

# TiCl<sub>3</sub>/PhN<sub>2</sub><sup>+</sup>-mediated radical addition of ethers to aldimines generated in situ under aqueous conditions

Angelo Clerici,<sup>a</sup> Rosalba Cannella,<sup>a</sup> Walter Panzeri,<sup>b</sup> Nadia Pastori,<sup>a</sup>  
Eva Regolini<sup>a</sup> and Ombretta Porta<sup>a,\*</sup>

<sup>a</sup>*Dipartimento di Chimica, Materiali e Ingegneria Chimica 'Giulio Natta', Politecnico di Milano, Sezione Chimica, Via Mancinelli 7, 20131 Milano, Italy*

<sup>b</sup>*CNR Istituto di Chimica del Riconoscimento Molecolare, Sezione 'A. Quilico', Via Mancinelli 7, 20131 Milano, Italy*

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**Abstract**—Ti(III)-mediated one-electron reduction of phenyldiazonium cation, followed by phenyl radical  $\alpha$ -H atom abstraction from ethers, leads to one-pot radical addition of ethers to the C-atom of imines generated in situ from the corresponding aldehydes and imines under aqueous conditions. The reaction is not limited to aromatic aldehydes and may be applied to imines generated in situ from formaldehyde and enolizable aldehydes.

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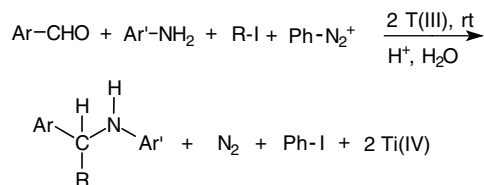
Intermolecular nucleophilic carbon radical addition to the C=N double bond of imines is a powerful method for the formation of C–C bonds, providing many advantages over the corresponding ionic chemistry,<sup>1</sup> which suffers some limitations associated with the strong basicity of the organometallic reagents usually employed.

The intramolecular radical addition to C=N bonds has been extensively investigated since 1980, however, the intermolecular version of the reaction has received significant attention by many research groups only in recent years.<sup>2,3</sup> So far, studies involving the reductive radical addition to simple aldimines are few in comparison to those dealing with various C=N containing functional groups, such as oxime ethers, glyoxylic oxime ethers, *N*-sulfonylimines, hydrazones and nitrones.<sup>2,3</sup> Simple aldimines are more prone to hydrolysis and, more importantly, have a slower radical addition rate than the former substrates,<sup>4</sup> due to the poor electrophilicity of the C=N bond. Imines also lack the potential for a stabilizing three-electron  $\pi$ -bond in the intermediate aminyl radical, as it occurs with oxime ethers and hydrazones.<sup>4</sup> However, the basic nitrogen of the C=N

bond offers a site for Lewis acid-complexation that will enhance the imine reactivity towards nucleophilic radicals.<sup>3d</sup> Naito and co-workers<sup>2b</sup> have adopted this approach to promote the BF<sub>3</sub> catalyzed radical addition to oxime ethers.

We recently reported<sup>5</sup> that under aqueous acidic conditions, Ti(IV) activates simple aldimines towards alkyl radical addition, via N-complexation;<sup>6</sup> this one-pot reaction (Scheme 1) involves an efficient iodine-atom transfer from alkyl iodides to phenyl radicals, arising from Ti(III) one-electron reduction of phenyldiazonium cations.

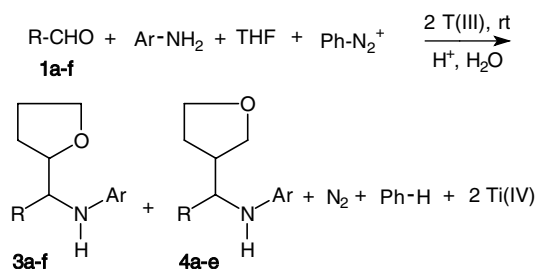
While investigating further this type of reaction, we found that, in the presence of THF as a solvent, phenyl radical promotes the addition of THF to the carbon atom of imines, leading to adducts **3** and **4** (3/4, 90:10) in a one-pot three-component reaction (Scheme 2).



Scheme 1.

**Keywords:** Titanium trichloride; One-electron reduction; Radical addition; Aldimines; Three-component reaction.

\* Corresponding author. Tel.: +39 02 2399 3063; fax: +39 02 2399 3180; e-mail: [ombretta.porta@polimi.it](mailto:ombretta.porta@polimi.it)



Scheme 2.

Tomioka and co-workers<sup>7</sup> have recently shown in a series of interesting papers that the methyl radical, generated from dimethylzinc/O<sub>2</sub>, abstracts an  $\alpha$ -H atom of ethers to generate  $\alpha$ -ethereal radicals, which add to tosylimines<sup>7a</sup> and imines.<sup>7b</sup> However, under Tomioka's oxidative conditions, phenyl radicals, arising from either diphenylzinc or benzoyl peroxide, are not operative in promoting radical addition of ethers to imines.<sup>7a</sup> Considering that (a) abstraction of an  $\alpha$ -H atom from THF by the phenyl radical has an absolute rate constant ( $4.8 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ )<sup>8</sup> about three orders of magnitude higher than that of C–H atom abstraction by methyl radical ( $10^2$ – $10^3 \text{ M}^{-1} \text{ s}^{-1}$ )<sup>9</sup> and that (b) aliphatic C–H bonds (CH<sub>3</sub>–H, BDE = 439 kJ mol<sup>−1</sup>)<sup>10</sup> are weaker than aromatic C–H bonds (Ph–H, BDE = 472 kJ mol<sup>−1</sup>),<sup>10</sup> a phenyl radical should abstract an H-atom from THF ( $\alpha$ -H–C, BDE = 385 kJ mol<sup>−1</sup>)<sup>10</sup> in a faster and more exothermic process than methyl radical.

We report here our preliminary results showing that, under reductive conditions, the phenyl radical does indeed promote the radical addition of ethers (THF, 1,4-dioxane and Et<sub>2</sub>O) to imines formed in situ and, notwithstanding the aqueous medium, the reaction is applicable even to formalimine and to imines of enolizable aliphatic aldehydes.

In planning the synthesis, we started first with a favorable equilibrium of imine formation by selecting 4-bromobenzaldehyde **1a** and *p*-methoxyphenyl(PMP)-amine **2** as reactive partners. Additionally, *p*-anisidine imines have the advantage that the resulting PMP-protected amines could be readily converted into the more versatile primary amines by CAN-oxidative removal of the N-PMP group.<sup>11</sup>

The reaction depicted in Scheme 2 smoothly occurs at room temperature by adding, portionwise over 3 h, the phenyldiazonium fluoroborate (4 mmol) to a homogeneous solution containing **1a** (2 mmol), **2** (3 mmol) and aqueous TiCl<sub>3</sub> (7 mmol, ca. 7 mL of a 15% commercially solution) in 10 mL of glacial CH<sub>3</sub>COOH and 10 mL of THF. After work up, **3a** was obtained in 62% isolated yield (Table 1, entry 3) as a 1:1 mixture of diastereomers; the minor  $\beta$ -THF adduct **4a** (**3a/4a**, 90:10) was not isolated and its structure was deduced by GC–MS analysis of the crude reaction mixture.

The competitive phenylation of the imine<sup>12</sup> was less than 5% (GC–MS analysis) and slow addition of the diazo-

**Table 1.** Radical addition of THF to an equilibrium mixture of **1a** and PMPNH<sub>2</sub> under different conditions

Entry	<b>2/1a</b> Molar ratio	PhN <sub>2</sub> <sup>+</sup> (equiv)	Ti(III) (equiv)	<b>3a+4a</b> Yield <sup>a</sup> (%)	<b>3a:4a</b> <sup>b</sup>
1	1.5	1.0	1.5	25	82:18
2	1.5	1.5	3.0	57	87:13
3	1.5	2.0	3.5	73 (62) <sup>c</sup>	90:10
4	3.0	2.0	3.5	85	90:10
5	1.0	2.0	3.5	55	87:13
6	— <sup>d</sup>	2.0	3.5	54	90:10

<sup>a</sup> Yields are based on the starting **1a** (2 mmol) and were determined by GC analysis with an internal standard.

<sup>b</sup> Compound **3a** is a 1:1 mixture of diastereomers; the ratio **3a/4a** was determined by GC–MS analysis.

<sup>c</sup> Isolated yield of **3a**.

<sup>d</sup> Preformed imine.

nium salt (e.g., low stationary concentration of phenyl radical) was essential to minimize side reactions involving the radical species, such as dimerization. In Table 1 are reported several approaches towards optimization of the yields obtained.<sup>13</sup>

We found that: (a) by increasing the amount of the diazonium salt (from 1 to 1.5 and 2 equiv), the yields improved from 25% to 57% and 73%, respectively (entries 1–3); (b) by using a **2/1a** molar ratio higher than the stoichiometric, the yields increased from 55% to 73% and 85%, respectively (entries 5, 3 and 4). Interestingly, comparable yields of **3a** were obtained starting from either a preformed imine or equimolar amount of **1a** and **2** (cf. entries 6 and 5). This means that the equilibrium concentration of the imine, in the aqueous co-solvent, is almost the same by using a preformed imine or an equimolar amount of **2** and **1**, but it may be increased at will by using an excess of either **1** or **2** (cf. entries 4 and 5).

With these results in hand we screened, under the conditions of entry 3, benzaldehyde **1b**, *p*-tolualdehyde **1c**, cyclohexylaldehyde **1d**, acetaldehyde **1e** and formaldehyde **1f** as reactive partners of PMPNH<sub>2</sub> and THF. The results, summarized in Table 2 (entries 1–6) show that, within experimental error, the isolated yields of **3a–f** are quite similar, indicating that the C-substituent of the imines has no influence on the imine reactivity: the polarization of the C=N bond, induced by Ti(IV)-complexation, overrides the polar effects of the substituents.

It is surprising that, under aqueous conditions, imines formed by in situ condensation of **2** with either acetaldehyde or formaldehyde afforded the desired **3e** and **3f**, respectively, (entries 5 and 6) in yields comparable to those obtained with aromatic aldehydes.

**Table 2.** Radical addition reaction of ethers to an equilibrium mixture of **1a–f** and PMPNH<sub>2</sub><sup>a</sup>

$\text{R}-\text{CH}=\text{O} + \text{H}_2\text{N}-\text{PMP} + \text{ether} \xrightarrow[\text{H}^+, \text{H}_2\text{O}, \text{rt}]{\text{PhN}_2^+, \text{Ti(III)}} \text{3a-k} + \text{4a-e}$					
Entry	R	Ether	3 Yield <sup>b</sup>	3:4 <sup>c</sup> (%)	
1	<i>p</i> -Br-C <sub>6</sub> H <sub>4</sub> <sup>d</sup>	<b>1a</b>	THF	<b>3a</b> (62)	90:10
2	C <sub>6</sub> H <sub>5</sub>	<b>1b</b>	THF	<b>3b</b> (60)	85:15
3	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>1c</b>	THF	<b>3c</b> (55)	85:15
4	Cyclohexyl <sup>e</sup>	<b>1d</b>	THF	<b>3d</b> (64)	Only <b>3d</b>
5	CH <sub>3</sub> <sup>e</sup>	<b>1e</b>	THF	<b>3e</b> (64)	86:14
6	H <sup>f</sup>	<b>1f</b>	THF	<b>3f</b> (58)+ <b>3ff</b> (7)	
7		<b>1a</b>	1,4-Dioxane	<b>3g</b> (63)	
8		<b>1b</b>	1,4-Dioxane	<b>3h</b> (65)	
9		<b>1a</b>	Et <sub>2</sub> O	<b>3i</b> (46)+ <b>3k</b> (20)	
10		<b>1b</b>	Et <sub>2</sub> O	<b>3j</b> (45)+ <b>3k</b> (20)	
11		<b>1e</b> <sup>c</sup>	Et <sub>2</sub> O	<b>3k</b> (56)	

<sup>a</sup> When not otherwise stated, the molar ratio of **1/2/PhN<sub>2</sub><sup>+</sup>/Ti(III)** is 1:1.5:2:3.5 and yields are based on the starting **1**.

<sup>b</sup> Isolated yield, dr 1:1.

<sup>c</sup> Determined by GC–MS.

<sup>d</sup> Reported by comparison from Table 1.

<sup>e</sup> Molar ratio of **1/2** is 2:1 and yields are based on the starting **2**.

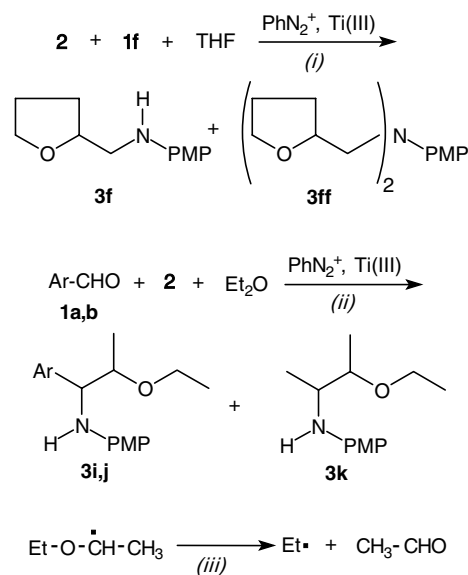
<sup>f</sup> Molar ratio of **1f/2** is 1:1.

Very likely, the successful radical addition to these rather unstable and polymerizable imines<sup>14</sup> is connected to the lack of steric hindrance at the C-atom,<sup>15</sup> which would render the radical addition faster than any side reaction involving either the CH<sub>2</sub>=N or the CH<sub>3</sub>CH=N bonds. In fact, even by using an equimolar amount of **2** and of the less hindered formaldehyde, a 7% of the tertiary amine **3ff** (Scheme 3, path i) was formed in addition to the expected **3f** (58%). The formation of **3ff** may be strongly increased by increasing the concentration of **1f** relative to **2**.

To the best of our knowledge this is the first reductive intermolecular radical addition to C=N bonds using a formaldimine for one-carbon homologation of ethers to 1,2-aminoethers.

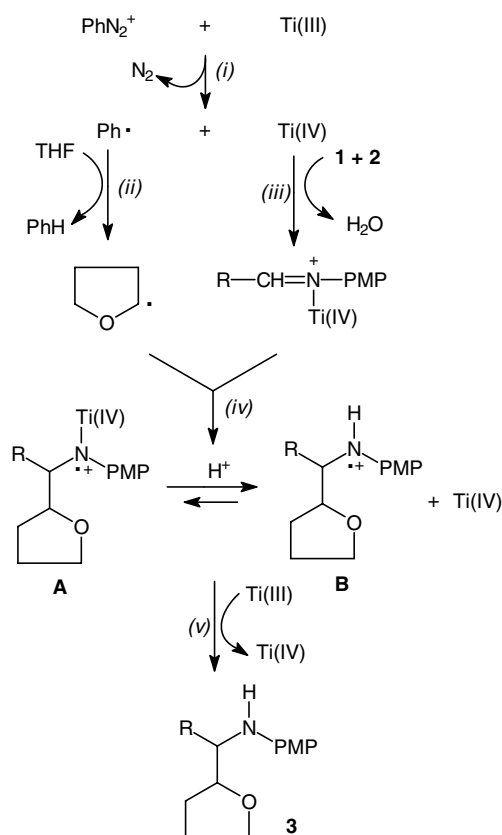
We finally made a preliminary survey on the scope of the method applying the one-pot protocol to 1,4-dioxane and diethyl ether. The reaction of **2** with either **1a** or **1b** in 1,4-dioxane, as a solvent, afforded the desired **3g** and **3h** in good isolated yield (entries 7 and 8) but in diethyl ether, as a solvent, (entries 9 and 10) adducts **3i** and **3j** were obtained in lower yield (45%) due to the concomitant formation of **3k** (20%) (Scheme 3, path ii).

We verified that **3k** is formed by Et<sub>2</sub>O radical addition to acetaldehyde–PMPNH<sub>2</sub> imine (entry 11). Thus, the formation of **3k**, in entries 9 and 10, involves that Et<sub>2</sub>O radical, resulting from selective α-H atom abstraction by phenyl radical, partially undergoes further decomposition into an ethyl radical and acetaldehyde (Scheme 3, path iii). Surprisingly, acetaldehyde com-

**Scheme 3.**

petes<sup>14</sup> with the aromatic aldehydes **1a** or **1b**, present from the beginning, in giving the reactive counterpart of Et<sub>2</sub>O radical.

The multiple role simultaneously played by Ti(III) and Ti(IV) ions in promoting the reaction is shown in Scheme 4 (THF as a solvent): (a) the one-electron

**Scheme 4.**

reduction of the phenyldiazonium cation<sup>16</sup> initiate the reaction by producing Ti(IV) and a phenyl radical (path i), which selectively abstracts an  $\alpha$ -H atom from THF (path ii) to generate an  $\alpha$ -ethereal radical;<sup>17</sup> (b) Ti(IV), owing to its high oxophilicity, would activate, through coordination, the carbonyl group toward amine condensation, favouring imine formation;<sup>18</sup> (c) Ti(IV), as a strong Lewis acid, further activates the imine toward radical addition (paths iii and iv); (d) a second equiv of Ti(III) readily reduces the resulting electrophilic aminium radical **B**,<sup>19</sup> affording the final product **3** after work up.

In summary, we have developed a promising new method for the reaction of an ether radical with imines. This radical addition procedure is convenient in terms of simplicity and generality (i.e., it is a one-pot four-component reaction applicable also to aliphatic imines difficult to isolate), as well as of reaction time. Moreover, an inexpensive readily-available reducing agent is employed which serves double duty as reductant and Lewis acid catalyst (in its higher oxidation state), and which decomposes to an environmentally sound chemical (TiO<sub>2</sub>).

Further studies on the synthetic implications of these results are under investigation in our laboratory.

### Acknowledgements

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### Supplementary data

Detailed experimental procedures and full spectra identification of products **3a–k** are provided. Supplementary data associated with this article can be found, in the on-line version, at doi:10.1016/j.tetlet.2005.09.158.

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