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ChemComm

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

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Received (in Corvallis, OR) 13th November 2001, Accepted 14th January 2002 First published as an Advance Article on the web 7th February 2002

Indoles are produced regioselectively and in moderate yields from the reactions of nitroaromatics with alkynes catalyzed by $[CpM(CO)_2]_2$ (1; $[(\eta^5-C_5H_5)Fe(CO)_2]_2$; $[(\eta^5-C_5Me_5)Fe(CO)_2]_2$; $[(\eta^5-C_5Me_5)Ru(CO)_2]_2$) 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 monoxide⁶ 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

ArNO₂ +
$$R$$
 CO $ArNH$ 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)).



Under similar conditions with $[(C_5Me_5)Fe(CO)_2]_2$ (1b) or $[(C_5Me_5)Ru(CO)_2]_2$ (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).



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 $[\rm Cp*Ru(\rm CO)_2]_2\text{-}catalyzed$ reductive annulation (eqn. 3)^a

Entry	ArNO ₂	R	R′	Yield (%) ^b
1	Ph	Ph	Н	39c,d
2	Ph	Ph	Me	34 ^c
3	Ph	Ph	Et	24
4	Ph	Ph	CO ₂ Et	24^{e}
5	Ph	$CH_3(CH_2)_4$	CH ₃	Traces
6	p-OCH ₃ -C ₆ H ₄	Ph	Н	38f
7	p-Cl-C ₆ H ₄	Ph	Н	23
8	p-CN-C ₆ H ₄	Ph	Н	31
9	m-CF ₃ -C ₆ H ₄	Ph	Н	44^{g}
10	2-Cl-C5H3N-4-NO2	Ph	Н	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.

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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 nitrosobenzene, 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 azobenzene¹⁶ (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 radicals¹⁸ and/or to undergo facile redox reactions¹⁹ 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.

We are grateful for financial support provided by the National Science Foundation and the Ministero dell'Universita' e della Ricerca Scientifica e Tecnologica (Italy).

Notes and references

- (a) R. J. Sundberg *Indoles*, Academic, London, UK, 1996R. J. Sundberg in *Comprehensive Heterocyclic Chemistry*, 2nd ed., vol. 2, ed. C. W. Bird, Pergamon, Oxford, UK, 1995, pp. 121–157.
- 2 B. Robinson *The Fischer Indole Synthesis*, John Wiley and Sons, New York, 1982, ref. 1a, p. 54–70.
- 3 P. G. Gassman, T. J. van Bergen, D. P. Gilbert and B. W. Cue, J. Am. Chem. Soc., 1974, 96, 5495; T. Sugasawa, M. Adachi, K. Sasakura and A. J. Kitagawa, Org. Chem., 1979, 44, 578; G. Bartoli, M. Bosco, R. Dalpozzo, G. Palmeri and E. J. Marcantoni, J. Chem. Soc., Perkin Transactions 1, 1991, 2757; J. R. Hwu, H. V. Patel, R. J. Lin and M. O. Gray, J. Org. Chem., 1994, 59, 1577.
- 4 L. S. Hegedus, Angew. Chem., Int. Ed. Engl., 1988, 27, 1113; J. J. Liin Alkaloids: Chemical and Biological Perspectives, 1999, 14, 437.
- R. C. Larock, E. K. Yum and M. D. Refvik, J. Org. Chem., 1998, 63, 7652; A. Arcadi, S. Cacchi and F. Marinelli, *Tetrahedron Lett.*, 1992, 33, 3915; S. Cacchi, G. Fabrizzi, F. Marinelli, L. Moro and P. Pace, Synlett, 1997, 1363; B. C. Soderberg, S. R. Rector and S. N. O'Neil, *Tetrahedron Lett.*, 1999, 40, 3657; B. C. Soderberg and J. A. Shriver, J.

Org. Chem., 1997, **62**, 5838; S. Tollari, S. Cenini, C. Crotti and E. Gianella, *J. Mol. Catal.*, 1994, **87**, 203; M. Akazome, T. Kondo and Y. Watanabe, *Chem. Lett.*, 1992, 769; M. Yamaguchi, M. Arisawa and M. Hirama, *J. Chem. Soc., Chem. Commun.*, 1998, 1399; Y. Nishiyama, R. Maema, K. Ohno, M. Hirose and N. Sonoda, *Tetrahedron Lett.*, 1999, **40**, 5717.

- 6 S. Cenini and F. Ragaini *Catalytic Reductive Carbonylation of Organic Nitro Compounds*, Kluwer Academic, Dordrecht, Netherlands, 1997.
- 7 A. Srivastava, Y. Ma, R. Pankayatselvan, W. Dinges and K. M. Nicholas, J. Chem. Soc., Chem. Commun., 1992, 853; R. S. Srivastava and K.M. Nicholas, *Tetrahedron Lett.*, 1994, 8739; R. S. Srivastava and K. M. Nicholas, J. Org. Chem., 1994, **59**, 5365; R. S. Srivastava, M. A. Khan and K. M. Nicholas, J. Am. Chem. Soc., 1996, **118**, 3311; R. S. Srivastava and K. M. Nicholas, J. Chem. Soc., Chem. Commun., 1996, 2335; R. S. Srivastava and K. M. Nicholas, J. Chem. Soc., Chem. Commun., 1996, 3302.
- 8 R. S. Srivastava and K. M. Nicholas, J. Chem. Soc., Chem. Commun., 1998, 2705; M. K. Kolel-Veetil, M. A. Khan and K. M. Nicholas, Organometallics, 2000, 19, 3754.
- 9 Product characterization details are available in the ESI[†].
- 10 [CpFe(CO)₂]₂ and [Cp*Fe(CO)₂]₂ are commercially available; [Cp*Ru(CO)₂]₂ was prepared by the reaction of Ru₃(CO)₁₂ with Cp*-H according to R. B. King, M. Z. Iqbal and A. D. King, *J. Organomet. Chem.*, 1979, **171**, 53.
- 11 The following procedure was used for all the catalytic reactions. A stainless steel autoclave fitted with a glass liner was charged with catalyst (0.15 mmol), nitro compound (3 mmol), alkyne (12 mmol), a spatula of 4 Å molecular sieves, and distilled solvent (dioxane or benzene, 10 ml). In a well-ventilated fume hood the autoclave was purged with CO three times and then pressurized to 750 psi. The vessel was then heated to 170° C for 48–72 h. After cooling, the autoclave was vented in the fume hood. Partial recovery of the catalyst (20–30%) can be achieved by precipitation with excess hexane. The solvent was removed by rotary evaporation and the products were isolated by flash chromatography over silica gel. Elution with 4:1 CH₂Cl₂–pet. ether afforded the products (yield, R_t): azoarene (5–15%, 0.7), azoxyarene (4–22 %, 0.5), indole (20–50%, *ca*. 0.3), arylamine (7–20%, 0.1).
- 12 Representatives of the following classes of complexes failed to catalyze indole formation: PdX_2L_2 , PdL_4 , $RuCl_2(C_6H_6)/L$, $Ru_3(CO)_{12}/L$; $Rh(CO)_2I_2^-$, (Me-Cp)Mn(CO)_3 and $[Cp*Cr(CO)_3]_3$ were also inactive.
- 13 J. Y. Merour and B. Joseph, Curr. Top. Org. Chem., 2001, 5, 471; M. Allegretti, A. Arcadi, F. Marinelli and L. Nicolini, Synlett, 2001, 609; K. Takeuchi, J. A. Bastian, D. S. Gifford-Moore, R. W. Harper, S. C. Miller, J. T. Mullaney, D. J. Sall, G. F. Smith, M. Zhang and M. J. Fisher, Bioorg. Med. Chem. Lett., 2000, 10, 2347; Q. Wu, J. A. Lavigne, Y. Tao, M. D'Iorio and S. Wang, Inorg. Chem., 2000, 39, 5248; R. E. Mewshaw and X. T. Shah, Patent Appl. US 6221863, 2001; L. Edwards, A. Slassi, A. Tehim and T. Xin Patent Appl. US 6191141, 2001 ; H. W. Pauls and W. R. Ewing, Curr. Top. Med. Chem., 2001, 1, 83; B. C. Askew, M. J. Breslin, M. E. Duggan, J. H. Hutchinson, R. S. Meissner, J. J. Perkins, T. G. Steele and M. A. Patane Patent Appl. 2001-2001 US 1953, 2001; P. J. Cox, T. N. Majid, J. Y. Q. Lai, A. D. Morley, S. Amendola, S. Deprets and C. Edlin Patent Appl. 2000-2000 GB 4993, 2000; P. Zakrzewski, M. Gowan, L. A. Trimble and C. K. Lau, Synthesis, 1999, 11, 1893; R. Fontan, C. Galvez and P. Viladoms, Heterocycles, 1981, 16, 1473; R. Beugelmans, B. Boudet and L. Quintero, Tetrahedron Lett, 1980, 21, 1943.
- 14 A. Penoni, J. Volkmann and K. M. Nicholas Org. Lett., in press.
- 15 R. J. Sundberg, M. Brenner, S. R. Suter and B. P. Das, *Tetrahedron Lett.*, 1970, 2715; R. J. Sundberg and R. W. Heintzelmen, *J. Org. Chem.*, 1974, **39**, 2546.
- 16 U. Durr and H. Kisch, Synlett, 1997, 1335.
- 17 J. Tsuji and Y. Mori, Bull. Chem. Soc. Jpn., 1969, **42**, 527; B. Giese and G. Thoma, Helv. Chim. Acta, 1991, **74**, 1143.
- 18 I. Kuksis and M. C. Baird, Organometallics, 1996, **15**, 4755; D. B. Moore, M. B. Simpson, M. Poliakoff and J. J. Turner, J. Chem. Soc., Chem. Commun., 1984, 972; B. D. Moore, M. Poliakoff and J. J. Turner, J. Am. Chem. Soc., 1986, **108**, 1819; P. E. Bloyce, A. K. Campen, R. H. Hooker, A. J. Rest, N. R. Thomas, T. E. Bitterwolf and J. E. Shade, J. Chem. Soc., Dalton Trans., 1990, 2833; A. J. Dixon, M. W. George, C. Hughes, M. Poliakoff and J. J. Turner, J. Am. Chem. Soc., 1992, **114**, 1719.
- 19 H. J. Schumann J. Organomet. Chem., 1985, 290, C34P. F. Boyle and K. M. Nicholas, J. Organomet. Chem., 1976, 114, 307; B. D. Dombek and R. J. Angelici, Inorg. Chim. Acta, 1973, 7, 345; J. E. Ellis and E. A. Flom, J. Organomet. Chem., 1975, 99, 26.