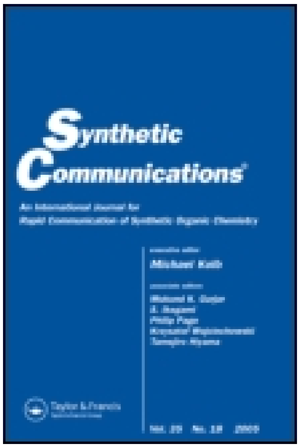

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Highly Efficient Heterobimetallic Iron-Magnesium-HMPA–Catalyzed Michael-type Friedel–Crafts Reactions of Indoles and Chalcones

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Abstract: A simple and novel bimetallic catalyst, an iron and magnesium complex (Fe-Mg-hexamethylphosphoramide (HMPA)), with dual activation was found to be an effective and promising catalyst for the Michael-type Friedel–Crafts reactions of indoles with chalcones. This novel catalytic system has the advantages of highly efficient, mild reaction conditions and exhibits high reactivity and selectivity, which make it a useful and attractive process for the synthesis of indole derivatives.

Keywords: Bimetallic catalysis, dual activation, Friedel–Crafts reaction, indoles, Michael addition

Homogeneous bimetallic or multimetallic catalysis has now been recognized as a promising tool in organic synthesis, because it is expected that

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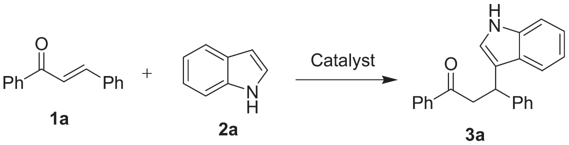
cooperative or successive interaction of two (or more) different metal centers with the substrate molecules gives rise to enhanced catalytic activities. Thus in some cases, bimetallic catalysts are superior to monometallic catalysts and promote new reactions that cannot be achieved by monometallic catalyst systems.[1] Recently, bimetallic catalysts have been attracting significant attention for organic transformations such as oxidation,[2] hydroxylation,[3] dihydroxylation,[4] carbonylation,[5] cross-coupling reactions,[6] reduction,[7] ring-opening,[8] multi-component coupling reactions,[9] and other reactions.[10] However, to the best of our knowledge, there are no reports on Michael-type Friedel–Crafts addition of indoles with electron-deficient olefins catalyzed by bimetallic complexes.

The Michael-type Friedel–Crafts addition of indoles to electron-deficient olefins and α,β-unsaturated enones is a very important process because it is involved in the total synthesis of bioactive indole alkaloids such as the hapalindoles and other 3-substituted indoles, which are important substructures and building blocks for the synthesis of natural products and therapeutic agents.[11] During past years, a variety of transition-metal salts, such as $Zr(OTf)_4$,[12] $Bi(OTf)_3$,[13] $CeCl_3 \cdot 7H_2O$-NaI,[14] $InBr_3$,[15] and other transition-metal-based Lewis acid catalysts[16] or organic molecular catalysts[17] have been used as efficient catalysts in the Michael-type Friedel–Crafts addition of indoles to electron-deficient olefins or α,β-unsaturated enones. However, some drawbacks still exist in previous synthetic methods, for example, the use of expensive stoichiometric amounts of Lewis acidic catalysts and toxic heavy metals. Hence, there is still a strong need for cheaper, simpler, and more efficient catalysts and procedures. In our continuing interest in developing new synthetic protocols for Michael-type Friedel–Crafts addition of indoles to enones, we report here an efficient method using a homogeneous heterobimetallic catalyst.

RESULTS AND DISCUSSION

The reaction of chalcone and indole was selected as a model (Scheme 1). We screened a series of transition-metal salts as catalyst (10 mol%) such as $PdCl_2(CH_3CN)_2$, $Mg(ClO_4)_2$, $MgCl_2$, $FeCl_3$, $ZnCl_2$, and $Cu(OAc)_2$. Unfortunately, no addition product was detected with these transition-metal salts at room temperature, so we then combined these transition-metal salts as



Scheme 1.

Table 1. Michael-type Friedel–Crafts reaction of indole with chalcone promoted by bimetallic complex (Fe-Mg-HMPA) catalyst

Entry[a]	Metal salt 1	Metal salt 2	Additive	Solvent	Reaction time (h)	Yield (%)[b]
1	$Mg(ClO_4)_2$	—	No[c] or HMPA	CH_2Cl_2	48	NR[d]
2	$FeCl_3$	$Mg(ClO_4)_2$	No[c]	CH_2Cl_2	24	Trace
3	$ZnCl_2$	$Mg(ClO_4)_2$	No[c] or HMPA	CH_2Cl_2	24	NR
4	$FeCl_3$	$Cu(OTf)_2$	No[c] or HMPA	CH_2Cl_2	24	Trace
5	$PdCl_2(CH_3CN)_2$	$Cu(OTf)_2$	No[c] or Et_3N	CH_3CN	24	NR
6	$Cu(OAc)_2$	$Mg(ClO_4)_2$	No[c] or HMPA	CH_2Cl_2	48	NR
7	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	No[c] or HMPA	CH_2Cl_2	48	NR
8	$InCl_3$	$Mg(ClO_4)_2$	No[c] or HMPA	CH_2Cl_2	48	Trace
9	$AgNO_3$	$Mg(ClO_4)_2$	No[c] or HMPA	CH_2Cl_2	48	NR
10	$PdCl_2(CH_3CN)_2$	$FeCl_3$	No[c] or HMPA	CH_2Cl_2	24	Trace
11	$Cu(OAc)_2$	$FeCl_3$	No[c] or HMPA	CH_2Cl_2	24	Trace
12	$FeCl_3$	$Mg(ClO_4)_2$	HMPA	CH_2Cl_2	12	63
13	$FeCl_3$	$Mg(ClO_4)_2$	HMPA	CH_3CN	12	55
14	$FeCl_3$	$Mg(ClO_4)_2$	HMPA	Toluene	12	53
15	$FeCl_3$	$Mg(ClO_4)_2$	HMPA	Et_2O	12	92
16	$FeCl_3$	$Mg(ClO_4)_2$	HMPA	THF	12	15
17	$FeCl_3$	$Mg(ClO_4)_2$	HMPA	CH_3OH	12	96
18	$FeCl_3$	$Mg(ClO_4)_2$	Et_3N or pyridine	CH_3OH	12	Trace
19	$FeCl_3$	$Mg(ClO_4)_2$	No[c]	CH_3OH	12	30
20	$FeCl_3$	$Mg(ClO_4)_2$	HMPA	CH_3OH	12	72[e]
21	$FeCl_3$	$Mg(ClO_4)_2$	HMPA	CH_3OH	12	58[f]
22	$Fe(ClO_4)_3$	—	HMPA	CH_3OH	12	48
23	$FeCl_3$	—	HMPA	CH_3OH	12	45
24	$Mg(ClO_4)_2$	—	HMPA	CH_3OH	12	Trace

[a] Reactions conditions: 10 mol% of transition-metal salt 1, 10 mol% of transition-metal salt 2, and 30 mol% HMPA: 0.55 mmol/0.5 mmol, of indole/chalcone; and 2 mL of solvent at room temperature for 12 h.

[b] Isolated yields.

[c] No addition of HMPA.

[d] No reaction.

[e] 5 mol% of $FeCl_3$ and 5 mol% of $Mg(ClO_4)_2$.

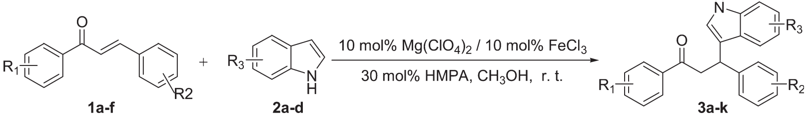
[f] 1 mol% of $FeCl_3$ and 1 mol% of $Mg(ClO_4)_2$.

bimetallic systems (some representative results are listed in Table 1, entries 1–11). Incidentally, we found that 63% of desired product **3a** was obtained when 10 mol% of $Mg(ClO_4)_2$ and 10 mol% of $FeCl_3$ were used as cocatalysts in the presence of 30 mol% HMPA in CH_2Cl_2 at room temperature for 12 h. With this encouraging result, we carried out the model reaction in different solvents. (Table 1, entries 12–18). Among the different solvents tested, CH_3OH and Et_2O were the most effective ones, and tetrahydrofuran (THF) gave the worst result with yields of 96%, 92%, and 15%, respectively. Moderate yields (50–60%) were obtained in lesser or nonpolar solvents such as CH_2Cl_2 and toluene. Interestingly, we found that HMPA was a crucial additive for this bimetallic catalytic system, other organic bases (Et_3N and pyridine) were inefficient (entry 18), and 30 mol% of HMPA exhibited better effect in this reaction after many trials (entry 17). In addition, even when the amounts of bimetallic catalysts [both $Mg(ClO_4)_2$ and $FeCl_3$] were reduced to 1 mol%, there was moderate yield (entry 21), which showed this bimetallic catalytic system has a dramatic effect in promoting the Michael-type Friedel–Crafts addition of indoles to chalcone. To assess whether the counteranions of Mg and Fe affect the course of this Michael reaction, the next studies were carried out employing $Fe(ClO_4)_3$, $FeCl_3$, or $Mg(ClO_4)_2$ alone under the same conditions (in CH_3OH). As expected, lower yields were obtained (entries 22–24). These results showed the remarkable synergistic effect between $FeCl_3$ and $Mg(ClO_4)_2$.

Under the optimized mild reaction conditions [10 mol% of $Mg(ClO_4)_2$, 10 mol% of $FeCl_3$, and 30 mol% HMPA, 1 equiv. chalcone, and 1.1 equiv. indole in CH_3OH at room temperature], we then investigated various indoles and enones for Michael-type Friedel–Crafts reactions (Scheme 2). As shown in Table 2, the yields of reaction are good except in the case of 5-Br substituted indole **2d** with enones (entry 11). For reaction of indole **2a** with enones bearing H-group, Cl-group, or methoxyl, moderate to good isolated yields could be obtained (entries 1 to 5). It is worth emphasizing that reacting N-substituted indole **2b** with different enones afforded the addition products with good to excellent yields (up to almost quantitative, entries 6 to 9). Nearly all reactions are clean, and the target compounds are obtained in good yields with no formation of side products such as dimers or trimers, which are normally observed when using strong acids.

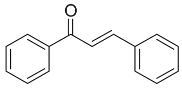
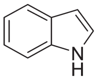
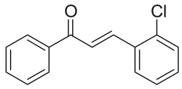
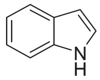
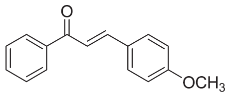
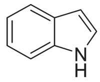
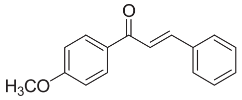
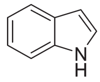
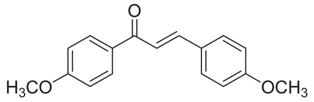
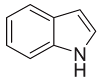
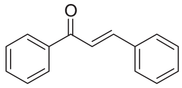
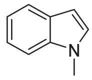
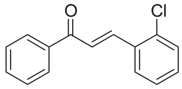
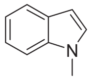
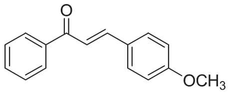
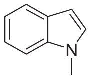
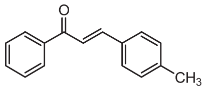
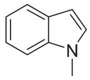
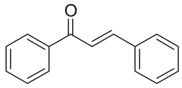
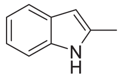
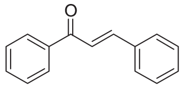
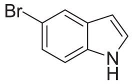
Although the correct mechanism of how the bimetallic iron and magnesium complex (Fe-Mg-HMPA) works is not yet clear, it seems that the catalyst acts as an efficient Lewis acid or the dual activation occurred with bimetallic iron and magnesium complex with both enone and indole. Further study of the mechanism of heterobimetallic iron–magnesium–catalyzed Michael-type Friedel–Crafts reactions is in progress.

In summary, we have demonstrated that simple bimetallic catalyst with dual activation was an effective and promising catalyst for the Michael-type Friedel–Crafts reactions of indoles with chalcones. This novel protocol,



Scheme 2.

Table 2. $Mg(ClO_4)_2$-$FeCl_3$-based bimetal complex (Fe-Mg-HMPA)–catalyzed Michael-type Friedel–Crafts reactions of indoles with chalcones

Entry[a]	Enone	Indole	Product	Yield (%)[b]
1		 2a	**3a**	96
2		 2a	**3b**	64
3		 2a	**3c**	83
4		 2a	**3d**	70
5		 2a	**3e**	82
6[c]		 2b	**3f**	99
7[d]		 2b	**3g**	90
8[c]		 2b	**3h**	94
9[c]		 2b	**3i**	98
10		 2c	**3j**	76
11		 2d	**3k**	32

[a]Unless noted, reactions conditions are 10 mol% of $Mg(ClO_4)_2$, 10 mol% of $FeCl_3$, and 30 mol% HMPA; 0.55 mmol/0.5 mmol of indole/chalcone; and 2 mL of CH_3OH at room temperature for 12 h.

[b]Isolated yields.

[c]Reaction time = 6 h.

[d]Reaction time = 8 h.

based on cheap and available Lewis acidic transition-metal catalysts, has the advantages of high efficiency, mild reaction conditions, high reactivity, and high selectivity, which make it a useful and attractive process for the synthesis of indole derivatives. Extension of this protocol to asymmetric catalysis is also in progress in our laboratories.

EXPERIMENTAL

All reaction flasks and solvents were used directly. Flash-column chromatography was performed over silica (100–200 mesh). 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. Infrared spectrometer (IR) spectra were recorded using a fourier transform infrared spectrometer (FT-IR) apparatus. Thin layer chromatography (TLC) was performed using silica gel.

Typical Michael-type Friedel–Crafts Reaction Procedure

$FeCl_3$ (0.1 mmol), $Mg(ClO_4)_2$ (0.1 mmol), and HMPA (0.3 mmol) were added into a solution of enone (1.0 mmol) and indole (1.1 mmol) in freshly distilled CH_3OH (4 mL). After stirring at room temperature for 12 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 (EtOAc–petroleum ether, 1:5) to gain the pure product. All the products are known,[17b] and structures were confirmed by mass spectrum (MS), nuclear magnetic resonance (NMR), and IR.

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