Organocatalytic versus Iron-Assisted β-Boration of Electron-Deficient Olefins

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In the light of current debates surrounding sustainable and green chemistry, iron has now become an attractive alternative to the most commonly used expensive noble metals in a number of homogenous catalytic reactions, as it is abundant, inexpensive, less toxic, and environmentally more acceptable.^[1] Despite the intense interest in the homogenous catalytic applications of iron complexes, the only known examples of iron-mediated C-B bond formation are the 1,4-hydroboration of 1,3-dienes to obtain linear (E)- γ disubstituted allylboranes,^[2] and the C-H activation/borylation of furans and thiophenes catalyzed by a half-sandwich iron N-heterocyclic carbene complex.^[3] Consequently, we became interested in exploring the benefits of iron in the β boration of electron-deficient olefins,^[4] comparing it with the known catalytic systems of copper^[5] and nickel^[6] complexes, and in particular with the most recently developed organocatalytic systems.^[7] In this study, we focused on the β boration of α , β -unsaturated esters and imines, which are highly versatile reactions to access polyfunctionalized molecules.

We started our study by exploring whether the addition of iron salts has any positive influence on the β -boration of α , β -unsaturated esters and imines with diboron reagents. Therefore, we selected bis(pinacolato)diboron (B₂pin₂) as the boron source, methanol as the proton source, ethylcrotonate **1a**, and (*E*)-1-phenyl-*N*-(4-phenylbutan-2-ylidene)methanamine **1b** as the substrates for the model reactions (Scheme 1).

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Scheme 1. β-boration model reaction of activated olefins.

The readily available iron(II) and iron(III) salts, Fe(acac)₂ (acac = acetylacetonate), $Fe(acac)_3$, $FeCl_2$, and $Fe(OMe)_2$ were selected as iron sources (2 mol% catalytic loading of iron). However, none of these salts were able to promote the β -boration reaction of **1a** and **1b**, even at 70 °C. However, the addition of a base (Cs_2CO_3) to the reaction medium favored the β -boration of ethylcrotonate (Table 1, entries 1– 4). The positive influence of base in this reaction was first observed in the case of the CuCl/KOAc catalyst.^[5a,b] The catalytic system Fe(acac)₂/PPh₃ (Fe/PPh₃=1:2) was also inactive, but the presence of the base, Cs_2CO_3 , allowed the β boration of ethylcrotonate in quantitative conversions, within 6 hours (Table 1, entries 5-8). Lowering the reaction temperatures substantially diminished the reaction rate (Table 1, entries 9 and 10). The catalytic activity observed for the Fe(acac)₂/PPh₃/Cs₂CO₃ system can be directly compared with the corresponding PPh₃/Cs₂CO₃ and Cs₂CO₃ catalysts^[7a] (Table 1, entries 8, 11, and 12). The base alone provides 45% conversion under the chosen catalytic conditions (Table 1, entry 12). Combining the base with phosphine increases the activity but the conversion is still moderate (Table 1, entry 11). The addition of the iron salt to the PPh₃/ Cs₂CO₃ system is strikingly beneficial; this results in complete conversion (Table 1, entry 8).

A similar trend has been observed for the β -boration of (*E*)-1-phenyl-*N*-(4-phenylbutan-2-ylidene)methanamine **1b**, which to the best of our knowledge, has only been β -borated with a copper catalyst modified with phosphine ligands.^[8] While Fe(acac)₂ did not show catalytic activity, its combination with Cs₂CO₃ resulted in 28% conversion (Table 2, entry 1). The benefits of the addition of base were also ob-

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Table 1.	Influence	of iron	on	catalytic	β-boration	of	ethylcrotonate.[a]
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Entry	Iron system	$Cs_2CO_3 [mol \%]$	$PPh_3 [mol \%]$	<i>T</i> [°C]	<i>t</i> [h]	Conv. [%] ^[b]
1	$Fe(acac)_2$	3	_	70	6/24	42/80
2	FeCl ₂	3	-	70	6	60
3	$Fe(OMe)_2$	3	-	70	6	15
4	$Fe(acac)_3$	3	-	70	6	56
5	$Fe(acac)_2$	3	4	70	6/24	26/99
6	$Fe(acac)_2$	6	4	70	6	73
7	$Fe(acac)_2$	12	4	70	6	87
8	$Fe(acac)_2$	15	4	70	6	99
9	$Fe(acac)_2$	15	4	45	6	54
10	$Fe(acac)_2$	15	4	25	6	21
11	_	15	4	70	6	54
12	-	15	-	70	6	45

[a] Standard conditions: ethylcrotonate/bis(pinacolato)diboron/Fe complex = 0.5:0.55:0.01. Fe/PPh₃=1:2. Cs₂CO₃: mol% with respect to the substrate, MeOH: (2.5 mol%). Solvent: THF (2 mL). [b] Determined by G.C.

served in the Fe(acac)₂/PPh₃ system, which provided the desired β -borated product in quantitative yield (Table 2, entries 2–4). Importantly, the PPh₃/Cs₂CO₃ organocatalytic system was not able to promote the β -boration of the imine substrate (Table 2, entry 5).

Recent evidence about the role of metal impurities in "iron-mediated" reactions^[9] prompted us to carefully exam-

cycloocta-1,5- $(cod)_2$ (cod =diene),^[11] under the standard conditions of the iron-mediated reactions. In these reactions, NaOtBu was used as a base in the stock solutions because of its high solubility in tetrahydrofuran (THF; Table 3, entries 1-3, 9, and 10). In subsequent experiments, we gradually decreased the concentration of the "in situ" formed, base-activated copper and nickel complexes from 5×10^{-3} M to $5 \times$ 10⁻⁶м. Both CuCl and CuOTf+4CH₃CN form considerably more active catalysts than

Fe(acac)₂ when applied in the same concentration, 5×10^{-3} M (Table 2, entries 1–3). The higher activity is even more obvious when the catalyst concentration is decreased by one magnitude, to 5×10^{-4} M (S/Cu=500), and the substrate is still quantitatively converted into the product (Table 2, entry 4). Further decreasing the concentration of the copper complex, the conversion quickly diminishes: at 5×10^{-5} M

Table 2. Influence of iron on catalytic β -boration of (E)-1-phenyl-N-(4-phenylbutan-2-ylidene)methanamine.^[a]

Entry	Iron system	$Cs_2CO_3 [mol \%]$	PPh ₃ [mol %]	<i>T</i> [°C]	<i>t</i> [h]	Conversion [%] ^[b]
1	$Fe(acac)_2$	15	-	70	6	28
2	$Fe(acac)_2$	3	4	70	6	32
3	$Fe(acac)_2$	9	4	70	6	74
4	$Fe(acac)_2$	15	4	70	6	99
5	-	15	4	70	6	-

[a] Standard conditions: (*E*)-1-phenyl-*N*-(4-phenylbutan-2-ylidene)methanamine/bis(pinacolato)diboron/Fe complex = 0.5:0.55:0:01. Fe/PPh₃=1:2. Cs₂CO₃: mol % with respect to the substrate, MeOH: (2.5 mol %). Solvent: THF (2.5 mL). [b] Determined by ¹H NMR spectroscopy.

ine the possible effect of traces of transition metals in our iron precursors. As a matter of fact, the $Fe(acac)_2$ catalyst precursor received from Sigma-Aldrich (99.95%) reportedly contains copper and nickel impurities in 6.1 and 43.0 ppm concentrations, respectively. Phosphine complexes of copper and nickel are well-known catalysts for β-boration of activated olefins.^[5,6] No other metals, known to be active in β boration of α,β -unsaturated carbonyl compounds, such as platinum, rhodium, and palladium were listed in the quality certificate of the product. Under standard reaction conditions, the concentration of the iron system is approximately 5×10^{-3} M (Table 1, foot note). Considering the heavy metal impurities reported by the provider, the catalytic system might contain "in situ" formed copper/phosphine, nickel/ phosphine complexes in 1.2×10^{-7} M and 9.2×10^{-7} M concentrations, respectively. To estimate the contribution of the impurities to the overall catalytic activity, we monitored the conversion as the function of the phosphine-complex concentration for both copper and nickel. As a comparison, we performed reactions using CuCl and CuOTf+4CH₃CN^[10] as transition-metal precursors, as well as with NiCl₂ and Nicopper concentration only 5% of the product can be observed, and at 5×10^{-6} M concentration, the substrate remains intact. Under the optimized conditions for the iron-mediated β -boration reactions, nickel complexes are much less active than the copper catalysts (Table 2, entries 9 and 10). Both NiCl₂ and Ni(cod)₂ provided incomplete conversions when applied in the

concentration of the iron precursor, and decreasing the concentration by one magnitude resulted in complete inactivity. Considering the high purity of the $Fe(acac)_2$ precursor (99.95%), and the activity versus concentration profiles of

Table 3. Conversions in β -boration of ethylcrotonate with bis(pinacolato)diboron as the function of the concentration of copper and nickel, typical heavy metal impurities of the Fe(acac)₂ precursor.^[a]

Entry	Precursor	Concentration [mol dm ⁻³]	Conversion [%] ^[b]
1	$Fe(acac)_2$	5×10^{-3}	45
2	CuCl	5×10^{-3}	99
3	CuOTf•4CH3CN	5×10^{-3}	99
4	CuOTf•4CH3CN	5×10^{-4}	99
5	CuOTf•4CH ₃ CN	2.5×10^{-4}	28
6	CuOTf•4CH3CN	1.25×10^{-4}	17
7	CuOTf•4CH ₃ CN	5×10^{-5}	5
8	CuOTf•4CH3CN	5×10^{-6}	0
9	NiCl ₂	5×10^{-3}	53
10	$Ni(cod)_2$	5×10^{-3}	51
11	$Ni(cod)_2$	$5 \times (10^{-4} - 10^{-6})$	0

[a] Standard conditions: ethylcrotonate =0.5 mmol, bis(pinacolato)diboron=0.55 mmol, metal/PPh₃/NaOtBu=1:2:5, T=70 °C, t=6 h. MeOH (2.5 mol%). Solvent: THF (2 mL). [b] Determined by G.C. the copper and nickel catalysts, one can conclude that the heavy metal impurities cannot contribute to the overall activity in the iron-mediated β -boration reactions.

Next, the scope of the iron-mediated β -boration was explored by using α,β -unsaturated esters, ketones, and imines as substrates. The Fe(acac)₂/PPh₃/Cs₂CO₃ system quantitatively converted isobutyl crotonate into the corresponding β -borated product, within 6 hours at 70 °C in tetrahydrofuran (Table 4, entry 1), despite the steric hindrance imparted by the isobutyl moiety. This is in sharp contrast to the moderate conversion (51%) obtained with the corresponding organocatalytic system, that is, in the absence of $Fe(acac)_2$ (Table 4, entry 2). The β -boration of acyclic α , β -unsaturated ketones, trans-4-hexen-3-one and trans-3-nonen-2-one, reached complete conversion with both the PPh₃/Cs₂CO₃ organocatalytic system and the iron-assisted system (Table 4, entries 3-6). However, complete conversion of cyclohexenone required the presence of the Fe(II) salt (Table 4, entries 7 and 8). Remarkably, the complete conversion of the β -boration of 1-azadienes, such as (E)-N-((E)-4-phenylbut3-en-2-ylidene)aniline and (E)-N-((E)-4-phenylbut-3-en-2ylidene)butan-1-amine, nicely demonstrates the benefits of the iron salt (Table 4, entries 9 and 11). In these cases, the organocatalytic system alone cannot promote the boronconjugate addition to the α , β -unsaturated imines (Table 4, entries 10 and 12).

In order to gain deeper insight into the role of iron in the β -boration reactions, we have explored two possibilities: a) an iron complex activates the diboron reagent, thus forming Fe–B bonds (by oxidative addition^[12] or transmetallation), and this promotes the boron-addition to the electrondeficient olefins in its inner coordination sphere; b) the substrate is activated by the iron salt through a Lewis acid–base interaction between the metal and the carbonyl or imino group, which polarizes the conjugated π -electron system of the substrate and facilitates the boron-addition. Towards this end, we first conducted NMR studies with: a) 1 equivalent of Fe(acac)₂ and 1 equivalent of B₂pin₂, b) 1 equivalent of Fe(acac)₂, 1 equivalent of B₂pin₂ and 1 equivalent of NaOtBu, c) 1 equivalent of B₂pin₂ and 1 equivalent of

Table 4. Influence of iron on catalytic β-boration of electron-deficient olefins with bis(pinacolato)diboron.^[a]

Entry	Iron system	$Cs_2CO_3 [mol\%]$	PPh ₃ [mol %]	Substrate	Product	Conversion [%] ^[b] [Yield] [%] ^[c]
1	Fe(acac) ₂	15	4	O O <i>i</i> Bu	BpinO JUI O <i>i</i> Bu	99[90%]
2	_	15	4	O U O/Bu	Bpin _O	51 ^[d]
3	Fe(acac) ₂	15	4	0 L	Bpin _O	99[88 %] ^[c]
4	_	15	4	0 L	Bpin _O	99[81 %] ^[d]
5	Fe(acac) ₂	15	4		BpinO	93[86%] ^[c]
6	_	15	4		BpinO	98
7	Fe(acac) ₂	15	4	O O	O Bpin	91[82 %] ^[c]
8	-	15	4	o	O Bpin	43
9	Fe(acac) ₂	15	4	Ph Ph	Ph Bpin N Ph	99
10	-	15	4	Ph Ph	Ph Bpin N Ph	0
11	Fe(acac) ₂	15	4	nBu N Ph	Bpin N Ph	99
12	_	15	4	nBu N Ph	Bpin N Ph	0

ESI-MS⁺ analyses of solutions of $Fe(acac)_2$ and $Fe(acac)_3$ in the presence of the two model substrates 1a and 1b. In the case of the combinations [Fe- $(acac)_2$]/1a, [Fe(acac)_2]/1b, and $[Fe(acac)_3]/1b$, the molecular ions [Fe(acac)₂]+-1a and [Fe-(acac)₂]⁺-**1b** are clearly observable. $[Fe(acac)_2]$ and the corresponding adducts with 1a and 1b are oxidized under the conditions of the ESI-MS⁺ analysis, which leads to the observation of the corresponding [Fe- $(acac)_{2}$]⁺, [Fe(acac)_{2}]⁺-1a, and $[Fe(acac)_2]^+$ -1b molecular ions. The $17e^-$ Fe(acac)₃ precursor can be observed as $[Fe(acac)_2]^+$ and $[Fe(acac)_3 + Na]^+$ by ESI-MS⁺. To act as a Lewis acid it needs to lose a ligand, in accordance with the observation of the $[Fe(acac)_2]^+-1b$ adduct. The analogous $[Fe(acac)_2]^+$ chalcone adduct has also been observed in the FeCl₃/acac-catalyzed Friedel-Crafts alkylation of indoles.^[13]

NaO*t*Bu. We have observed that the diboron reagent is only

affected by the base, independ-

ently of the presence or absence of $Fe(acac)_2$. In order to study possible interactions between the iron precursors and the substrates, we performed

[a] Standard conditions: ethylcrotonate/bis(pinacolato)diboron/Fe complex=0.5:0.55:0.01. Fe/PPh₃=1:2. Cs₂CO₃: mol% with respect to the substrate, MeOH: (5 mol%). Solvent: THF (2.5 mL), T=70 °C, t=6 h. [b] Determined by G.C. and ¹H NMR spectroscopy. [c] Isolated yield. [d] Ref. [9].

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Scheme 2. Iron-mediated β-boration reaction of activated olefins.

Based on these experimental results, we suggest a preactivation of the substrates by the Lewis acidic Fe(II) and Fe(III) salts (Scheme 2), as it has been proposed for the iron-catalyzed Michael additions and other conjugate addition reactions.^[14] The boron nucleophile is generated upon the interaction of the bis(pinacolato)diboron and the organocatalyst.^[7a] Thus, the reaction is facilitated by two catalytic systems, which function independently. The synergetic effect of the transition-metal and the PPh₃/Cs₂CO₃ catalytic system is particularly striking in the case of the imine substrates. Neither the iron salt nor the PPh₃/Cs₂CO₃ system alone can activate these substrates, however, their combination leads to complete conversions.

Experimental Section

Experimental procedure for the iron-mediated β -boration of α , β -unsaturated esters, ketones, and imines with bis(pinacolato)diboron. The iron precursor (0.01 mmol) and PPh₃ (0.02 mmol of phosphorus) were placed in a Schlenk tube, and dissolved in THF (2 mL) under argon. The suspension was stirred for 10 min and Cs₂CO₃ (0.075 mmol, 15 mol%) was added. Afterwards, the substrate (0.5 mmol) and bis(pinacolato)diboron (0.55 mmol) were added. Finally, MeOH (100 µL, 2.5 mol%) was added, and the mixture was allowed to stir for 6h at 70 °C. The reaction mixture was cooled to room temperature. An aliquot (0.2 mL) was taken from the solution. It was diluted with CH₂Cl₂ (1 mL) and analyzed by G.C. to determine conversion. After G.C. analysis, the same aliquot was gently concentrated on a rotary evaporator at room temperature, and analyzed by ¹H NMR spectroscopy to confirm the conversion previously observed by G.C.. In each case, both methods indicated that one single product was formed from the substrate. The differences in the conversions obtained with the two methods are within 5% in most cases.

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