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Expedient Synthesis of N-Fused Indoles: A C−F Activation and C−H Insertion Approach**

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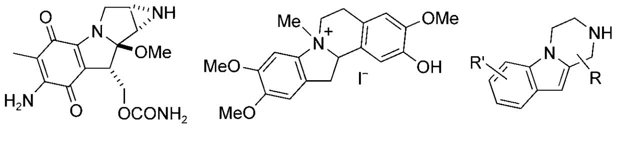
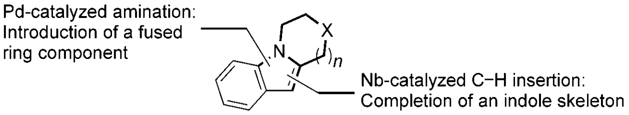
Indoles are versatile components of many natural and synthetic biologically active compounds, and a vast number of pharmaceuticals containing the indole skeleton are being used for therapeutic purposes.[1] N-fused indoles are indole derivatives that have great biological and pharmaceutical importance. For example, mitomycin C[2] and cryptaustoline[3] possess the N-fused indole structure (Scheme 1). These and related indole alkaloids exhibit antitumor[4] and tubulin polymerization inhibitory[5] activities. Pyrazino[1,2-*a*]indoles behave as 5-HT_{2c} receptor agonists[6] and are related to the treatment of hyperglycemia and other diseases by controlling appetite.



Scheme 1. Biologically active N-fused indoles.

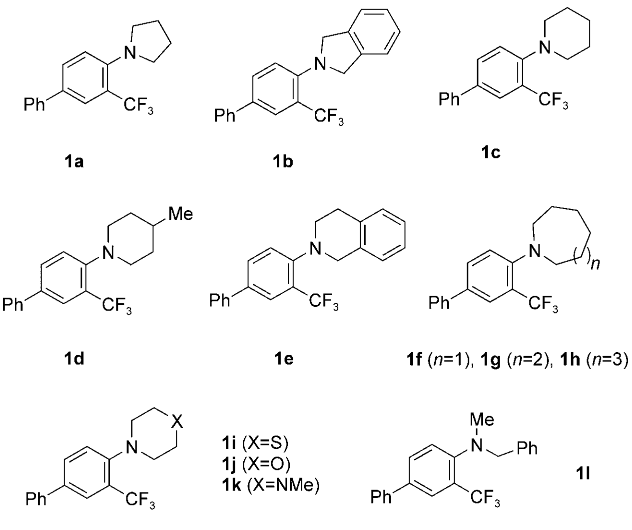
Despite the importance of N-fused indole derivatives, the synthesis of this class of compounds has not yet been fully developed: alkyl chain elongation and ring closure on an existing indole platform have been reported by many research groups (for example, by intramolecular alkylation,[7a] radical cyclization,[7b–e] and other methods[7f]). Transannulation reactions[8] also afford N-fused indoles. In recent years, many transition-metal-catalyzed reactions have been reported.[9] However, the ring-closure strategy still poses many problems and most importantly, a multistep synthesis of the substrates is required regardless of the synthetic strategy selected.

Herein we describe an expedient synthesis of N-fused indoles by means of a direct, catalytic C−H carbenoid insertion approach. Our strategy consists of two steps: 1) a cyclic amine is introduced into *o*-(trifluoromethyl)bromobenzene as a fused ring component by a palladium-catalyzed amination reaction, and 2) a niobium-catalyzed $C(sp^3)$−H insertion reaction completes the indole core skeleton (Scheme 2). The well-established amination reaction, originally explored by Buchwald and co-workers,[10] will ensure the flexibility of the fused-ring substructure. Insertion reactions of a niobium fluorocarbenoid center, which is generated from a CF_3 group attached to an aromatic nucleus, into a $C(sp^2)$−H bond were developed recently by our group.[11–13]



Scheme 2. Our strategy.

Scheme 3 shows precursors which were prepared in good yields mainly by the Buchwald amination reaction (see the Supporting Information for details).[10] Notably, CF_3 groups, which would generate the key carbenoid centers, were not affected by the C−N coupling conditions.



Scheme 3. List of insertion precursors **1**.

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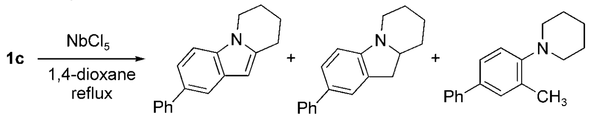
With the insertion precursors **1** in hand, the key C–H insertion reaction was examined (Table 1). Initially, **1c** was treated with lithium aluminum hydride in the presence of 1.5 equivalents of niobium(V) chloride.[10a] To our delight, piperidinoindole **2c** and piperidinoindoline **3** were obtained in 20 % yield each, with **1c** recovered in 52 % yield (Table 1, entry 1). The conversion rate improved dramatically when sodium aluminum hydride was used, giving **2c** and **3** in yields of 27 % and 46 %, respectively (Table 1, entry 2; 30 mol % niobium(V) chloride).[14,15] In contrast, alkoxy-substituted aluminum hydride reagents were unreactive, resulting in the recovery of starting material **1c** (Table 1, entries 3 and 4) even when an equimolar amount of niobium(V) chloride was used.[16]

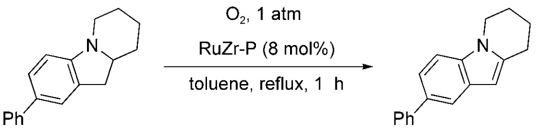
Table 1: Optimization of the reaction conditions.



2c **3** **4**

Entry	NbCl$_5$	Reducing agent[a]	*t* [h]	Yield [%]		
				2c	**3**	**1c**
1	1.5 equiv	LiAlH$_4$ (10)	49	20	20	52
2	30 mol %	NaAlH$_4$ (4)	23	27	46	–[b]
3	1.0 equiv	LiAl(O*t*Bu)H$_3$ (10)	72	–	–	[c]
4	1.0 equiv	Red-Al (19)[d]	24	–	–	[c]

[a] The amount of reducing agent (equiv) is indicated in parenthesis. [b] **4** was obtained in 15 % yield. [c] **1c** was recovered as the sole product (yields were not determined). [d] Red-Al = sodium bis(methoxyethoxy)-aluminum hydride.



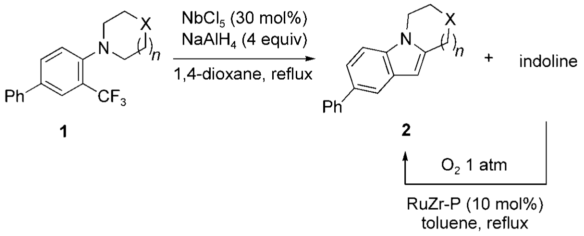
3 **2c**, quant.

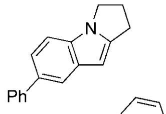
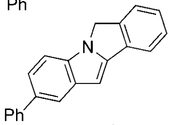
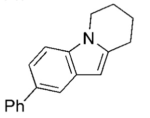
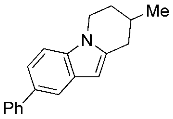
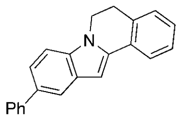
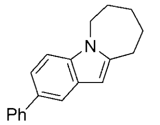
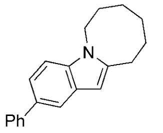
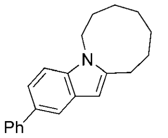
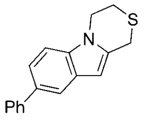
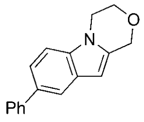
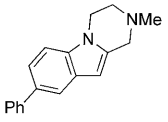
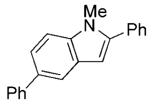
Scheme 4. Ruthenium-catalyzed dehydrogenation of indoline **3**.

Dehydrogenation of isolated **3** proceeded smoothly in the presence of a ruthenium catalyst (Scheme 4). Indoline **3** afforded indole **2c** in quantitative yield when treated with 8 mol % ruthenium zirconium phosphate[17] under dioxygen at atmospheric pressure. 2,6-Dichloro-3,5-dicyano-*p*-benzoquinone (DDQ) was found to be less efficient for this aromatization, giving 75 % yield of **2c** upon heating for 11 h in toluene (1 equiv, RT to 50 °C; not shown).

Precursors **1a–l** were subjected to niobium-catalyzed C–H insertion conditions and the isolated indolines were then dehydrogenated with the ruthenium catalyst. Table 2 shows the overall yields of indoles **2a–l** from the consecutive reactions. The C–H insertion step was found to proceed smoothly with a range of cyclic amino groups: indoles with five- to nine-membered fused-ring substructures were syn-

Table 2: Synthesis of N-fused indoles.

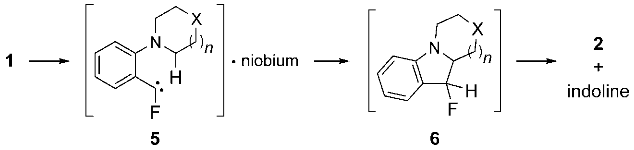


Entry	Precursor	Product	*t* [h][a]	Yield [%][b]
1	**1a**		6	65, **2a**
2	**1b**		5	78, **2b**
3	**1c**		23	70, **2c**
4	**1d**		13	64, **2d**
5	**1e**		6.5	68, **2e**
6	**1f**		19	71, **2f**
7	**1g**		4	87, **2g**
8	**1h**		6	85, **2h**
9	**1i**		15	52, **2i**
10	**1j**		25	59, **2j**
11	**1k**		13	57, **2k**
12	**1l**		19	56,[c] **2l**

[a] Reaction time of the C–H insertion step. [b] Overall yield of two contiguous reactions. [c] 1-Benzyl-5-phenylindole was obtained in 11 % yield.

thesized in good to high yields (Table 2, entries 1–8). Oxygen, sulfur, and nitrogen atoms in the cyclic amino groups did not interfere with the insertion, and the corresponding heteroatom-containing N-fused indoles were obtained in good yields (Table 2, entries 9–11). Acyclic **1l** also underwent insertion, with the reaction proceeding mainly at an electronically favored benzylic site (Table 2, entry 12). This result clearly contrasts with the result of the $[Rh_2(S\text{-dosp})_4]$-catalyzed insertion (dosp = *N*-(*p*-dodecylphenylsulfonyl)prolinato),[18] in which the sterically less hindered methyl site is preferred.

Mechanistically, the C–H insertion reaction can be rationalized similarly to our previous C(sp^2)–H insertion reactions (Scheme 5):[10c] fluorine-substituted carbenoid intermediate **5** is generated in the reaction medium and then the carbenoid center undergoes insertion into a C–H σ bond adjacent to a nitrogen atom. Dehydrofluorination of the resulting fluoroindoline **6** (not detected) gives indole **2**.[19] Hydrodefluorination of **6**, however, gives indolines (for example, **3**).[20] Further studies to gain a full understanding of the niobium-catalyzed C–H insertion reaction are ongoing.



Scheme 5. Proposed reaction pathway.

In summary, we have developed a new route to biologically and pharmaceutically important N-fused indole derivatives. Indoles with a nine-membered ring substructure (maximum ring size) and with a heteroatom-containing ring substructure could be synthesized in good yields. The combined use of a palladium-catalyzed amination reaction and a newly developed niobium-catalyzed C(sp^3)–H insertion reaction has resulted in a facile, short-step synthesis.

Experimental Section

Niobium(V) chloride (27 mg, 0.10 mmol, 30 mol %) and sodium aluminum hydride (65 mg, 1.2 mmol) were added to a solution of **1c** (103 mg, 0.338 mmol) in dioxane (3.3 mL). The reaction mixture was refluxed for 23 h and then quenched with water at 0 °C. Purification by column chromatography (SiO_2, hexane/dichloromethane 3:1) gave indole **2c** (23 mg, 0.091 mmol) and indoline **3** (39 mg, 0.16 mmol) in 27 and 46 % yield, respectively. Commercially available ruthenium zirconium phosphate (40 mg, 10 mol % Ru, Kanto Co.) was added to a solution of isolated **3** in toluene (1.5 mL). Dioxygen (1 atm) was introduced into the flask and the reaction mixture was heated at reflux for 24 h. The reaction mixture was filtered through a small pad of silica gel and purified by column chromatography (SiO_2, hexane/dichloromethane 3:1) to give indole **2c** (36 mg, 0.14 mmol, 43 % based on **1c**) .

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Keywords: carbenoids · fused-ring systems · indoles · insertion · niobium

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[19] Thin-layer chromatographic analysis of the reaction mixture suggests that the indole is generated in the reaction medium. However, partial autooxidation of the indoline to the indole during work-up was also observed.

[20] When a reaction of **1c** was quenched with D_2O, **3** with 0.59 deuterium atoms at a benzylic position was obtained. This result suggests that the benzylic anion is reductively formed from the presumed intermediate **6** and that protonation of the anionic intermediate gives **3**.