Ambiphilic molecules for trapping reactive intermediates: interrupted Nazarov reaction of allenyl vinyl ketones with Me₂PCH₂AlMe₂

Josée Boudreau, Marc-André Courtemanche, Vanessa M. Marx, D. Jean Burnell, and Frédéric-Georges Fontaine

Département de Chimie and Centre de recherche sur la propriété des interfaces et de la catalyse (CERPIC), Université Laval, 1045 Avenue de la Médecine, Québec (Québec), Canada, G1V 0A6

Department of Chemistry, Dalhousie University, P. O. Box 15000, Halifax, Nova Scotia, Canada B3H 4R2

E-mails: frederic.fontaine@chm.ulaval.ca and jean.burnell@dal.ca

This is the peer reviewed version of the following article: [Ambiphilic molecules for trapping reactive intermediates: interrupted Nazarov reaction of allenyl vinyl ketones with Me₂PCH₂AlMe₂, Chem. Commun. 2012, 48, 11250 – 11252], which has been published in final form at [10.1039/c2cc35257e].
Ambiphilic molecules for trapping reactive intermediates: interrupted Nazarov reaction of allenyl vinyl ketones with Me₂PCH₂AlMe₂

Josée Boudreau,a Marc-André Courtemanche,a Vanessa M. Marx,b D. Jean Burnell*a and Frédéric-Georges Fontaine*a

Received (in XXX, XXX) Xth XXXXXXXX 20XX, Accepted Xth XXXXXXXX 20XX
DOI: 10.1039/b000000x

The addition of the ambiphilic molecule Me₂AlCH₂PMe₂ (1) to the allenyl vinyl ketone 2 gave a trapped Nazarov reaction product. Under kinetic control, the addition of the phosphine was on the methylated carbon, contrary to expected steric and electronic considerations. Computational data pointed to hydrogen bonding between the phosphine and the methyl group guiding the regiochemistry of this reaction. This product rearranged to provide the expected, regioisomeric Nazarov product. With additional 1 this compound yielded a Michael-addition product via a retro-Nazarov process.

In the past decade, there has been considerable interest in the properties of group XIII ambiphilic molecules, notably as sensors,1 as ligands for transition metals2 and for the activation of small molecules such as CO₂3, H₂4 and O₂.5 It was also demonstrated that ambiphilic molecules could trap active intermediates in Lewis base-initiated organic transformations. Notably, it was shown by Bourissou that phenylazides and diethyl azodicarboxylate, reagents used in the Staudinger and Mitsunobu reactions, respectively, could be activated by the phosphine of phosphine-boranes to lead to intermediates stabilized by the intramolecular Lewis acid.6 Recently, it was also demonstrated that phosphine-boranes could act as organocatalysts for Michael additions7 and in the activation of ketones and esters.8 The Nazarov cyclization is a 4π electrocyclic process promoted by Lewis acids that leads to the synthesis of cyclopentenones from divinyl ketones.9 An interrupted version of the Nazarov reaction has been developed, in which a nucleophile traps the oxallyl cation intermediate.10 Allenyl vinyl ketones (AVKs) are particularly well suited for the interrupted Nazarov cyclization.11 Previous studies have shown that AVKs are typically trapped by nucleophiles at positions (a) or (b), but mostly (a), or by [3+2] or [4+3] cyclizations of an alkene or diene at positions (a) and (c) (Scheme 1).12 In a joint experimental and theoretical study, it was shown that the selectivity for nucleophilic addition at position (a) can be attributed to an electronic bias (the carbon at position (a) is a better electrophile) rather than steric effects (methyl group at position (c)).13 Herein, we report not only that the Lewis acid alane moiety in ambiphilic compound (Me₂PCH₂AlMe₂) efficiently initiates the Nazarov cyclization of AVK 2, but that the phosphine moiety can selectively trap the oxallyl cation at position (a) or (c), which to our knowledge is unprecedented.

Scheme 1. Interrupted Nazarov cyclization.

Ambiphilic molecule (PMe₂CH₂AlMe₂) (1) instantly reacts with allenyl vinyl ketone 2 at 23 °C in benzene-d₆ to give a bright yellow solution of the interrupted Nazarov cyclization products 3 and 4, in which the oxallyl cations are trapped at the (c) and (a) positions (Scheme 2). The ability of Lewis basic moieties, such as the ketone moiety in 2, to break the dimeric structure of 1 has been demonstrated on several occasions, notably using CO₂3f and THF14 (see ESI). The regioisomers 3 and 4 are present in a 3:7 ratio after 40 minutes; however, a complete conversion to product 4 is observed within 20 hours at 23 °C. 13C[1H] NMR spectroscopy reveals that in compound 4, the pendant phosphine moiety has trapped the oxallyl cation in position (a), since the 13C[1H] resonance for C(a) at δ 43.0 appears as a doublet with a 1J_{C-P} coupling constant of 55.4 Hz. The 1J_{H-H} coupling appears as a triplet at δ 2.04 in the 1H NMR spectrum, where the 3.0 Hz coupling constant can be attributed to the 2J_{H-H} coupling with both protons of the terminal vinyl group, which is confirmed by the gDQ COSY 2D NMR spectrum. The 31P[1H] resonate at δ 29.0 for compound 4 reveals 3J_{H-P} coupling for the terminal vinyl protons and both protons of the cyclopentene core, as well as for the diastereotopic P-CH₃ and methylene groups of the ambiphilic compound. 2DNOESY confirms the relative stereochemistry depicted in Scheme 2 (See ESI).

Scheme 2. Results of interrupted Nazarov cyclization using ambiphilic molecule (Me₂AlCH₂PMe₂) (1).

Attack at the (a) position was expected for AVK 2.13 However, under kinetic control, trapping by the nucleophilic phosphine
mioity was observed at position (c), going against both the electronic and steric bias expected for the oxyallyl cation. Immediately after mixing compounds 1 and 2 in dichloromethane-d$_2$ at -25 °C, NMR spectroscopy at -50 °C allowed characterization of 3 as the predominant species (> 90 %). Under these conditions, the $^1$H and $^{13}$C($^1$H) NMR spectra are again in accordance with a cyclopentene core, however both the $^1$H and $^1$C C(c)-CH$_3$ resonances now exhibit coupling with the phosphorous atom; $^3$J$_{C-P}$ and $^3$J$_{H-P}$ couplings of 3.6 and 1.2 Hz, respectively. The $^3$J$_{C-P}$ coupling of 65.9 Hz is now observed for the C(c) $^{13}$C resonance at δ 78.9. For compound 3, attack of the phosphine moiety on the face opposite of the phenyl group is supported by the dipolar coupling between one of the P-CH$_3$ groups and the proton on the carbon atom also bearing the phenyl group (see ESI). Density functional theory calculations at the B3LYP/6-31g(d,p) level of theory confirm that 4 is thermodynamically favoured over 3 by approximately 10 kcal/mol both products being thermodynamically downhill with respect to the isolated reagents (Figure 1).

The presence of species 3 as a kinetic product is nevertheless surprising because steric hindrance due to the presence of the methyl group on C(c) should encourage the energy of the activation barrier compared to the attack of the phosphine on unsubstituted carbon C(a). Furthermore, it was previously established that the delocalization index obtained by QTAIM (quantum theory of atoms in molecules) calculations also favour “attack” at position C(a), although the charges on C(a) and C(c) are quite similar. It appears that when reacting with ambiphilic phosphine-alane 1, stabilization of the oxyallyl cation occurs by electronic density transfer through an interaction between the intramolecular phosphine moiety and the methyl group on C(c). All attempts to find reaction intermediates using DFT calculations resulted either in interrupted Nazarov cyclization products 3 and 4, or in the structure depicted in Figure 2, in which the lone pair of the phosphine moiety is oriented towards one of the hydrogen atoms on the methyl group in position (c). The H-P distance of 2.54 Å falls in the range expected for a methyl group involved in a hydrogen bond (2.3 to 2.7 Å). The corresponding ΔG was calculated to be at 5.1 kcal/mol compared to the isolated reagents, but it is well known that the value of ΔS in such an interaction is usually underestimated. Although the hydrogen bond is relatively weak (estimated to be 4-5 kcal/mol), it appears to be sufficiently strong to promote the generation of 3.

Figure 2. DFT model for intermediate that could explain the formation of kinetic product 3.

A transition state was localized on the potential energy surface that corresponds to slippage of the phosphine moiety from C(c) to C(a) without complete dissociation (see ESI); however, as it would correspond to an activation barrier of 54.3 kcal/mol, it seems likely that transformation of product 3 into 4 occurs through dissociation of the phosphine moiety and rearrangement of the cyclic core to allow binding of the phosphine moiety to C(a). In attempts to trap a reaction intermediate with a pendant phosphine, NBu$_3$Cl and Me$_2$SiCH$_2$CH=CH$_2$ were added to 2 prior to addition of 1, but no reaction was observed with either of these reactants. Scheme 3. Formation of the Michael’s addition product in presence of an excess of 1.

Addition of a slight excess of 1 catalyzes the formation of product 5, which is formally the product of a Michael addition on the AVK 2. The $^3$J$_{H-P}$ coupling constants of the terminal allylic protons; 22 Hz (cis) and 44 Hz (trans) in the $^1$H NMR spectra confirm the position of the phosphorus atom. Other signals have been thoroughly assigned according to the proposed structure 5 (See ESI). Dipolar coupling between the terminal alkyl group and allylic protons confirms formation of the Z-isomer which is favored over the E-isomer by greater than 25 kcal/mol as determined by DFT calculations (see ESI, 5'). Interestingly, addition of an excess of PMe$_3$ to product 4 did not yield any reaction, even after 4 hours. In fact, only unreacted 4 and free PMe$_3$ were observed in the $^1$H NMR spectra. This suggests that the alane moiety is of particular importance in the catalytic transformation of 4 into 5.

Attempts to obtain high resolution mass spectra for compounds 3, 4 and 5 resulted in hydrolysis of the phosphine-alane moiety and oligomerization to what can be tentatively identified as compounds 10*, 11* and 12* based on the exact mass data (see ESI for structure and characterization). In fact, addition of one equivalent of water to a benzene-$d_6$ solution of 4, results, apart from the precipitation of what can be assumed to be mixed aluminum oxides/hydroxides, in a $^1$H NMR spectrum extremely similar to compound 5, albeit the absence of resonances corresponding to aluminum alkyl moieties and the very broad resonance close to free PMe$_3$.

Figure 3. Allyl vinyl ketones used with 1.

AVKs 7 and 8 are poorer substrates for Nazarov reactions than 2. Therefore it was not surprising that upon addition of 1 these AVKs afforded complex mixtures of products. AVK 9 had behaved like 2 under some Nazarov conditions, but under other conditions it had dimerized via a Nazarov reaction and [3+2] cyclization of the second molecule. AVK 9 was examined with 1 at 23 °C. The energy barrier between 3 and 4 was small, and that barrier was somewhat different with 9 because only Nazarov product 4-OMe, along with a small amount of 5-OMe, was observed by NMR. Addition an excess of 1 generated 5-OMe from 4-OMe quantitatively. This transformation, like the formation of 5 from 4, must include a retro-Nazarov reaction with a low barrier since forcing conditions are not required. The need for an excess of 1 is consistent with the P-to-cyclopentene bond of 4 (or 4-OMe) being ruptured only association of that P to
the Al of a second, free molecule of 1. The resulting cationic intermediate can undergo the \textit{retro}-Nazarov and reclosure of the P onto the central allene carbon to generate 5 (or 5-OMe). Thus, \textit{Nazarov} reactions of 2 and related AVKs could be reversible until the addition of a nucleophile creates a strong bond.

**Scheme 4. Results of interrupted Nazarov cyclization using 9**

In conclusion, we have shown that amphiphilic molecule 1 does not only initiate \textit{Nazarov} cyclisation of allenyl vinyl ketones such as 2, but it permits trapping and characterisation of an unprecedented kinetic \textit{Nazarov} product 3. Rearrangement of 3 at room temperature generates thermodynamically favoured \textit{Nazarov} product 4. However, with a slight excess of 1, the \textit{Nazarov} product 4 gives 5. This study represents an important first direct observation of sequential reactions, including \textit{Nazarov} and \textit{retro}-\textit{Nazarov} reactions, taking place in the acid-mediated reaction of an allenyl vinyl ketone, and reversibility in some of its \textit{Nazarov} reactions is indicated.

We are grateful to NSERC (Canada), CFI (Canada), CCVC (Québec), and CERPIC (Université Laval) for financial support. J.B., M.-A.C., and V.M.M. would like to acknowledge NSERC and FQRNT for scholarships.

**Notes and references**

* Département de Chimie et Centre de Recherche sur la Catalyse et les Interfaces (CERPIC), Université Laval, 1045 Avenue de la Médecine, Québec, Québec, Canada. G1V 0A6; Fax: 1(418)656-7916; Tel: 1(418)655-5140; E-mail: frederic.fontaine@chem.ulaval.ca.

Department of Chemistry, Dalhousie University, P. O. Box 15000, Halifax, Nova Scotia, Canada B3H 4R2. E-mail: jean.burnell@dal.ca.

† Electronic Supplementary Information (ESI) available: Full NMR characterization and atomic coordinates for DFT models. See DOI: 10.1039/b000000x/


