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A practical, catalytic and selective deprotection of a Boc group in *N,N´*-diprotected amines using iron(III)-catalysis

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A selective, catalytic and practical method for removing a Boc group from several *N, N´*-diprotected amino acids and amine derivatives using iron(III) salts as sustainable catalysts is described. The process is clean, not being necessary a purification step. A theoretical study rationalizing the results with several metals is presented.

Iron occupies an important place amongst the biologically relevant metals and there is growing interest in using their salts as sustainable catalysts for organic transformations. A multitude of biological systems and functions rely upon the chemistry of iron-containing enzymes. It is one of the most abundant and inexpensive metals in the earth´s crust, being an attractive metal for man-made synthetic transformations as no severe toxicity and side effects exist. Therefore, iron salts fulfil the criteria to be a perfect sustainable catalyst.[1]

The *tert*-butyloxycarbonyl (Boc) group is one of the most widely used amino protecting groups. This group is usually used in combination with other orthogonal protecting groups, and its removal should be easy, practical and clean, avoiding waste. The most common methods for its removal use excess of an organic acid such as TFA or mineral acids such as sulphuric acid, hydrochloric acid and phosphoric acid in large scale.[2] However, the production of waste salt due to the neutralization is inevitable. Despite advances in this area,[3] only a few methods can be found to selectively deprotect an alkoxycarbonyl group in *N, N*-dicarbamoyl (or amide)-protected amines,[4] sometimes using hazardous compounds.[5] Therefore a catalyst which would lead to simple and clean work-ups is desirable. During our work directed to the synthesis of unsaturated α-amino acid derivatives to use in the aza-Prins cyclization, we found that iron(III) salts could efficiently catalyse the selective deprotection of *N*-Boc, which meet all requirements for a sustainable and greener chemical process. This promising result prompted us to explore the use of iron(III) salts as sustainable metal catalysts in the *N*-Boc deprotection.

Herein, we report the cleavage of *N*-Boc using catalytic amounts of iron(III) salts. A selective cleavage of the *N*-Boc group even in the presence of an *N*-Cbz group, is possible.

First, we decided to test different iron salts and compare them with other metal salts, in most cases, sustainable metals catalysts (Table 1).[1b]

Table 1 Optimization of *N*-Boc cleavage of *N, N*-Ts, Boc-amines in a sustainable context[a]
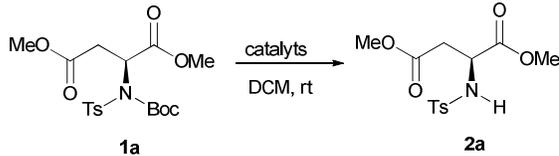
Entry	Catalyst	mol.	Time	Yield [%]
1	FeCl$_3$	1.0	15 min	>99
2	FeCl$_3$	0.5	45 min	>99
3	FeCl$_3$	0.3	2 h	>99
4	FeCl$_3$	0.2	10 h	>99
5	FeCl$_3$	0.1	24 h	80
6	FeBr$_2$	1.0	24 h	>99
7	FeCl$_2$	1.0	24 h	NR[b]
8	Fe(OTf)$_3$	1.0	15 min	D[c]
9	Fe(OTf)$_3$	0.3	30 min	>99
10	FeCl$_3$·6H$_2$O	1.0	12 h	>99
11	Fe(acac)$_3$	1.0	24 h	NR[b]
12	Fe(acac)$_3$/TMSCl	0.1/1	24 h	>99
13	FeCl$_3$/TMSCl	0.1/1	45 min	>99
14	InCl$_3$	1.0	8 h	>99
15	InCl$_3$	0.3	12 h	>99
16	RuCl$_3$	1.0	24 h	NR[b]
17	AuCl$_3$	1.0	45 min	>99
18	AuCl$_3$	0.3	12 h	84
19	NiCl$_2$	1.0	24 h	NR[b]
20	MnBr$_2$	1.0	24 h	NR[b]
21	CuCl$_2$	1.0	24 h	NR[b]
22	CuCl	1.0	24 h	NR[b]
23	ZnCl$_2$	1.0	12 h	56
24	MoCl$_3$	1.0	12 h	>99
25	MoCl$_3$	0.3	12 h	35
26	MgCl$_2$	1.0	24 h	NR[b]

[a] The reaction was conducted with 0.5 mmol of **1a** in 5 mL of DCM at room temperature. No inert atmosphere is necessary. [b] NR = No reaction. [c] D = Decomposition

We chose the dimethyl ester *N,N*-Boc,Ts-amino acid **1a**, derived from *L*-aspartic acid, as the substrate to study this selective *N*-Boc deprotection. Very good results with different metal salts, from indium(III) chloride to several iron salts through other transition metals like gold(III), were obtained (Table 1).

Using stoichiometric amounts, several salts of iron, indium, gold and molybdenum afforded quantitative yields of the desired products (Table 1, entries 1, 6, 10, 14, 17 and 24). FeCl$_3$ led to shorter reaction times (15 min) and a cleaner reaction (Table 1, entry 1). No column chromatography was necessary after work-up. Besides iron(III) salts only a few sustainable metals deprotected the *N*-Boc group, obtaining the best results with MoCl$_3$ (Table 1, entries 19-26). The other iron salts (except Fe(OTf)$_3$)) and indium(III) chloride behave similarly but with longer reaction times. The deprotection with Fe(OTf)$_3$, AuCl$_3$ and MoCl$_3$ lead to a waste after the work-up being necessary a further chromatography purification (Table 1, entries 8, 17 and 24 respectively).[6]

To our delight, the removal of *N*-Boc works with substochiometric amounts of several metals with excellent yields (Table 1, entries 3, 9, 15, and 18). Decreasing the amount of FeCl$_3$ increased the reaction time but the yields remained almost quantitative except with 0.1 equiv. that lead to 80% in 24 h (Table 1, entry 5). However, the combination of this amount of FeCl$_3$ with 1 equiv. of trimethysilyl chloride (TMSCl) increased the yield to 99% and decreased the reaction time to 45 min (Table 1, entry 13). Control experiments confirmed that in the absence of the iron salts no reaction was observed (Table 2, entry 2).

In the first experiments, the reaction was conducted under strict moisture free conditions, dry CH$_2$Cl$_2$ at room temperature under inert atmosphere, with excellent yields. The reactions works equally well using FeCl$_3$ of 99.999% of purity.

In a further step, we obtained the same results without inert atmosphere, showing that moisture is not implicated in the deprotection of *N*-Boc group.

From all metals tested above, we have chosen FeCl$_3$ as the best catalyst because it is cheap and sustainable, leads to a clean reaction with excellent yield and short reaction time, and it does not require a chromatographic purification. Taking into consideration all this data, we found the best conditions to be FeCl$_3$ (1 or 0.3 equiv.) or the combination FeCl$_3$/TMSCl (Table 1, entries 1, 3 and 13 respectively). With this methodology we have scaled the reaction up to 2 grams.

To explore the scope and limitations of our method, we investigated several α-amino acids with different *N*-protecting groups and functionalities. The deprotection of *N*-Boc is effective when the nitrogen bears other protecting groups (PG^1) such as tosyl, mesyl, nosyl, acetate, Boc and Cbz (Table 2). The possibility to alternate whatever of the three iron salt options lead to the *N*-Boc deprotection with excellent yields. The method works very well with internal double bonds present in the molecule (Table 2, entries 3-5). In this case, the best yield was obtained using 1 equiv. of iron(III) chloride which led to quantitative yields and the double bond was unaffected. No isomerization of the *cis*-double bond was observed. The reaction works really well with amino acids bearing an aromatic group such as phenylalanine derivatives (Table 2, entries 27-29), failing when a free hydroxyl group is present (Table 2, entries 30-32).

In the presence of other functional groups such as esters (glutamic acid derivatives) the *N*-Boc deprotection works well when the other *N*-protecting group is tosyl or mesyl (Table 2, entries 6-11). The same behavior was observed when PG^1 was a nosyl group and aspartic acid derivatives were used as starting materials (Table 2, entries 12-14).

On the other hand, we found that our method selectively deprotected an *N*-Boc group in *N,N*-di-Boc-protected α-amino acids (Table 2,

entries 15-17). We found the procedure to be highly general, yielding the corresponding *N*-Boc amino derivatives (Table 2, entries 18-20).[7]

Considering that the metal catalysis works with the *N, N*-di-Boc moiety, we wondered if this methodology could be extended to other situations in which the nitrogen is doubly protected with an additional alkoxycarbonyl group as Cbz. To our surprise, the procedure removes selectively, and with excellent yield, the *N*-Boc group leading the *N*-Cbz monoprotected amino acid derivatives (Table 2, entries 24-26). The complete and selective deprotection of *N*-Boc group was obtained using substoichiometric amounts of iron(III) chloride (Table 2, entries 25 and 26).[8] With this method we are able to distinguished between two alkoxycarbonyl groups, improving the results of other methods developed in our group.[9]

When the additional protecting group is a carboxylic acyl derivative (e.g acetate) the cleavage of the *N*-Boc group needed more time but remained as efficient using 1 equiv. of iron(III) chloride (Table 2, entry 21). After 12 h, the reactions with substochiometric amounts of iron(III) chloride were not complete (Table 2, entries 22 and 23). It should be noted that the *N*-Boc deprotection of α-amino acids occurs without any detectable racemization.[10]

Table 2. Iron(III) salts catalyse *N*-Boc Cleavage [a,b]

Entry	R	PG^1	PG^2	FeCl$_3$/ TMSCl (equiv)	Yield [%]
1	CH$_2$COOMe	H	Boc	1/0	NR
2	CH$_2$COOMe	Ts	Boc	0/1	NR
3	CH$_2$(CH=CH)(CH$_2$)$_2$CH$_3$-(Z)	Ts	Boc	1/0	>99
4	CH$_2$(CH=CH)(CH$_2$)$_2$CH$_3$-(Z)	Ts	Boc	0.1/1	84
5	CH$_2$(CH=CH)(CH$_2$)$_2$CH$_3$-(Z)	Ts	Boc	0.3/0	83
6	CH$_2$COOMe	Ms	Boc	1/0	>99
7	CH$_2$COOMe	Ms	Boc	0.1/1	>99
8	CH$_2$COOMe	Ms	Boc	0.3/0	>99
9	CH$_2$COOMe	Ts	Boc	1/0	>99
10	CH$_2$COOMe	Ts	Boc	0.1/1	>99
11	CH$_2$COOMe	Ts	Boc	0.3/0	>99
12	COOMe	Ns	Boc	1/0	>99
13	COOMe	Ns	Boc	0.1/1	94
14	COOMe	Ns	Boc	0.3/0	>99
15	H	Boc	Boc	1/0	70
16	H	Boc	Boc	0.1/1	86
17	H	Boc	Boc	0.3/0	90
18	CH$_2$COOMe	Boc	Boc	1/0	69
19	CH$_2$COOMe	Boc	Boc	0.1/1	92
20	CH$_2$COOMe	Boc	Boc	0.3/0	91
21	COOMe	Ac	Boc	1/0	>99[d]
22	COOMe	Ac	Boc	0.1/1	59[c]
23	COOMe	Ac	Boc	0.3/0	76[c]
24	CH$_2$COOMe	Cbz	Boc	1/0	85
25	CH$_2$COOMe	Cbz	Boc	0.1/1	>99
26	CH$_2$COOMe	Cbz	Boc	0.3/0	>99
27	Ph	Ts	Boc	1/0	95
28	Ph	Ts	Boc	0.1/1	>99
29	Ph	Ts	Boc	0.3/0	80
30	CH$_2$CH$_2$OH	Ts	Boc	1/0	--[e]
31	CH$_2$CH$_2$OH	Ts	Boc	0.1/1	--[e]
32	CH$_2$CH$_2$OH	Ts	Boc	0.3/0	--[e]

[a] The reaction was conducted with 0.5 mmol of **1a** in 5 mL of DCM at room temperature. No inert atmosphere is necessary. [b] NR = No reaction. [c] H NMR yield. [d] 12 h of reaction time. [e] Decomposition of the starting material.

Next, we wondered about the relation between *N*-Boc deprotection and the functional groups present in the molecule. We focused on the presence of the ester of the α-amino acid and the other protecting group of the nitrogen (Table 3). The method works equally well when the carboxylic group of the α-amino acid is not present in the molecule. The cleavage of the *N*-Boc group in the amines occurs with very good yield when the nitrogen of the amine bears a tosyl group (Table 3, entries 1-3). However, the cleavage of *N*-Boc protected secondary amines was not successful (Table 3, entries 4-6). No reaction was observed with an *N*-Boc protected primary amine (PG¹=H) (Table 2, entry 1).

Then, to study the influence of the metal and protecting group of the amine in the *N*-Boc deprotection, we carried out DFT theoretical calculations at the B3LYP/Def2-SVP level. The polarizable continuum model (PCM) implemented in Gaussian 03 was used with methylene chloride as solvent.[11] We performed these calculations over the simplified structure of *tert*-butyl *N*-methyl-*N*-sulfonylmethylcarbamate associated with the following Lewis acids; FeCl₃, InCl₃, CuCl₂, MoCl₃, AuCl₃, MgCl₂ and RuCl₃. As a result of this study, previous to the *N*-Boc removal three structures were possible. 1) The structure **I** in which the carbonyl and sulfonyl groups are chelating the metal. 2) The structure **II** where only the sulfonyl group is coordinated to the metal. 3) The structure **III** where only the carbonyl group is coordinated to the metal (Fig 1).

Table 3. Deprotection of *N*-Boc, *N*-substituted aliphatic amines [a,b]

Entry	Substrate	FeCl₃/ TMSCl (equiv)	Product	Yield [%]
1	(butenyl)N(Ts)(Boc)	1/0 0.1/1 0.3/0	(butenyl)N(Ts)(H)	94 81 89
2	(pentenyl)₃N(Ts)(Boc)	1/0 0.1/1 0.3/0	(pentenyl)₃N(Ts)(H)	>99 95 97
3	(propyl)N(Ts)(Boc)	1/0 0.1/1 0.3/0	(propyl)N(Ts)(H)	>99 98 >99
4	(diallyl)N(Boc)	1/0 0.1/1 0.3/0	--	NR NR NR
5	(diisopropyl)N(Boc)	1/0 0.1/1 0.3/0	--	NR NR NR
6	(proline)N(Boc)(OMe)	1/0 0.1/1 0.3/0	--	NR NR NR

[a] The reaction was conducted with 0.5 mmol of amide/amine in 5 mL of DCM at room temperature. No inert atmosphere is necessary. [b] NR = No reaction.

Iron(III), indium (III) and ruthenium(III) have two complexes, being the most unstable the most reactive for iron and ruthenium. In the case of FeCl₃ the reactive complex-**III** is 2,15 kcal/mol more unstable than the complex FeCl₃-**II**. The stability gap between both ruthenium(III) complexes differ in 1.42 kcal/mol. In the case of indium(III), the complex InCl₃-**I** is 1.04 kcal/mol more stable. Next, we decided to study the influence of the sulfonyl group and the different metals on the O-C(CH₃)₃ bond (Table 4). We studied the

bond order of O-C(CH₃)₃ bond using a recent definition of bond order, called the Laplacian bond order (LBO).[12] It should be emphasized that the LBO is a definition of covalent bond order rather than total bond order.[13]

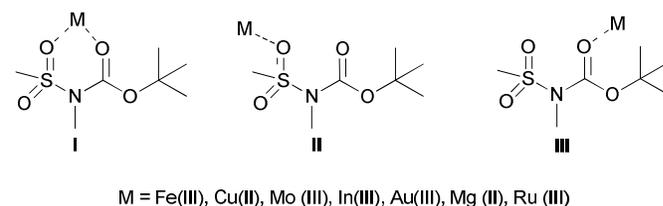M = Fe(III), Cu(II), Mo (III), In(III), Au(III), Mg (II), Ru (III)

Figure 1. Metal complexes involved in the *N*-Boc deprotection of *tert*-butyl *N*-methyl-*N*-sulfonylmethylcarbamate

We performed the LBO studies over two simplified models; **A** with *N*-sufonylmethyl and **B** with *N*-methyl (Table 4). A very good correlation between LBO values and C-O bond lengths (Å) in model **A** was observed (Table 4).[14]

**Table 4.** Influence of sulfonyl group and Lewis acid in the bond length of O-C(CH₃)₃ bond [a,b]

	A		**B**

Entry	Lewis acid	C-O bond (Å) A	LBO A	C-O bond(Å) B	LBO B
1	---	1.480	0.17566	1.467	0.21497
2	H⁺	1.548	0.05957	1.522	0.09472
3	Mg²⁺	1.519	0.10053	1.493	0.14376
4	MoCl₃-**I**	1.513	0.11258	1.491	0.14760
5	FeCl₃-**III**	1.507	0.11844	1.493	0.12909
6	AuCl₃-**I**	1.508	0.11913	1.493	0.14595
7	InCl₃-**I**	1.509	0.12015	1.490	0.15513
8	MgCl₂-**I**	1.505	0.12552	1.493	0.16528
9	RuCl₃-**III**	1.501	0.12839	1.488	0.15714
10	CuCl₂-**I**	1.501	0.13535	1.488	0.15922
11	FeCl₃-**II**	1.492	0.15322	--	--
12	InCl₃-**II**	1.490	0.15708	--	--
13	RuCl₃-**II**	1.489	0.16037	--	--

[a] **I**, **II** or **III** indicate which type of complex is implicate. [b] In the model **B** the only possible interaction with the metal is through the carbonyl of the Boc group.

The LBO value decreases with all the metals, being the lowest with a protic acid (Table 4, entry 2, model **A**). The presence of the metal produces a weakening of the O-C(CH₃) bond due to an enlargement of this bond, that favor the *N*-Boc deprotection (Table 4, entries 4-7, model **A**). This bond becomes more ionic leading to a greater decarboxilative ability according to the mechanism where the rupture of the O-C(CH₃)₃ bond is assumed to be the rate-controlling process.[15] Also, we have found that the effective limit for the LBO value is around that for MgCl₂ (Table 4, entry 8, model **A**). All the metals with a LBO value > 0.125 do not contribute to remove the *N*-

Boc group (Table 4, entries 8-13, model **A**). In all the cases, the metals that favor the deprotection present coordination with the carbonyl of the ester group. The process is inhibited when the metal coordination is through the sulfonyl group (Table 4, entries 11, 12 and 13, model **A**).

A simplified mechanism according with the experimental and theoretical results is shown in Scheme 1.
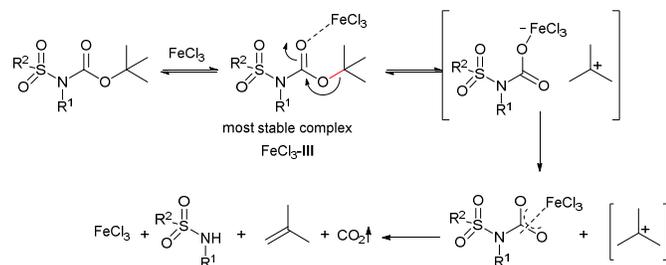
Scheme 1. Plausible mechanism of *N*-Boc deprotection catalyzed by iron (III) chloride.

Several factors contribute to facilitate the deprotection of the *N*-Boc group. The presence of an electron withdrawing group attached to the nitrogen, the adequate metal at the Lewis acid and its counteranion. The results of a geometric optimization of model **B** show the importance of the electron withdrawing group to favor the removal of *N*-Boc group. In all the metal cases with this model, the LBO value is higher than 0.125, therefore the removal of the Boc group is not favored (Table 4, entries 3-10, model **B**). Only with protic acid the LBO values is lower than 0.125 justifying the deprotection (Table 4, entry 2, model **B**).

The nature of the counteranion is another important factor. Sometimes, in the cationic complexes, the counteranion is assumed to be quite separated from the complexed cation. We can observe this effect comparing the results of magnesium salts; $MgCl_2$ and counteranion-free Mg^{2+} (Table 4, entries 3 and 8 respectively, model **A**).[16] With chloride as counter anion, the $MgCl_2$ is unable to produce the removal of *N*-Boc. However, with perchlorate as counteranion the deprotection of *N*-Boc occurs with good yield although with the necessity of increasing the reaction temperature.[5a] This difference of reactivity is due to a high ionic character of the perchlorate ion with a weak tendency to coordinate metal ions, which enhances the Lewis acid power of the metals counterions.[16] In our case, the iron(III)chloride is a strong enough Lewis acid to produce this deprotection with substoichiometric amounts in a sustainable and green context, not being necessary to modulate the counteranion.

In conclusion, we have developed a catalytic, general and selective method to deprotect *N*-Boc using catalytic amounts of iron(III) chloride as sustainable catalyst. The method is clean, not being necessary further chromatography purification. A DFT study, in combination with LBO method with different metals is presented and supported the importance of the electronwithdrawing in the *N*-Boc group deprotection. The iron(III) chloride is active in the unstable complex through weakening the O-C bond of the *tert*-butyl group leading to an easier decarboxylation. With this catalyst we can selective cleave the *N*-Boc group even in the presence of an *N*-Cbz group. Thus, the *N*-Boc deprotection falls into a sustainable and greener context.

Notes and references

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6   $Fe(OTf)_3$ is a strong Lewis acid that produces decomposition of the **1a** using 1 equiv. (Table 1, entry 8). However very good results with substochiometric amounts were obtained, being necessary a further chromatography (Table 1, entry 9).

7   The yields of glutamic derivatives were much better than the shorter alanine derivatives. The reaction crude only shows the final deprotected amine.

8   With *N*-Ts,Cbz dimethyl ester of aspartic acid, the deprotection of Cbz group took place in 70% yield. The reaction is slower lasting 12 h and using the combination $FeCl_3$/TMSCl.

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EWG = Boc, Cbz, Ac, Ts, Ns and Ms