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Iron–Palladium Association in the Preparation of Indoles and One-Pot Synthesis of Bis(indolyl)methanes

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Indoles were prepared by annulation of the parent alkynylanilines with the use of a new $FeCl_3$–$PdCl_2$ catalytic combination. High yields were obtained by using low loadings of the transition-metal complex ($FeCl_3$–$PdCl_2$: 2 and 1 mol-%, respectively). One-pot accesses to bis(indolyl)methanes and trisubstituted indoles through annulation/Friedel–Crafts alkylation and annulation/1,4-Michael addition sequences, in which $FeCl_3$ acts both as a cooxidant and a Lewis acid are described.

Introduction

Indoles are ubiquitous substructures of natural or synthetic biologically active products. It is thus not surprising that this benzo-fused heterocycle continuously attracted the attention of the scientific community from the initial discovery, over 120 years ago, of the Fischer indole synthesis[1] until the most recent metal-catalyzed alternative procedures.[2] Among the latter, transition-metal-catalyzed hydroamination of *o*-alkynylaniline derivatives to 2-substituted indoles is one of the most efficient approaches (Figure 1).

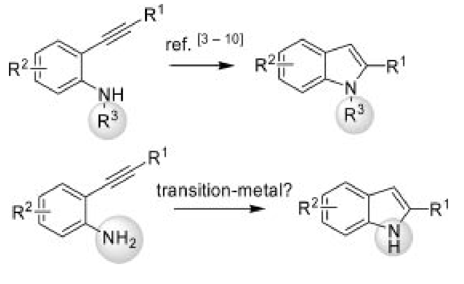
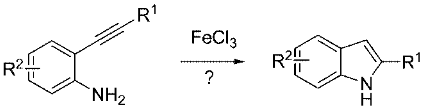


Figure 1. Transition-metal-catalyzed indol syntheses.

Usually, activation of carbon–carbon triple bonds toward intramolecular nucleophilic attack of proximate nucleophiles can be achieved through precoordination to organo–transition-metal complexes. In this context, procedures that rely on the use of palladium salts appeared particularly versatile in both homo-[3] and heterogeneous[4] catalysis. This intense research area is not restricted to palladium chemistry. Indeed, gold,[5] copper,[6] platinum,[7] molybdenum,[8] iridium,[9] indium[10] or rhodium,[11] have recently proved efficient for the preparation of substituted indoles.[12] Only a few methods dealing with unprotected primary *o*-alkynylanilines are described to use expensive metal sources and/or high catalyst loadings: as Ir-,[9] Au-,[5] In-,[10] Pd-[13,14] and Cu-based complexes.[6c] Therefore, the development of efficient catalytic systems for the preparation of indoles from the corresponding primary *o*-alkynylaniline is still of high interest.

On the basis of our previous experience in indole[15] synthesis and our recent interest in iron(III)-catalyzed hydroamination of vinylarenes,[16] our initial plan was to synthesize the indole moiety through iron π activation of the triple bonds of *o*-alkynylanilines [Equation (1)]. Moreover, as a result of the Lewis acidity of the iron complex, further one-pot transformations might be envisaged such as the one-pot hydroamination/Friedel–Crafts alkylation sequence towards bis(indolyl)methanes [Equation (2)].



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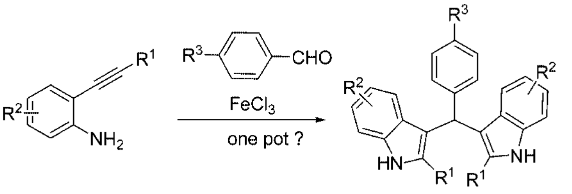
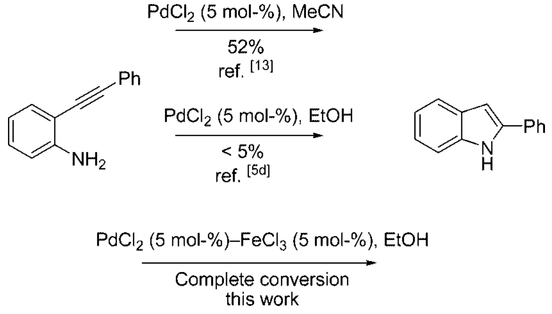


(2)

Results and Discussion

Although the very first experiments with substrate **1** in the presence of iron chloride (10 mol-%) in dichloroethane (DCE) at 80 °C were successful, the reaction rapidly appeared to be nonreproducible. After considerable experimentation, it appeared that the success of the annulation reaction was dependent on the preparation procedure of the starting alkynylanilines and their purification.[17] The question of traces of palladium or copper in the reaction mixture was then posed. Indeed, when the reaction was carried out in the presence of $PdCl_2$ (10 mol-%) and $FeCl_3$ (10 mol-%), indole **2** was obtained in 89% isolated yield (Table 1, Entry 1). In contrast, the same reaction run with CuI (10 mol-%) and $FeCl_3$ (10 mol-%) did not afford the expected indole nucleus (Table 1, Entry 2). Control experiments in the presence of $PdCl_2$ (10 mol-%), but in the absence of iron, only lead to the formation of trace amounts of indole **2** (Table 1, Entry 3).

This first set of experiments clearly evidenced that both Pd and Fe are required for the formation of indole starting from alkynylanilines under our conditions (80 °C in DCE). In addition to our results, disparate reports in the literature deserve some comments: whereas a 52% yield was reported by Utimoto[13] when the reaction was carried out in MeCN in the presence of $PdCl_2$ (5 mol-%), the same reaction in EtOH[5d] led to a very low yield (5%), which evidences the major role played by the solvent in these cyclizations (Scheme 1). Our own experiment, performed in ethanol in the presence of both $FeCl_3$ (5 mol-%) and $PdCl_2$ (5 mol-%), showed complete conversion to **2**. These results suggest that two different mechanisms may account for the formation of the indole nucleus.

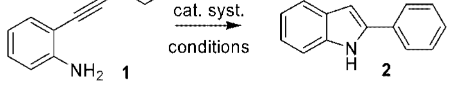


Scheme 1.

Although the π activation of the triple bond by an iron species could not be totally ruled out, one hypothesis on the role of iron in these cyclizations is that it may facilitate the in situ reoxidation of Pd^0 to Pd^{II}. Indeed, the use of a stoichiometric amount of $PdCl_2$ led to a quantitative conversion of the starting alkynylaniline into expected indole **2** (Table 1, Entry 4). Moreover, the use of another cooxidant, such as benzoquinone and $CuCl_2$ (Table 1, Entries 8, 9) in association with $PdCl_2$ evidenced the required presence of an oxidant to complete the catalytic cycle and confirmed our hypothesis. Because all reactions were carried out in open-air flasks, the presence of oxygen may account for the cascade reoxidation of Fe^{II} to Fe^{III} and Pd^0 to Pd^{II}, which allows the use of catalytic amounts of $FeCl_3$.

Thus, the cyclization might proceed along two different mechanistic paths depending on the solvent. On the one hand, in acetonitrile, palladium might play the role of Lewis acid (or more precisely the role of π acid according to Fürstner[18]) without any redox transformation in the catalytic cycle. On the other hand, in EtOH or DCE, the palladium is reduced to Pd^0 in a mechanism related to Wacker reactions, thus demanding a reoxidation step to complete the catalytic cycle.

Table 1. Optimization of the synthesis of 2-phenylindole.



Entry	Catalytic system				Time [h]	Conditions	Conversion [%][a] (isolated yield, %)
	Oxidant	Equiv.	[M]	Equiv.			
1	$FeCl_3$	0.1	$PdCl_2$	0.1	2	DCE 80°	quant. (89)
2	$FeCl_3$	0.1	CuI	0.1	2	DCE 80°	–
3	–	–	$PdCl_2$	0.05	4	DCE 80°	traces
4	–	–	$PdCl_2$	1	12	DCE r.t.	quant.
5	$FeCl_3$	0.05	$PdCl_2$	0.01	2	DCE 80°	>95 (88)
6	$FeCl_3$	0.02	$PdCl_2$	0.01	2	DCE 80°	60
7	$FeCl_3$	0.02	$PdCl_2$	0.01	4	DCE 80°	quant. (88)
8	benzoquinone	1.5	$PdCl_2$	0.01	2	DCE 80°	48
9	$CuCl_2$	0.02	$PdCl_2$	0.01	4	DCE 80°	quant.

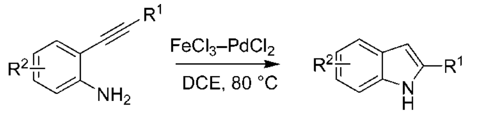
[a] Determined by ^1H NMR spectroscopic data of the crude reaction mixture.

The present conditions compare favourably with previously described conditions in terms of catalyst loading (1 mol-% $PdCl_2$ vs. 5 mol-%) and yields (89% vs. 52%). Moreover, the presence of a Lewis acid such as $FeCl_3$ paves the way to further one-pot transformations. Consequently, optimization of the catalytic system, scope and limitations of this methodology were next examined.

Optimization of reaction conditions as well as both Pd^{II} and Fe^{III} sources and loadings were next examined. It is worth noting that several other Pd^{II} and Fe^{III} sources as well as solvents were tested, such as Na_2PdCl_4 or $PdCl_2TPP_2$, $Fe(acac)_3$ or $Fe(NO_3)_3$ and toluene or dioxane. If some combinations gave similar results, the best results were obtained by using the $PdCl_2/FeCl_3$ combination in DCE. Attempts to decrease Pd and Fe loadings to 0.01 equiv. and 0.05–0.02 equiv., respectively, led to promising results, as indole **2** could be obtained in 88% yield (Table 1, compare Entries 5–7). The use of 0.02 equiv. of $FeCl_3$ required longer reaction times. Indeed, 4 h at 80 °C were required to ensure completion of the reaction and allow the isolation of indole **2** in 88% yield (Table 1, Entry 7).

The scope of the reaction was then surveyed by using various electron-withdrawing and -donating substituents on the aromatic side and heterocyclic or aliphatic moieties on the alkyne. Results obtained in these reactions are summarized in Table 2.

Table 2. $FeCl_3$-catalyzed synthesis of substituted indoles.



Entry	R^2	R^1	Product	Isolated yield (%)[a]
1	H	Ph	**2**	88
2	5-Cl	Ph	**3**	83
3	5-NO_2	Ph	**4**	82
4	4-Me	Ph	**5**	80
5	H	CO_2Et	**6**	n.r.[b]
6	H	4-NO_2Ph	**7**	40[c]
7	H	4-MeOPh	**8**	76[c]
8	H	2-thienyl	**9**	50

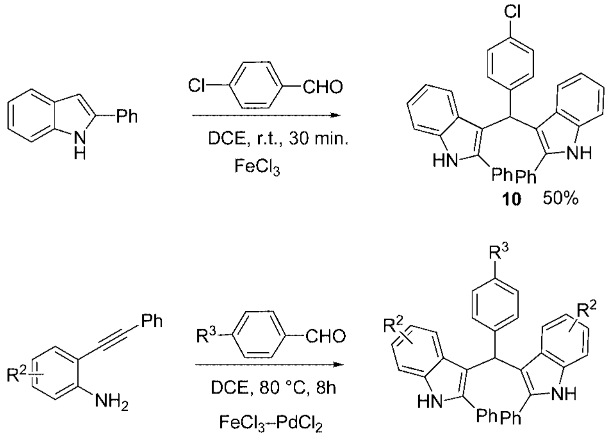
[a] Unless otherwise stated, $FeCl_3$ (2 mol-%) and $PdCl_2$ (1 mol-%), 4 h at 80 °C. [b] No reaction. [c] 20 h.

The reactivities of alkynylanilines substituted by various functional groups such as Cl, NO_2 and Me (Table 2, Entries 2–4) were similar to those of compound **1** and allowed the formation of the indole nucleus in high yields (80–83%). The electronic effect of the substituent of the alkyne moiety was also examined. Electron-rich substituents such as 4-MeOPh or 2-thienyl (Table 2, Entry 7, 8) fairly yielded the expected indole under standard reaction conditions (2 mol-% catalyst). In contrast, electron-poor substituents (4-NO_2Ph; Table 2, Entry 6) required longer reaction times for lower yields. In addition, substrates with strongly withdrawing groups such as CO_2Et did not react even after prolonged heating times.

Keeping in mind the one pot transformation of alkynylanilines to bis(indolyl)methanes, the use of an iron complex could be advantageous and act as both the reoxidant and the Lewis acid.

Further use of the iron–palladium combination in a one-pot, two-step sequence was next investigated. Bis(indolyl)-methanes are known bioactive compounds,[19] and they are usually obtained through Friedel–Crafts alkylation of indoles under acidic or Lewis acid catalysis.[19a,20] If $FeCl_3$ is able to stepwise promote the reoxidation of Pd^0 in the annulation and catalyze Friedel–Crafts alkylation reactions, one interesting issue would be the one-pot transformation of alkynylanilines to substituted bis(indolyl)methanes.

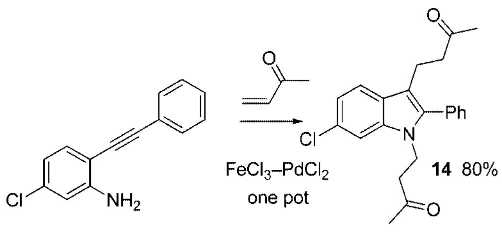
We first tried to prepare bis(indolyl)methane **10** from indole **2** and 4-chlorobenzaldehyde under the aforementioned conditions (DCE, 2 mol-% $FeCl_3$) at room temperature. Under these conditions, expected compound **10** was isolated in a fair 50% yield. The one-pot annulation and Friedel–Crafts alkylation sequence was next examined. When the appropriate alkynyl starting material was treated with the benzaldehyde derivative (0.5 equiv.) and $FeCl_3$ (2 mol-%)–$PdCl_2$ (1 mol-%) in DCE, bis(indolyl)methanes **10**–**13** were obtained in yields ranging from 40 to 59%, thus providing one-pot access to bis(indolyl)methanes (Scheme 2).



10 R^2 = H; R^3 = Cl 59%
11 R^2 = 5-Cl; R^3 = H 42%
12 R^2 = 5-NO_2; R^3 = H 40%
13 R^2 = H; R^3 = H 51%

Scheme 2.

Further extension of the iron–palladium combination and dual role of $FeCl_3$ is also shown in Scheme 3. In the presence of a Michael acceptor such as methyl vinyl ketone



Scheme 3.

and $FeCl_3$ (2 mol-%)–$PdCl_2$ (1 mol-%) in DCE, trisubstituted indole **14** was selectively obtained in high yield (80%) from the parent alkynylaniline.

Conclusions

We reported a selective synthesis of N–H indoles from the parent anilines by using a new $FeCl_3$–$PdCl_2$ catalytic combination in DCE. Low loadings of the transition-metal complexes ($FeCl_3$–$PdCl_2$ 2 and 1 mol-%, respectively) have proved efficient in the annulation reaction. One-pot annulation/Friedel–Crafts alkylation and annulation/1,4-Michael addition sequences were successfully developed, which provided access to both bis(indolyl)methanes and trisubstituted indoles, respectively. This provides evidence for the dual cooxidant and Lewis acid role of $FeCl_3$ and extends the scope of the iron–palladium combination.

Supporting Information (see footnote on the first page of this article): General procedures for the annulation of alkynylanilines, annulation/Friedel–Crafts alkylation and annulation/1,4-Michael addition sequences as well as spectroscopic data.

Acknowledgments

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