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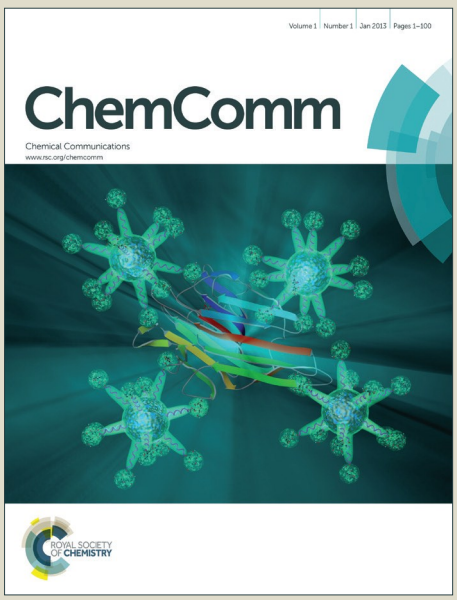

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Nazarov Cyclization of 1,4-Pentadien-3-ols: Preparation of Cyclopenta[*b*]indoles and Spiro[indene-1,4´-quinoline]s †

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The first Lewis acid–catalyzed intramolecular interrupted Nazarov cyclization of 1,4-pentadien-3-ols is described. Using $FeBr_3$ as the catalyst, a series of new substituted cyclopenta[*b*]indoles was prepared—through a sequence of Nazarov cyclization, nucleophilic amination, and isomerization—with good yields and high diastereo- and regioselectivities. A similar catalytic process was also developed for the synthesis of structurally interesting spiro[indene-1,4´-quinoline]s.

Indoles and their derivatives, especially multicyclic indole compounds, are seemingly ubiquitous in natural products and pharmaceutical agents, acting as important key structural motifs in many bioactive molecules.[1] Among them, cyclopenta[*b*]indoles occupy a significant place in the fields of natural products and medicinal chemistry. There are numerous biologically active indole alkaloids and medicinally important compounds containing a cyclopenta[*b*]indole unit as a core structure, including yuehchukene,[2] fischerindoles,[3] terpendoles,[4] bruceollines,[5] malasseziacitrin,[6] and the drug laropiprant.[7] Traditionally, cyclopenta[*b*]indoles have been constructed through Fischer indole synthesis from corresponding phenylhydrazines and cyclopentanones.[8] The major drawbacks of the classic Fischer indole synthesis, however, are the limited substrate scope and the lack of regioselectivity. Although intramolecular Friedel–Crafts cyclizations of indole with alkenes can also provide access to cyclopenta[*b*]indoles, this approach can require multistep preparations of starting materials and harsh reaction conditions.[9] Consequently, the development of new methodologies for the construction of the cyclopenta[*b*]indole scaffold under mild reaction conditions with high efficiency and selectivity remains an active research area.[10] Methods involving both pyrrole and cyclopentane ring formation in a single step are particularly desirable.[11]

The Nazarov cyclization, a primary tool for the preparation of cyclopentenone compounds, has been applied widely in the synthesis of natural products and bioactive molecules.[12] In particular, the interrupted Nazarov cyclization has been developed extensively for rapid access to complex functionalized cyclopentenones.[13] Although the Nazarov cyclization of divinyl ketones has been studied thoroughly, examples of Nazarov cyclization based on 1,4-pentadien-3-ols are relatively scarce.[14] In the limited examples, 1,4-pentadien-3-ols were treated with a Brønsted or Lewis acid to form pentadienyl cations, which underwent 4π-electrocylic ring closure to afford the cyclopentadiene products.[14b,d,i] The broader application of this transformation has been hampered, however, by lack of control with respect to the position of the double bonds.[14a,b,i] For example, Hall reported recently that the arylboronic acid–catalyzed Nazarov reaction of divinyl alcohol furnished a 1:2.2 mixture of regioisomeric cyclopentadienes.[14a] Moreover, to the best of our knowledge, the interrupted Nazarov cyclization of 1,4-pentadien-3-ols has not been reported previously. As a means of controlling the regiochemistry of the Nazarov cyclization of 1,4-pentadien-3-ols, we envisioned intramolecular trapping of the allylic cation by an appended aniline unit (Scheme 1). Accordingly, treatment of 3-(2-anilinyl)-1,4-pentadien-3-ol (**1**) with either a Brønsted or Lewis acid should produce the pentadienyl cation **2**, which, upon Nazarov cyclization, should form the allylic cation **3**. Potentially, the steric bias endowed by the substitution around the cyclopentene cation would control its trapping by the aniline unit on the less-hindered side,

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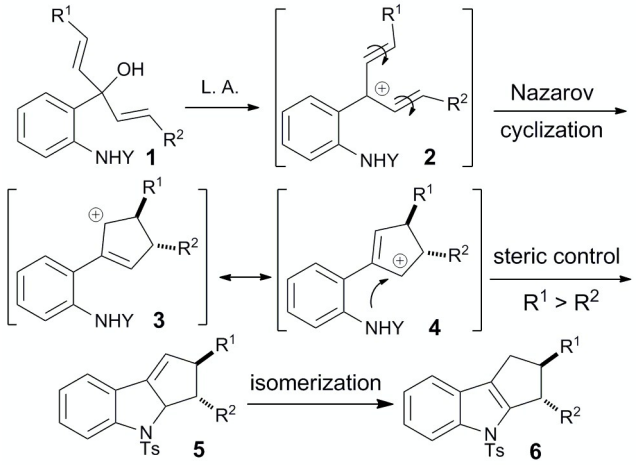


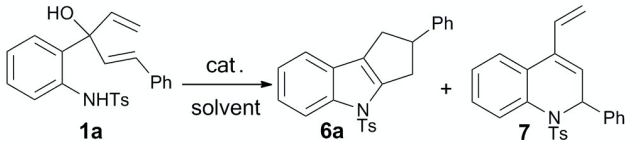
Scheme 1 Intramolecular Interrupted Nazarov Cyclization of 1,4-Pentadien-3-ols

selectively forming the single regioisomer **5**, which is likely to isomerize to the indole **6**.

To explore the feasibility of this transformation, we chose (*E*)-3-(2-tosylamidophenyl)-1-phenylpenta-1,4-dien-3-ol (**1a**) as the model substrate (Table 1). Treatment of **1a** with 30 mol % $FeBr_3$ in $CHCl_3$ at 50 °C gave 2-phenyl-4-tosyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole (**6a**) as the sole product in 75% yield through the expected reaction sequence (entry 1). The structure of **6a** was confirmed through X-ray crystallographic analysis.[15] Employing $FeCl_3$, $AlCl_3$, or $ZrCl_4$ as the catalyst resulted in a markedly lower yield (10-55%) of the desired product (entries 2-4). In contrast, changing the catalyst to $AuCl_3$ or HBr led to the production of 2-pentyl-1-tosyl-4-vinyl-1,2-dihydroquinoline (**7**), presumably through intramolecular allylic amination of the pentadienyl cation precursor of the Nazarov cyclization (entries 5 and 6).[16] A lower yield of **6a** (60%) was afforded when using CH_2Cl_2 as the solvent (entry 7). An even less polar solvent (toluene) provided an even lower yield and worse selectivity of the product **6a**, while THF and MeCN delivered the 1,2-dihydroquinoline by-product **7** exclusively (entries 8–10). Increasing the catalyst loading to 40-100 mol % did not improve the reaction's outcome (entries 11 and 12). Lowering the catalyst loading to 20-5 mol % provided only a moderate yield of the cyclopenta[*b*]indole **6a**, along with the by-product **7** (entries 13 and 14). A similar result was obtained when diluting the original mixture fivefold (entry 15). It seems that the reaction pathway is highly dependent on the catalyst's concentration in the reaction system. Gratifingly, this intramolecular interrupted Nazarov cyclization could be easily performed on a 4 mmol scale, giving the desired product **6a** in 73% yield (entry 16).

With the optimized conditions in hand, the scope of the reaction was examined using a variety of disubstituted 1,4-pentadien-3-ols (Table 2). *N*-Methanesulfonyl, *N*-benzenesulfonyl, *N*-(4-chloro)benzenesulfonyl, and *N*-(4-methoxy)benzenesulfonyl (*E*)-3-(2-aminophenyl)-1-phenylpenta-1,4-dien-3-ols all functioned well in the cascade reaction, albeit with slightly lower reaction yields (cf. **6a** vs **6b-e**). Disubstituted 1,4-pentadien-3-ols with either electron-donating or -withdrawing substituents on the 2-aminophenyl ring were suitable for this transformation, giving **6f-h** in 59-81% yields. The $FeBr_3$-catalyzed synthesis of cyclopenta[*b*]-indole compounds tolerated methyl, methoxyl, fluoro, chloro,

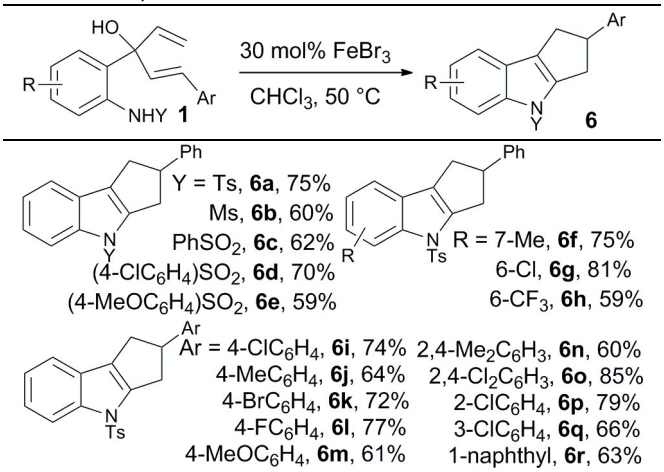
Table 1 Optimization of Reaction Conditions[a]



entry	catalyst	solvent	temp/ °C	time/ h	yield (%)[b] 6a	7
1	$FeBr_3$	$CHCl_3$	50	0.5	75	–
2	$FeCl_3$	$CHCl_3$	50	0.5	55	–
3	$AlCl_3$	$CHCl_3$	50	0.5	10	–
4	$ZrCl_4$	$CHCl_3$	50	0.5	10	40
5	$AuCl_3$	$CHCl_3$	50	0.5	–	71
6	HBr	$CHCl_3$	50	0.5	–	40
7	$FeBr_3$	CH_2Cl_2	40	0.5	60	–
8	$FeBr_3$	toluene	50	2	30	40
9	$FeBr_3$	THF	50	2	–	46
10	$FeBr_3$	CH_3CN	50	1	–	68
11	$FeBr_3$[c]	$CHCl_3$	50	0.5	70	–
12	$FeBr_3$[d]	$CHCl_3$	50	0.5	65	–
13	$FeBr_3$[e]	$CHCl_3$	50	0.5	40	48
14	$FeBr_3$[f]	$CHCl_3$	50	0.5	–	80
15	$FeBr_3$[g]	$CHCl_3$	50	0.5	42	45
16	$FeBr_3$[h]	$CHCl_3$	50	0.5	73	–

[a] Unless otherwise stated, all reactions were performed with 0.2 mmol of **1a** and 0.06 mmol of the catalyst in 2 mL of the solvent. [b] Isolated yield. [c] 0.08 mmol of $FeBr_3$ was used. [d] 0.2 mmol of $FeBr_3$ was used. [e] 0.04 mmol of $FeBr_3$ was used. [f] 0.01 mmol of $FeBr_3$ was used. [g] 10 mL of $CHCl_3$ was used. [h] Reaction performed on a 4 mmol scale.

Table 2 Intramolecular Interrupted Nazarov Cyclizations of Disubstituted 1,4-Pentadien-3-ols[a,b]

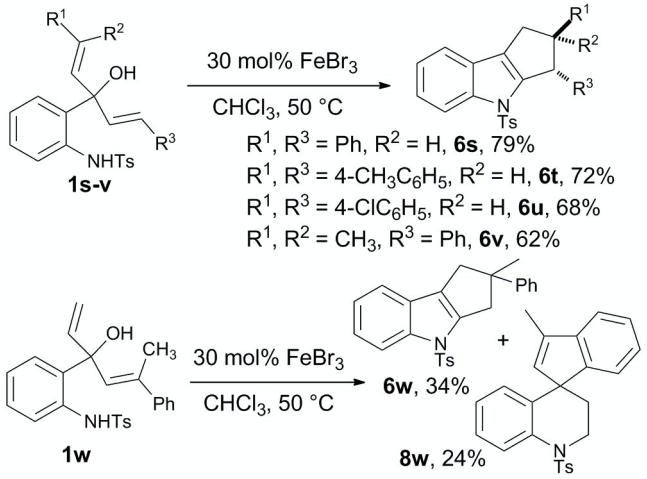


[a] **1** (0.2 mmol) and $FeBr_3$ (0.06 mmol) were reacted in $CHCl_3$ (2 mL) at 50 °C for 0.5 h. [b] Isolated yield.

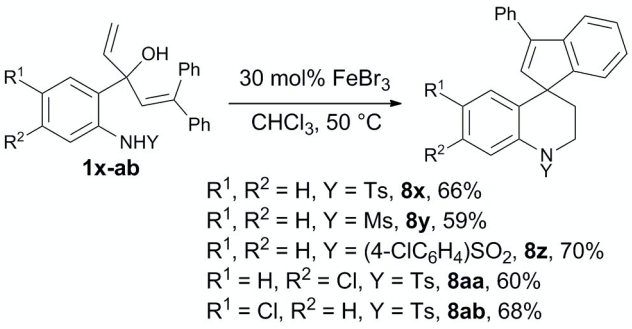
and bromo groups on the phenyl ring of the 1-phenyl-1,4-pentadien-3-ols, affording the desired products **6i–q** in good yields. 1-Naphthyl-1,4-pentadien-3-ol also provided its desired product **6r** in 63% yield.

As conjectured, the intramolecular amination of the allylic cation intermediate **3**↔**4** occurred away from the sterically more demanding substituent. Encouraged by these results, several polysubstituted 1,4-pentadien-3-ols (**1s-w**) were synthesized to examine the reaction's regio- and diastereoselectivities and the substituent effects of the 1,4-pentadien-3-ol (Scheme 2). The (*E*,*E*)-3-(2-tosylaminophenyl)-1,5-diarylpenta-1,4-dien-3-ols **1s-u** reacted well, giving only their *trans* products **6s-u**. The relative configuration of the *trans* isomer was established unequivocally through X-ray crystallographic analysis of compound **6t**.[15,17] The tetrasubstituted 1,4-pentadien-3-ol **1v** also gave a good yield of a single product (**6v**). Again, the reaction's regioselectivity appeared to be induced by steric bias. When (*E*)-3-(2-tosylaminophenyl)-1-methyl-1-phenylpenta-1,4-dien-3-ol (**1w**) was applied, however, both the cyclopenta[*b*]indole **6w** (34%) and the spiro[indene-1,4′-quinoline] **8w** (24%) were isolated, with the latter formed presumably through Nazarov cyclization on the benzene ring and subsequent $FeBr_3$-catalyzed intramolecular hydroamination of the monosubstituted alkene moiety.[18,19]

Because of their importance in natural products synthesis and pharmaceuticals, various methods have been developed for the preparation of quinoline derivatives.[20] Surprisingly, efficient synthetic pathways for the construction of structurally interesting spiro[indene-1,4′-quinoline] frameworks are very rare. We envisioned that changing the methyl group on the C-1 atom of **1w** to a phenyl group might stabilize the carbocation at the C-1 position of the substrate and improve the reaction's selectivity to afford the spiro[indene-1,4′-quinoline] product. Gratifyingly, the use of various *N*-sulfonyl 3-(2-sulfonamidoaryl)-1,1-diphenylpenta-1,4-dien-3-ols **1x-ab** as substrates furnished several unusual spiro[indene-1,4′-quinoline] compounds **8x-ab** as sole products in yields of 59-70% (Scheme 3). The Nazarov cyclization/hydroamination cascade leading to the spiro[indene-1,4′-quinoline] framework could accommodate *N*-tosyl, *N*-mesyl, *N*-4-



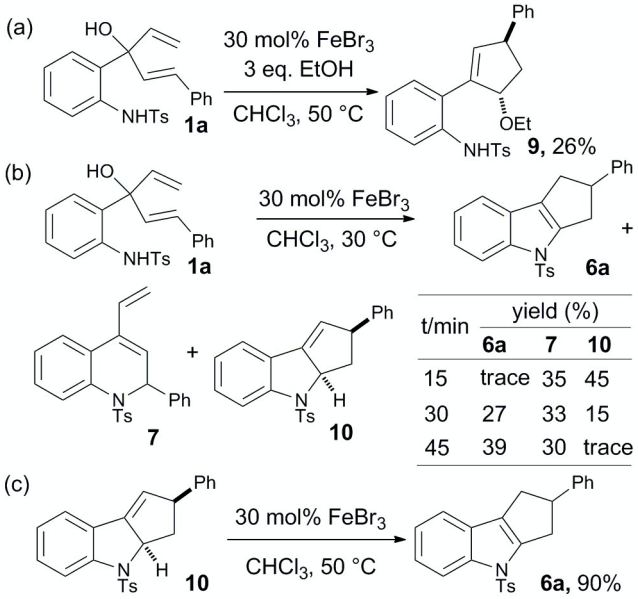
Scheme 2 Nazarov Cyclizations of Polysubstituted 1,4-Pentadien-3-ols



Scheme 3 Synthesis of Spiro[indene-1,4′-quinoline]s

chlorobenzenesulfonyl, and chloro groups on the substrates. The structures of compounds **6v** and **8y** were confirmed using X-ray crystallography.[15]

To further verify the reaction mechanism proposed in Scheme 1, three different sets of experiments were conducted (Scheme 4). When the reaction was run in the presence of three equivalents of EtOH, the putative carbocation underwent solvolysis to form the ethyl ether **9** in 26% yield. Moreover, the key reaction intermediate 2,3,3a,4-tetrahydrocyclopenta[*b*]indole **10** was isolated as a single *cis* diastereoisomer when the reaction was conducted at 30 °C. The ratio of the products **6a**, **7**, and **10** was highly dependent on the reaction time. After 15 min, **7** and **10** were obtained in yields of only 35 and 45%, respectively. As the reaction progressed, the yield of **6a** increased and the yield of **10** decreased, while the yield of **7** remained almost constant. When the indoline **10** was subjected to the optimized reaction conditions, the cyclopenta[*b*]indole **6a** was isolated in 90% yield. These results corroborate the notion that this cyclopenta[*b*]indole synthesis involves an intramolecular interrupted Nazarov cyclization and isomerization sequence, with the 2,3,3a,4-tetrahydrocyclopenta[*b*]indole **10** as the key reaction intermediate. The structures of compounds **9** and **10** were confirmed using X-ray crystallography.[15]



Scheme 4 Mechanistic Studies

In conclusion, new Lewis acid–catalyzed cascade reactions based on Nazarov cyclization of 1,4-pentadien-3-ols have been developed, providing substituted cyclopenta[*b*]indoles and spiro[indene-1,4′-quinoline]s in good yields. The advantages of this approach are the use of inexpensive and environmentally friendly $FeBr_3$ as the catalyst, relatively mild reaction conditions, and exclusive regio- and diastereoselectivities. This facile and efficient methodology appears to be a useful tool for the synthesis of biologically important cyclopenta[*b*]indole and spiro[indene-1,4′-quinoline] derivatives.

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