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# Construction of α-amido-indanones *via* formal allenamide hydroacylation–Nazarov cyclization†

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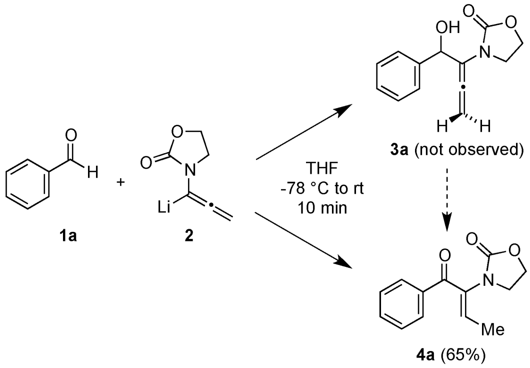
**A two-step modular synthesis of an α-hydroxycyclopentenone and α-amido-indanones has been developed based on the Nazarov cyclization of 2-amido-1,4-pentadien-3-ones, readily accessed *via* formal hydroacylation of allenamides.**

The Nazarov reaction has become a well-established protocol for constructing a diverse array of five-membered carbocycles, notably since the disclosure of silicon-directed Nazarov reactions by Denmark and co-workers.[1] Recent efforts toward expanding its synthetic versatility have been devoted to several aspects including the development of catalytic and asymmetric variants,[2a,b] interception of intermediates derived from the cyclization,[2c] and the use of unconventional substrates and activations.[2d] However, the efficiency in terms of step/atom economy for the preparation of conventional Nazarov precursors, namely 1,4-dien-3-ones, remains an underemphasized subject. Traditional approaches for their syntheses from simple ketones involved aldol or Knoevenagel condensations,[3] which generally required harsh basic or acidic conditions. Horner–Wadsworth–Emmons or related Wittig-type olefinations have also been employed to install the alkenes conjugated with the carbonyl, but the stoichiometric production of phosphorus-containing side products is undesirable.[4] A [3 + 2] cycloaddition–oxidative rearrangement sequence has been revealed to specifically target the syntheses of polarized divinyl or aryl vinyl ketones.[5] On the other hand, coupling reactions between a variety of vinylmetallic donors and supplemental fragments offered a flexible route to cross-conjugated dienones with various substitution patterns, although the preparation of necessary starting materials may be tedious in some cases.[6] Therefore, economical and operationally simple procedures for dienone synthesis are still demanded in Nazarov chemistry.

Recently, Hsung and co-workers' described a regioselective functionalization of allenamides with a range of electrophiles such as stannyl or silyl chlorides and alkyl halides.[7] Inspired by their work, we envisioned that aldehyde (*e.g.* **1a**) could be used as an alternative electrophilic trap for α-lithiated allenamides, where the allenyl alcohol **3a** thus formed could be isomerized to cross-conjugated ketone **4a** under suitable conditions.[8] Fortuitously, we found that **4a** was directly generated in lieu of the expected product **3a** in a one-pot operation (Scheme 1). We set out to explore the scope of this intriguing transformation, which constitutes a metal-free formal hydroacylation of the allenamide,[9] and attempted to elucidate its mechanism. Herein, we describe our preliminary studies on this novel route to α-amidodienones, and the applications of the products in the Nazarov cyclization.[10]



**Scheme 1** A one-pot synthesis of Nazarov precursors from simple aldehydes and allenamides.

As shown in Table 1 (entries 1–7), aryl aldehydes with distinct *para*-substituents reacted with lithiated allenamide **2** uniformly resulting in the formation of oxazolidinone-substituted aryl vinyl ketones in moderate to low yields.[11] The results indicated that strong polarizing groups such as carboxylate or methoxy group at the *para* position are detrimental to the overall process. There is no obvious trend between yields and substituent effects; it may simply reflect the fact that addition of **2** to the carbonyl carbon and the presumed isomerization of the allenylic hydrogen are favored by different electronic factors.[12] Furthermore, 2-furfural was employed to capture **2** providing an efficient synthesis of heteroaryl vinyl ketone (entry 8). Analogously, the reaction between simple unsaturated aldehyde **1i** and α-deprotonated allenamide gave the corresponding divinyl ketone **4i** in moderate yield (entry 9). The geometry of the conjugated alkene was assigned based on observed TROESY correlations between vinyl and aryl protons.

While the substrate scope has been briefly examined, we embarked on an investigation of the reaction mechanism. Deuterated benzaldehyde *d*-**1a** was prepared and treated with

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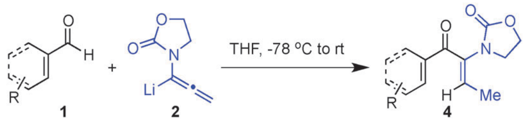
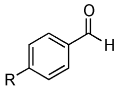
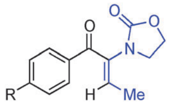
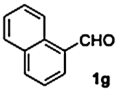
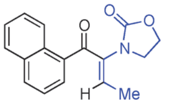
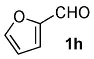
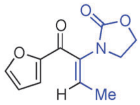
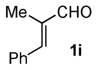
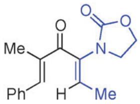
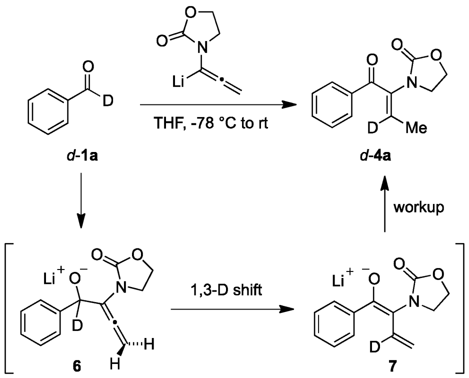
**Table 1** The overall hydroacylation of allenamides **2**[a]



| Entry | Aldehyde | Product | Yield[b] (%) |
|---|---|---|---|
| |  |  | |
| 1 | R = H, **1a** | R = H, **4a** | 65 |
| 2 | R = Me, **1b** | R = Me, **4b** | 44 |
| 3 | R = OMe, **1c** | R = OMe, **4c** | 18 |
| 4 | R = SMe, **1d** | R = SMe, **4d** | 52 |
| 5 | R = Cl, **1e** | R = Cl, **4e** | 46 |
| 6 | R = $CO_2Me$, **1f** | R = $CO_2Me$, **4f** | 14 |
| 7 |  **1g** |  **4g** | 52 |
| 8 |  **1h** |  **4h** | 33 |
| 9 |  **1i** |  **4i** | 35 |

[a] Standard procedure: to a homogeneous solution of allenamide **2** (0.5 mmol) in anhydrous THF under an argon atmosphere, 1.2 equiv. *n*-BuLi was added dropwise at −78 °C. After 45 min, freshly distilled aldehyde **1** (1.1 equiv.) was added at −78 °C, then the reaction was warmed to rt. The reaction was quenched with sat. aq. $NH_4Cl$, followed by extraction, drying ($MgSO_4$), and chromatographic purification. [b] Isolated yields based on allenamides.



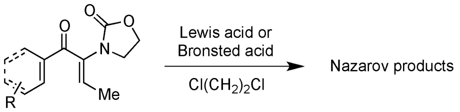
**Scheme 2** A plausible mechanism for this overall hydroacylation of allenamides supported by the deuterium labelling experiment.

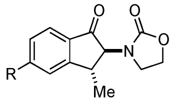
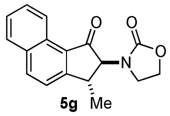
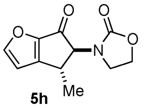
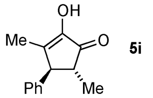
**2** to furnish *d*-**4a** as the only identifiable product where the deuterium was incorporated at the β-carbon and no **4a** was detected even in the crude $^1H$ NMR spectrum. As depicted in Scheme 2, this result supports the hypothesis that a concerted 1,3-deuteride shift is the operating pathway for the generation of *d*-**4** from allenyl alkoxide **6**, rather than the alternative proton transfer mechanism involving external acid or base.[8d] As reported by Hsung, the isomerization of α-allylated allenamides generally required additional promoters (heat or acid) to give triene products.[8,13] In this case, the facile 1,3-D shift furnishing intermediate aryl diene **7** was likely facilitated by alkoxide substitution at the deuterium-labeled center.[14] Notably, the allenylation of unsaturated aldehydes with terminally substituted propargyl-metal species has ample precedent in the literature.[15] To the best of our knowledge, those reactions resulted in aryl or vinyl allenyl alcohols with no evidence of the corresponding isomerizations. From this, we infer that the oxazolidinone group plays an important role in mediating the 1,3-deuteride shift.[8d]

Next, we commenced to identify optimal catalytic conditions[2a] for triggering the Nazarov reaction of **4**, where the α-amido group was expected to advantageously polarize the pentadienyl system, thus lowering the electrocyclization barriers.[10,16] In the event, a catalyst screening with **4a** showed that only indium(III) triflate was an effective catalytic promoter (DCE, 80 °C) providing **5a** in 65% yield, a surprising contrast to the recent observation that $Sc(OTf)_3$ displays superior reactivity in catalyzing the Nazarov cyclization of heteroaromatic substrates.[17] Subsequently, we turned our attention to use commercially available superacids as catalysts.[2a] The cyclization of **4a** using a substoichiometric amount of triflic acid gave partial conversion of the starting material, but the optimized reaction conditions (Table 2, entry 5) entailed excess TfOH with mild heating (65 °C). For substituted aryl vinyl ketones, $In(OTf)_3$ displayed little to no reactivity, demonstrating that subtle electronic changes exert a large effect on catalysis of the Nazarov reaction. Nevertheless, **4b–4f** did undergo efficient cyclization in the presence of triflic acid, with negligible effects of substitution (entries 6–10). Naphthyl substrate **4g** could potentially undergo competing Friedel–Crafts type cyclization to furnish the phenalan skeleton;[18] however, exclusive reaction *via* the Nazarov pathway was observed, using either TfOH or $In(OTf)_3$ (entries 11 and 12). 2-Furyl vinyl ketones are generally considered to be unreactive substrates for the Nazarov reaction.[6c,17] Nonetheless, **4h** underwent cyclization with triflic acid, though not with indium(III) triflate (entry 13 *vs.* 14). This result is analogous to the report of Flynn and co-workers, wherein the authors attributed cyclization of conventionally inert substrates to the potent activation exerted from the oxazolidinone auxiliary.[10] Given our observations that Nazarov reactions of aryl and 2-furyl ketones **4a–h** are quite sensitive to acid strength,[19] we propose an equally important role to the superacid (TfOH), perhaps through formation of highly reactive dicationic intermediate **8** or protosolvated species **9** might be equally essential (Fig. 1).[20] Finally, it should be noted that Lewis acid-catalyzed cyclization of non-aromatic substrate **4i** deviated from the typical eliminative termination, furnishing hydrolysis product **5i** (entries 14 and 15), in contrast to the reactivity observed by the Flynn group in related cases.[10]

In summary, we have described a novel approach to amido-substituted Nazarov precursors through 1-step coupling of simple aldehydes and a lithiated allenamide. As supported by a deuterium labelling study, the reaction mechanism appears to entail sequential carbonyl addition–1,3-sigmatropic rearrangement. In the context of the Nazarov reaction, triflic acid

**Table 2** Nazarov cyclizations of oxazolidinone-substituted cross-conjugated ketones **4**[a]



| Entry | Dienone | Acid (equiv.)/$T$ (°C) | Nazarov products | Yield[b] (%) (ratio)[c] |
|---|---|---|---|---|
| | | |  | |
| 1 | **4a** | $FeCl_3$ (0.2)/80 | R = H, **5a** | NR |
| 2 | **4a** | $Sc(OTf)_3$ (0.2)/80 | R = H, **5a** | Trace |
| 3 | **4a** | $Eu(OTf)_3$ (0.2)/80 | R = H, **5a** | NR |
| 4 | **4a** | $In(OTf)_3$ (0.2)/80 | R = H, **5a** | 65 (20 : 1) |
| 5 | **4a** | $CF_3SO_3H$ (5)/65 | R = H, **5a** | 98 (20 : 1) |
| 6 | **4b** | $CF_3SO_3H$ (5)/65 | R = Me, **5b** | 87 (20 : 1) |
| 7 | **4c** | $CF_3SO_3H$ (5)/65 | R = OMe, **5c** | 88 (4 : 1) |
| 8 | **4d** | $CF_3SO_3H$ (5)/65 | R = SMe, **5d** | 97 (20 : 1) |
| 9 | **4e** | $CF_3SO_3H$ (5)/65 | R = Cl, **5e** | 94 (20 : 1) |
| 10 | **4f** | $CF_3SO_3H$ (5)/65 | R = $CO_2Me$, **5f** | 91 (20 : 1) |
| 11 | **4g** | $In(OTf)_3$ (0.2)/80 |  **5g** | 76 (20 : 1) |
| 12 | **4g** | $CF_3SO_3H$ (5)/65 | | 97 (20 : 1) |
| 13 | **4h** | $In(OTf)_3$ (0.2)/80 |  **5h** | NR |
| 14 | **4h** | $CF_3SO_3H$ (5)/65 | | 65 (3 : 1) |
| 14 | **4i** | $Sc(OTf)_3$ (0.2)/80 |  **5i** | 96 |
| 15 | **4i** | $BF_3 \cdot OEt_2$ (1.1)/−78 | | 81 |

[a] To a stirred solution of **4** in DCE at the indicated temperature, acid was added to the mixture. Once the starting material was consumed (based on TLC), the reaction was quenched with sat. aq. $NaHCO_3$, followed by extraction, drying ($MgSO_4$) and chromatographic purification. [b] Isolated yields; NR = no reaction. [c] *cis*/*trans* isomers were inseparable and the ratios were determined by $^1H$ NMR.

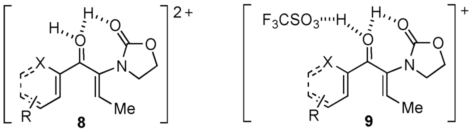


**Fig. 1** Proposed superelectrophilic intermediates.

was found to be a superior promoter for the aromatic or heteroaromatic substrates. Alternatively, the cyclization of divinyl ketones proceeded smoothly under mild conditions where the oxazolidinone served as a traceless activating group. An extension of the aforementioned overall hydroacylation process to other heteroatom-substituted allenes will be further explored.

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