CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201100519

Substituent-Controlled Reactivity in the Nazarov Cyclisation of Allenyl Vinyl Ketones

Vanessa M. Marx, Rhonda L. Stoddard, Gavin S. Heverly-Coulson, and D. Jean Burnell*[a]

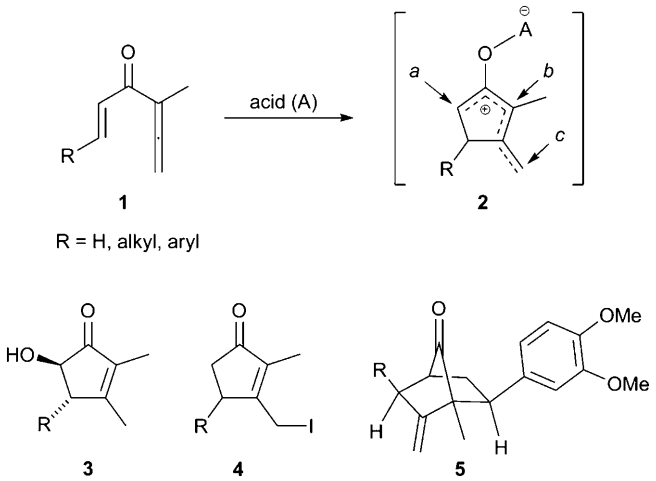
Abstract: Alkyl substitution α to the ketone of an allenyl vinyl ketone enhances Nazarov reactivity by inhibiting alternative pathways involving the allene moiety and through electron donation and/or steric hindrance. This substitution pattern also accelerates Nazarov cyclisation by increasing the population of the reactive conformer and by stabilising the oxyallyl cation intermediate. Furthermore, α substitution by an alkyl group does not alter the regioselectivity of interrupted Nazarov reactions when the oxyallyl cation intermediate is intercepted by addition of an oxygen nucleophile, or by [4+3] cyclisation with acyclic dienes. The regioselectivity of the Nazarov process for allenyl vinyl ketones was determined to be a result of an electronic bias in the oxyallyl cation intermediate. Computational data are consistent with this observation.

Keywords: allenes · carbocations · cyclic compounds · cycloaddition · Nazarov reaction

Introduction

The Nazarov reaction[1] of dialkenyl ketones and its more recently investigated variant, the "interrupted" Nazarov reaction,[2] are powerful tools for the construction of five-membered rings. Although strong acids may be required to induce cyclisation for divinyl ketone substrates, the reaction proceeds more rapidly when the substrate is activated by substitution α to the carbonyl group.[3] An alternative means of activation involves an allene used in the place of one of the alkene units.[4,5] Allenyl ethers cyclise spontaneously following their generation from propargyl precursors,[4] but allenyl vinyl ketones (AVKs) of general structure **1** are easily isolable and can be stored for prolonged periods. However, in the presence of acid, compound **1** undergoes rapid Nazarov cyclisation (Scheme 1), and the intermediate oxyallyl cation **2** has a propensity to be intercepted by nucleophilic species rather than to follow the traditional elimination pathway.[6] This interrupted Nazarov reaction has been exploited to provide a variety of products, such as **3**, **4** and **5**, by capture at positions *a*, *c*, or *a* and *b* of **2** by heteroatom- or carbon-based nucleophiles.

Although previous studies have demonstrated that some AVKs with general structure **1** are valuable substrates for a diverse range of interrupted Nazarov cyclisations, structure **1** represents a single pattern of substitution. The substituent on the alkene terminus of the AVK (R in **1**) has been varied, and the course of the Nazarov reaction did not change significantly. However, it was not known if the regiochemistry of the trapping process (e.g., in the formation of **3** and **5**) might be explained simply by steric hindrance imparted by the methyl group at position *b* in **2** or if there is an electronic bias in oxyallyl cation **2**. Before AVKs can be exploited fully for the synthesis of complex structures possessing five-membered rings, it is crucial that the implications of substitution on the AVK, especially α to the carbonyl group, be understood in terms of reactivity and regioselectivity in the trapping process. The results of a computational and experimental study addressing this important issue are presented herein.



Scheme 1. Nazarov cyclisation of AVK **1** and representative products formed by interception of oxyallyl cation **2**.

[a] Dr. V. M. Marx, R. L. Stoddard, G. S. Heverly-Coulson, Prof. D. J. Burnell
Department of Chemistry, Dalhousie University
Nova Scotia, B3H 4R2 (Canada)
Fax: (+1) 902-494-1310
E-mail: jean.burnell@dal.ca

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201100519.

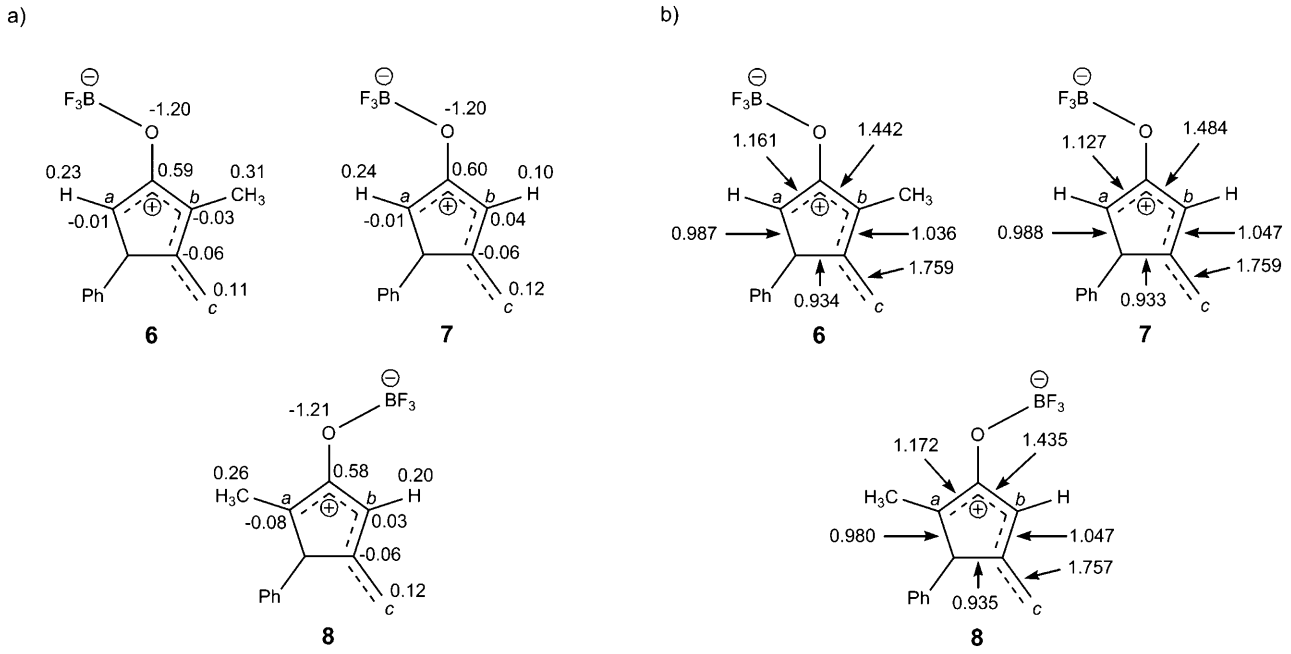
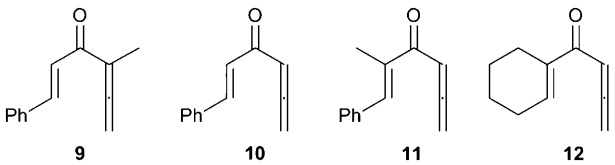


Figure 1. a) Selected atomic charges and b) delocalisation indices for oxyallyl cations **6–8**, in their lowest-energy conformations, as calculated by QTAIM methods (RI-MP2/cc-pvdz).[9]

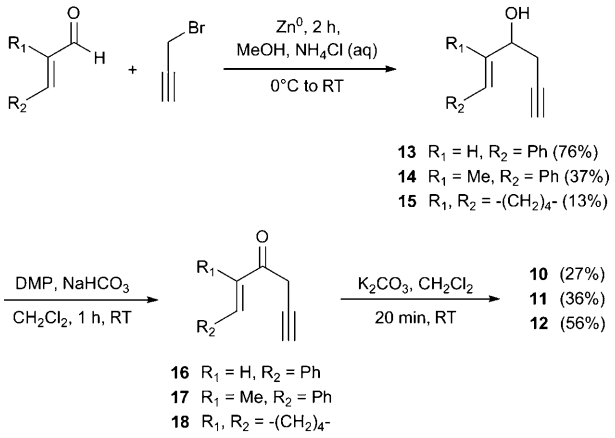
Results and Discussion

An increased amount of positive charge borne largely at position *a* in **6** (Figure 1), rather than at positions *b* or *c*, might play a significant role in the high regioselectivity observed for position *a* in the interrupted Nazarov reactions of AVKs of general structure **1**. Thus, a computational examination of oxyallyl cation **6**, derived from Nazarov cyclisation of AVK **9** with BF_3 as the acid, was carried out with the intent of locating any significant electronic bias in the oxyallyl cation. In addition, to specifically probe the electronic role of substitution α to the carbonyl group, oxyallyl cation **7**, bearing no α-substituent, and oxyallyl cation **8**, derived from a compound with an α-methyl substituent on the alkenyl side of the carbonyl group, were also examined computationally (Figure 1). Species **7** and **8** would be derived from the BF_3-mediated Nazarov cyclisations of AVKs **10** and **11**, respectively.



By using the quantum theory of atoms in molecules (QTAIM),[7] the atomic charges on all of the atoms in **6**, **7** and **8** were determined computationally (Figure 1a). There were no significant differences between **6**, **7** and **8** in the lengths of the bonds between adjacent sp^2 carbon atoms, but important differences were revealed in the delocalisation indices (Figure 1b),[8] which are estimates of bond population by pairs of electrons. Regardless of the presence or position of the methyl group, the bond from the oxygen-bearing carbon to *b* and the carbon–carbon bond to *c* had larger indices than the bond from the oxygen-bearing carbon to *a*, which points to position *a* as the most electrophilic carbon in all three oxyallyl cations. Thus, if steric differences are negligible, AVKs **9–11** should exhibit similar regioselectivities in interrupted Nazarov processes.

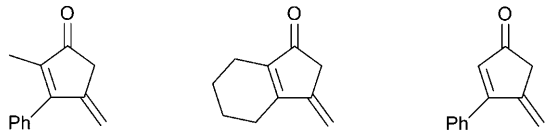
AVKs **10–12** were synthesised to compare experimentally with AVK **9** (Scheme 2). The zinc-mediated Barbier-type coupling of propargyl bromide with the corresponding α,β-unsaturated aldehydes[10] was more satisfactory than a procedure that uses more costly indium.[6a] The use of indium in



Scheme 2. Preparation of AVKs **10–12**.

lieu of zinc gave a 1:1 mixture of the propargyl alcohol and the allenyl alcohol and attempts to prepare the AVKs by oxidation of the allenyl alcohols were unsuccessful with a variety of oxidants, including $(COCl)_2/Et_3N$, iodoxybenzoic acid, $BaMnO_4$, MnO_2, the Dess–Martin periodinane (DMP) and a DMP/$NaHCO_3$ combination.[11] Oxidation of propargyl alcohols **13–15**, however, was accomplished successfully by using DMP/$NaHCO_3$. Other reagents, such as CrO_3/H_2SO_4, $(COCl)_2/Et_3N$ and even DMP alone, resulted in decomposed material, and $BaMnO_4$ and MnO_2 did not react with the starting material. Oxidation of **13** was accompanied through isomerisation of **16** to give AVK **10** directly, whereas AVKs **11** and **12** required a separate base-mediated isomerisation step with **17** and **18** as the intermediate productsYES. Although both K_2CO_3 and triethylamine were equally effective for the base-induced isomerisation of **17** to **11**, Na_2CO_3 and $NaHCO_3$ failed to produce **11** in acceptable yield.

AVK **9** was amenable to purification by chromatography over silica gel.[6a] AVK **10** also proved to be stable with silica gel, but AVKs **11** and **12** were much less so. In the presence of silica gel, **11** and **12** produced some of the corresponding Nazarov elimination products **19** (41%) and **20** (14%). This

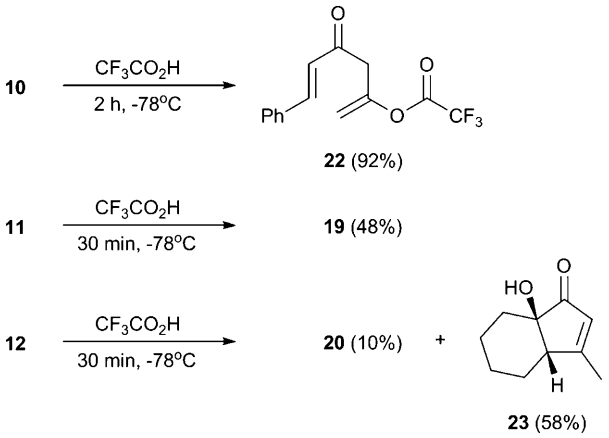


19 **20** **21**

observation parallels the reactivity observed by Hashmi et al.[5a] for AVKs with this substitution pattern, which also underwent rapid Nazarov cyclisation promoted by the weakly acidic silica gel. Purification of AVKs **11** and **12** was also attempted by chromatography using basic alumina; however, this resulted in decomposition. Thus, the two-step yields of **11** and **12** were determined without purification, by ^{1}H NMR spectroscopy by using 1,3,5-trimethoxybenzene as an internal standard. It is important to note that AVKs **11** and **12** decomposed rapidly at room temperature, either neat or in CH_2Cl_2. These compounds could only be stored for less than 24 h in CH_2Cl_2 (0.1 M) at −20 °C.

Treatment of **11** and **12** with BF_3•OEt_2 at −78 °C for 10 min led to complex mixtures, although 23% of Nazarov product **20** was isolated following the reaction of the latter. On the other hand, compound **10** was much more tolerant of the acid and after one hour Nazarov product **21** was obtained in 64% yield.

AVK **10** reacted cleanly in the presence of TFA, but the product was compound **22**, the result of conjugate addition to the allene (Scheme 3). AVK **11** yielded Nazarov elimination product **19** in 48% yield, although AVK **12** gave mainly **23**, which represents an intercepted Nazarov product in which the oxygen nucleophile attacked position *a*. The relative stereochemistry of **23** was confirmed by X-ray crystallographic analysis of the 3,5-dinitrobenzoate of **23** (Figure 2).[12]



Scheme 3. Reactions of AVKs **10–12** with trifluoroacetic acid.

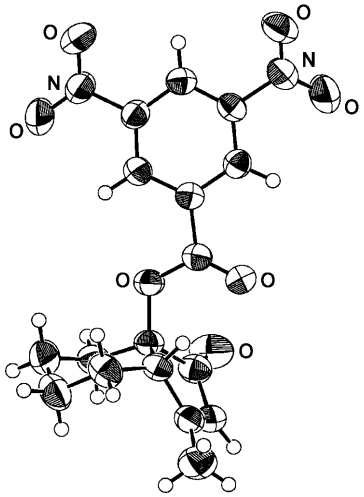
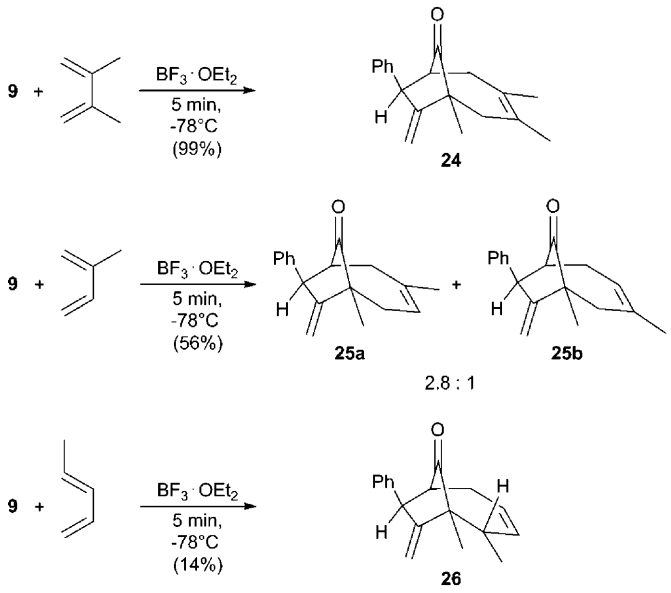


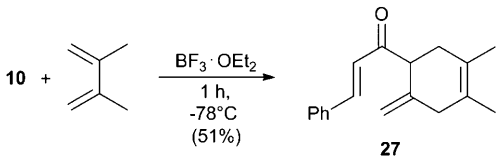
Figure 2. X-ray crystal structure of dinitrobenzoate **23a**.

Although AVK **9** yielded [3+2] cyclisation products, such as **5**, if Nazarov cyclisation was induced with BF_3•OEt_2 in the presence of electron-rich alkenes,[6c] similar products were not seen with **10–12** and NMR analysis of the product mixtures suggested that the bulk of the material reacted directly with the allene moiety of the AVK. Cation **6**, derived from AVK **9**, also underwent [4+3] cyclisations[13] with substituted butadiene derivatives to give bicyclo[4.2.1]nonenone derivatives **24–26** (Scheme 4).

AVK **10** reacted with 2,3-dimethylbutadiene, but the major product was Diels–Alder adduct **27** (Scheme 5). In contrast, AVK **11** underwent rapid Nazarov cyclisation followed by [4+3] cyclisation in the presence of 2,3-dimethylbutadiene to afford bicyclo[4.2.1]nonenone derivative **28**[14] in good yield (Scheme 6). AVK **12** reacted similarly to provide **31**. Both **11** and **12** gave regioisomeric [4+3] cyclisation products (**29a** and **b**, and **32a** and **b**) upon reaction in the presence of isoprene.[15] Nazarov reactions in the presence of *trans*-piperylene gave **30** and **33** and the regioselectivity of these [4+3] cyclisations was the same as was seen with



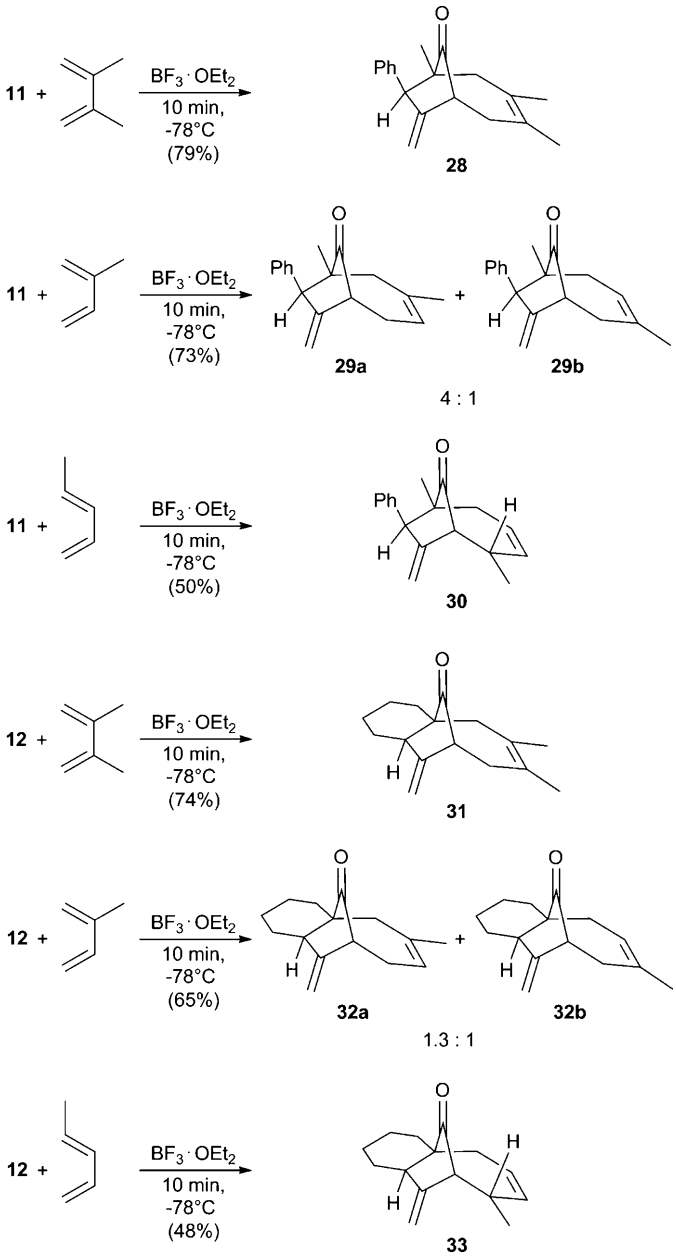
Scheme 4. [4+3] Cyclisations of AVK **9**.[6c]



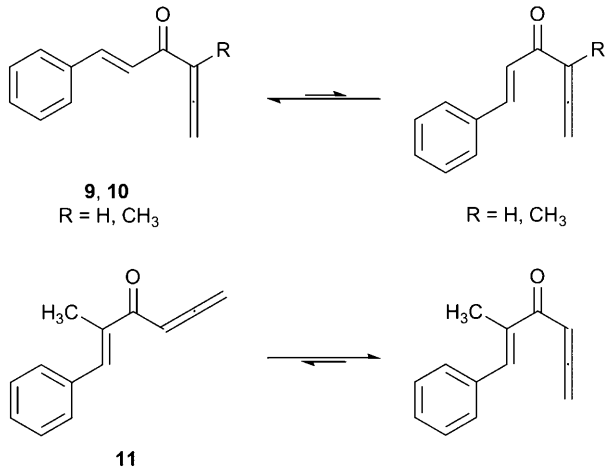
Scheme 5. [4+2] Cyclisation of AVK **10** with 2,3-dimethylbutadiene.

AVK **9**, that is, **26**.[6c,14,15] These provide experimental corroboration of the computational result that the electronic bias in the oxyallyl cations derived from AVKs **9** and **11** (i.e., **6** and **8**) is the same, regardless of the position of the alkyl substituent. That **26**, **30** and **33** were obtained as single stereoisomers is consistent with the [4+3] cyclisation being through a concerted, though likely asynchronous, reaction with an extended geometry.

The computational and experimental data presented herein concerning substituent-controlled reactivity in the Nazarov cyclisation of allenyl vinyl ketones are in accord with the following rationalisation. The most inherently electrophilic site on the oxyallyl cation intermediate is position *a* (the α-alkenyl position) and alkyl substitution on position *a* does not change this. However, substitution by an alkyl group can significantly change the outcome of Nazarov cyclisations. Although AVK **10** is capable of cyclisation, as shown by the formation of **21** in the presence of BF_3·OEt_2, attempts to elicit an interrupted Nazarov process are predicted to be pre-empted by the more rapid acid-mediated reaction of the allene, as in the formation of **22** and **27**. It is proposed that an alkyl group on the allene (as in **9**) attenuates the reactivity at the central carbon of the allene, by electron donation and/or by steric hindrance, allowing the Nazarov pathway to dominate. Furthermore, it is hypothesised that an alkyl group on the alkene or the allene accelerates the Nazarov reaction. It can be seen in Figure 1a that the methyl groups in oxyallyl cations **7** and **8** bear a significant atomic charge that should facilitate the formation of the oxyallyl cation intermediate. In addition, calculations revealed that the alkyl group on the alkene in **11** exerts a significant influence on the conformation, and thus the reactivity, of the AVK (Scheme 7). An s-*trans*–s-*trans* arrangement must resemble the transition state geometry for the Nazarov cyclisation. An s-*trans* conformation of the carbonyl and the allene must be favoured because this feature is seen in the lowest energy conformers of **9**, **10** and **11**. However, without a methyl group on the alkene, the s-*cis* conformation is preferred for the carbonyl–alkene moiety leading to s-*cis*–s-



Scheme 6. Nazarov reactions with subsequent [4+3] cyclisations of AVKs **11** and **12**.



Scheme 7. Conformations of AVKs calculated at RI-MP2/cc-pvdz.[9]

trans conformations for AVKs **9** and **10** being lower in energy than the s-*trans*–s-*trans* conformation by more than 12 kJ mol^{-1}. In contrast, the s-*trans*–s-*trans* conformation is the lowest-energy conformation for AVK **11** by 5.5 kJ mol^{-1} over the s-*cis*–s-*trans* conformation because the methyl group on the alkene induces an unfavourable through-space interaction with the allene when the alkene–carbonyl moiety is in an s-*cis* conformation. Enhancement of Nazarov reactivity though the influence of an α substituent on conformation has previously been observed for divinyl ketones.[1c]

Interrupted Nazarov processes, however, are expected to be less efficient with **11** and **12** than with **9** because the more substituted position *a* offers more steric hindrance. This is shown by comparison of the yields of trapped products from AVK **9**, which are nearly quantitative in the reaction with TFA and with BF_3•OEt_2 and 2,3-dimethylbutadiene, with the yields of the analogous processes with AVKs **11** and **12**. This steric hindrance also explains why AVK **11** gave conventional, eliminated Nazarov product **19** with TFA, whereas AVK **9** yielded only the interrupted Nazarov product.[6a]

Conclusion

The presence of an alkyl group α to the ketone on either the alkene or the allene of an AVK has a significant impact on the efficiency of Nazarov and interrupted Nazarov reactions. AVKs lacking an α substituent can undergo a conventional Nazarov cyclisation, but the interrupted variant of the reaction is not feasible. Interrupted Nazarov reactions can be expected with an AVK bearing an α substituent. An alkyl substituent on the allene is beneficial as it inhibits alternative allene reactions and may accelerate the Nazarov reaction. An alkyl substituent on the alkene accelerates the Nazarov reaction, but interception of the intermediate oxyallyl cation by a nucleophile is retarded by steric hindrance. Overall, with alkyl substitution, the efficiency of the interrupted Nazarov process is dependent on steric hindrance about position *a*, although the electronic bias in favour of position *a* in the intermediate oxyallyl cation is responsible for the regioselectivity. These findings will be invaluable in the design of feasible synthetic approaches involving Nazarov cyclisations of AVKs.

Experimental Section

General considerations: Dichloromethane was distilled from calcium hydride. Ethyl acetate and hexanes were distilled. Flash column chromatography used 230–400 mesh silica gel. Melting points were acquired by using a Fisher–Johns apparatus and are uncorrected. IR spectra (FT) were recorded with an FT instrument by using CsI plates. ^{1}H NMR spectra were acquired at 500 MHz and ^{13}C NMR spectra at 125 MHz as solutions in $CDCl_3$. All HRMS were collected through positive-ion electrospray ionisation (ESI). For computational methods see the Supporting Information.

***(E)*-2-Methyl-1-phenylhex-1-en-5-yn-3-ol (14)**: Propargyl bromide (12 g, 0.10 mol) was combined with α-methyl-*trans*-cinnamaldehyde (10 mL, 0.08 mol) in a mixture of a saturated aqueous solution of ammonium chloride and methanol (5:1, 200 mL) and stirred in an ice bath. Zinc dust (6.7 g, 0.10 mol) was added in four portions, over 20 min. Additional zinc dust (10.3 g, 0.16 mol) was then added in four portions, over 10 min, and the mixture was stirred vigorously at RT for 1 h. The mixture was filtered through Celite, and the aqueous layer was extracted thoroughly with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Flash column chromatography of the residue (10% diethyl ether in pentane) yielded **14** (5.5 g, 37%) as a colourless oil. ^{1}H NMR: δ = 7.34 (2H, m), 7.23 (2H, m), 7.11 (1H, m), 6.60 (1H, m), 4.37 (1H, m), 2.58 (2H, m), 2.19 (1H, d, J = 3.7 Hz), 2.09 (1H, t, J = 2.7 Hz), 1.89 ppm (3H, d, J = 1.4 Hz); ^{13}C NMR: δ = 138.4, 137.2, 129.0, 128.1, 126.6, 126.5, 80.6, 75.5, 70.9, 26.1, 13.5 ppm; IR (film): $\tilde{\nu}$ = 3380, 3297, 2128, 1605 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{14}ONa^+$: 209.0937; found: 209.0941. NMR data match the literature.[16,17]

(*E*)-2-Methyl-1-phenylhex-1-en-5-yn-3-one (17) and (*E*)-2-methyl-1-phenylhexa-1,4,5-trien-3-one (11): DMP (1.5 g, 3.5 mmol) was added to a vigorously stirring solution of alcohol **14** (0.5 g, 2.7 mmol) and sodium bicarbonate (2.3 g, 27 mmol) in CH_2Cl_2 (25 mL) at RT. After 45 min, saturated aqueous solutions of sodium bicarbonate (25 mL) and sodium thiosulphate (25 mL) were added, as well as a small amount of diethyl ether, and the mixture was stirred until both layers went clear. The mixture was extracted thoroughly with CH_2Cl_2 and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum, yielding crude **17** as a pale yellow oil. ^{1}H NMR: δ = 7.58 (1H, q, J = 1.4 Hz), 7.43 (4H, m), 7.37 (1H, m), 3.74 (2H, d, J = 2.8 Hz), 2.29 (1H, t, J = 2.8 Hz), 2.10 ppm (3H, d, J = 1.4 Hz); ^{13}C NMR: δ = 194.8, 140.5, 135.8, 135.4, 129.8, 128.8, 128.5, 77.3, 72.9, 29.7, 13.3 ppm; IR (film): $\tilde{\nu}$ = 1641 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{12}ONa^+$: 207.0780; found: 207.0781. Without further purification, propargyl ketone **17** from the initial step was redissolved in CH_2Cl_2 (25 mL) and potassium carbonate (0.41 g, 3.0 mmol) was added. After stirring at RT for 20 min, the solution was filtered and concentrated under vacuum, yielding **11** (0.18 g, 36%) as a red oil. ^{1}H NMR: δ = 7.50 (1H, m), 7.41 (5H, m), 6.34 (1H, t, J = 6.6 Hz), 5.21 (2H, d, J = 6.6 Hz), 2.12 ppm (3H, d, J = 1.9 Hz); ^{13}C NMR: δ = 215.8, 193.0, 139.3, 137.2, 135.7, 133.2, 129.7, 128.4, 92.5, 78.5, 13.9 ppm; IR (film): $\tilde{\nu}$ = 1967, 1943, 1650, 1601 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{13}ONa^+$: 185.0961; found: 185.0968. Note: the yield of AVK **11** in the crude reaction mixture was determined by ^{1}H NMR spectroscopy by using 1,3,5-trimethoxybenzene as an internal standard and was used without further purification.

2-Methyl-4-methylene-3-phenylcyclopent-2-enone (19): SiO_2 (0.12 g, 2.7 mmol) was added to a solution of AVK **11** (0.10 g, 0.54 mmol) in CH_2Cl_2 (5 mL) at RT and stirred overnight. The mixture was filtered and

concentrated under vacuum and flash column chromatography (10–20% ethyl acetate in hexanes) of the residue yielded **19** (0.041 g, 41%) as a yellow oil. ^{1}H NMR: δ = 7.47 (3H, m), 7.34 (2H, m), 5.29 (1H, s), 5.22 (1H, s), 3.19 (2H, s), 1.88 ppm (3H, s); ^{13}C NMR: δ = 205.2, 164.5, 143.7, 141.1, 133.2, 128.8, 128.5 (4C), 110.9, 39.7, 9.4 ppm; IR (film): $\tilde{\nu}$ = 1703, 1612 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{13}O^+$: 185.0961; found: 185.0962.

4-Methylene-3-phenylcyclopent-2-enone (21): BF_3·OEt_2 (0.070 mL, 0.60 mmol) was added to a solution of AVK **10** (0.070 g, 0.41 mmol) in CH_2Cl_2 (40 mL) at −78 °C. The solution was stirred for 1 h and then poured into a separatory funnel containing a saturated solution of sodium bicarbonate. The organic layer was removed and the aqueous layer was extracted with additional CH_2Cl_2 (×2). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. Flash column chromatography (10–20% EtOAc in hexanes) of the residue provided **21** (0.045 g, 64%) as a yellow oil. ^{1}H NMR: δ = 7.47 (5H, m), 6.37 (1H, m), 5.51 (1H, m), 5.43 (1H, m), 3.22 ppm (2H, m); ^{13}C NMR: δ = 204.5, 170.6, 143.6, 133.4, 133.3, 130.1, 128.9 (2C), 128.4 (2C), 113.8, 41.5 ppm; IR (film): $\tilde{\nu}$ = 1721, 1695, 1610 cm^{-1} (w); HRMS (ESI): *m/z* calcd for $C_{12}H_{10}ONa^+$: 193.0624; found: 193.0628. ^{1}H NMR data match the literature.[18]

(3a*R,7a*S**)-3a,4,5,6,7,7a-Hexahydro-7a-hydroxy-3-methyl-1*H*-inden-1-one (23)**: TFA (0.20 mL, 2.6 mmol) was added to a solution of AVK **12** (0.080 g, 0.54 mmol) in CH_2Cl_2 (55 mL) at −78 °C and this mixture was stirred for 30 min. The mixture was poured into a separatory funnel containing a saturated solution of sodium bicarbonate, the organic layer was removed and the aqueous layer was extracted with additional CH_2Cl_2 (× 2). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum. The crude product was then subjected to column chromatography (Al_2O_3, basic, activated, 20% EtOAc in hexanes then MeOH), which provided **20** (0.009 g, 10%) and **23** (0.052 g, 58%) as yellow oils. For **20**: ^{1}H NMR: δ = 5.24 (1H, s), 5.11 (1H, s), 2.98 (2H, s), 2.45 (2H, m), 2.26 (2H, m), 1.76 (2H, m), 1.70 ppm (2H, m); ^{13}C NMR: δ = 204.9, 165.7, 143.9, 143.1, 107.1, 40.1, 23.1, 22.0, 21.8, 20.6 ppm; IR (film): $\tilde{\nu}$ = 1704, 1641 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_{12}ONa^+$: 171.0780; found: 171.0785. For **23**: ^{1}H NMR: δ = 5.94 (1H, m), 2.76 (1H, m), 2.64 (1H, br s), 2.10 (3H, t, *J* = 1.3 Hz), 1.89 (1H, m), 1.72 (1H, m), 1.61 (4H, m), 1.46 (1H, m), 1.27 ppm (1H, m); ^{13}C NMR: δ = 210.9, 179.1, 126.9, 78.1, 50.3, 32.3, 22.9, 20.7, 18.8, 17.7 ppm; IR (film): $\tilde{\nu}$ = 3437, 1695, 1610 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_{14}O_2Na^+$: 189.0886; found: 189.0884.

(3a*R,7a*S**)-3a,4,5,6,7,7a-Hexahydro-3-methyl-1-oxo -1*H*-inden-7a-yl-3,5-dinitrobenzoate (23a)**: Triethylamine (1 mL, 7.2 mmol) and then 3,5-dinitrobenzoylchloride (0.48, 2.1 mmol) were added to a solution of **23** (0.17 g, 1.0 mmol) and 4-(dimethylamino)pyridine (0.13 g, 1.1 mmol) in CH_2Cl_2 (25 mL) at RT. The solution was stirred for 18 h, diluted with ethyl acetate and washed successively with aqueous solutions of HCl (1 M), NaOH (10%), saturated $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and concentrated under vacuum. Flash column chromatography (10–25% EtOAc in hexanes) of the residue provided **23a** (0.24 g, 67%) as a peach-coloured solid. M.p. 176–179 °C (CH_2Cl_2); ^{1}H NMR: δ = 9.24 (1H, m), 9.12 (2H, m), 6.14 (1H, s), 3.39 (1H, m), 2.18 (3H, s), 2.14 (1H, m), 1.87 (2H, m), 1.70 (4H, m), 1.42 ppm (1H, m); ^{13}C NMR: δ = 203.3, 176.1, 161.4, 148.8, 133.8, 129.8 (2C), 128.3, 122.8, 85.6, 47.0, 30.0, 22.4, 20.5, 18.8, 17.7 ppm; IR (film): $\tilde{\nu}$ = 1720, 1619 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}N_2O_7Na^+$: 383.0850; found: 383.0847.

***(E)*-1-(3,4-Dimethyl-6-methylenecyclohex-3-enyl)-3-phenylprop-2-en-1-one (27)**: BF_3·OEt_2 (1.1 equiv) was added to a solution of AVK **10** (0.070 g, 0.41 mmol) and 2,3-dimethylbutadiene (0.25 mL, 2.2 mol) in CH_2Cl_2 (40 mL) at −78 °C. The solution was stirred for 1 h and poured into a separatory funnel containing a saturated solution of sodium bicarbonate. The aqueous layer was extracted thoroughly with CH_2Cl_2. The combined organic solutions were dried over Na_2SO_4 and concentrated under vacuum. Flash column chromatography of the residue (2.5% EtOAc in hexanes) yielded **27** (0.051 g, 51%) as an off-white solid. M.p. 71–74 °C (CH_2Cl_2/pentane); ^{1}H NMR: δ = 7.63 (1H, d, *J* = 16 Hz), 7.55 (2H, m), 7.38 (3H, m), 6.97 (1H, d, *J* = 16 Hz), 4.98 (1H, m), 4.86 (1H, m), 3.57 (1H, t, *J* = 5.7 Hz), 2.74 (1H, d, *J* = 19 Hz), 2.69 (1H, d, *J* = 19 Hz), 2.63 (1H, br d, *J* = 19 Hz), 1.65 (1H, br d, *J* = 19 Hz), 1.68 (3H, s), 1.62 ppm (3H, s); ^{13}C NMR: δ = 199.4, 144.8, 142.6, 134.9, 130.6, 129.1 (2C), 128.6 (2C), 124.8, 124.3, 124.1, 110.9, 54.2, 39.6, 34.4, 19.0, 18.9 ppm; IR (film): $\tilde{\nu}$ = 1695, 1614 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{20}ONa^+$: 275.1406; found: 275.1403.

(1*R,6*S**,8*S**)-1,3,4-Trimethyl-7-methylene-8-phenylbicyclo[4.2.1]non-3-en-9-one (28)**: BF_3·OEt_2 (1.1 equiv) was added to a solution of AVK **11** (0.10 g, 0.54 mmol) and 2,3-dimethylbutadiene (0.30 mL, 2.7 mol) in CH_2Cl_2 (55 mL) at −78 °C. The solution was stirred for 10 min and poured into a separatory funnel containing a saturated solution of sodium bicarbonate. The aqueous layer was extracted thoroughly with CH_2Cl_2. The combined organic solutions were dried over Na_2SO_4 and concentrated under vacuum. Flash column chromatography (2.5% EtOAc in hexanes) of the residue yielded **28** (0.11 g, 79%) as a colourless oil. ^{1}H NMR: δ = 7.22 (2H, m), 7.17 (1H, m), 6.92 (2H, m), 5.11 (1H, t, *J* = 1.9 Hz), 4.87 (1H, t, *J* = 1.9 Hz), 3.63 (1H, m), 3.24 (1H, m), 2.54 (1H, br d, *J* = 16 Hz), 2.42 (1H, dd, *J* = 16, 7.7 Hz), 2.25 (1H, d, *J* = 16 Hz), 2.18 (1H, d, *J* = 16 Hz), 1.81 (3H, s), 1.72 (3H, s), 0.68 ppm (3H, s); ^{13}C NMR: δ = 222.9, 152.1, 144.5, 129.1, 128.6, 128.1, 126.7, 126.5, 111.1, 57.9, 54.9, 53.4, 50.6, 41.7, 24.6, 23.9, 20.3 ppm; IR (film): $\tilde{\nu}$ = 1743, 1597 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{22}ONa^+$: 289.1563; found: 289.1556.

Acknowledgements

The Natural Sciences and Engineering Research Council of Canada, the Killam Trusts and Dalhousie University are thanked for providing the financial support for this work. We are grateful to Dr. T. Stanley Cameron for the X-ray crystal structure of **23a**, Dr. M. Lumsden for assistance with nuclear magnetic resonance experiments and Mr. Xiao Feng for the collection of mass spectrometry data.

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Received: February 16, 2011
Published online: June 7, 2011

