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Highly efficient bimetallic iron-palladium catalyzed Michael-type Friedel–Crafts reactions of indoles with chalcones

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Iron–palladium is a superior bimetallic catalyst in the presence of acetylacetone (Acac) with remarkable synergistic effect for the Michael-type Friedel–Crafts reactions of indoles with chalcones. This catalytic system has the advantages of mild reaction conditions, smaller amount of metal salts, high yields of the desired products and operational simplicity, which make it a useful and promising process for the synthesis of indole derivatives. Copyright © 2008 John Wiley & Sons, Ltd.

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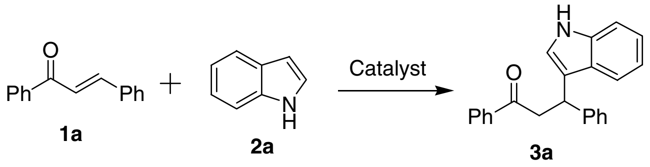
Keywords: bimetallic catalysis; Lewis acid; Michael addition; Friedel–Crafts Reaction; indoles; chalcones

Introduction

The bifunctional, bimetallic catalysts have been applied to various organic transformations in recent decades,[1–3] such as cyanation,[4] Friedel–Crafts acylation,[5] Friedel–Crafts alkylation,[6–8] oxidation,[9] hydroformylation,[10] allylic etherification,[11] nitro-Mannich reaction[12] and other rections.[13–15] Heterobimetallic catalysts offer superior results in terms of efficiency and selectivity relative to the individual ones. Mechanistic studies suggest that the synergistic functions of two metal active sites make substrates more reactive in the transition state and control their positions so that the functional groups are proximal to each other. Moreover, the cooperative effects also enable transformations that have never been possible using conventional catalysts employing only Lewis acidity. With our continuous research in developing novel catalysts in Michael-type Friedel–Crafts reactions,[16,17] we report the efficient Michael-type Friedel–Crafts addition of indoles with chalcones catalyzed by an iron–palladium bimetallic catalytic system.

The development of new efficient, clean and highly selective synthetic methods of indole derivatives has attracted much attention because of their important role as versatile building bocks in the synthesis of biologically active compounds and natural products.[18,19] Since the 3-position of indole is the preferred site for the electrophilic substitution reaction, the introduction of functionalized alkyl frameworks at this position by means of a Friedel–Crafts reaction involving the use of various electrophilic reagents constitutes a well-established strategy. Among the Friedel–Crafts reactions, the Michael-type Friedel–Crafts addition of indoles to α,β-unsaturated enones has been investigated widely. Recently, a variety of Lewis acids have been used to promote this reaction, such as $Zr(OTf)_4$,[20] $NaAuCl_4 \cdot 2H_2O$,[21] I_2,[22] SmI_3,[23] $Hf(OTf)_4$,[24] GaI_3,[25] $HfCl_4$,[26] $NO^+BF_4^-$[27] and aziridin-2-yl methanols.[28] Although numerous advances have been achieved, there are still some drawbacks in previous synthetic methods, such as the need for large amounts of expensive and toxic metal salts or drastic reaction conditions. Moreover, these catalysts often do not work when using chalcones as Michael acceptors. Therefore, the development of cheaper, simpler and more efficient catalysts for Friedel–Crafts type reactions of indoles and chalcones is highly desirable.



Scheme 1.

Results and Discussion

To establish suitable Friedel–Crafts reaction conditions, we selected the reation of indole with chalcone as a model (Scheme 1). First of all, we screened various bimetallic systems in which iron salts were regarded as center metals, such as Fe–Pd, Fe–In, Fe–Cu, Fe–Zn and Fe–Ni systems. All the results are listed in Table 1. In the iron–palladium system, we incidentally found that 84% of desired product **3a** was obtained when 5 mol% of $FeCl_3$ and 5 mol% of $PdCl_2$ were used as cocatalysts in CH_3OH at room temperature after

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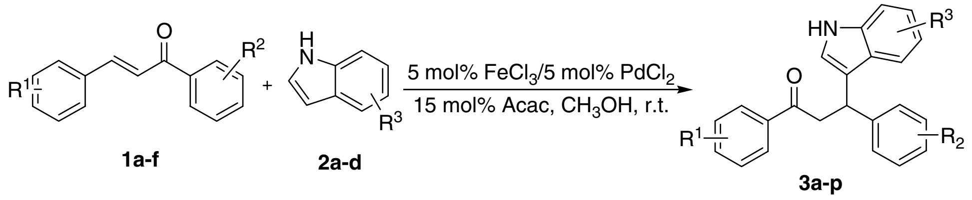
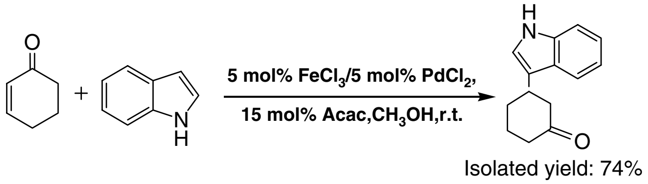


Scheme 2.



Scheme 3.

24 h (Table 1, entry 2), but the reaction did not occur when other palladium salts were used under the same conditions (entries 3–5). In addition, only trace product was detected with $FeCl_3$ or $PdCl_2$ alone (entries 1 and 6), which showed this bimetallic catalytic system has a dramatic effect in promoting this reaction. Subsequently, we obtained the desired product with yields of 39 and 60% by replacing $FeCl_3$ with $Fe(NO_3)_3 \cdot 9H_2O$ and $FeCl_3 \cdot 6H_2O$ respectively (entries 7 and 8). The yield could have a remarkable improvement by increasing the temperature to 50 °C (entry 9). Therefore, we could conclude that $FeCl_3$ was the most suitable iron salts for this reaction and iron salts with crystal water could result in decreased yield. In the iron–copper system, $Cu(OTf)_2$ and $CuSO_4 \cdot 5H_2O$ could only give lower yields of the desired product, and the reaction did not proceed at all with other copper salts (entries 11 and 12). Similarly, only poor to moderate yields were obtained when using Fe–Zn or Fe–Ni as a bimetallic catalytic system (entries 13–20). All the results indicated that $FeCl_3$ and $PdCl_2$ were the optimized bimetallic catalysts and there was a remarkable synergistic effect between them.

In order to further improve the yields of the Friedel–Crafts product, we reviewed the effect of various additives on the reaction between indole and chalcone (Table 2). Unexpectedly, we found that, in the presence of 10 mol% of $FeCl_3$ and 10 mol% of $PdCl_2$ in CH_3OH at room temperature, the reaction afforded the desired product **3a** in 68% yield when 30 mol% hexamethyl phosphoric triamide (HMPA) was used as additive (Table 2, entry 1). The reaction became very sluggish when using *trans*-1,2-cyclohexanediamine and triphenyl phosphorous as additives, which was presumably ascribed to the negative effect of base additive on the reaction (entries 2 and 3). Considering that it is difficult to react iron metal with ligands, addition to some protic reagents could favor the reaction. In the subsequent study, we were pleased to find that, in the presence of 5 mol% of $FeCl_3$ and 15 mol% of acetylacetone (Acac) at room temperature in CH_3OH as solvent, the reaction proceeded smoothly to afford product **3a** in 75% yield (entry 4). Encouraged by this result, we carried out the reaction in the presence of 5 mol% of $FeCl_3$–$PdCl_2$ and 15 mol% Acac in CH_3OH at room temperature, and the yield increased to 99% (entry 9). Then we screened some dicarbonyl compounds as additives. Among various dicarbonyl compounds used for this transformation, Acac was found to be the most effective one in terms of yield (entries 9–13). In addition, we investigated the impact of solvents on the model reaction (entries 14–22). Among the various solvents tested, CH_3OH was found to be the best solvent with a yield of 95% (entry 14); moderate yield (59%) was obtained in ethanol (entry 15). It should be noted that this reaction could be occur in pure H_2O under similar reaction conditions (entry 22). We presume that, besides being a solvent, CH_3OH can provide an acidic environment for the reaction.

To investigate the generality of this method, the reaction of various indoles and different enones was examined under the optimized reaction condtions (5mol% of $FeCl_3$, 5mol% of $PdCl_2$ and 15mol% Acac, 1 equiv. chalcone and 1.1 equiv. indole in CH_3OH at room temperature; Scheme 2). All of the results are summarized in Table 3. To sum up, the yields of the products were higher than those catalyzed by the Fe–Mg–HMPA system. Compared with previously reported results, the dramatic improvement of this work is the smaller amount of bimetallic catalysts needed, half that needed for the Fe–Mg–HMPA catalysts. In general, the reactions proceeded smoothly with high selectivities for various indoles **2a–d** with enones in moderate to good isolated yields at room temperature (up to 99%). The process worked noticeably

Table 1. Michael-type Friedel–Crafts reaction of indole with chalcone promoted by bimetallic catalyst in the absence of any ligand

Entry[a]	Metal salt 1	Metal salt 2	Solvent	Reaction time (h)	Yield (%)[b]
1	$FeCl_3$	–	CH_3OH	24	Trace
2	$FeCl_3$	$PdCl_2$	CH_3OH	24	84
3	$FeCl_3$	$Pd(NO_3)_2 \cdot 2H_2O$	CH_3OH	13	Trace
4	$FeCl_3$	$PdCl_2(CH_3CN)_2$	CH_3CN	13	NR[c]
5	$FeCl_3$	$PdCl_2(CH_3CN)_2$	CH_2Cl_2	24	Trace
6	–	$PdCl_2$	CH_3OH	24	Trace
7	$Fe(NO_3)_3 \cdot 9H_2O$	$PdCl_2$	CH_3OH	24	39
8	$FeCl_3 \cdot 6H_2O$	$PdCl_2$	CH_3OH	24	60
9	$FeCl_3$	$PdCl_2$	CH_3OH	18	92[d]
10	$FeCl_3$	$InCl_3$	CH_3OH	24	Trace
11	$FeCl_3$	$Cu(OTf)_2$	CH_3OH	18	11
12	$FeCl_3$	$CuSO_4 \cdot 5H_2O$	CH_3OH	36	15
13	$FeCl_3$	$ZnCl_2 \cdot 2H_2O$	CH_3OH	41	13
14	$FeCl_3$	$ZnBr_2$	CH_3OH	41	11
15	$FeCl_3$	$Zn(OTf)_2$	CH_3OH	40	14
16	$FeCl_3$	$Ni(OTf)_2$	CH_3OH	41	11
17	$FeCl_3$	$Ni(ClO_4)_2$	CH_3OH	41	11
18	$FeCl_3$	$Ni(OAc)_2 \cdot 4H_2O$	CH_3OH	41	10
19	$FeCl_3$	$Ni(NO_3)_2 \cdot 6H_2O$	CH_3OH	35	43
20	$FeCl_3$	$NiCl_2 \cdot 6H_2O$	CH_3OH	40	Trace

[a] Reaction conditions: 5 mol% of $FeCl_3$, 5 mol% of $PdCl_2$, 0.55 mmol/0.5 mmol of indole/chalcone and 2 ml of solvent at room temperature for 24 h.
[b] Isolated yields.
[c] No reaction.
[d] The reaction was carried out at 50 °C.

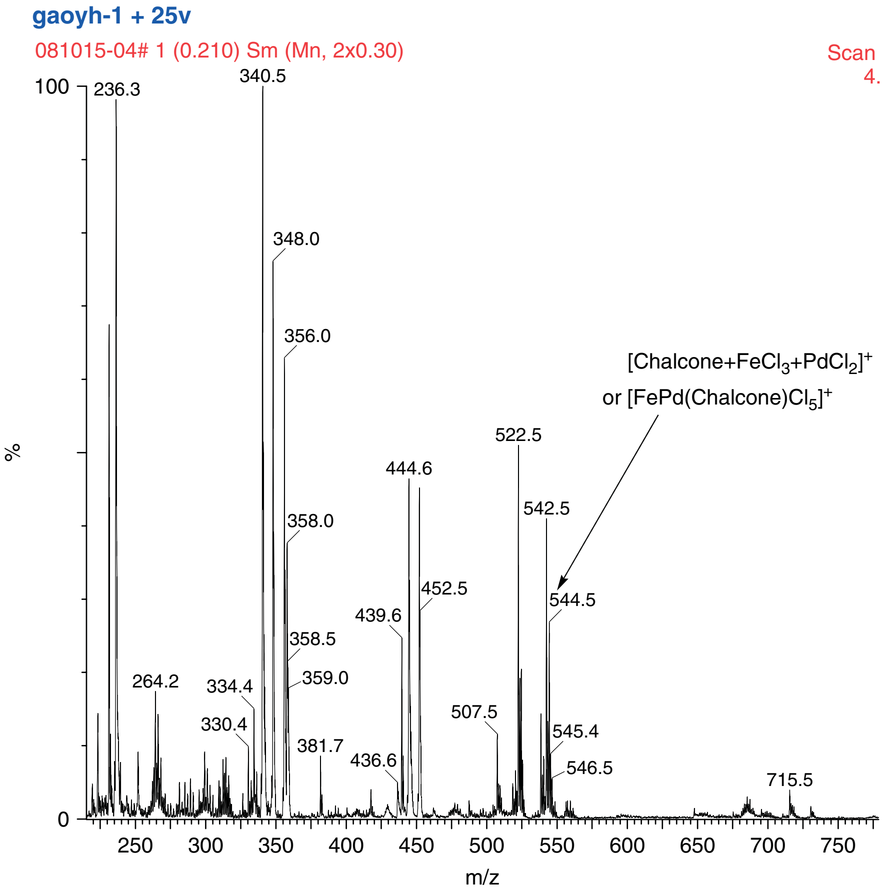


Figure 1. ESI mass spectrum of the $FeCl_3$–$PdCl_2$–chalcone intermediate in MeOH.

more efficiently for *N*-substituted indole **2b** with different enones and the yields of addition products were good to excellent (entries 7–11). Unfortunately, the reaction of 5-Br substituted indole **2d** with chalcone afforded only the desired products in 54% yield (entry 15). In addition, we found that the electron effect of enones' substituents had a profound impact on the yields of the reaction. For the same indole, enones with electron-donating substituents would give higher yields than those with electron-withdrawing substituents (entries 8–11), and the trend also applied to indoles. Interestingly, the enones with *ortho*-substituents afforded higher yields than those with *para*-substituents (entries 10 and 11). It is reasonable that the *ortho*-substituted group favored the interaction of the activated olefin bond with the catalyst, which increased the reactivity of enone in the Friedel–Crafts reaction of indole. Almost all reactions are clean and give the C_3-substitution product exclusively, and the target compounds are obtained in good yields with no formation of side products such as dimers or polymers, which are frequently encountered under the influence of strong protic acids.

In addition, the optimal conditions also was applied for the cyclic enones. For example, the F–C alkylation product of indole with cyclohex-2-enone under the optimized reaction condtions was obtained in 74% yield.

To investigate the mechanism of bimetallic iron and palladium-catalyzed Michael-type Friedel–Crafts addition of indoles with chalcones, another catalytic procedure was investigated. $FeCl_3$, $PdCl_2$ and acetylacetone were mixed and stirred for 2 h, then chalcone and indole were added to the catalyst mixture. After 24 h, the yield was almost the same as that of the reported procedure (96% yield). Besides the investigations on the catalysis performances, we also monitored the intermediate from the Fe–Pd catalyst and chalcone by ESI-MS, without addition of indole (Fig. 1). The main peak of the spectrum was characterized as a bimetallic complex of Fe–Pd with chalcone by HR-ESI-MS ($m/z = 544.5$): $[FePd(Chalcone)Cl_5]^+$. In addition, we performed IR analysis of the present bimetallic catalytic system and the expected interaction was comfirmed by the correspoding spectrum (*see* Supporting Information). The mixture of chalcone and $PdCl_2$ resulted in the appearance of a new peak (1688 cm^{-1}) in comparison with chalcone, and there was almost no difference for the other peak. Interestingly, the mixture of $FeCl_3$ and chalcone gave a larger difference in the IR spectrum: the diagnostic peaks of chalcone, 1661, 1604 and 1573 cm^{-1}, were shifted to 1646, 1598 and 1572 cm^{-1}, respectively. Based on the catalytic performance and ESI and IR spectrum, it is more reasonable that a bimetallic iron and palladium complex was formed and acted as a super Lewis acid in this Michael-type Friedel–Crafts addition of indoles with chalcones.

Conclusion

In summary, we have demonstrated that iron–palladium–acetylacetone is a superior bimetallic catalytic system with strong Lewis acidic activity for the Michael-type Friedel–Crafts reactions of indoles with chalcones. This catalytic system has the advantages of mild reaction conditions, smaller amount of metal salts, higher

Table 2. Michael-type Friedel–Crafts reaction of indole with chalcone catalyzed by $FeCl_3$ and $PdCl_2$ under various additives and different sovlents

Entry[a]	Metal salt 1	Metal salt 2	Ligand	Solvent	Yield (%)[b]
1	$FeCl_3$	$PdCl_2$	Hexamethyl phosphoric triamide	CH_3OH	68[c]
2	$FeCl_3$	$PdCl_2$	*trans*-1,2-Cyclohexanediamine	CH_3OH	Trace
3	$FeCl_3$	$PdCl_2$	Triphenyl phosphorous	CH_3OH	10
4	$FeCl_3$	–	Acetylacetone	CH_3OH	75
5	$FeCl_3$	–	Dibenzoylmethane	CH_3OH	80
6	$FeCl_3$	–	2-Acetylcyclohexanone	CH_3OH	69
7	–	$PdCl_2$	Acetylacetone	CH_3OH	46
8	–	–	Acetylacetone	CH_3OH	11
9	$FeCl_3$	$PdCl_2$	Acetylacetone	CH_3OH	99
10	$FeCl_3$	$PdCl_2$	*t*-Butyl acetoacetate	CH_3OH	96
11	$FeCl_3$	$PdCl_2$	Diethyl malonate	CH_3OH	95
12	$FeCl_3$	$PdCl_2$	Ethyl acetoacetate	CH_3OH	97
13	$FeCl_3$	$PdCl_2$	Benzoylacetone	CH_3OH	88
14[d]	$FeCl_3$	$PdCl_2$	Acetylacetone	CH_3OH	95
15[d]	$FeCl_3$	$PdCl_2$	Acetylacetone	Ethanol	59
16[d]	$FeCl_3$	$PdCl_2$	Acetylacetone	Et_2O	45
17[d]	$FeCl_3$	$PdCl_2$	Acetylacetone	CH_2Cl_2	68
18[d]	$FeCl_3$	$PdCl_2$	Acetylacetone	CH_3CN	26
19[d]	$FeCl_3$	$PdCl_2$	Acetylacetone	THF	26
20[d]	$FeCl_3$	$PdCl_2$	Acetylacetone	Toluene	39
21[d]	$FeCl_3$	$PdCl_2$	Acetylacetone	Acetone	66
22[d]	$FeCl_3$	$PdCl_2$	Acetylacetone	H_2O	12

[a] Reaction conditions: 5 mol% of $FeCl_3$, 5 mol% of $PdCl_2$ and 15 mol% of ligand, 0.55 mmol/0.5 mmol of indole/chalcone and 2 ml of Solvent at room temperature for 24 h.
[b] Isolated yields.
[c] 10 mol% of $FeCl_3$, 10 mol% of $PdCl_2$, and 30 mol% of Ligand.
[d] 5 mol% of $FeCl_3$, 5 mol% of $PdCl_2$, and 10 mol% of ligand.

yields of desired products and operational simplicity, which makes it a useful and promising process for the synthesis of indole derivatives. Further studies to address extension to the asymmetric process and the comprehension of the reaction mechanism are currently underway.

Experimental

General

All reaction flasks and solvents were dried according to standard methods prior to use. Flash column chromatography was performed over silica. NMR spectra were recorded on a 400 MHz spectrometer. ^{13}C NMR spectra were obtained with broadband proton decoupling. For spectra recorded in $CDCl_3$, unless noted, chemical shifts were recorded relative to the internal TMS (tetramethylsilane) reference signal. IR spectra were recorded using an FTIR apparatus. Thin-layer chromatography was performed using silica gel. $FeCl_3$ was purchased from Alfa Aesar Chemical Company. $PdCl_2$ was purchased from Shanxi Kaida Chemical Engineering Co. Ltd. Reagent-grade acetylacetone was purchased from common commercial sources and was used directly.

Table 3. $FeCl_3$–$PdCl_2$–acetylacetone catalyzed Michael-type Friedel–Crafts reactions of indoles with chalcones

Entry[a]	R_1	R_2	R_3	Product	Yield (%)[b]
1	H	H	H	**3a**	99
2	H	*p*-OCH_3	H	**3b**	90
3	*p*-OCH_3	H	H	**3c**	93
4	*p*-OCH_3	*p*-OCH_3	H	**3d**	72
5	H	*p*-Cl	H	**3e**	60
6	H	*o*-Cl	H	**3f**	77
7	H	H	*N*-CH_3	**3g**	92
8	H	*p*-OCH_3	*N*-CH_3	**3h**	97
9	*p*-OCH_3	H	*N*-CH_3	**3i**	98
10	H	*p*-Cl	*N*-CH_3	**3j**	84
11	H	*o*-Cl	*N*-CH_3	**3k**	96
12	H	H	2-CH_3	**3l**	87
13	H	*p*-Cl	2-CH_3	**3m**	76
14	H	*p*-OCH_3	2-CH_3	**3n**	87
15	H	H	5-Br	**3o**	54
16	H	*p*-Cl	5-Br	**3p**	83

[a] Reaction conditions: 5 mol% of $FeCl_3$, 5 mol% of $PdCl_2$ and 15 mol% of Acac, 0.55 mmol/0.5 mmol of indole/chalcone and 2 ml of CH_3OH at room temperature for 24 h.
[b] Isolated yields.

Representative experimental procedure of Michael-type Friedel–Crafts reaction

$FeCl_3$ (0.025 mmol), $PdCl_2$ (0.025 mmol), and acetylacetone (0.075 mmol) were added into a solution of enone (0.5 mmol) and indole (0.55 mmol) in freshly distilled CH_3OH (2 ml). After stirring at room temperature for 24 h, the mixture was diluted with H_2O (10 ml) and extracted with EtOAc (3 × 15 ml). The combined organic layers were dried (Na_2SO_4), concentrated *in vacuo* and purified by column chromatography on silica gel (200–300 mesh, gradient eluted with EtOAc–petroleum ether = 1 : 10–1 : 5) to gain the pure product. All the products are known[16,17] and structures were confirmed by MS, NMR and IR.

Supporting information

Supporting information may be found in the online version of this article.

Acknowledgements

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