Hydrogen Transfer

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C–H Activation in S-Alkenyl Sulfoximines: An Endo 1,5-Hydrogen Migration**

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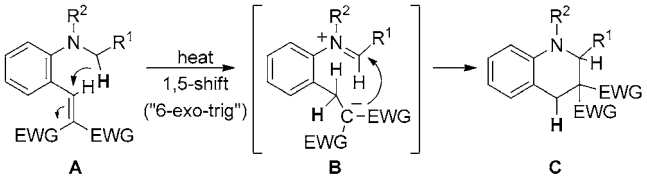
In memory of Richard N. Loeppky

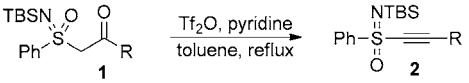
The concept of C–H activation has fascinated chemists for quite a long time. It has been studied with a variety of substrates using metal catalysis, and research in this area continues unabated.[1] Metal-free processes are also known.[2] One particular example of such a C–H activation proceeds through a mechanism that, at least formally, involves the 1,5-sigmatropic shift of a hydride to an electron-deficient site, with concomitant formation of some reactive ionic or zwitterionic species, depending on the nature of the species that undergoes the process.

This interesting and important reaction is part of a process that involves the so-called "*tert*-amino effect".[3] For example, heating a compound, such as **A**, results in a hydride shift in what appears to be a pericyclic process to produce zwitterion **B** (Scheme 1). Collapse of **B** produces **C**. There are a number of other transannular and related carbocationic 1,5-hydride shifts that are not pericyclic, but result in C–H activation via ionic intermediates.[4]



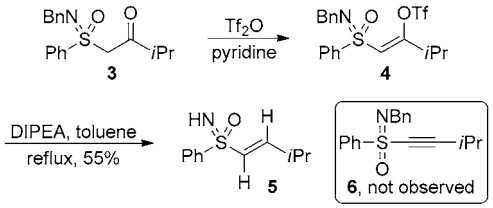
Scheme 1. *Tert*-amino effect.

We recently reported the synthesis of a series of S-alkynyl sulfoximines **2** by dehydration of the corresponding β-ketosulfoximines **1** [Eq. (1)], all of which bore a TBS group



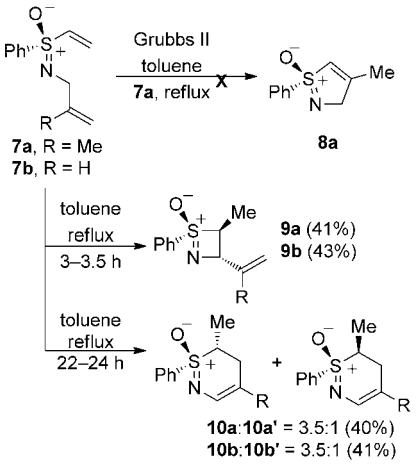
(1)

on the nitrogen atom of the sulfoximine.[5] An attempt to prepare **6**, however, resulted in the formation of **5** by a process we assumed to be an intramolecular redox/C–H activation process (Scheme 2). This result stimulated our interest in this process as a general phenomenon.



Scheme 2. Intramolecular redox reaction.

Around the same time, we were interested in producing the cyclic sulfoximine **8a** through an intramolecular ring-closing metathesis process. We thus heated sulfoximine **7a**[6] in the presence of Grubbs' second generation catalyst in toluene, but obtained only recovered starting material.[7] We subsequently heated **7a** in toluene for 3.5 hours and obtained the cyclic species **9a** in 41% yield of isolated product (Scheme 3) along with **7a** (8%), **10a** (26%), and **10a′** (6%).[8] The structure and stereochemistry of **9a** were established by ^{1}H NMR and NOE experiments. The thermal



Scheme 3. Intramolecular redox reaction and C–C bond formation with vinyl sulfoximines.

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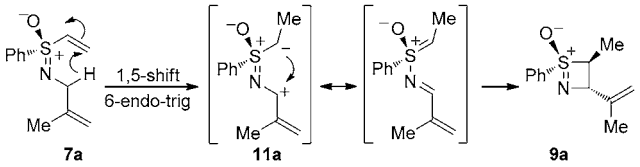
process also worked with **7b**, affording **9b** in 43% yield. Interestingly, if the reaction was allowed to proceed for around 24 hours, thiazines **10** were isolated as a mixture of diastereomers. The stereochemistry of **10a** was verified by X-ray crystallography. To the best of our knowledge, cyclic sulfoximines, such as **9a/b**, are unknown. It also appears that dihydrothiazines, such as **10a/b**, have not been reported.

The mechanism for this reaction presumably begins with an intramolecular hydride migration in **7a** to generate **11a** (Scheme 4). This type of hydride shift appears to be unique. Generally, examples of the *tert*-amino effect and related reactions with ethers involve 6-*exo*-trig or 7-*endo*-trig migrations, if one includes the migrating hydrogen atom in the



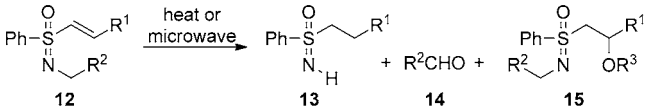
Scheme 4. Proposed mechanism for the formation of **9a** from **7a**.

count, regardless of the specific mechanism.[9] However, 6-*endo*-dig migrations are proposed in pericyclic processes, such as those that occur in the Crabbe homologation.[10] Furthermore, processes that can be characterized as a 6-*endo*-trig hydride transfer are known, but not common.[11] Lastly, there are other types of hydride transfer that are 6-*exo*-dig,[12] 5-*exo*-trig,[13] 8-*exo*-trig,[14] and 7-*exo*-trig[15] processes and others,[16] the characterization of which is vague using this nomenclature.

Ring closure can be formulated as the intramolecular collapse of the zwitterion **11a** or an electrocyclization. Though at present we favor the former explanation, a more definitive answer must await mechanistic studies. For reasons that remain unclear, no other example of cyclization has been observed in our studies of other substrates under similar conditions.

To further explore the scope of the hydride shift, we examined several changes in the substrate as well as the reaction conditions (Table 1). At lower temperatures, conjugate addition of a nucleophilic solvent could be observed, as in the conversion of **12a** to **15a** (entry 1). However, at 170°C or with a longer reaction time, the product of an intramolecular redox reaction, **13a**, was produced (entries 2 and 3). This behavior was reproduced in one other system (entries 4 and 5). Polar solvents facilitate the reaction, as in the examples already mentioned. The redox process occurs with alkenyl sulfoximines that are disubstituted (entries 4–6), but proceeds better with simple vinyl sulfoximines. We note that N-allylic substituents participate in the reaction (entries 7–8), and in these cases no cyclization to heterocycles was observed. Interestingly, three different benzyl substituents afforded products in nearly the same yield (entries 9, 11, and 12). Finally, we recorded the yield of aldehydes produced in this process in several cases. Whether these aldehydes are formed as a result of adventitious water or a different mechanism is not clear at present (entries 8, 9, 11, and 12).

Table 1: Formation of N–H sulfoximines.



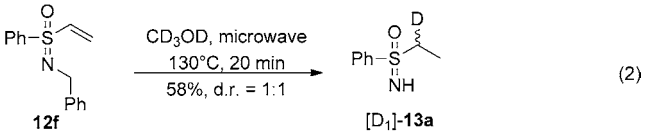
Entry	12	R^1	R^2	13	Yield [%]	14	Yield [%]
1[a,h]	**a**	H	Me	**a**	–	**a**	–
2[b]	**a**	H	Me	**a**	72	**a**	–
3[c,i]	**a**	H	Me	**a**	34	**a**	–
4[a,j]	**b**	*n*Pr	Ph	**b**	–	**b**	–
5[b]	**b**	*n*Pr	Ph	**b**	42	**b**	–
6[d]	**c**	Ph	Ph	**c**	52	**b**	–
7[e]	**d**	2-furyl	vinyl	**d**	39	**c**	–
8[f]	**e**	H	PhCHCH	**a**	83	**d**	76
9[f]	**f**	H	Ph	**a**	81	**b**	60
10[g]	**f**	H	Ph	**a**	62	**b**	–
11[f]	**g**	H	4-OMe-C_6H_4	**a**	86	**e**	80
12[f]	**h**	H	4-Br-C_6H_4	**a**	82	**f**	34

[a] MeOH, microwave, 130°C, 30 min. [b] *n*PrOH, microwave, 170°C, 20 min. [c] *n*PrOH, microwave, 130°C, 2 h. [d] *n*PrOH, microwave, 170°C, 1.5 h. [e] Toluene/H_2O, microwave, 190°C, 2.5 h. [f] Toluene/*n*BuOH, reflux, 4 h. [g] THF/MeOH, microwave, 130°C, 20 min. [h] **15a** (R^3 = Me) was produced in 77% yield. [i] **15a′** (R^3 = *n*Pr) was isolated in 50% yield. [j] **15b** (R^3 = Me) was produced in 62% yield (d.r. = 1:1).

Some aspects of the mechanism of this reaction have been evaluated. Heating **12f** at 130°C in deuterated methanol afforded [D_1]-**13a** as a 1:1 mixture of diastereomers, as expected based on the formation of a zwitterionic intermediate [Eq. (2)]. When the dideuterated sulfoximine [D_2]-**12f** was heated in a mixture of toluene and butanol for 8 hours, the expected deuterated product [D_1]-**13a′** was produced in 64% yield [Eq. (3)]. Interestingly, under the same reaction conditions, **12f** required less than 2 hours to give **13a** in 81% yield (Table 1, entry 9). Though this is a very qualitative observation, it suggests a kinetic isotope effect of around 4, in keeping with a rate-determining step in which hydride transfer occurs.[17,18]

In order to assess the stereochemistry of the hydride transfer, we heated [D_2]-**12b** at 170°C in a mixture of toluene and water[19] to afford [D_1]-**13b** in 83% yield with a 3:1 ratio of diastereomers [Eq. (4)].

In an effort to trap the putative sulfoximine-stabilized carbocation formed in this process, we used ethylene glycol as the polar cosolvent. Heating a solution of **12e** in a 1:1 mixture of toluene/ethylene glycol produced the expected sulfoximine



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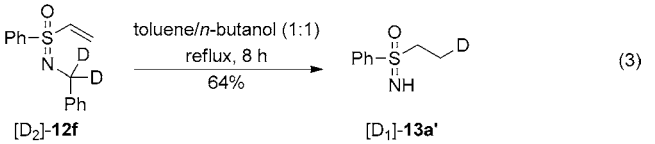

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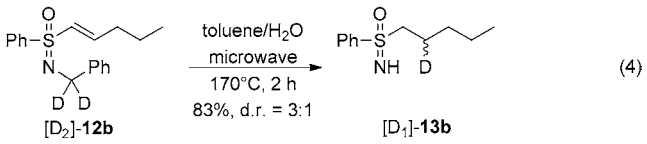
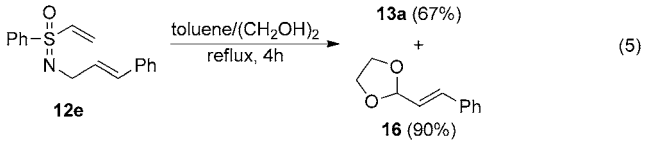


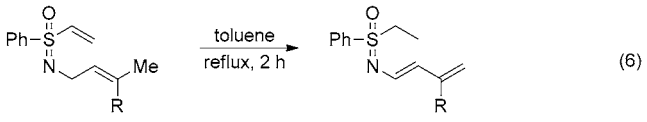
(4)

13a in 67% yield and the cinnamaldehyde acetal **16** in 90% yield [Eq. (5)].[20]



(5)

We wondered if a simple elimination reaction from an allylic cation would be possible, and therefore explored the intramolecular redox reaction with **17a** and **17b** [Eq. (6)]. To our delight, when **17a** was simply heated to reflux in toluene for 2 hours, the diene **18a** was isolated in 95% yield as a mixture of E:Z = 7:1. The conversion of **17b** to a mixture of E:Z = 4:1 occurred nearly quantitatively.[21] Chiral N-dienyl dienes, such as **18a/b**, are not known and potentially useful in cycloaddition processes, such as the Diels–Alder reaction.



(6)

In summary, we have disclosed an intramolecular redox C–H activation process of alkenyl sulfoximines. The process is proposed to proceed through a 6-*endo*-trig hydride transfer to produce a zwitterionic intermediate. This intermediate can close to novel heterocycles, produce N–H alkyl sulfoximines, or form novel, chiral, N-dienyl sulfoximines. This preliminary work raises many questions about the scope of the reaction and how it may be catalyzed. Further results will be reported in due course.

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Keywords: C–H activation · hydrogen transfer · intramolecular redox reaction · *tert*-amino effect · vinyl sulfoximines

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[6] Experimental details on the synthesis of sulfoximines **7a/b** are provided in the Supporting Information.

[7] However, a compound closely related to **7b** did react with the Grubbs catalyst to afford **8b**. Details of this process will be reported elsewhere.

[8] The yields of **7a**, **10a**, and **10a′** were determined by integration of the ^{1}H NMR spectrum of the crude product relative to **9a**, for which a yield of isolated product is given.

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[17] Aliquots from each reaction were withdrawn at intervals of 2 hours and examined by ^{1}H NMR spectroscopy. The reaction of **12 f** was complete in less than two hours, and the reaction of [D_2]-**12 f** was complete at some point between six and eight hours.

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[19] Water was added to see if a hydroxylic species, even an insoluble one, would allow the reaction to occur, particularly after alcoholic cosolvents gave multiple products. Further studies of the process in the presence of water need to be conducted.

[20] A mixture of **13 a**, ethylene glycol, and cinnamaldehyde afforded **16** in 55 % yield under the same conditions.

[21] Products **18** were obtained as clean mixtures of isomers. They are very unstable on silica gel. The major products were isolated by passing through a very small amount of alumina.

