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REGIOSELECTIVITY OF INTRAMOLECULAR NITRILE OXIDE–ALLENE CYCLOADDITIONS

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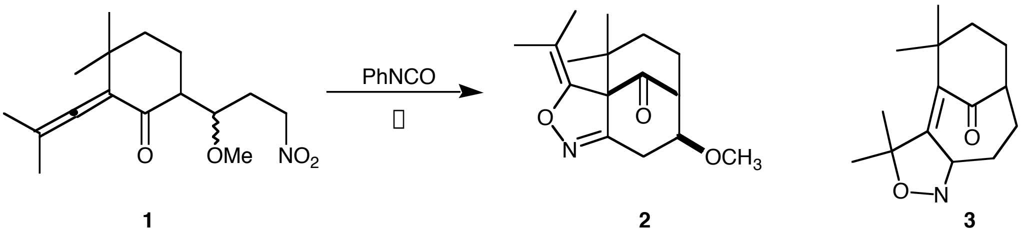
Abstract–Studies on the intramolecular nitrile oxide–allene cycloaddition are reported. The reaction shows a preference for reaction of the more remote □-bond.

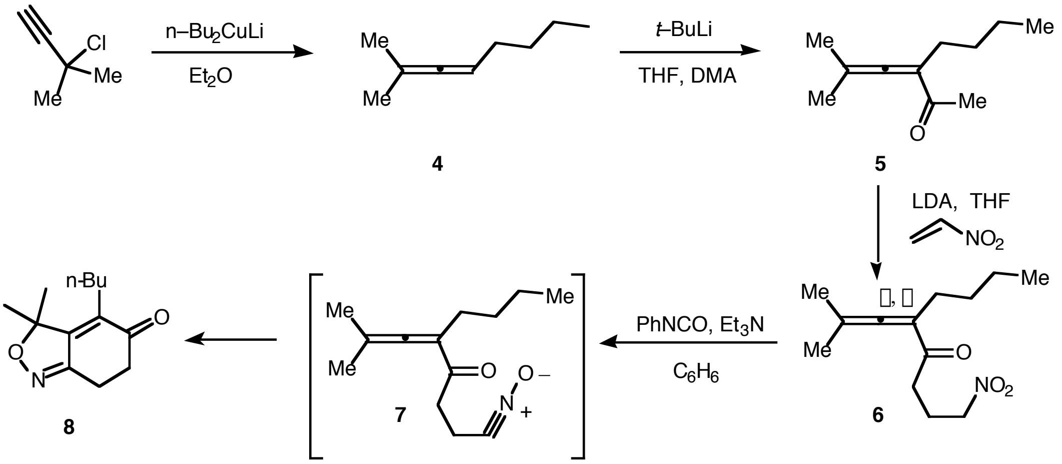
Previously, we reported an intramolecular nitrile oxide–allene cycloaddition route to triacylmethanes.[1] It was suggested that potential formation of a strained bridgehead double bond contributed to the regioselectivity as only **2** was produced in the event (Scheme 1).[2] It was decided to study the cycloaddition in another setting because many instances would not involve a bridgehead olefin as in **1**□ **3**.[3] We report here that the regioselection is turned over in two fused bicyclic systems.

Scheme 1



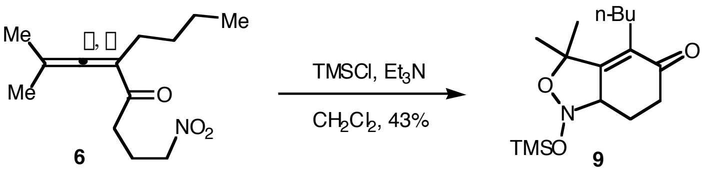
As shown in Scheme 2, 3,3-dimethylpropargyl chloride reacted with dibutyl cuprate to afford allene (**4**) (55%).[4] The allene was deprotonated with LDA and quenched with dimethylacetamide which yielded the methyl ketone (**5**) in 53% yield.[5] The anion derived from **5** underwent Michael addition to nitroethylene to yield 68% of **6.** Dehydration of **6** using phenyl isocyanate generated the nitrile oxide (**7**) *in situ*, which led to the production of isoxazoline (**8**) in the absence of the regioisomer (75%).[6,7]

Scheme 2



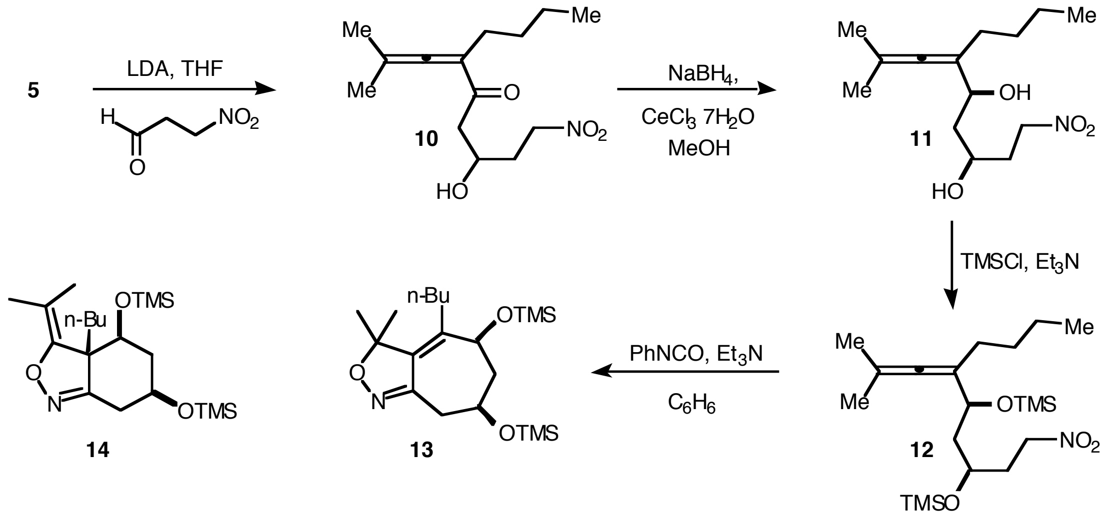
Other reaction conditions did not alter the regioselectivity. For example, treatment of **6** with Boc$_2$O and 4-DMAP produced **8** in 48% yield, and generation of the silyl nitronate produced **9** in 43% yield (Scheme 3). Under no circumstances did the □,□ double bond react.

Scheme 3



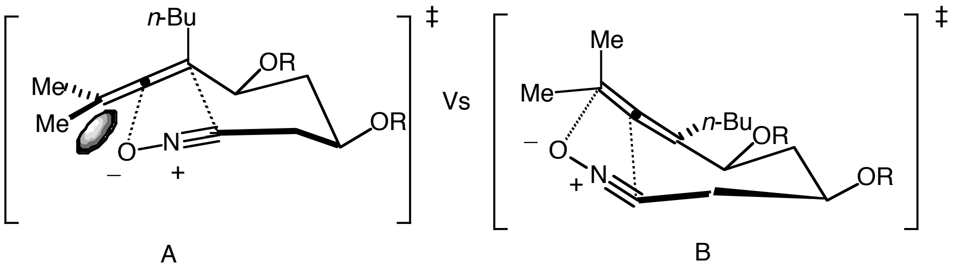
To see if electronic factors were playing a role in the selectivity, the oxidation state of the ketone was adjusted. Condensation of the anion of **5** with 3-nitropropanal gave **10,** Luche reduction of which afforded diol (**11**) (49% for two steps).[8] Double silylation of **11** afforded bis–TMS protected **12** in 90% yield, and treatment of **12** with phenyl isocyanate was found to produce **13** in the absence of **14** (45%).[7,9]

Scheme 4



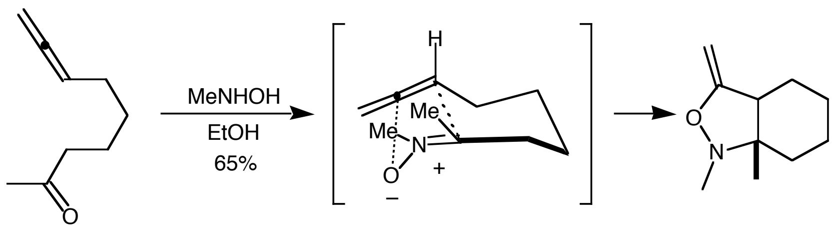
The results can be rationalized through a chairlike transition state in which the n-butyl group is pseudoaxial, (i.e. A, in Figure 1). In A, the nitrile oxide approaches the □ bond in the same plane as the allene methyls whereas B involves approach of the oxygen in an orthogonal plane. If one assumes that the axial alkyl group raises the energy of the chair, transition state B is lower in energy which would lead to products like **8**, **9** and **13**.

Figure 1



These results stand in contrast to the nitrone allene cycloaddition of terminal allenes in which it has been shown that the internal □–bond of the allene is more reactive.[10] In **15**, for example, it is an H atom as opposed to an n–butyl group which would be processed through the chairlike transition state in an axial position.

Scheme 5



15 **16**

In conclusion, the INOC (intramolecular nitrile oxide cycloaddition) reaction is subject to regioselectivity control when a bulky group is present in the □–position of the allene.[11]

ACKNOWLEDGMENT

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11. Data for new compounds prepared: **6**, ^{1}H NMR ($CDCl_3$) □ 4.42 (t, *J*=6.6 Hz, 2H), 2.71 (t, *J*=6.9 Hz, 2H), 2.26 (q, *J*=6.8 Hz, 2H), 2.15 (t, *J*=7.1 Hz, 2H), 1.82 (s, 6H), 1.25–1.35 (m, 4H),

0.87–0.93 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 209.53, 200.10, 107.21, 100.56, 74.87, 34.94, 30.08, 26.36, 22.25, 19.57 (2C), 13.89; HRMS (EI) calcd for $C_{13}H_{21}NO_3$ *m/z* 239.1521, found *m/z* 239.1516; **8**, ^{1}H NMR ($CDCl_3$) δ 2.95, (t, *J*=7.4 Hz, 2H), 2.61 (t, J=7.4 Hz, 2H), 2.29, (m, 2H), 1.55 (s, 6H), 1.34–1.37 (m, 4H), 0.89 (t, *J*=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.69, 156.60, 152.35, 134.83, 85.91, 35.28, 32.19, 25.39 (2C), 25.30, 23.10, 19.97, 13.74; HRMS (EI) calcd for $C_{13}H_{19}NO_2$ *m/z* 221.1416; found *m/z* 221.1420; **9**, ^{1}H NMR ($CDCl_3$) δ 4.22 (m, 1H), 2.85 (td, *J*=15.8, 9.8 Hz, 1H), 2.12–2.28 (m, 3H), 1.80 (s, 3H), 1.73 (s, 3H), 1.54–1.59 (m, 2H), 1.25–1.42 (m, 4H), 0.92 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.8, 133.3, 128.9, 92.1, 74.0, 34.4, 27.5, 26.7, 25.6, 23.1, 22.96, 18.9, 14.1, -0.42(3C); HRMS (EI) calcd for $C_{16}H_{29}NO_3Si$ *m/z* 311.1917; found 311.1928; **10**, ^{1}H NMR ($CDCl_3$) δ 4.54 (t, *J*=5.2 Hz, 2H), 4.06 (m, 1H), 3.59 (s, 1H), 2.83 (dd, 1H), 2.62 (dd, *J*=17.1, 8.9 Hz,1H), 2.00–2.15 (m, 4H), 1.80 (s, 6H), 1.22– 1.32 (m, 4H), 0.85 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 210.06, 202.00, 107.59, 100.97, 72.15, 65.17, 44.87, 33.46, 29.91, 26.02, 22.11, 19.43, 13.79; HRMS (EI) calcd for $C_{14}H_{23}NO_4$ *m/z* 269.1627; found *m/z* 269.1639; **11**, ^{1}H NMR ($CDCl_3$) δ 4.52–4.59 (m, 2H), 4.23–4.27 (m, 1H), 4.00–4.10 (m, 1H), 3.40 (s, 1H), 2.80 (s, 1H), 2.07–2.19 (m, 3H), 1.81–1.91 (m, 3H), 1.80 (s, 6H), 1.34–1.43 (m, 4H), 0.89 (t, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 195.94, 106.37, 102.01, 72.57, 69.57, 65.82, 40.80, 34.45, 29.89, 28.90, 22.30, 20.84 (2C), 13.94; HRMS (EI) calcd for $C_{14}H_{25}NO_4$ $-H_2O$ *m/z* 253.1678, found *m/z* 253.1690; Anal Calcd for $C_{14}H_{25}NO_4$: C, 61.99; H, 9.23; N, 5.17. Found: C, 61.02; H, 8.95; N, 5.00; **12**, ^{1}H NMR ($CDCl_3$) δ 4.44 (t, *J*=7.1 Hz, 2H), 4.14 (t, *J*=6.8 Hz, 1H), 3.84 (m, 1H), 1.72–2.06 (m, 6H), 1.69 (s, 3H), 1.66 (s, 3H), 1.26–1.42 (m, 4H), 0.89 (t, *J*=4.5 Hz, 3H), 0.11 (s, 9H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 198.36, 104.38, 96.74, 72.36, 72.35, 67.43, 44.31, 34.48, 29.90, 25.81, 22.57, 20.63, 20.32, 14.08, 0.27, (6C); HRMS (EI) calcd for $C_{20}H_{41}NO_4Si_2$ *m/z* 4115.2574; found *m/z* 415.2575; **13**, ^{1}H NMR ($CDCl_3$) δ 4.68–4.71 (m, 1H), 4.11–4.14 (m, 1H), 3.10 (dd, *J*=14.7, 5.2 Hz,1H), 2.58 (dd, *J*=14.6, 8.1 Hz, 1H), 2.12–2.23 (m, 2H), 1.87–1.93 (m, 1H), 1.63–1.66 (m, 1H), 1.53 (s, 3H), 1.48 (s, 3H), 1.26–1.45 (m, 4H), 0.93 (t, *J*=6.7 Hz, 3H), 0.16 (s, 9H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.36, 145.05, 140.07, 86.82, 68.35, 65.69, 48.24, 35.01, 32.36, 30.56, 26.72(2C), 23.11, 13.90, 0.18 (3C), -0.02 (3C); HRMS (EI) calcd for $C_{20}H_{39}NO_3Si_2$ *m/z* 397.2469; found *m/z* 397.2473.