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Anti-Markovnikov rearrangement in sulfur mediated allylic C–H amination of olefins†

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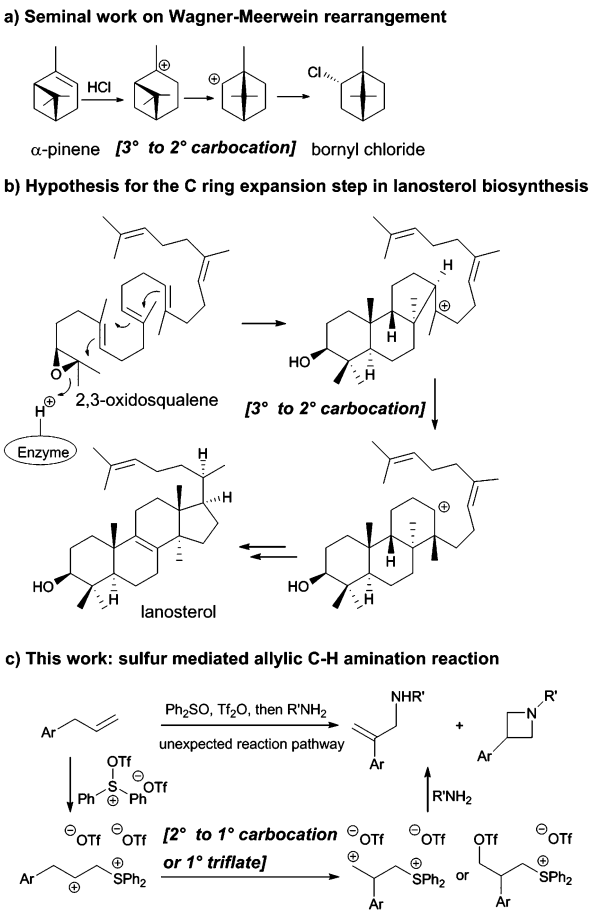
Cationic rearrangement reactions usually follow Markovnikov's rule to give more substituted carbocations as stable intermediates. During our study on sulfur mediated allylic C–H amination of olefins, very rare cases of anti-Markovnikov rearrangement from secondary carbocations toward primary carbocations or primary triflates were observed.

The essence of Markovnikov's rule is the stability of cationic intermediates: tertiary carbocations are more stable than the corresponding secondary ones, which are more stable than the corresponding primary ones. Most organic chemistry textbooks would state the general trend for cationic rearrangement reactions: less stable carbocations would rearrange toward the more stable ones, *i.e.* primary carbocations would rearrange toward the secondary ones, and secondary carbocations would rearrange toward the tertiary ones, through hydride shift, alkyl shift, or aryl shift.[1,2] On the other hand, anti-Markovnikov rearrangement reactions which convert tertiary carbocations to secondary ones are also well-known. Indeed, the seminal work on Wagner–Meerwein rearrangement was intrigued by the conversion of α-pinene to bornyl chloride, a secondary chloride rather than the expected tertiary chloride (Scheme 1a).[3,4] In this case, the release of ring strain for the four-membered ring is apparently the thermodynamic driving force for such abnormal anti-Markovnikov rearrangement. Another famous example is Corey's hypothesis of anti-Markovnikov rearrangement in the biosynthetic pathway of lanosterol, a precursor for many steroids including cholesterol, for its C-ring expansion from a tertiary carbocation to a secondary one (Scheme 1b),[5,6] a much debated puzzle for the past two decades which has led to a number of experimental and theoretical studies.[7–13] However, to the best of our knowledge, secondary to primary carbocation rearrangement has not been reported in the literature. During our study on sulfur mediated allylic C–H functionalization of olefins,[14] serendipitous observation of some rearranged products led us to believe the possibility of such hitherto unknown chemistry involving anti-Markovnikov rearrangement from secondary carbocations toward primary carbocations or primary triflates (Scheme 1c).



Scheme 1 Anti-Markovnikov rearrangement reactions.

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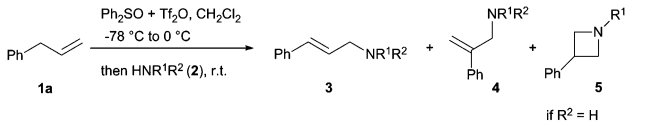
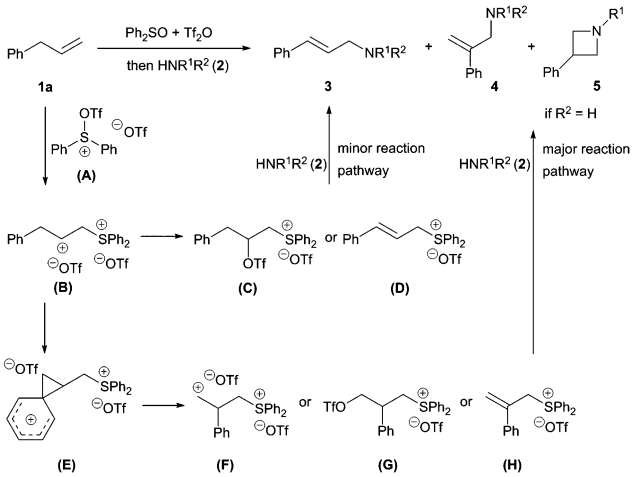
Table 1 Sulfur mediated allylic C–H amination of allylbenzene with different amine nucleophiles[a]



Entry	2	R^1	R^2	3, yield[b] (%)	4, yield[b] (%)	5, yield[b] (%)
1	i-Pr_2NH (**2a**)	i-Pr	i-Pr	**3aa**, 12	**4aa**, 70	—
2	Et_2NH (**2b**)	Et	Et	**3ab**, 16	**4ab**, 47	—
3	*n*-Pr_2NH (**2c**)	*n*-Pr	*n*-Pr	**3ac**, 18	**4ac**, 56	—
4	i-PrNH_2 (**2d**)	i-Pr	H	**3ad**, 8[c]	**4ad**, 50	**5ad**, 18[c]
5	BnNH_2 (**2e**)	Bn	H	**3ae**, 9	**4ae**, 26	**5ae**, 32
6	*n*-PrNH_2 (**2f**)	*n*-Pr	H	**3af**, 9	**4af**, 50	**5af**, 35
7	*t*-BuNH_2 (**2g**)	*t*-Bu	H	**3ag**, 14[c]	**4ag**, 48	**5ag**, 20[c]

[a] Reaction conditions: 1 eq. of **1a** (0.4 mmol) and 1.2 eq. of Ph_2SO in 2 mL of CH_2Cl_2 was treated with 1.2 eq. of Tf_2O at −78 °C, and then warmed up to 0 °C, added 5 eq. of **2** in 1 mL of CH_2Cl_2, and reacted at room temperature before aqueous quenching. [b] Isolated yields after repeated flash column chromatography and preparative thin layer chromatography. [c] NMR yield based on an isolated mixture of **3** and **5**, see the ESI for mixture spectra.



Scheme 2 Proposed reaction mechanism involving anti-Markovnikov rearrangement.

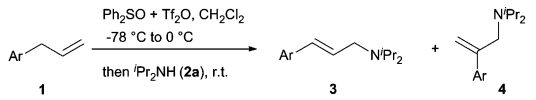
The experiment that initiated this study was very straightforward: electrophilic addition of allylbenzene (**1a**) with the sulfur reagent generated from diphenylsulfoxide and triflic anhydride[15–19] followed by nucleophilic substitution with various amine nucleophiles (**2**) should give allylic C–H amination product **3** with concomitant double bond migration (Table 1). A similar reaction sequence has previously been accomplished in Mukaiyama group's study using α-methylstyrene as an olefin substrate.[18,19] However, when terminal olefin **1a** was examined under these conditions, the originally expected products **3aa** to **3ag** turned out to be the minor products, while the major products were **4aa** to **4ag**. If primary amine nucleophiles (**2d** to **2g**) were used instead of secondary amine nucleophiles (**2a** to **2c**), azetidine products **5ad** to **5ag** were also generated in up to 35% isolated yield. The formation of abnormal products **4** and **5** indicates that some rearrangement step must be taking place during these reactions.

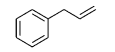
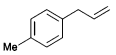
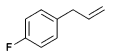
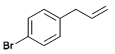
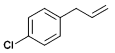
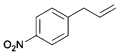
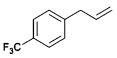
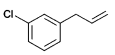
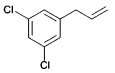
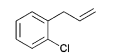
These observations led us to propose the reaction mechanism involving anti-Markovnikov rearrangement as shown in Scheme 2. Reaction of highly electrophilic sulfur reagent **A**[15–19] with allylbenzene (**1a**) should follow Markovnikov's rule, *i.e.* the terminal position of olefin would be the nucleophilic reacting site, to give secondary carbocation **B**. For the minor reaction pathway, **B** could lead to secondary triflate **C** or allyl sulfonium salt **D**; after the addition of amine nucleophile **2**, triflate **C** would also be converted to **D** through an elimination reaction, which would then undergo an S_N2 type reaction at the allylic position to generate the originally expected product **3**. On the other hand, for the major reaction pathway, secondary carbocation **B** might rearrange through phenonium ion **E** to give the corresponding primary carbocation **F**, which could lead to primary triflate **G** or allylic sulfonium salt **H**; alternatively, phenonium ion **E** could be opened by a triflate anion to directly give primary triflate **G**. In the presence of amine nucleophile **2**, elimination of **G** should generate allylic sulfonium salt **H**, which would then undergo an S_N2 type reaction at the allylic position to give the observed major product **4**; when R^2 = H, primary amine nucleophile **2** could also undergo a double S_N2 type reaction with triflate **G** to give the azetidine product **5**. The variable product distribution shown in Table 1 should be the consequence of different reaction rates between these intermediates with different amine substrates.

We believe that the thermodynamic driving force for the conversion of secondary carbocation **B** to primary carbocation **F** or primary triflates **G** could be the result of intramolecular electrostatic repulsion in dicationic intermediates.[20–25] For dicationic intermediate **B**, the cationic carbon center and the cationic sulfur center are separated by only one carbon atom, and thus experience more severe repulsion; on the other hand, for intermediate **F**, the cationic carbon center and the cationic sulfur center are separated by two carbon atoms, and have less severe intramolecular electrostatic repulsion. Anti-Markovnikov rearrangement reactions from secondary carbocations toward primary carbocations or primary triflates are thus possible because the secondary carbocations are now the thermodynamically less stable intermediates.

As shown in Table 2, we then conducted a survey of various substituted allylbenzenes (**1b** to **1j**) to compare the product ratio of **3** and **4**. We expect that the competition between the rearrangement pathway (from **B** to **F**, **G** or **H**) and the normal reaction pathway (from **B** to **C** or **D**) would be influenced by the electronic nature of different aryl migrating groups. Indeed, compared with substrates with more electron-rich aryl groups, substrates with more electron-deficient aryl groups generally give less rearranged products. While the **3** : **4** ratio for allylbenzene substrate **1a** is around 1 : 4 (Table 2, entry 1), 4-methyl substituted allylbenzene **1b** gave a 1 : 9 ratio (entry 2). 4-Halogen substituted allylbenzenes (**1c**, **1d** and **1e**) gave a ratio of around 1 : 3 (entries 3–5), still favouring the rearranged products **4ca**, **4da** and **4ea**. While 4-nitro substituted allylbenzene **1f** gave nearly equal amounts of products **3fa** and **4fa** (entry 6), 4-trifluoromethyl substituted allylbenzene **1g** gave the rearranged product as a minor product (entry 7). This trend is in good accordance with our proposed carbocation rearrangement reaction mechanism,

Table 2 Sulfur mediated allylic C–H amination with different aryl migrating groups

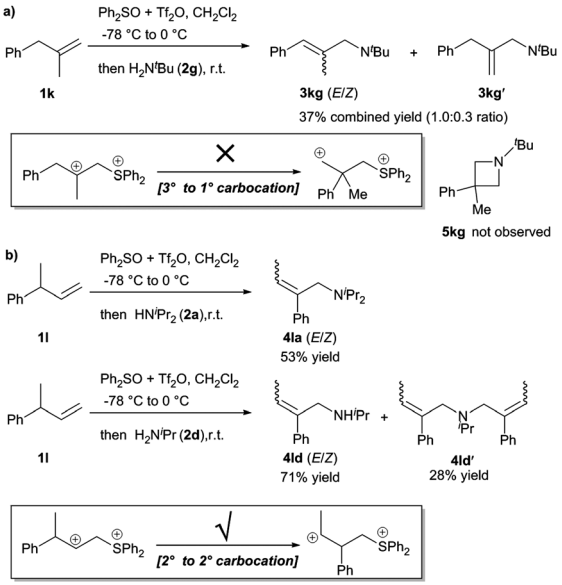


Entry	1		3, yield[a] (%)	4, yield[a] (%)	3 : 4 ratio[b]
1		**1a**	**3aa**, 12	**4aa**, 70	18 : 82
2		**1b**	**3ba**, 9	**4ba**, 58	10 : 90
3		**1c**	**3ca**, 17	**4ca**, 38	26 : 74
4		**1d**	**3da**, 20	**4da**, 67	27 : 73
5		**1e**	**3ea**, 22	**4ea**, 50	27 : 73
6		**1f**	**3fa**, 20	**4fa**, 24	46 : 54
7		**1g**	**3ga**, 40	**4ga**, 22	60 : 40
8		**1h**	**3ha**, 26	**4ha**, 43	39 : 61
9		**1i**	**3ia**, 46	**4ia**, 24	60 : 40
10		**1j**	**3ja**, 44	**4ja**, 4	92 : 8

[a] Isolated yields after flash column chromatography. [b] ^{1}H NMR ratio for the crude reaction mixture, see the ESI for mixture spectra.

since the tendency for aryl shift should decrease with more electron-deficient aryl groups. In addition, the trend (entries 5 and 8–10) for 4-chloro (**1e**), 3-chloro (**1h**), 3,5-dichloro (**1i**), and 2-chloro (**1j**) substituted allylbenzenes seems to indicate that the steric effect was also important for the rearrangement to occur: for *ortho*-substituted substrate **1j**, presumably the phenonium type intermediate (similar to structure **E** in Scheme 2) would be very much hindered from forming, and thus very little rearranged product **4ja** was produced (entry 10); on the other hand, *para*-substituted substrate **1e** would have the least sterically hindered migrating group, and thus gave more rearranged product **4ea** (entry 5). Substrate **1h** with only one *meta*-chloro substituent should be more electron-rich and less sterically hindered than 3,5-dichloro substituted substrate **1i**, and thus the aryl migration product **4ha** was formed in a higher ratio compared with **4ia** (entries 8 and 9).

For the reaction between **1a** and **2a**, we also examined the concentration effect and the temperature effect. If we doubled or quadrupled the amount of CH_2Cl_2 solvent used for the first step, which decreased the concentration of substrate **1a** from 0.2 M to 0.1 M or 0.05 M, the **3aa** : **4aa** ratio turned out to be 18 : 82 or 19 : 81, which remained virtually unchanged. This suggests that the reaction rates for both competing pathways shown in Scheme 2 changed proportionally by the change in the substrate concentration. On the other hand, if triflic anhydride was added at −45 °C instead of −78 °C, the **3aa** : **4aa** ratio would change to 25 : 75, indicating the reaction rates for the two competing pathways were influenced differently by the increase of reaction temperature.



Scheme 3 Attempts for tertiary to primary carbocation rearrangement and secondary to secondary carbocation rearrangement.

We next examined the possibility of tertiary to primary carbocation rearrangement, and secondary to secondary carbocation rearrangement reactions, which could be driven by intramolecular electrostatic repulsion in dicationic intermediates. As shown in Scheme 3, with substrate **1k** and amine nucleophile **2g**, only the normal allylic C–H amination products **3kg** and **3kg′** were formed, indicating the absence of phenyl shift, which would result in a tertiary to primary carbocation rearrangement and give the corresponding azetidine type substitution product **5kg**. In this case, intramolecular electrostatic repulsion is not enough to overcome the energetic cost for anti-Markovnikov rearrangement of a relatively more stable tertiary carbocation. In contrast, with substrate **1l** and amine nucleophiles **2a** and **2d**, only rearranged allylic C–H amination products **4la** and **4ld**/**4ld′** were formed, indicating the high tendency for a secondary to secondary carbocation rearrangement in these cases, which should decrease the intramolecular electrostatic repulsion in the corresponding dicationic intermediates.

In conclusion, we have observed a new type of anti-Markovnikov rearrangement reactions converting secondary carbocations toward primary carbocations or primary triflates in sulfur mediated allylic C–H amination of terminal olefins, which could be driven by intramolecular electrostatic repulsion in dicationic intermediates. These reactions also provide a direct method for converting terminal olefins to the corresponding allylic amines or azetidines.

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