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THE SUBTLE CO-CATALYTIC INTERVENTION OF BENZOPHENONE IN RADICAL CATION MEDIATED CYCLIZATION — AN IMPROVED SYNTHESIS OF 2-(3',4'-DIMETHOXYPHENYL) INDOLINE

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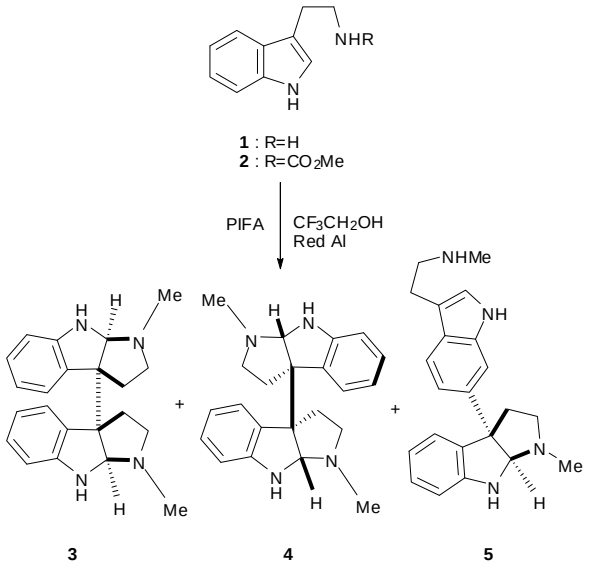
Abstract - The addition of benzophenone to a $FeCl_3/CH_2Cl_2$ mixture in the presence of 3',4'-dimethoxy-2-acetamidostilbene **17** unexpectedly leads to a dramatic improvement in yield of the indoline **20** from 38% (previously reported by us) to 75.4%, after careful examination of a variety of reaction conditions. A catalytic cycle has been proposed that involves not only stilbene radical cations but also Fe^{2+} promoted benzophenone ketyl radical formation which enhances cyclisation, suppresses dimerization and accounts for the virtually quantitative recovery of the benzophenone.

With the publication of a major review,[1] the bisindolines will continue to be in the forefront of research in the natural product/synthetic organic area. Malaysian *Psychotria rostrata* has brought forth bisindolines (specifically the pyrroloindoline structures) such as hodgkinsine, (-)-calycanthine, (+)-chimonanthine and calycosidine.[2] Hodgkinsine A, for example, has demonstrated cytotoxic activity against Vero African green monkey kidney cells.[3] Although recent reviews on synthetic methodology have perhaps given more attention to indole construction, Takayama's synthesis of meso-chimonanthine **3** from the tryptamine **1** and **2** by exploitation of PIFA in CF_3CH_2OH[4] is significant (Scheme 1). The same transformation can be achieved all be it in lower yield by use of thallium trifluoroacetate.[5] Although Takayama did not discuss the mechanism of these intriguing transformations in his original paper, we believe these results can be explained by a radical cationic cascade[6] process promoted by phenyl iodine bistrifluoroacetate (PIFA). Ley[7] has exploited solid supported phenyliodine diacetate in the construction of a spirocyclic cyclohexadienone in which radical cations (single electron transfer) were invoked. Since the chemistry depicted in Scheme 1 has mechanistic implications for our own studies to be described later, we will

apply the radical cascade hypothesis, which we invoked in our previously reported stereoselective bisindoline synthesis,[8] to Takayama's syntheses.

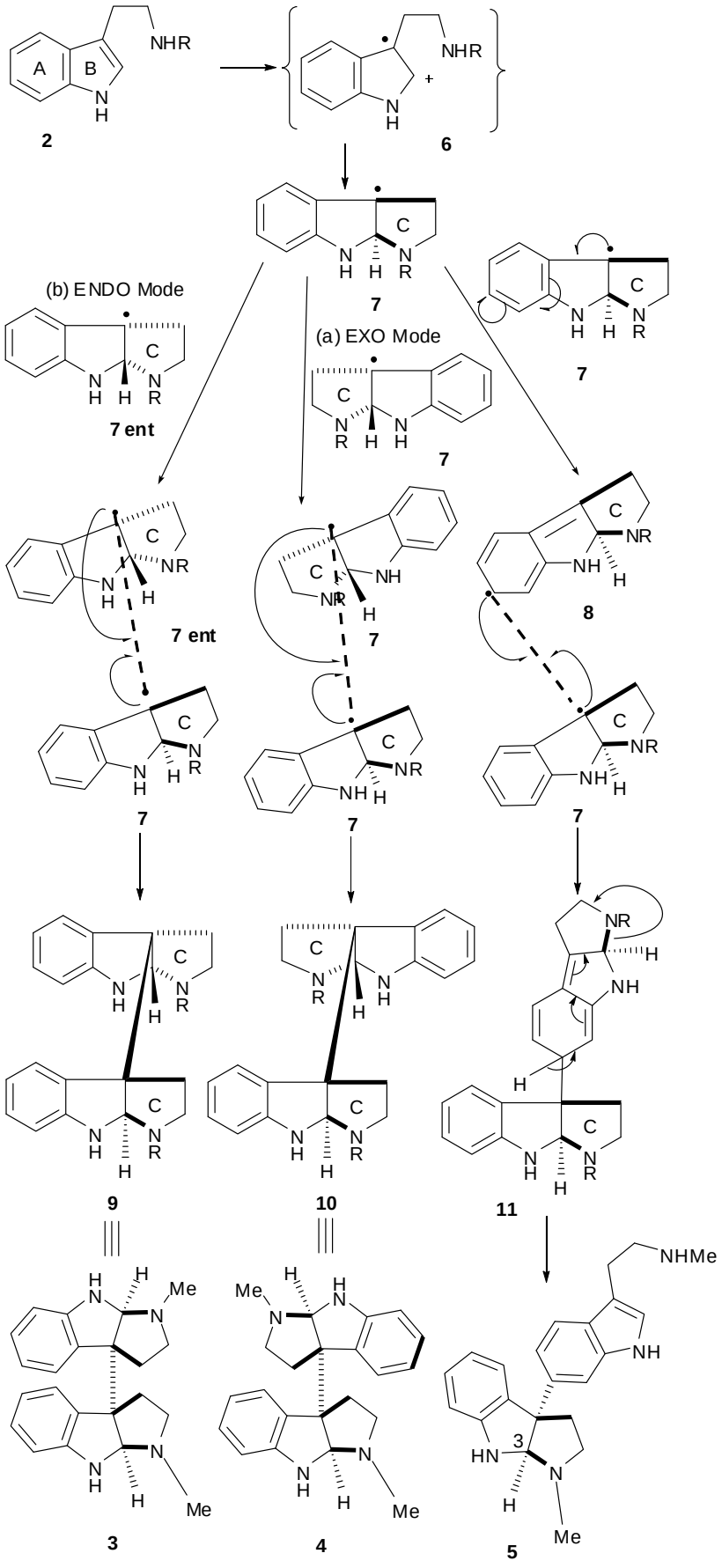


Scheme 1. Takayama's synthesis of meso-chimonanthine **3** from tryptamine **1** and **2** by exploitation of iodobenzene bistrifluoroacetate

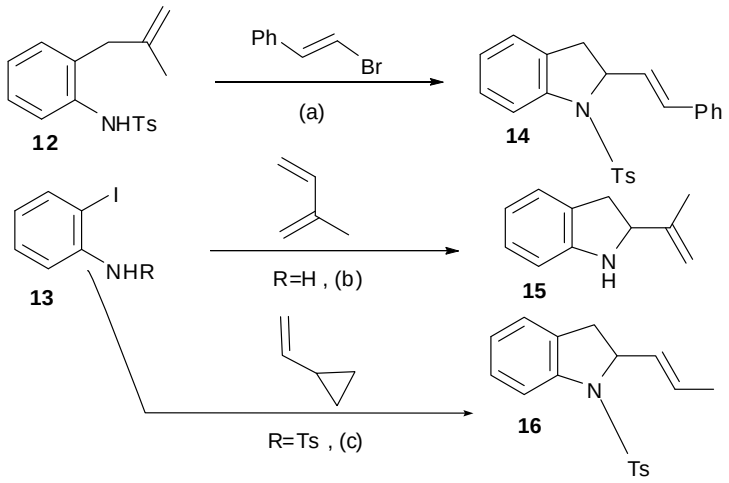
This mechanistic explanation that accounts for both stereochemical and regiospecific issues is shown in Scheme 2. The pathway described in Scheme 2 is revealing. Racemic chimonanthine **4** is formed by combination of pyrroloindolyl radical **7** (exo mode). **7** is of course derived from the radical cation **6**. Mesochimonanthine **3** is obtained by combination of **7** with its enantiomorph (**ent 7**). The "dimer" **5** is the result of combination of the delocalized radical **8** with **7**. This explains the C(3)–C(7') bond in **5**. We have employed a similar analysis (radical combination) to our previously published bisindoline syntheses[8] that accounts for the observed stereoselectivity complete with enthalpy of formation data (AMI-annealing method). The suggestion that the biosynthesis of compounds related to the pyrrolidinoindolines (e.g., **4** and **5**) might involve radical cations has been made by Overman[9] and Crich.[10]

Indoline natural products such as (+)-vinblastine,[11] duocarmycin[12] and phakellistaton **3**[13] show significant pharmacological potency, and not surprisingly, provided the impetus for many creative attempts to construct the indoline ring. These successful attempts include intramolecular (pyridazine) inverse electron demand Diels Alder methodology,[14] aryl radical addition,[15] organozincate addition,[16] aza-Cope Mannich rearrangement[17] and copper mediated aryl amination.[18]

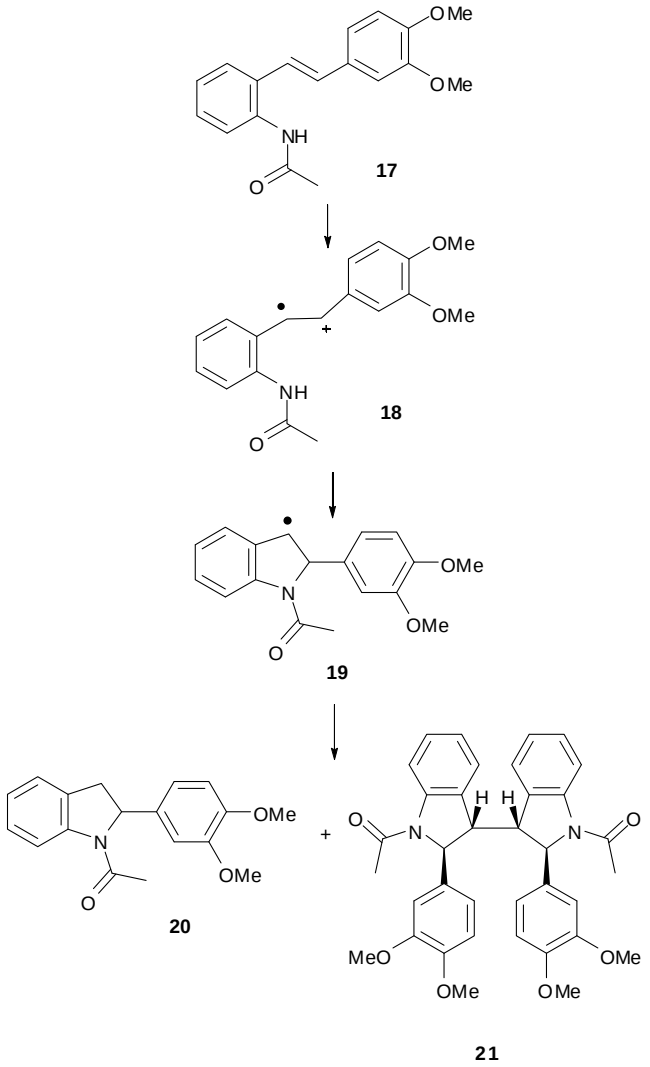
Many of the transformations have been applied to the synthesis of 3-substituted indolines. With respect to the 2-substituted indolines a conservative selection of methods that employ protected anilines may be summarized (Scheme 3).



Scheme 2. Our proposed mechanism for Takayama synthesis of chimonanthine



Scheme 3. Creative attempts to construct the indoline ring[22] *Reagents and conditions*: (a) $Pd(OAc)_2$, Na_2CO_3, Bu_4NCl, DMF, 100 °C, 62%. (b) $Pd(OAc)_2$, PPh_3, Et_3N, 125-130 °C, 72%. (c) $Pd(OAc)_2$, KOAc, Bu_4NCl, DMF, 80 °C, 77%



Scheme 4. Oxidative coupling of protected amino stilbene **17**

Our interest in radical cation mediated methods for the construction of C-2 aryl substituted indolines goes back to our earlier report[19] which provides the background for our domino construction of the indoline **20** and the bisindoline **21** from *o*-acetamidostilbenes **17** (Scheme 4).[8]

In our earlier reported syntheses, we employed very dilute $FeCl_3$ solutions. Here we have repeated this transformation using "anhydrous"[20] $FeCl_3$ (3 or 5 equiv) in CH_2Cl_2 obtaining results in good agreement with those previously reported. These results are shown in Table 1.

Table 1. Investigation of the $FeCl_3$ oxidative coupling in the absence of benzophenone or maleic anhydride

Entry	**17** (equiv)	Conditions	Yield % **20**	**21**
1	1.0	$FeCl_3$ (3.0 equiv), acetone : MeCN (5ml:5ml), 30-32 ^oC	No reaction	
2	1.0	$FeCl_3$ (3.0 equiv), acetone : MeCN : MeOH (4.5ml:4.5ml:1.0ml), 30-32 ^oC	No reaction	
3	1.0	$FeCl_3$ (0.01 equiv), acetone : MeCN : MeOH (4.5ml:4.5ml:1.0ml), 30-32 ^oC	No reaction	
4	1.0	$FeCl_3$ (1.0 equiv), acetone : MeCN : MeOH (4.5ml:4.5ml:1.0ml), -78-0 ^oC	No reaction	
5	1.0	$FeCl_3$ (0.12 equiv), acetone : MeCN : MeOH (20.0ml:20.0ml:10.0ml), 30-32 ^oC	No reaction	
6	1.0	$FeCl_3$ (3.0 equiv), CH_2Cl_2 (9.0ml), 30-32 ^oC	37	11

[a] silica gel was weighed together with the $FeCl_3$ in the weighing bottle, mixed and added to the reaction flask.

In the light of Itoh's report[21] of the ferric perchlorate catalysed cycloaddition of benzoquinone to styrene derivatives, we thought it would be timely to revisit our earlier investigations. The result of this re-examination of our earlier studies with a view to controlling radical cation reactivity is described below.

We subjected acetamido stilbene **17**, prepared according to our previously published method, to $FeCl_3$ oxidation under a variety of conditions including solvent mixtures: acetone, MeCN and MeOH. Most of the reactions were run at 30-32 ^oC, see Scheme 4. With one exception, starting material was recovered unchanged. (Table 1, Entries 1 to 5). However, when 3 equivalents of anhydrous $FeCl_3$ in CH_2Cl_2 were employed, the indole **20** and the bisindoline **21** were obtained in yields of 36.9% and 10.6% respectively (See Table 1, Entry 6).

In the second series of experiments, we reacted the acetamido stilbenes with "anhydrous" $FeCl_3$ in the presence of maleic anhydride in either toluene or CH_2Cl_2 at temperatures varying from 30 ^oC to 70 ^oC. Table 2, Entry 5, indicates that the highest yield for the indoline was 72.6% with only trace amounts of the bisindoline. However, heating the reaction mixture in toluene at 60 ^oC – 70 ^oC gives only 56.7% of

indoline **20** (Table 2, Entry 4).

Table 2. $FeCl_3$ / stilbene **17** oxidation in the presence of maleic anhydride (MA)

Entry	**17** (equiv)	Conditions	Yield % **20**	**21**
1	1.0	$FeCl_3$ (0.0 equiv), MA (1.66 equiv), toluene (25mL), 60-70 ^oC	No reaction	
2	0.0	$FeCl_3$ (1.0 equiv), MA (1.0 equiv), toluene (25mL), 60-70 ^oC	No reaction	
3	0.0	$FeCl_3$ (1.0 equiv), MA (1.0 equiv), CH_2Cl_2 (25mLl), 30-32 ^oC	No reaction	
4	1.0	$FeCl_3$ (1.41 equiv), MA (1.12 equiv), toluene (25mL), 60-70 ^oC	57	2
5	1.0	$FeCl_3$ (1.0 equiv), MA (1.0 equiv), CH_2Cl_2 (25mL), 30-32 ^oC	73	4

In the final series of experiments (Table 3), the stilbene was again treated with $FeCl_3$ but now in the presence of benzophenone. It was found that of all the solvents tried: acetone, CH_2Cl_2, MeCN and toluene, stirring the stilbene with equimolar quantities of $FeCl_3$ and benzophenone in CH_2Cl_2, gave the highest yield of indoline **20** 75.4% (See Table 3, Entry 6). Recovery of benzophenone was 99%. No bisindoline **21** could be observed in the reaction mixture. This represents a two fold increase in yield for the bisindoline compared to the 38% we reported in our previous communication. Replacing CH_2Cl_2 with toluene and heating in the presence of $^1/_{12}$ of an equivalent of benzophenone produced the indoline in 78.3% yield (Table 3, Entry 9).

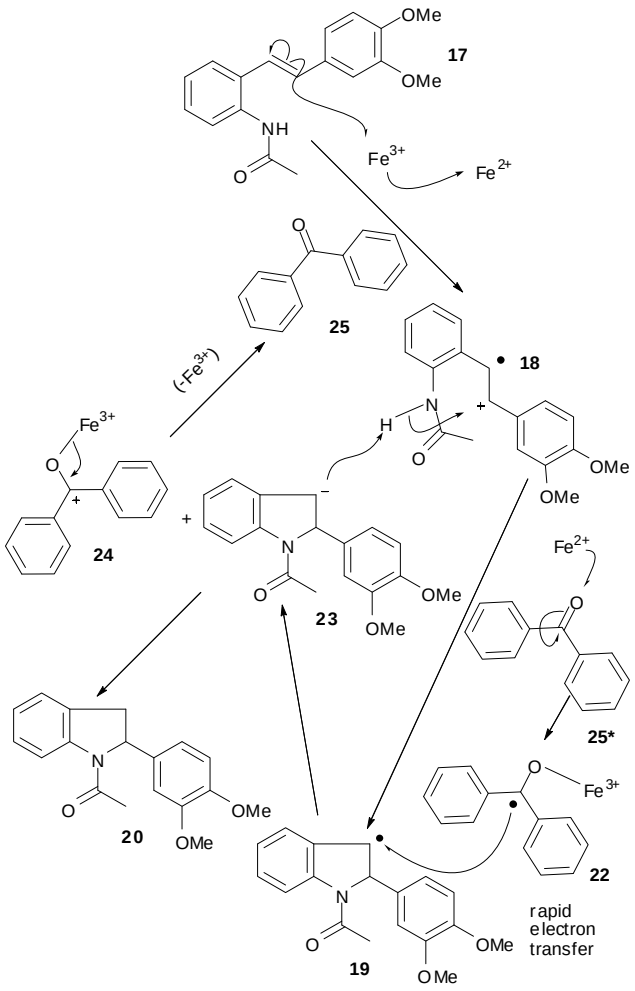
Table 3. $FeCl_3$ / stilbene **17** oxidation in the presence of benzophenone (Bzph)

Entry	**17** (equiv)	Conditions	Yield % **20**	**21**
1	1.0	$FeCl_3$ (1.2 equiv), Bzph (1.0 equiv), toluene (25mLl), 60-70 ^oC	61	Trace[a]
2	1.0	$FeCl_3$ (0.0 equiv), Bzph (1.0 equiv), toluene (25mL), 60-70 ^oC	No reaction	
3	1.0	$FeCl_3$ (0.0 equiv), Bzph (1.0 equiv), MeCN (25mL), 30-32 ^oC	No reaction	
4	1.0	$FeCl_3$ (1.0 equiv), Bzph (1.0 equiv), MeCN (25mL), 30-32 ^oC	No reaction	
5	1.0	$FeCl_3$ (0.0 equiv), Bzph (1.0 equiv), CH_2Cl_2 (25mL), 30-32 ^oC	No reaction	
6	1.0	$FeCl_3$ (1.0 equiv), Bzph (1.0 equiv), CH_2Cl_2 (25mLl), 30-32 ^oC	75	Trace[a]
7	1.0	$FeCl_3$ (0.0 equiv), Bzph (1.0 equiv), acetone (25mL), 30-32 ^oC	No reaction	
8	1.0	$FeCl_3$ (1.0 equiv), Bzph (1.0 equiv), acetone (25mL), 30-32 ^oC	No reaction	
9	1.0	$FeCl_3$ (1.0 equiv), Bzph (1/12 equiv), toluene (25mL), 75-80 ^oC	78	8

[a] TLC shows formation of **21**, but in quantities too small to be isolated.

With respect to the increased efficiency of the stilbene radical-cation cyclization and the suppression of the bisindolization (see Table 2, Entries 4 and 5 and Table 3, Entries 6 and 9), a catalytic cascade hypothesis which has considerable explanatory power is provided (see Scheme 5). The stilbene **17** is oxidized ($Fe^{3+} \rightarrow Fe^{2+}$) to produce the radical cation **18** (Scheme 4) as we have previously described. Cyclization can proceed to give the indolyl radical **19** as described in our previous report. However, a critical event not previously observed, now occurs in the presence of benzophenone which is now effectively reduced by the Fe^{2+} to yield the ketyl radical **22** (Scheme 5).[23]

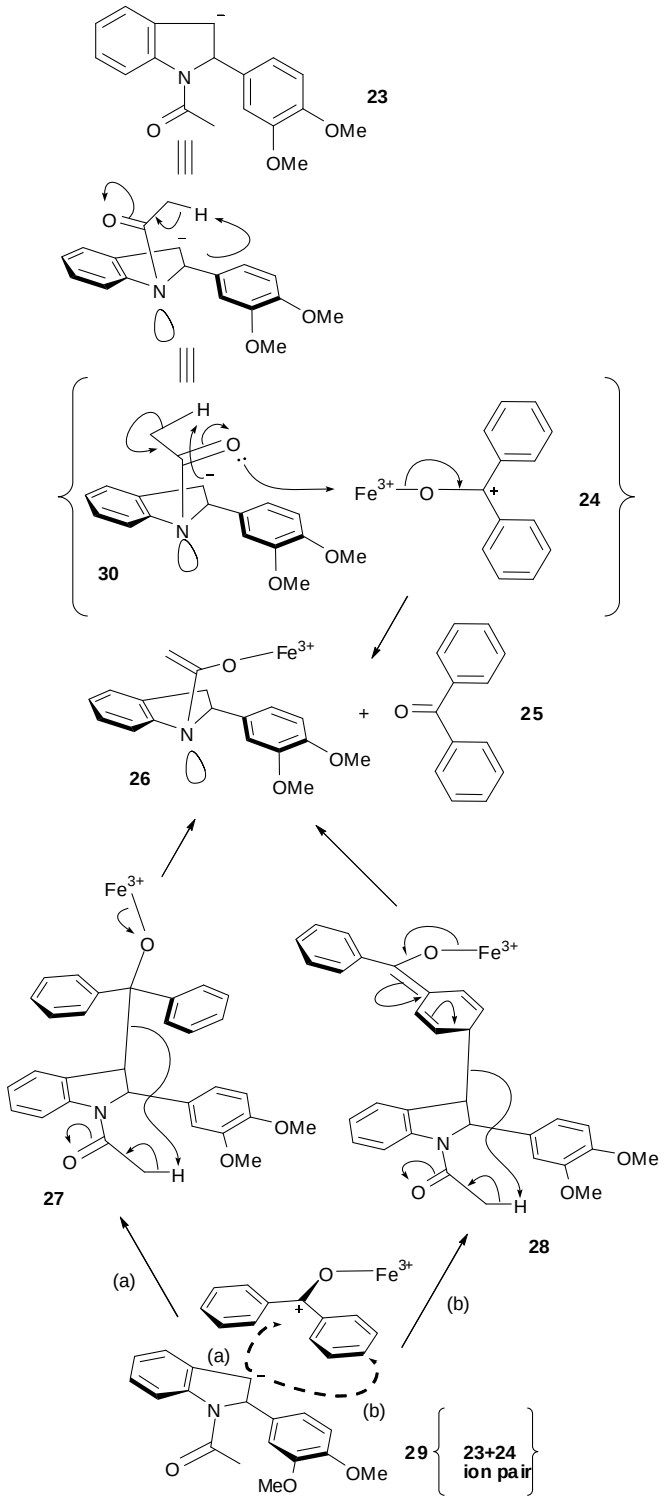
The intermediacy of this species is crucial because we propose that rapid electron transfer from **22** to the indolyl radical **19** will generate the moderately stabilized carbanion **23** which now deprotonates the previously formed radical cation **18** thus promoting the required cyclisation of **18** to **19** thereby increasing the concentration of **19** which is fed back into the cycle. The protonation of **23** will of course yield the desired indoline **20**. Notice that from **23** bisindolyzation (see **21**, Scheme 4) is prohibited. As we will see the anion **23** is not the only candidate for a source of base (see Scheme 6). However, at this juncture two points should be noted.



Scheme 5. Ketyl radical **22** / indolyl anion **23** catalytic cycle

Firstly, the rapid proton transfer will produce the doubly resonance stabilized cation **24** which collapses to regenerate both the Fe^{3+} and the benzophenone **25** thereby explaining the virtually quantitative recovery of **25**. As an indication of the essentially catalytic nature of the process reduction to $^{1}/_{12}$ of an equivalent of benzophenone produces the indoline **20** in 78.3% yield plus 7.7% bisindoline (Table 3, Entry 9). The second significant fact is the generation and involvement of the anion **23** in Scheme 5, which functioning

as a base, dramatically improves the efficiency of the cyclization and hence the increased yield of indoline **20**. Two questions remain. Are there other candidates for the potential base (see **23** in Scheme 5) and why is bisindoline **21** formation (Scheme 4) now suppressed at least substantially? These two questions are not unrelated. The anion **23** in Scheme 6 could receive additional stabilization by ion pair formation, a beneficiary of stabilizing π-π interactions (See **29**, Scheme 6).[24]



Scheme 6. Interconversion of **23** to **26** via various pathways

Within the arrangement **29**, nucleophilic attack via either paths (a) or (b) would produce intermediates **27** and **28** respectively both of which would collapse to the enolate **26**. Thus the anion **23** in Scheme 6 could be replaced by the stronger base – the enolate **26**. Notice that the involvement of species **27**, **28** or **29** could effectively account for the almost complete suspression of bisindoline **21** formation (Scheme 4).

Conversion of the carbanion **23** to the more stable enolate **26** could conceivably occur via the six-membered chair transtition state **30** (Scheme 6) in which the lone pair on the carbonyl is engaged with the Fe^{3+} chelate (the benzophenoxy cation **24**). This quite logically gives rise to the Fe^{3+} enolate **26** and the regenerated benzophenone **25** (Scheme 6).[25]

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a JEOL JMN LA-400 spectrometer at 400MHz. The spectroscopic data has been described in detail elsewhere.[8] Coupling constants (*J*) are reported in Hz. All solvents were of analytical grade and were distilled before use. TLC: precoated Kieselgel 60 F_{254} aluminium plates (Merck). Column Chromatography: Silica gel 60, 40-63 microns (Mallinckrodt). Centrifugal chromatography: Silica gel 60 PF_{254} containing gypsum (Merck).

$FeCl_3$ oxidative coupling of 17 in a variety of conditions: Protected amino stilbene (**17**) (0.0526 g, 0.177 mmol) was dissolved in 9mL of CH_2Cl_2. Anhydrous $FeCl_3$ (CAS No. 10025-77-1) (0.0896 g, 0.552 mmol) was added to the mixture. The mixture was allowed to stir at rt (30-32 ^{o}C) and was monitored by TLC. After the consumption of the starting material, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The crude product obtained after evaporation under reduced pressure was subjected to centrifugal chromatography using hexane with increasing proportions of EtOAc. Two pure compounds, **20** (36.9% yield) and **21** (10.6% yield) were isolated. The procedure was repeated by varying the amount of $FeCl_3$ and different solvent mixtures.

$FeCl_3$ oxidative coupling of 17 in the presence of maleic anhydride (CAS NO. 108-31-6): Protected amino stilbene (**17**) (0.0223 g, 0.0751 mmol) and maleic anhydride (0.0093 g, 0.0948 mmol) were dissolved in 25mL of CH_2Cl_2. Anhydrous $FeCl_3$ (CAS No. 10025-77-1) (0.0162 g, 0.0999 mmol) was added to the mixture. The mixture was allowed to stir at rt (30-32 ^{o}C) and was monitored by TLC. After the consumption of the starting material, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The crude product obtained after evaporation under reduced pressure was subjected to centrifugal chromatography using hexane with increasing proportions of EtOAc. Two pure compounds, **20** (72.6% yield) and **21** (3.8% yield), were isolated.

$FeCl_3$ oxidative coupling of 17 in the presence of benzophenone: Protected amino stilbene (**17**)

(0.0267 g, 0.0899 mmol) and benzophenone (0.0014 g, 0.0768 mmol) (CAS No. 119-61-9) was gently warmed up (60-70 ^{o}C) in 25mL of CH_2Cl_2. Anhydrous $FeCl_3$ (CAS No. 10025-77-1) (0.0146 g, 0.09 mmol) was then added to the mixture. The mixture was allowed to stir and was monitored by TLC. After the consumption of the starting material, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The crude product obtained after evaporation under reduced pressure was subjected to centrifugal chromatography using hexane with increasing proportions of EtOAc. Two pure compounds, **20** (78.3% yield) and **21** (7.7% yield) were isolated.

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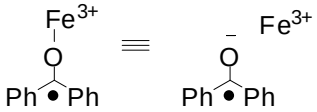
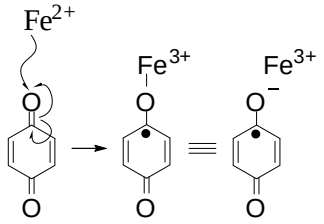
23. (a) Our ketyl radical may also be described by the radical anion:



I II

Compare with Itoh's version (see Ref. 21):



(b) As an alternative to Fe^{2+} ketyl radical formation, we have considered the posibility of light promoted n → π* excitation of benzophenone to the corresponding radical (where a proton donating solvent is present). However such radicals are either converted to benzhydryl alcohol or benzpinacol, which we do not observe in our reactions. See - M. B. Smith and J. March, 'March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,' 5th ed., John Wiley & Sons, Canada, 2001, p. 321 and p. 1560.

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25. $TiCl_4$/Zn/Benzophenone ketyl radical formation is known (See: (a) J. Gao, M. Hu, J. Chen, S. Yuan, and W. Chen, *Tetrahedron Lett.*, 1993, **34**, 1617. (b) P. I. Dalko, *Tetrahedron*, 1995, **51**, 7579), we have no reason to rule out the possibility of Fe^{2+} benzophenone ketyl radicals. Itoh's Fe^{2+} benzoquinone ketyl radical mechanism (Ref. 21) bears a close similarity to our Fe^{2+} benzophenone

ketyl radical (see **25** → **22**, Scheme 5) and Ref. 23. We could write a similar mechanism for the formation of Fe^{2+} maleic anhydride radical anion and utilise this species to explain enhance indolisation (See, Table 3). Light induced radical cation formation in the presence if 4,4'-bisdimethyl amino benzophenone is known (See: L. F. Tietze, G. Brasche, and K. M. Gericke, 'Domino Reactions in Organic Synthesis', Wiley-VCH, Germany, 2006, p. 345), but in the light of our observations (See, Table 3, Entries 2, 3, 5 and 7), radical cation formation solely by benzophenone is unlikely in our case.