Radical Addition-Initiated Domino Reactions of Conjugated Oxime Ethers

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The application of conjugated oxime ethers to the synthesis of complex chemical scaffolds using domino radical reactions has been described in detail. The triethylborane-mediated hydroxysulfenylation reaction allows for the regioselective construction of a carbon–sulfur bond and a carbon–oxygen bond in a single operation for the formation of β-hydroxy sulfides. This reaction proceeds via a radical pathway involving regioselective thiol addition and the subsequent trapping of the resulting α-imino radical with O₂, where the imino group enhances the stability of the intermediate radical. Hydroxyalkylation reactions that occur via a carbon radical addition reaction followed by the hydroxylation of the resulting N-borylenamine with O₂ have also been developed. We investigated sequential radical addition aldol-type reactions in detail to explore the novel domino reactions that occur via the generation of N-borylenamine. The radical reaction of a conjugated oxime ether with triethylborane in the presence of an aldehyde affords γ-butyrolactone via sequential processes including ethyl radical addition, the generation of N-borylenamine, an aldol-type reaction with an aldehyde, and a lactonization reaction. A novel domino reaction has also been developed involving the [3,3]-sigmatropic rearrangement of N-boryl-N-phenoxyenamine. The triethylborane-mediated domino reactions of O-phenyl-conjugated oxime ethers afforded the corresponding benzofuro[2,3-b]pyrrol-2-ones via a radical addition/[3,3]-sigmatropic rearrangement/cyclization/lactamization cascade.

Key words  domino reaction; radical reaction; oxime ether; hydroxylation; aldol reaction; [3,3]-sigmatropic rearrangement

1. Introduction

Domino reactions are transformations involving two or more bond-forming reactions in a single operation, where the initial transformation in the domino process provides a functionality that can undergo subsequent transformations to produce increasingly elaborate structures. Domino reactions can therefore be used to construct complex molecules from simple substrates in a straightforward, efficient, elegant manner without the need to isolate any of the individual intermediates.1,2 Furthermore, domino reactions are generally considered to be much more environmentally friendly than traditional single-step batch reactions because they require fewer reagents and solvents and generate less waste. Based on these factors, there has been considerable interest in the design of new type of domino reaction, although work in this area can be challenging.

As part of our ongoing research on the development of novel domino reactions,3–9 we have recently focused our attention on the radical reactions of conjugated imines. Conjugated imines can be used as versatile building blocks for the efficient construction of nitrogen-containing heterocycles, as well as amino acids and amines, because they contain several reactive sites.10,11 Although conjugated imines have been used as electrophiles and nucleophiles in inter- and intramolecular addition reactions, as well as heterodienes in cycloaddition reactions, reports pertaining to the use of conjugated imines in radical reactions are few.12 It was envisioned that the versatility of conjugated imines would allow them to be used as substrates in radical-mediated domino reactions. Of the various different types of conjugated imine available, we selected conjugated oxime ether. It was thought that the addition of a radical species (Z·) to a conjugated oxime ether would proceed smoothly to generate a stable radical intermediate, which could undergo further transformations in situ (Chart 1). In this review, we present a comprehensive overview of our studies on domino radical reactions involving the generation of an α-alkoxyimino radical or an N-alkoxyaminyl radical.

2. Sequential Radical Addition and Aerobic Hydroxylation Reaction

2.1 Hydroxysulfenylation16 Free radical-mediated hydroxysulfenylation reactions, which are traditionally also known as thiol-oxygen cooxidation reactions, were originally developed as attractive routes for the construction of valuable functionalized products.17–22 The overall scope of hydroxysulfenylation reactions, however, has been limited by their requirement for electron-rich olefins as radical acceptors, and much less is known about the hydroxysulfenylation reactions...
of electron-deficient olefins, most likely because the competitive nonradical Michael addition of the thiol would impede the radical process. With this in mind, we anticipated that the scope of the hydroxysulfenylation reaction could be improved considerably by enhancing the stability of the intermediate radical and reducing the ability of the Michael acceptor to participate in an ionic process. It was envisioned that regioselective addition of a thiyl radical to the activated double bond of 1 would lead to the exclusive formation of the α-imino radical intermediate A, which would be stabilized through a resonance interaction with the imine moiety as well as homocoujngative interaction between the p-orbital on the trigonal carbon and the unoccupied 3d orbitals on the sulfur atom (Chart 2). The α-imino radical A could then be trapped with molecular oxygen to afford the corresponding alcohol 2.

We initially investigated the hydroxysulfenylation of conjugated oxime ether 3 with thiophenol in the presence of triethylborane as a radical initiator under an atmosphere of dry air (Chart 3, Eq. 1). The reaction proceeded as anticipated to give the β-hydroxy sulfide 4 in 85% yield, without the formation of the simple Michael adduct. In marked contrast, the reaction of the cyclohexenone (5) under the same conditions afforded the corresponding Michael adduct 6 exclusively (Chart 3, Eq. 2). These results clearly indicated that the ionic Michael addition reaction could be completely suppressed by converting the ketone to the corresponding oxime ether.

Possible reaction pathways for these transformations are shown in Charts 4 and 5. Triethylborane reacts immediately with thiophenol to give PhSBEt₂ (Chart 4), which would act as a radical initiator by reacting with triplet oxygen to generate a thiyl radical (Chart 4). Regioselective addition of the thiyl radical to the conjugated oxime ether 3 would give the α-imino radical.

Masafumi Ueda was born in Kobe in 1976 and graduated from Kobe Pharmaceutical University in 1999 under the supervision of Professor Takeaki Naito. In 2000, he was appointed research assistant at Kobe Pharmaceutical University in the research group of Profs. Takeaki Naito and Okiko Miyata and was subsequently promoted to Assistant Professor in 2001. After obtaining his Ph.D. from Osaka University in 2006, he joined the group of Professor Peter Wipf at Pittsburgh University as a postdoctoral associate and returned to Kobe Pharmaceutical University to continue his research in 2008. He became a lecturer at Kobe Pharmaceutical University in 2009 and was then promoted to Associate Professor in 2013. He has received several awards, including the Pharmaceutical Society of Japan Kinki Branch Award for Young Scientists in 2004, the Fuji Photo Film Award in Synthetic Organic Chemistry, Japan, in 2005, the Mitsubishi Chemical Award in Synthetic Organic Chemistry, Japan, in 2012, and the Pharmaceutical Society of Japan Award for Young Scientists in 2014. His research interests include the development of new synthetic methodologies using radical chemistry and transition metal catalysis, as well as the design and synthesis of bioactive compounds with potential pharmaceutical applications.
Radical B would then be trapped with molecular oxygen to give peroxyradical C, which would extract an H radical from thiophenol to afford hydroperoxide D with the concomitant formation of a thiyl radical. Subsequent reduction of D with thiophenol would give the desired \( \beta \)-hydroxy sulfide 4 and diphenyl disulfide \(^{27,28}\) (Chart 5).

We subsequently proceeded to investigate the reactivity of conjugated oxime ether 7 bearing an ester moiety,\(^{29}\) because we believed that this compound would exhibit excellent reactivity toward the thiyl radical (Chart 6). Initial evaluation of this substrate revealed that the ester group of 7 did not affect the regioselectivity of the reaction, with the addition of the thiyl radical occurring exclusively at the \( \beta \)-position of the oxime ether group to give product 8a in 75% yield. Several other thiols were also investigated in the reaction, including substituted aryl mercaptans and an aliphatic thiol, which all reacted smoothly to give the desired products.

This hydroxysulfenylation method was also extended to a series of cyclic and acyclic conjugated oxime ethers 9–13 (Table 1). Good diastereoselectivity was observed with substrate 9 bearing Oppolzer’s camphorsultam, which gave the chiral \( \beta \)-hydroxy sulfide 14 in 70% yield\(^{30–34}\) (Table 1, entry 1). The acyclic ketoxime ether 10 also reacted smoothly to afford the desired product with high stereoselectivity (Table 1, entry 2). The application of the hydroxysulfenylation reaction conditions to substrate 12 gave the \( \beta \)-hydroxy sulfide 17 with low trans/cis selectivity (Table 1, entry 4). In contrast, substrate 13 gave \( \beta \)-hydroxy sulfide 18 as a single diastereomer under the same conditions (Table 1, entry 5). The reaction is therefore characterized by its broad scope and experimental simplicity, and the fact that it allows for the regio- and stereoselective introduction of a \( \beta \)-hydroxy sulfide.

### Chart 5. Proposed Hydroxysulfenylation Reaction Pathway

![Chart 5. Proposed Hydroxysulfenylation Reaction Pathway](image)

### Chart 6. Hydroxysulfenylation Reaction of Conjugated Oxime Ether 7

![Chart 6. Hydroxysulfenylation Reaction of Conjugated Oxime Ether 7](image)

### Table 1. Generality of Hydroxysulfenylation Reaction

| Entry | Substrate | Product | Yield (%) | Stereoselectivity |
|-------|-----------|---------|-----------|-------------------|
| 1     | 7         | 8a      | 75%       | anti: syn = 10:1, >10:1 dr |
| 2     | 7         | 8b      | 78%       | anti: syn = 20:1  |
| 3     | 7         | 8c      | 63%       | trans: cis = 10:1 |
| 4     | 7         | 8d      | 58%       | trans: cis = 3:2  |
| 5     | 7         | 8e      | 58%       | trans: cis = >20:1|
oselective construction of carbon–sulfur and carbon–oxygen bonds in a single operation, representing a highly efficient approach to the synthesis of β-hydroxy sulfides.

2.2 Hydroxyalkylation Free radical-mediated hydroxyalkylation reactions involving both carbon–carbon bond formation and oxygenation processes represent an attractive approach for the preparation of complex molecules. With this in mind, we investigated the triethylborane-induced hydroxyalkylation reaction of conjugated imines in the context of our previous study on hydroxysulfenylation. In the hydroxysulfenylation reaction, the intermediate radical generated by the addition of the thiyl radical to the carbon–carbon double bond is stabilized by a homoconjugative interaction between the carbon–centered radical and the sulfur atom, and this stabilization process is critical to the success of the transformation. It could therefore be difficult to conduct hydroxyalkylation reactions without such stabilizing functional groups.

To achieve an efficient oxygenation reaction, O₂ gas (3.6 equiv.) was bubbled into a mixture of conjugated oxime ether and triethylborane (3.0 equiv.) in toluene (Table 2, entry 1). As expected, the hydroxyalkylation reaction proceeded in a regioselective manner to give the desired product 19a in 78% yield as an E/Z mixture with anti/syn ratio of 2 : 1. This reaction proceeded smoothly in the absence of a reducing agent such as tributyltin hydride, because triethylborane plays an important role in the reduction of the hydroperoxy radical or hydroperoxide to the corresponding hydroxyl group. The importance of triethylborane to the reduction process was effectively demonstrated by the significant decrease in the chemical yield observed when the amount of triethylborane was reduced to 1.0 equiv. (Table 2, entry 2). The hydroxyalkylation reaction was also found to be strongly influenced by the solvent. For example, the reaction of 7 in CH₂Cl₂ produced the simple Michael-type product 20 in 92% yield (Table 2, entry 3). Interestingly, the use of trimethylaluminum (Me₃Al) as an additive promoted the hydroxyalkylation reaction, even in CH₂Cl₂, to give 19a in 69% yield (Table 2, entry 4).

A possible mechanism of this reaction is shown in Chart 7. The first step in this reaction would involve the regioselective addition of the alkyl radical to 7, followed by the trapping of the aminyl radical with triethylborane to generate the N-borylenamine. N-Borylenamine would then undergo either an ene-type reaction with molecular oxygen or an addition reaction involving the borylperoxy radical to form the borylperoxide. The reduction of G with triethylborane, followed by hydrolysis of the resulting borinate H, would give alcohol 19a. According to this mechanism, triethylborane would act as a multirole reagent inducing the radical initiation, radical termination, and reduction reactions.

Several experiments were conducted in support of our proposed reaction mechanism (Chart 8). In marked contrast to ester 7, the reaction of carboxylic acid 21 under the optimized hydroxyalkylation conditions gave the Michael-type adduct 22. This difference in the reactivity of the two substrates was attributed to the intermediate N-borylenamine, which would have been immediately protonated by the free carboxylic acid (Eq. 1). This observation supported the presence of borylenamine as a key intermediate in the proposed aerobic hydrox-
ylation mechanism. In addition, $^1$H-NMR and MS analysis of a mixture containing 7, triethylborane, and a catalytic amount of $O_2$ in $C_5D_4N$ indicated that compound 7 had been completely converted into N-borylenamine F (Eq. 2). The subsequent treatment of F with oxygen gas afforded the desired product 19a in 63% yield. An alternative mechanistic hypothesis was also proposed, where the hydroxyl group was derived from $H_2O$, but this suggestion was subsequently excluded based on an $H_2^{18}O$ labeling experiment, which led to the exclusive formation of unlabeled 19a$^{59}$ (Eq. 3).

$$\text{EtO}_{2}C_{6}H_{4}N=\text{O}^{\text{N}^{\text{Bn}}} \xrightarrow{\text{R}_{1}} \text{Et}_{2}B_{2}O_{3}, \text{Me}_{3}Al \xrightarrow{\text{CH}_{2}Cl_{2}, \text{rt}} \text{EtO}_{2}C_{6}H_{4}N=\text{O}^{\text{N}^{\text{Bn}}}$$

**Chart 9.** Generality of the Hydroxyalkylation Reaction

A range of alkyl iodides was examined as carbon radical precursors in the iodine atom-transfer reaction$^{59}$ (Chart 9, Eq. 1). The results of this examination revealed that only secondary and bulky tertiary alkyl radicals reacted well under the optimized conditions to afford the desired products 19b–d in moderate yields. The acrolein derivative 23 also reacted smoothly under similar conditions to give the secondary alcohol 24 in 60% yield (Eq. 2).

3. Sequential Radical Addition and Aldol-Type Reaction

Having confirmed that N-borylenamine was formed as an intermediate in the triethylborane-initiated addition of an alkyl radical to a conjugated oxime ether, we proceeded to investigate the reaction of the N-borylenamine intermediate with electrophiles. In an attempt to develop a highly efficient and stereoselective carbon–carbon bond-forming reaction involving a novel hybrid radical-ionic reaction process,$^{56-59}$ we investigated the domino radical addition aldol-type reaction of conjugated oxime ethers.

Prior to exploring the aldol-type reaction, we initially investigated the stereoselectivity resulting from the addition of a carbon radical to a chiral conjugated oxime ether 9 bearing camphorsultam.$^{60}$ The addition of an ethyl radical to 9 was performed in the presence of triethylborane in $CH_2Cl_2$ at room temperature (Chart 10). The reaction proceeded in a regio- and stereoselective manner to give the desired product 25 in 97% yield. The diastereomeric purity of 25 was determined to be greater than 95% de by $^1$H-NMR analysis. The stereochemical preference of this reaction can be rationalized as follows. With regard to the conformation of 9, the *anti* (sulfonyl and carbonyl groups) and *s-cis* (carbonyl group and C≡C bond) planar rotamer would be favored over the other rotamers. The alkyl radical would therefore prefer to add to the *si* (bottom) face, presumably because of steric interactions between the axial oxygen of the sulfonyl group.$^{61}$

It is noteworthy that the radical reaction gave the *α*-deuterated product 25-*d* when it was conducted in the presence of $D_2O$ (Chart 11). This result suggested that the N-borylenamine 1 could act as a nucleophile.

With these results in mind, we proceeded to investigate the sequential radical addition aldol-type reaction using paraformaldehyde (Table 3). Triethylborane was added to a mixture of 9 and paraformaldehyde, which resulted in the formation of the ethylated product 25 and *trans-*γ-butyrolactone 26 in 53% and 44% yields, respectively (Table 3, entry 1). The *γ*-butyrolactone 26 was formed via the diastereoselective addition of the ethyl radical to 9, followed by the sequential trapping of the borylenamine intermediate 1 with paraformaldehyde, and intramolecular lactonization with concomitant removal of the chiral auxiliary. To the best of our knowledge, this reaction represents the first reported example of the electrophilic trapping of an N-borylenamine generated through a radical process. This domino reaction was promoted by the addition of $Me_3Al$ as a Lewis acid. When the reaction was conducted in the presence of $Me_3Al$ at reflux, the desired lactone 26 was formed exclusively in 72% yield (Table 3, entry 3). The enantiomeric purity of *trans-*γ-butyrolactone 26 was determined to be 90% e.e.

The scope and utility of this new domino radical-ionic reaction were evaluated in the asymmetric synthesis of a variety of different γ-butyrolactones using a broad range of aldehydes (Table 4). The reaction with benzaldehyde gave the *trans, trans* isomer 27a as the major product, which was accompanied by small amounts of other diastereomers (Table 4, entry 1). Benzaldehydes bearing an electron-donating or electron-withdrawing substituent on their aromatic ring reacted in a similar manner to benzaldehyde, with the different substituents having very little impact on the chemical yield or the stereoselectivity, and 27b and 27c were obtained in good yields (Table 4, entries 2 and 3). 2-Furfural and cinnamaldehyde also reacted smoothly under similar reaction conditions (Table 4, entries 4 and 5). The *trans, trans* stereoselectivity observed in this reaction can be explained by invoking a six-membered-ring transition state. NMR studies revealed that N-borylenamine existed as the E isomer. The more sterically stable conformer of (E)-borylenamine would react with the
Me₃Al-activated aldehyde in such a way as to avoid the occurrence of any unfavorable steric interactions between the allylic substituents (Chart 12).

The discovery of this new sequential radical addition/aldol-type reaction prompted us to explore the domino reaction of alkynyl oxime ether, which ultimately led to the development of a novel method for the construction of tetrasubstituted olefins (syn-adduct) and highly substituted butenolides (anti-adduct) (Table 5). When the domino reaction of with benzaldehyde and triethylborane was conducted in the presence of Me₃Al, compounds 29a and 30a were formed as the products via the regioselective addition of the ethyl radical followed by the aldol-type reaction of the resulting intermediate N-borylaminooallene M, but the reaction occurred with low selectivity (Table 5, entry 1). When the reaction was conducted with aliphatic aldehyde, there was a slight preference for the formation of furanones 30b and 30c (Table 5, entries 2 and 3). Interestingly, the use of the bulky secondary isopropyl iodide afforded furanone 30d as a single product in 77% yield (Table 5, entry 4). The use of a bulky tert-butyl radical also led to the exclusive formation of 30e in excellent yield (Table 5, entry 5). The domino reactions of the enolizable cyclohexanecarboxaldehyde proceeded smoothly to afford the corresponding furanones 30f–h stereoselectively in good

Table 3. Radical Addition-Aldol Type Reaction with Paraformaldehyde

| Entry | Lewis acid | T (°C) | Yield (%) | Selectivity trans : cis |
|-------|------------|--------|-----------|------------------------|
| 1     | None       | Reflux | 44        | 35                     |
| 2     | Me₃Al      | 20     | 41        | 42                     |
| 3     | Me₃Al      | Reflux | 72        | —                      |

*a* Enantiopurity of the trans-isomer was determined to be 90% e.e.

Table 4. Radical Addition-Aldol Type Reaction

| Entry | R      | Product | Yield (%) | trans, trans: Isomers |
|-------|--------|---------|-----------|-----------------------|
| 1     | Ph     | 27a     | 73        | 4 : 1                 |
| 2     | 4-MeOC₆H₄ | 27b | 84        | 3 : 1                 |
| 3     | 4-ClC₆H₄ | 27c  | 84        | 5 : 1                 |
| 4     | 2-Furyl | 27d  | 68        | 4 : 1                 |
| 5     | PhCH=CH | 27e  | 71        | 2 : 1                 |

Chart 12. Stereochemical Features of the Reaction
yields (Table 5, entries 6–8).

The stereoselectivity of this reaction can be explained using the six-membered transition states N and O, which are shown in Chart 13. The tetrasubstituted olefin 29 would be formed via the syn-addition of N-borylamoallene to the Me₃Al-activated aldehyde via transition state N. The anti-trapping of N-borylaminoallene with an aldehyde followed by the lactonization of borate Q would afford furanone 30 via transition state O. The use of relatively large alkyl groups for R¹ and R² would lead to a preference for conformation O with lower levels of steric repulsion, which would result in the formation of furanone 30 via the anti-addition of an electrophile.

This methodology was successfully applied to a series of domino reactions involving vinylcyclopropyl oxime ether 31 and a variety of different aldehydes. The triethylborane-initiated addition of a thyl radical to vinylcyclopropyl oxime ether 31 in the presence of p-chlorobenzaldehyde gave the β-hydroxy oxime ether 32a in 80% yield via sequential thyl radical addition, cyclopropane ring opening, and aldol-type reactions (Table 6, entry 1). We subsequently evaluated the scope of the reaction using different thiophenols and aldehydes. Thiophenols bearing an electron-donating or electron-withdrawing group were well tolerated under these conditions (Table 6, entries 2 and 3). In terms of the electrophile, p- and o-methoxybenzaldehydes and 2-thiophenecarboxaldehyde performed effectively as good trapping agents (Table 6, entries 4–6). The reaction also worked well with an aliphatic cyclohexylaldehyde, which gave the β-hydroxy oxime ether 32g in good yield (Table 6, entry 7).

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Table 5. Domino Alkyl Radical Addition/Aldol-Type Reaction with Various Aldehyde

| Entry | R¹I | R²CHO | Product (yield %) |
|-------|-----|-------|-------------------|
| 1     | —   | PhCHO | 29a (36) (R¹=Et)  |
| 2     | —   | Me₂CHCHO | 29b (28) (R¹=Et) |
| 3     | —   | c-C₆H₄CHO | 29c (31) (R¹=Et) |
| 4     | i-Pr | PhCHO | — | 30d (77) |
| 5     | t-Bu | PhCHO | — | 30e (93) |
| 6     | i-Pr | c-C₆H₄CHO | — | 30f (63) |
| 7     | c-C₆H₄I | c-C₆H₄CHO | — | 30g (68) |
| 8     | t-Bu | c-C₆H₄CHO | — | 30h (68) |

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Table 6. Thiyl Radical Addition and Aldol-Type Reaction of Vinylcyclopropyl Oxime Ether 31

| Entry | ArSH | RCHO | Product a) | Yield (%) |
|-------|------|------|------------|-----------|
| 1     | PhSH | 4-CIC₆H₄CHO | 32a | 80        |
| 2     | 4-MeOC₆H₄SH | 4-CIC₆H₄CHO | 32b | 82        |
| 3     | 4-CIC₆H₄SH | 4-CIC₆H₄CHO | 32c | 85        |
| 4     | 4-CIC₆H₄SH | 4-MeOC₆H₄CHO | 32d | 83        |
| 5     | 4-CIC₆H₄SH | 2-MeOC₆H₄CHO | 32e | 84        |
| 6     | 4-CIC₆H₄SH | 2-ThiophenelyCHO | 32f | 83        |
| 7     | 4-CIC₆H₄SH | c-C₆H₄CHO | 32g | 78        |

a) Diastereomeric ratios were 9:1–7:3.
It was envisioned that the addition of an alkyl radical to the O-phenyl-conjugated oxime ether 33 would afford the N-boryl-N-phenoxyenamine S, which would undergo sequential [3,3]-sigmatropic rearrangement and cyclization reactions to give the 2-borylaminodihydrobenzofuran T (Chart 14). Because T has a highly nucleophilic amine moiety, lactamization would readily occur to produce the tetrahydrobenzofuro[2,3-b]pyrrol-2-one 34.

Benzofuro[2,3-b]pyrroles are unique skeletons, but efficient routes for the synthesis of these compounds are relatively scarce. In addition, these compounds have not been biologically evaluated in great detail, despite their biological potential. The development of straightforward, flexible, and general synthetic methods for the construction of compounds containing this scaffold from relatively simple substrates is therefore highly desirable.

Our research efforts were initially focused on the O-phenyl-conjugated oxime ether 35, which contains an ethoxycarbonyl group (Table 7). Treatment of 35 with triethylborane in benzene at room temperature did not afford the desired product, but resulted instead in the formation of a complex mixture. This failure was attributed to the reaction conditions being unsuitable for rearrangement and lactamization reactions (Table 7, entry 1). When the reaction was conducted in the presence of Me₃Al, the desired benzofuro[2,3-b]pyrrol-2-one 37 was obtained as a 1:1 mixture of diastereomers at the C3 position (Table 7, entry 2). The reaction temperature played a significant role in this process, and the chemical yield improved significantly when the reaction was conducted in benzene at reflux (Table 7, entry 3). An investigation of the effect of the ester moiety on the reaction revealed that the yield could be improved by changing from an ethyl ester to a pentafluorophenyl ester (Table 7, entry 4). It is noteworthy that the domino reaction of 36a proceeded even in the absence of Me₃Al at room temperature to furnish the benzofuro[2,3-b]pyrrol-2-one 37 in high yield (Table 7, entry 7). The pentafluorophenoxy group not only enhanced the lactamization reaction but also improved the reactivity toward the nucleophilic ethyl radical. To the best of our knowledge, this reaction represents the first reported example of the [3,3]-sigmatropic rearrangement of an N-borylenamine generated through a radical process.

Table 7. Optimization Studies for the Formation of Benzofuro[2,3-b]pyrrol-2-one 37

| Entry | Substrate | Additive | Temperature | Yield (%) |
|-------|-----------|----------|-------------|-----------|
| 1     | 35 (R=Et) | —        | rt          | nd        |
| 2     | 35 (R=Et) | Me₃Al    | rt          | 50        |
| 3     | 35 (R=Et) | Me₃Al    | reflux      | 64        |
| 4     | 36a (R=C₆F₅) | Me₃Al | reflux | 88        |
| 5     | 36a (R=C₆F₅) | Me₃Al | reflux | 75        |
| 6     | 36a (R=C₆F₅) | —   | reflux | 81        |
| 7     | 36a (R=C₆F₅) | —   | rt   | 95        |

| Entry | Substrate | Additive | Temperature | Yield (%) |
|-------|-----------|----------|-------------|-----------|
| 8     | 36a (R=C₆F₅) | —   | reflux | 95        |

*Ratio of stereoisomer: endo/exo = 1:1.

4. Sequential Radical Addition and [3,3]-Sigmatropic Rearrangement

It was envisioned that the addition of an alkyl radical to the O-phenyl-conjugated oxime ether 33 would afford the N-boryl-N-phenoxyenamine S, which would undergo sequential [3,3]-sigmatropic rearrangement and cyclization reactions to give the 2-borylaminodihydrobenzofuran T. Because T has a highly nucleophilic amine moiety, lactamization would readily occur to produce the tetrahydrobenzofuro[2,3-b]pyrrol-2-one 34.

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To investigate the molecular diversity of this transforma-
tion, we also conducted the reaction with a tert-butyl radical (Chart 15). Interestingly, the domino reaction proceeded stereoselectively to afford exo-38a as a single stereoisomer.

We then proceeded to investigate the substituent effect on the phenyl group of the oxime moiety. The use of a substrate bearing a trifluoromethyl group at the para position afforded 5-trifluoromethylbenzofuro[2,3-b]pyrrole 38b in 76% yield. A slightly lower yield was observed for product 38c bearing a methyl group as an electron-donating substituent. Notably, a bromo group was tolerated under these radical reaction conditions, thereby facilitating further transformations. Although moderate steric hindrance effects were observed for substrates bearing a substituent at the ortho position of their phenyl ring (e.g., 36e and 36f), the corresponding 7-substituted benzofuro[2,3-b]pyrrol-2-ones 38e and 38f were obtained in moderate yields.

The rationale for high stereoselectivity is depicted in Chart 16. The N-boryl-N-phenoxenamine V would undergo a [3,3]-sigmatropic rearrangement via a six-membered transition state that effectively minimized the steric repulsion between the tert-butyl and phenyl groups, which would allow for stereoselective formation of syn-α-arylimine W. Given that the subsequent cyclization of W would be reversible, an equilibrium would exist between cis-X and trans-X. The irreversible lactamization would then push the equilibrium toward the formation of the sterically favored cis-fused tricyclic compound 38a.

Finally, we demonstrated the asymmetric synthesis of benzofuro[2,3-b]pyrrol-2-ones (Chart 17). The reaction of the chiral conjugated oxime ether 39 bearing Oppolzer’s camphorsultam with triethylborane led predominately to the formation of the endo-isomer 40 in 57% yield with 93% e.e. Although the removal of a chiral auxiliary during a diastereoselective reaction is generally tedious, the use of the domino reaction in this case allowed for the rapid release of the chiral auxiliary.

5. Conclusion

We have developed a novel domino reaction involving conjugated oxime ethers which proceeds via the generation of an α-alkoxyimino radical or an alkoxyaminyl radical. This triethylborane-mediated hydroxysulfenylation reaction allows for the construction of a carbon–sulfur bond and a carbon–oxygen bond in a single operation to provide 1,3-hydroxy sulfides. We also found that the hydroxyalkylation reaction of conjugated oxime ethers with triethylborane under an O₂ atmosphere proceeded effectively via the addition of a carbon radical followed by the hydroxylation of the resulting N-borylenamine with O₂. To explore this novel domino reaction, which occurred via the formation of N-borylenamine, we conducted several sequential radical addition/aldol-type reactions. The radical reaction of a conjugated oxime ether with triethylborane in the presence of an aldehyde afforded a γ-butyrolactone via a sequential process involving ethyl radical addition, the generation of N-borylenamine, an aldol-type reaction with an aldehyde, and lactonization. We also developed a domino reaction involving sequential radical addition and [3,3]-sigmatropic rearrangement reactions. The triethylborane-mediated domino reaction of the O-phenyl-conjugated oxime ether produced benzofuro[2,3-b]pyrrol-2-ones, which can otherwise be difficult to access using existing synthetic methods, via a radical addition/[3,3]-sigmatropic rearrangement/cyclization/lactamization cascade. The application of these methods to the synthesis of biologically active compounds, as well as in studies directed toward the development of domino reactions involving transition metal catalysts, are currently underway in our laboratory.

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References

1) Tietze L. F., Brasche G., Gericke K. M., “Domino Reactions in Organic Chemistry,” Wiley-VCH, Weinheim, 2006.
2) Tietze L. F., Chem. Rev., 96, 115–136 (1996).
3) Ueda M., Miyabe H., Nishimura A., Miyata O., Takeno Y., Nat. Org. Lett., 5, 3835–3838 (2003).
4) Miyata T., Takahashi S., Tamura A., Ueda M., Nat. Org. Lett., Tetrahedron, 64, 1270–1284 (2008).
5) Ueda M., Sato A., Ikeda Y., Miyoishi T., Naito T., Miyata O., Org. Lett., 12, 2594–2597 (2010).
6) Ueda M., Ikeda Y., Sato A., Yotomo Y., Kikuchi M., Shono H., Miyoishi T., Naito T., Miyata O., Tetrahedron, 67, 4612–4615 (2011).
7) Ueda M., Sugita S., Sato A., Miyoishi T., Miyata O., J. Org. Chem., 77, 9344–9351 (2012).
8) Jithunsa M., Ueda M., Miyabe H., Angew. Chem. Int. Ed., 59, 9230–9236 (2020).
9) Jithunsa M., Hachiya I., Mizota I., Chem. Commun. (Camb.), 65, 9230–9236 (2020).
10) Jithunsa M., Hachiya I., Mizota I., Chem. Commun. (Camb.), 2009, 874–899 (2009).
11) Shimizu M., Hachiya I., Mizota I., Chem. Commun. (Camb.), 2009, 874–899 (2009).
12) Booth S. E., Jenkins P. R., Swain C. J., Sweeney J. B., J. Chem. Soc., Perkin Trans. 1, 1994, 3499–3508 (1994).
13) Taut P., Fällis A. G., J. Org. Chem., 64, 6960–6968 (1999).
14) Lucarini M., Pedulli G. F., Lazzari D. J., J. Org. Chem., 65, 2723–2727 (2000).
15) Ueda M., Miyabe H., Shimizu H., Sugino H., Miyata O., Naito T., Angew. Chem. Int. Ed., 47, 5600–5604 (2008).
16) Iriuchijima S., Maniwa K., Sakakibara T., Tsuhashi G., J. Org. Chem., 79, 1170–1171 (1974).
17) Beckwith A. L. J., Wagner R. D., J. Am. Chem. Soc., 101, 7099–7100 (1979).
18) Kershuk E. E., Hoos R., Szpilman A. M., Konstantinovski L., Posner G. H., Bachi M. D., Tetrahedron, 58, 2461–2467 (2002).
19) O’Neill P. M., Stocks P. A., Pugh M. D., Arajou N. C., Kershuk E. E., Bickley J. F., Ward S. A., Bray P. G., Pasmi E., Davies J., Verissimo E., Bachi M. D., Angew. Chem. Int. Ed., 43, 4193–4197 (2004).
20) O’Neill P. M., Mukhtar A., Ward S. A., Bickley J. F., Davies J., Bachi M. D., Stocks P. A., Org. Lett., 6, 3035–3038 (2004).
21) Surendra K., Krishnamoorthy N. S., Sridhar R., Rao K. R., J. Org. Chem., 71, 5819–5821 (2006).
22) Bucheral X., Uziel J., Jügel S., J. Org. Chem., 66, 4504–4510 (2001).
23) Jo O., “S-Centered Radicals,” ed. by Alfassi Z. B., Wiley, Chichester, 1999, pp. 193–224.
24) Krusci P.), Kochi J. K., J. Am. Chem. Soc., 93, 846–869 (1971).
25) Gillman H., Nelson J. F., J. Am. Chem. Soc., 59, 935–937 (1937).
26) Dong Z., Liu J., Mao S., Huang X., Yang B., Ren X., Luo G., Shen J., J. Am. Chem. Soc., 126, 16395–16404 (2004).
27) Back T. G., Kuzma D., Parvez M., J. Org. Chem., 70, 9230–9236 (2005).
64) Rahaman H., Ueda M., Miyata O., Naito T., Org. Lett., 11, 2651–2654 (2009).
65) Ueda M., Ito Y., Ichii Y., Kakiuchi M., Shono H., Miyata O., Chemistry, 20, 6763–6770 (2014).
66) Sheradsky T., Tetrahedron Lett., 7, 5225–5227 (1966).
67) Tsuritani T., Shinokubo H., Oshima K., J. Org. Chem., 68, 3246–3250 (2003).
68) Padwa A., Nara S., Wang Q., J. Org. Chem., 70, 8538–8549 (2005).
69) Avril J.-L., Marçot B., Coquillay M., De Rango C., Moskowitz H., Mayrargue J., New J. Chem., 23, 743–748 (1999).
70) Harada K., Kajit E., Takahashi K., Zen S., Chem. Pharm. Bull., 42, 1562–1566 (1994).
71) Connor D. T., Von Strandmann M., J. Org. Chem., 38, 3874–3877 (1973).