Formal C–H Amination of Cyclopropenes

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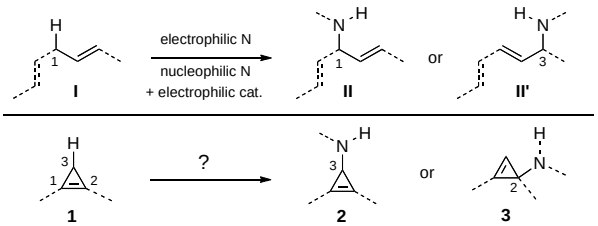
A novel C(sp^3)–H amination of trimethylsilyl-substituted cyclopropenes is described. This C–H amination proceeds via a tandem regioselective ene reaction between cyclopropene and azodicarboxylate to generate a hydrazodicarboxylate intermediate followed by its site-selective allylic transposition.

Allylic C–H amination (**I** → **II** or **II'**), by which simple alkene feedstocks can be transformed to a nitrogen-containing molecules, invites vibrant academic and industrial interests.[1] Due to the relatively weaker allylic/bisallylic C–H bonds, their selective functionalization to C–N bonds is possible with either electrophilic nitrogen sources[2] or nitrogen nucleophiles in combination with electrophilic metal catalysts.[3] In this context, we were intrigued by the C–H amination of cyclopropenes (**1** → **2** or **3)** because, in its nature, the C(3)–H bond in cyclopropene **1** is bisallylic, therefore, its reactivity should mirror that of typical bisallylic C–H bonds.

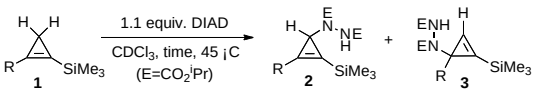


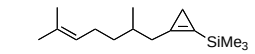
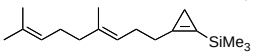
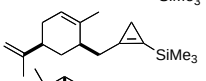
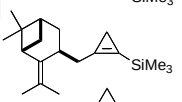
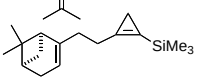
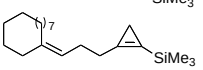
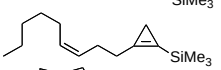
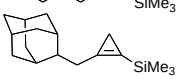
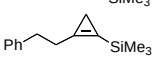
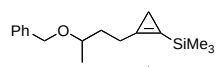
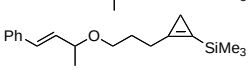
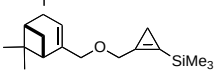
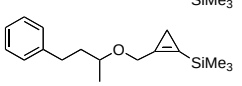
Scheme 1 Allylic C–H amination

Cyclopropenes have high chemical reactivity:[4] the unsubstituted parent cyclopropene undergoes dimerization and polymerization even at –25 °C.[5a] Substituted cyclopropenes are more stable, yet they dimerize at higher temperature.[5b–5e] A radical[5b] and an Alder-ene mechanism[5a] were proposed, and comprehensive quantum mechanical studies by Dowd and Houk[6] provided good mechanistic pictures into these processes. Despite the broad theoretical and mechanistic interests in dimerizations of cyclopropenes,[7] only sporadic ene reactions with other enophiles were reported.[8]

To gauge the cross ene reactivity of cyclopropenes, citronellal-derived silyl cyclopropene **1a**[9] was treated with diisopropyl azodicarboxylate (DIAD, 1.1 equiv) in $CDCl_3$ at 45 °C (entry 1 in Table 1). After 40 hours two products were isolated, which were identified as **2a** and **3a**. Surprisingly, the major product **2a** was not the expected ene product but a C–H amination product, although the minor compound **3a** was indeed derived from the expected ene reaction. The high chemoselectivity for the cyclopropene moiety over the trisubstituted alkene is noteworthy.[10]

Table 1. C–H amination of silyl cyclopropenes[a]



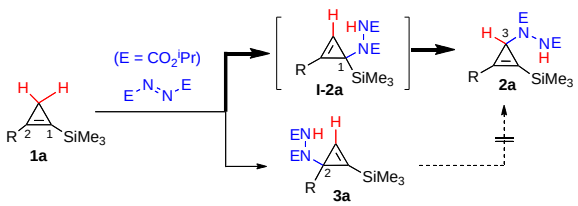
Entry		Cyclopropene	Time (h)	**2** : **3**[b]	Yield (%)[c]
1	**1a**		20	6 : 1	93
2	**1b**		40	12 : 1	90
3	**1c**		18	8 : 1	91
4	**1d**		40	6 : 1	87
5	**1e**		40	4 : 1	93
6	**1f**		3[d,e]	3 : 1	85
7	**1g**		40	2.5 : 1	85
8	**1h**		40	2.3 : 1	88
9	**1i**		40	7 : 1	97
10	**1j**		3.5[e]	1.5 : 1	95
11	**1k**		40	3 : 1	95
12	**1l**		40	2 : 1	90
13	**1m**		15	1 : 1	90
14	**1n**		15	1 : 1	92
15	**1o**		15	1 : 3	88

[a] Unless otherwise indicated, reactions were performed with 0.5 mmol of cyclopropenes in 1 mL $CDCl_3$ at 45 °C for the indicated time. [b] Based on the crude NMR. [c] Isolated yields. [d] With DEAD at rt. [e] For a specified period of time at rt followed by silica gel treatment.[11]

With this encouraging result, we further examined the reaction scope of various cyclopropenes (Table 1). Similar to **1a**, other cyclopropenes containing an additional alkene substituent (**1b**–**h**) provided **2b**–**h** and **3b**–**h** in good yields (entries 2–8). However, the ratio of **2**:**3** varies significantly ranging from 12:1 to 2.3:1 depending on the nature of the alkyl group at C2. Cyclopropenes **1i** and **1j** containing bulky saturated adamantylmethyl and hydrocinnamyl substituents behaved similarly, providing product mixtures of **2i/2j** and **3i/3j**, respectively (entries 9 and 10). The high selectivity for

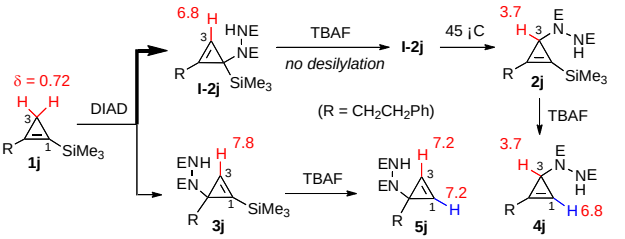
1i (7:1) compared to that of **1j** (1.5:1) is most likely due to the steric effect of the substituents. Cyclopropenes that contain an ether linkage (**1k**–**1o**) provided products **2k**–**2o** and **3k**–**3o** in high yields but with low selectivity (entries 11–15). Especially, these ether-containing substrates showed a different selectivity trend probably due to the inductive effect of the oxygen atoms, even culminating in a reversed 1:3 ratio of C–H amination product **2o** and ene product **3o** (entry 15).

Once a general trend of the ene reaction is established, we probed the mechanism of the C–H amination yielding **2**. Toward this end, the reaction of **1a** and diisopropyl azodicarboxylate (DIAD, 1.0 equiv) was monitored by NMR spectroscopy in $CDCl_3$ at 45 °C (Scheme 2). While **1a** gradually decreased, two new products grew in a roughly 6:1 ratio. As the reaction proceeded, the minor compound constantly grew but the major turned into another compound. After 40 hours, two products were isolated, and they were identified as **2a** and **3a**. In this monitoring, we were able to identify that the initially formed compound was a regioisomeric ene product **I-2a**, which then rearranged to **2a**. On the other hand, the other minor regioisomer **3a** did not rearrange to **2a** even at an elevated temperature, thus it was accumulated. The relatively facile rearrangement of **I-2a** to the final product **2** via an allylic transposition of the C–N bond[12] is assumed to be mainly the consequence of the steric pressure of the trimethylsilyl group.



Scheme 2. [1,3]-transposition of Alder-ene products

To further confirm the identity of the intermediates and products **2** and **3**, the ene reaction products derived from **1j** were desilylated with tetrabutylammonium fluoride (Scheme 3**)**. It is interesting to note that **I-2j** is resistant to desilylation but the regioisomer **3j** was readily desilylated, giving **5j**. However, the isolated **I-2j** rearranged to **2j** at 45 °C, which was then treated with TBAF to provide **4j**. Upon desilylation of **2j**, the C3–H at 3.8 ppm remained same but a new vinyl proton signal appeared at 6.7 ppm, a characteristic chemical shift of the vinyl proton on the alkyl- substituted double bond of cyclopropene. On the other hand, **3j** displaying a vinyl proton signal at 7.7 ppm, a characteristic signal for the proton on the silyl-substituted double bond of cyclopropene, provided a new compound upon desilylation, which now shows two identical vinyl protons at 7.3 ppm, the characteristic chemical shift of 3,3-disubstituted cyclopropene. From the NMR signal assignment, we deduced the structures of **I-2j**, **2j** and **3j** as assigned (see supporting information for details).



Scheme 3. Mechanistic study via desilylation

Additional proof for the formation of intermediates and their conversion to final products was established by ^{13}C-labeled cyclopropene **1p** (Figure 1). The distribution of the ^{13}C-label in combination of ^{1}H signal monitoring proved the formation of intermediate **I-2p** and its allylic transposition to the final product. The ^{13}C-label was ultimately distributed in two major products. The compound containing sp^2-hybridized ^{13}C-label (138 ppm) shows a new signal at 3.7 ppm, while the other compound containing sp^3-hybridized ^{13}C-label (46 ppm) shows a signal at 7.8 ppm. From these data, the structures of these compounds could be assigned unambiguously as **2p** and **3p**, respectively. This ^{13}C-label-based structural assignment for **1p** is consistent with that of the chemical derivatization through desilylation of **2j** and **3j** derived from **1j**. In addition, the reaction profile showed that the intensity of **3p** remained constant after **1p** disappeared completely, which clearly indicates that only **I-2p** but not **3p** rearranged to **2p**.

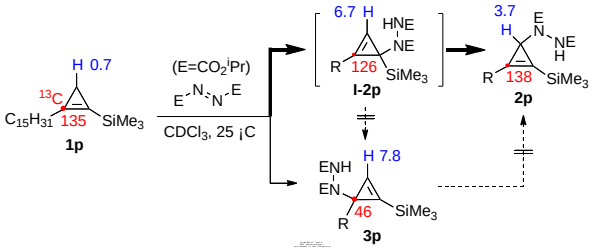
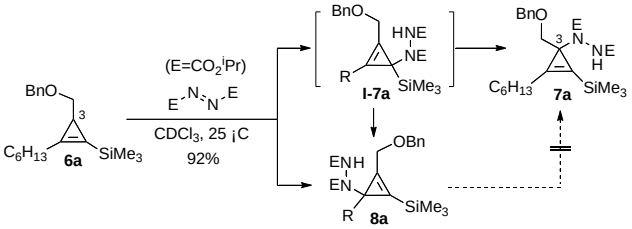


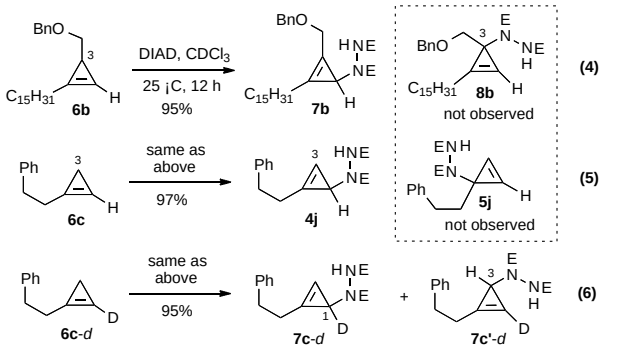
Figure 1. Reaction profile of a ^{13}C-labeled cyclopropene

Next, we examined the C–H amination of **6a** that contains an extra alkyl substituent at C3 (Scheme 4). A mixture of C3–H amination product **7a** and a regioisomeric ene product **8a** was isolated in 92% yield (1.7:1 ratio). Reaction monitoring indicates the formation of intermediate **I-7a**, which rearranged to both **7a** and **8a**. It was also found that the extra C3-substituent significantly retards the ene reaction, and thus even after 20 h cyclopropene **6a** still remained, whereas C3-unsubstituted **1p** reached completion within 3 h.



Scheme 4. Reaction profile of C–H a C3-substituted cyclopropene

The ene reaction of **6b** containing a C3-substituent but devoid of silyl substituent at C1 **(**Eq 4 in Scheme 5**)**, and **6c** containing no substituent at C1 and C3 were also examined **(**Eq 5**)**. As expected, **6b** provided only **7b** in 95% yield without **8b**, and the reaction was much faster than that of trisubstituted cyclopropene **6a**. The lack of forming C3–H amination products **8b** is most likely due to a high barrier for the rearrangement of **7b**.



Scheme 5. Alder-ene reaction of nonsilylated cyclopropenes

Similarly, C2-monosubstituted cyclopropene **6c** afforded regioisomer **4j** without forming **5j**. In case of **4j**, we surmised that there should be a degenerate allylic transposition (Eq 5). To examine this possibility, the reaction of a deuterium-labeled **6c**-*d* was monitored with ^{1}H NMR spectroscopy (Eq 6). At ambient temperature in $CDCl_3$, **6c**-*d* underwent a rapid ene reaction to form **7c**-*d*, confirmed by the C3-vinyl proton signal at 6.8 ppm but lacking C1 proton signal at 3.7 ppm. It was found that **7c**-*d* remained unchanged even at 80 °C, which indicates that **7c**-*d* never rearranged to isotopomer **7c'**-*d*. With this observation, we conclude that the allyic transpositions of **7b, 4j** and **7c**-*d* derived from nonsilylated cyclopropenes have much higher activation barrier than those derived from silyl cyclopropenes.

In conclusion, we have disclosed a novel C–H amination of silylcyclopropenes. This amination involves a rapid Alder-ene reaction followed by an allylic transposition of the quaternary hydrazodicarboxylate intermediate from the carbon bearing the trimethylsilyl group. DFT calculation-based mechanistic studies on this C–H amination of cyclopropenes will be reported in due course.

Notes and references

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† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/
‡ These authors contributed equally.

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[10] The amination occurs on the C(sp^3)–H bond as opposed to the C(sp^2)–H functionalization with deprotonated cyclopropenyl metal species in the C–H amination with diphenylcyclopropenylidene, see: S. D. McGregor, W. M. Jones, *J. Am. Chem. Soc.*, 1968, **90**, 123.

[11] It was found that the silica gel treatment accelerated the rearrangement of intermediates (**I-2f** and **I-2j**) to the final product **2f** and **2j.**

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Table of Contents

A novel C(sp^3)−H amination of silylated cyclopropenes via a regioselective ene reaction with azodicarboxylate followed by its site-selective allylic transposition is described.