Nazarov Reaction

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Organoaluminum-Mediated Interrupted Nazarov Reaction**

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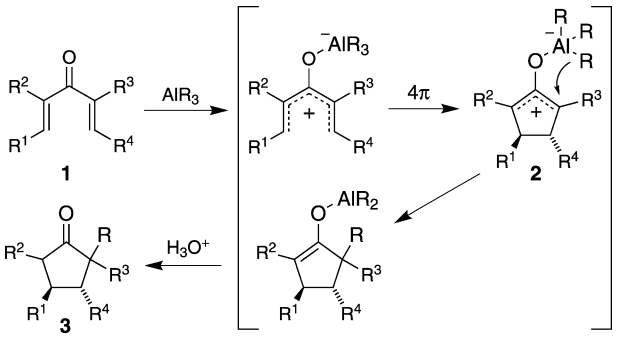
There has been considerable recent interest in the Nazarov reaction,[1] especially with respect to catalytic asymmetric variants,[2] alternative substrates,[3] and domino or cascade processes initiated by the electrocyclization step.[4] The domino or cascade process, termed the "interrupted Nazarov" reaction, often entails nucleophilic trapping of the 2-oxidocyclopentenyl cation formed after electrocyclization, using either intra- or intermolecular traps. The result, introduction of the nucleophilic group α to a cyclopentanone carbonyl carbon atom, represents a formal umpolung approach to functionalized cyclopentanoids. However, to date this chemistry has been largely limited to π-nucleophiles (allyl silanes, enol derivatives, electron-rich arenes) as well as certain heteroatomic traps,[5] and introduction of simple alkyl groups by this method has been elusive.[6]

Triorganoaluminum compounds are intrinsically Lewis acidic, yet their formation of Lewis acid–base complexes can permit the transfer of one of the aluminum substituents to an activated substrate.[7] For example, trialkylaluminum reagents have been used in epoxide opening,[8] S_N'- type reactions,[9] and acetal cleavages.[10] On the other hand, the use of trivalent aluminum compounds to initiate Nazarov cyclization has been quite rare.[11,12] We envisaged a new type of interrupted Nazarov reaction employing triorganoaluminum reagents, in which one of the groups on aluminum could migrate to an allyl terminus of cyclized intermediate **2**, affording, after quenching of the resulting aluminum enolate, substituted cyclopentanones **3** in which R might include previously inaccessible alkyl or aryl groups (Scheme 1) by metal-mediated delivery.[13] Herein we describe the realization of this chemistry.



Scheme 1. Triorganoaluminum-mediated interrupted Nazarov reaction.

The ability of triorganoaluminum reagents to effect Nazarov electrocyclization was uncertain, as was the potential for premature methyl addition to the activated dienones. At the outset, we chose to examine the behavior of several dienones in the presence of excess trimethylaluminum (Table 1). In the event, dienones **1a–d** afforded methylated cyclopentanones **3a–d** in excellent yield upon treatment with 2.5 equivalents of Me_3Al at low temperature in dichloromethane in the presence of 4 Å molecular sieves[14] (entries 1–4). Notably, in all cases the product was obtained as a single (all-*trans*) diastereomer,[15] indicating complete stereoselectivity in the enolate protonation step.

Compound **1e** was converted into cyclopentanone **3e** in reduced yield (entry 5). We attribute this to the requirement for higher temperature (−25 °C) in the cyclization step, which permits minor amounts of the competing 1,2-addition of methyl to give alcohol **4e**. This undesired side-reaction becomes the exclusive pathway in the case of unsymmetrically substituted dienone **1f**, lacking a substituent at C-4. In this case, dienol **4f** was obtained in good yield, presumably owing to slower electrocyclization and greater accessibility of the carbonyl to attack by the relatively small methyl nucleophile.[16]

Other unsymmetrically substituted dienones (**1g–j**) did undergo the desired interrupted Nazarov process, allowing an examination of regioselectivity in the methyl addition step (entries 7–9). Substrate **1g**, lacking an R^4 substituent, underwent clean cyclization and methylation at the terminus adjacent to the unsubstituted carbon to afford **3g** as an 11:1 *trans*/*cis* mixture. The dihydropyran-containing substrate **1h** also gave an excellent yield of bicyclic products **3h** and **3h′**. In this case, methyl delivery was completely regio- and stereoselective to afford a *cis* ring-fusion, but an approximately 2:1 mixture of epimers was obtained at the site of the former enolate. The relative configuration of the major epimer **3h** was determined by single-crystal X-ray diffraction.[15] The nearly symmetrical dienone **1i**,with *n*Pr and Me substitution at C-2 (R^2) and C-4 (R^3), gave a mixture of three products in high yield, and with surprisingly high regioselectivity for methylation on the methyl-substituted carbon in preference to the propyl-substituted position. Finally, dienone **1j** provided a mixture of regioisomers **3j** and **3j′** in excellent yield. Methyl migration occurred preferentially at the carbon adjacent to the 4-methoxyphenyl group.

Having established the generality of the methylation reaction, we now sought to explore the range of organo-

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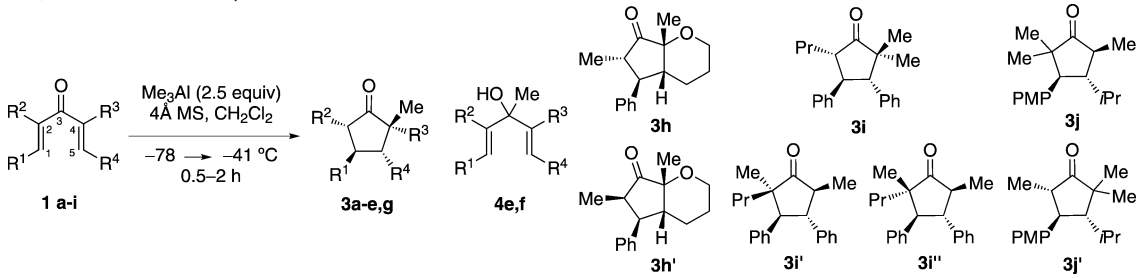
Table 1: $AlMe_3$-Mediated Nazarov Cyclization.[a]



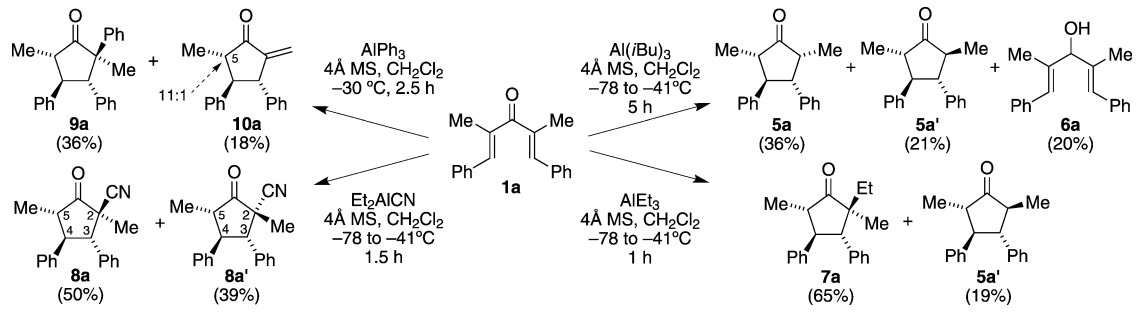
Entry	Substrate	R^1	R^2	R^3	R^4	Product(s)	Yield [%][b]
1	**1a**	Ph	Me	Me	Ph	**3a**	92
2	**1b**	4-ClC_6H_4	Me	Me	4-ClC_6H_4	**3b**	92
3	**1c**	4-$MeOC_6H_4$	Me	Me	4-$MeOC_6H_4$	**3c**	82
4	**1d**	2-furyl	Me	Me	2-furyl	**3d**	94
5[c]	**1e**	*i*Pr	Me	Me	*i*Pr	**3e**[d]	54
6	**1f**	Ph	Me	H	Ph	**4f**	74
7	**1g**	Ph	Me	Me	H	**3g** (11:1)[e]	79
8	**1h**	-$(CH_2)_3O$-		Me	Ph	**3h/3h′** (2.3:1)[f]	79
9	**1i**	Ph	*n*Pr	Me	Ph	**3i/3i′/3i″** (7.1:1.1:1.0)[g]	84
10	**1j**	4-$MeOC_6H_4$	Me	Me	*i*Pr	**3j/3j′** (2:1)[h]	93

[a] Standard procedure: 2.5 equivalents of $AlMe_3$ (2.0 M solution in $PhCH_3$) were added to a solution of **1** in CH_2Cl_2 (0.1 M) with activated 4 Å molecular sieves at −78 °C. The reaction mixture was transferred into a bath at −41 °C, and stirred until complete consumption of starting material (TLC); PMP = 4-methoxyphenyl. [b] Yields are based on isolated product after chromatography. [c] The reaction was carried out at −25 °C. [d] 1,2-Adduct **4e** was also obtained in ca. 23% yield. [e] Ratio of diastereomers (*trans*/*cis*), measured by integration of benzylic methine proton signals in the ^{1}H NMR spectrum. [f] Ratio reflects isolated yields of **3h** and **3h′**. [g] Ratio of regioisomers/diastereomers determined by integration of benzylic methine proton signals in ^{1}H NMR spectrum. Only partial characterization of **3i″** was possible owing to inseparable mixtures, so structural assignment is tentative. [h] Ratio of regioisomers, measured by integration of benzylic methane proton signals in ^{1}H NMR spectrum.

aluminum reagents (2.5 equiv in all cases) able to initiate the Nazarov process and deliver a substituent to the cyclized intermediate using dienone **1a** as a test substrate (Scheme 2). Triisobutylaluminum effected Nazarov cyclization of **1a**, but without subsequent transfer of an *i*Bu group. Instead, diastereomeric cyclopentanones **5a** and **5a′** were obtained, presumably through transfer of hydride from an isobutyl substituent.[17] Minor amounts of dienol **6a** were also isolated. We considered the possibility that these reduced products resulted from the presence of diisobutylaluminum hydride.[18] However, treatment of **1a** with DIBAL-H under the same conditions afforded only **6a**, suggesting that the Nazarov cyclization and subsequent hydride transfer were mediated by $(i\text{Bu})_3$Al.

Triethylaluminum also afforded ethylated cyclopentanone **7a** in good yield, with exclusive delivery of the ethyl group from the face opposite the adjacent phenyl substituent. Minor amounts of the reductive Nazarov product **5a′** were also obtained, suggesting that the β-hydrogen atom of the ethyl ligands is transferable, analogous to what was seen with $(i\text{Bu})_3$Al. The relative configuration of **7a** was confirmed by single-crystal X-ray diffraction.[15]

Diethylaluminum cyanide was also examined. Though potentially capable of transferring either an ethyl or cyano group, this reagent furnished only the diastereomeric cyanides **8a** and **8a′**, in excellent yield but as a nearly equal mixture of stereoisomers. In comparison to NMR data for other adducts derived from **1a** (e.g., **3a** and **7a**), both **8a** and **8a′** were judged to have a *trans* relationship between the Ph and Me groups at C-4 and C-5, while a *cis* relationship between the C-2 Me and C-3 Ph was apparent for **8a**.[19] Further evidence that these isomers did not differ in config-

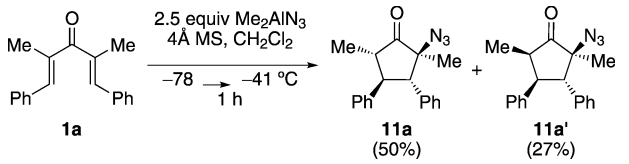


Scheme 2. Variation of the R_3Al reagent.

uration at C-5 was seen by the failure of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) epimerization to interconvert **8a** and **8a′**.

Phenylation at the α position to afford cyclopentanone **9a** was also possible, albeit in modest yield. While there have been reports of intermolecular arylation by interrupted Nazarov reaction, these cases have employed highly electron-rich aromatic or heteroaromatic traps.[20] To our knowledge, this is the first report of trapping of the Nazarov intermediate with a simple phenyl group. It is notable that higher temperature and longer reaction times were required with Ph_3Al. Significant amounts of exocyclic elimination products **9a** were also obtained, as an 11:1 mixture of epimers at C-5.

In situ generated organoaluminum also broadens the generality of the methodology. It has been reported that organoazides participate in both intermolecular[21] and intramolecular[22] [3+3] cycloadditions with oxyallyl zwitterions, in addition to domino Nazarov cyclization/Schmidt rearrangement to form dihydropyridones[5b] or peroxy bridged indolizidinones.[5c] We now report the unprecedented α carbon azidation of the oxyallyl intermediate. Subjecting divinylketone **1a** to solution of freshly prepared Me_2AlN_3[23] afforded a mixture of epimeric adducts **11a** and **11a′** in good yield (Scheme 3). Single-crystal X-ray diffraction allowed the unambiguous assignment of the relative stereochemistry of



Scheme 3. Intramolecular azide trapping.

major isomer **11a**.[15] Isomer **11a′** interconverted with **11a** on treatment with DBU, confirming that they are epimeric at C-5.[24] The high 1,2-diastereoselection seen with azide contrasts sharply with the unselective trapping observed for cyanide (Scheme 2). The origins of this difference are unclear at present, but are under further study.

We have described the first example of a 4π electrocyclic process employing triorganoaluminum reagents. Use of these organoaluminum compounds allowed the incorporation of simple alkyl groups, as well as phenyl, cyano, and azido moieties. Highly substituted cyclopentanones are accessible, in some cases with good diastereoselectivity. Further studies involving incorporation of other groups and additive effects to suppress 1,2-addition are underway, and will be described in due course.

Experimental Section

Representative procedure of organoaluminum mediated cyclization (**3a**): 2.5 equivalents of $AlMe_3$ (0.26 mL, 2.0 M solution in toluene) were added to a solution of **1a** (55 mg, 0.21 mmol) in CH_2Cl_2 (2.1 mL, 0.1 M) under an argon atmosphere with activated 4 Å MS (100 mg) at −78 °C. The reaction mixture was then transferred into a bath at −41 °C, and stirred until complete consumption of **1a** was observed by TLC (30 min). The reaction was quenched with 2 M aq.HCl (1 mL) and warmed to room temperature. After separation of the phases, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine, and dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel; 20:1 hexane:EtOAc) gave **3a** (53 mg, 92 %) as a white solid: R_f 0.43 (hexanes/EtOAc 9:1); m.p. 134–136 °C; IR (film): $\tilde{\nu}$ =3027, 3003, 2927, 1726, 1601, 1498, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.22 (m, 6H), 7.18–7.12 (m, 4H), 3.34 (d, J = 12.3 Hz, 1H), 3.30 (dd, J = 12.3, 10.5 Hz, 1H), 2.42 (dq, J = 10.5, 7.0 Hz, 1H), 1.12 (s, 3H), 1.17 (d, J = 7.0 Hz, 3H), 0.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 222.0 140.7, 137.0, 129.1, 128.6, 128.0, 127.7, 126.8, 126.8, 58.4, 51.9, 50.7, 49.7, 24.0, 20.2, 13.5; HR-MS (EI, M^+) for $C_{20}H_{22}O$ calcd: 278.1671, found: m/z 278.1670.

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[14] Triorganoaluminum reagents are highly sensitive to traces of water, and inclusion of molecular sieves in the reaction mixture was found to improve reproducibility.

[15] CCDC 915117 (**3a**), 915118 (**3h**), 915119 (**7a**), 915120 (**8a′**), and 915121 (**11a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[24] Catalytic amounts of DBU were added to an NMR tube containing **11a′** and the reaction was monitored by ^{1}H NMR spectroscopy over 15 h. During this time, 40 % conversion into **11a** was observed.

