyl-substituted tetrahydrofuran (±)-**3k** from ω-cyclopropylphenylpentenol **1j** requires an efficient ring-opening process. Although it is not possible from the existing data to distinguish whether the cycloaliphatic ring fragments prior or after tetrahydrofuran formation, this type of reactivity restricts the set of possible intermediates to radicals, radical cations, or carbenium ions.[17]

Scheme 4. Alkylative Termination of Aerobic Cobalt-Catalyzed Alkenol Ring Closure



[a] 50/50 mixture of diastereomers at C^{α}.

(ii) 1,4-Dihydroarenes, $BrCCl_3$, and DBM are efficient radical trapping reagents[18] but typically do not react with cations.[19,20]

(iii) The notable driving force for addition to electron-deficient olefins revealed the nucleophilic behavior of cyclized intermediates. Primary, secondary, and tertiary carbon radicals are nucleophilic intermediates.[21]

Although the systematics of carbon−carbon bond formation in the aerobic cobalt catalyzed alkenol oxidation merit future attention, the observed selectivities can be rationalized on the basis of rate constants of free radical elementary reactions that typically proceed under kinetic control.[21] Addition of primary carbon radicals to acrylonitrile, for example, occurs with a rate constant of $\sim 4 \times 10^5$ M^{-1} s^{-2} (20 °C).[22] The rate constant for H-atom abstraction from CHD by $\bullet C_2H_5$ is 6×10^4 M^{-1} s^{-2} (27 °C).[23] A rate constant of $\sim 2 \times 10^8$ M^{-1} s^{-2} (26 °C) was determined for Br-atom transfer from $BrCCl_3$ onto primary and secondary carbon radicals using the radical clock technique.[24] By considering given reactant concentrations and product distributions obtained from such mixtures, selectivity associated with the conversion of **1a** is explicable, if the rate constant of alkylative trapping of the cyclized intermediates were 1 order of magnitude higher than that of its reaction with the reductant, i.e., CHD. The rate constant for bromination of the cyclized intermediate with $BrCCl_3$ must exceed that of the addition to acrylonitrile by at least 2 orders of magnitude. This argumentation almost perfectly matches the information obtained from the experimental data.

The proposed mechanistic scheme furthermore allows us to explain the unsatisfactory yield of acceptor-substituted bromocyclization product **3c** (Table 1, entry 10). Br-atom trapping of cyclized intermediates requires homolytic displacement of $\bullet CCl_3$ from $BrCCl_3$ by carbon radicals.[25,26] A Hammett correlation suggests that partial negative charge develops at CCl_3 in the transition state as the Br-atom is transferred from $BrCCl_3$ onto a positively polarized carbon radical center. The radical that is left in the course of cyclization of **1c** is expected for reasons of electron-withdrawing capabilities of the CO_2Me-substituent to react notably slower with $BrCCl_3$, due to a marked lowering of its SOMO energy and thus reduced ability to serve as an electron donor according to the polar transition state model. For reasons of almost equivalent group electronegativities of intermediates associated with homolytic displacement at CHD, polar effects are expected to be less relevant for explaining relative transition state energies of intermediates associated with carbon radical reductions.

The chemistry associated with the final step of cobalt-catalyzed aerobic alkenol oxidation, in conclusion, is uncontradictively explicable with the existence of free carbon radicals. If combinations of XH-acidic nucleophiles (X = e.g. O, N) and olefins other than those described in the present report were able to provide free carbon radicals, the new methodology would have the potential to supplement existing well-established tin or silicon hydride based methods for conducting carbon radical chemistry under reductive conditions, however, on the basis of a catalytic reaction.[27]

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Supporting Information Available: Experimental procedures, 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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Lebenslauf

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