Highly diastereoselective ionic/radical domino reactions: single electron transfer induced cyclization of bis-sulfoxides†‡

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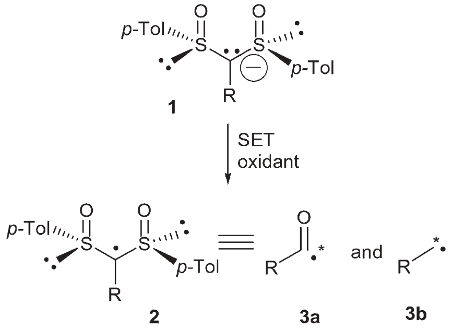
SET oxidation of bis-sulfinyl anions has enabled the uses of bis-sulfinyl radical as a synthetic equivalent of chiral acyl and methylene radicals involved in tandem reactions leading to the enantioselective construction of various carbo- and heterocyclic derivatives.

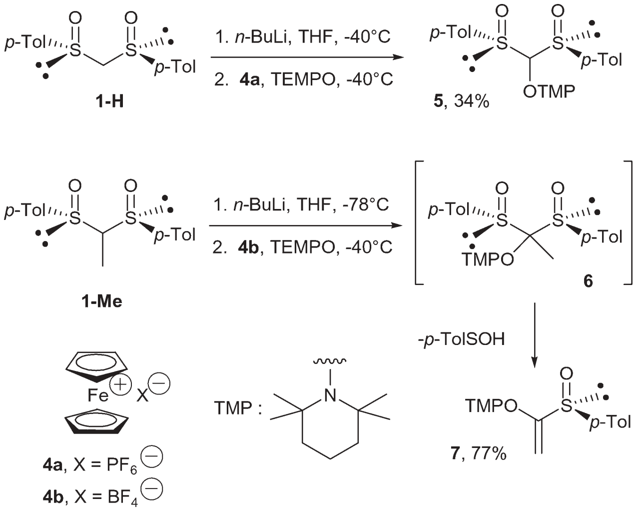
The development of tin free radical reactions[1] constitutes one of the most important challenges in order to anchor the popularity of radical chemistry in synthesis and widen its fields of application.[2] Among all possible alternatives, single electron transfer (SET) that allows the generation of radicals by a redox process constitutes an intriguing approach. Notably, one electron oxidation of electron rich centers has been established as a highly versatile method for the generation of carbon-centered radicals.[3] Neutral carbonyl compounds are transformed into α-keto radicals by employing $Mn(OAc)_3$[4] or ceric ammonium nitrate (CAN).[5] Enolate oxidation has been reported using a variety of reagents,[3,6] and ester enolate oxidations have been particularly studied by Jahn.[7] Some of these processes could be elegantly incorporated in ionic/radical domino reactions[8] to give various carbo- and heterocycles and they could be tailored for the total synthesis of natural products.[7b,c] In a seminal report, Dulcère and Rodriguez disclosed an ionic/radical tandem reaction with CAN as SET reagent involving conjugate addition on nitroalkenes.[9] Of paramount importance would be an extension of these reactions that allows the synthesis of enantiopure products.

In this context, we decided to investigate the reactivity of bis-sulfinyl[10] radicals[11,12] of type **2** (Scheme 1). These new radical entities would correspond to synthetic equivalents of chiral acyl[13] or methylene radical synthons **3a** and **3b**, a highly unexplored approach in organic synthesis.[14] Generation of the radical species would be ensured by the SET oxidation of the easily formed carbanionic intermediate **1**.[15]



Scheme 1 Principle of a chiral acyl and methylene radicals.

In order to probe our design, we examined the possibility of generating the C-centered radical of unsubstituted bis-sulfinylmethane (Scheme 2). We devised the following sequence. (S_S,S_S)-bis(*p*-tolylsulfinyl) methane **1-H** was deprotonated with *n*-BuLi at −40 °C. To the resulting anion **1** were added simultaneously ferrocenium hexafluorophosphate **4a** as the oxidative reagent and TEMPO, as a radical trap. Evolution of the reaction is evidenced by the formation of orange $FeCp_2$ resulting from the Fe(III) to Fe(II) reduction. After usual workup, we were pleased to isolate the desired product **5**, albeit in a relatively low yield (34%).[16] We suspected that some aggregates were formed and compromised a good conversion (about 50% of starting material was recovered). Moreover, the final product **5** showed moderate stability. We also studied methyl-substituted bis-sulfoxide **1-Me**, anticipating that different aggregation states would arise, and that the oxidative process would be improved. This proved to be the case since in this reaction, vinylsulfoxide **7** was isolated in 77% yield. Presumably,



Scheme 2 Evidence of bis-sulfinyl radical.

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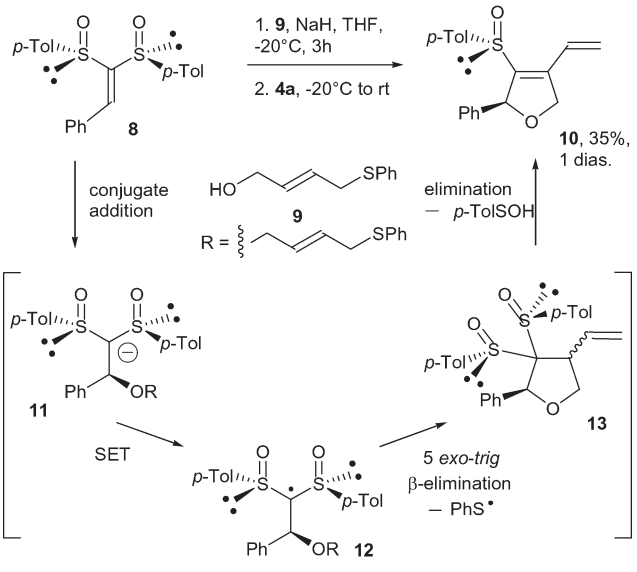
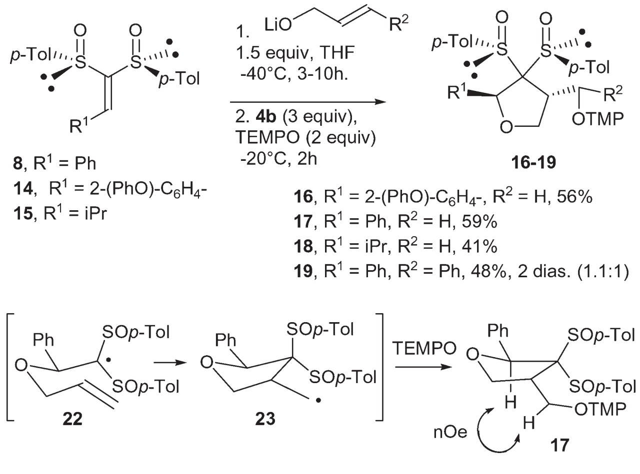
‡ In memory of our dear colleague and friend Charles Mioskowski.



Scheme 3 Tandem ionic/radical reaction: cyclization.



Scheme 4 Radical cyclization and TEMPO trapping.

the radical trapping adduct **6** undergoes loss of sulfenic acid which alleviates steric crowding to deliver **7**.

The feasibility of this approach being established, we examined further transformations that would require an intramolecular trapping step. We focused on Michael addition–oxidation tandems on precursors bearing an adequately positioned unsaturation (Scheme 3). Initially, we added the lithium alkoxide of allylic alcohol to alkylidene bis-sulfoxide **8**.[10] After oxidation, a minute amount ($< 10\%$) of a compound resulting from a 5-*exo-trig* radical process was isolated. This encouraging result suggested to us that an optimization of the termination step would give a clean and fast end to the radical process and should improve the overall yield of the sequence. Our first approach relied on the use of the sodium alkoxide derived from **9**, anticipating that a fast β-elimination of a thiyl radical would fulfil this goal. Presumably, as reported before, a completely diastereoselective conjugate addition to **8** provided **11** on which the (*R*) absolute configuration of the benzylic center is set.[10a] The carbanionic intermediate was then oxidized by the Fe(III) salt to give bis-sulfinyl radical **12** that would intramolecularly add to the pendant alkene *via* a 5-*exo-trig* cyclization process. The newly formed radical evolves through a β-fragmentation process generating **13** that contains a tetrahydrofuran motif and a terminal double bond. Here also, decongestive β-elimination of sulfenic acid with concomitant formation of a conjugated diene moiety proceeded, and provided dihydrofuran **10** in 35% yield as a single diastereoisomer. Although the diastereoselectivity of the cyclization could not be known through this example, diene **10** should exhibit interesting synthetic potential for cycloaddition reactions or conjugate additions.

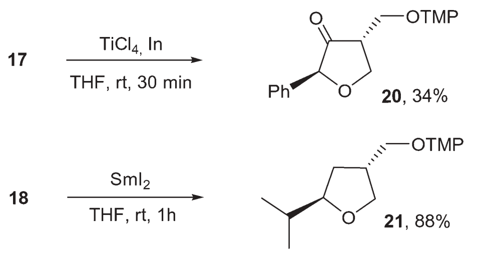
Radical trapping reagents like TEMPO are very powerful species for efficient termination of radical reactions[17] and should result in optimized yields. After Michael addition, the oxidative cyclization–TEMPO trapping tandem yielded tetrahydrofuran derivatives **16–19** in good yields (41 to 59%)[18] and as single diastereoisomers from the corresponding alkylidenes **8**, **14** and **15** (Scheme 4).[19] Cinnamyl alcohol was used in this tandem process and the resulting secondary benzylic radical was trapped by TEMPO. Two diastereoisomers (**19**), presumably epimers at the exocyclic benzylic position, were isolated in this sequence in a 1.1 : 1 ratio.[20]

NOE interactions between the benzylic proton and the two protons adjacent to the alkoxyamine function on **17** established a *trans* relationship between the phenyl and the CH_2OTMP substituents. This determination is consistent with a favored pathway through pseudo-chair transition state **22** that minimizes steric interactions to give **23**.[21]

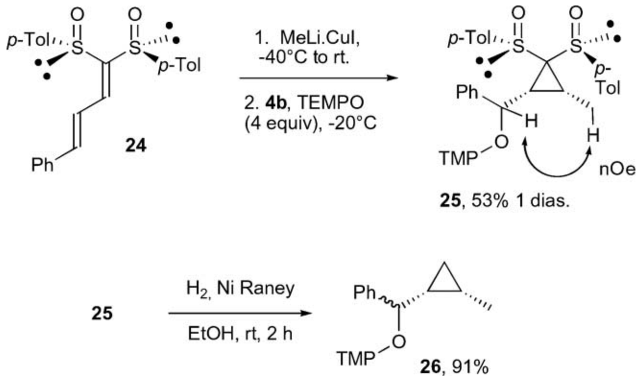
Gratifyingly, derivatization to dihydrofuranone or tetrahydrofuran products (**20** and **21**) was accomplished (Scheme 5). The compound **20** was obtained from **17** through a $TiCl_4$/In treatment in 34% yield while the product **21** was obtained through an unprecedented chemoselective SmI_2 (6 equiv.) promoted reduction in THF in 88% yield.[13c] These transformations are important and promising for some other synthetic developments.[22]

With these efficient tandem processes in hand, we decided to investigate less usual cyclization reactions like 3-*exo-trig* ring closures in order to generate cyclopropane derivatives. We recently reported the conjugate addition of organocopper reagent onto dienyl bis-sulfoxide substrates that proceeds with high diastereoselectivity.[10b] Thus, addition of 4 equiv. of [MeCu,LiI] to **24** followed by the addition of **4b** and TEMPO afforded cyclopropyl derivative **25** in 53% yield as a single *cis* diastereomer (Scheme 6).[23] This remarkable sequence features a reversible 3-*exo-trig* cyclization[24] whose driving force is the fast trapping by TEMPO. Reductive desulfinylation furnished **26** in good yield.

In conclusion, we report the first uses of bis-sulfinyl radicals that serve as synthetic equivalents of chiral acyl or methylene radicals. The generation of such radicals has been accomplished by SET



Scheme 5 Derivatization of bis-sulfoxide derivatives.



Scheme 6 Formation of a cyclopropyl derivative by a 3-*exo-trig* cyclization.

oxidation of an anionic intermediate. Based on Michael additions–oxidation tandems, this tin free radical chemistry provides the first asymmetric entry into the versatile construction of various carbo- and heterocyclic derivatives. Further applications of this process are underway.

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18 Uncyclized Michael adducts (10–15%) and suspected sulfinyl elimination products were observed in a lot of reactions.

19 An alternative mechanism relying on a carbanionic cyclization followed by β-elimination of thiophenate (PhS^-) or addition to the oxoammonium species could be involved. We thank one referee for this suggestion. However, control experiments have shown that TEMPO does not reduce **4b** to ferrocene, and that no cyclization product is obtained upon warming at rt without ferrocenium even in the presence of TEMPO.

20 This absence of selectivity could be rationalized by a poorly diastereoselective ring closure or TEMPO trapping. Another explanation could be the thermal isomerization of the benzylic center. See U. Jahn, P. Hartmann, I. Dix and P. G. Jones, *Eur. J. Org. Chem.*, 2001, 3333.

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