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Oxidative tandem alkoxide conjugate addition to nitroalkenes/radical 5-*exo* cyclizations—a versatile synthesis of functionalized 3-nitrotetrahydrofurans

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ABSTRACT

Structurally diverse functionalized 4-(1-haloalkyl)-3-nitrotetrahydrofurans were conveniently obtained in moderate to good yield and moderate to very good diastereoselectivity by an oxidative tandem process consisting of conjugate addition reaction of lithium allyloxides to nitroalkenes followed by SET oxidation of the resulting nitronates. This triggers a radical cyclization; ligand transfer from the oxidant provides the products. The influence of the counter ion of the initial alkoxide and intermediate nitronate, the solvent and additives on the outcome of the tandem process was investigated. Optimal conditions for the tandem reactions consist of using butyllithium as the base for deprotonation in DME as the solvent. Cupric halides proved to be the SET oxidants of choice in the tandem reactions. A stereochemical model for the radical cyclization and ligand transfer steps is proposed.

1. Introduction

Tandem, cascade or domino reactions enjoy a high popularity in organic chemistry since they allow the time and resource-efficient assembly of molecules in a one-pot operation.[1] Several bonds are formed (and sometimes also cleaved) in the course of the sequence. A significant advantage is offered by the use of very simple precursors as starting materials, from which a considerable increase of the complexity of a carbon framework is achieved throughout the sequence. Most tandem reactions are developed on the basis of a carefully chosen intermediate type or a pericyclic process. So far, most of the known strategies consist of a defined order of reaction steps based on only one intermediate type (organometallic species[2] or radicals[3] or carbocations[4] or carbenes[5]). This defines the scope but also the limitations of the tandem process, since species-typical reactivity patterns have to be obeyed.

These inherent limitations may be overcome by switching the redox state in a domino process, since the reactivities of intermediates of different oxidation state are often complementary to each other. This can be achieved by incorporation of single electron transfer (SET) steps in tandem reactions. However, such reaction sequences will only succeed if the electron transfer steps are quantitative and fast compared to all other reaction steps. Thus, the development of such sequences is more complex and represents a formidable challenge, since multiple intermediate types and the SET steps must be controlled. Most of the work on the realization of such 'multiple intermediate' sequences have so far been developed in the reductive direction mediated by reagents, such as samarium diiodide[6] or titanocene chloride.[7] In the area of oxidatively induced tandem processes, radical-(cationic) reactions of neutral (di)carbonyl compounds induced by $Mn(OAc)_3$[8] or ceric ammonium nitrate (CAN)[9] or electrochemically induced sequences of electron-rich alkenes[10] are notable.

Our interest concentrates on the development of oxidative tandem methodology combining the advantages of organometallic, radical, and carbocationic intermediates. Recently, we introduced oxidative radical cyclizations using enolates as precursors to avoid toxic tin hydrides as a radical source.[11] Based on that, efficient tandem anionic-radical processes for the rapid assembly of hetero- and carbocyclic compounds[12] were developed. In this context we became interested in coupling oxa-Michael additions[13] as the anionic reaction step with radical cyclizations for the synthesis of tetrahydrofuran derivatives,[14] which are structural elements in a large number of biologically active molecules, such as lignans, acetogenins, macrolides, and terpenoids. Here, we provide a full account on the realization of such sequences[15] applying allylic alkoxides and nitroalkenes.[16] This approach affords highly functionalized tetrahydrofurans and has potential in natural product

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synthesis.[17] Moreover, this anionic-radical tandem strategy is unique, since purely anionic addition/cyclizations do not work for alkene units in the allylic alcohol part (vide infra), and complementary to the behavior of propargylic nitro ethers, which can be cyclized anionically.[18] Alternative radical processes consisting of intermolecular alkoxyl radical addition and subsequent cyclization steps are generally not efficient,[19] whereas a few individual α-nitro radical cyclizations[20] and additions[21] are known.

2. Results

Initial experiments focused on the synthesis of β-nitro ethers **3Aa**,**3Ba** by conjugate addition[22] of allylic alkoxides **1A**,**B** to nitroalkene **2a** under reliable conditions in optimal yields using the least excess of one component to establish the envisaged tandem process most efficiently (Scheme 1, Table 1).[23] Best yields of **3Aa** and complete conversion were achieved by deprotonation of 1.5 equiv of **1A** with an equimolar amount of strong alkali metal base in THF or DME at −78 °C for 15–30 min, followed by addition of 1.0 equiv of **2a** at −78 °C (entries 1–5). In contrast, the magnesium alkoxide of **1A** provided **3Aa** only in low yield (entry 6), while amine bases, such as DBU initiated polymerization of **2a**. Cinnamic alkoxide **1B** reacted much more slowly than **1A**, but also gave complete conversion to **3Ba** in good yield at −45 °C (entry 7). Attempts to increase the reactivity of the alkoxide of **1B** by adding aggregate-modifying additives, such as anhydrous LiCl prior to deprotonation, or HMPA[24] thereafter, gave inferior results. While LiCl retarded the reaction rate but did not alter the product formation (entry 8), HMPA triggered the competitive undesired consumption of **2a**, most probably by Michael addition-initiated polymerization of **3Ba**$^-$ with **2a** (entry 9). Since nitronates **3**$^-$ may be susceptible to retro-Michael reactions promoted by these additives thus diminishing the yield, both additives were also introduced into the reaction mixture after complete formation of **3Ba**$^-$. Here, the isolated yield of **3Ba** (85% and 78%, respectively) did not decrease, thus ruling out significant reversibility of the conjugate addition under the reaction conditions (vide infra). When sodium hydride was used as the base, a further Michael addition of **3Ba**$^-$ to **2a** competed significantly to afford **4Ba** as a single diastereomer of unassigned relative configuration in 24% yield (entry 10). It should be noted here that the reaction mixture must be quenched with glacial acetic acid for optimal yields of **3**.

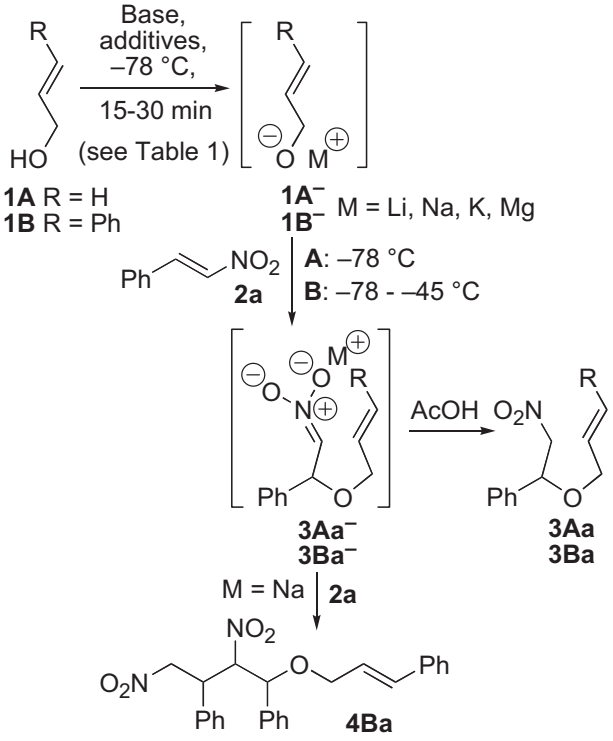
Table 1
Optimization of the conjugate addition of allylic alcohols **1A** and **1B** to nitrostyrene **2a**

Entry	1	Base[a]	Solvent	Additives (equiv)	3[b] (%)	Other products[b]
1	**A**	*n*-BuLi[c]	THF	—	74	**2a** (25%)[d]
2	**A**	*n*-BuLi[c]	DME	—	97	—
3	**A**	NaH[e]	THF	—	87	—
4	**A**	NaHMDS[f]	THF	—	97	—
5	**A**	KHMDS[g]	THF	—	94[h]	—
6	**A**	MeMgCl[i]	THF	—	48	**2a** (48%)[d]
7[j]	**B**	*n*-BuLi[c]	THF	—	83	**2a** (9%)[d]
8[j]	**B**	*n*-BuLi[c]	THF	LiCl (10)[k]	62	**2a** (30%),[d] **1B** (53%)[d]
9[j]	**B**	*n*-BuLi[c]	THF	HMPA (6)[l,m]	37	**1B** (73%)[d]
10[j]	**B**	NaH[e]	THF	—	46	**4Ba** (24%)

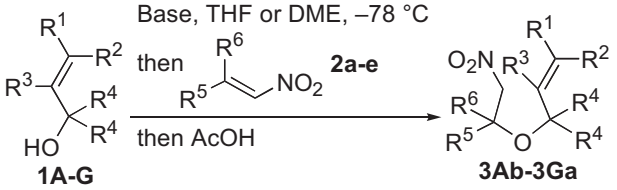
[a] Compound **1** (1.0 equiv) at −78 °C, ratio **1**:**2a** 1.5 mmol:1 mmol unless otherwise stated.
[b] Isolated yields.
[c] Hexanes (1.6 M).
[d] Recovered s.m., isolated.
[e] Suspension (80%) in mineral oil, ratio NaH/**1A**/**2a** 2:1.5:1.
[f] THF (2.0 M), ratio NaHMDS/**1A**/**2a** 1.4:1.4:1.
[g] Toluene (0.5 M), ratio KHMDS/**1A**/**2a** 1:1:1.
[h] Determined by ^{1}H NMR.
[i] THF (3.0 M), ratio MeMgCl/**1A**/**2a** 1.8:1.5:1, reaction time two days at room temperature.
[j] Reaction temperature −45 °C.
[k] Added before deprotonation of **1B**.
[l] No **2a** detected.
[m] Added after deprotonation of **1B**.

With optimized conditions for the conjugate addition of alkoxides to nitroalkenes in hand, the substrate scope of the oxa-Michael addition with respect to various nitroalkenes **2a**–**e** and achiral allylic alcohols **1A**–**G** was determined (Scheme 2, Table 2).

In general, lithium alkoxides derived from substituted allylic alcohols **1C**–**F** underwent the conjugate addition to nitrostyrene **2a** efficiently to give β-nitro ethers **3Ca**–**3Fa** in good to excellent yields (entries 1–2, 4–5). Sodium alkoxides proved again much less efficient in the conjugate addition (entry 3). Even the sterically most congested allylic alcohol **1G** afforded nitro ether **3Ga** in DME after longer reaction time at −40 to 0 °C in a reasonable crude yield of 67%. Extensive decomposition was, however, observed on flash chromatography, so that only 24% of pure **3Ga** was isolated (entry 6). Other nitroalkenes, such as **2b**–**d** were also applicable in the oxa-Michael addition giving the adducts **3Ab**–**3Dd** in good yields (entries 7–13). Generally, the addition proceeded with similar yields in DME and THF. A difference was, however, found in the cyclization step (vide infra). The addition of **1D** to β-disubstituted **2e** did not go to completion and the addition product **3De** was isolated in moderate yield (entry 14). Additionally, some unidentified and polymeric material formed after longer reaction times. β-Methylnitrostyrene gave only undefined polymeric material in the addition with **1D** using a number of bases.[25]



Scheme 1. Optimization of conjugate addition of **1A**,**B** to **2a**.



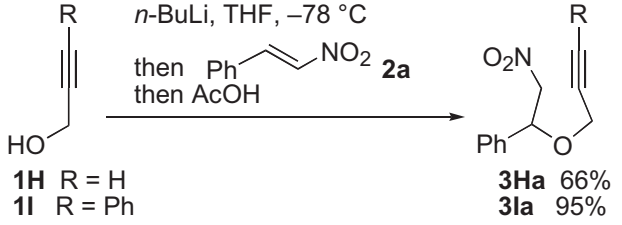
Scheme 2. Conjugate addition of alkoxides **1A**–**G** to nitroalkenes **2a**–**e**.

Table 2
Scope of conjugate additions of allylic alkoxides **1A**–**G** to nitroalkenes **2a**–**e**[a]

Entry	1	R^1	R^2	R^3	R^4	2	R^5	R^6	Solvent	3 (%)
1[b]	**C**	Me	H	H	H	**a**	Ph	H	DME	**3Ca** (93)
2[b]	**D**	Me	Me	H	H	**a**	Ph	H	THF	**3Da** (97)
3[c]	**D**	Me	Me	H	H	**a**	Ph	H	THF	**3Da** (20)
4[b]	**E**[d]	H	H	Me	H	**a**	Ph	H	DME	**3Ea** (67)
5[b]	**F**	H	H	H	Me	**a**	Ph	H	DME	**3Fa** (70)[e]
6[b]	**G**	Me	Me	H	Me	**a**	Ph	H	DME	**3Ga** (24)[f]
7[b]	**A**	H	H	H	H	**b**	4-$MeOC_6H_4$	H	THF	**3Ab** (95)
8[b]	**A**	H	H	H	H	**c**	Et	H	THF	**3Ac** (63)
9[b]	**B**	Ph	H	H	H	**c**	Et	H	DME	**3Bc** (55)
10[b]	**C**	Me	H	H	H	**c**	Et	H	DME	**3Cc** (75)
11[b]	**D**	Me	Me	H	H	**c**	Et	H	THF	**3Dc** (75)
12[b]	**B**	Ph	H	H	H	**d**	*i*-Pr	H	DME	**3Bd** (95)
13[b]	**D**	Me	Me	H	H	**d**	*i*-Pr	H	DME	**3Dd** (73)[g]
14[b]	**D**	Me	Me	H	H	**e**	$-(CH_2)_5-$		DME	**3De** (52)

[a] Substrate **1** (1.5 mmol), **2** (1 mmol), isolated yields.
[b] *n*-BuLi (1.6 M in hexanes) as the base.
[c] NaH as the base. Additionally, 33% of **4Da** (cf. Scheme 1) was isolated as a 2:1 diastereomeric mixture.
[d] Reaction time 3 h at −50 °C.
[e] Compound **2a** (11%) recovered.
[f] Isolated yield after chromatography. The crude yield of **3Ga** was 67% as determined by ^{1}H NMR. This compound is apparently very sensitive to acidic conditions; 6% of **2a** recovered.
[g] An experiment in THF gave exactly the same result.

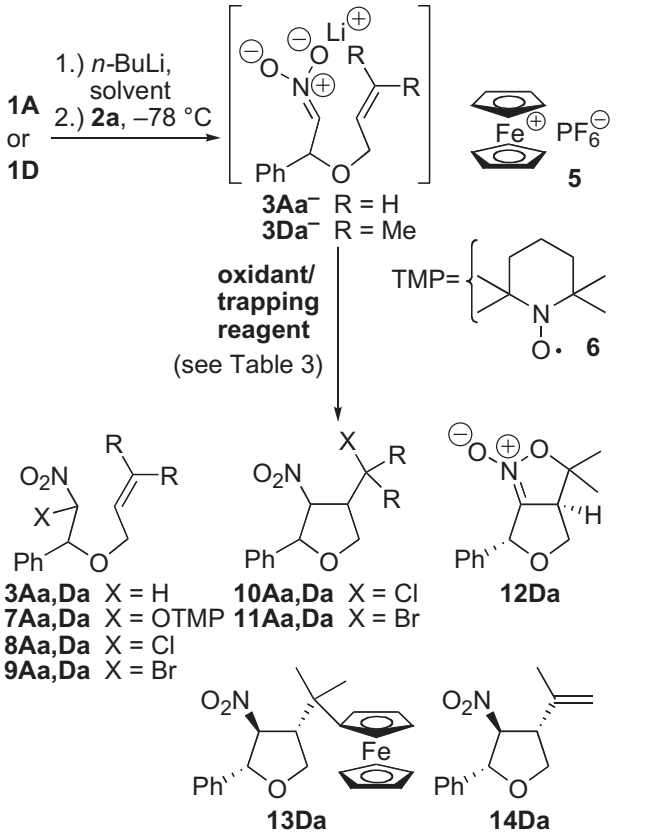
The conjugate addition of propargylic alcohols **1H** and **1I** to nitrostyrene **2a** furnished nitro ethers **3Ha** and **3Ia** in good yields (Scheme 3).



Scheme 3. Conjugate additions of propargylic alkoxides **1H** and **1I** to nitrostyrene **2a**.

Based on the optimized conditions for the alkoxide conjugate addition, the oxidative tandem alkoxide conjugate addition/radical 5-*exo* cyclization sequences were studied in detail. Application of ferrocenium hexafluorophosphate **5**, known to be one of the best and most general SET oxidants for carbanions, enolates, and radicals,[11,12] and TEMPO **6** in the tandem addition/cyclization reaction of **1A** or **1D** and **2a** resulted exclusively in the acyclic TEMPO-trapping products **7Aa** and **7Da** in high yields (Scheme 4, Table 3, entries 1, 2).[26] These experiments indicated that the nitronates **3**$^-$ were oxidized to α-nitro radicals, but that the cyclization step was slow compared to coupling by TEMPO **6**. To check the general cyclization ability of α-nitro radicals under these conditions, the oxidative sequence was repeated with **1D**, **2a**, and **5** in the absence of **6**, since it was known that the cyclized radical will stabilize by a second SET oxidation to a carbocation.[11] The addition/cyclization sequence indeed gave cyclic products **12Da**–**14Da** in reasonable combined yield together with small amounts of **3Da** (entry 3).

The structure and configuration of compound **13Da** was determined by X-ray crystallography (Fig. 1).[27] The all-trans orientation of the substituents in pseudo-equatorial positions is established, with relative configuration *R**,*S**,*S** at C2, C3, C4, respectively; the compound crystallizes with two similar molecules in the asymmetric unit (rms deviation 0.15 Å). The ferrocene unit is located underneath the tetrahydrofuran ring, while the exocyclic methyl groups point outward. The tetrahydrofuran rings adopt



Scheme 4. Screening of SET oxidants in tandem alkoxide conjugate addition/radical 5-*exo* cyclization/termination reactions of **1A**,**D** to **2a** (Stereochemistry of **10**,**11** omitted for clarity, vide infra).

Table 3
Addition/SET/cyclization of **1A**,**D** and **2a** using different oxidants[a]

Entry	1	Oxidant (equiv)/ termination[b]	T^c (°C)	Solvent[d]	3, 7, 8, 9 (%)	10, 11, 14 (%)	12 (%)	13 (%)
1	**A**	**5** (1.2)/**6**	0	DME	**7Aa** (88)[e]	—	—	—
2	**D**	**5** (1.6)/**6**	0	DME	**7Da** (93)[e]	—	—	—
3	**D**	**5** (1.6)	0	DME	**3Da** (18)	**14Da** (9)	55	14
4	**D**	$CuCl_2$ (1.0)/**6**	0	DME	**7Da** (87)[f]	—	—	—
5[g]	**A**	$CuCl_2$ (3.5)	−60	DME	**3Aa** (10)	**10Aa** (69)	—	—
6[h]	**A**	$CuCl_2$ (3.0)	0	DME	**3Aa** (3)	**10Aa** (78)[i]	—	—
7[j]	**A**	$CuBr_2$ (3.0)	0	THF	**9Aa** (35)[k]	**11Aa** (49)[l]	—	—
8[m]	**A**	$Cu(OTf)_2$ (2.0)	0	THF	**3Aa** (73)	—	—	—

[a] Substrate **1** (1.5 mmol), **2a** (1 mmol).
[b] TEMPO **6** (1.0 equiv) used.
[c] Oxidation temperature.
[d] Concentration 0.1 M with respect to **2a**.
[e] 1.1:1 *anti*/*syn*-mixture, diastereomers not assigned.
[f] 1:1 *anti*/*syn*-diastereomeric mixture, diastereomers not assigned.
[g] Compound **2a** (7%) was recovered, **10Aa** is a 2.1:1 2,3-*trans*-3,4-*cis*/2,3-*cis*-3,4-*trans*-diastereomeric mixture.
[h] Compound **2a** (11%) was recovered.
[i] Isolated as a 1.6:1 2,3-*trans*-3,4-*cis*/2,3-*cis*-3,4-*trans*-diastereomeric mixture, traces of **16Aa** detected (vide infra).
[j] Compound **2a** (12%) was recovered.
[k] 2:1 *anti*/*syn*-mixture, diastereomers not assigned.
[l] Isolated as a 2.8:1 2,3-*trans*-3,4-*cis*/2,3-*cis*-3,4-*trans*-diastereomeric mixture (vide infra).
[m] Reaction time 1 h, 26% of **2a** recovered.

distorted envelope conformations, whereby the oxygen atoms lie 0.56/0.55 Å out of the plane of the other four atoms.

The application of anhydrous $CuCl_2$ as the oxidant in the presence of **6** provided **7Da** in high yield (entry 4). Initiation of the cyclization of **3Aa**$^-$, resulting from anionic conjugate addition of **1A** to **2a** at −78 °C in dry DME using $CuCl_2$ in the absence of **6** at −60 °C, provided a 69% yield of tetrahydrofuran **10Aa** as a 2.1:1

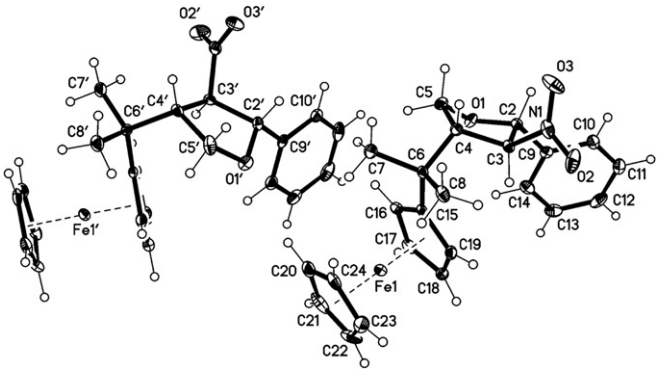
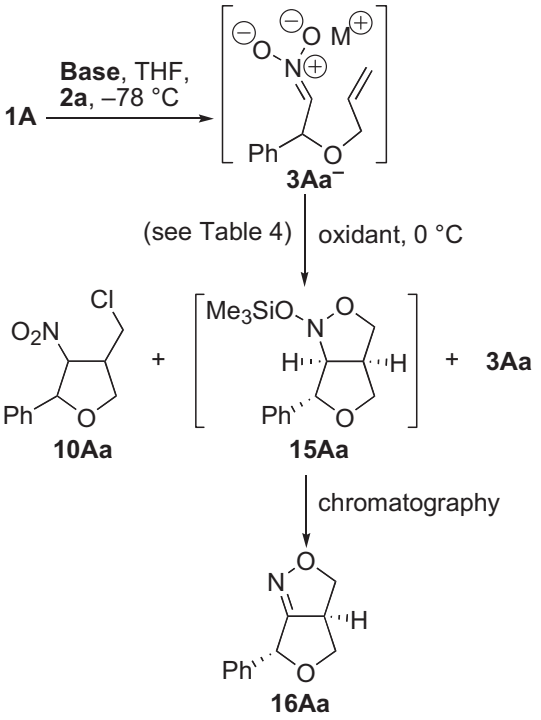


Fig. 1. X-ray crystallographic view of ferrocene adduct **13Da**.

diastereomeric mixture (entry 5). The yield of **10Aa** improved to 78% when $CuCl_2$ was added at 0 °C (entry 6). Cupric bromide proved also effective as a SET oxidant/ligand transfer reagent, providing **11Aa**; however, a significant amount of β-bromo-β-nitro ether **9Aa** was also formed (entry 7). In contrast, $Cu(OTf)_2$ did not oxidize **3Aa**$^-$ but promoted a slow retro-Michael reaction of **3Aa**$^-$ to **2a** (entry 8). Other common SET oxidants, such as copper(II) dicarboxylates,[28] $FeCl_3$,[29] $Fe(acac)_3$,[29] or $Mn(OAc)_3$[8] were not effective in the tandem reactions.

The outcome of the Cu(II)-promoted addition/cyclization sequence depended strongly on the applied base/counterion of nitronates **3**$^-$ (Scheme 5, Table 4). Compared to standard *n*-BuLi (entries 1, 2), LDA gave only a low yield of cyclization product **10Aa** (entry 3). When LiHMDS was used as the base, bicyclic **16Aa** was surprisingly isolated as an additional product besides **3Aa** and **10Aa** (entry 4); it became the major product in unoptimized yield, when NaHMDS or KHMDS were used as the base (entries 5, 7, 8). It was found that the crude material of the cyclization reactions after workup did not contain **16Aa** but unstable bicyclic **15Aa**. This compound was characterized by NMR, but it undergoes rapid



Scheme 5. Screening of bases for tandem alkoxide conjugate additions of **1A** to **2a**/radical 5-*exo* cyclization/ligand transfer reactions (Stereochemistry of **10Aa** omitted for clarity).

Table 4
Addition/cyclization sequences of **1A** and **2a** using various bases[a]

Entry	Base	Oxidant (equiv)	Solvent[b]	**3Aa** (%)	**10Aa** (%) (dr)[c]	**16Aa** (%)	**2a** (%)[d]
1	*n*-BuLi	$CuCl_2$ (3.0)	DME	3	78 (1.6:1)	Trace	11
2	*n*-BuLi	$CuCl_2$ (2.5)	THF	7	65 (4.1:1)	Trace	7
3	LDA	$CuCl_2$ (3.0)	THF	60	16	4	20
4	LiHMDS	$CuCl_2$ (2.5)	THF	3	39 (8:1)	15	4
5	NaHMDS	$CuCl_2$ (2.5)	THF	47	—	46[e]	10
6	NaH	$CuCl_2$ (2.5)	THF	11	Traces	12	12
7	KHMDS	$CuCl_2$ (2.5)	THF	21	—	40[e]	11
8	KHMDS	$Cu(OTf)_2$ (2.5)	THF	19	—	21	16
9	KO^{t}Bu	$CuCl_2$ (2.5)	THF	75	—	—	24
10	MeMgCl	$CuCl_2$ (2.5)	THF	36	2	—	32

[a] Substrate **1A** (1.5 mmol), **2a** (1 mmol).
[b] Concentration 0.1 M with respect to **2a**.
[c] 2,3-*trans*-3,4-*cis*/2,3-*cis*-3,4-*trans*-diastereomeric ratio in parentheses (vide infra).
[d] Compound **2a** was recovered.
[e] Compound **15Aa** is the major product in the crude reaction mixture, but conversion to **16Aa** occurs during chromatography.

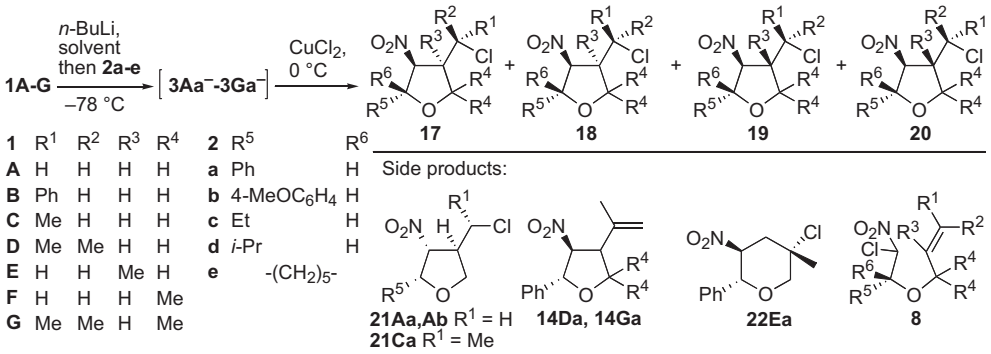
elimination of TMSOH to form the stable bicyclic isoxazoline **16Aa** in moderate yields (entries 4–5, 7–8).[30]

NaH, KO^{t}Bu or MeMgCl proved to be unsuitable bases in the sequences, since nitronates **3Aa**$^-$ were oxidized much more slowly (entries 6, 10) or not at all (entry 9) by $CuCl_2$. Thus, the conditions of nitronate generation and the presence of an amine or HMDS influence the course of the tandem reactions significantly.[31] In all experiments involving Cu(II) salts, a certain amount of nitrostyrene **2a** was recovered, which was not present prior to addition of the copper salts as indicated by TLC (entries 1–9).

The applicability of other solvents was investigated briefly. Acetonitrile can be used in the sequences (50% yield of **10Da**); however, it underwent apparently slow anionic polymerization under the reaction conditions, thus making workup impractical. In toluene, the oxidative cyclization was very slow (16% yield of **10Da**) because of the insufficient solubility of $CuCl_2$ and a passivation effect of the surface by insoluble reduced CuCl.

With optimal conditions in hand the scope of tandem alkoxide conjugate addition/SET-oxidation/radical 5-*exo* cyclization/ligand transfer reactions mediated by $CuCl_2$ was determined for substrates **1A**–**G** and **2a**–**e**. 2-Substituted 4-(1-haloalkyl)-3-nitrotetrahydrofurans **17**–**21** were isolated in moderate to good yields and diastereoselectivities (Scheme 6, Table 5). It was notable that the tandem reactions led to higher yields in DME than in THF (entries 1, 7, 24 vs 3, 8, 25). The optimum temperature for the oxidative step of the reaction sequences was 0 °C. The oxidation proceeded, however, with unhindered substrates in comparable yield even at −60 °C (entries 2, 9), but the improvement of the diastereoselectivity was marginal (entries 1, 8 vs 2, 9). In some cases, even a considerable variation of the diastereoselectivity was found (entries 1, 2 vs 3, vide infra). The yields of oxidative cyclizations did not decrease when the tandem reactions were performed at slightly elevated temperature (entries 6, 12, 15). However, in some cases the diastereoselectivity of the cyclization and of ligand transfer worsened considerably (entry 5 vs 6). Normally anhydrous $CuCl_2$ was used in the tandem reactions; however, cupric chloride dihydrate also served as an efficient oxidant with only a slight decrease of the yield (entry 10).

In case of substrate **1E**, the cyclization rate was retarded due to the substituents at the 2-position of the allylic alkoxide. An increase of the temperature improved the yield of **17Ea** (entry 11 vs 12), but chlorine transfer to the acyclic radical leading to the formation of **8Ea** could not be suppressed. A further temperature increase to 50 °C led to no further improvement (entry 13). This reaction was the only instance in which small amounts of 6-*endo* cyclization product **22Ea** formed as a single diastereomer. When the allylic



Scheme 6. Scope of the tandem alkoxide conjugate addition/radical 5-*exo* cyclization/ligand transfer reactions.

Table 5
Tandem alkoxide conjugate addition/radical 5-*exo* cyclization/ligand transfer reactions promoted by $CuCl_2$[a]

Entry	1	2	Solvent	Yield[b] **17**–**21**	Diastereomeric ratio			Other products Yield (%)
					17+**18** (**17**/**18**)[c]	**19**+**20** (**19**/**20**)[c]	**21**	
1[d]	**A**	**a**	DME	78	1.6 (—)	0 (—)	1	**3Aa** (2), **2a** (11)
2[e,f]	**A**	**a**	DME	69	2.1 (—)	0 (—)	1	**3Aa** (10), **2a** (7)
3	**A**	**a**	THF	65	40 (—)	1 (—)	8	**3Aa** (7), **2a** (7)
4	**B**	**a**	DME	47 (70)	2.1 (5:1)	1 (4:1)	0	**3Ba** (3), **2a** (33)
5[d]	**C**	**a**	DME	65 (74)	5.6 (4.6:1)	1 (5:1)	Trace	**3Ca** (3), **2a** (13)
6[g,h]	**C**	**a**	DME	68 (77)	6.5 (2.8:1)	1.4 (1.7:1)	1	**2a** (12)
7	**D**	**a**	DME	73	1.3 (—)	1 (—)	0	**3Da** (20), **14Da** (1)
8[d]	**D**	**a**	THF	64 (72)	1.5 (—)	1 (—)	0	**3Da** (7), **14Da** (2), **2a** (12)
9[e]	**D**	**a**	THF	41	1.6 (—)	1 (—)	0	**3Da** (26), **2a** (9)
10[g,i]	**D**	**a**	THF	58 (72)	1.4 (—)	1 (—)	0	**3Da** (6), **14Da** (4), **2a** (20)
11[f]	**E**	**a**	DME	16 (24)	1 (—)	0 (—)	0	**3Ea** (12), **8Ea** (20),[j] **22Ea** (6), **2a** (34)
12[f,h]	**E**	**a**	DME	37 (60)	7.5 (—)	1 (—)	0	**8Ea** (17)[j], **22Ea** (4), **2a** (39)
13[g,k]	**E**	**a**	DME	37 (50)	1 (—)	0 (—)	0	**8Ea** (26)[l], **22Ea** (6), **2a** (25)
14[d]	**F**	**a**	DME	42 (52)	9.4 (—)	1 (—)	0	**3Fa** (1), **2a** (20)
15[d,h]	**F**	**a**	DME	45 (59)	10 (—)	1 (—)	0	**2a** (24)
16[m]	**G**	**a**	DME	24	2 (—)	1 (—)	0	**2a** (8), **14Ga** (8)[n]
17	**A**	**b**	THF	52 (76)	2.75 (—)	Traces	1	**3Ab** (15), **2b** (32)
18[f]	**A**	**b**	DME	46 (76)	13 (—)	1 (—)	9	**3Ab** (8), **2b** (40)
19[d]	**A**	**c**	DME	61	5.9 (—)	0 (—)	1	**3Ac** (4)
20	**B**	**c**	DME	70	3.7 (3.4:1)	1 (2:1)	0	—
21	**B**	**d**	DME	55	1.6 (2.5:1)	1 (2.6:1)	0	**3Bd** (9)
22[d]	**C**	**c**	DME	58	4.3 (6.7:1)	1 (1.9:1)	0	—
23[d]	**D**	**c**	DME	50	1.7 (—)	1 (—)	0	—
24	**D**	**d**	DME	44	1.8 (—)	1 (—)	0	**3Dd** (15)
25	**D**	**d**	THF	38	1.5 (—)	1 (—)	0	**3Dd** (11)
26[d]	**D**	**e**	DME	34 (40)	2.5 (—)	1 (—)	0	**2e** (15)

[a] Standard conditions: 1.5 mmol **1** and BuLi, 1 mmol **2**, 2.5 mmol anhydrous $CuCl_2$, 0 °C.
[b] Isolated yield, numbers in parentheses indicate yield based on recovered **2**.
[c] The sum indicates the relative amount of ring diastereomers; the ratio in parentheses indicates the diastereomeric ratio at the exocyclic stereocenter with respect to a defined ring stereoisomer.
[d] $CuCl_2$ (3.0 equiv) was used.
[e] Oxidation at −60 °C.
[f] $CuCl_2$ (3.5 equiv) was used.
[g] $CuCl_2$ (4.0 equiv) was used.
[h] Oxidation temperature +30 °C.
[i] $CuCl_2 \cdot 2H_2O$ was used.
[j] Compound **8Ea** consists of a 2.4:1 *anti*/*syn*-mixture of unassigned diastereomers.
[k] Oxidation temperature +50 °C, 4.0 equiv $CuCl_2$ was added in one portion.
[l] Compound **8Ea** consists of a 1.8:1 *anti*/*syn*-mixture of unassigned diastereomers.
[m] oxa-Michael addition for 1 h at −50 °C, then 3 h at 20 °C until completed, then 3.0 equiv $CuCl_2$ at 0 °C.
[n] Diastereomeric ratio at 4-position 1:1.

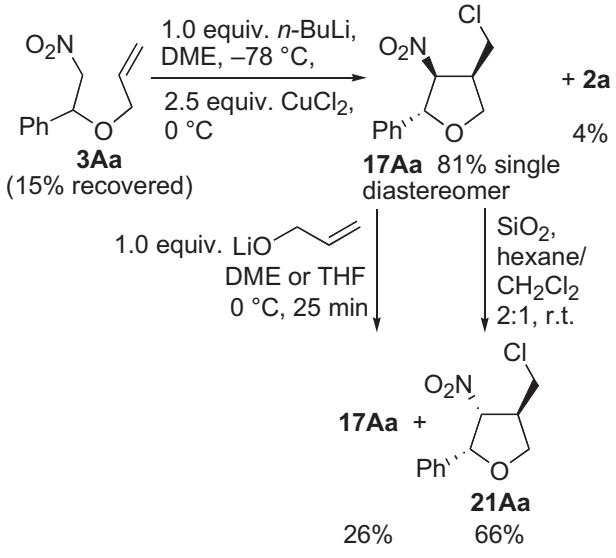
alcohol was disubstituted in 1-position, as in **1F** and **1G**, the yield of cyclized products was moderate (entries 14–16). At least for **1G** the lower yield may be ascribed to a competitive action of $CuCl_2$ as a Lewis acid, promoting the decomposition of **3Ga** (vide supra). With nitroalkenes disubstituted in β-position, the yield of cyclization products **17De** and **19De** decreased, probably associated with slower Michael addition steps (entry 26).

All substrate combinations except those involving **1A** underwent the addition/cyclization sequences with exclusive 2,3-*trans*-selectivity. The cyclization diastereoselectivity was generally good for **1E** and **1F** (entries 11–15). The tandem reactions involving crotyl alcohol **1C** also gave a reasonable diastereoselectivity (entries 5, 6, 22). On the other hand, tandem processes involving alkene units with sterically more demanding substituents at the alkene terminus, such as **1B**, **1D**, and **1G**, cyclized generally only with low diastereoselectivity. It is notable that chlorine transfer occurred with surprisingly good diastereoselectivities if the cyclic radical was prochiral (entries 4, 5, 22). The substitution pattern of **2** was

only of minor importance for the diastereoselectivity, although especially for **2a** and **2b** epimerization has to be taken into account.

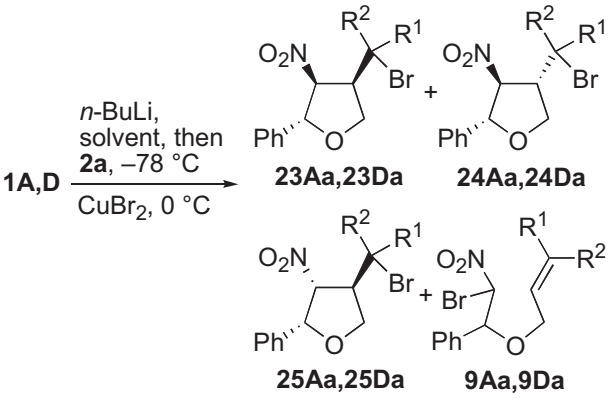
The tandem reactions involving **1A** and nitrostyrenes **2a**,**b** deserve a comment (entries 1–3, 17–19). As mentioned above, exclusive 2,3-*trans*-selectivity was observed for most substrates in the tandem process leading to **17**–**20**. In the original communication,[15] the relative configuration of the minor cyclization product was assigned therefore to be **19Aa** by analogy.[12] Further experiments and the reaction behavior of '**19Aa**–**Ac**' subsequently cast serious doubts on the correctness of this assignment; it was shown that the correct structure of the minor cyclization diastereomer in addition/cyclization sequences of **1A** with **2a**–**c** is in fact **21Aa**–**Ac** (entries 1–3, 17–19). Authentic **19Aa** was detected in trace amounts on large-scale preparations of **17Aa**.

The correction of stereochemical assignment stems from a crucial experiment, which was initially conceived as a simple test of the performance of the tandem reactions versus a stepwise procedure (Scheme 7). This experiment indeed showed that the tandem process is more efficient than a stepwise procedure with isolation of **3Aa**. More significantly, however, the oxidative cyclization of **3Aa**$^-$, generated by deprotonation with exactly 1 equiv of *n*-BuLi, provided **17Aa** as a single diastereomer, in stark contrast to the 2:1 diastereomeric mixture in the tandem process (Table 5, entries 1, 2), but more closely related to the result in THF (entry 3). This indicated that epimerization rather than simple cyclization diastereoselectivity was responsible for the formation of the minor diastereomer. Two experiments revealed the factors responsible for the facile epimerization. First, when diastereomerically pure **17Aa** was subjected to 1 equiv of the lithium alkoxide of **1A** at 0 °C for 25 min, a facile epimerization to a separable 1:2 mixture of **17Aa**/**21Aa** was observed. Secondly, **17Aa** was subjected to silica gel in the chromatography solvent system hexane/CH_2Cl_2 (2:1) and the mixture was stirred at room temperature for 15 h. Epimerization leading to a separable 1:2 mixture of **17Aa**/**21Aa** was also found under acidic conditions. These results rule out **19Aa**, but prove **21Aa** to be the minor diastereomer in the tandem process. The configuration of **21Aa** was assigned by NOE difference experiments (See the Supplementary data) and an intramolecular alkylation reaction.[32] Thus, the tandem reaction of **1A** and **2a** was highly diastereoselective to give **17Aa**, but the diastereoselectivity was compromised by the basic reaction conditions and the acidity during flash chromatography.



Scheme 7. Oxidative radical cyclization of **3Aa** and epimerization of **17Aa**.

Copper bromide as the oxidant gave similar results in the tandem reactions (Scheme 8, Table 6). The yields of cyclized products **23**–**25** were slightly lower than those of the corresponding chlorides (vide supra), and significant amounts of acyclic β-bromo-β-nitro ethers **9** were formed in these sequences. Based on the knowledge gained in the epimerization experiments (vide supra), a tandem reaction of **1A** and **2a** with minimal workup and purification times led to a slight increase of the yield, but a significant improvement of the diastereomeric ratio of bromomethyltetrahydrofurans **23Aa** and **25Aa** (entry 2).



Scheme 8. Use of $CuBr_2$ as oxidant and ligand transfer reagent in the tandem reactions.

Table 6
Bromotetrahydrofurans from addition/cyclization sequences using $CuBr_2$[a]

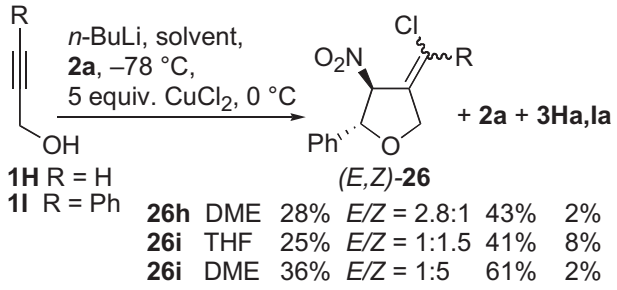
Entry	1	Solvent	**23**+**24**+**25** (%)[b]	**23**/**24**/**25**	**9** % (dr[c])
1[d]	**A**	DME	52	1:0:1.4	18 (2:1)
2[e]	**A**	DME	62	11:0:1	9 (1.7:1)
3[f]	**D**	DME	69	2:1:0	15 (1.5:1)
4[g]	**D**	THF	42	1.2:1:0	24 (3:1)

[a] Substrate **1A** (1.5 mmol), **2a** (1 mmol).
[b] Isolated yield.
[c] *anti*/*syn*-mixture of unassigned diastereomers.
[d] Anhydrous $CuBr_2$ (2.0 equiv).
[e] $CuBr_2$ (2.5 equiv). Fast workup and flash chromatography to avoid epimerization.
[f] $CuBr_2$ (2.8 equiv).
[g] $CuBr_2$ (3.0 equiv).

The relative ring configurations of almost all diastereomers **17**–**21** were assigned by NOE and NOESY experiments (See the Supplementary data). The configuration at the exocyclic stereocenter in compounds **17**–**20Ba** and **17**–**20Ca** was unambiguously assigned by intramolecular alkylation reactions with inversion and other follow-up reactions.[32] The configuration at the exocyclic stereocenter of **17**–**20Bc**, **17**–**20Bd**, and **17**–**20Cc** was assigned by comparison of the NMR spectra with those of **17**–**20Ba** and **17**–**20Ca**. The following spectral properties of the diastereomeric tetrahydrofurans are also diagnostic. The ring protons of diastereomers **17** and **18** are similar to each other, as are those of **19** and **20**. Diastereomers **17** and **18** display generally an H4 resonance upfield-shifted by 0.3–0.5 ppm relative to diastereomers **19** and **20**. Moreover the coupling constant between H2 and H3 amounts to 1.3–3.0 Hz for **17** and **18**, while this value is 5–7 Hz for **19** and **20**. The ^{13}C NMR resonances of the chlorine-bearing carbon atoms are also diagnostic. The resonances of **17** and **18** are again similar to each other, as are those of **19** and **20**. Those of **17** and **18** are, however, 3–6 ppm upfield-shifted compared to **19** and **20**. The bromine derivatives **23** and **24** display similar properties.

The applicability of propargylic alkoxides in the sequences was also checked (Scheme 9). Propargyl alcohol **1H** underwent the

oxidative cyclization in DME giving **26h** in 28% yield as a 2.8:1 *E*/*Z*-mixture. 3-Phenylpropargylalcohol **1I** furnished 4-(chlorobenzylidene)-3-nitro-2-phenyltetrahydrofuran **26i** in 25% yield as a 1:1.5 *E*/*Z*-diastereomeric mixture in THF at 0 °C. In DME, the yield increased to 36% and a higher *E*/*Z*-ratio of 1:5 was observed. The relative configuration and the double bond geometry of compounds **26** was determined by NOESY experiments (See the Supplementary data). From all three experiments surprisingly large amounts of **2a** were recovered although the conjugate addition reactions of **1H** and **1I** to **2a** were complete.



Scheme 9. Tandem conjugate addition/radical 5-*exo* cyclization/ligand transfer reactions using propargylic alcohols.

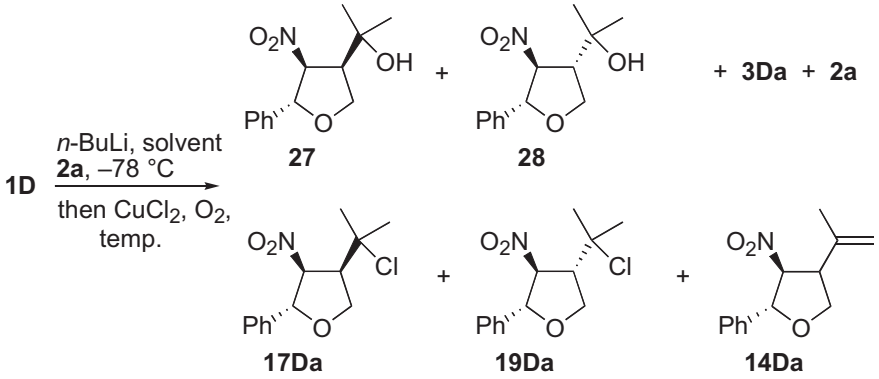
To broaden the scope of the tandem reaction further, other oxidation/termination modes, namely using molecular oxygen, were explored for the addition/cyclization sequences (Scheme 10). The conjugate addition of allylic alkoxide **1D** to **2a** was performed as described above under nitrogen atmosphere. When the addition step was complete as judged by TLC, dry oxygen was bubbled through the reaction mixture[33] and $CuCl_2$ was added. The reaction outcome was dependent on the temperature. When $CuCl_2$ was added at 0 °C in THF or DME solution, the major cyclized product proved to be a diastereomeric mixture of the cyclized alcohols **27** and **28**. In addition, minor amounts of the cyclized ligand transfer products **17Da** and **19Da** were formed. Nitro ether **3Da** and also **2a** were recovered in notable amounts, especially in THF. When the reaction temperature was lowered to −30 °C, the yield of **27** and **28** remained the same, but a decrease in the yield of **17Da** and **19Da** to 5% was found. In addition, **3Da**, **2a**, and a small amount of **14Da** were also isolated. Thus, the use of molecular oxygen to terminate the reaction sequence is limited by the insufficient chemoselectivity of trapping of the cyclized radical.

3. Discussion

The reaction course of the addition/cyclization sequences with cupric halides (X=Cl, Br) as SET oxidants is best rationalized as follows (Scheme 11). After deprotonation of the allylic alcohol **1** by the chosen base, the derived alkoxide undergoes a conjugate addition to the nitroalkene **2**; the rate of this step is dependent on the nucleophilicity of the allylic alkoxide. Qualitatively, lithium prenyl oxide **1D** added faster than crotyl oxide **1C**, allyloxide **1A** and cinnamyl oxide **1B**. The rate of alkoxide addition is also dependent on steric features of **1** and **2**. The addition reaction rate decreased as the degree of substitution at the β-position of the nitroalkene and the 1-position of the alkoxide increases. With tertiary alkoxides, such as **1G** even fragmentations of the nitronates **3Ga**$^-$ became competitive. It is mandatory to use strong bases, such as alkyllithium or alkali metal bis(trimethylsilyl)amides, promoting irreversible deprotonation of **1** to the alkoxide, because equilibrium deprotonation triggers polymerization of the nitroalkenes **2**. The alkali β-alkoxy nitronates **3**$^-$ resulting from addition of **1** are relatively stable under the reaction conditions. The conjugate addition reaction is apparently not reversible. Incomplete additions and retro-oxa-Michael additions were, however, observed when more strongly Lewis acidic magnesium alkoxides were used or when external Lewis acids, such as $Cu(OTf)_2$ were present in the reaction mixture.

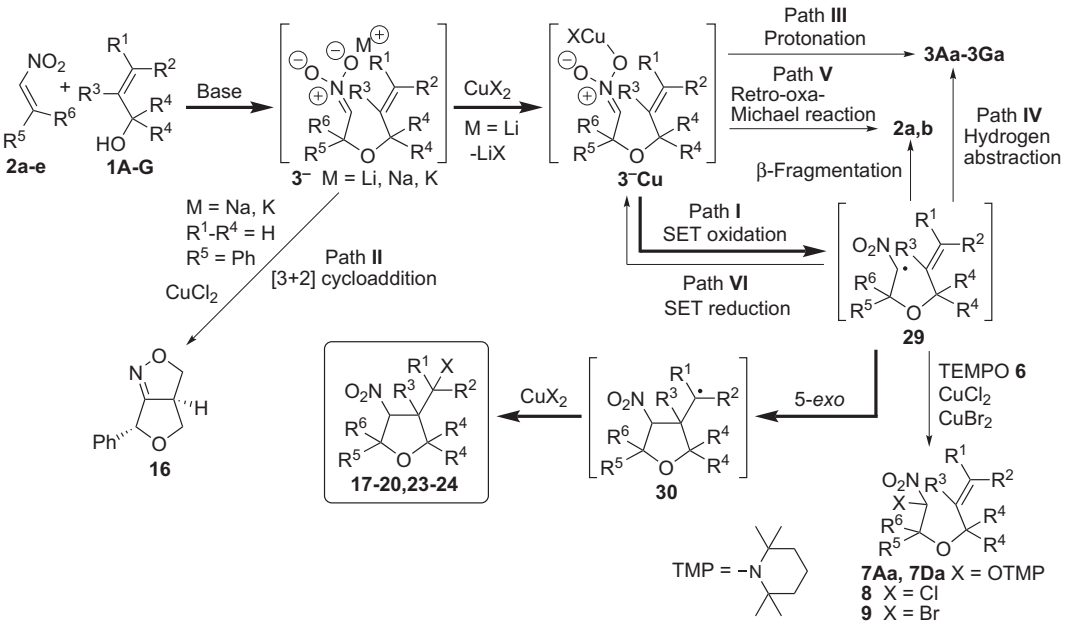
The counter ion in **3**$^-$ and the choice of the SET oxidant affect the further course of the tandem reactions. The lithium cation proved to be the counter ion of choice for the SET oxidations of **3**$^-$ (Scheme 11, Path **I**). Of the oxidants tried, only cupric halides and ferrocenium hexafluorophosphate **5** oxidized nitronates **3**$^-$ efficiently to α-nitro radicals **29**. The SET oxidation should proceed with cupric halides as inner-sphere oxidants via initial transmetalation of **3**$^-$ to **3**$^-$**Cu**. It was, however, important that basic amines, such as the coformed diisopropylamine from LDA, were not present in the reaction mixture, since they retarded SET oxidation considerably, probably by coordination to the Cu(II) ion.

The reaction course switched completely when sodium or potassium nitronates **3**$^-$ were employed (Path **II**). Their $CuCl_2$-induced tandem reactions did not afford ligand transfer-derived products **17**–**20** but bicyclic isoxazoline **16**, especially when hexamethyldisilazides were used as bases. Since sodium and potassium nitronates are expected to be oxidized with more difficulty,[31] these tandem reactions are in fact not anionic/radical



Solvent	temp.	27/28	(d.r.)	17Da/19Da	(d.r.)	3Da	2a	14Da
THF	0 °C	29%	1.6:1	12%	1:1	40%	18%	-
DME	0 °C	33%	1.5:1	4%	1:1	6%	10%	-
THF	–30 °C	28%	1:1	5%	3:1	30%	18%	2%

Scheme 10. Tandem alkoxide conjugate addition/radical 5-*exo* cyclization/oxygenation reactions in the presence of molecular oxygen.



Scheme 11. Mechanistic rationalization of product formation in the tandem reactions.

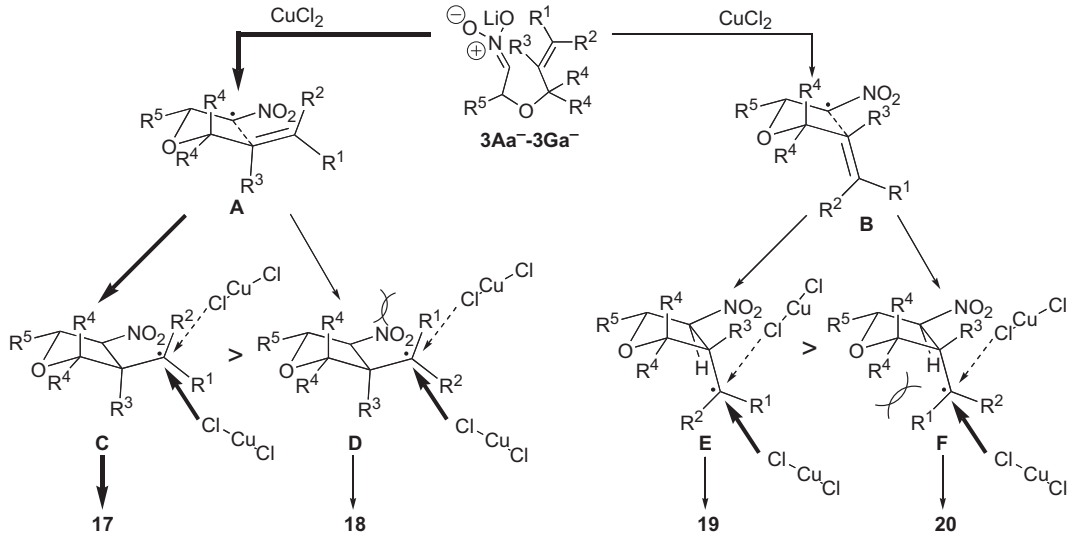
reactions. It is more likely that **16** forms by a tandem alkoxide conjugate addition/[3+2] cycloaddition process,[30] which proceeds by O-silylation of nitronate **3**$^-$ by co-formed HMDS and subsequent promotion of the cycloaddition by Cu(II) salts acting merely as a Lewis acid rather than as a SET oxidant (Table 4). The mechanism and the potential of these reactions are interesting in its own right and will be investigated in due course. It should be noted here that the much stronger SET oxidant ceric ammonium nitrate (CAN) was applied for similar cyclizations of a number of sodium nitronates, thus being complementary to the present tandem reactions.[16a,b]

The fate of α-nitro radicals **29** generated by SET oxidation is determined by the efficiency of the radical traps present. With TEMPO **6**, radicals **29** are trapped completely to **7**. The cyclizations of **29** to **30** must thus be considerably slower compared to cyclizations of related α-carbonyl radicals.[11,12] Ligand transfer from $CuCl_2$ fitted in contrast much better to the slower cyclization of **29**. When $CuCl_2$ and **6** competed for **29**, TEMPO adduct **7** was formed as the exclusive product. Thus ligand transfer of $CuCl_2$ to α-nitro radicals is slow and enables the efficient radical 5-*exo* cyclization of unhindered **29** to **30** at 0 °C. However, when the substitution pattern of **29** leads to a retardation of the 5-*exo* cyclization, as in that of radical **29Ea** derived from methallylic alcohol **1E**, ligand transfer from $CuCl_2$ to **29** competed to some extent, giving chloro nitro ethers **8Ea**. Ligand transfer from $CuBr_2$ to **29** proved to be faster than that from $CuCl_2$, since acyclic bromo nitro ethers **9** formed always.

The small amounts of β-nitro ethers **3** formed in the majority of the reactions result either from incomplete oxidation of **3**$^-$ and subsequent protonation (Path **III**) or from hydrogen abstraction of **29** from the ethereal solvents (Path **IV**). Since no deuterium incorporation into **3** was observed after the reaction mixtures were quenched with D_2O, the latter pathway is supported. The very general recovery of significant amounts of nitrostyrenes **2a**,**b** (but not **2c**,**d**) was unexpected, since the anionic conjugate additions always went to completion as indicated by TLC and isolation of an aliquot of **3**. The re-isolated amounts of **2a** were especially high in tandem reactions, where the oxidation does not occur, such as in experiments using $Cu(OTf)_2$ (Table 3, entry 8; Table 4, entry 8), and also in such tandem reactions where the cyclization rate is retarded (Table 5, entries 11–13; Scheme 9). Since it can be safely assumed that all nitronates **3**$^-$ undergo SET oxidation by $CuCl_2$ with very similar rates, the re-formation of **2a**,**b** can most probably be traced to two competing processes: First, Cu(II) salts promote a retro-oxa-Michael reaction by acting as Lewis acids prior to oxidation. This explains why **2a**,**b** form in all reactions, even when no oxidation proceeds (Path **V**). The especially large amounts of recovered **2a**,**b** during slow cyclizations indicate that back electron transfer from Cu(I) to radical **29** returning **3**$^-$**Cu** may compete to a certain extent with radical 5-*exo* cyclization to **30** (Path **VI**).[34] An alternative direct β-fragmentation of β-allyloxy-α-nitro radicals **29** to **2a**,**b** and an allyloxyl radical seems to be less likely. This is also supported by the especially large amounts of re-formed **2a** in the tandem processes involving propargylic alkoxides **1H**,**I**, which can be traced to a potential reversibility of the radical cyclization process, thus extending the lifetime of **29**.

Once cyclized, radicals **30** usually underwent efficient ligand transfer from the cupric halides to afford the cyclic products **17**–**20** or **23**–**25**. These reactions are known to be very fast with rate constants in the range of $1–5\times10^8$ M^{-1} s^{-1}.[35] Chlorine transfer competed even with coupling of **30** with oxygen to a certain extent, which occurs with rate constants of $\approx10^9$ M^{-1} s^{-1} (Scheme 10).[36] When the cyclized radical **30** is further oxidizable by outer-sphere SET oxidant **5** in the absence of radical traps carbocation-derived products **12Da**–**14Da** form (cf. Scheme 4). However, the selectivity of these tandem reactions must be further improved.

The stereoselectivity of the sequences was most strongly influenced by the substitution pattern of the alkene unit. The observed diastereomeric ratios can be explained best by a Beckwith–Houk transition state for the radical cyclizations (Scheme 12).[37] With all substitution patterns of the alkene function, chair transition state **A**, giving products **17**/**18** with exclusive 2,3-*trans*-diastereoselectivity and a 3,4-*cis*-stereochemistry, was preferred over boat transition state **B**, which leads to minor diastereomers **19**/**20** with a 3,4-*trans*-relationship. For prochiral cyclized radicals **C**–**F** ($R^1 \neq R^2$), ligand transfer from $CuCl_2$ is preferred via more strain-free conformations **C** and **E**, respectively, while rotamers **D** and **F** display unfavorable strain of substituents R^1 and R^4. The ligand transfer to **C** occurs preferentially from the less hindered front face, affording **17** as the



Scheme 12. Diastereoselectivity of the oxidative radical 5-*exo* cyclizations and ligand transfer of **3Aa**$^-$–**3Ga**$^-$.

major diastereomer of the sequences. Similarly, ligand transfer to **E** affording **19** is preferred in the minor diastereomeric series, though face selectivity is somewhat less pronounced.

Especially high cyclization diastereoselectivities are observed for R^1–R^3=H and also for R^1–R^2=H and R^3=Me. However, because of the highly acidic nature of the nitro function, the least-substituted compounds **17Aa**–**Ac** subsequently epimerized to **21Aa**–**Ac** displaying a 2,3-*cis*-stereochemistry under the reaction conditions, thus compromising the good overall diastereoselectivity. To achieve optimal results, reaction and especially workup and chromatography purification times should be kept as short as possible. In some cases, it may be better to perform the addition and cyclization steps separately as indicated in Scheme 7, since epimerization is prevented through the less basic conditions starting from nitro ethers **3Aa** and an equimolar amount of base to generate **3Aa**$^-$. The lowest cyclization diastereoselectivities were observed for prenol-derived radicals. Here, $A^{1,3}$-strain levels the energy differences of both transition states **A** and **B**.

4. Conclusions

The presented anionic-radical tandem reactions consisting of conjugate addition of alkoxides to nitroalkenes and radical 5-*exo* cyclizations connected by SET oxidation of the intermediate nitronates by $CuCl_2$ or $CuBr_2$ are a convenient strategy for obtaining functionalized tetrahydrofurans in a single step from very simple precursors. Several parameters that influence the outcome of the reaction sequences, such as the counter ion in the allylic alkoxide and the nitronates, applicable SET oxidants, solvents or the reaction temperature were investigated. Under optimized conditions, the substrate scope of allylic alcohols **1** and nitroalkenes **2** is broad. Propargylic alcohols are, however, less useful. Anhydrous $CuCl_2$ proved to be the SET oxidant of choice. However, $CuBr_2$, and with some restrictions ferrocenium hexafluorophosphate, can also be applied in the reaction sequences. The tandem reactions display interesting stereochemical features. The diastereoselectivity of the radical 5-*exo* cyclizations and also the ligand transfer were moderate to excellent. Thus a good potential of the tandem process for application in target-oriented synthesis can be expected. Future work is certainly necessary to improve the diastereoselectivity of the cyclizations by minimizing epimerization. Methods to conduct the anionic addition step asymmetrically have to be devised, since the diastereoselectivity of the subsequent radical cyclizations can be predicted on the basis of the present study. Investigations along these lines are underway.

5. Experimental section

5.1. General

All reactions were conducted in flame-dried glassware under nitrogen atmosphere. THF, DME, CH_2Cl_2, Et_2O, MeCN, toluene, $CuCl_2$, $CuBr_2$, and **5** were dried following standard methods under nitrogen atmosphere. TLC plates POLYGRAM SIL G/UV_{254} (Macherey–Nagel) were used for monitoring reactions. Flash column chromatographic separations were performed on silica gel 60 (Fluka, 230–400 mesh). IR spectra were taken on a Bruker Tensor 27 spectrometer (Dura Sample Diamant-ATR, 1 Reflexion). UV spectra were recorded on a Varian Cary 100 spectrometer. ^1H and ^{13}C NMR spectra were recorded, unless otherwise noted, in $CDCl_3$ on Bruker DRX 400, AV 300 or AC 200 spectrometers at 400, 300 or 200, and 100, 75 or 50 MHz, respectively. Connectivity was determined by ^1H–^1H COSY experiments. Relative configurations were determined by NOE or NOESY experiments. ^{13}C NMR assignments were obtained from DEPT and HSQC experiments. EI-mass spectra were recorded on Finnigan MAT 95 spectrometers at 70 eV. ESI-mass spectra were obtained on a Finnigan MAT 95XLT, sample concentration approx. 50 μg/mL in MeOH, spray voltage pos. mode: 1.3–1.8 kV, spray voltage neg. mode: 1.1–2.3 kV, HRMS resolution: 10,000 (10% valley definition). Combustion analyses were performed at the Microanalytical Laboratories of the Technical University of Braunschweig. Allylic alcohol **1G** and nitroalkenes **2c**–**e** were synthesized according to literature procedures.[38]

5.2. β-(Allyloxy) nitroalkanes 3 (general procedure)

At −78 °C under N_2, *n*-BuLi (0.937 mL, 1.5 mmol, 1.6 M solution in hexane) was added via syringe to a stirred solution of allylic alcohol **1** (1.5 mmol) in 10 mL dry DME or THF. After 15 min, a solution of nitroalkene **2** (1.0 mmol) in 1 mL dry DME or THF was added. The reaction mixture was warmed to 0 °C after 10 min and maintained at this temperature until complete by TLC. The reaction mixture was quenched with acetic acid (0.086 mL, 1.5 mmol), diluted with 30 mL diethyl ether, filtered through a pad of silica gel, and concentrated in vacuum. The crude oily products were purified by flash column chromatography (hexane/EtOAc 10:1). β-Nitro

ethers **3Aa**,[23c,h] **3Ba**,[23h] **3Ca**,[23b] **3Ea**,[23b] **3Ab**,[23c] **3Ac**,[23c] and **3Ha**[39] are known compounds and their analytical data are in agreement with the published values.

*5.2.1. 2-Nitro-1-phenyl-1-(prenyloxy)ethane (**3Da**).* Colorless oil, yield 228 mg (97%). R_f=0.56, hexane/EtOAc 10:1; IR (neat) 3064, 3032, 2974, 2915, 2879, 1553, 1452, 1378, 1086, 1065, 1014 cm^{-1}; MS (EI) *m*/*z* 150 (4), 104 (100), 103 (12), 85 (30), 77 (15), 69 (45), 57 (21); Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C 66.36 H 7.28 N 5.95. Found: C 66.31 H 7.47 N 6.20. ^{1}H NMR (400 MHz) δ 1.53 (s, 3H), 1.73 (d, *J*=0.4 Hz, 3H), 3.85 (dd, *J*=11.4, 7.5 Hz, 1H), 3.93 (dd, *J*=11.4, 6.6 Hz, 1H), 4.38 (dd, *J*=12.7, 3.5 Hz, 1H), 4.62 (dd, *J*=12.7, 10.0 Hz, 1H), 5.10 (dd, *J*=10.0, 3.5 Hz, 1H), 5.29 (m, 1H), 7.36–7.41 (m, 5H); ^{13}C NMR (100 MHz) δ 17.9 (q), 25.7 (q), 65.5 (t), 77.2 (d), 80.5 (t), 119.9 (d), 126.8 (d), 129.0 (d, 3C), 136.7 (s), 138.5 (s).

*5.2.2. 1-(2-Methyl-3-buten-2-yloxy)-2-nitro-1-phenylethane (**3Fa**).* Purified by flash chromatography hexane/Et_2O 5:1. Colorless oil, yield 165 mg (70%). R_f=0.62, hexane/Et_2O 5:1; IR (neat) 3088, 3065, 3031, 2980, 2931, 1552, 1454, 1416, 1379, 1224, 1145, 1086, 1064, 964, 926 cm^{-1}; MS (EI) *m*/*z* 220 (10), 150 (30), 107 (18), 104 (100), 78 (11), 77 (16), 71 (28), 69 (76); Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C 66.36 H 7.28 N 5.95. Found: C 66.44 H 7.37 N 6.15. ^{1}H NMR (200 MHz) δ 1.10 (s, 3H), 1.24 (s, 3H), 4.30 (dd, *J*=11.9, 3.8 Hz, 1H), 4.52 (dd, *J*=11.9, 9.7 Hz, 1H), 5.07 (dd, *J*=10.6, 1.1 Hz, 1H), 5.10 (dd, *J*=17.7, 1.1 Hz, 1H), 5.16 (dd, *J*=9.7, 3.8 Hz, 1H), 5.67 (dd, *J*=17.7, 10.6 Hz, 1H), 7.29–7.40 (m, 5H); ^{13}C NMR (50 MHz) δ 25.8 (q), 26.8 (q), 72.7 (d), 77.4 (s), 81.8 (t), 114.6 (t), 126.4 (d), 128.3 (d), 128.7 (d), 140.0 (s), 142.9 (d).

*5.2.3. 1-(2,4-Dimethyl-3-penten-2-yloxy)-2-nitro-1-phenylethane (**3Ga**).* The crude yield as determined by NMR amounted to 67%. After column chromatography only 64 mg (24%) of **3Ga** was isolated as a colorless oil. The compound is very acid sensitive. An optimization was not performed. Despite many attempts, neither a satisfactory combustion analysis nor reasonable mass spectral data were obtained. R_f=0.35, hexane/EtOAc 10:1; ^{1}H NMR (200 MHz) δ 1.16 (s, 3H), 1.28 (s, 3H), 1.61 (d, *J*=1.3 Hz, 3H), 1.63 (d, *J*=1.3 Hz, 3H), 4.33 (dd, *J*=11.8, 4.3 Hz, 1H), 4.59 (dd, *J*=11.8, 9.0 Hz, 1H), 5.09 (quint, *J*=1.3 Hz, 1H), 5.21 (dd, *J*=9.0, 4.3 Hz, 1H), 7.27–7.39 (m, 5H); ^{13}C NMR (50 MHz) δ 19.1 (q), 27.4 (q), 28.7 (q), 28.9 (q), 72.9 (d), 77.4 (s), 81.8 (t), 126.6 (d), 128.2 (d), 128.6 (d), 129.1 (d), 136.4 (s), 140.4 (s).

*5.2.4. 2-(Cinnamyloxy)-1-nitrobutane (**3Bc**).* Colorless oil, yield 130 mg (55%). R_f=0.21, hexane/EtOAc 10:1; IR (neat) 3028, 2970, 2936, 2880, 1550, 1461, 1451, 1421, 1383, 1142, 1075, 1050, 966 cm^{-1}; MS (EI) *m*/*z* 235 (M^+, 4), 133 (69), 131 (45), 118 (11), 117 (100), 115 (92), 105 (82), 104 (61), 103 (24), 91 (50), 89 (11), 79 (22), 77 (38), 65 (12), 63 (11), 55 (70), 51 (25); Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C 66.36 H 7.28 N 5.95. Found: C 66.38 H 7.49 N 5.96. ^{1}H NMR (200 MHz) δ 0.92 (t, *J*=7.4 Hz, 3H), 1.59 (m, 2H), 4.03 (ddt, *J*=8.1, 6.0, 4.1 Hz, 1H), 4.13 (dd, *J*=6.1, 1.5 Hz, 2H), 4.32 (dd, *J*=12.4, 4.1 Hz, 1H), 4.43 (dd, *J*=12.4, 8.1 Hz, 1H), 6.16 (dt, *J*=15.9, 6.1 Hz, 1H), 6.53 (dt, *J*=15.9, 1.5 Hz, 1H), 7.18–7.36 (m, 5H); ^{13}C NMR (50 MHz) δ 9.2 (q), 24.9 (t), 70.8 (t), 77.0 (d), 78.6 (t), 125.3 (d), 126.5 (d), 127.8 (d), 128.5 (d), 132.9 (d), 136.5 (s).

*5.2.5. 2-(Crotyloxy)-1-nitrobutane (**3Cc**).* Colorless oil, yield 130 mg (75%). R_f=0.35, hexane/EtOAc 10:1; IR (neat) 2970, 2938, 2881, 2861, 1552, 1383, 1087, 1043, 967 cm^{-1}; GC–MS (EI) *m*/*z* 113 (3), 102 (32), 72 (65), 71 (98), 57 (80), 55 (100), 53 (25); Anal. Calcd for $C_8H_{15}NO_3$ (173.21): C 55.47 H 8.73 N 8.09. Found: C 55.26 H 8.94 N 7.87. ^{1}H NMR (200 MHz) δ 0.92 (t, *J*=7.4 Hz, 3H), 1.60 (m, 2H), 1.66 (dd, *J*=6.1, 1.2 Hz, 3H), 3.90–4.04 (m, 3H), 4.35 (dd, *J*=12.3, 4.2 Hz, 1H), 4.41 (dd, *J*=12.3, 7.9 Hz, 1H), 5.47 (m, 1H), 5.66 (m, 1H); ^{13}C NMR (50 MHz) δ 9.2 (q), 17.7 (q), 25.0 (t), 71.0 (t), 76.9 (d), 78.6 (t), 127.0 (d), 130.2 (d).

*5.2.6. 1-Nitro-2-(prenyloxy)butane (**3Dc**).* Colorless oil, yield 140 mg (75%). R_f=0.34, hexane/EtOAc 10:1; IR (neat) 2972, 2934, 2881, 1552, 1449, 1382, 1123, 1084, 1049, 981 cm^{-1}; GC–MS (EI) *m*/*z* 172 (3), 102 (18), 85 (100), 83 (22), 71 (52), 69 (80), 67 (15), 57 (14), 55 (60), 53 (12); Anal. Calcd for $C_9H_{17}NO_3$ (187.24): C 57.73 H 9.15 N 7.48. Found: C 57.10 H 9.40 N 7.42. Despite many attempts, a better matching analysis was not obtained. ^{1}H NMR (400 MHz) δ 0.93 (t, *J*=7.5 Hz, 3H), 1.59 (m, 2H), 1.62 (s, 3H), 1.70 (s, 3H), 3.93–4.03 (m, 3H), 4.35 (dd, *J*=12.3, 4.2 Hz, 1H), 4.41 (dd, *J*=12.3, 8.0 Hz, 1H), 5.26 (m, 1H); ^{13}C NMR (100 MHz) δ 9.5 (q), 18.2 (q), 25.2 (t), 26.0 (q), 66.8 (t), 77.0 (d), 79.0 (t), 120.7 (d), 138.2 (s).

*5.2.7. 2-(Cinnamyloxy)-3-methyl-1-nitrobutane (**3Bd**).* Colorless oil, yield 236 mg (95%). R_f=0.35, hexane/EtOAc 10:1; IR (neat) 3028, 2963, 2933, 2875, 1553, 1466, 1451, 1383, 1074, 967 cm^{-1}; MS (EI) *m*/*z* 249 (M^+, 3), 189 (5), 133 (56), 132 (12), 131 (25), 117 (89), 116 (21), 115 (70), 105 (100), 103 (14), 92 (24), 91 (35), 79 (12), 78 (13), 77 (24), 69 (58), 57 (17), 51 (18); HRMS (EI) calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1362; Anal. Calcd for $C_{14}H_{19}NO_3$ (249.31): C 67.45 H 7.68 N 5.62. Found: C 67.95 H 7.73 N 5.25. ^{1}H NMR (200 MHz) δ 0.98 (d, *J*=6.9 Hz, 3H), 0.99 (d, *J*=6.9 Hz, 3H), 1.98 (dsept, *J*=6.9, 5.1 Hz, 1H), 3.98 (ddd, *J*=8.1, 5.1, 4.1 Hz, 1H), 4.21 (dt, *J*=6.1, 1.1 Hz, 2H), 4.44 (dd, *J*=12.4, 4.1 Hz, 1H), 4.47 (dd, *J*=12.4, 8.1 Hz, 1H), 6.20 (dt, *J*=15.9, 6.1 Hz, 1H), 6.58 (dt, *J*=15.9, 1.1 Hz, 1H), 7.23–7.41 (m, 5H); ^{13}C NMR (50 MHz) δ 17.8 (q), 17.9 (q), 30.3 (d), 71.7 (t), 77.3 (t), 80.8 (d), 125.4 (d), 126.5 (d), 127.8 (d), 128.5 (d), 132.8 (d), 136.5 (s).

*5.2.8. 3-Methyl-1-nitro-2-(prenyloxy)butane (**3Dd**).* Purified by flash column chromatography hexane/Et_2O 5:1. Colorless oil, yield 147 mg (73%). R_f=0.62, hexane/Et_2O 5:1; IR (neat) 2967, 2934, 2915, 2878, 1553, 1468, 1449, 1423, 1382, 1224, 1076, 1052, 998 cm^{-1}; MS (EI) *m*/*z* 200 ([M–H]$^+$, 2), 85 (46), 69 (100), 57 (24), 55 (25), 53 (22); Anal. Calcd for $C_{10}H_{19}NO_3$ (201.26): C 59.68 H 9.52 N 6.96. Found: C 59.79 H 9.80 N 6.88. ^{1}H NMR (400 MHz) δ 0.96 (d, *J*=6.9 Hz, 3H), 0.98 (d, *J*=6.9 Hz, 3H), 1.65 (d, *J*=1.1 Hz, 3H), 1.74 (d, *J*=1.1 Hz, 3H), 1.95 (dsept, *J*=6.9, 5.3 Hz, 1H), 3.88 (ddd, *J*=8.1, 5.3, 4.1 Hz, 1H), 4.00 (dd, *J*=11.6, 7.5 Hz, 1H), 4.05 (dd, *J*=11.6, 7.5 Hz, 1H), 4.40 (dd, *J*=12.4, 4.1 Hz, 1H), 4.45 (dd, *J*=12.4, 8.1 Hz, 1H), 5.29 (tquint, *J*=7.5, 1.1 Hz, 1H); ^{13}C NMR (100 MHz) δ 17.5 (q), 17.6 (q), 17.7 (q), 25.4 (q), 30.0 (d), 67.2 (t), 77.0 (t), 80.3 (d), 120.0 (d), 137.6 (s).

*5.2.9. 1-(3-Methylbut-2-enyloxy)-1-(nitromethyl)cyclohexane (**3De**).* Colorless oil, yield 118 mg (52%). R_f=0.44, hexane/EtOAc 10:1; IR (neat) 2934, 2860, 1547, 1449, 1379, 1050, 1028 cm^{-1}; MS (ESI) *m*/*z* 250 (M+Na^+, 100); Anal. Calcd for $C_{12}H_{21}NO_3$ (227.30): C 63.41 H 9.31 N 6.16. Found: C 63.64 H 9.51 N 6.04. ^{1}H NMR (400 MHz) δ 1.24–1.34 (m, 1H), 1.43–1.68 (m, 7H), 1.70 (d, *J*=0.9 Hz, 3H), 1.75 (d, *J*=1.0 Hz, 3H), 1.89 (m, 2H), 3.98 (d, *J*=6.9 Hz, 2H), 4.50 (s, 2H), 5.33 (m, 1H); ^{13}C NMR (100 MHz) δ 18.0 (q), 21.5 (t, 2C), 25.3 (t), 25.9 (q), 32.9 (t, 2C), 58.1 (t), 74.9 (s), 80.4 (t), 120.7 (d), 136.7 (s).

*5.2.10. 2-Nitro-1-phenyl-1-(3-phenylpropargyloxy)ethane (**3Ia**).* Purified by flash column chromatography hexane/Et_2O 5:1. Colorless oil, yield 267 mg (95%). R_f=0.40, hexane/Et_2O 5:1; IR (neat) 3062, 3033, 2905, 2856, 2240, 1553, 1490, 1417, 1379, 1260, 1085, 1066, 1027, 917 cm^{-1}; MS (EI) *m*/*z* 281 (M^+, 1), 220 (10), 149 (14), 132 (28), 131 (46), 115 (100), 104 (57), 102 (26), 91 (20), 89 (19), 78 (20), 77 (46), 66 (12), 63 (14), 51 (32), 50 (14). Anal. Calcd for $C_{17}H_{15}NO_3$ (281.31): C 72.58 H 5.37 N 4.98. Found: C 72.39 H 5.34 N 4.99. ^{1}H NMR (200 MHz) δ 4.18 (d, *J*=15.9 Hz, 1H), 4.41 (d, *J*=15.9 Hz, 1H), 4.45 (dd, *J*=12.8, 3.5 Hz, 1H), 4.72 (dd, *J*=12.8, 9.9 Hz, 1H), 5.43 (dd, *J*=9.9, 3.5 Hz, 1H), 7.27–7.36 (m, 3H), 7.37–7.46 (m, 7H); ^{13}C

NMR (50 MHz) δ 57.1 (t), 76.9 (d), 80.1 (t), 83.7 (s), 87.2 (s), 122.3 (s), 127.1 (d), 128.3 (d), 128.5 (d), 129.1 (d), 129.3 (d), 131.7 (d), 135.5 (s).

5.3. 1-(2-Allyloxy-1-nitro-2-phenylethoxy)-2,2,6,6-tetramethylpiperidine (7Aa)

n-BuLi (0.938 mL, 1.5 mmol, 1.6 M in hexane) was added via syringe to a stirred solution of **1A** (0.102 mL, 1.5 mmol) in 10 mL dry DME at −78 °C. After 15 min, a solution of **2a** (149 mg, 1.0 mmol) in 1 mL dry DME was added. The reaction mixture was warmed slowly to −30 °C and maintained at this temperature until complete, as indicated by TLC. A thoroughly homogenized mixture of dry **5** (258 mg, 0.78 mmol) and **6** (156 mg, 1.0 mmol) was added in portions with vigorous stirring as fast as it was consumed, as indicated by discoloration of the mixture. After consumption more dry **5** (125 mg, 0.38 mmol) was added at the same temperature in 5 portions until the reaction mixture became green-blue and inhomogeneous. After 30 min, the reaction was quenched with AcOH (0.2 mL, 3.2 mmol) and 4 drops of water. The inhomogeneous green-blue mixture was diluted with 20 mL diethyl ether and filtered through a pad of silica gel. The solution was evaporated in vacuum and the crude product was purified by flash chromatography (hexane/EtOAc, gradient 80:1 to 10:1). Orange oil, yield 320 mg (88%) as an inseparable 1.1:1 mixture of unassigned *anti*/*syn*-diastereomers. R_f=0.61, hexane/EtOAc 10:1; IR (neat) 3067, 3009, 2976, 2935, 2874, 1561, 1455, 1366, 1129, 1092, 1066, 991, 927 cm^{-1}; MS (EI) *m*/*z* 362 (M$^+$, 9), 347 (25), 156 (56), 147 (68), 140 (100), 124 (25), 123 (20), 107 (11), 105 (55), 98 (12), 91 (39), 83 (73), 77 (21), 69 (58), 58 (93), 56 (50), 55 (79); Anal. Calcd for $C_{20}H_{30}N_2O_4$ (362.46): C 66.27 H 8.34 N 7.73. Found: C 66.30 H 8.38 N 7.66. *Diastereomer* **1**: ^{1}H NMR (400 MHz) δ 0.86 (s, 3H), 1.12 (s, 3H), 1.17−1.55 (m, 6H), 1.24 (s, 3H), 1.42 (s, 3H), 3.94 (m, 2H), 4.69 (d, *J*=8.1 Hz, 1H), 5.11 (m, 1H), 5.20 (m, 1H), 5.83 (m, 1H), 5.88 (d, *J*=8.1 Hz, 1H), 7.24−7.32 (m, 5H); ^{13}C NMR (100 MHz) δ 16.5 (t), 19.8 (q), 20.1 (q), 31.3 (q), 32.3 (q), 40.3 (t), 40.4 (t), 59.6 (s), 61.9 (s), 70.3 (t), 80.0 (d), 116.9 (d), 117.0 (t), 127.7 (d), 128.2 (d), 128.84 (d), 133.5 (d), 134.5 (s). *Diastereomer* **2**: ^{1}H NMR (400 MHz) δ 0.48 (s, 3H), 0.56 (s, 3H), 0.92 (s, 3H), 1.04 (s, 3H), 1.17−1.45 (m, 6H), 3.74 (m, 1H), 3.94 (m, 1H), 4.74 (d, *J*=8.6 Hz, 1H), 5.17 (m, 2H), 5.67 (d, *J*=8.6 Hz, 1H), 5.73 (m, 1H), 7.33−7.38 (m, 3H), 7.43−7.45 (m, 2H); ^{13}C NMR (100 MHz) δ 16.4 (t), 19.4 (q), 20.1 (q), 31.0 (q), 32.0 (q), 40.3 (t, 2C), 59.8 (s), 61.3 (s), 70.1 (t), 78.7 (d), 115.9 (d), 117.6 (t), 128.1 (d), 128.2 (d), 128.82 (d), 133.1 (d), 135.5 (s).

5.4. 2,2,6,6-Tetramethyl-1-[1-nitro-2-phenyl-2-(prenyloxy) ethoxy]piperidine (7Da)

n-BuLi (0.938 mL, 1.5 mmol, 1.6 M in hexane) was added via syringe to a stirred solution of **1D** (0.152 mL, 1.5 mmol) in 10 mL dry DME at −78 °C. After 15 min, a solution of **2a** (149 mg, 1.0 mmol) in 1 mL dry DME was added. The reaction mixture was slowly warmed to 0 °C and maintained at this temperature until complete as indicated by TLC. A thoroughly homogenized 1:1 mixture of anhydrous $CuCl_2$ (135 mg, 1.0 mmol) and **6** (156 mg, 1.0 mmol) was quickly added in portions with vigorous stirring. After it was consumed, as detected by a lightening of the initially coffee-brown mixture, additional anhydrous $CuCl_2$ (135 mg, 1.0 mmol) was added. After 30 min, the reaction was quenched with 12 drops of saturated NH_4Cl solution. The inhomogeneous mixture was diluted with 80 mL diethyl ether and washed with 100 mL saturated NH_4Cl solution. After separation the aqueous layer was extracted four times with diethyl ether. The organic layers were combined and dried with Na_2SO_4. The organic layer was evaporated in vacuum and the crude product was purified by flash chromatography (hexane/EtOAc 10:1). Orange oil, yield 340 mg (87%) as an inseparable 1.1:1 mixture of unassigned *anti*/*syn*-diastereomers. R_f=0.64, hexane/EtOAc 10:1; IR (neat) 3008, 2975, 2934, 2875, 1561, 1454, 1379, 1366, 1124, 1087, 1065, 991, 980 cm^{-1}; MS (EI) *m*/*z* 390 (M$^+$, 1), 375 (4), 186 (13), 156 (20), 143 (13), 140 (19), 126 (11), 107 (30), 105 (73), 91 (14), 83 (17), 79 (13), 77 (30), 69 (100), 58 (30), 55 (38); Anal. Calcd for $C_{22}H_{34}N_2O_4$ (390.52): C 67.66 H 8.78 N 7.17. Found: C 67.69 H 8.80 N 7.08. *Diastereomer* **1**: ^{1}H NMR (400 MHz) δ 0.90 (s, 3H), 1.15 (s, 3H), 1.19−1.55 (m, 6H), 1.27 (s, 3H), 1.44 (s, 3H), 1.54 (s, 3H), 1.73 (s, 3H), 3.92 (dd, *J*=11.3, 6.6 Hz, 1H), 3.99 (dd, *J*=11.3, 6.6 Hz, 1H), 4.69 (d, *J*=7.9 Hz, 1H), 5.31 (t, *J*=6.6 Hz, 1H), 5.89 (dd, *J*=7.9, 0.4 Hz, 1H), 7.25−7.33 (m, 5H); ^{13}C NMR (100 MHz) δ 16.7 (t), 17.9 (q), 19.9 (q), 20.3 (q), 25.6 (q), 31.6 (q), 32.4 (q), 40.5 (t), 40.6 (t), 59.8 (s), 62.0 (s), 66.0 (t), 79.7 (d), 117.2 (d), 120.3 (d), 127.9 (d), 128.3 (d), 128.8 (d), 135.1 (s), 137.3 (s). *Diastereomer* **2**: ^{1}H NMR (400 MHz) δ 0.51 (s, 3H), 0.59 (s, 3H), 0.96 (s, 3H), 1.08 (s, 3H), 1.19−156 (m, 6H), 1.49 (s, 3H), 1.71 (s, 3H), 3.79 (dd, *J*=11.2, 6.9 Hz, 1H), 3.91 (dd, *J*=11.2, 6.9 Hz, 1H), 4.75 (d, *J*=8.6 Hz, 1H), 5.23 (t, *J*=6.9 Hz, 1H), 5.70 (d, *J*=8.6 Hz, 1H), 7.34−7.41 (m, 3H), 7.47−7.49 (m, 2H); ^{13}C NMR (100 MHz) δ 16.5 (t), 17.7 (q), 19.6 (q), 20.3 (q), 25.6 (q), 31.2 (q), 32.1 (q), 40.4 (t), 40.5 (t), 60.0 (s), 61.5 (s), 65.7 (t), 78.7 (d), 116.2 (d), 119.5 (d), 128.3 (d, 3C), 128.4 (d, 2C), 136.0 (s), 138.7 (s).

5.5. Tandem addition/cyclization mediated by 5 in the absence of TEMPO 6

n-BuLi (0.938 mL, 1.5 mmol, 1.6 M in hexane) was added via syringe to a stirred solution of **1D** (0.152 mL, 1.5 mmol) in 10 mL dry DME at −78 °C. After 15 min, a solution of **2a** (149 mg, 1.0 mmol) in 1 mL dry DME was added. The reaction mixture was warmed slowly to −60 °C and maintained at this temperature until complete as indicated by TLC. Dry **5** (662 mg, 2.0 mmol) was added in portions with vigorous stirring as fast as it was consumed as indicated by discoloration of the mixture. After 30 min, the reaction was quenched with 12 drops of saturated NH_4Cl solution. The inhomogeneous green-blue mixture was diluted with 20 mL diethyl ether and filtered through a pad of silica gel. The solution was evaporated in vacuum and the crude product was purified by flash chromatography (hexane/EtOAc, gradient 80:1 to 2:1).

5.5.1. 3,3-Dimethyl-6(R)-phenyl-3a(R*),4-dihydro-3H,6H-furo[3,4-c]isoxazole-1-oxide (**12Da**).* Solid, which quickly degrades at room temperature and in the presence of traces of acid. Yield 128 mg (55%). Mp 68 °C; R_f=0.32, hexane/EtOAc 3:1; IR (neat) 3032, 2979, 2942, 2881, 1672, 1456, 1373, 1288, 1249, 1224, 1169, 1143, 1007, 963 cm^{-1}; MS (EI) *m*/*z* 233 (M$^+$, 1), 145 (100), 127 (15), 117 (35), 115 (99), 105 (83), 91 (13), 89 (10), 88 (10), 77 (38), 69 (22), 58 (10), 55 (13); MS (ESI) *m*/*z* 256 (M+Na$^+$, 100); HRMS (ESI) $C_{13}H_{15}NO_3$ calcd for [M+Na$^+$] 256.0950, found 256.0947; Anal. Calcd for $C_{13}H_{15}NO_3$ (233.26): C 66.94 H 6.48 N 6.00. Found: C 66.90 H 6.28 N 5.80. ^{1}H NMR (400 MHz, C_6D_6) δ 0.93 (s, 3H), 0.95 (s, 3H), 3.24 (dt, *J*=8.3, 2.0 Hz, 1H), 3.38 (t, *J*=8.3 Hz, 1H), 3.47 (dd, *J*=8.3, 2.0 Hz, 1H), 5.61 (d, *J*=2.0 Hz, 1H), 7.07−7.11 (m, 1H), 7.14−7.19 (m, 2H), 7.48−7.50 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 22.3 (q), 26.6 (q), 56.8 (d), 65.6 (t), 75.3 (d), 84.4 (s), 126.2 (d), 128.3 (d), 128.7 (d), 138.0 (s), 216.1 (s).

5.5.2. 4(S)-(1-Ferrocenyl-1-methylethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**13Da**).* Orange solid, yield 58 mg (14%) as a single diastereomer. Mp 85 °C; R_f=0.45, hexane/EtOAc 10:1; IR (neat) 3101, 3083, 3060, 2985, 2962, 2936, 2869, 1542, 1469, 1453, 1370, 1323, 1292, 1095, 1075, 1029, 990, 766 cm^{-1}; UV ($CHCl_3$, 1.56×10^{-4} M) λ_{max} 240, 439 nm; MS (EI) *m*/*z* 419 (M$^+$, 99), 372 (10), 227 (100), 212 (17), 199 (17), 186 (33), 121 (40), 77 (11), 55 (25); Anal. Calcd for $C_{23}H_{25}FeNO_3$ (419.29): C 65.88 H 6.01 N 3.34. Found: C 66.01 H 6.16 N 3.49. ^{1}H NMR (400 MHz) δ 1.28 (s, 6H), 3.00 (m, 1H), 3.98 (m, 2H), 4.01 (m, 1H), 4.03 (d, *J*=2.7 Hz, 1H), 4.09 (m, 2H), 4.11 (s, 5H), 4.64 (t, *J*=6.9 Hz, 1H), 4.94 (d, *J*=6.9 Hz, 1H), 7.06−7.09

(m, 2H), 7.25–7.26 (m, 3H); ^{13}C NMR (100 MHz) δ 26.1 (q), 26.2 (q), 35.3 (s), 57.5 (d), 66.1 (d), 66.3 (d), 67.7 (d, 2C), 68.5 (d, 5C), 69.6 (t), 85.9 (d), 93.8 (d), 96.2 (s), 125.7 (d, 2C), 128.6 (d, 3C), 137.6 (s).

5.6. Tandem addition/cyclization mediated by cupric chloride in the presence of NaHMDS

At −78 °C under N_2, NaHMDS (0.70 mL, 1.4 mmol, 2.0 M solution in THF) was added via syringe to a stirred solution of **1A** (0.102 mL, 1.4 mmol) in 10 mL dry THF. After 40 min, at −70 °C a solution of **2a** (149 mg, 1.0 mmol) in 1 mL dry THF was added via syringe. The reaction mixture was warmed to −50 °C and maintained at this temperature until completion (TLC monitoring). The reaction mixture was warmed to 0 °C and anhydrous $CuCl_2$ (336 mg, 2.5 mmol) was added at the same temperature in one portion with vigorous stirring. After 30 min, the reaction was quenched with 0.5 mL of a saturated NH_4Cl solution and stirred for 30 min at 20 °C. The inhomogeneous mixture was diluted with 15 mL diethyl ether and filtered through a pad of silica gel. The solution was evaporated in vacuum and the crude product was purified by flash column chromatography (hexane/Et_2O, gradient 5:1 to 1:1).

5.6.1. 6(R)-Phenyl-1-trimethylsilyloxy-3a(R*),6a(S*)-tetrahydrofuro [3,4-c]isoxazole (**15Aa**).*[40] Purified by flash chromatography hexane/Et_2O, gradient 5:1 to 1:1. Colorless oil. R_f=0.38, hexane/Et_2O 1:1; ^{1}H NMR (200 MHz) δ 0.00 (s, 9H), 3.28 (m, 1H), 3.53 (dd, J=9.1, 7.1 Hz, 1H), 3.74 (bd, J=7.1 Hz, 1H), 3.87 (dd, J=8.4, 6.8 Hz, 1H), 4.25 (dd, J=8.4, 6.6 Hz, 1H), 4.26 (t, J=8.4 Hz, 1H), 4.39 (d, J=6.8 Hz, 1H), 7.12–7.29 (m, 5H); ^{13}C NMR (50 MHz) δ −0.6 (q), 46.0 (d), 71.5 (t), 73.8 (t), 83.8 (d), 87.7 (d), 125.6 (d), 127.6 (d), 128.4 (d), 140.3 (s).

5.6.2. 6(R)-Phenyl-3a(R*),4-dihydro-3H,6H-furo[3,4-c]isoxazole (**16Aa**).*[23a,b,h,40] Purified by flash chromatography hexane/Et_2O, gradient 5:1 to 1:1. Colorless solid. For yields and ratios, see Table 4. Mp 77 °C; R_f=0.29, hexane/Et_2O 1:1; IR (neat) 3068, 3036, 3009, 2945, 2917, 2873, 2857, 1501, 1457, 1451, 1358, 1200, 1097, 1008, 975, 947 cm^{-1}; MS (EI) m/z 189 (M^+, 36), 188 (65), 112 (16), 105 (100), 77 (56), 57 (17), 54 (18), 51 (23); Anal. Calcd for $C_{11}H_{11}NO_2$ (189.21): C 69.83 H 5.86 N 7.40. Found: C 69.67 H 5.85 N 7.39. ^{1}H NMR (400 MHz) δ 3.82 (dd, J=9.5, 8.3 Hz, 1H), 4.07 (dd, J=12.3, 8.2 Hz, 1H), 4.24 (m, 1H), 4.44 (dt, J=8.3, 0.7 Hz, 1H), 4.59 (dd, J=9.4, 8.2 Hz, 1H), 5.61 (s, 1H), 7.31–7.44 (m, 5H); ^{13}C NMR (100 MHz) δ 54.8 (d), 70.3 (t), 73.3 (d), 74.0 (t), 126.0 (d), 128.8 (d), 129.0 (d), 137.7 (s), 170.6 (s).

5.7. General procedure for the conjugate addition/radical 5-*exo* cyclization reactions in the presence of cupric chloride or cupric bromide

At −78 °C under N_2, *n*-BuLi (0.938 mL, 1.5 mmol, 1.6 M solution in hexane) was added via syringe to a stirred solution of allylic alcohols **1** (1.5 mmol) in 10 mL dry DME or THF. After 15 min, a solution of nitroalkenes **2** (1.0 mmol) in 1 mL dry DME or THF was added. The reaction mixture was warmed to 0 °C after 10 min and maintained at this temperature until completion (TLC monitoring). Anhydrous $CuCl_2$ (336 mg, 2.5 mmol) or $CuBr_2$ (558 mg, 2.5 mmol) was added at the same temperature in one portion with vigorous stirring. After 30 min, the reaction was quenched with two drops of saturated NH_4Cl solution. The inhomogeneous green-brown mixture was diluted with 30 mL diethyl ether or dichloromethane and filtered through a pad of silica gel. The solution was evaporated in vacuum and the crude product was purified by flash column chromatography (hexane/EtOAc, gradient 10:1 to 2:1). Dichloromethane was the preferred solvent for filtration of larger scale reactions or those involving a larger excess $CuCl_2$, since it retained copper species better on silica.

*5.7.1. 4-(Chloromethyl)-3-nitro-2-phenyltetrahydrofurans (**17Aa**, **19Aa**, **21Aa**).* Purified by flash chromatography hexane/EtOAc, gradient 10:1 to 5:1. For yields and ratios, see Table 5 and Scheme 7. The following analyses were performed on the diastereomeric mixture before further separation. MS (EI) m/z 243/241 (M^+, 1/3), 197/195 (3/8), 196/194 (5/14), 145 (100), 105 (50), 91 (19), 86 (13), 77 (28); Anal. Calcd for $C_{11}H_{12}ClNO_3$ (241.67): C 54.67 H 5.00 N 5.80. Found: C 54.84 H 4.91 N 5.65.

5.7.1.1. 4(R)-(Chloromethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**17Aa**).* Colorless oil. R_f=0.50, hexane/EtOAc 5:1; ^{1}H NMR (400 MHz) δ=3.04 (dquint, J=10.3, 7.6 Hz, 1H), 3.50 (dd, J=11.3, 7.6 Hz, 1H), 3.60 (dd, J=11.3, 7.6 Hz, 1H), 4.05 (dd, J=10.3, 8.6 Hz, 1H), 4.44 (dd, J=8.6, 7.6 Hz, 1H), 5.01 (dd, J=7.6, 3.1 Hz, 1H), 5.49 (d, J=3.1 Hz, 1H), 7.27–7.37 (m, 5H); ^{13}C NMR (100 MHz) δ 39.3 (t), 45.7 (d), 71.3 (t), 85.0 (d), 93.2 (d), 125.2 (d), 128.7 (d), 128.9 (d), 138.5 (s).

5.7.1.2. 4(S)-(Chloromethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**19Aa**).* Colorless oil formed in trace amounts in large scale setups. R_f=0.45, hexane/EtOAc 5:1; ^{1}H NMR (300 MHz) δ 3.40 (m, 1H), 3.59 (dd, J=11.3, 7.1 Hz, 1H), 3.69 (dd, J=11.3, 6.9 Hz, 1H), 4.15 (dd, J=9.5, 3.7 Hz, 1H), 4.33 (dd, J=9.5, 3.7 Hz, 1H), 4.82 (dd, J=6.2, 4.4 Hz, 1H), 5.27 (d, J=6.2 Hz, 1H), 7.35–7.41 (m, 5H); ^{13}C NMR (75 MHz) δ 43.9 (t), 48.1 (d), 70.8 (t), 85.0 (d), 93.5 (d), 125.7 (d), 128.907 (d), 128.949 (d), 137.5 (s).

5.7.1.3. 4(R)-(Chloromethyl)-3(R*)-nitro-2(R*)-phenyltetrahydrofuran (**21Aa**).* Colorless solid. Mp 65 °C; R_f=0.44, hexane/EtOAc 5:1; IR (KBr) 3070, 3049, 3033, 3016, 2978, 2958, 2896, 2868, 1549, 1510, 1453, 1381, 1366, 1339, 1305, 1278, 1097, 1072, 1062, 980, 852, 814 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.61 (m, 1H), 3.65 (dd, J=11.3, 6.2 Hz, 1H), 3.76 (dd, J=11.3, 5.1 Hz, 1H), 3.83 (dd, J=9.1, 7.2 Hz, 1H), 4.62 (dd, J=9.1, 8.0 Hz, 1H), 5.21 (d, J=6.3 Hz, 1H), 5.28 (dd, J=6.3, 3.1 Hz, 1H), 7.29–7.37 (m, 5H); ^{13}C NMR (100 MHz) δ 43.4 (t), 46.7 (d), 70.6 (t), 84.3 (d), 93.2 (d), 126.3 (d), 128.8 (d), 129.3 (d), 134.2 (s).

*5.7.2. 4-(Chlorobenzyl)-3-nitro-2-phenyltetrahydrofurans (**17Ba**–**20Ba**).* Purified by flash chromatography hexane/Et_2O 5:1. Yield 150 mg (47%) as an 8.8:1.8:4:1 mixture of **17Ba**/**18Ba**/**19Ba**/**20Ba**. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3064, 3022, 3004, 2968, 2941, 2905, 1553, 1480, 1365, 1335, 1230, 1115, 1061, 1028, 943, 928, 711, 695 cm^{-1}; MS (CI) m/z 335/337 ($[M+NH_4]^+$, 32/100), 300 (21), 299 (55), 285 (51), 283 (41), 254 (37), 252 (20), 250 (35), 237 (10), 179 (10), 162 (28), 106 (10); Anal. Calcd for $C_{17}H_{16}ClNO_3$ (317.77): C 64.26 H 5.08 N 4.41. Found: C 64.25 H 4.96 N 4.19.

5.7.2.1. 4(R)-((R*)-Chlorobenzyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**17Ba**).* Colorless solid, for yields and ratios, see Table 5. Its relative configuration is supported by a X-ray crystal structure analysis, from which the configuration can be derived unambiguously. The structure is, however, not publishable due to extensive disorder. For the assignment of the configuration, see Ref. 32 and the Supplementary material. Mp 117 °C; R_f=0.50, hexane/Et_2O 5:1; ^{1}H NMR (400 MHz) δ 3.44 (tt, J=10.9, 7.5 Hz, 1H), 4.55 (dd, J=10.9, 8.5 Hz, 1H), 4.56 (dd, J=7.5, 2.5 Hz, 1H), 4.81 (dd, J=8.5, 7.5 Hz, 1H), 5.14 (d, J=10.9 Hz, 1H), 5.49 (d, J=2.5 Hz, 1H), 7.30–7.45 (m, 10H); ^{13}C NMR (100 MHz) δ 51.3 (d), 59.5 (d), 73.0 (t), 87.3 (d), 93.5 (d), 125.3 (d), 127.4 (d), 129.0 (d), 129.24 (d), 129.5 (d), 129.8 (d), 138.6 (s), 139.0 (s).

5.7.2.2. 4(R)-((S*)-Chlorobenzyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**18Ba**).* Colorless oil as an inseparable mixture with **17Ba** and **19Ba**. For the assignment of the configuration, see

the Supplementary data. R_f=0.50, hexane/Et_2O 5:1; ^1H NMR (400 MHz) δ 3.33 (m, 1H), 3.77 (m, 1H), 4.03 (dd, J=11.2, 8.6 Hz, 1H), 4.99 (d, J=11.2 Hz, 1H), 5.28 (dd, J=6.5, 2.2 Hz, 1H), 5.50 (d, J=2.2 Hz, 1H), 7.26–7.40 (m, 10H); ^{13}C NMR (50 MHz) δ 52.6 (d), 58.2 (d), 70.7 (t), 86.3 (d), 94.0 (d), 125.1 (d), 126.87 (d), 126.91 (d), 128.9 (d), 129.0 (d), 129.5 (d), 137.1 (s), 138.8 (s).

5.7.2.3. 4(S)-((S*)-Chlorobenzyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**19Ba**).* Colorless oil as a partially separable mixture with **17Ba** and **18Ba**. For the assignment of the configuration, see Ref. 32 and the Supplementary data. R_f=0.50, hexane/Et_2O 5:1; ^1H NMR (400 MHz) δ 3.79 (ddt, J=9.6, 7.0, 4.1 Hz, 1H), 4.39 (dd, J=9.5, 7.0 Hz, 1H), 4.50 (dd, J=9.5, 4.1 Hz, 1H), 4.51 (m, 1H), 4.85 (d, J=9.6 Hz, 1H), 5.25 (d, J=5.8 Hz, 1H), 7.21–7.39 (m, 10H); ^{13}C NMR (100 MHz) δ 53.8 (d), 62.7 (d), 71.0 (t), 85.2 (d), 93.7 (d), 125.59 (d), 127.3 (d), 128.89 (d), 128.94 (d), 129.2 (d), 129.4 (d), 137.5 (s), 137.9 (s).

5.7.2.4. 4(S)-((R*)-Chlorobenzyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**20Ba**).* Colorless oil. For the assignment of the configuration, see the Supplementary data. R_f=0.35, hexane/Et_2O 5:1; ^1H NMR (400 MHz) δ 3.81 (m, 1H), 3.82 (dd, J=10.3, 3.3 Hz, 1H), 4.09 (dd, J=10.3, 7.5 Hz, 1H), 4.76 (d, J=10.7 Hz, 1H), 5.13 (dd, J=6.0, 3.7 Hz, 1H), 5.20 (d, J=6.0 Hz, 1H), 7.36–7.45 (m, 10H); ^{13}C NMR (100 MHz) δ 54.2 (d), 63.1 (d), 70.5 (t), 86.0 (d), 94.9 (d), 125.7 (d), 127.4 (d), 129.0 (d, 3C), 129.2 (d), 129.37 (d), 137.2 (s), 138.5 (s).

*5.7.3. 4-(1-Chloroethyl)-3-nitro-2-phenyltetrahydrofurans (**17Ca**–**21Ca**).* Purified by flash chromatography hexane/EtOAc, gradient 10:1 to 5:1. For yields and ratios, see Table 5. The following analyses were performed on the diastereomeric mixture before further separation. MS (CI) m/z 292/290 ($[M+NH_3+NH_4]^+$, 4/13), 275/273 ($[M+NH_4]^+$, 30/100), 239 (43), 238 (30), 226 (23), 222 (70), 209 (20), 206 (30), 191 (14), 188 (35); Anal. Calcd for $C_{12}H_{14}ClNO_3$ (255.70): C 56.37 H 5.52 N 5.48. Found: C 56.64 H 5.43 N 5.29.

5.7.3.1. 4(R)-(1(S*)-Chloroethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**17Ca**).* Colorless solid as a partially separable mixture with **18Ca**–**20Ca**. For the assignment of the configuration, see Ref. 32 and the Supplementary data. Mp 78 °C; R_f=0.58, hexane/EtOAc 5:1; IR (KBr) 3064, 3035, 3024, 2992, 2925, 2896, 1551, 1478, 1449, 1391, 1365, 1341, 1317, 1285, 1244, 1160, 1094, 1074, 1063, 1027, 935, 788, 737, 704 cm^{-1}; ^1H NMR (400 MHz) δ 1.56 (d, J=6.5 Hz, 3H), 2.88 (tt, J=10.8, 7.3 Hz, 1H), 4.04 (dq, J=10.8, 6.5 Hz, 1H), 4.29 (dd, J=10.8, 8.8 Hz, 1H), 4.59 (dd, J=8.8, 7.3 Hz, 1H), 4.94 (dd, J=7.3, 2.1 Hz, 1H), 5.57 (d, J=2.1 Hz, 1H), 7.31–7.45 (m, 5H); ^{13}C NMR (100 MHz) δ 24.59 (q), 51.7 (d), 53.7 (d), 72.6 (t), 86.2 (d), 93.4 (d), 125.1 (d), 128.7 (d), 129.0 (d), 138.9 (s).

5.7.3.2. 4(R)-(1(R*)-Chloroethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**18Ca**).* Colorless oil as a partially separable mixture with **17Ca**, **19Ca**, and **20Ca**. For the assignment of the configuration, see Ref. 32 and the Supplementary data. R_f=0.50, hexane/EtOAc 5:1; ^1H NMR (400 MHz) δ 1.5416 (d, J=6.6 Hz, 3H), 2.87 (ddt, J=10.9, 8.2, 6.5 Hz, 1H), 4.148 (dq, J=10.9, 6.6 Hz, 1H), 4.15 (dd, J=10.9, 8.2 Hz, 1H), 4.35 (t, J=8.2 Hz, 1H), 5.16 (dd, J=6.5, 2.0 Hz, 1H), 5.47 (d, J=2.0 Hz, 1H), 7.33–7.43 (m, 5H); ^{13}C NMR (100 MHz) δ 24.6 (q), 52.5 (d), 52.9 (d), 70.4 (t), 85.9 (d), 94.2 (d), 125.0 (d), 128.6 (d), 128.9 (d), 138.8 (s).

5.7.3.3. 4(S)-(1(R*)-Chloroethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**19Ca**).* Colorless oil as partially separable mixture with **17Ca**, **18Ca**, and **20Ca**. For the assignment of the configuration, see Ref. 32 and the Supplementary data. R_f=0.44, hexane/EtOAc 5:1; ^1H NMR (400 MHz) δ=1.5424 (d, J=6.5 Hz, 3H), 3.35 (dq, J=8.1, 6.5 Hz, 1H), 4.25 (quint, J=6.5 Hz, 1H), 4.27 (dd, J=9.4, 6.5 Hz, 1H), 4.334 (dd, J=9.4, 8.1 Hz, 1H), 4.84 (dd, J=7.0, 6.5 Hz, 1H), 5.26 (d, J=7.0 Hz, 1H), 7.33–7.42 (m, 5H); ^{13}C NMR (100 MHz) δ 23.1 (q), 53.3 (d), 57.0 (d), 69.5 (t), 84.8 (d), 93.3 (d), 125.82 (d), 128.9 (d), 129.0 (d), 137.24 (s).

5.7.3.4. 4(S)-(1(S*)-Chloroethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**20Ca**).* Colorless oil as a partially separable mixture with **17Ca**–**19Ca**. For the assignment of the configuration, see the Supplementary data. R_f=0.44, hexane/EtOAc 5:1; ^1H NMR (400 MHz) δ 1.57 (d, J=6.7 Hz, 3H), 3.40 (dddd, J=7.9, 6.7, 5.1, 4.5 Hz, 1H), 4.10 (quint, J=6.7 Hz, 1H), 4.13 (dd, J=9.6, 4.5 Hz, 1H), 4.333 (dd, J=9.6, 7.9 Hz, 1H), 5.01 (dd, J=6.6, 5.1 Hz, 1H), 5.19 (d, J=6.6 Hz, 1H), 7.34–7.43 (m, 5H); ^{13}C NMR (100 MHz) δ 23.4 (q), 53.6 (d), 57.2 (d), 70.5 (t), 85.6 (d), 93.7 (d), 125.80 (d), 128.9 (d), 129.0 (d), 137.16 (s).

5.7.3.5. 4(R)-(1(S*)-Chloroethyl)-3(R*)-nitro-2(R*)-phenyltetrahydrofuran (**21Ca**).* Colorless liquid as a partially separable mixture with **17Ca**, **18Ca**, and **20Ca**. It forms from **17Ca** during column chromatography. For the assignment of the configuration, see Ref. 32 and the Supplementary data. R_f=0.50, hexane/EtOAc 5:1; ^1H NMR (400 MHz) δ 1.54 (d, J=6.8 Hz, 3H), 3.50 (ddt, J=8.7, 5.1, 3.9 Hz, 1H), 3.94 (t, J=8.7 Hz, 1H), 4.33 (dq, J=6.8, 5.1 Hz, 1H), 4.54 (t, J=8.7 Hz, 1H), 5.16 (d, J=6.6 Hz, 1H), 5.22 (dd, J=6.6, 3.9 Hz, 1H), 7.25–7.39 (m, 5H); ^{13}C NMR (100 MHz) δ=23.6 (q), 51.7 (d), 56.9 (d), 68.5 (t), 84.3 (d), 93.5 (d), 126.1 (d), 128.4 (d), 128.9 (d), 133.9 (s).

*5.7.4. 4-(1-Chloro-1-methylethyl)-3-nitro-2-phenyltetrahydrofurans (**17Da**, **19Da**).* Purified by flash chromatography hexane/EtOAc, gradient 10:1 to 5:1. For yields and ratios, see Table 5. The following analyses were performed on the diastereomeric mixture before further separation. MS (CI) m/z 306/304 ($[M+NH_3+NH_4]^+$, 3/10), 289/287 ($[M+NH_4]^+$, 24/100), 273/271 (5/10), 256/254 (8/20), 237 (23), 220 (23), 202 (19), 145 (7); Anal. Calcd for $C_{13}H_{16}ClNO_3$ (269.72): C 57.89 H 5.98 N 5.19. Found: C 58.19 H 6.12 N 4.93.

5.7.4.1. 4(R)-(1-Chloro-1-methylethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**17Da**).* Colorless solid. Mp 110 °C; R_f=0.47, hexane/EtOAc 10:1; IR (KBr) 3089, 3064, 3031, 3019, 2995, 2979, 2905, 1548, 1378, 1137, 1103, 1073, 724, 699 cm^{-1}; ^1H NMR (400 MHz) δ 1.60 (s, 3H), 1.62 (s, 3H), 2.85 (ddd, J=11.2, 8.0, 6.2 Hz, 1H), 4.45 (dd, J=11.2, 8.0 Hz, 1H), 4.49 (t, J=8.0 Hz, 1H), 4.97 (dd, J=6.2, 1.3 Hz, 1H), 5.58 (br s, 1H), 7.27–7.39 (m, 5H); ^{13}C NMR (100 MHz) δ 30.3 (q), 32.2 (q), 55.3 (d), 65.7 (s), 69.1 (t), 85.1 (d), 92.2 (d), 125.1 (d), 128.5 (d), 128.91 (d), 139.4 (s).

5.7.4.2. 4(S)-(1-Chloro-1-methylethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**19Da**).* Colorless oil as a partially separable mixture with **17Da**. R_f=0.47, hexane/EtOAc 10:1; ^1H NMR (200 MHz) δ 1.57 (s, 3H), 1.59 (s, 3H), 3.43 (ddd, J=8.2, 6.1, 5.3 Hz, 1H), 4.27 (dd, J=9.3, 5.3 Hz, 1H), 4.34 (dd, J=9.3, 8.2 Hz, 1H), 4.97 (dd, J=7.1, 6.1 Hz, 1H), 5.16 (d, J=7.1 Hz, 1H), 7.32–7.38 (m, 5H); ^{13}C NMR (50 MHz) δ 30.81 (q), 30.84 (q), 57.7 (d), 69.3 (s), 69.8 (t), 86.0 (d), 93.9 (d), 125.8 (d), 128.87 (d), 129.0 (d), 137.1 (s).

*5.7.5. 4-(Chloromethyl)-4-methyl-3-nitro-2-phenyltetrahydrofurans (**17Ea**,**19Ea**).* Purified by flash chromatography hexane/Et_2O 20:1, then hexane/EtOAc 10:1. For yields and ratios, see Table 5. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3065, 3033, 2980, 2877, 1547, 1455, 1366, 1085, 1064, 947, 741, 697 cm^{-1}; MS (EI) m/z 210/208 (2/5), 159 (100), 105 (10), 91 (10), 77 (11); Anal. Calcd for $C_{12}H_{14}ClNO_3$ (255.70): C 56.37 H 5.52 N 5.48. Found: C 56.76 H 5.58 N 5.21.

5.7.5.1. 4(R)-(Chloromethyl)-4-methyl-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**17Ea**).* Colorless oil. R_f=0.32, hexane/Et_2O 20:1; ^1H NMR (400 MHz) δ 1.43 (s, 3H), 3.56 (d, J=11.2 Hz, 1H), 3.64 (d,

J=11.2 Hz, 1H), 3.94 (d, J=9.1 Hz, 1H), 4.22 (d, J=9.1 Hz, 1H), 4.71 (d, J=6.2 Hz, 1H), 5.55 (d, J=6.2 Hz, 1H), 7.31–7.41 (m, 5H); ^{13}C NMR (100 MHz) δ 22.7 (q), 46.7 (t), 49.7 (s), 76.9 (t), 83.9 (d), 99.0 (d), 125.3 (d), 128.7 (d), 128.9 (d), 138.5 (s).

5.7.5.2. 4(S)-(Chloromethyl)-4-methyl-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**19Ea**).* Colorless oil as a partially separable mixture with **2a**, **3Ea**, and **17Ea**. R_f=0.28, hexane/Et$_2$O 20:1; ^{1}H NMR (400 MHz) δ 1.25 (s, 3H), 3.59 (d, J=11.3 Hz, 1H), 3.68 (d, J=11.3 Hz, 1H), 3.93 (d, J=9.4 Hz, 1H), 4.23 (d, J=9.4 Hz, 1H), 4.85 (d, J=6.9 Hz, 1H), 5.59 (d, J=6.9 Hz, 1H), 7.31–7.46 (m, 5H); ^{13}C NMR (100 MHz) δ 17.0 (q), 50.0 (s), 50.1 (t), 76.1 (t), 82.9 (d), 95.8 (d), 125.6 (d), 128.8 (d), 129.0 (d), 137.9 (s).

5.7.6. 5(S)-Chloro-5(S*)-methyl-3(S*)-nitro-2(R*)-phenyltetrahydropyran (**22Ea**).* Purified by flash chromatography hexane/Et$_2$O 20:1, then hexane/EtOAc 10:1. Colorless oil, for yields and ratios, see Table 5. R_f=0.30, hexane/EtOAc 10:1; IR (neat) 3067, 3037, 2975, 2930, 2883, 2848, 1547, 1375, 1271, 1098, 1084, 1019, 759, 699 cm^{-1}; MS (EI) m/z 257/255 (M$^+$, 0.2/0.5), 210/208 (15/55), 173 (50), 132 (17), 115 (12), 107 (35), 105 (100), 91 (35), 79 (14), 77 (30), 51 (13); Anal. Calcd for $C_{12}H_{14}ClNO_3$ (255.70): C 56.37 H 5.52 N 5.48. Found: C 57.00 H 5.65 N 5.24. ^{1}H NMR (400 MHz) δ 1.62 (s, 3H), 2.43 (dd, J=13.5, 11.8 Hz, 1H), 2.71 (ddd, J=13.5, 4.2, 2.6 Hz, 1H), 3.66 (d, J=12.6 Hz, 1H), 4.00 (dd, J=12.6, 2.6 Hz, 1H), 4.59 (d, J=9.8 Hz, 1H), 5.02 (ddd, J=11.8, 9.8, 4.2 Hz, 1H), 7.29–7.36 (m, 5H); ^{13}C NMR (100 MHz) δ 28.0 (q), 43.7 (t), 65.5 (s), 77.2 (t), 81.1 (d), 85.2 (d), 127.0 (d), 128.8 (d), 129.4 (d), 135.9 (s).

*5.7.7. 2-Chloro-1-(methallyloxy)-2-nitro-1-phenylethane (**8Ea**).* Purified by flash chromatography hexane/Et$_2$O 20:1, then hexane/EtOAc 10:1. Pale yellow oil as a partially separable *anti*/*syn*-mixture of unassigned diastereomers. For yields and ratios, see Table 5. R_f=0.44 and 0.35, hexane/Et$_2$O 20:1; IR (neat) 3068, 3035, 2978, 2935, 2914, 2873, 1570, 1555, 1454, 1353, 1087, 1071, 764, 699 cm^{-1}; MS (EI) m/z 257/255 (M$^+$, 1/3), 210/208 (25/75), 173 (35), 138/140 (23/66), 135 (13), 132 (22), 128 (12), 115 (14), 107 (63), 105 (100), 103 (19), 91 (50), 79 (18), 77 (35), 55 (17), 51 (11); Anal. Calcd for $C_{12}H_{14}ClNO_3$ (255.70): C 56.37 H 5.52 N 5.48. Found: C 56.56 H 5.74 N 5.37. *Diastereomer* **1**: ^{1}H NMR (400 MHz) δ 1.63 (s, 3H), 3.66 (d, J=12.2 Hz, 1H), 3.89 (d, J=12.2 Hz, 1H), 4.81 (m, 1H), 4.85 (m, 1H), 5.06 (d, J=4.9 Hz, 1H), 5.83 (d, J=4.9 Hz, 1H), 7.29–7.33 (m, 5H); ^{13}C NMR (100 MHz) δ 19.3 (q), 73.4 (t), 80.6 (d), 94.5 (d), 114.2 (t), 127.6 (d), 128.98 (d), 129.6 (d), 134.1 (s), 140.51 (s). *Diastereomer* **2**: ^{1}H NMR (400 MHz) δ 1.55 (s, 3H), 3.60 (d, J=12.0 Hz, 1H), 3.76 (d, J=12.0 Hz, 1H), 4.74 (m, 1H), 4.77 (d, J=9.0 Hz, 1H), 4.81 (m, 1H), 5.73 (d, J=9.0 Hz, 1H), 7.32–7.35 (m, 5H); ^{13}C NMR (100 MHz) δ 19.2 (q), 73.6 (t), 81.8 (d), 91.5 (d), 114.0 (t), 128.3 (d), 128.8 (d), 129.7 (d), 133.7 (s), 140.47 (s).

*5.7.8. 3-(Chloromethyl)-2,2-dimethyl-4-nitro-5-phenyltetrahydrofurans (**17Fa**, **19Fa**).* Purified by flash chromatography hexane/EtOAc, gradient 10:1 to 5:1. For yields and ratios, see Table 5. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3066, 3033, 2977, 2938, 2909, 1550, 1451, 1370, 1316, 1088, 1060, 1027, 919, 732, 697 cm^{-1}; MS (EI) m/z 224/222 (4/10), 173 (100), 129 (28), 128 (15), 105 (18), 91 (10), 77 (18); Anal. Calcd for $C_{13}H_{16}ClNO_3$ (269.72): C 57.89 H 5.98 N 5.19. Found: C 58.31 H 6.31 N 5.54.

5.7.8.1. 3(R)-(Chloromethyl)-2,2-dimethyl-4(S*)-nitro-5(R*)-phenyltetrahydrofuran (**17Fa**).* Colorless oil. R_f=0.44, hexane/EtOAc 10:1; ^{1}H NMR (400 MHz) δ 1.47 (s, 3H), 1.55 (s, 3H), 2.83 (ddd, J=9.8, 8.9, 6.9 Hz, 1H), 3.55 (dd, J=11.5, 6.9 Hz, 1H), 3.73 (dd, J=11.5, 8.9 Hz, 1H), 5.11 (dd, J=9.8, 5.8 Hz, 1H), 5.47 (d, J=5.8 Hz, 1H), 7.32–7.41 (m, 5H); ^{13}C NMR (100 MHz) δ 21.6 (q), 29.7 (q), 39.5 (t), 55.0 (d), 82.5 (d), 83.9 (s), 95.2 (d), 125.91 (d), 129.1 (d), 129.2 (d), 138.9 (s).

5.7.8.2. 3(S)-(Chloromethyl)-2,2-dimethyl-4(S*)-nitro-5(R*)-phenyltetrahydrofuran (**19Fa**).* Colorless oil as a partially separable mixture with **17Fa**. R_f=0.29, hexane/EtOAc 10:1; ^{1}H NMR (400 MHz) δ 1.39 (s, 3H), 1.58 (s, 3H), 3.25 (dt, J=8.0, 6.9 Hz, 1H), 3.63 (dd, J=11.5, 8.0 Hz, 1H), 3.73 (dd, J=11.5, 6.9 Hz, 1H), 4.76 (t, J=8.0 Hz, 1H), 5.34 (d, J=8.0 Hz, 1H), 7.32–7.38 (m, 5H); ^{13}C NMR (100 MHz) δ 24.3 (q), 29.0 (q), 42.2 (t), 55.5 (d), 81.0 (d), 82.7 (s), 95.0 (d), 125.85 (d), 128.9 (d), 129.0 (d), 137.7 (s).

*5.7.9. 3-(1-Chloro-1-methylethyl)-2,2-dimethyl-4-nitro-5-phenyltetrahydrofurans (**17Ga**, **19Ga**).* Purified by flash chromatography hexane/Et$_2$O 5:1. Yield 72 mg (24%) as a 2:1 mixture of **17Ga** and **19Ga**. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3066, 2982, 2938, 2905, 1552, 1454, 1388, 1367, 1093, 1063, 760, 699 cm^{-1}; MS (EI) m/z 252/250 (1/3), 173 (100), 157 (32), 142 (15), 129 (20), 128 (10), 115 (15), 105 (24), 91 (14), 77 (20); Anal. Calcd for $C_{15}H_{20}ClNO_3$ (297.78): C 60.50 H 6.77 N 4.70. Found: C 60.56 H 6.69 N 4.76.

5.7.9.1. 3(R)-(1-Chloro-1-methylethyl)-2,2-dimethyl-4(S*)-nitro-5(R*)-phenyltetrahydrofuran (**17Ga**).* Colorless oil as a partially separable mixture with **19Ga**. R_f=0.50, hexane/Et$_2$O 5:1; ^{1}H NMR (400 MHz) δ 1.65 (s, 3H), 1.73 (s, 3H), 1.74 (s, 3H), 1.81 (s, 3H), 2.66 (d, J=8.7 Hz, 1H), 5.22 (dd, J=8.7, 4.0 Hz, 1H), 5.63 (d, J=4.0 Hz, 1H), 7.32–7.38 (m, 5H); ^{13}C NMR (100 MHz) δ 23.8 (q), 32.5 (q), 33.17 (q), 33.22 (q), 64.3 (d), 66.2 (s), 81.4 (d), 85.1 (s), 95.8 (d), 125.3 (d), 128.5 (d), 128.9 (d), 139.9 (s).

5.7.9.2. 3(S)-(1-Chloro-1-methylethyl)-2,2-dimethyl-4(S*)-nitro-5(R*)-phenyltetrahydrofuran (**19Ga**).* Colorless oil as a partially separable mixture with **17Ga**. R_f=0.40, hexane/Et$_2$O 5:1; ^{1}H NMR (300 MHz) δ 1.60 (s, 3H), 1.61 (s, 3H), 1.63 (s, 3H), 1.72 (s, 3H), 3.24 (d, J=7.7 Hz, 1H), 5.16 (t, J=7.7 Hz, 1H), 5.20 (d, J=7.7 Hz, 1H), 7.35–7.38 (m, 5H); ^{13}C NMR (75 MHz) δ 26.0 (q), 31.1 (q), 31.6 (q), 33.0 (q), 64.1 (d), 68.6 (s), 81.2 (d), 84.3 (s), 95.5 (d), 125.9 (d), 128.8 (d), 128.9 (d), 138.0 (s).

*5.7.10. 4-(Chloromethyl)-2-(4-methoxyphenyl)-3-nitrotetrahydrofurans (**17Ab**, **19Ab**, **21Ab**).* Purified by flash chromatography hexane/Et$_2$O, gradient 5:1 to 2:1. For yields and ratios, see Table 5. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3011, 2960, 2935, 2866, 2839, 1612, 1552, 1510, 1467, 1377, 1308, 1249, 1221, 1172, 1080, 1028, 983, 852, 814 cm^{-1}; MS (EI) m/z 273/271 (M$^+$, 3/10), 175 (100), 135 (40), 121 (10), 77 (18); Anal. Calcd for $C_{12}H_{14}ClNO_4$ (271.70): C 53.05 H 5.19 N 5.16. Found: C 53.20 H 5.18 N 5.02.

5.7.10.1. 4(R)-(Chloromethyl)-2(R*)-(4-methoxyphenyl)-3(S*)-nitrotetrahydrofuran (**17Ab**).* Colorless oil. R_f=0.35, hexane/Et$_2$O 2:1; ^{1}H NMR (300 MHz) δ 3.10 (dquint, J=10.3, 7.7 Hz, 1H), 3.55 (dd, J=11.3, 7.7 Hz, 1H), 3.66 (dd, J=11.3, 7.7 Hz, 1H), 3.811 (s, 3H), 4.07 (dd, J=10.3, 8.7 Hz, 1H), 4.48 (dd, J=8.7, 7.7 Hz, 1H), 5.02 (dd, J=7.7, 3.4 Hz, 1H), 5.47 (d, J=3.4 Hz, 1H), 6.89–6.94 (m, 2H), 7.22–7.27 (m, 2H); ^{13}C NMR (75 MHz) δ 39.4 (t), 45.9 (d), 55.4 (q), 71.3 (t), 85.0 (d), 93.3 (d), 114.3 (d), 126.7 (d), 130.4 (s), 159.9 (s).

5.7.10.2. 4(S)-(Chloromethyl)-2(R*)-(4-methoxyphenyl)-3(S*)-nitrotetrahydrofuran (**19Ab**).* Colorless oil. R_f=0.32, hexane/Et$_2$O 2:1; ^{1}H NMR (300 MHz) δ 3.10 (m, 1H), 3.57 (dd, J=11.3, 7.1 Hz, 1H), 3.71 (dd, J=11.3, 6.8 Hz, 1H), 3.814 (s, 3H), 4.13 (dd, J=9.5, 3.7 Hz, 1H), 4.31 (dd, J=9.5, 7.2 Hz, 1H), 4.79 (dd, J=6.4, 4.5 Hz, 1H), 5.18 (d, J=6.4 Hz, 1H), 6.89–6.94 (m, 2H), 7.27–7.31 (m, 2H); ^{13}C NMR (75 MHz) δ 44.1 (t), 48.0 (d), 55.3 (q), 70.6 (t), 77.2 (d), 93.5 (d), 114.3 (d), 126.7 (d), 130.4 (s), 159.9 (s).

5.7.10.3. 4(R)-(Chloromethyl)-2(R*)-(4-methoxyphenyl)-3(R*)-nitrotetrahydrofuran (**21Ab**).* Colorless solid. Mp 89 °C; R_f=0.29, hexane/Et_2O 2:1; ^1H NMR (300 MHz) δ 3.57–3.65 (m, 2H), 3.69–3.81 (m, 2H), 3.77 (s, 3H), 4.58 (m, 1H), 5.15 (d, *J*=6.4 Hz, 1H), 5.21 (dd, *J*=6.4, 3.1 Hz, 1H), 6.83–6.88 (m, 2H), 7.21–7.26 (m, 2H); ^{13}C NMR (75 MHz) δ 43.1 (t), 46.3 (d), 55.2 (q), 70.2 (t), 83.8 (d), 92.9 (d), 113.9 (d), 125.8 (s), 127.3 (d), 160.0 (s).

*5.7.11. 4-(Chloromethyl)-2-ethyl-3-nitrotetrahydrofurans (**17Ac**, **21Ac**).* Purified by flash chromatography hexane/Et_2O 5:1. Yield 118 mg (61%) as a 5.9:1 mixture of **17Ac** and **21Ac**. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 2969, 2938, 2880, 1548, 1463, 1361, 1113, 1086, 1052, 936, 732 cm^{-1}; MS (CI) *m/z* 213/211 ($[M+NH_4]^+$, 11/38), 197 (30), 195 (28), 177 (21), 166/164 (4/16), 161 (100), 144 (30), 128 (10), 126 (50); Anal. Calcd for $C_7H_{12}ClNO_3$ (193.63): C 43.42 H 6.25 N 7.23. Found: C 43.83 H 6.36 N 6.97.

5.7.11.1. 4(R)-(Chloromethyl)-2(R*)-ethyl-3(S*)-nitrotetrahydrofuran (**17Ac**).* Colorless oil. R_f=0.35, hexane/Et_2O 5:1; ^1H NMR (400 MHz) δ 0.96 (t, *J*=7.5 Hz, 3H), 1.64 (m, 2H), 2.95 (dquint, *J*=10.4, 7.7 Hz, 1H), 3.48 (dd, *J*=11.3, 7.7 Hz, 1H), 3.59 (dd, *J*=11.3, 7.7 Hz, 1H), 3.85 (dd, *J*=10.4, 8.7 Hz, 1H), 4.18 (dd, *J*=8.7, 7.7 Hz, 1H), 4.32 (dt, *J*=6.6, 3.6 Hz, 1H), 4.85 (dd, *J*=7.7, 3.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 9.4 (q), 27.4 (t), 39.3 (t), 46.5 (d), 70.5 (t), 85.4 (d), 90.7 (d).

5.7.11.2. 4(R)-(Chloromethyl)-2(R*)-ethyl-3(R*)-nitrotetrahydrofuran (**21Ac**).* Colorless oil as a partially separable mixture with **17Ac**. R_f=0.27, hexane/Et_2O 5:1; ^1H NMR (400 MHz) δ 1.01 (t, *J*=7.4 Hz, 3H), 1.51 (m, 2H), 3.44 (m, 1H), 3.53 (dd, *J*=11.4, 6.8 Hz, 1H), 3.58 (dd, *J*=9.1, 7.1 Hz, 1H), 3.67 (dd, *J*=11.4, 5.5 Hz, 1H), 3.92 (dt, *J*=7.7, 5.8 Hz, 1H), 4.36 (dd, *J*=9.1, 8.2 Hz, 1H), 5.01 (dd, *J*=5.8, 2.9 Hz, 1H); ^{13}C NMR (100 MHz) δ 10.6 (q), 22.7 (t), 43.3 (t), 46.6 (d), 69.8 (t), 83.3 (d), 91.3 (d).

*5.7.12. 4-(Chlorobenzyl)-2-ethyl-3-nitrotetrahydrofurans (**17Bc**–**20Bc**).* Purified by flash chromatography hexane/EtOAc, gradient 10:1 to 5:1. Yield 189 mg (70%) as a 8.6:2.5:2:1 mixture of **17Bc**/**18Bc**/**19Bc**/**20Bc**. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3066, 3034, 2970, 2938, 2880, 1550, 1457, 1357, 1253, 1118, 1092, 1056, 938, 701 cm^{-1}; MS (CI) *m/z* 306/304 ($[M+NH_3+NH_4]^+$, 3/9), 289/287 ($[M+NH_4]^+$, 18/60), 253 (65), 251 (45), 234 (100), 222 (28), 220 (26), 139 (10); Anal. Calcd for $C_{13}H_{16}ClNO_3$ (269.72): C 57.89 H 5.98 N 5.19. Found: C 57.87 H 6.06 N 5.12.

5.7.12.1. 4(R)-((R*)-Chlorobenzyl)-2(R*)-ethyl-3(S*)-nitrotetrahydrofuran (**17Bc**).* Colorless oil. R_f=0.44, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 0.93 (t, *J*=7.5 Hz, 3H), 1.58 (m, 1H), 1.68 (m, 1H), 3.30 (tt, *J*=11.1, 7.3 Hz, 1H), 4.25 (m, 1H), 4.26 (dd, *J*=11.1, 8.7 Hz, 1H), 4.32 (dd, *J*=7.3, 3.2 Hz, 1H), 4.49 (dd, *J*=8.7, 7.3 Hz, 1H), 5.03 (d, *J*=11.1 Hz, 1H), 7.31–7.40 (m, 5H); ^{13}C NMR (100 MHz) δ 9.4 (q), 28.0 (t), 51.9 (d), 59.1 (d), 72.1 (t), 87.5 (d), 90.7 (d), 127.1 (d), 129.2 (d), 129.5 (d), 138.4 (s).

5.7.12.2. 4(R)-((S*)-Chlorobenzyl)-2(R*)-ethyl-3(S*)-nitrotetrahydrofuran (**18Bc**).* Colorless oil as an inseparable mixture with **17Bc** and **20Bc**. R_f=0.38, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 1.02 (t, *J*=7.4 Hz, 3H), 1.64–1.80 (m, 2H), 3.26 (tt, *J*=11.3, 7.2 Hz, 1H), 3.49 (dd, *J*=8.7, 7.2 Hz, 1H), 3.81 (dd, *J*=11.3, 8.7 Hz, 1H), 4.30 (m, 1H), 4.94 (d, *J*=11.3 Hz, 1H), 5.08 (dd, *J*=7.2, 2.9 Hz, 1H), 7.35–7.40 (m, 5H); ^{13}C NMR (100 MHz) δ 9.54 (q), 28.1 (t), 53.7 (d), 58.2 (d), 70.1 (t), 86.9 (d), 91.4 (d), 126.9 (d), 129.1 (d), 129.387 (d), 139.0 (s).

5.7.12.3. 4(S)-((S*)-Chlorobenzyl)-2(R*)-ethyl-3(S*)-nitrotetrahydrofuran (**19Bc**).* Colorless oil. R_f=0.45, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 0.98 (t, *J*=7.4 Hz, 3H), 1.65–1.79 (m, 2H), 3.70 (ddt, *J*=9.6, 6.9, 4.3 Hz, 1H), 4.07 (m, 1H), 4.18 (dd, *J*=9.6, 6.9 Hz, 1H), 4.25 (dd, *J*=6.3, 4.3 Hz, 1H), 4.27 (dd, *J*=9.6, 4.3 Hz, 1H), 4.86 (d, *J*=9.6 Hz, 1H), 7.33–7.39 (m, 5H); ^{13}C NMR (100 MHz) δ 9.53 (q), 26.5 (t), 53.5 (d), 62.9 (d), 70.2 (t), 85.6 (d), 91.2 (d), 127.3 (d), 129.26 (d), 129.39 (d), 139.0 (s).

5.7.12.4. 4(S)-((R*)-Chlorobenzyl)-2(R*)-ethyl-3(S*)-nitrotetrahydrofuran (**20Bc**).* Colorless oil as an inseparable mixture with **17Bc** and **18Bc**. R_f=0.38, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 1.05 (t, *J*=7.4 Hz, 3H), 1.82–1.94 (m, 2H), 3.60 (dd, *J*=9.8, 3.5 Hz, 1H), 3.68 (ddt, *J*=10.8, 7.0, 3.5 Hz, 1H), 3.89 (dd, *J*=9.8, 7.0 Hz, 1H), 4.05 (m, 1H), 4.74 (d, *J*=10.8 Hz, 1H), 4.87 (dd, *J*=6.3, 3.5 Hz, 1H), 7.35–7.41 (m, 5H); ^{13}C NMR (100 MHz) δ 9.6 (q), 26.8 (t), 54.0 (d), 63.4 (d), 70.0 (t), 86.2 (d), 92.6 (d), 127.4 (d), 129.1 (d), 129.29 (d), 138.1 (s).

*5.7.13. 4-(Chlorobenzyl)-2-isopropyl-3-nitrotetrahydrofurans (**17Bd**–**20Bd**).* Purified by flash chromatography hexane/Et_2O 10:1. Yield 156 mg (55%) as a 4.1:1.6:2.6:1 mixture of **17Bd**/**18Bd**/**19Bd**/**20Bd**. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3034, 2964, 2936, 2877, 1551, 1469, 1456, 1370, 1353, 1254, 1089, 1062, 953, 797, 765, 699 cm^{-1}; MS (EI) *m/z* 157 (8), 129 (18), 128 (10), 125 (20), 115 (13), 111 (100), 105 (68), 91 (30), 71 (12), 69 (70); Anal. Calcd for $C_{14}H_{18}ClNO_3$ (283.75): C 59.26 H 6.39 N 4.94. Found: C 59.26 H 6.39 N 4.71.

5.7.13.1. 4(R)-((R*)-Chlorobenzyl)-2(R*)-isopropyl-3(S*)-nitrotetrahydrofuran (**17Bd**).* Colorless oil as an inseparable mixture with **18Bd**–**20Bd**. R_f=0.39, hexane/Et_2O 10:1; ^1H NMR (400 MHz) δ 0.88 (d, *J*=6.8 Hz, 3H), 0.95 (d, *J*=6.8 Hz, 3H), 1.81 (oct, *J*=6.8 Hz, 1H), 3.22 (tt, *J*=11.1, 7.3 Hz, 1H), 4.05 (dd, *J*=6.8, 3.4 Hz, 1H), 4.25 (dd, *J*=11.0, 8.7 Hz, 1H), 4.37 (dd, *J*=7.3, 3.4 Hz, 1H), 4.49 (dd, *J*=8.7, 7.3 Hz, 1H), 5.00 (d, *J*=11.0 Hz, 1H), 7.31–7.35 (m, 2H), 7.36–7.40 (m, 3H); ^{13}C NMR (100 MHz) δ 17.8 (q), 17.96 (q), 32.31 (d), 52.4 (d), 59.0 (d), 72.1 (t), 89.3 (d), 91.5 (d), 127.1 (d), 129.2 (d), 129.5 (d), 138.4 (s).

5.7.13.2. 4(R)-((S*)-Chlorobenzyl)-2(R*)-isopropyl-3(S*)-nitrotetrahydrofuran (**18Bd**).* Colorless oil as an inseparable mixture with **17Bd**, **19Bd**, and **20Bd**. R_f=0.41, hexane/Et_2O 10:1; ^1H NMR (400 MHz) δ 0.94 (d, *J*=6.8 Hz, 3H), 1.00 (d, *J*=6.8 Hz, 3H), 1.89 (m, 1H), 3.12–3.26 (m, 1H), 3.47 (dd, *J*=8.6, 7.3 Hz, 1H), 3.82 (dd, *J*=11.4, 8.6 Hz, 1H), 4.09 (dd, *J*=7.0, 3.3 Hz, 1H), 4.93 (d, *J*=11.3 Hz, 1H), 5.13 (dd, *J*=7.1, 3.3 Hz, 1H), 7.36–7.40 (m, 5H); ^{13}C NMR (100 MHz) δ 17.91 (q), 17.95 (q), 32.35 (d), 54.3 (d), 58.2 (d), 70.1 (t), 90.0 (d), 90.9 (d), 126.8 (d), 129.1 (d), 129.3 (d), 139.0 (s).

5.7.13.3. 4(S)-((S*)-Chlorobenzyl)-2(R*)-isopropyl-3(S*)-nitrotetrahydrofuran (**19Bd**).* Colorless oil as an inseparable mixture with **18Bd**. R_f=0.39, hexane/Et_2O 10:1; ^1H NMR (400 MHz) δ 0.95 (d, *J*=6.5 Hz, 3H), 0.97 (d, *J*=6.5 Hz, 3H), 1.90 (oct, *J*=6.5 Hz, 1H), 3.62 (tdd, *J*=9.9, 6.6, 3.9 Hz, 1H), 3.94 (t, *J*=6.5 Hz, 1H), 4.18 (dd, *J*=9.6, 6.6 Hz, 1H), 4.28 (dd, *J*=9.6, 3.9 Hz, 1H), 4.32 (dd, *J*=6.5, 3.9 Hz, 1H), 4.82 (d, *J*=9.9 Hz, 1H), 7.31–7.35 (m, 2H), 7.36–7.40 (m, 3H); ^{13}C NMR (100 MHz) δ 17.8 (q), 18.25 (q), 31.3 (d), 54.3 (d), 62.5 (d), 70.3 (t), 89.5 (d), 89.7 (d), 127.3 (d), 129.3 (d), 129.41 (d), 138.1 (s).

5.7.13.4. 4(S)-((R*)-Chlorobenzyl)-2(R*)-isopropyl-3(S*)-nitrotetrahydrofuran (**20Bd**).* Colorless oil as an inseparable mixture with **17Bd**–**19Bd**. R_f=0.39, hexane/Et_2O 10:1; ^1H NMR (400 MHz) δ 1.04 (d, *J*=6.5 Hz, 3H), 1.05 (d, *J*=6.5 Hz, 3H), 2.01 (oct, *J*=6.5 Hz, 1H), 3.53–3.60 (m, 2H), 3.89 (dd, *J*=10.0, 6.8 Hz, 1H), 3.93 (t, *J*=6.5 Hz, 1H), 4.70 (d, *J*=11.1 Hz, 1H), 5.00 (dd, *J*=6.5, 3.3 Hz, 1H), 7.35–7.40 (m, 5H); ^{13}C NMR (100 MHz) δ 17.9 (q), 18.27 (q), 31.5 (d), 54.9 (d), 63.0 (d), 69.9 (t), 90.0 (d), 91.5 (d), 127.5 (d), 129.1 (d), 129.37 (d), 138.7 (s).

*5.7.14. 4-(1-Chloroethyl)-2-ethyl-3-nitrotetrahydrofurans (**17Cc–20Cc**).* Purified by flash chromatography hexane/EtOAc, gradient 10:1 to 5:1. Yield 121 mg (58%) as a 11:1.6:1.9:1 mixture of **17Cc**/**18Cc**/**19Cc**/**20Cc**. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 2971, 2936, 2880, 1549, 1460, 1384, 1357, 1283, 1243, 1087, 1071, 1052, 939, 907, 781, 683 cm^{-1}; MS (CI) *m/z* 227/225 ($[M+NH_4]^+$, 2/7), 213/211 (5/15), 191 (23), 178 (37), 175 (100), 160 (33), 158 (90), 142 (13), 140 (45), 114 (11), 69 (12); Anal. Calcd for $C_8H_{14}ClNO_3$ (207.65): C 46.27 H 6.80 N 6.75. Found: C 46.25 H 6.86 N 6.34.

5.7.14.1. 4(R)-(1(S*)-Chloroethyl)-2(R*)-ethyl-3(S*)-nitrotetrahydrofuran (**17Cc**).* Colorless oil as a partially separable mixture with **18Cc–20Cc**. R_f=0.34, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 1.00 (t, *J*=7.5 Hz, 3H), 1.60 (d, *J*=6.5 Hz, 3H), 1.62–1.71 (m, 2H), 2.77 (tt, *J*=10.8, 7.3 Hz, 1H), 4.01 (dq, *J*=10.8, 6.5 Hz, 1H), 4.08 (dd, *J*=10.8, 8.8 Hz, 1H), 4.32 (dd, *J*=8.8, 7.3 Hz, 1H), 4.37 (m, 1H), 4.77 (dd, *J*=7.3, 2.8 Hz, 1H); ^{13}C NMR (100 MHz) δ 9.6 (q), 24.7 (q), 28.00 (t), 52.9 (d), 53.6 (d), 71.9 (t), 86.8 (d), 90.9 (d).

5.7.14.2. 4(R)-(1(R*)-Chloroethyl)-2(R*)-ethyl-3(S*)-nitrotetrahydrofuran (**18Cc**).* Colorless oil as a partially separable mixture with **17Cc**, **19Cc**, and **20Cc**. R_f=0.44, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 0.96 (m, 3H), 1.49 (d, *J*=6.4 Hz, 3H), 1.59–1.69 (m, 2H), 2.76 (m, 1H), 3.89 (dd, *J*=11.2, 8.3 Hz, 1H), 4.04 (m, 1H), 4.05 (t, *J*=8.0 Hz, 1H), 4.23 (dt, *J*=6.8, 2.8 Hz, 1H), 4.92 (dd, *J*=7.0, 2.8 Hz, 1H); ^{13}C NMR (100 MHz) δ 9.5 (q), 24.5 (q), 27.98 (t), 52.6 (d), 54.0 (d), 69.7 (t), 86.5 (d), 91.5 (d).

5.7.14.3. 4(S)-(1(R*)-Chloroethyl)-2(R*)-ethyl-3(S*)-nitrotetrahydrofuran (**19Cc**).* Colorless oil as a partially separable mixture with **17Cc**, **18Cc**, and **20Cc**. R_f=0.34, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 0.964 (m, 3H), 1.52 (d, *J*=6.7 Hz, 3H), 1.70–1.80 (m, 2H), 3.22 (m, 1H), 3.94 (m, 1H), 4.03 (m, 1H), 4.04 (m, 1H), 4.11 (m, 1H), 4.71–4.75 (m, 1H); ^{13}C NMR (100 MHz) δ 9.5 (q), 23.4 (q), 26.2 (t), 51.9 (d), 57.0 (d), 68.1 (t), 83.6 (d), 92.0 (d).

5.7.14.4. 4(S)-(1(S*)-Chloroethyl)-2(R*)-ethyl-3(S*)-nitrotetrahydrofuran (**20Cc**).* Colorless oil as a partially separable mixture with **17Cc–19Cc**. R_f=0.34, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 0.96 (m, 3H), 1.49 (d, *J*=6.4 Hz, 3H), 1.70–1.80 (m, 2H), 3.36 (m, 1H), 3.73 (t, *J*=8.6 Hz, 1H), 3.90 (m, 1H), 4.28 (m, 1H), 4.30 (m, 1H), 4.98 (dd, *J*=6.1, 3.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 10.5 (q), 23.5 (q), 26.0 (t), 53.4 (d), 57.2 (d), 68.6 (t), 85.6 (d), 91.3 (d).

*5.7.15. 4-(1-Chloro-1-methylethyl)-2-ethyl-3-nitrotetrahydrofurans (**17Dc**, **19Dc**).* Purified by flash chromatography hexane/EtOAc, gradient 10:1 to 5:1. Yield 121 mg (50%) as a 1.7:1 mixture of **17Dc** and **19Dc**. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 2972, 2935, 2897, 1552, 1461, 1375, 1365, 1219, 1131, 1101, 1057, 1030, 887, 779 cm^{-1}; MS (CI) *m/z* 239 ($[M+NH_4]^+$, 1), 203 (13), 189 (8), 156 (19), 139 (100), 137 (45); Anal. Calcd for $C_9H_{16}ClNO_3$ (221.68): C 48.76 H 7.27 N 6.32. Found: C 48.81 H 7.27 N 6.09.

5.7.15.1. 4(R)-(1-Chloro-1-methylethyl)-2(R*)-ethyl-3(S*)-nitrotetrahydrofuran (**17Dc**).* Colorless solid. Mp 53 °C; R_f=0.30, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 0.95 (t, *J*=7.2 Hz, 3H), 1.49 (sext, *J*=7.2 Hz, 1H), 1.59 (m, 1H), 1.61 (s, 3H), 1.64 (s, 3H), 2.80 (dt, *J*=11.2, 6.9 Hz, 1H), 4.20 (dd, *J*=8.3, 6.9 Hz, 1H), 4.24 (dd, *J*=11.2, 8.3 Hz, 1H), 4.39 (dt, *J*=7.2, 1.5 Hz, 1H), 4.81 (dd, *J*=6.9, 1.5 Hz, 1H); ^{13}C NMR (100 MHz) δ 9.8 (q), 28.5 (t), 30.6 (q), 31.8 (q), 56.8 (d), 65.9 (s), 68.3 (t), 85.7 (d), 89.7 (d).

5.7.15.2. 4(S)-(1-Chloro-1-methylethyl)-2(R*)-ethyl-3(S*)-nitrotetrahydrofuran (**19Dc**).* Colorless oil. This compound could not be purified to homogeneity. R_f=0.35, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 0.98 (t, *J*=7.4 Hz, 3H), 1.51 (s, 3H), 1.56 (s, 3H), 1.73 (m, 2H), 3.29 (dt, *J*=8.4, 5.9 Hz, 1H), 3.97 (dd, *J*=9.4, 5.9 Hz, 1H), 4.05 (m, 1H), 4.13 (m, 1H), 4.73 (t, *J*=5.9 Hz, 1H); ^{13}C NMR (100 MHz) δ 9.5 (q), 25.8 (t), 30.8 (q), 31.2 (q), 57.4 (d), 68.9 (t), 69.3 (s), 85.9 (d), 91.4 (d).

*5.7.16. 4-(1-Chloro-1-methylethyl)-2-isopropyl-3-nitrotetrahydrofurans (**17Dd**, **19Dd**).* Purified by flash chromatography hexane/Et_2O 5:1. For yields and ratios, see Table 5. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3039, 2985, 2959, 2901, 1551, 1467, 1377, 1223, 1131, 1103, 1053, 1024, 901, 781 cm^{-1}; MS (EI) *m/z* 194/192 (1/3), 148/146 (3/8), 111 (100), 71 (14), 69 (62), 68 (18), 55 (10); Anal. Calcd for $C_{10}H_{18}ClNO_3$ (235.71): C 50.96 H 7.70 N 5.94. Found: C 51.05 H 7.70 N 6.11.

5.7.16.1. 4(R)-(1-Chloro-1-methylethyl)-2(R*)-isopropyl-3(S*)-nitrotetrahydrofuran (**17Dd**).* Colorless solid. Mp 57 °C; R_f=0.53, hexane/Et_2O 5:1; ^1H NMR (400 MHz) δ 0.94 (d, *J*=7.0 Hz, 3H), 0.99 (d, *J*=7.0 Hz, 3H), 1.64 (s, 3H), 1.68 (s, 3H), 1.77 (oct, *J*=7.0 Hz, 1H), 2.75 (dt, *J*=11.4, 7.1 Hz, 1H), 4.214 (dd, *J*=8.4, 7.1 Hz, 1H), 4.216 (dd, *J*=7.0, 2.2 Hz, 1H), 4.26 (dd, *J*=11.4, 8.4 Hz, 1H), 4.91 (dd, *J*=7.1, 2.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 17.8 (q), 18.0 (q), 30.4 (q), 31.4 (q), 32.1 (d), 57.3 (d), 65.7 (s), 68.0 (t), 88.1 (d), 89.6 (d).

5.7.16.2. 4(S)-(1-Chloro-1-methylethyl)-2(R*)-isopropyl-3(S*)-nitrotetrahydrofuran (**19Dd**).* Colorless oil as a partially separable mixture with **17Dd**. R_f=0.62, hexane/Et_2O 5:1; ^1H NMR (400 MHz) δ 1.00 (d, *J*=7.0 Hz, 3H), 1.01 (d, *J*=7.0 Hz, 3H), 1.56 (s, 3H), 1.60 (s, 3H), 1.97 (oct, *J*=7.0 Hz, 1H), 3.27 (dt, *J*=8.4, 6.1 Hz, 1H), 3.92 (dd, *J*=7.0, 6.1 Hz, 1H), 3.99 (dd, *J*=9.2, 6.1 Hz, 1H), 4.17 (dd, *J*=9.2, 8.4 Hz, 1H), 4.90 (t, *J*=6.1 Hz, 1H); ^{13}C NMR (100 MHz) δ 18.0 (q), 18.3 (q), 30.8 (q), 31.0 (q), 31.2 (d), 58.3 (d), 69.0 (t), 69.3 (s), 90.0 (d), 90.2 (d).

*5.7.17. 3-(1-Chloro-1-methylethyl)-4-nitro-1-oxaspiro[4.5]decanes (**17De**, **19De**).* Purified by flash chromatography hexane/EtOAc, gradient 10:1 to 5:1. Yield 89 mg (34%) as a 2.5:1 mixture of **17De** and **19De**. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 2992, 2970, 2933, 2897, 2857, 1551, 1360, 1131, 1045, 829, 776 cm^{-1}; UV ($CHCl_3$, 0.111×10^{-3} M) λ_{max} 239, 232 nm; MS (EI) *m/z* 217/215 (10/36), 179 (35), 177 (10), 161 (34), 149 (45), 145 (11), 139 (17), 137 (20), 123 (19), 121 (20), 109 (21), 107 (23), 105 (14), 103 (15), 99 (25), 97 (75), 95 (77), 93 (38), 91 (20), 85 (10), 83 (35), 81 (70), 79 (39), 77 (30), 69 (100), 67 (45), 57 (12), 55 (55), 53 (18); MS (ESI) 286/284 ($[M+Na^+]$, 35/100); HRMS (ESI) calcd for $C_{12}H_{20}{}^{35}ClNNaO_3$ 284.1029, found 284.1026; Anal. Calcd for $C_{12}H_{20}ClNO_3$ (261.74): C 55.06 H 7.70 N 5.35. Found: C 55.45 H 7.79 N 5.37.

5.7.17.1. 3(R)-(1-Chloro-1-methylethyl)-4(S*)-nitro-1-oxaspiro[4.5]decane (**17De**).* Colorless solid. Mp 91 °C; R_f=0.44, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 1.34–1.80 (m, 10H), 1.61 (s, 3H), 1.65 (s, 3H), 3.28 (ddd, *J*=11.3, 8.4, 5.4 Hz, 1H), 4.19 (t, *J*=8.4 Hz, 1H), 4.38 (dd, *J*=11.3, 8.4 Hz, 1H), 4.95 (d, *J*=5.4 Hz, 1H); ^{13}C NMR (100 MHz) δ 22.9 (t), 23.0 (t), 25.2 (t), 30.9 (q), 31.4 (q), 32.3 (t), 37.8 (t), 56.0 (d), 66.9 (s), 67.3 (t), 85.5 (s), 92.6 (d).

5.7.17.2. 3(S)-(1-Chloro-1-methylethyl)-4(S*)-nitro-1-oxaspiro[4.5]decane (**19De**).* Colorless oil. R_f=0.62, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 1.18–1.35 (m, 2H), 1.54 (s, 3H), 1.56 (s, 3H), 1.57–1.77 (m, 7H), 1.90–1.99 (m, 1H), 3.46 (dt, *J*=8.6, 6.9 Hz, 1H), 3.85 (dd, *J*=9.1, 8.6 Hz, 1H), 4.18 (t, *J*=8.6 Hz, 1H), 4.82 (d, *J*=6.9 Hz, 1H); ^{13}C NMR (100 MHz) δ 21.8 (t), 22.1 (t), 25.0 (t), 30.6 (t), 34.5 (t), 31.3 (q), 31.7 (q), 56.2 (d), 66.1 (s), 69.0 (t), 84.6 (s), 96.1 (d).

5.8. SET-oxidation/radical 5-*exo* cyclization of 3Aa

At −78 °C under N_2, *n*-BuLi (0.246 mL, 0.394 mmol, 1.6 M solution in hexane) was added via syringe to a stirred solution of **3Aa** (68 mg, 0.328 mmol) in 4 mL dry DME or THF. After 15 min the reaction mixture was warmed to 0 °C and anhydrous $CuCl_2$ (119 mg, 0.89 mmol) was added at the same temperature in one portion with vigorous stirring. After 30 min, the reaction was quenched with one drop of saturated NH_4Cl solution. The inhomogeneous mixture was diluted with 10 mL diethyl ether and filtered through a pad of silica gel. The solution was evaporated in vacuum and the crude product was purified by flash column chromatography (hexane/EtOAc, gradient 10:1 to 2:1). Yield 81% as a single diastereomer.

5.9. Epimerization of 17Aa by lithium allyloxide

To **1A** (19.2 mg, 0.33 mmol) in 3 mL anhydrous THF was added *n*-BuLi (0.21 mL, 0.33 mmol, 1.6 M solution in hexane) via syringe at −78 °C. The mixture was stirred for 15 min and warmed to 0 °C. Diastereomerically pure **17Aa** (76 mg, 0.33 mmol) was added and the mixture was stirred for 25 min. The reaction mixture was quenched with two drops of a saturated NH_4Cl solution, diluted with Et_2O, filtered through a pad of silica gel, and concentrated under reduced pressure. The resulting oil (70 mg) consisted of a 1:2.5 mixture of **17Aa**/**21Aa**.

5.10. 4-(Bromomethyl)-3-nitro-2-phenyltetrahydrofurans (23Aa, 25Aa)

Purified by flash chromatography hexane/EtOAc, gradient 10:1 to 5:1. For yields and ratios, see Table 6. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3064, 3031, 2969, 2948, 2885, 1547, 1451, 1361, 1295, 1229, 1114, 1089, 1067, 933, 737, 698 cm^{-1}; MS (EI) *m*/*z* 240/238 (4/5), 145 (100), 117 (15), 105 (18), 91 (12), 77 (19); Anal. Calcd for $C_{11}H_{12}BrNO_3$ (286.12): C 46.18 H 4.23 N 4.90. Found: C 46.36 H 4.12 N 4.80.

5.10.1. 4(R)-(Bromomethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**23Aa**).* Colorless oil. R_f=0.50, hexane/EtOAc 5:1; ^1H NMR (400 MHz) δ 3.12 (m, 1H), 3.33 (dd, *J*=10.5, 8.5 Hz, 1H), 3.45 (dd, *J*=10.5, 7.2 Hz, 1H), 4.07 (dd, *J*=10.4, 8.7 Hz, 1H), 4.51 (dd, *J*=8.7, 7.5 Hz, 1H), 5.03 (dd, *J*=7.3, 3.1 Hz, 1H), 5.55 (d, *J*=3.1 Hz, 1H), 7.30–7.41 (m, 5H); ^{13}C NMR (100 MHz) δ 25.6 (t), 45.7 (d), 72.1 (t), 85.1 (d), 93.8 (d), 125.2 (d), 128.7 (d), 128.9 (d), 138.5 (s).

5.10.2. 4(R)-(Bromomethyl)-3(R*)-nitro-2(R*)-phenyltetrahydrofuran (**25Aa**).* Colorless oil. R_f=0.62, hexane/EtOAc 10:1; ^1H NMR (400 MHz) δ 3.50 (dd, 10.6, 6.4 Hz, 1H), 3.60 (dd, 10.6, 5.6 Hz, 1H), 3.65 (m, 1H), 3.80 (dd, *J*=9.1, 7.2 Hz, 1H), 4.63 (dd, *J*=9.1, 7.8 Hz, 1H), 5.23 (m, 2H), 7.30–7.37 (m, 5H); ^{13}C NMR (100 MHz) δ 31.1 (t), 46.2 (d), 71.4 (t), 83.9 (d), 93.9 (d), 126.0 (d), 128.5 (d), 129.0 (d), 133.8 (s).

*5.10.3. 1-Allyloxy-2-bromo-2-nitro-1-phenylethane (**9Aa**).* Purified by flash chromatography hexane/EtOAc, gradient 10:1 to 5:1. Pale yellow unstable oil. For yields and ratios, see Table 6. R_f=0.59, hexane/EtOAc 5:1; IR (neat) 3068, 3032, 3017, 2909, 2869, 1564, 1454, 1351, 1061, 987, 929 cm^{-1}; GC–MS (EI) *m*/*z* 183/181 (25/27), 147 (100), 119 (12), 105 (61), 103 (20), 91 (53), 77 (32), 51 (11); Anal. Calcd for $C_{11}H_{12}BrNO_3$ (286.12): C 46.18 H 4.23 N 4.90. Found: C 46.78 H 4.22 N 4.65. Despite many attempts, a better matching combustion analysis was not obtained for this unstable compound. *Diastereomer* **1**: ^1H NMR (400 MHz) δ 3.88 (ddt, *J*=12.7, 6.5, 1.3 Hz, 1H), 4.09 (ddt, *J*=12.7, 5.1, 1.5 Hz, 1H), 5.03 (d, *J*=6.4 Hz, 1H), 5.23 (dq, *J*=10.4, 1.5 Hz, 1H), 5.26 (dq, *J*=17.1, 1.3 Hz, 1H), 5.87 (dddd, *J*=17.1, 10.4, 6.5, 5.1 Hz, 1H), 6.01 (d, *J*=6.4 Hz, 1H), 7.35–7.45 (m, 5H); ^{13}C NMR (100 MHz) δ 70.5 (t), 80.9 (d), 83.9 (d), 118.6 (t), 127.6 (d), 129.0 (d), 129.7 (d), 133.1 (d), 134.5 (s). *Diastereomer* **2**: ^1H NMR (400 MHz) δ 3.79 (ddt, *J*=12.6, 6.5, 1.3 Hz, 1H), 3.96 (ddt, *J*=12.6, 5.1, 1.5 Hz, 1H), 4.96 (d, *J*=9.5 Hz, 1H), 5.17 (dq, *J*=14.2, 1.5 Hz, 1H), 5.18 (dq, *J*=10.8, 1.3 Hz, 1H), 5.75 (dddd, *J*=14.2, 10.8, 6.5, 5.1 Hz, 1H), 5.88 (d, *J*=9.5 Hz, 1H), 7.40–7.42 (m, 5H); ^{13}C NMR (100 MHz) δ 70.7 (t), 80.1 (d), 82.0 (d), 118.4 (t), 128.4 (d), 128.8 (d), 129.8 (d), 133.0 (d), 134.0 (s).

5.11. 4-(1-Bromo-1-methylethyl)-3-nitro-2-phenyltetrahydrofurans (23Da, 24Da)

Purified by flash chromatography hexane/Et_2O 5:1. For yields and ratios, see Table 6. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3064, 3031, 2992, 2975, 2902, 1545, 1487, 1376, 1299, 1218, 1129, 1101, 1071, 1057, 934, 732, 698 cm^{-1}; MS (EI) *m*/*z* 315/313 (M^+, 1/1), 268/266 (4/4), 187 (8), 186 (10), 146 (62), 145 (100), 128 (30), 117 (50), 115 (26), 107 (18), 105 (64), 91 (35), 79 (16), 77 (39), 69 (15), 51 (10); Anal. Calcd for $C_{13}H_{16}BrNO_3$ (314.18): C 49.70 H 5.13 N 4.46. Found: C 49.85 H 5.11 N 4.32.

5.11.1. 4(R)-(1-Bromo-1-methylethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**23Da**).* Colorless solid. Mp 103 °C; R_f=0.41, hexane/Et_2O 5:1; ^1H NMR (400 MHz) δ 1.80 (s, 3H), 1.87 (s, 3H), 2.99 (ddd, *J*=11.5, 7.7, 6.1 Hz, 1H), 4.50 (dd, *J*=11.5, 8.3 Hz, 1H), 4.58 (dd, *J*=8.3, 7.7 Hz, 1H), 5.02 (dd, *J*=6.1, 1.3 Hz, 1H), 5.63 (s, 1H), 7.30–7.44 (m, 5H); ^{13}C NMR (100 MHz) δ=31.6 (q), 33.4 (q), 56.3 (d), 59.8 (s), 69.8 (t), 85.3 (d), 92.4 (d), 125.1 (d), 128.6 (d), 129.0 (d), 139.3 (s).

5.11.2. 4(S)-(1-Bromo-1-methylethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**24Da**).* Colorless oil. R_f=0.35, hexane/Et_2O 5:1; ^1H NMR (300 MHz) δ 1.75 (s, 3H), 1.77 (s, 3H), 3.37 (ddd, *J*=8.5, 6.2, 5.0 Hz, 1H), 4.28 (dd, *J*=9.5, 5.0 Hz, 1H), 4.36 (dd, *J*=9.5, 8.5 Hz, 1H), 4.97 (dd, *J*=7.2, 6.2 Hz, 1H), 5.17 (d, *J*=7.2 Hz, 1H), 7.36–7.41 (m, 5H); ^{13}C NMR (75 MHz) δ 32.3 (q), 32.6 (q), 58.4 (d), 65.3 (s), 70.8 (t), 86.1 (d), 94.8 (d), 125.9 (d), 128.9 (d), 129.1 (d), 137.0 (s).

*5.11.3. 2-Bromo-2-nitro-1-phenyl-1-(prenyloxy)ethane (**9Da**).* Purified by flash chromatography hexane/Et_2O 5:1. Pale yellow oil. For yields and ratios, see Table 6. R_f=0.53, hexane/Et_2O 5:1; IR (neat) 3065, 3032, 2975, 2913, 2878, 1565, 1453, 1352, 1203, 1059, 1026, 981, 944, 905, 764, 713, 697 cm^{-1}; GC–MS (EI) *m*/*z* 183/181 (55/57), 150 (55), 117 (15), 107 (22), 105 (24), 103 (25), 91 (13), 85 (90), 77 (60), 69 (100), 57 (30), 53 (12), 51 (20); Anal. Calcd for $C_{13}H_{16}BrNO_3$ (314.18): C 49.70 H 5.13 N 4.46. Found: C 49.79 H 5.25 N 4.34. *Diastereomer* **1**: ^1H NMR (400 MHz) δ 1.54 (d, *J*=0.8 Hz, 3H), 1.75 (d, *J*=0.4 Hz, 3H), 3.92 (dd, *J*=11.6, 8.2 Hz, 1H), 4.02 (dd, *J*=11.6, 6.5 Hz, 1H), 4.98 (d, *J*=6.5 Hz, 1H), 5.31 (m, 1H), 5.99 (d, *J*=6.5 Hz, 1H), 7.35–7.42 (m, 5H); ^{13}C NMR (100 MHz) δ 18.0 (q), 25.8 (q), 65.9 (t), 80.6 (d), 84.0 (d), 119.4 (d), 127.6 (d), 128.9 (d), 129.60 (d), 134.8 (s), 139.4 (s). *Diastereomer* **2**: ^1H NMR (400 MHz) δ 1.49 (d, *J*=0.7 Hz, 3H), 1.72 (s, 3H), 3.83 (dd, *J*=11.5, 7.7 Hz, 1H), 3.90 (ddd, *J*=11.5, 6.6, 0.7 Hz, 1H), 4.92 (d, *J*=9.6 Hz, 1H), 5.20 (m, 1H), 5.85 (d, *J*=9.6 Hz, 1H), 7.40–7.42 (m, 5H); ^{13}C NMR (100 MHz) δ 17.9 (q), 25.7 (q), 66.2 (t), 80.2 (d), 81.7 (d), 119.3 (d), 128.4 (d), 128.8 (d), 129.65 (d), 134.5 (s), 139.3 (s).

5.12. (*E*)- and (*Z*)-4-(Chloromethylene)-3(*S**)-nitro-2(*R**)-phenyltetrahydrofuran (26h)

Purified by flash chromatography hexane/Et_2O 5:1. The double bond geometry was determined by a NOESY experiment, see the Supplementary data. Colorless oil as a partly separable 2.8:1 *E*/*Z*-mixture, yield 67 mg (28%). $R_{f(Z)}$=0.60, hexane/Et_2O 5:1; $R_{f(E)}$=0.50, hexane/Et_2O 5:1; IR (neat) 3075, 3034, 2860, 1671, 1552, 1455, 1364, 1335, 1310, 1085, 1061, 1026, 921, 827, 750, 696 cm^{-1}; UV ($CHCl_3$,

0.42×10^{-3} M) λ_{max} 240 nm; MS (EI) *m/z* 241/239 (M^+, 1), 194/192 (35/95), 157 (58), 133 (12), 129 (100), 128 (60), 127 (30), 105 (20), 91 (20), 77 (50), 63 (14), 51 (50); Anal. Calcd for $C_{11}H_{10}ClNO_3$ (239.65): C 55.13 H 4.21 N 5.84. Found: C 55.02 H 4.23 N 5.83. *(E)-Isomer*: ^{1}H NMR (400 MHz) δ 4.73 (m, 2H), 5.41 (d, *J*=4.5 Hz, 1H), 5.52 (ddt, *J*=4.5, 1.2, 0.4 Hz, 1H), 6.47 (q, *J*=1.9 Hz, 1H), 7.34–7.44 (m, 5H); ^{13}C NMR (100 MHz) δ 70.5 (t), 85.7 (d), 91.5 (d), 119.0 (d), 125.6 (d), 128.98 (d), 129.00 (d), 135.9 (s), 137.4 (s). *(Z)-Isomer*: ^{1}H NMR (200 MHz) δ 4.79 (dd, *J*=2.7, 1.6 Hz, 1H), 4.83 (d, *J*=2.7 Hz, 1H), 5.34 (m, 1H), 5.68 (d, *J*=4.0 Hz, 1H), 6.54 (dt, *J*=2.6, 1.5 Hz, 1H), 7.31–7.43 (m, 5H); ^{13}C NMR (50 MHz) δ 71.6 (t), 84.8 (d), 91.4 (d), 118.9 (d), 125.5 (d), 129.0 (d, 3C), 135.8 (s), 137.0 (s).

5.13. (*E*)- and (*Z*)-4-(Chlorobenzylidene)-3(*S**)-nitro-2(*R**)-phenyltetrahydrofuran (26i)

Purified by flash chromatography hexane/Et_2O 5:1. The double bond geometry was determined by a NOESY experiment, see the Supplementary data. Colorless oils, as a partly separable *E*/*Z*-mixture, for yields and ratios, see Scheme 9. $R_{f(Z)}$=0.52, hexane/Et_2O 5:1; $R_{f(E)}$=0.44, hexane/Et_2O 5:1; IR (neat) 3063, 3032, 2909, 2863, 1672, 1551, 1446, 1358, 1220, 1086, 1063, 1027, 928, 895, 731, 694 cm^{-1}; UV ($CHCl_3$, 0.785×10^{-4} M) λ_{max} 245 nm; MS (ESI) *m/z* 338 ($[M+Na]^+$, 100); Anal. Calcd for $C_{17}H_{14}ClNO_3$ (315.75): C 64.67 H 4.47 N 4.44. Found: C 64.65 H 4.55 N 4.57. *(Z)-Isomer*: MS (EI) *m/z* 271/269 (9/30), 233 (12), 205 (35), 129 (25), 105 (100), 91 (20), 77 (70), 51 (25), 50 (13); ^{1}H NMR (400 MHz) δ 4.96 (dd, *J*=14.3, 1.0 Hz, 1H), 4.99 (dt, *J*=14.3, 0.6 Hz, 1H), 5.30 (ddd, *J*=2.5, 1.0, 0.6 Hz, 1H), 5.58 (d, *J*=2.5 Hz, 1H), 7.20–7.45 (m, 10H); ^{13}C NMR (100 MHz) δ 71.9 (t), 86.9 (d), 92.3 (d), 125.3 (d), 127.6 (d), 128.8 (d), 128.89 (d), 129.0 (d), 130.0 (d), 131.1 (s), 134.2 (s), 136.2 (s), 137.5 (s). *(E)-Isomer*: MS (EI) *m/z* 271/269 (6/20), 205 (23), 202 (12), 129 (13), 105 (100), 91 (10), 77 (30), 69 (15), 51 (10); ^{1}H NMR (400 MHz) δ 4.66 (dd, *J*=13.0, 0.6 Hz, 1H), 4.97 (dd, *J*=13.0, 1.6 Hz, 1H), 5.41 (d, *J*=4.7 Hz, 1H), 5.70 (dd, *J*=4.7, 1.6 Hz, 1H), 7.37–7.42 (m, 5H), 7.42–7.44 (m, 5H); ^{13}C NMR (100 MHz) δ 71.0 (t), 85.5 (d), 94.3 (d), 125.7 (d), 127.8 (d), 128.6 (d), 128.95 (d, 3C), 130.1 (d), 131.5 (s), 133.5 (s), 136.0 (s), 137.6 (s).

5.14. 4-(1-Hydroxy-1-methylethyl)-3(*S**)-nitro-2(*R**)-phenyltetrahydrofurans 27 and 28

At −78 °C under N_2, *n*-BuLi (0.937 mL, 1.5 mmol, 1.6 M in hexane) was added via syringe to a stirred solution of **1D** (129 mg, 1.5 mmol) in 10 mL dry DME or THF. After 15 min, a solution of **2a** (149 mg, 1.0 mmol) in 1 mL dry DME or THF was added. The reaction mixture was warmed to 0 °C after 10 min and maintained at this temperature until completion (TLC monitoring). A strong stream of dry O_2 was bubbled through the solution and anhydrous $CuCl_2$ (268.9 mg, 2.0 mmol) was added simultaneously in small portions with vigorous stirring. After 30 min, the reaction was quenched with two drops of saturated NH_4Cl solution. The inhomogeneous green-brown mixture was diluted with 30 mL Et_2O and filtered through a pad of silica gel. The solution was concentrated under reduced pressure and the crude product was purified by flash column chromatography (hexane/EtOAc, gradient 10:1 to 2:1). For yields and ratios, see Scheme 10. The following analyses were performed on the diastereomeric mixture before further separation. R_f=0.15, hexane/EtOAc 10:1; IR (neat) 3434, 2999, 2972, 2933, 2910, 2881, 1549, 1476, 1381, 1335, 1182, 1101, 1063, 1045, 930 cm^{-1}; MS (CI) *m/z* 269 ($[M+NH_4]^+$, 100), 222 (45), 205 (39), 189 (16), 162 (85), 160 (10); Anal. Calcd for $C_{13}H_{17}NO_4$ (251.28): C 62.14 H 6.82 N 5.57. Found: C 61.99 H 6.94 N 5.59.

5.14.1. 4(R)-(1-Hydroxy-1-methylethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**27**).* Colorless solid. Mp 113 °C; ^{1}H NMR (400 MHz) δ 1.27 (s, 3H), 1.38 (s, 3H), 1.68 (br s, 1H), 2.58 (dt, *J*=9.8, 6.2 Hz, 1H), 4.43 (d, *J*=9.8 Hz, 2H), 5.00 (dd, *J*=6.2, 1.3 Hz, 1H), 5.59 (s, 1H), 7.26–7.41 (m, 5H); ^{13}C NMR (100 MHz) δ 28.7 (q), 30.2 (q), 53.3 (d), 68.5 (t), 69.15 (s), 84.9 (d), 92.1 (d), 125.1 (d), 128.3 (d), 128.78 (d), 139.7 (s).

5.14.2. 4(S)-(1-Hydroxy-1-methylethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**28**).* Colorless oil. ^{1}H NMR (200 MHz) δ 1.22 (s, 3H), 1.24 (s, 3H), 1.90 (br s, 1H), 3.12 (dt, *J*=8.3, 5.6 Hz, 1H), 4.17 (dd, *J*=9.4, 5.6 Hz, 1H), 4.26 (dd, *J*=9.4, 8.3 Hz, 1H), 4.96 (dd, *J*=7.0, 5.6 Hz, 1H), 5.16 (d, *J*=7.0 Hz, 1H), 7.28–7.40 (m, 5H); ^{13}C NMR (50 MHz) δ 27.5 (q), 28.3 (q), 56.3 (d), 69.24 (t), 70.7 (s), 85.7 (d), 93.1 (d), 125.8 (d), 128.82 (d, 3C), 137.6 (s).

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Supplementary data

Experimental procedures, analytical characterization and configuration assignment of all new compounds. Copies of ^{1}H and ^{13}C NMR spectra. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.12.010.

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