Radical Reactions

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Repairing the Thiol-Ene Coupling Reaction**

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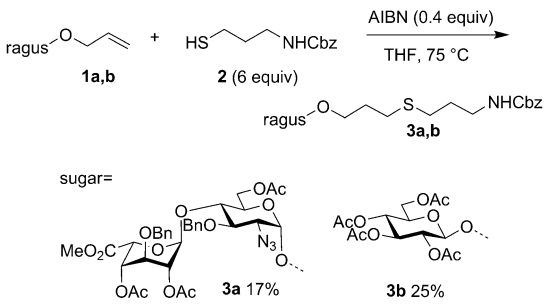
In memory of André Lubineau

Abstract: *Thiol-ene coupling (TEC) reactions emerged as one of the most useful processes for coupling different molecular units under reaction mild conditions. However, TEC reactions involving weak C–H bonds (allylic and benzylic fragments) are difficult to run and often low yielding. Mechanistic studies demonstrate that hydrogen-atom transfer processes at allylic and benzylic positions are responsible for the lack of efficiency of the radical-chain process. These competing reactions cannot be prevented, but reported herein is a method to repair the chain process by running the reaction in the presence of triethylborane and catechol. Under these reaction conditions, a unique repair mechanism leads to an efficient chain reaction, which is demonstrated with a broad range of anomeric O-allyl sugar derivatives including mono-, di-, and tetrasaccharides bearing various functionalities and protecting groups.*

Discovered more than a century ago,[1] the radical addition of thiols to alkenes [also called the thiol-ene coupling (TEC) reaction] became very popular during the last two decades with applications in polymer science, biology, and bioorganic chemistry[2] with particular emphasis on glycochemistry.[2,3] The mild reaction conditions, atom economy, and regioselectivity of the process satisfy essential requirements of the click concept.[3d] This prompted us to evaluate TEC procedures[4] for functionalizing the allyl moiety of fully protected fragments of glycosaminoglycans (GAGs)[4a,5] with N-Cbz-protected 3-aminoethanethiol. Treatment of the allyl azidodisaccharide **1a** with 6 equivalents of the thiol **2** in the presence of 2,2′-azobis(2-methylpropionitrile) (AIBN) afforded the addition product **3a** in only 17% yield. To test whether such failure was due to the presence of an azide,[6] the reaction was repeated with the glucopyranoside **1b**,[7] thus leading to a poor 25% yield of **3b** (Scheme 1). A closer look at the literature revealed that TEC reactions involving O-allyl derivatives or O-benzyl-protected saccharides in organic solvents require the use of a large excess of thiols (typically 15 equivalents),[4c,8] and moderate to low yields were reported for simple model systems.[9,10] Therefore, a detailed study of this reaction was undertaken to develop a more efficient and reliable procedure. We report herein that the use of Et_3B as an initiator and catechol as a co-reagent allows highly efficient coupling reactions by an unprecedented chain-reaction repair process.



Scheme 1. Thermally initiated TEC reaction with allyl glycosides. Cbz = benzyloxycarbonyl, THF = tetrahydrofuran.

The TEC reaction between dodecanethiol and two simple model allyl ethers were investigated first. Under thermal conditions, *trans*-**4** afforded only 62% of the expected anti-Markovnikov adduct **5** (Scheme 2a).[11] A significant amount of the regioisomer **6** was observed, and more surprisingly, epimerization on the cyclohexyl ring took place to a great extent in both **5** and **6**.[12] Traces of the O,S-acetal **7** were also isolated and the enolether **8** was observed as a transient species during the reaction. The allyl benzyl ether **9** was examined next (Scheme 2b). The addition of dodecanethiol to **9** proceeded slowly and required large amounts of an initiator to eventually furnish the adduct **10** in a moderate 55% yield along with 7% of the corresponding regioisomer **11**. Benzaldehyde, 1-phenyl-1,1- (didodecylsulfanyl)methane, and 3-dodecylsulfanylpropan-1-ol were also detected.

The results obtained with *trans*-**4** and **9** demonstrate that the well-established hydrogen atom abstraction from weak C–H bonds by thiyl radicals[13] represents the major issue in TEC reactions involving allylic ene partners or benzyl-

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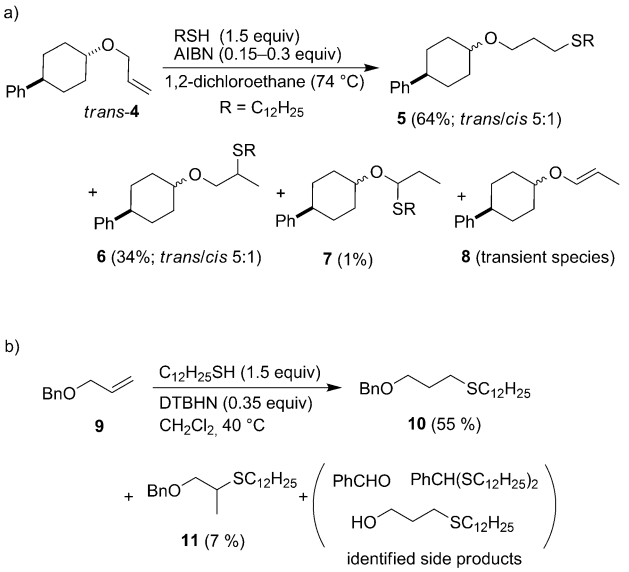
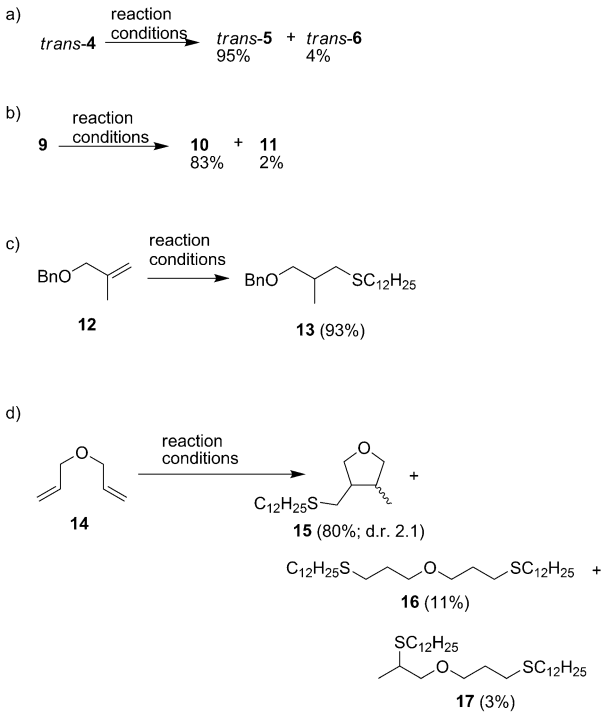


Scheme 2. Thermally initiated TEC reaction with allyl ethers *trans*-**4** and **9**. DTBHN = di-*tert*-butylhyponitrite.



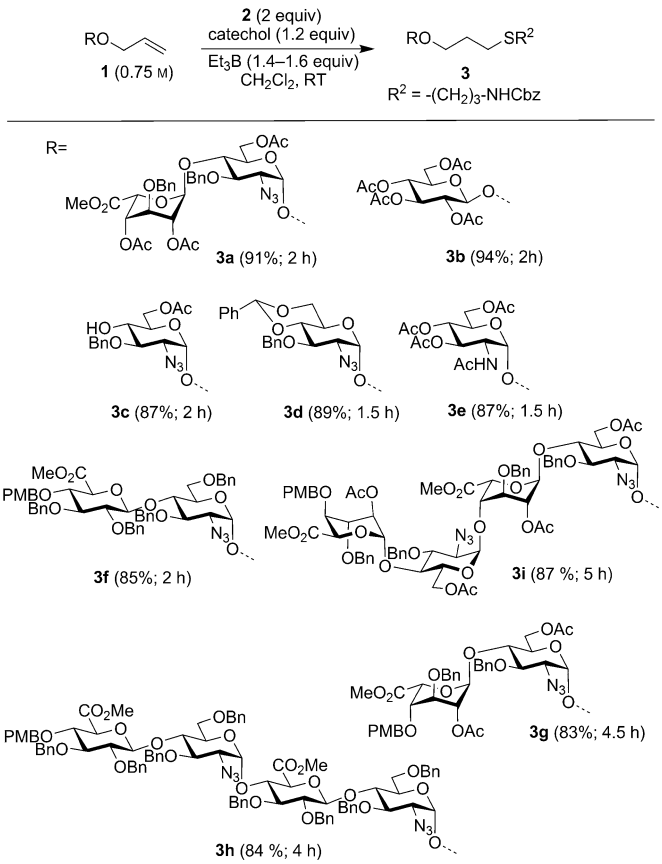
Scheme 3. The catechol/BEt_3 TEC reaction with allyl ethers *trans*-**4**, **9**, **12**, and **14**. Reaction conditions: $C_{12}H_{25}SH$ (1.5 equiv), Et_3B (1.2 equiv), TBC (1.2 equiv), CH_2Cl_2, RT, 4 h.

protected substrates. The stable allylic and benzylic radicals thus generated accumulate and eventually terminate the chain through recombination or disproportionation reactions.[14] We anticipated that reduction of the undesired stabilized radicals by an external reagent could regenerate the starting substrate and repair the radical chain process. However, this external reagent has to meet very strict requirements: 1) it should have a weakly bound hydrogen atom to permit hydrogen-atom transfer to stabilized allylic and benzylic radicals; 2) the resulting radical should not react with the alkene but should be readily converted into the intermediate thiyl radical to regenerate the chain process; 3) if possible, it should possess a low toxicity and be commercially available and cheap. Based on these requirements, we decided to investigate the use of catechols in the presence of triethylborane.[15]

The TEC reaction between dodecanethiol and *trans*-**4** was investigated first (Scheme 3a). For this study, 4-*tert*-butylcatechol (TBC) was preferred to catechol because of its better solubility in organic solvents.[15] To our great satisfaction, the reaction proceeded in almost quantitative yields with good selectivity for the anti-Markovnikov adduct when the reaction was run in the presence of TBC (1.2 equiv) and Et_3B (1.3 equiv). Under these reaction conditions (room temperature), the *trans*/*cis* isomerization process was almost completely suppressed (*trans*/*cis* > 200:1). A similar result was observed with the model substrate **9**. By running the reaction under the optimized Et_3B/catechol conditions, a yield of 83% for the formation of **10** was obtained and only 2% of the regioisomer **11** were detected (Scheme 3b). The reaction was also tested with 2-methylallyl benzyl ether (**12**), which was converted into **13** in 93% yield as a single product (Scheme 3c). The radical nature of the reaction was unambiguously demonstrated by running the reaction with the radical probe **14** (Scheme 3d). The reaction afforded the furan **15**, resulting from a 5-*exo*-trig cyclization process, in 80% together with small amount of the bis(addition) products **16** (11%) and **17** (3%).[16]

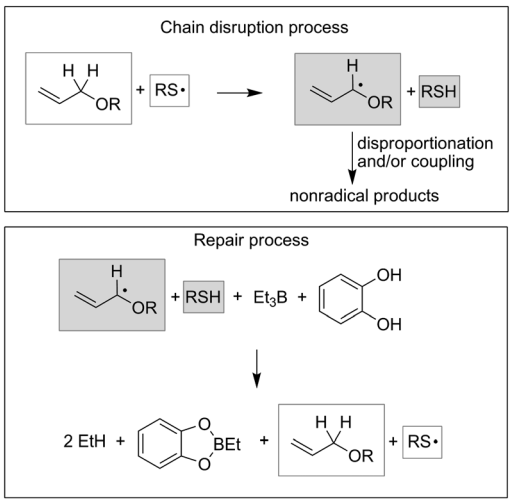
The optimized reaction conditions were tested with a wide range of allyl glycosides including mono-, di-, and tetrasaccharides (Scheme 4).[17] Within 4 hours, full conversion and excellent yields of the isolated products were obtained[18] by using only two equivalents of the thiol on a reaction scale ranging from 40–80 mg of the allyl glycosides to 1.16 g of disaccharide **1f**. This procedure proved to be superior to the thermal reactions (compare to results in Scheme 1: **1a**: 91% versus 17%; **1b**: 83% versus 25%).[19,20]

Alkylthiyl radicals add to nonactivated terminal olefins at rates close to $k_{add} = 10^6\,M^{-1}s^{-1}$ (ca. 300 K).[21] The reverse fragmentation process is much slower ($k_{frag} = 10^5\,s^{-1}$; ca. 300 K).[22] Thiols are excellent hydrogen-atom donors toward alkyl radicals ($k_H = 10^7\,M^{-1}s^{-1}$, ca. 300 K).[23] Thus, assuming a moderately high concentration of the thiol ($\geq$0.1 M), the reduction of the 2-(alkylthio)alkyl radical will be faster than its fragmentation. Moreover, the high rate constants for the two elementary steps of the transformation predict a long-chain mechanism leading to fast, selective, and efficient reactions.[24] However, hydrogen atom abstraction by thiyl radicals from allylic[25] and benzylic positions[26] may cause the unexpected failures of TEC reactions. Hydrogen-atom transfer from C–H bonds adjacent to a heteroatom is particularly efficient (rate constants 10^3–$10^7\,M^{-1}s^{-1}$).[27] The S–H bond dissociation energies (BDE) of alkanethiols are around 87–88 kcal mol^{-1}. Thus, the hydrogen abstraction by an alkanethiyl radical from allylic and benzylic C–H bonds (BDE 79–87 kcal mol^{-1})[28] is exothermic and the equilibrium



Scheme 4. The catechol/BEt_3 TEC reaction with allyl glycosides. PMB = *para*-methoxybenzyl.

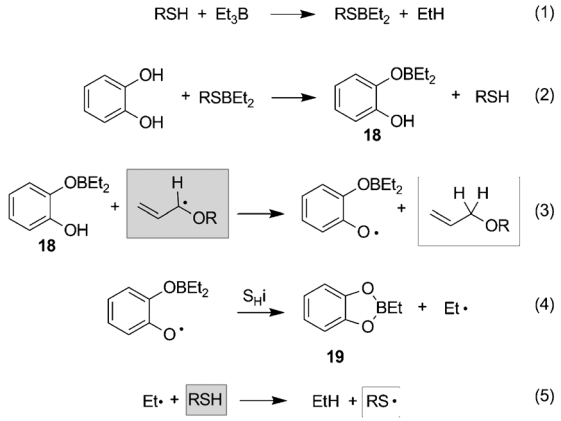
lies on the side of the C-centered radical. The main termination reactions involve coupling and disproportionation of stabilized allylic and benzylic radicals (Scheme 5, chain disruption process).[29] The long-chain mechanism operating under the optimized Et_3B/catechol conditions is particularly striking since only traces of oxygen in a degased



Scheme 5. Disruption and repair processes.

solution are sufficient to drive all reactions to completion. Our data suggest that an efficient repair process is occurring in which the undesired allylic radical and the thiol are converted back into the starting allyl ether and the thiyl radical (Scheme 5, repair process). The repair process described in Scheme 5 for allylic radicals is expected to be valid for any kind of radicals resulting from undesired hydrogen-atom transfer such as benzyl radical and α-heteroatom-substituted alkyl radicals.

Addition of triethylborane to a solution of alkene, dodecanethiol, and 4-*tert*-butylcatechol starts an important ethane evolution, even in carefully degased solutions.[30] When a RSH/TBC/Et_3B 1:1:1 ratio is used, a new borinic ester attributed to the structure **18** is the sole compound observed by ^{11}B NMR spectroscopy ($\delta = 56.3$ ppm). Under our reaction conditions, all the catechol is converted into **18** according to Equations (1) and (2) (Scheme 6). The mono-

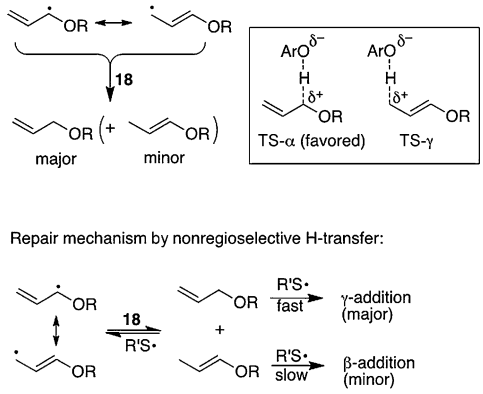


Scheme 6. Repair mechanism operating in the catechol/BEt_3 TEC reaction.

borinate **18** acts as a hydrogen donor with allylic (or benzylic) radicals [Eq. (3)]. This step is close to thermoneutral or slightly exothermic (BDE of O–H bonds in catechols lie close to 80 kcal mol^{-1}).[31] After the hydrogen-atom transfer step, the resulting aryloxyl radical undergoes a rapid 5-*exo* cyclization which produces an ethyl radical [Eq. (4)], which reinitiates the chain upon reaction with the thiol [Eq. (5)].[15] At the end of the reaction with *trans*-**4**, the ^{11}B NMR spectrum reveals that around 15% of **18** has been converted into the B-ethylcatecholborane **19** ($\delta = 35.8$ ppm).[32]

The repair mechanism proposed here works best with 1-alkoxyallyl radicals if the reduction regioselectively provides the allylether over the enolether (Scheme 7, top). The reduction of the allyl radical is expected to be faster at the most-electron-rich carbon atom, thus favoring the regeneration of the allylether over the isomerization to the enolether.[33] Interestingly, according to the Curtin–Hammett principle, a nonregioselective hydrogen-transfer could also explain the repair mechanism (Scheme 7, bottom).

In conclusion, the high reactivity of thiyl radicals induces unwanted degradations by hydrogen abstraction, thus resulting in disruption of the chain reaction. To overcome this



Scheme 7. Regioselectivity issue and the origin of the repair mechanism.

problem, we developed a new TEC procedure which allows restoration of the chain process. Although the concept of the repair process is well known in biological systems, the procedure described here represents a unique example where a repair process is used to increase the efficiency of a synthetic method involving a radical chain reaction.

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[11] At the dilution of 0.3 M used in all experiments, the concentration in thiol at the end of the reaction is 0.15 M, thus giving a pseudo-first-order rate of hydrogen-atom transfer to an alkyl radical of around 3×10^6 s^{-1}, which is still more than ten times faster than the fragmentation of the 2-(alkylthio)alkyl radical intermediate.
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[17] The allyl glycosides **1a–i** were prepared according to reported procedures. See the Supporting Information for references.
[18] See the Supporting Information.
[19] See the procedure from Oshima et al. (see Ref. [20a]) as it involves Et_3B initiation in methanol to give yields between 30% and 50%. Under these reaction conditions, full conversion required a much longer reaction time ($\geq$ 24 h) compared to the reaction in the presence of catechol ($\leq$ 4 h).
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