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Iron-Mediated Domino Interrupted Iso-Nazarov/Dearomative (3 + 2)-Cycloaddition of Electrophilic Indoles

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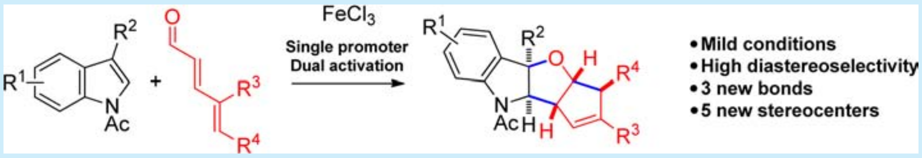
Supporting Information



ABSTRACT: An efficient domino reaction combining different classes of pericyclic reactions leads to chiral complex polycyclic indoline-based architectures from achiral starting materials under mild conditions. This practical method is based on the ability of iron(III) chloride to promote both 4π electrocyclizations of 2,4-dienals and the C2−C3 umpolung of *N*-acetylindoles during the dearomative (3 + 2) cycloadditions.

Whether in natural or bioinspired synthetic products, three-dimensional polycyclic frameworks are omnipresent in intricate architectures that exhibit a vast array of biological properties.[1] The development of highly efficient chemical processes that generate multiple bonds in a single operation is a straightforward approach to construct molecular complexity and structural diversity.[2] More specifically, domino or cascade reactions that merge different classes of pericyclic reactions enable a rapid and efficient access to a large variety of fused and bridged ring systems.[3] Brønsted or Lewis acid promoted Nazarov cyclizations[4] that follow a typical conrotatory 4π electrocyclic behavior have been incorporated in a series of elegant transformations.[5] Beyond the classical version that generates the reactive 3-oxopentadienyl cation intermediate by using divinyl ketones, myriad polyunsaturated precursors have been recently investigated.[6] These oxyallyl cations can be trapped by carbon- or heteroatom-based nucleophiles through an interrupted Nazarov process,[7] but they can also be engaged in cycloaddition reactions as 1,3-dipoles.[8] Such domino sequences usually provide carbocycles, especially through (4 + 3)- or (3 + 2)-cycloadditions.[9] In contrast, the concomitant formation of a C−C and a C−O bond has been far less investigated. In 1998, West and co-workers described the formation of tricyclic architectures via an intramolecular trapping of oxyallyl cation by a pendant alkene.[10] Intermolecular versions using alkynes[11] or allylsilanes[12] have also been recently reported (Scheme 1, eq 1). The acid-promoted iso-Nazarov reaction was formalized in 2003 by Trauner as the electrocyclization of 1-oxopentadienyl cation intermediate generated through the cyclization of a conjugated dienal.[13] The synthetic utility of the resulting oxyallyl cations in an interrupted iso-Nazarov process has been scarcely studied.[14]

As a part of our program devoted to the development of new methodologies for the construction of polycyclic scaffolds from polyunsaturated aldehydes,[15] we propose here a novel strategy that employs an iso-Nazarov cyclic oxyallyl cation intermediate as a dipole in a dearomative cycloaddition reaction. Dearomatization of indoles through cycloadditions is an efficient strategy to create polycyclic indoline-based compounds.[16] The innate C3-nucleophilic character of indoles has been largely exploited in cycloaddition/annulation and particularly in (3 + 2)-cycloadditions.[17] The C3-position generally reacts with the electrophilic atom of the dipole, while the C2 indole position reacts with the dipole's nucleophilic atom (Scheme 1, eq 2).[18,19] We have recently established that the association of *N*-acetylindoles and $FeCl_3$ results in the reversal of classical polarity of the C2 and C3-positions on the indoles during hydroarylation reactions.[20,21] This fact opens an opportunity to achieve (3 + 2)-cycloadditions with the C2═C3 indole bond[22] with an inverted regioselectivity compared to known cycloadditions of indoles. More specifically, the combination of *N*-acetylindoles and $FeCl_3$ should yield cycloadducts through the formation of a bond between the C3-carbon of the indole and the nucleophilic atom of the dipole as well as a bond between the C2-carbon of the indole and the electrophilic atom of the dipole.

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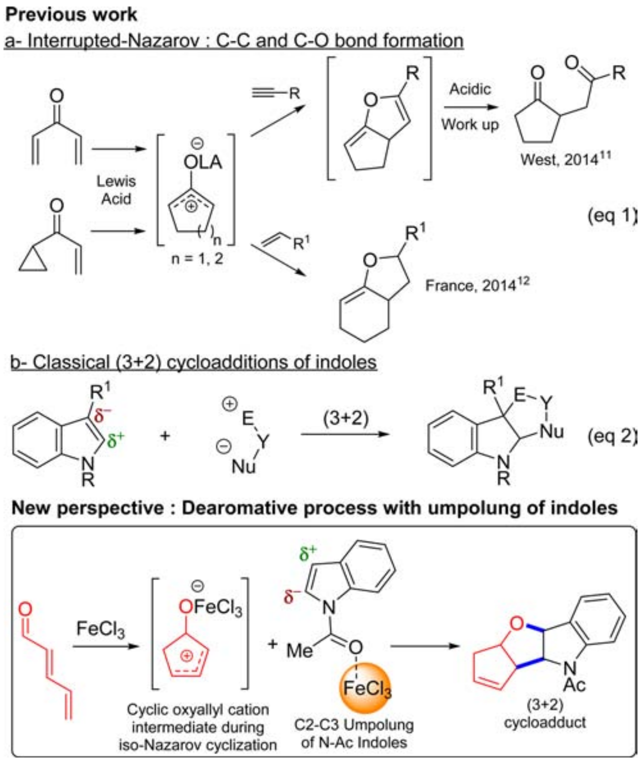
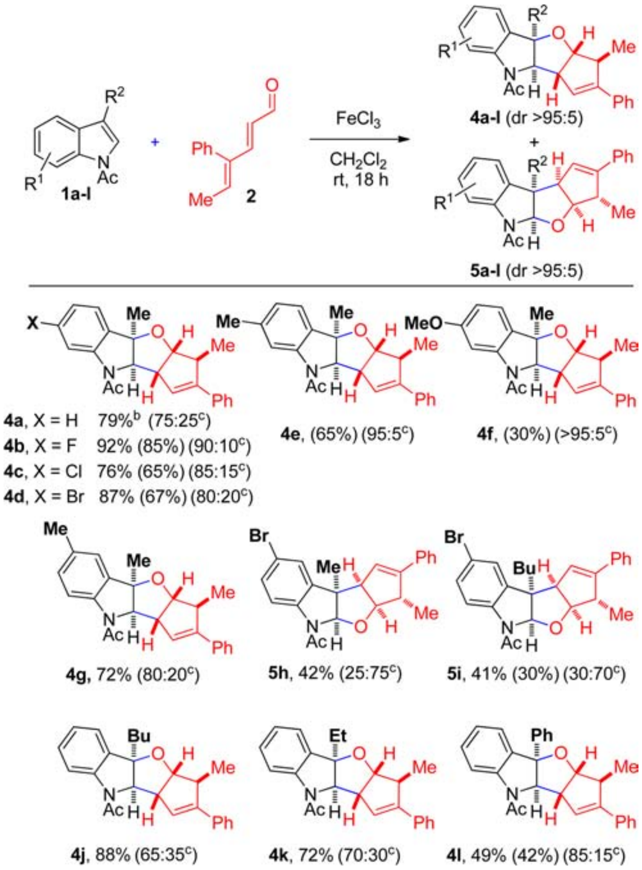
Scheme 1. Interrupted Nazarov Reactions in Cycloadditions or Annulations



Here, we present our efforts to develop a novel domino sequence initiated by an iso-Nazarov reaction of a 2,4-dienal to form a cyclic oxyallyl cation that would undergo a dearomative (3 + 2)-cycloaddition with indoles (Scheme 1). Different Brønsted (TfOH, TsOH) or Lewis acids (cationic gold species, silver salts, platinium(II) chloride, or dimethylaluminum chloride) have been shown to promote the iso-Nazarov reaction. Nevertheless, it would be highly desirable to select a unique Lewis acid that could activate both the 2,4-dienal and the *N*-acetylindole partners. The ability of $FeCl_3$ to promote interrupted vinylogous iso-Nazarov reactions, as recently pointed out by Mischne,[13g] merged with our established activation of *N*-acetylindoles by iron(III) chloride makes this Lewis acid the ideal dual promotor.

A careful survey of the reaction revealed that merging *N*-acetylskatole **1a** with 2 equiv of 4-phenylhexa-2,4-dienal **2** and 2 equiv of anhydrous iron(III) chloride in dichloromethane were the optimized conditions (Scheme 2).[23] After extensive study of the reaction conditions, the expected domino reaction proceeded smoothly to afford a mixture of two regioisomeric polycycles **4a** and **5a** in 79% yield and in a 75/25 ratio.[24] Worthy of note is the formation of tetracyclic core molecules bearing five contiguous stereocenters including a quaternary carbon from simple and readily available starting materials. The major cycloadduct **4a** (dr >95:5[24]) arises from the reaction between the oxygen of the dipole and the C3-position of the indole and validates our strategy to overturn the innate reactivity of indoles in cycloadditions. The minor cycloadduct **5a** (dr >95:5[24]) was produced from the classical reactivity of indoles in cycloadditions. We then evaluated the scope of the transformation. We first explored the reaction between 4-phenylhexa-2,4-dienal **2** with an array of substituted *N*-acetylindoles (Scheme 2). *N*-Acetyl-3-methylindoles bearing substituents on the C6 position were first engaged in the domino process. Excellent results were observed with halogen atoms (6-F, 6-Cl, and 6-Br), as yields between 65 and 85% and regioisomeric ratios from 80/20 to 90/10 were recorded for **4b**, **4c**, and **4d**. 6-Substituted skatole derivatives with an electron-donating substituent were also used in the reaction. The presence of a methyl group on the C6 position afforded indoline **4e** in 65% yield and with an excellent selectivity (rr 95:5). Although a high level of selectivity was maintained (rr >95:5), a more electron-donating group such as 6-OMe led to a lower yield (**4f**, 30% yield) because of the propensity of the starting *N*-acetylindole to dimerize. Results were more contrasted with the skatole derivatives bearing a substituent on the C5 position. When *N*-acetyl-3,5-dimethylindole was used in the reaction, fused heterocycles **4g**/**5g** were isolated in 72% yield with a 80/20 ratio. Surprisingly, replacing the methyl group with a bromine atom at the C5 position has a drastic effect on the selectivity of the transformation.

Scheme 2. Substrate Scope of Indoles[a]

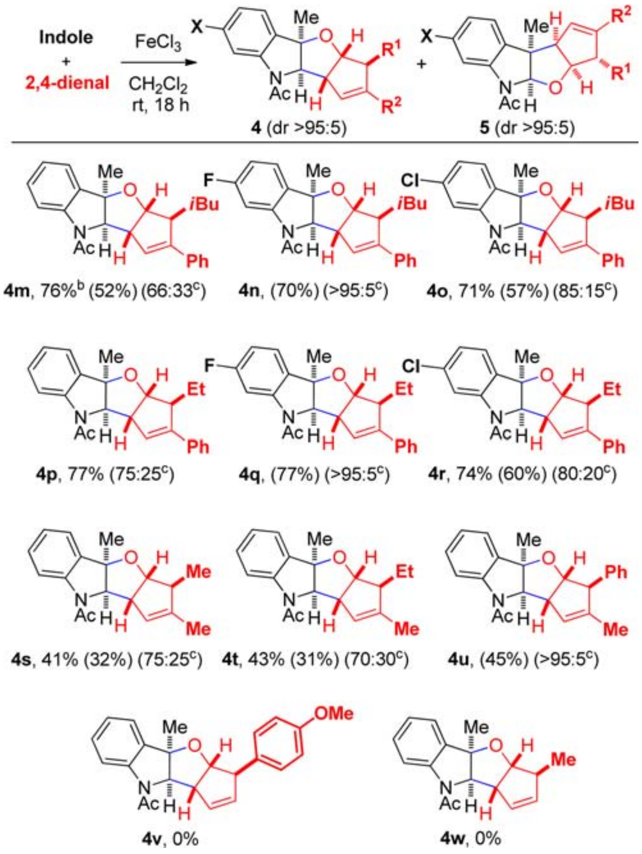


[a]Reactions run with 1 equiv of indole **1**, 2 equiv of 4-phenyl hexa-2,4-dienal **2**, and 2 equiv of $FeCl_3$ in CH_2Cl_2; only the major regioisomer is represented in the table. [b]Yield of a mixture of **4** and **5**. Yields in parentheses refer to the isolated yield of the major regioisomer. [c]Regioisomeric ratio of **4**/**5** was determined by ^1H NMR of the crude mixture.

In this case, indoline **5h** was isolated in 42% yield with a reversal of the regioselectivity. A similar result in terms of yield and selectivity was obtained with *N*-acetyl-3-butyl-5-bromoindole as shown by the formation of indoline **5i** as the major regioisomer. This intriguing finding remains unclear to us, but in the latter case, the presence of a bulkier group at the C3 position was not the origin of the inversed selectivity since *N*-acetyl-3-butylindole produced the expected compound **4j** as the major isomer. *N*-Acetyl-3-ethylindole delivered **4k** with 72% yield (rr 70/30). Not only did 3-alkylindole derivatives undergo this sequence, but an indole core bearing a phenyl group on the C3 position was also amenable to the reaction to afford polycycle **4l** in 42% yield with a good level of selectivity (rr 85:15). The scope of the reaction with respect to unsaturated aldehydes was then examined (Scheme 3). From the outset, we speculated that the reaction could be strongly influenced by the nature of the substituents borne by the 2,4-dienal, especially on the C4 position, which could have an effect on the stability of the cyclic oxyallyl cation intermediate. Aldehydes bearing a phenyl on the C4 position delivered yields superior to 52% whatever the nature of the alkyl chain at C5 (*i*-Bu or Et) as shown by the isolation of compounds **4m**−**r**. When we replaced the C4-phenyl group by a methyl group, the yield decreased as described in the cases of **4s**−**u** (31−45%) with, respectively, a methyl, ethyl, or phenyl group at C5. These results could be explained by the greater stabilization of the carbocation intermediate by a phenyl group at C4 over a methyl group.

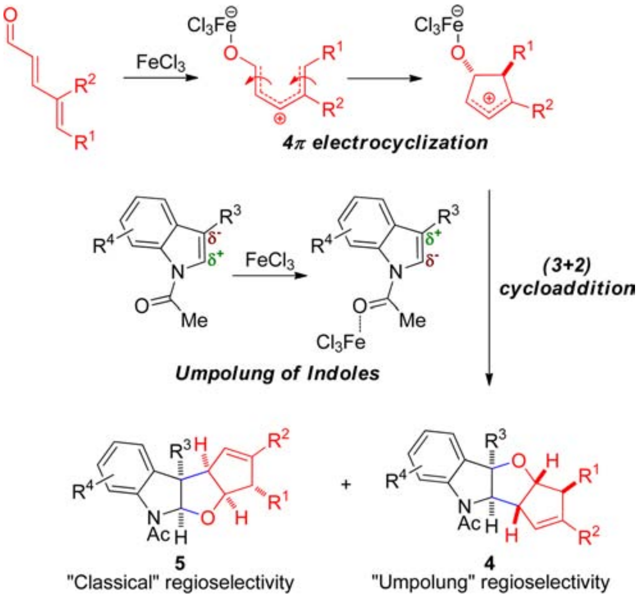
Indeed, no reaction occurred in the absence of substitution at C4 as in the case of 5-(4-methoxyphenyl)penta-2,4-dienal and hexa-2,4-dienal. On the basis of experimental results, the well-established Nazarov reaction, and our own experience in the field of umpolung of indoles, a plausible mechanism is postulated in Scheme 4 to account for the construction of the polycyclic skeletons. Complexation of iron(III) chloride by the carbonyl group of the dienal and the subsequent isomerization of the C2−C3 double bond would result in the formation of a cyclic oxyallyl cation via a conrotatory 4π electrocyclization. The stereospecific process would lead to the creation of two adjacent stereocenters with a *trans* relationship. In the meantime, the complexation of $FeCl_3$ by the oxygen of the *N*-acetylindole would generate an activated dipolarophile with an electrophilic C3 position which would trap the cyclic delocalized cation through a (3 + 2)-cycloaddition to yield tetracyclic indolines **4** as the major product. In most cases, regioisomer **5** is also observed as the minor cycloadduct.

Scheme 3. Substrate Scope of 2,4-Dienals[a]



[a] Reactions run with 1 equiv of indole, 2 equiv of 2,4-dienal, and 2 equiv of $FeCl_3$ in CH_2Cl_2. Only the major regioisomer is represented in the table [b] Yield of a mixture of **4** and **5**. Yields in parentheses refer to isolated yield of the major regioisomer. [c] Regioisomeric ratio of **4**/**5** was determined by ^1H NMR of the crude mixture.

Scheme 4. Proposed Mechanism



In summary, we have developed an efficient domino process constituted by an electrocyclization of a dienal and a dearomative cycloaddition of indoles for the stereoselective elaboration of complex polyheterocyclic structures with the creation of three bonds, two cycles, and five contiguous stereogenic centers including a quaternary carbon. The originality of this method lies in the unprecedented deployment of the iso-Nazarov dipole in a dearomative reaction with C3-electrophilic *N*-acetylindoles as well as the inverted regioselectivity observed compared to known cycloadditions of indoles. The use of cheap and nontoxic $FeCl_3$ as a unique promotor is crucial for both events of these reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02613.

Experimental procedures and compound characterization data including NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(22) We have already described one example of an $FeCl_3$-mediated [2 + 2] intramolecular cycloaddition from an alkene-containing N-Ac indole which led to a 3,3-spiroindoline; see ref 20e.

(23) See the Supporting Information for details.

(24) The structures of both compounds were assigned on the basis of 2D NMR experiments and correlations, and the regioisomeric and diasteromeric ratios were determined by ^{1}H NMR. See the Supporting Information for details.