A novel and direct synthesis of indoles *via* catalytic reductive annulation of nitroaromatics with alkynes†

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Indoles are produced regioselectively and in moderate yields from the reactions of nitroaromatics with alkynes catalyzed by [CpM(CO)₂]₂ (1; [(η⁵-C₅H₅)Fe(CO)₂]₂; [(η⁵-C₅Me₅)-Fe(CO)₂]₂; [(η⁵-C₅Me₅)Ru(CO)₂]₂) under carbon monoxide.

Indoles are among the most abundant and important classes of N-heterocycles, being present in the form of innumerable natural products and bioactive compounds. Accordingly, chemists have long sought methods for the preparation of indoles and numerous approaches continue to be reported toward this end.[1] Especially attractive, but rare, are reactions which directly produce indoles by annulation of commercially available N-aromatic precursors, as typified by the Fischer indole synthesis in which aromatic hydrazines and ketones are condensed.[2,3] The need for broad substrate scope, more accessible starting materials, improved regioselectivity, milder reaction conditions, and functional group tolerance has also stimulated the development of numerous transition metal-promoted routes to indoles,[4] most of which, however, are intramolecular cyclizations requiring an ortho-substituted N-aromatic substrate.[5]

The ability of metal complexes to induce C–N bond formation by the reduction of nitroaromatic compounds with carbon monoxide[6] and our continuing goal to develop direct nitrogenation reactions of hydrocarbons,[7] led us recently to develop a novel and regioselective, iron-catalyzed synthesis of allyl amines by the reductive amination of olefins with nitroaromatics (eqn. (1)).[8]

$$ArNO_2 + \underset{}{\diagup\!\!\!\diagdown}R \xrightarrow[\text{[CpFe(CO)}_2]_2]{CO} ArNH\underset{}{\diagup\!\!\!\diagdown}R + CO_2$$

(1)
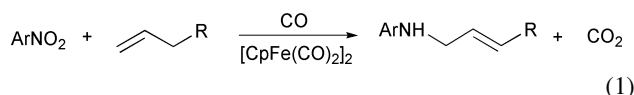
Anticipating a new route to propargyl- and/or allenylamines, we began to examine the corresponding reactions of nitroaromatics and alkynes but have found, remarkably, that *indoles are the major products of these reactions*.

In our initial experiments 1-phenylpropyne and nitrobenzene were heated together with [CpFe(CO)₂]₂ (**1a**) under CO pressure (dioxane, 170 °C, 750 psi, 24 h); GC/MS monitoring indicated the formation of a major product (*ca.* 20%) with the mass of the expected amine (*m/e* 207) as well as lesser quantities of aniline (12%), azo- (15%) and azoxybenzene (8%). Isolation of this material in fact showed it to be 2-methyl-3-phenylindole (**2a**)[9] rather than the isomeric propargyl- or allenylamine (eqn. (2)).

(2)
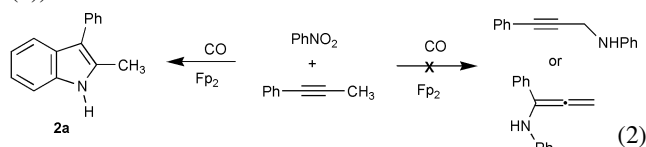
Under similar conditions with [(C₅Me₅)Fe(CO)₂]₂ (**1b**) or [(C₅Me₅)Ru(CO)₂]₂ (**1c**) as the catalyst phenyl acetylene and nitrobenzene afforded 3-phenylindole regiospecifically (**2b**,

† Electronic supplementary information (ESI) available: analytical data for the product indoles. See http://www.rsc.org/suppdata/cc/b1/b110370a/

30–40% yield). Using the PhNO₂/PhC≡CH reaction for a catalyst survey and optimization study (eqn. (3), X,Y=H, Z=CH, R=Ph, R′=H) both Fe- and Ru-cyclopentadienyl derivatives, **1a–c**[10] proved to be effective catalysts for the production of 3-phenylindole. Moderate yields (20–40%) were obtained in dioxane or benzene operating above 500 psi of CO and 160 °C with a 2–4 : 1 PhC≡CH : PhNO₂ ratio and 5 mol% catalyst; under these conditions the Ru-complex **1c** gave the best yield (39%). For these reactions the N-mass balance was 80–90%.[11] Notably, several cyclopentadienyl complexes of other metals, non-Cp-Ru compounds, and various Pd–phosphine complexes, which are active in other nitroarene reductive reactions, failed to promote indole formation.[12]

An initial survey of nitroarene and alkyne substrates indicates that the reaction has significant scope as a method for the selective preparation of substituted indoles (eqn. (3), Table 1).

[Mp]₂= [(η⁵-CpFe(CO)₂]₂ (**1a**), [(η⁵-C₅Me₅)Fe(CO)₂]₂ (**1b**), [(η⁵-C₅Me₅)Ru(CO)₂]₂ (**1c**)

(3)
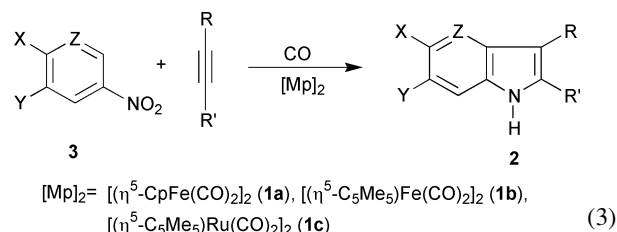
Although electron-neutral or -deficient nitroarenes react more rapidly, both electron rich and electron deficient substrates gave comparable yields of indoles in their reactions with phenylacetylene (entries 1,6–10). The unsymmetrical *m*-CF₃-derivative (entry 9) reacted with phenylacetylene to give a (3:2) mixture of 3-phenyl-4-CF₃- and 3-phenyl-6-CF₃-indoles but the 3-aryl specificity was preserved. The electron poor nitropyridine derivative (entry 10) is an especially effective substrate for annulation, illustrating direct access to azaindoles which are of considerable importance as clinical, fluorescent and metal-

Table 1 Preparation of indoles by [Cp*Ru(CO)₂]₂-catalyzed reductive annulation (eqn. 3)[a]

Entry	ArNO₂	R	R′	Yield (%)[b]
1	Ph	Ph	H	39[c,d]
2	Ph	Ph	Me	34[c]
3	Ph	Ph	Et	24
4	Ph	Ph	CO₂Et	24[e]
5	Ph	CH₃(CH₂)₄	CH₃	Traces
6	*p*-OCH₃-C₆H₄	Ph	H	38[f]
7	*p*-Cl-C₆H₄	Ph	H	23
8	*p*-CN-C₆H₄	Ph	H	31
9	*m*-CF₃-C₆H₄	Ph	H	44[g]
10	2-Cl-C₅H₃N-4-NO₂	Ph	H	53[h]

[a] 5 mol% **1c**, benzene, 750 psi CO, 170 °C, 48 h (see ref. 11 for procedure). [b] Isolated, after chromatography. [c] GC yield, naphthalene internal reference. [d] Reaction carried out in dioxane. [e] 2 : 1 mixture of 2,3-regioisomers. [f] 45% conversion after 120 h. [g] 3:2 mixture of 4,6-regioisomers. [h] 3.5 : 1 mixture of 4- and 6-azaindoles.

complexing agents.[13] The most effective reactions occur with alkynes possessing at least one aryl or carboalkoxy group (entries 1–4 *vs.* 5). As above, phenylacetylene and arylalkyl alkynes reacted with complete regioselectivity (>99%), placing the aryl substituent at the 3-position (entries 1–3, 6–10), while ethyl phenylpropiolate afforded a 2:1 mixture of 3-phenyl/2-phenyl regioisomers.

The mechanistic pathway for this remarkable transformation, which involves N-centered reduction, C–H activation, and the formation of both C–N and C–C bonds is presently unknown but the following initial observations are informative. No reaction occurs in the absence of either catalyst or carbon monoxide, consistent with the precedented ability of metal carbonyl complexes to promote deoxygenation of nitro compounds.[3] Under the same conditions employed for the nitroarene/alkyne reactions, a mixture of *nitroso*benzene, phenylacetylene and **1c** also was converted to 3-phenylindole, faster and in greater yield (18 h, 53% yield),[14] suggesting the intermediacy of the nitrosoarene (free or coordinated) in the nitroarene reactions. On the other hand no carbazole was detected in the reaction of *o*-nitrobiphenyl with PhC≡CH (**1c**, benzene, 170 °C, 750 psi), rendering unlikely the intermediacy of a free aryl nitrene.[15] Similarly, possible formation of the indoles by metal-promoted heterocyclization of azobenzene[16] (present as a by-product) was excluded by the failure of the latter to be converted to 3-phenylindole under the catalytic reaction conditions. It is also noteworthy, both mechanistically and synthetically, that complex **1c** is largely recovered following catalytic runs. The unique activity of the dinuclear [CpM(CO)$_2$]$_2$ complexes **1** to catalyze the reductive aminations of alkenes and alkynes by nitroarenes is extraordinary, considering their stable, eighteen electron count and very limited catalytic history.[17] The ability of **1** to dissociate to seventeen electron organometallic radicals[18] and/or to undergo facile redox reactions[19] may be relevant to their special catalytic activity.

The presently disclosed novel annulation reaction provides a direct and regioselective route to indoles from nitroaromatics, the most readily available of N-functionalized aromatic compounds, and alkynes. Although the indole yields presently are only moderate, the directness, regioselectivity and neutral reaction conditions of this annulation route portend its wide synthetic utility. Our current efforts are centered on identifying more active and efficient catalyst systems and on exploring the synthetic scope and the mechanism of this remarkable transformation.

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12 Representatives of the following classes of complexes failed to catalyze indole formation: PdX$_2$L$_2$, PdL$_4$, RuCl$_2$(C$_6$H$_6$)/L, Ru$_3$(CO)$_{12}$/L; Rh(CO)$_2$I$_2^-$, (Me-Cp)Mn(CO)$_3$ and [Cp*Cr(CO)$_3$]$_3$ were also inactive.
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