Cyclizations

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Interrupted Imino-Nazarov Cyclization of 1-Aminopentadienyl Cation and Related Cascade Process**

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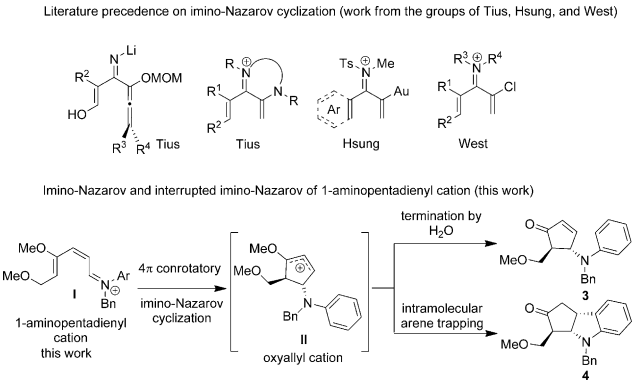
Abstract: *Facile 4π conrotatory imino-Nazarov cyclization of a 1-aminopentadienyl cation generated from condensation an aldehyde and secondary aniline in the presence of a catalytic amount of a Lewis acid has been developed. Silver(I)-catalyzed intramolecular arene trapping of the resulting cyclic oxyallyl cation leads to formation of tricyclic indoline-fused cyclopentanone. The use of lanthanide salts allows transformation after the initial trapping to afford tetrahydroquinoline-fused cyclopentenone in a concise manner.*

Five-membered carbocyclic scaffolds are ubiquitous in both natural products and biologically important molecules.[1] Development of facile cyclization reactions which allow rapid construction of five-membered carbocyclic frameworks has thus attracted immense interest in the synthetic community. In this context, the classical Nazarov reaction, involving $4\pi e^-$ conrotatory electrocyclization of pentadienyl cation, arguably represents one of the most efficient methods to access a diverse array of carbocycles.[2] The synthetic utility of the Nazarov cyclization is further enhanced by the possibility of trapping the oxyallyl cation with nucleophiles both intra- and intermolecularly in a process termed the interrupted Nazarov reaction.[3] Recent years have seen a wide range of nucleophiles being employed to capture the cation, thus rendering the formation of highly functionalized cyclopentanones as well as intriguing polycyclic skeletons which contain five-membered carbocycles.[4]

A relatively new variant of the Nazarov reaction which has received less attention is the imino-Nazarov cyclization, which essentially involves electrocyclic ring closure of the pentadienyl system bearing an imino group instead of the conventional ketone functionality. Since the pioneering work reported by Tius et al. on the lithiated imino-Nazarov reaction,[5] literature examples pertaining to this special class of Nazarov reaction remain scarce. The lack of success in developing an imino-Nazarov cyclization stems from the inherent challenge associated with higher stability of the pentadienyl cation, relative to the corresponding cyclic allyl cation, owing to stabilization by a nitrogen atom.[6] Later, Tius and co-workers disclosed the use of enamine-iminium ion formation in facilitating an imino-Nazarov cyclization.[7] The work of Hsung and co-workers on gold-catalyzed cyclization of allenamides demonstrated that diminishing nitrogen stabilization through incorporation of an electron-withdrawing tosyl group proved to be an effective solution to drive the electrocyclization forward.[8] More recently, the group of West reported silver-assisted ring opening of 2,2-dichlorocyclopropanes to access a 3-aminopentadienyl cation capable of undergoing imino-Nazarov cyclization, including a few examples of interrupted process (Scheme 1).[9]



Scheme 1. Literature precedence and present work on imino-Nazarov and related interrupted process. MOM = methoxymethyl, Ts = 4-toluenesulfonyl.

Our recent interest in the synthesis of cyclopentanoid compounds[10] prompted us to investigate the possibility of a diene iminium ion, of the type shown in Scheme 1, to undergo an imino-Nazarov cyclization, and to explore the related interrupted process. The resonance forms of such iminium ions, 1-aminopentadienyl cations, have been invoked as intermediates which undergo facile 4π electrocyclization in the synthesis of cephalotaxine and agelastatin A[11] as well as in the aza-Piancatelli reaction.[12] In addition, the iminium ion **I** is expected to serve as an excellent substrate for the imino-Nazarov cyclization because of the polarized nature of the conjugated π system.[13] The presence of an electron-donating methoxy group at C4 should lead to selective resonance stabilization of the cyclic oxyallyl cation **II** which provides sufficient driving force for efficient cyclization to occur.[14] Hydrolysis of **II** following an imino-Nazarov reaction would then furnish the 4-aminocyclopentenone product **3**. The focus of this present work, however, would be the capture of the oxyallyl cation by a sufficiently nucleophilic pendant aryl

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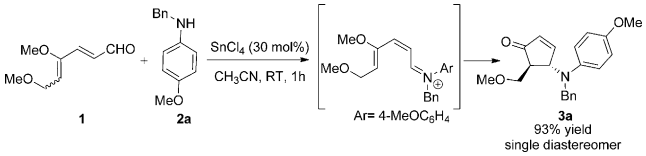
group in a 5-exo cyclization reaction to afford the indoline-fused cyclopentanone product **4** in one step. Some biologically active indole alkaloids isolated from Aspidosperma such as kopsanone, tuboxenine, and vindolinine have been shown to possess a similar tricyclic core structure.[15]

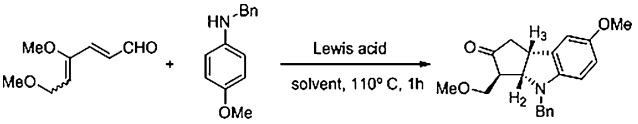
At the outset of this study, we envisioned that **I** could be generated from the condensation of an aldehyde and amine in the presence of a catalytic Lewis acid. 4,6-Dimethoxyhexa-2,4-dienal (**1**), which can be readily prepared from 3,4,6-tri-*O*-methyl D-glucal in three steps (see the Supporting Information), and *N*-benzyl 4-methoxyaniline (**2a**) were chosen as model substrates to test whether the imino-Nazarov cyclization of the resulting iminium ion intermediate is indeed feasible. A short survey of a series of Lewis acid catalysts quickly revealed that treatment of **1** and **2a** in the presence of $SnCl_4$ in CH_3CN at room temperature for 1 hour resulted in formation of 4-aminocyclopentenone **3a** in 93% yield (Scheme 2). Interestingly, only one diastereomer of **3a** was observed, although the reaction was carried out using an inseparable 5:4 *Z*/*E* mixture of the dienal **1**. The relative stereochemistry of the newly formed stereocenters is established to be *trans* based on comparison with our previous work.[10] This result indicates that isomerization of the putative 1-aminopentadienyl cation occurred to primarily give an isomer which led to formation of thermodynamically favored *trans* diastereomer after a conrotatory ring closure. Initial efforts to intercept the oxyallyl cation with the proximal pendant 4-methoxyphenyl substituent by increasing reaction temperature and prolonging reaction time proved futile.



Scheme 2. Imino-Nazarov reaction of iminium ion generated from condensation of **1** and **2a**.

We then turned our attention to systematically screening other metal Lewis acid catalysts to promote the trapping of the oxyallyl cation by electrophilic aromatic substitution of a nearby arene functionality. To our delight, by using 30 mol% of either $Mg(OTf)_2$, $Cu(OTf)_2$, or $FeCl_2$ and heating the reaction mixture to 110°C for 1 hour, the desired interrupted imino-Nazarov cyclization ensued smoothly to give the indoline-fused cyclopentanone **4a** in moderate yield in the range of 37–45% (Table 1, entries 1–3). An improvement in reaction yield was observed when $InBr_3$ and AgOTf was employed as the Lewis acid catalyst, thus giving the desired product in 73 and 78% yield, respectively (entries 4 and 5). Finally, after careful evaluation of other silver(I) salts, $AgClO_4$ was identified as the best catalyst to effect this transformation (entries 6–9). Solvents other than acetonitrile, such as nitromethane and THF, failed to facilitate the formation of the desired interrupted imino-Nazarov product (entries 13 and 14). When a mixture of acetonitrile and water in a ratio of 9:1 was used as the reaction solvent, a competing

Table 1: Screening of reaction conditions for interrupted imino-Nazarov reaction.[a]



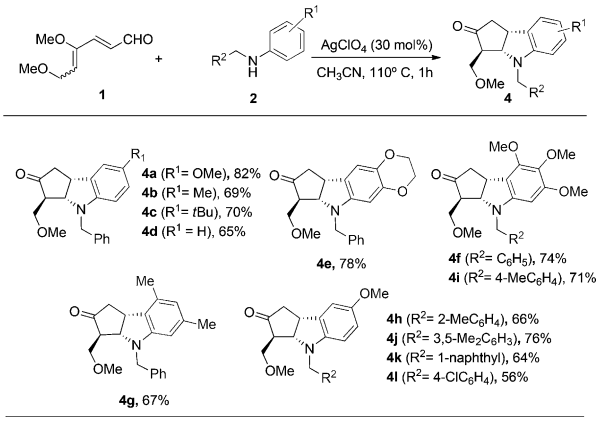
Entry	Catalyst (mol%)	Solvent	Yield [%][b]
1	$Mg(OTf)_2$ (30)	CH_3CN	45
2	$Cu(OTf)_2$ (30)	CH_3CN	37
3	$FeCl_2$ (30)	CH_3CN	39
4	$InBr_3$ (30)	CH_3CN	73
5	AgOTf (30)	CH_3CN	78
6	$AgNO_3$ (30)	CH_3CN	–[c]
7	$AgSbF_6$ (30)	CH_3CN	73
8	$AgNTf_2$ (30)	CH_3CN	75
9	$AgClO_4$ (30)	CH_3CN	82
10	$AgClO_4$ (20)	CH_3CN	67
11	$AgClO_4$ (40)	CH_3CN	53
12[f]	$AgClO_4$ (30)	CH_3CN	55
13	$AgClO_4$ (30)	THF	–[e]
14	$AgClO_4$ (30)	CH_3NO_2	–[d]
15	$AgClO_4$ (30)	CH_3CN/H_2O (9:1)	–[e]

[a] Unless otherwise specified, all reactions were carried out using the dienal **1** (0.1 mmol, 1 equiv) and aniline **2a** (0.1 mmol, 1 equiv) with catalyst in 1 mL of solvent ($c = 0.1$ M). [b] Yields of isolated products. [c] No reaction even after prolonged reaction time. [d] Starting materials decomposed. [e] 4-aminocyclopentenone **3** product was obtained predominantly. [f] Reaction was carried out at 80°C. Tf = trifluoromethanesulfonyl.

termination pathway through hydrolysis of the oxyallyl cation became prominent and thus formation of **3a** was observed (Table 1, entry 15). Stereocenters formed during ring fusion is assigned *cis*, considering attack from the opposite face of the oxyallyl cation would be disfavored because of geometrical constraints. The stereochemical assignment was further confirmed by two-dimensional NMR studies wherein strong correlations between H2 and H3 in the NOESY spectrum of **4a** were observed.

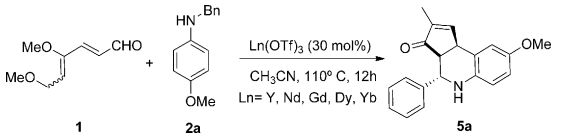
Having established the optimized reaction conditions, the scope of this transformation with respect to the secondary aniline was explored by varying the substituents (R^1) on the aniline ring as well as the phenyl ring (R^2) of the benzyl group (Scheme 3). Replacing the *para* substituent of the aniline ring with weaker electron-donating groups, such as methyl and *tert*-butyl, resulted in a lower yield of **4b** and **4c**, respectively, as compared to 82% yield for the **4a**. As expected, the presence of multiple electron-rich substituents aniline led to an efficient reaction which afforded **4e**–**g** in relatively good yields. It is noteworthy that unsymmetrical *N*-benzyl 3,4-(ethylenedioxy) aniline furnished the sterically less demanding product **4e** regioselectively. Variation of the phenyl ring (R^2) of the benzyl substituent of the secondary aniline affords the desired products **4h**–**l** in moderate to good yields. It is notable that, in all cases, the resulting indoline-fused cyclopentanones were obtained exclusively as single diastereomers.

In the course of our study, a serendipitous discovery was made when the reaction was performed in the presence of lanthanide metal catalysts, that is, the tetrahydroquinoline-



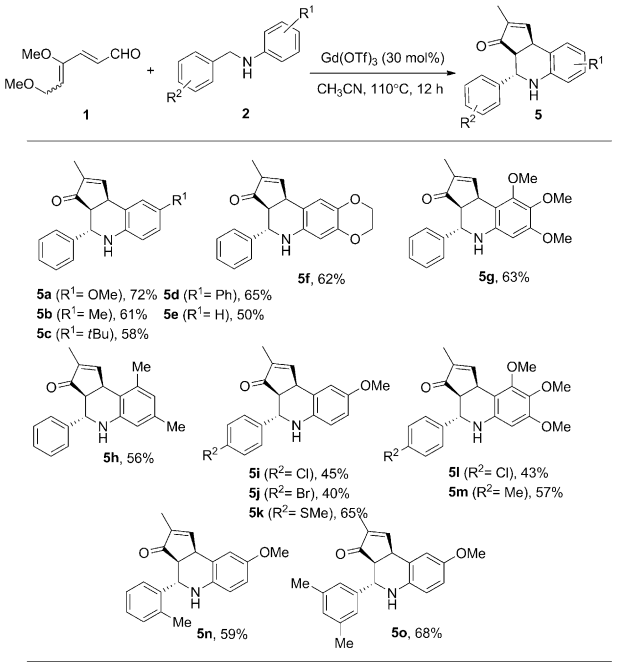
Scheme 3. Substrate scope of silver(I)-catalyzed interrupted imino-Nazarov reaction.

fused cyclopentenone product **5a** was formed instead of the product expected from intramolecular interrupted imino-Nazarov reaction (Scheme 4). Some tetrahydroquinolines fused with five-membered carbocycles have been shown to be pharmacologically relevant compounds, for instance, as agonists of large-conductance calcium-activated potassium channel (BKCa) and positive allosteric modulator of α7 nicotinic acetylcholine receptor.[16] Among various lanthanide metal triflate salts tested (for details see the Supporting Information), $Gd(OTf)_3$ emerged as the catalyst of choice, thus furnishing **5a** in 72% yield as a single diastereomer. The unusual result observed when $Gd(OTf)_3$ is employed as a catalyst, can be attributed to its mild nature and high oxophilicity.[17] The structure and relative stereochemistry of **5a** was unambiguously elucidated based on single-crystal X-ray analysis (see the Supporting Information).



Scheme 4. Lanthanide(III) triflate-catalyzed formation of the tetrahydroquinoline-fused cyclopentenone **5a**.

Encouraged by our preliminary finding, exploration of the substrate scope of this transformation was undertaken by performing the reaction using differently substituted secondary anilines (**2**) under the standard reaction conditions (Scheme 5). In general, electron-donating substituents on the aniline ring are well-tolerated, thus giving a variety of tetrahydroquinoline-fused cyclopentenones (**5a**–**h**) as single diastereomers in relatively good yield, considering the overall process is a multistep cascade reaction. Reaction with secondary anilines bearing an electron-withdrawing substituent on the phenyl ring of the benzyl group (Cl and Br) afforded the corresponding tetrahydroquinoline-fused cyclopentenones **5i**, **5j**, and **5l** in moderate yield. In the case of a substrate containing an electron-donating substituent (SMe) on phenyl ring of the benzyl group, the reaction proceed

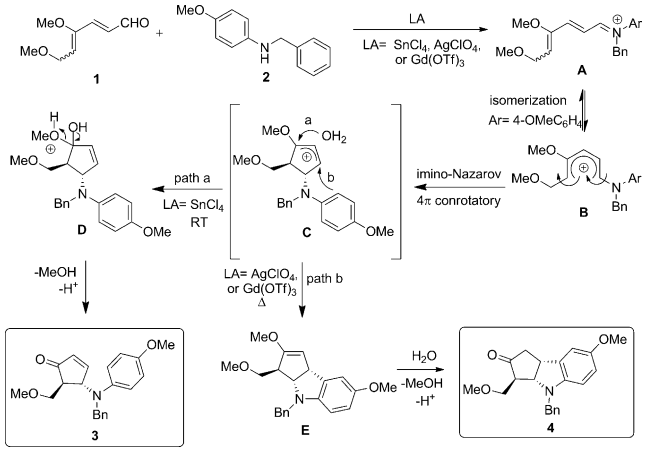


Scheme 5. Substrate scope of $Gd(OTf)_3$-catalyzed cascade transformation.

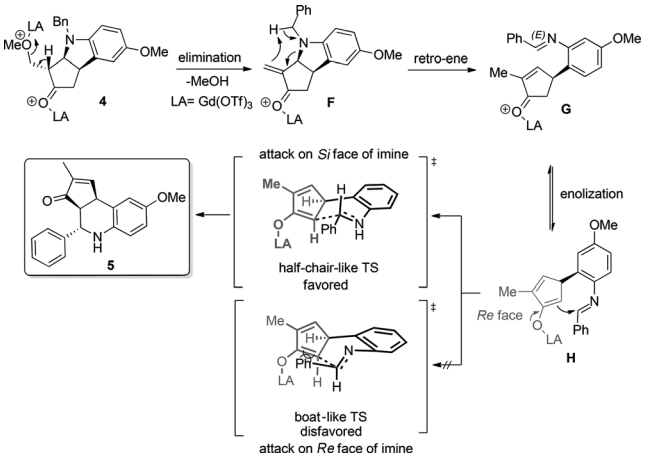
smoothly to furnish cyclopentenone **5k**. Additionally, *ortho*- and *meta*-substitution patterns on the phenyl ring of the benzyl group do not affect the efficiency of the cascade transformation significantly, as compounds **5n** and **5o** were obtained in 59 and 68% yield, respectively. The relative assignment of the stereochemistry of **5f** was also determined by X-ray crystallography, while those of other products were assigned by analogy, based on similarity in coupling constants to those of **5a** and **5f**.

On the basis of observed experimental results and well-established chemistry of Nazarov reaction, plausible reaction mechanisms to account for the formation of **3** and **4** are described in Scheme 6. Initial Lewis acid catalyzed condensation of an aldehyde and secondary aniline generates the corresponding iminium ion **A**. Isomerization of *Z* and E isomers of the 1-aminopentadienyl cation occurs readily such that the imino-Nazarov cyclization is stereoconvergent. In this case, only the *Z* isomer **B** undergoes a facile 4π symmetry-allowed conrotatory ring closure to afford the cyclic oxyallyl cation **C** with trans configuration.[18] Depending on the judicious choice of catalyst, the cyclic oxyallyl cation can then go through different pathways. When $SnCl_4$ is employed as the Lewis acid, termination by reaction with water gives **3**. In contrast, when $AgClO_4$ or $Gd(OTf)_3$ are used under heating conditions, intramolecular arene trapping of the oxyallyl intermediate by pendant aryl groups prevails over termination by water to furnish the tricyclic enol ether intermediate **E**, which upon hydrolysis results in formation of **4**.

To gain further insight into the reaction mechanism for formation of the tetrahydroquinoline-fused cyclopentenone product, an isotope-labelling experiment was carried out using [D_2]*N*-benzyl 4-methoxyaniline ([D_2]-**2a**) which is fully

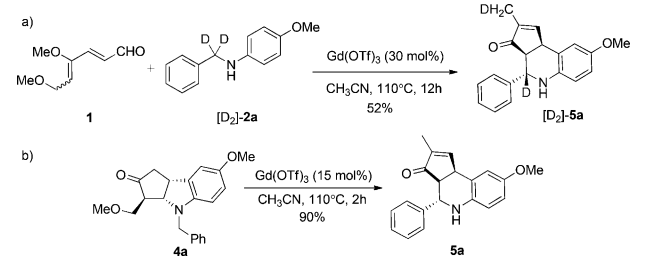


Scheme 6. Proposed mechanism for formation of the 4-aminocyclopentenone **3** and indoline **4**.



Scheme 8. Mechanistic hypothesis for cascade transformation of indoline **4** into tetrahydroquinoline **5**.

deuterated at the benzylic position (Scheme 7a). Interestingly, one deuterium atom was incorporated into the methyl group on the cyclopentenone ring of the tetrahydroquinoline



Scheme 7. Deuterium-isotope-labelling experiment and conversion of compound **4a** into **5a** upon treatment with $Gd(OTf)_3$.

product [D_2]-**5a** whereas the other one remained at the position α to the nitrogen atom. In addition, treatment of **4a** in the presence of 15 mol% of $Gd(OTf)_3$ at 110°C in CH_3CN led to the formation of **5a** in 90% yield (Scheme 7b). Based on these experimental results, we postulated a mechanistic pathway for the formation of **5** from **4** as depicted in Scheme 8. The mild nature and highly oxophilic properties of $Gd(OTf)_3$ allowed additional transformation of **4** to occur. Through a Lewis acid catalyzed elimination of the methoxy group, the intermediate cyclopentanone bearing an *exo* alkene group (**F**) is formed. This intermediate is prone to undergoing a retro-ene-type reaction to give the intermediate **G**,[19] which upon enolization would be converted into the enolate **H**.[20] Highly diastereofacial selective intramolecular Mannich reaction between the enolate and imine is hypothesized to proceed from the *Re* face of the enolate onto the *Si* face of the imine through a favored half-chair-like transition state (TS). Alternative attack from the *Re* face of enolate to the *Re* face of imine would lead to an unfavorable boatlike TS which is much higher in energy because of steric hindrance created by an eclipsing interaction between the bulky phenyl and the cyclopentadiene enolate.

In conclusion, we have described an efficient imino-Nazarov cyclization of an iminium ion generated from simple condensation of an aldehyde and secondary aniline. Moreover, we have developed an interrupted imino-Nazarov process by intramolecular arene trapping of the cyclic oxyallyl cation in the presence of a silver(I) catalyst to provide convenient access to indoline-fused cyclopentanones. We also discovered that lanthanide salts are able to effect further transformation through an elimination, retro-ene, and a Mannich reaction sequence, and thus elaborated tetrahydroquinoline-fused cyclopentenone can be synthesized in a single operation. Further investigation of the scope and synthetic application of the work described here, as well as extension to intermolecular interrupted process are currently underway and will be reported in due course.

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