Iron-catalyzed dehydrogenative phosphonation of *N*,*N*-dimethylanilines†

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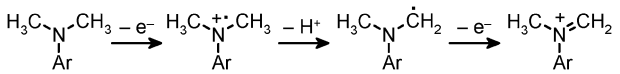
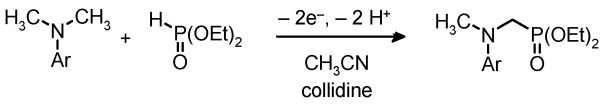
Iron(II) and iron(III) salts catalyze the oxidative α-phosphonation of *N*,*N*-dimethylanilines with dialkyl H-phosphonates in the presence of *tert*-butylhydroperoxide.

α-Aminophosphonates and related α-aminophosphonic acids are important mimics for structurally analogous α-amino-carboxylic acids in which the planar carboxylic group is replaced by a sterically more demanding tetrahedral phosphonic acid moiety.[1,2] Furthermore, α-aminophosphonates and the corresponding phosphonopeptides possess useful biological activity[2–5] and have been studied, for example, as protease[2,3] and human collagenase inhibitors,[2] catalytic antibodies,[2,6] neuroactive compounds,[2] agrochemicals,[2] antibacterial,[7] antimicrobial,[8] antifungal,[9] anticancer,[5] and antithrombotic agents.[2] The Kabachnik–Fields and the Pudovik reaction which rely on reactions of dialkyl H-phosphonates[5] with iminium or imine species, respectively, are generally applicable for the synthesis of differently substituted α-aminophosphonates.[10] The unbroken interest in both types of reactions is reflected by continuous methodological advancements[11] which include microwave-assisted transformations[12] as well as stereoselective[13] and metal-catalyzed or organocatalytic enantioselective syntheses.[14,15]

On the other hand, only few syntheses of α-aminophosphonates from tertiary amines have been reported. Electrochemical activation of ring-substituted *N*,*N*-dimethylanilines has previously been studied,[16] but only moderate yields (<30% at rt, in MeCN) of α-phosphonated products were obtained with P-nucleophiles.[17] Nevertheless, the work by Geniès *et al*. showed that during anodic oxidation of mixtures of diethyl phosphonate and *N*,*N*-dimethyl-*p*-toluidine (**1**) only the latter was oxidized to generate nitrogen-centered radical cations which, after proton loss, underwent a second one-electron oxidation (Scheme 1).[17a,b] The intermediate iminium ions were sufficiently reactive to be intercepted by the diethyl phosphonate that survived the oxidative reaction conditions. Hence, products were formed with a new C–P bond in place of the C(sp^3)–H and H–P bonds in the reagents (Scheme 2).[17a,b]



Scheme 1 Generation of iminium ions through anodic oxidation of tertiary amines.[17a,b]



Scheme 2 Electrochemical cross-coupling of tertiary amines with diethyl H-phosphonate (supporting electrolyte: collidine–H^+ ClO_4^-).[17a,b]

These observations prompted us to investigate whether an iron-catalyzed oxidative cross coupling[18–20] could be used for the selective transformation of a C–H bond[21] of the *N*-methyl group of an aromatic tertiary amine into a C–P bond. To the best of our knowledge, such a metal-catalyzed oxidative activation of C(sp^3)–H bonds with subsequent formation of a new C–P bond had been unknown at the time when we started our work.

Very recently, Baslé and Li reported an aerobic CuBr-catalyzed phosphonation of the benzylic position in *N*-aryl tetrahydroisoquinolines (MeOH, 60 °C) with dialkyl H-phosphonates[22] as a novel application of the very versatile cross-dehydrogenative-coupling (CDC) method.[23]

Herein, we report on the synthesis of α-aminophosphonates by selective oxidation of *N*,*N*-dimethylanilines in the presence of iron salts as catalysts and dialkyl H-phosphonates.

We started our studies by exploring potential catalyst systems for the oxidative phosphonation of *N*,*N*-dimethyl-*p*-toluidine (**1**) with diethyl phosphonate at room temperature in the presence of different iron salts and varied the solvent[24] and the oxidant (Table 1).

Methanol was the best solvent for the $FeCl_2$-catalyzed phosphonation of the *N*-methyl group in **1** with diethyl phosphonate in the presence of *tert*-butylhydroperoxide (entry 1, Table 1).[24] This result agrees with our previous observations for the $FeCl_2$-catalyzed α-cyanation of **1** and other tertiary amines with *tert*-butylhydroperoxide and trimethylsilyl cyanide.[20] Analogously, Baslé and Li reported the aerobic CuBr-catalyzed phosphonation of *N*-aryl-tetrahydroisoquinolines to be most efficient in methanol.[22,25]

Further iron salts were also investigated as catalysts.[26] Significantly lower yields of **2** were obtained when $FeCl_2$ was replaced by FeF_2, $Fe(OAc)_2$, or $Fe(ClO_4)_2$ (entries 2–4, Table 1). On the other hand, the iron(III) salts $FeBr_3$ or $FeCl_3$ proved to be comparably active (entries 5 and 6, Table 1) as $FeCl_2$.

Only trace amounts of phosphonation product **2** could be isolated when the reaction was performed either without catalyst (entry 7, Table 1), under conditions similar to those described by Baslé and Li[22] [$HP(O)(OEt)_2$ (2 equiv.), O_2 (1 atm), 10 mol% CuBr, MeOH, 60 °C, 24 h], or in the

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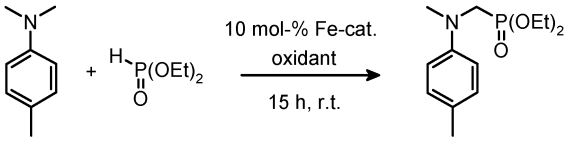
Table 1 Optimization of the catalyst[a]



1 **2**

	Catalyst	Oxidant	Yield[b] (%)
1	**$FeCl_2$**	***tert*-BuOOH**	**84**
2	FeF_2	*tert*-BuOOH	43
3	$Fe(OAc)_2$	*tert*-BuOOH	19
4	$Fe(ClO_4)_2 \cdot H_2O$	*tert*-BuOOH	55
5	$FeBr_3$	*tert*-BuOOH	66
6	$FeCl_3$	*tert*-BuOOH	76
7	None	*tert*-BuOOH	Trace
8	$FeCl_2$	$(tert\text{-}BuO)_2$	Trace
9	$FeCl_2$	Benzoyl peroxide	37
10	$FeCl_2$	Cumylhydroperoxide	27
11	$FeCl_2$	O_2 (1 atm)	61[c]

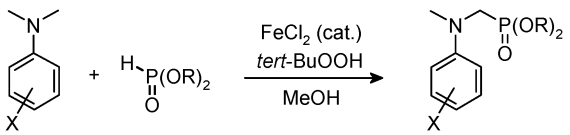
[a] Reaction conditions: *N*,*N*-dimethyl-*p*-toluidine (1.0 mmol), diethyl H-phosphonate (2.0 mmol), peroxide (2.5 mmol), and methanol (2.0 mL), dry N_2 atmosphere. [b] Yield of isolated product after column chromatography on silica gel. [c] Extended reaction time: 36 h.

presence of di-*tert*-butylperoxide as oxidant instead of *tert*-butylhydroperoxide (entry 8, Table 1). The use of other peroxides gave moderate yields of **2** (entries 9 and 10, Table 1). With dioxygen as oxidant, however, a promising level of the phosphonation of **1** was achieved at extended reaction time (entry 11, Table 1).

The substrate variability of the $FeCl_2$-catalyzed oxidative phosphonation was then investigated by combining different dialkyl phosphonates with different ring-substituted *N*,*N*-dimethylanilines (Table 2).

Di-isopropyl phosphonate (entry 6 in Table 2) was found to be a comparably reactive phosphonation reagent towards

Table 2 $FeCl_2$-catalyzed oxidative phosphonation of X-substituted *N*,*N*-dimethylanilines with dialkyl H-phosphonates[a]



Entry	X	$FeCl_2$/mol%	R	*t*/h	*T*/°C	Yield[b] (%)
1	*p*-OMe	15	Me	36	rt	77
2	—	15	Et	18	rt	83
3	—	15	*i*-Pr	18	rt	80
4	*p*-Me	10	Me	24	rt	78
5	—	10	Et	15	rt	84
6	—	10	*i*-Pr	15	rt	74
7	H	20	Et	14	rt	71
8	*p*-Br	15	Me	24	60	84
9	—	15	Et	24	rt	80
10	—	15	*i*-Pr	24	60	68
11	*m*-NO_2	30	Et	36	Reflux	57

[a] Reaction conditions: amine (1.0 mmol), iron(II) chloride (0.1–0.3 mmol), dialkyl H-phosphonate (2.0 mmol), methanol (2.0 mL), and *tert*-butylhydroperoxide (2.5 mmol), dry N_2 atmosphere. [b] Yields of isolated products after column chromatography on silica gel (for the characterization of new compounds, see the ESI†).

N,*N*-dimethyl-*p*-toluidine (**1**) as diethyl phosphonate. The position adjacent to nitrogen in **1** was also efficiently phosphonated with dimethyl phosphonate, though this reaction required longer reaction times than the corresponding transformations with the diethyl or di-isopropyl derivatives (entries 4–6). This behavior was observed also for reactions with further tertiary amines (entries 1–3), however, the differences were so small (entries 8–10) that a conclusive reactivity order for the three dialkyl H-phosphonates used in this work could not be derived from the results summarized in Table 2.

N,*N*-Dimethylanisidine could be α-phosphonated in good yields at room temperature (entries 1–3) when the amount of catalyst was slightly increased. The products are valuable synthetic intermediates because they contain two different, easily removable groups, the *p*-methoxyphenyl and the alkyl substituents of the phosphonic ester moiety,[15b] and can, therefore, be stripped down to the phosphonic acid analogue of *N*-methyl glycine.

The unsubstituted *N*,*N*-dimethylaniline was efficiently converted at room temperature (entry 7) in the presence of 20 mol% $FeCl_2$. Under similar reaction conditions, *N*-phenylpyrrolidine[27] and *N*-phenyl-1,2,3,4-tetrahydroisoquinoline[28] were found to be poor substrates for the phosphonation.

Nevertheless, even *N*,*N*-dimethylaniline derivatives that carried electron-withdrawing substituents (entries 8–11) could be converted successfully at elevated reaction temperature. For the *m*-nitro derivative a moderate yield was obtained with the most reactive dialkyl phosphonate in the presence of 30 mol% catalyst under reflux conditions (entry 11).

Because many different iron species are conceivable[18c] that might be involved in the phosphonation reaction presented in this work, we do not want to speculate about the mechanism at this point of our studies. Detailed mechanistic studies will be the subject of future investigations.

In summary, within short time two different approaches for metal-catalyzed oxidative α-phosphonations of tertiary amines have been reported that use the concept of $C(sp^3)$–H activation with subsequent C–P bond formation. The scope of the aerobic copper(I)-catalyzed version by Li[22] and the substrate variability of the iron-catalyzed system with *tert*-butylhydroperoxide as oxidant described in this work complement each other and add a new method to the synthetic tool kit of chemists which allows for the formation of new C–P bonds at unfunctionalized starting materials.

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27 After 24 h at 60 °C residual *N*-phenylpyrrolidine and only 21% of the corresponding α-phosphonation product were detected by GC-MS.
28 We observed the quantitative consumption of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (24 h, rt). However, a complex product mixture was obtained, and we could not isolate the corresponding α-aminophosphonate from the reaction of the amine with $HP(O)(OEt)_2$.