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Intramolecular Oxygen Radical Additions to α,β-Unsaturated Esters. Diastereoselective Tandem Cyclofunctionalization and Hydrogen Transfer Reactions.

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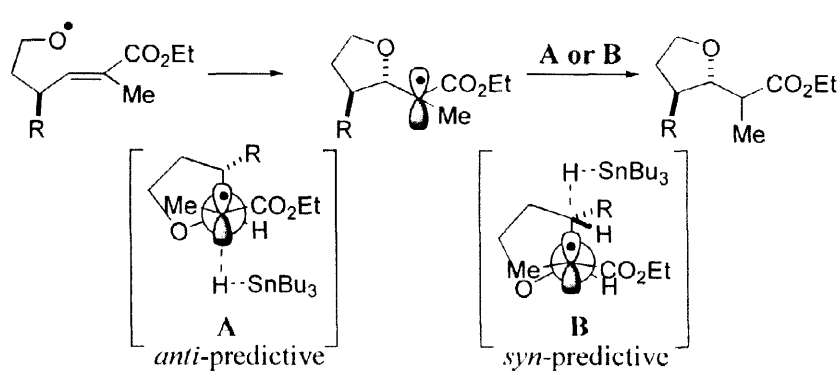
Abstract: The efficiency of a tandem process featuring an oxy radical cyclization and hydrogen transfer reaction of the resultant carbon-based radical has been demonstrated. This methodology affords 2,3-*trans*-disubstituted tetrahydrofurans by creating two new contiguous stereogenic centers with high levels of 1,2-induction in each step.

Diastereoselective radical-based processes involving acyclic substrates have attracted considerable interest in recent years.[1,2,3] Our group has focused mainly on the reactivity of radicals flanked by an ester and a heteroatom-bearing stereogenic center. Not only has asymmetric induction been demonstrated in hydrogen transfers, allylations, and atom transfer reactions,[4] but both the sense and extent of diastereoselection can be controlled by Lewis acid chelation in these reactions.[5,6]

We have recently embarked on a study directed at generating such radicals in the penultimate step of a tandem sequence to induce two new contiguous stereogenic centers from a single neighboring asymmetric site. This methodology would constitute an extension to the diastereoselective processes involving radicals generated by homolytic cleavage of a C-X bond (X = halide, Se or S), studies of which have served well in identifying factors governing radical facial discrimination. The tandem sequence (Scheme 1) features, in its initial step, the intramolecular addition of an oxy radical to an α,β-unsaturated ester to afford a radical exocyclic to a tetrahydrofuran ring. Based on our previous work, such a radical is anticipated to undergo reduction to give predominantly a product with *anti* relative configuration at the α- and β-carbons. Enhanced *anti* selectivity has been observed particularly in reactions of such exocyclic radicals.[4d,5d] To rationalize the radical facial preference of the hydrogen transfer, we and other research groups have proposed the *anti* predictive transition state **A**, which is stabilized by steric and electronic effects.[1,2,4]



Scheme 1

While the hydrogen transfer step of our tandem process is well-documented, there is a relative paucity of studies on oxygen-based radicals.[7] Carbon-based radical cyclizations constitute the majority of stereoselective radical reactions,[8] but oxy radicals remain relatively unstudied due to the lack of suitable means by which they are generated. Access to these radicals through the fragmentation of arylsulfenic acid *O*-esters[7c] and N-alkoxypyridine-2-1H-thiones[7b] has been reported recently. Because of the ease of their preparation and

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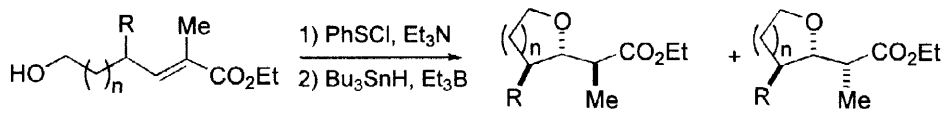
fragmentation, the arylsulfenic acid *O*-esters were chosen as precursors to the oxy radicals in our study. Oxy radicals are believed to be electrophilic; the few examples reported so far involve their cyclization onto electron-rich olefins[7] with rates[7c] of cyclization on the order of 5.2 x 10^8 s^{-1}. The electrophilicity of oxy radicals is further supported by the bimolecular rate of hydrogen abstraction from Bu_3SnH (~10^8 $M^{-1}s^{-1}$, 30 °C).[9] Since the radical cyclization planned in this study involves an electron-deficient olefin, these data suggest that cyclization may be considerably slower than reduction. However, this concern could be evaluated only through experimentation, and so we decided to probe a) the electronic and steric influence of R on the oxy radical cyclization through alkyl, alkoxy, and silyloxy substituents, and b) the effect of ring size on the oxy radical cyclization.

Olefins **1**[10] and **4a** were prepared after two steps [DIBAL, CH_2Cl_2, -78 °C; $Ph_3P{=}CHCO_2Et$, THF, 25 °C] from γ–butyrolactone and α-methyl-γ-butyrolactone respectively.[4d] To prepare olefins **4b** and **4c**,[5a] dihydrofuran was treated with *m*CPBA (H_2O-Et_2O, 82%) to give the hemiacetal which was subjected to $Ph_3P{=}CHCO_2Et$ (THF, reflux, 53%). Protection of the of the allylic alcohol gave either **4b** (Ag_2O, MeI, MeCN, reflux, 15 h, 74%) or **4c** (*t*$BuMe_2SiCl$, imid., DMF, 15 h, 62%). The O-alkylbenzenesulphenates were prepared by treating each alcohol (**1**, **4a**, **4b**, **4c** or **7**[4d]) with benzenesulfenyl chloride and Et_3N in THF.

Table 1. Tandem Cyclofunctionalization and Hydrogen Transfer Reactions[a]



1, 4, 7 **2, 5, 8** *anti* **3, 6, 9** *syn*

Entry	Substrate	n	Products (*anti*/*syn*)	Solvent	Temp. (°C)	Yield (%)[b]
1	**1**: R = H	1	**2/3** : 6/1[c]	benzene	23	--[d]
2	**1**: R = H	1	**2/3** : 6/1	benzene	23	75[e]
3	**1**: R = H	1	**2/3** : 6/1	THF	23	51 (74)
4	**1**: R = H	1	**2/3** : 9/1[f]	THF	-23	61 (85)
5	**1**: R = H	1	**2/3** : --	THF	-45	--[g]
6	**1**: R = H	1	**2/3** : --	CH_2Cl_2	23	<10[g]
7	**4a**: R=Me	1	**5a/6a** : 16/1	THF	23	59 (86)
8	**4a**: R=Me	1	**5a/6a** : 22/1[h]	THF	-23	56 (82)
9	**4b**: R=OMe	1	**5b/6b** : 7/1	THF	23	51 (68)
10	**4c**: R=OTBDMS	1	**5c/6c** : 13/1	THF	23	52 (52)
11	**4c**: R=OTBDMS	1	**5c/6c** : 25/1	THF	-23	~5[g]
12	**4a**: R=Me	1	**5a/6a** : 14/1[i]	THF	23	52
13	**4a**: R=Me	1	**5a/6a** : 1.8/1[j]	THF	23	79
14	**7**: R=H	2	**8/9** : --	THF	23	--[g]

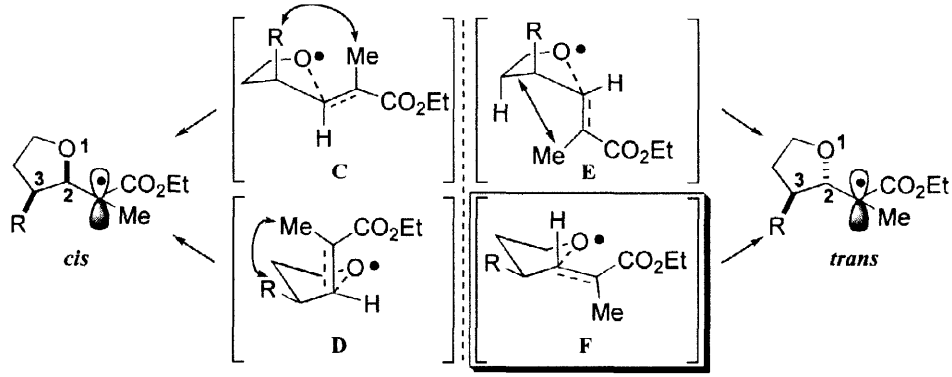
[a]Conditions: 1.0 equiv of PhSCl, 2.2 equiv of Et_3N, THF, -78°C for 15 min and then 1 h at 23°C. The salt was removed by gravity filtration and the filtrate was concentrated. Subsequent reductions were performed by using a substrate concentration of 0.03M in the solvent shown above and slow addition of 2.0 equiv of Bu_3SnH over 3 h via syringe pump. Initiation was accomplished using Et_3B. [b]Isolated yields of cyclic products over 2 steps and, in parentheses, yields determined by NMR using benzyl alcohol as internal standard. [c]Bu_3SnH was added in a single aliquot. [d]1.5:1 ratio of cyclized and reduced (oxy) products. [e]5:1 ratio of cyclized and reduced (oxy) products (similar ratio was also observed for entries 3-14). [f]Reduction of the same radical arising from a tetrahydrofuranyl tertiary iodide at -30° C in toluene gave a 11:1 *anti*/*syn* ratio; see ref. 12. [g]Major product from reduction of oxy radical. [h]Reduction of a tertiary iodide (to generate the same radical) with Bu_3SnH at -30°C in toluene gave a 52/1 *anti*/*syn* ratio; see ref. 12. [i]Bu_3SnD was used instead of Bu_3SnH. [j]The reaction was conducted in EtOH using a catalytic amount of EtONa, 24 h.

In the initial attempt at tandem radical cyclization-hydrogen transfer, the addition of Bu_3SnH in one aliquot (0.02 M) gave a 50:50 mixture of cyclized product and olefinic alcohol **1** (entry 1, Table 1). To favor cyclization over reduction of the oxy radical, the Bu_3SnH was slowly introduced *via* syringe pump and a 6:1 mixture of tetrahydrofurans favoring the *anti* relative configuration at the α- and β-carbons (with respect to the ester) was obtained in good yield (entry 2). While a similar product ratio with some erosion in the yield[11] was

observed when THF was used instead of benzene (entry 3), little cyclization occurred when the reaction was performed in CH_2Cl_2 (entry 6).

While neither the stereochemical outcome nor yield of the cyclization was noticeably affected by the methyl substitution (R) in the substrate (**4a**), the *anti* selectivity in the reduction of the cyclized radical was increased to 16:1 (cf. entries 3 and 7). On the other hand, an erosion of the *anti/syn* ratio was observed when the methyl group (R) was replaced by an electronegative group such as a methoxy (7:1, entry 9) or a silyloxy (13:1, entry 10). These observations are consistent with other results that have been attributed to the σ-donating ability of the R groups in the hyperconjugative stabilization of the radical (**A**, Scheme 1).[12] However, the electronegative alkoxy and siloxy R groups also affect the radical cyclization, as evidenced by the lower NMR yields (entries 9-11). In comparison with an electron-rich R group (e.g. Me), the inductive effect produced by an electronegative allylic group may enhance the electrophilicity of the olefin sufficiently to slow the reaction with the electrophilic oxy radical; consequently, reduction would become a more competitive pathway for the oxy radical. It is interesting to note that no tetrahydropyrans arising from 6-exo cyclization of the oxy radical were observed (entry 14); oxy radical reduction occurred much faster than 6-membered ring formation.

In an attempt to increase the diastereoselectivity of the hydrogen transfer of the cyclic radical, the reaction temperature was lowered, leading to modest enhancements in *anti* selectivity at -23 °C for **1** (cf. entries 3 and 4) and for **4a** (cf. entries 7-8).



Scheme 2

Although increased selectivity was also observed at -23 °C for **4c** (cf. entries 10-11), the allylic siloxy substitution retarded the cyclization due perhaps to a combination of electronic (*vide supra*) and steric effects in the transition state (*vide infra*); only reduction of the oxy radical was observed. At -45 °C, no cyclization was observed even for **1** (entry 5).

Interestingly, 2,3-*cis*-disubstituted tetrahydrofurans were not detected in any of the oxy radical cyclizations. Presumably the oxy radical cyclization proceeds through a "chair-like" transition state (Scheme 2), which is supported by calculation[7e,f] and is analogous to a hexenyl radical cyclization.[13] Compared to the transition states leading to *trans* cyclization, the transition states predictive of the *cis*-isomer seem less favored; **C** is destabilized by an 1,3-allylic interaction[14] between the R and α-methyl groups, while **D** suffers from two gauche interactions. By contrast, the transition states leading to the 2,3-*trans* disubstituted tetrahydrofuranyl radical appear either free of destabilizing steric interactions (**F**) or only slightly disfavored by one gauche interaction (**E**).

Since the products could conceivably arise through an ionic process (such as intramolecular Michael addition to the unsaturated ester by an alcohol arising either from the reduction of the oxy radical or from the hydrolysis of sulfenate ester), experiments were designed to ascertain the mechanism of these reactions. Two experiments in particular supported the intermediacy of radicals; firstly, the use of Bu_3SnD (entry 12) gave deuterated esters (**5a** and **6a**) in a ratio and yield similar to that obtained from the use of Bu_3SnH (entry 7). Secondly, these reactions can be inhibited by 1,3-dinitrobenzene (only sulphenates were recovered). Interestingly, the subjection of **4a** to catalytic NaOEt in EtOH afforded in good yield the 2,3-*trans*-disubstituted tetrahydrofurans (entry 13). Although *trans* cyclization was observed exclusively, protonation of

the resultant enolate exhibited little selectivity (1.8:1, entry 13). Taken together, these data indicate that radical-based processes contribute to most, if not all, of the observed products.[15]

In conclusion, we have demonstrated the efficiency of a tandem process which features an intramolecular oxygen radical addition to an α,β-unsaturated ester and hydrogen transfer reaction of the resultant carbon-based radical. This methodology affords 2,3-*trans*-disubstituted tetrahydrofurans by creating two new contiguous stereogenic centers with high levels of 1,2-induction in both tandem steps. Studies aimed at developing other tandem processes that generate an *exo*-cyclic radical in the penultimate step are ongoing.

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