

## Pyrethroid insecticides. Chapter III: Synthesis of 3-phenoxymandelonitrile

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To the memory of friends and dedicated chemists: Profs Bertrand Castro (Sanofi, France), Istvan Marko (UCL, Belgium), Pierre Potier (ICSN, France), and Heinz Viehe (UCL, Belgium)

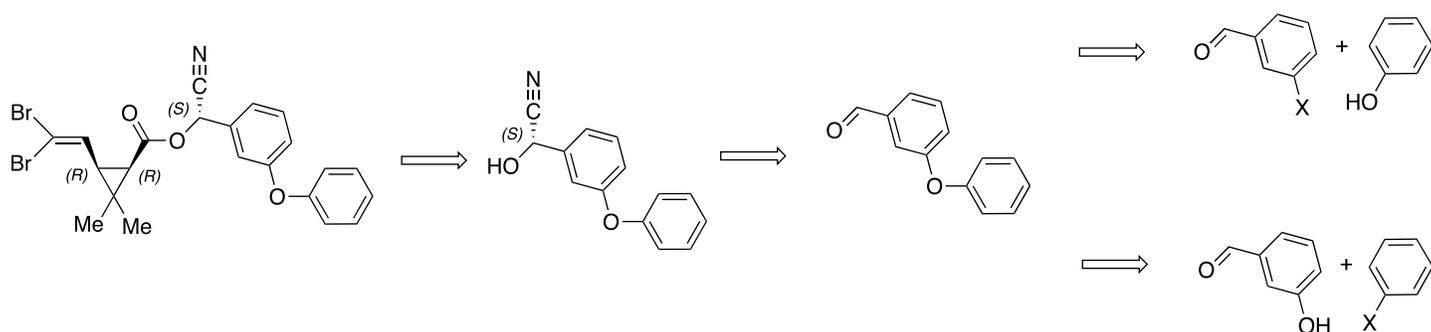
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### Abstract

Racemic and enantiopure 3-phenoxymandelonitrile are valuable building blocks for the synthesis of pyrethrin insecticides cypermethrin and deltamethrin. Their synthesis involves two crucial steps: the synthesis of 3-phenoxybenzaldehyde which is produced through ether coupling, and its hydrocyanation.



**Keywords:** 3-phenoxymandelonitrile, hydroxycyanation, Ullmann coupling, Buchwald-Hartwig coupling, diaryl ethers

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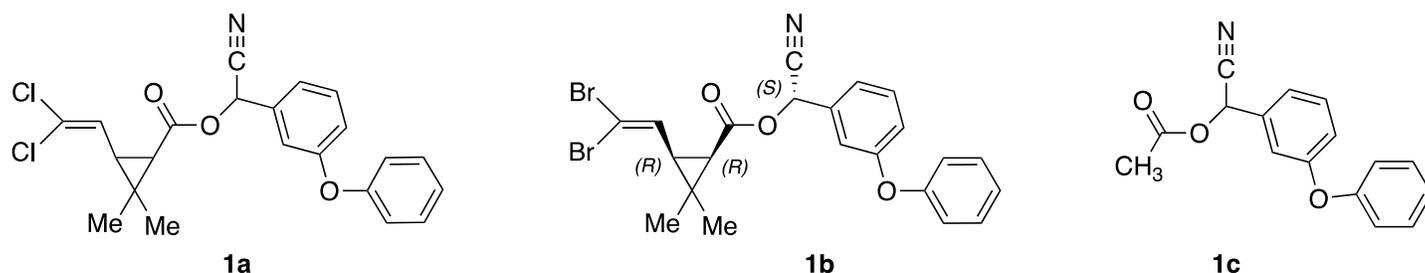
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## 1. Introduction: Retrosynthetic Routes to 3-phenoxymandelonitrile

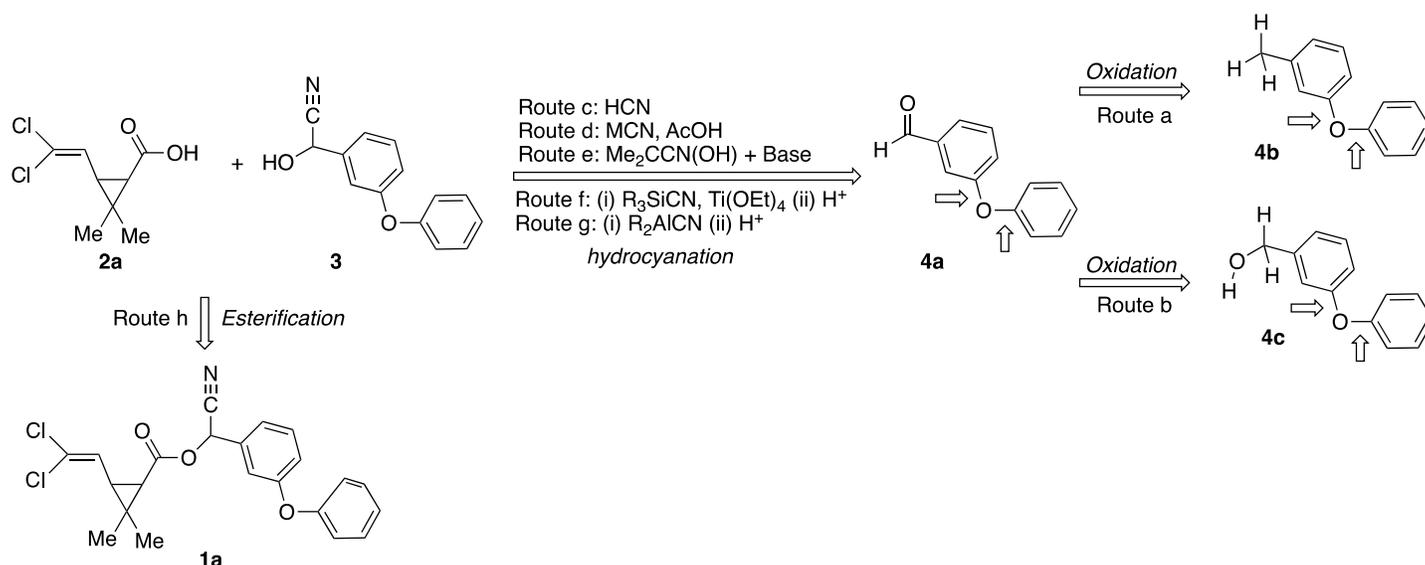
Permethrins **1a** and **1b**, the unnatural members of the pyrethroid family exhibit exceptional insecticidal properties properly adjusted for being used in agriculture (Scheme 1).<sup>1</sup> They are more active than natural pyrethrins and their half-life is sufficiently long to allow reasonable protection in a harsh environment of sunlight and rain and sufficiently short to allow consumption of unaltered fruits and vegetables, at the required time, with no trace of the insecticide. Their structures differ in many aspects from that of the natural products and

although both series possess the basic structure of cyclopropane carboxylic esters (Chapter 1)<sup>1</sup> they exhibit important differences not only in the carboxyl moiety (*cis* instead of *trans* stereochemistry, two halogens instead of two methyl groups) but also in the alkoxy moiety (3-phenoxymandelonitrile instead of rethrolone) which completely differs from that present in the natural pyrethrin. They are more active than natural pyrethrins and their half-life is sufficiently long to allow reasonable protection in a harsh environment of sunlight and rain and sufficiently short to allow consumption of fruits and vegetables, at the required time, no residual insecticide. Their structures differ in many aspects from those of the natural products and although both series possess the basic structure of cyclopropanecarboxylic esters (Chapter 1)<sup>1</sup> they exhibit important differences not only in the carboxyl moiety (*cis* instead of *trans* stereochemistry, two halogens instead of two methyl groups) but also in the alkoxy moiety (3-phenoxymandelonitrile instead of rethrolone) which completely differs from that present on the natural pyrethrin.



**Scheme 1.** Chemical structures of cypermethrin (**1a**), deltamethrin (**1b**) and acetyl 3-phenoxymandelonitrile (**1c**).

As was already pointed out in Chapter I, cypermethrin (**1a**) is a mixture of all possible stereoisomers but deltamethrin (**1b**) is a single stereoisomer. Their synthesis including the commercial ones imply the esterification of permethrinic acids (**2a**) and (1*R*,3*R*)-*cis*-**2b** with racemic (*R,S*)-**3** and enantiopure (*S*)-(**3**) 3-phenoxymandelonitrile respectively.<sup>1</sup>

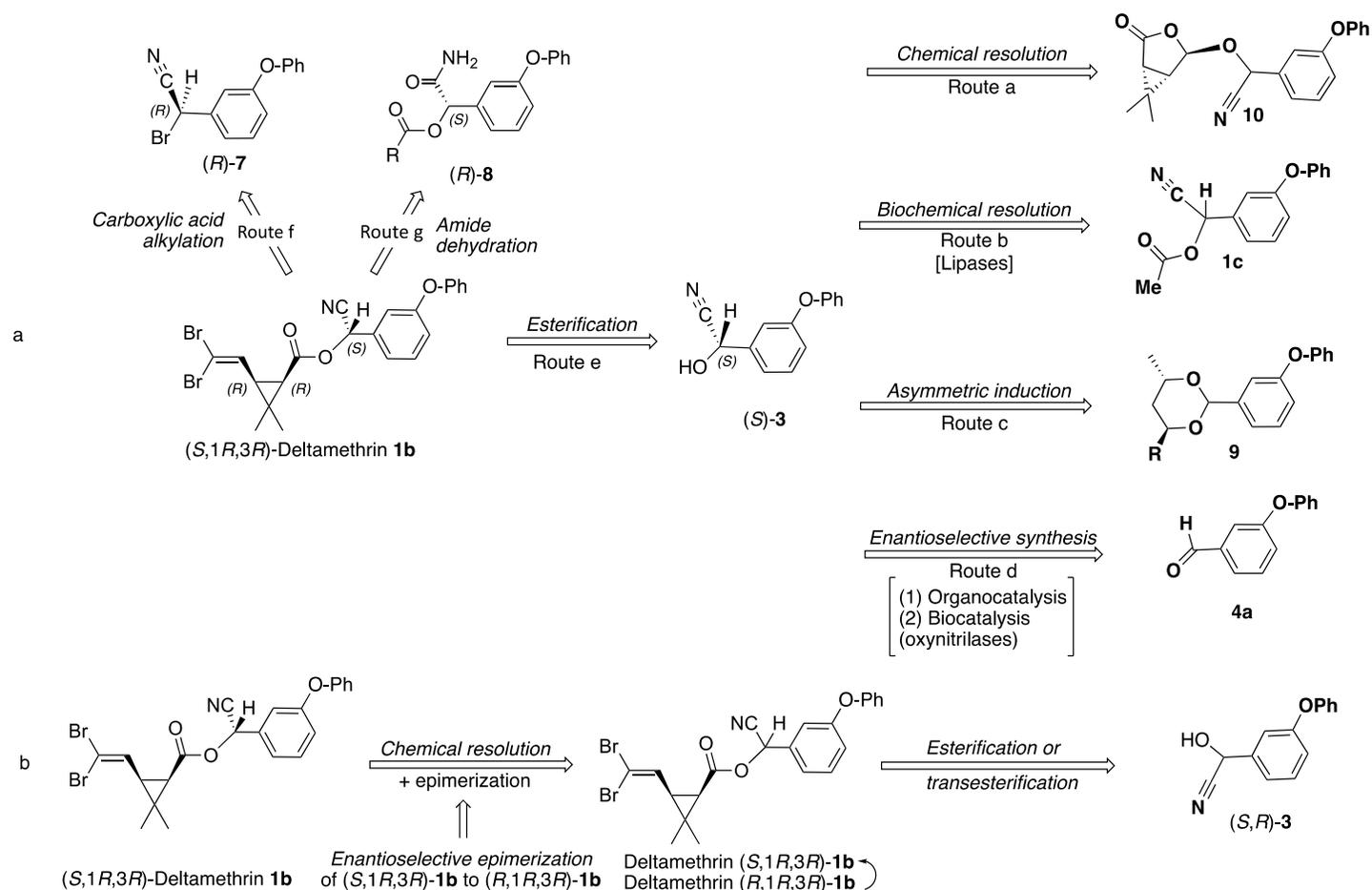


**Scheme 2.** Racemic 3-phenoxymandelonitrile (**3**): retrosynthesis and use in the synthesis of cypermethrin.

The esterification step will be reported in Chapter IV, the synthesis of 3-phenoxymandelonitrile is the subject of the present chapter. It mainly involves 3-phenoxybenzaldehyde (**4a**) as the key intermediate. The retrosynthetic analyses of racemic **1a** and enantiomerically pure **1b** that emphasize the access to the cyanohydrin from 3-phenoxybenzaldehyde are reported in Scheme 2 and in Scheme 3 respectively.

The esterification step (Scheme 2, Route h) is not a simple task since the cyanohydrin component **3** is quite labile especially if the esterification is carried out on an industrial scale. The synthesis of enantiopure (*S*,1*R*,3*R*)-**1b** bears even more complexity (Scheme 3, entry a, Routes e,f,g; entry b). Epimerization can either proceed (i) by decomposition of the cyanohydrin **3** to its constituents **4a** and cyanide in a reversible process during the esterification reaction involving the enantiopure deltamethrinic acid (1*R*,3*R*)-*cis*-(**2b**) and (*S*)-(**3**) 3-phenoxymandelonitrile or (ii) by epimerization of the resulting ester (*S*,1*R*,3*R*)-(**1b**) at its sensitive benzylic site that also bears the activating cyano group.

The propensity of deltamethrin to be epimerized under mild conditions has been purposefully used by synthesizing, as it will be discussed later in this chapter, the diastereomeric mixture of (*S*,1*R*,3*R*)-*cis*-**1b** and (*R*,1*R*,3*R*)-*cis*-**1b** from enantiopure deltamethrinic acid (1*R*,3*R*)-*cis*-**2b** and the racemic cyanohydrin (*R*,*S*)-**3** followed by a combination of epimerization at the benzylic site of deltamethrin and constant separation of the enantiopure deltamethrin (*S*,1*R*,3*R*)-*cis*-**1b** that allow complete conversion of the deltamethrin epimer (*R*,1*R*,3*R*)-*cis*-**1b** to deltamethrin (*S*,1*R*,3*R*)-*cis*-**1b** the most biologically active stereoisomer (Scheme 3, entry b).

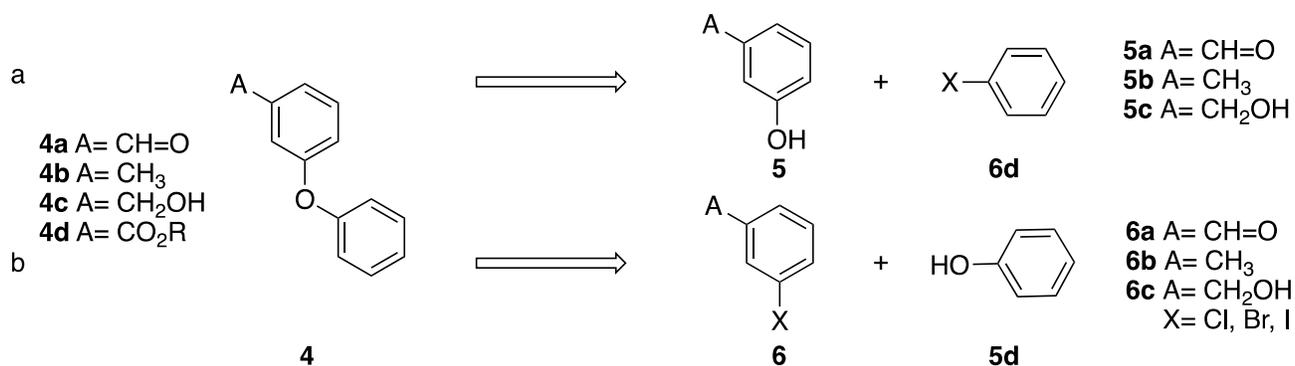


**Scheme 3.** Strategy used for the synthesis of enantiopure deltamethrin (*S*,1*R*,3*R*)-(**1b**).

3-Phenoxymandelonitrile (**3**) has been synthesized from 3-phenoxybenzaldehyde (**4**) and a large array of reagents that include hydrogen cyanide (Scheme 2, Route c) eventually prepared *in situ* by reaction of metal cyanides with acids (Scheme 2, Route d) or resulting from the base catalyzed decomposition of acetone cyanohydrin (**13a**) (transcyanation, Scheme 2, Route e), trimethylsilyl cyanide and an acid catalyst (Scheme 2, Route f) or dialkyl aluminum cyanides also in the presence of acid catalyst (Scheme 2, Route g).

The enantiopure (S)-3-phenoxymandelonitrile (S)-(**3**) has been, as expected, isolated from the racemic mixture of stable derivatives by chemical (Scheme 3, Route a) and biochemical (Reaction of lipases on the acetate, Scheme 3, Route b) methods, by asymmetric induction on prochiral precursors (Scheme 3, Route c) implying organocatalysis or biocatalysis (Scheme 3, Route d) mimicking the aptitude of nature to produce such type of compounds to protect from predators or to use an easy access to a functionalized single carbon reagent.

All approaches require 3-phenoxybenzaldehyde (**4a**) as starting material (Scheme 1). Its synthesis could (and has been) achieved by generating the diaryl ether functionality by forming any of the two C-O ether bonds. Alternative methods involve oxidation of 3-phenoxytoluene (**4b**) (Scheme 2, route a) or 3-phenoxybenzyl alcohol (**4c**), (Scheme 2, route b) and eventually reduction of 3-phenoxybenzoic acid (**4d**) as precursors. Those precursors also possess an ether functionality that generation can be achieved using the same strategy as above. The related retrosynthetic analyses are shown in Scheme 4.



**Scheme 4.** Retrosyntheses of 3-phenoxybenzaldehyde and related compounds.

The selection of the route to 3-phenoxybenzaldehyde (**4a**) depends on the availability of their precursors **5** and **6**, the availability of the method and their cost as well as their suitability to be implemented at the industrial level. In case of the intermediary synthesis of 3-phenoxytoluene (**4b**) and 3-phenoxybenzyl alcohol (**4c**) the ease and cost of their transformation to 3-phenoxybenzaldehyde (**4a**) must also be considered.

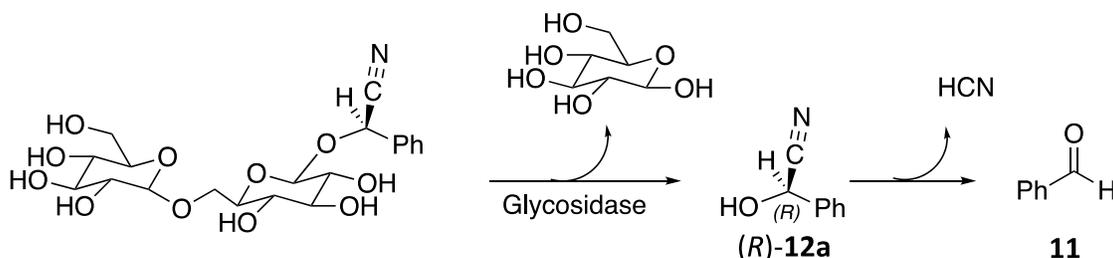
The synthesis of **3a** mainly relies on two methods: (i) the synthesis of cyanohydrins from aldehydes and more precisely from benzaldehydes especially the synthesis of enantiopure cyanohydrins<sup>2-9</sup> (ii) the synthesis of diaryl ethers by forming the O-C bond that originally involved the Ullmann reaction and related transformations that often require harsh conditions.<sup>10-14</sup> Recent publications on the mechanism of the Ullmann reaction<sup>15,16</sup> provide useful information that were not available at the time, in the mid-1970s, original industrial syntheses have been achieved. New methods of synthesis of diaryl ethers have appeared since then and we take this opportunity to include them in this presentation and to compare them with the original ones.<sup>17-20</sup>

## 2. Syntheses of Cyanohydrins from Aromatic Aldehydes

### 2.1. Generalities concerning cyanohydrins

In the mid-1960s, at the time the first industrial syntheses of cypermethrin and deltamethrin were achieved,<sup>17-20</sup> the synthetic methods to produce cyanohydrins from carbonyl compounds were quite limited although the addition of hydrogen cyanide to aldehydes was the first reaction, the mechanism of which was investigated in organic chemistry.<sup>21</sup> Lapworth demonstrated that the reaction was base catalyzed, with the role of the base being to convert hydrogen cyanide into the nucleophilic cyanide ion.<sup>22</sup> It was also reported that some higher organisms such as plants (>3000 species)<sup>4,5</sup> were able to perform cyanogenesis.<sup>4</sup> The process involved in almonds is shown in Scheme 5. It leads first to (*R*)-mandelonitrile (benzaldehyde cyanohydrin) (**12a**), a compound that possesses a skeleton close to that of the required compound **3**. (*R*)-mandelonitrile breaks down then to hydrogen cyanide and benzaldehyde (**11**) on catalysis by hydroxynitrile lyase (abbreviated to HNL; also named as oxynitrilase).<sup>5,23,24</sup>

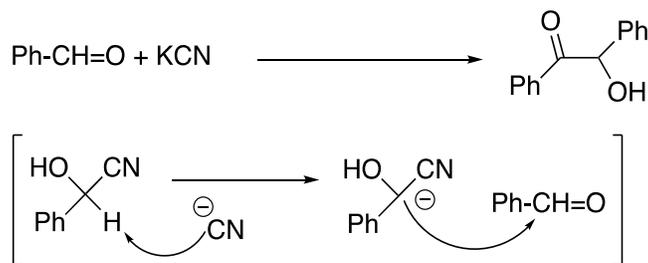
In the mid-1960s, application of these results to the synthesis of deltamethrin (*S*,1*R*,3*R*)-*cis*-(**1b**) was not conceivable since the technology was undeveloped and furthermore the outcome of this biochemical process was opposite to the one requested since it delivers a cyanohydrin possessing the inverted (*R*)-stereochemistry at its benzylic chiral center. Since then, a great deal of work has been carried out in this field, efficient protocols have been developed, valuable microorganism and enzymes identified, especially those that selectively generate the (*S*)-enantiomer of the desired cyanohydrin, and improved results have been achieved by engineering the enzymes as will be reported below (Section 2.4.3.2).



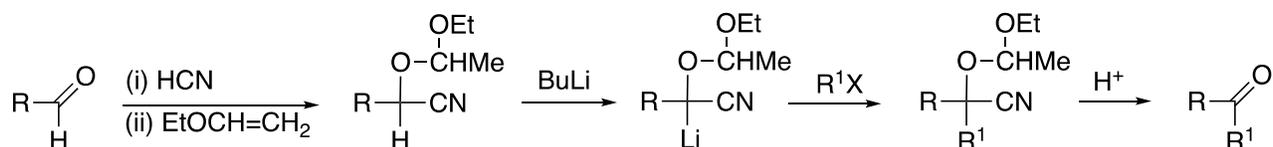
**Scheme 5.** Cyanogenesis pathway in almonds: breakdown of the cyanogenic glycoside amygdalin leading to (*R*)-mandelonitrile (**12a**), precursor of hydrogen cyanide and benzaldehyde (**11**).

Cyanohydrins are stable in acidic media but epimerize in basic media. The latter reaction involves the production of the cyanide ion and generation of the aldehyde in an equilibrated process that return to the cyanohydrin. This reaction is detrimental for enantioselective synthesis since it promotes the formation of racemic mixtures. It however offers the opportunity to synthesize cyanohydrines from aldehyde by trans-hydrocyanation from for example acetone cyanohydrin (**13a**) avoiding the use of toxic hydrogen cyanide (Scheme 6).

Epimerization also occurs by metalation at the carbon bearing the cyano and the hydroxyl group or protected hydroxyl group (alkoxy, acetoxy and silyloxy), especially if this site is benzylic as in the case in our concern. This is reminiscent of the benzoin condensation reaction (Scheme 6)<sup>22</sup> and the Stork acylation equivalent reaction (Scheme 7)<sup>25</sup> and related reactions.<sup>3</sup>



**Scheme 6.** Benzoin condensation and proposed mechanism.



**Scheme 7.** Stork "acyl anion equivalent" reaction and synthesis of ketones from aldehydes.

## 2.2. Syntheses of racemic mandelonitrile and protected species from benzaldehyde as models for the synthesis of racemic 3-phenoxymandelonitrile

Cyanohydrins have been synthesized from aldehydes and ketones using a large variety of reagents and conditions. Most of these reactions have been carried out on benzaldehyde. We have collected them as model for the reactivity of the closely related 4-phenoxybenzaldehyde (**3**).

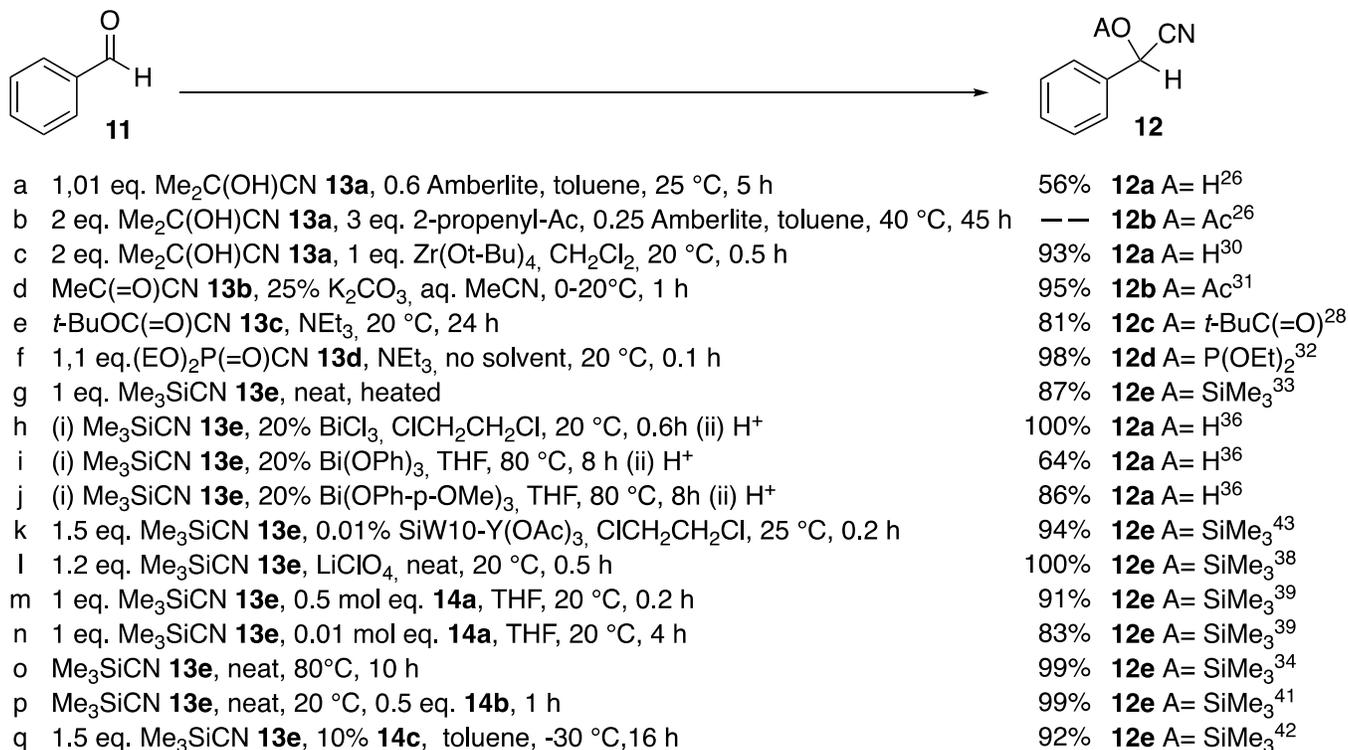
Hydrogen cyanide (HCN) is not reactive enough towards carbonyl compounds and requires base catalysis to add reversibly.<sup>2-10</sup> Alternatively, metal cyanides (sodium or potassium) can be used but in the presence of acetic acid.<sup>2-10</sup>

Acetone cyanohydrin (**13a**) also reacts with aldehydes allowing under suitable catalysis, their transhydroxycyanation (Scheme 8, entries a-c).<sup>26</sup> This reagent offers the advantage to be easily handled and to release HCN slowly in toluene in the presence of an ion exchange resin such as Amberlite (Amberlite type IRA 904, hydroxide involvement). Accordingly, benzaldehyde has been transformed to racemic mandelonitrile (Scheme 8, entries a,b).<sup>26</sup> Careful investigation of the process shows that: (i) the equilibrium involving acetone cyanohydrin and benzaldehyde is slowly reached after five hours [hydroxide (0.025 eq.), benzaldehyde (**11**) (1 eq.), acetone cyanohydrin (**13a**) (1.2 eq.), dry toluene, 25 °C resulting in a mixture of: benzaldehyde (**11**) (43%), mandelonitrile **12a** (55%); acetone (82%), acetone cyanohydrin (**13a**) (17%)]<sup>26</sup> and (ii) racemization of *R*-mandelonitrile takes about 1 h under closely related conditions (toluene, 40°C).<sup>26</sup>

Those features have been used purposefully, to produce a single enantiomer of mandelonitrile **12a**<sup>26</sup> and related aromatic aldehydes,<sup>27</sup> by performing the transhydroxycyanation reaction on benzaldehyde (**11**) in the presence of a lipase and isopropenyl acetate.<sup>26,27</sup> It takes advantage of the observations that isopropenyl acetate is able, in the presence of a lipase, to transform mandelonitrile to its acetate but is unable to do so on acetone cyanohydrin (**13a**) due to steric hindrance. Acetylcyanation offers the advantage to shift the equilibrium and to get the cyanoacetate **12b** which is stable against dehydrocyanation. This however requires the inclusion of a deacetylation step to recover the requested cyanohydrin that is not an easy task as it will be reported below (Scheme 16).

The synthesis of acetyl mandelonitrile (**12b**), as a racemate, has been also achieved from benzaldehyde, acetone cyanohydrin (**13a**) and isopropenyl acetate in modest yield (49 %) using Cp\*<sub>2</sub>Sm(thf)<sub>2</sub> as a chemical catalyst.<sup>29</sup>

Several other conditions and catalysts have been successfully used to perform the cyanation of benzaldehyde. For example, it has been reported that zirconium(IV) *t*-butoxide favors the transhydroxycyanation of benzaldehyde (**11**) from acetone cyanohydrin (**13a**) (Scheme 8, entry c).<sup>30</sup> Otherwise acetoxy nitriles can be synthesized directly from the benzaldehyde and acetyl cyanide **13b** in the presence of potassium carbonate (Scheme 8, entry d).<sup>31</sup>

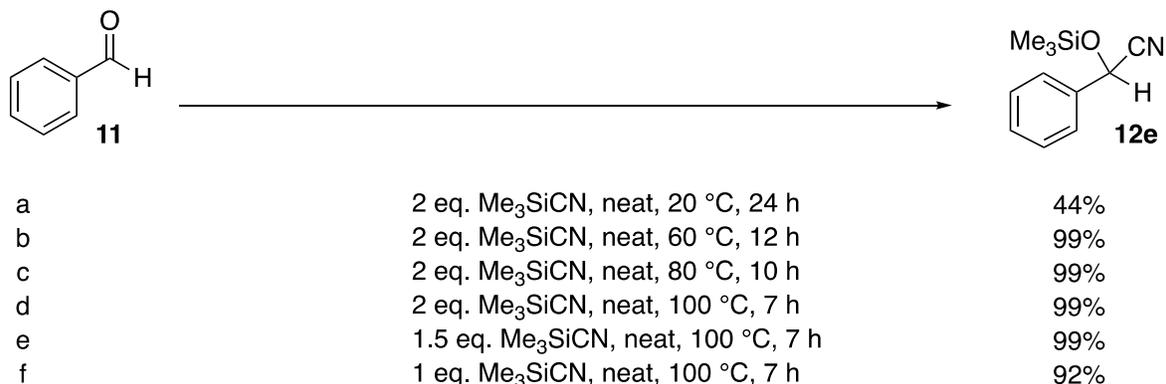


**Scheme 8.** Synthesis of mandelonitrile and O-protected forms from benzaldehyde.<sup>26,28,30-34,36,38,39,41-43</sup>

Similarly, *t*-butyl cyanofornate (**13c**) reacts with benzaldehyde (**11**) to provide *t*-butyloxocarbonyl mandelonitrile **12c** through triethylamine catalysis (Scheme 8, entry e),<sup>28</sup> and diethyl cyanophosphonate (**13d**) reacts with (**11**) extremely rapidly at room temperature (0.1h) in the presence of triethylamine (10%, neat) to produce the diethyl phosphonate **12d** in almost quantitative yield (Scheme 8, entry f).<sup>32</sup>

Trimethylsilylcyanide (TMSCN) (**13e**) is by far the most efficient reagent for the addition of a cyano group to aldehydes and ketones as well. The reaction was originally carried out by heating the two reactants in neat form for several hours (Scheme 8, entry g) and related conditions are listed in Scheme 9.<sup>33,34</sup>

It has been suggested<sup>33</sup> that replacing a proton in HCN for silicon in Me<sub>3</sub>SiCN (**13e**) favors the cyanation of benzaldehyde (**11**) by *ca.* 20 kcal mol<sup>-1</sup>. Furthermore, the stability of the TMS adduct **12e**, conferred by an energetically favorable Si-O bond, (i) prevents the reverse cyanation reaction from occurring and hence removes a potential pathway for racemization for enantiopure compounds (ii) offers an easy synthesis and recovery of the related cyanohydrin **12a** by desilylation on hydrolysis (1 N HCl, rt, 6 h) that occurs with complete stereocontrol.<sup>35</sup>



**Scheme 9.** Synthesis of trimethylsilyl mandelonitrile from benzaldehyde and trimethylsilyl cyanide.<sup>33</sup>

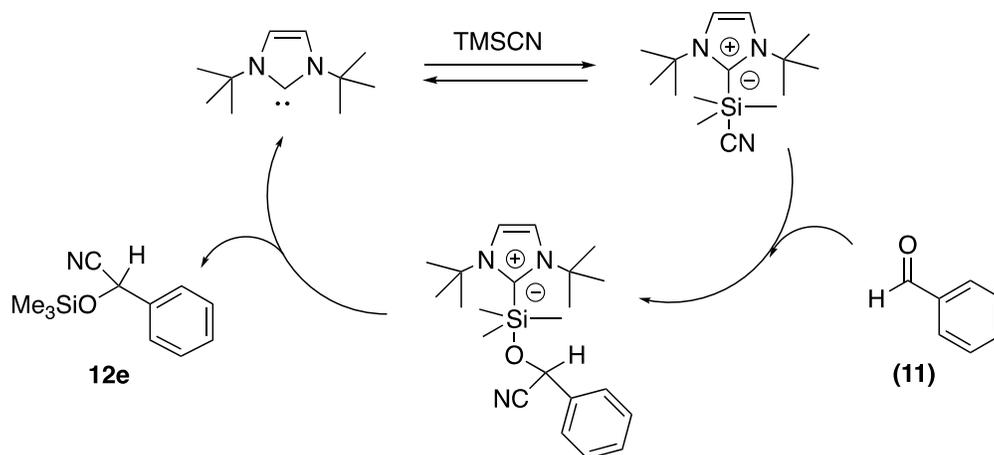
Careful investigation of the process shows that the reaction already occurs at room temperature, is best achieved around 100 °C with 1.5 equivalent of trimethylsilyl cyanide (Scheme 9) and does not suffer from limitations often reported in catalyzed reactions.<sup>34</sup> It has been also reported that it proceeds more rapidly and at much lower temperature when carried out in the presence acidic or basic catalysts including Lewis acids and Lewis bases.<sup>33</sup>

Acid catalysts that have been successfully used involves zinc iodide,<sup>33</sup> aluminium trichloride<sup>33</sup> in chlorinated solvents such as chloroform, and dichloromethane, benzene or toluene,<sup>33</sup> bismuth trichloride in dichloroethane (Scheme 8, entries h)<sup>36</sup> and triarylbismuth derivatives in THF (Scheme 8, entries i,j).<sup>36</sup>

Basic/nucleophilic catalysts such as potassium cyanide-18-crown-6 complex,<sup>33</sup> or amines (tertiary amines such as triethylamine, TMEDA, secondary amines such as diisopropylamine and 2,2,6,6-tetramethyl piperidine,<sup>37</sup> tributylphosphine,<sup>37</sup> triphenylarsine<sup>37</sup> and triphenylantimony,<sup>37</sup> have successfully been used as catalysts for cyanation of several aldehydes but have not apparently been used on benzaldehyde.

Yttrium-pillared silicotungstate dimer [SiW10-Y(OAc)<sub>3</sub>], a member of the family of polyoxometalates (POMs), (Scheme 8, entry k) efficiently catalyzes the silylcyanation of benzaldehyde (**11**) (TON 9400, TOF 37 6000 h<sup>-1</sup>).<sup>43</sup>

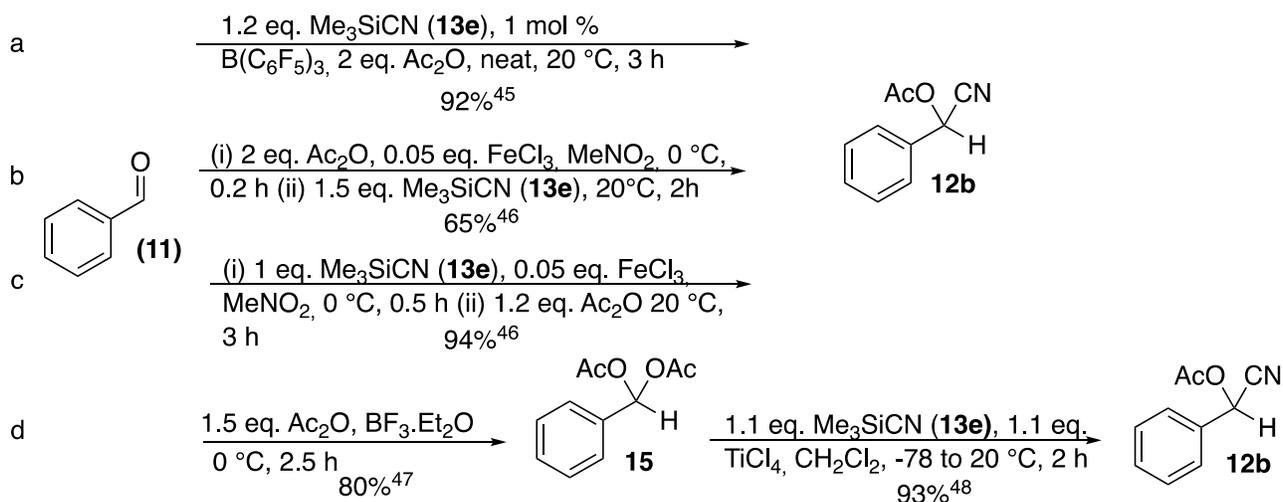
Other reactions have been successfully carried out using lithium perchlorate (Scheme 8, entry l),<sup>38</sup> or N-heterocyclic carbenes in dichloromethane as well as in acetonitrile (Scheme 8, entries m,n).<sup>39,40</sup> The mechanism of the latter process is reported in Scheme 10.<sup>39,40</sup>



**Scheme 10.** Proposed mechanism for the cyanosilylation of benzaldehyde by activation of TMSCN by N-heterocyclic carbenes.<sup>39,40</sup>

Aluminum monohydride complex [LiAlH(OTf)] (**14b**) catalyzes at 20 °C the reaction of TMSCN (**13e**) with benzaldehyde (**11**) and gives an almost quantitative yield of **12e** within 1 h with 0.5 mol % loading of the catalyst (Scheme 8, entry p).<sup>41</sup> It takes longer time (5 h) when loading of the catalyst is reduced to 0.1 mol %.<sup>41</sup> This is also the case for bifunctional thiourea (**14c**)–Brønsted acid copperative catalytic system that works efficiently at -30 °C even with no more than 10% catalyst loading to provide trimethylsilyl mandelonitrile (**12e**) in very good yield (Scheme 8, entry q).<sup>42</sup> Finally, the ionic liquid [bmim]BF<sub>4</sub> has been demonstrated to be an efficient and environmentally friendly reaction medium as well as reaction promoter for the synthesis of *O*-acetyl cyanohydrin from an aldehyde, TMSCN (**13e**), and acetic anhydride.<sup>44</sup> Not only does it not require the use of Lewis acid or any special activation but also the recovered ionic liquid could be reused for subsequent runs without loss of its activity.<sup>44</sup>

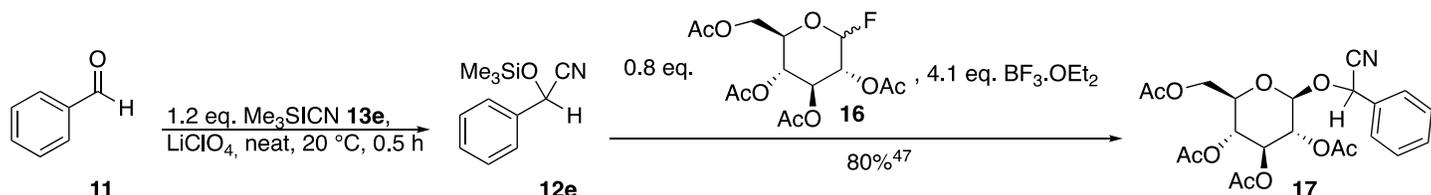
Several catalysts have been used to promote the synthesis  $\alpha$ -acetoxybenzonnitrile from benzaldehyde (**11**) and TMSCN (**13e**) (Scheme 11) and the reaction has been extended to a large panel of aldehydes. Best results have been obtained on reacting, neat, a mixture of benzaldehyde (**11**), trimethylsilyl cyanide (**13e**), acetic anhydride, and 1% tris(pentafluorophenyl)borane as an efficient Lewis acid catalyst stable to air and humidity (Scheme 11, entry a).<sup>45</sup>



**Scheme 11.** Synthesis of acetylmandelonitrile and 1,1-diacetoxytoluene from benzaldehyde.<sup>45-48</sup>

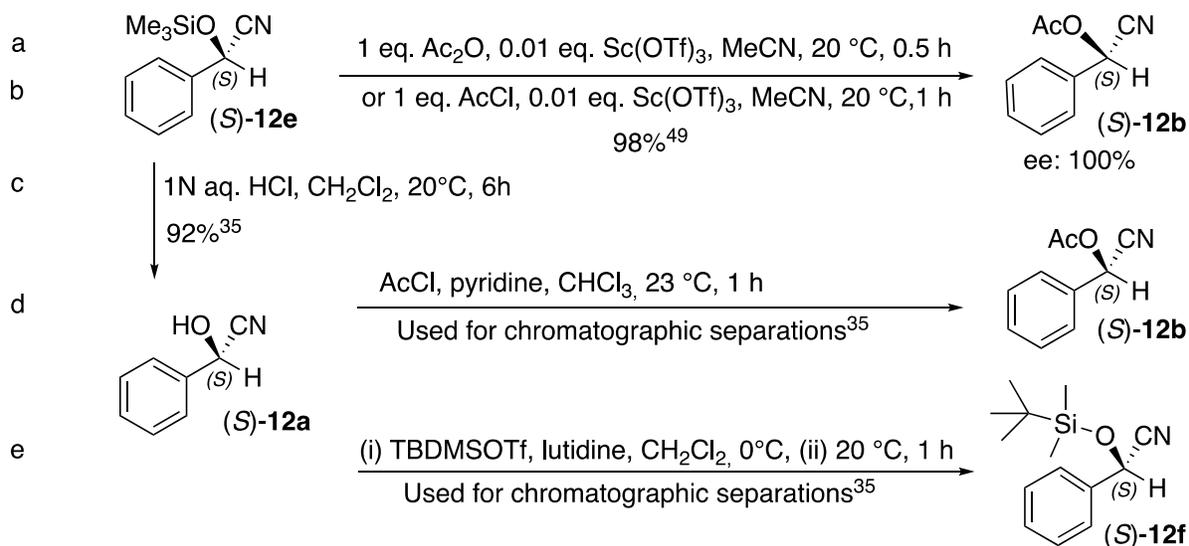
The same reaction has been carried out with ferric chloride in nitromethane with an even lower amount of catalyst than above.<sup>46</sup> It is interesting to note that better yields are observed, all things being equal, if the reaction is carried out in one pot and two steps with acetic anhydride being added first to the mixture of the other reactants rather than trimethylsilyl cyanide (**13e**) (Scheme 11, entry c compare to b).<sup>46</sup>

Reaction of acetic anhydride with the silyloxy-cyanide **12e** in the presence of a catalytic amount (5%) of FeCl<sub>3</sub> produces the  $\alpha$ -acetoxybenzyl cyanide **12b** in almost quantitative yield.<sup>46</sup> Otherwise, the later has been produced in two distinct steps that involve the intermediate synthesis of the gem-diacetate **15** from benzaldehyde (**11**) and acetic anhydride catalyzed by boron trifluoride-etherate,<sup>47</sup> and its subsequent reaction with trimethylsilyl cyanide (**13e**) in the presence of a stoichiometric amount of titanium tetrachloride (Scheme 11, entry d).<sup>48</sup> A related reaction that involves **12e** and the glycosyl fluoride **16** is depicted in Scheme 12.<sup>38</sup>



**Scheme 12.** Glycosylation of trimethylsilyl mandelonitrile.<sup>47</sup>

It has been also reported that  $\alpha$ -silyloxybenzyl cyanide (**12e**) reacts with acetic anhydride in the presence of scandium triflate to produce  $\alpha$ -acetoxybenzyl cyanide (**12b**) in very high yield and with complete retention of configuration (Scheme 13).<sup>49</sup> These non-aqueous conditions are especially useful since they deliver *O*-acyl cyanohydrins, which are more stable than their *O*-TMS precursors and can be readily analyzed by chiral HPLC.<sup>50</sup>



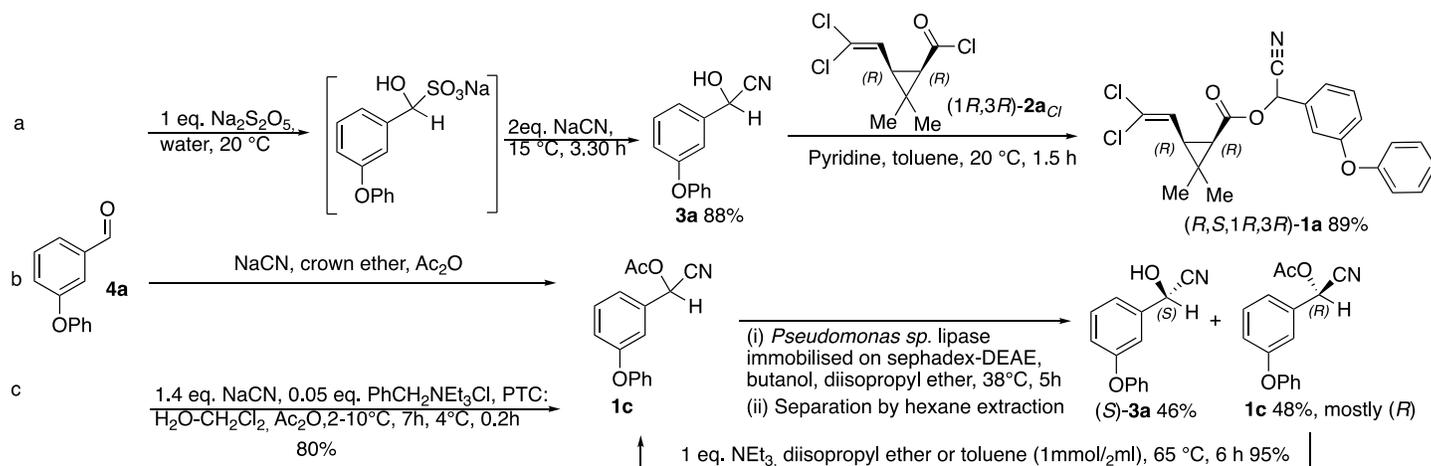
**Scheme 13.** Transformations of enantiopure trimethylsilyl mandelonitrile to the related mandelonitrile, acetyl or TBDMS-mandelonitriles.<sup>35,49</sup>

Hydrolysis of  $\alpha$ -silyloxybenzyl cyanide (**12e**) is efficiently achieved, in 6 h, upon reaction with 1N aqueous hydrochloric acid in biphasic medium (dichloromethane/water) and delivers mandelonitrile (**12a**) with complete retention of configuration.<sup>35</sup> Reactions of the latter with acyl chloride/pyridine (Scheme 13, entry d) or with *t*-butyldimethylsilyl chloride produce the  $\alpha$ -acetyl-derivative **12b** and the  $\alpha$ -*t*-butyldimethylsilyloxybenzyl cyanide (**12f**) in high yield and with complete retention of configuration.

### 2.3. Syntheses of racemic 3-phenoxymandelonitrile from 3-phenoxybenzaldehyde

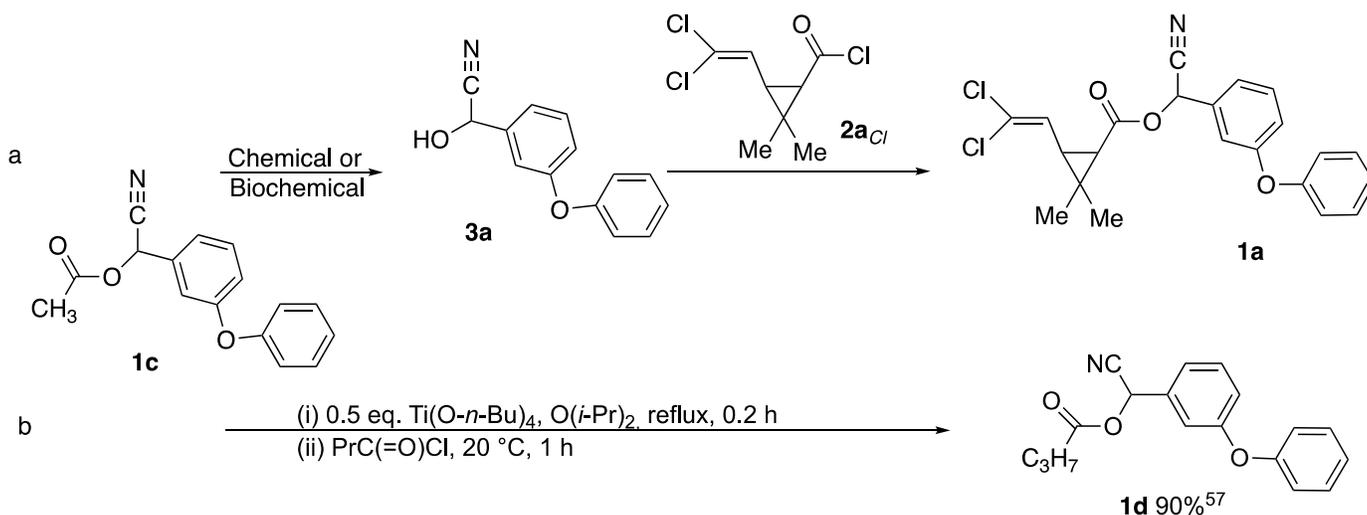
The synthesis of racemic 3-phenoxymandelonitrile (**3**) and related compounds bearing a “protected” hydroxyl group has been carried out from 3-phenoxybenzaldehyde (**4a**) using some of the conditions depicted above. It is however crucial that in all the cases the resulting compounds allow, under smooth conditions, to produce cypermethrin (**1a**) or racemic deltamethrin (**1b**) on reaction of a suitable precursor: directly or after deprotection. Racemic 3-phenoxymandelonitrile (**3**) and related compounds bearing a “protected” hydroxyl group have been also used, after resolution, to produce the enantiopures  $(S)$ -3-phenoxymandelonitrile (**3**) and enantiopure deltamethrin ( $S,1R,3R$ )-(**1b**) (Scheme 3f and 3h).

The racemic cyanohydrin (**3**) has been successfully prepared from 3-phenoxybenzaldehyde (**4a**) and sodium cyanide through its bisulfite adduct (Scheme 14, entry a)<sup>50</sup> and has been used to produce a diastereoisomeric mixture of cypermethrin (**1a**) from the enantiopure cypermethrinic acid chloride (*1R,3R*)-**2a<sub>Cl</sub>** (Scheme 14, entry a).<sup>50</sup> Sodium cyanide, in the presence of crown ether<sup>51,52</sup> or in a two-phase system in the presence of benzyl triethyl ammonium acetic anhydride<sup>53-55</sup> produces as intermediary the cyanohydrin **3** that is directly transformed to the corresponding acetate **1c** on reaction with acetic anhydride present in the medium.



**Scheme 14.** Synthesis of acyl 3-phenoxymandelonitrile and related applications.<sup>51-53,55</sup>

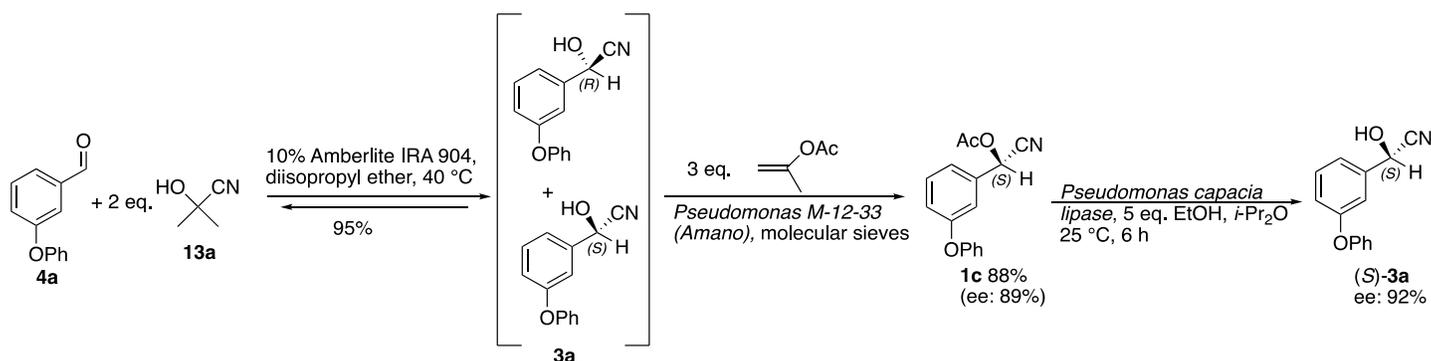
Performing the acetylation of cyanohydrins *in situ* offers not only the advantage to drive the equilibrium towards the formation of the  $\alpha$ -cyanoacetate but also to produce a product much more stable than the cyanohydrins that have the propensity to revert to the aldehydes and, in case of enantiopure cyanohydrins, to epimerize. Thus, the formation of the cypermethrin (**1a**) and deltamethrin (**1b**) from the related acetate (**1c**) requires either a robust deacetylation method to transform **1c** to the cyanohydrin **3a** (Scheme 15, entry a) or a direct method to transesterify **1c** directly to **1a** or **1b** as for example reported for the acetoxy to butyroxyl exchange reported in Scheme 15, entry b.<sup>57</sup>



**Scheme 15.** Single- or multi-step transesterification reactions from acetyl 3-phenoxymandelonitrile.<sup>57</sup>

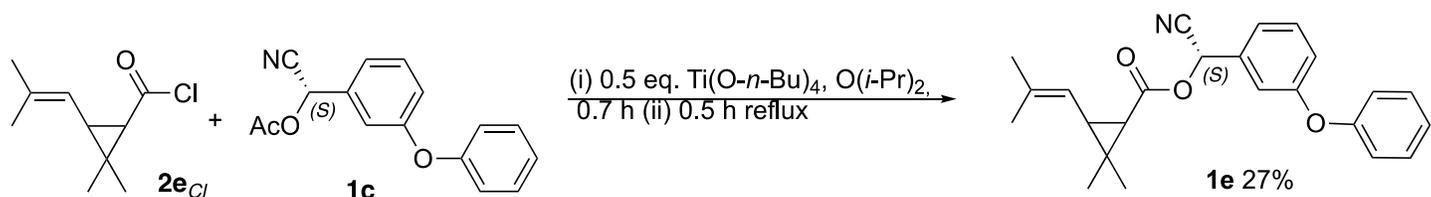
The recovery of cyanohydrins from their acetylated derivatives, especially enantiopure ones, has failed in many cases<sup>27</sup> for the reasons discussed above.<sup>26,27,60</sup> Ester hydrolysis in acidic media proved unsatisfactory because hydrolysis of the cyano group takes place faster than that of the ester.<sup>60</sup>

Best results have been obtained performing a transesterification using lipases and an alcohol<sup>27,55,56</sup> such as ethanol in large excess, which is able to deprotect **1c** to produce smoothly 3-phenoxymandelonitrile (*S*)-(**3a**) (Scheme 16, third step).<sup>27</sup> The process is highly stereoselective and therefore only applies to a single enantiomer of the racemate.<sup>27,55,56</sup> A different solution to such a problem is depicted below (Scheme 32).



**Scheme 16.** Enantioselective synthesis of (*S*)-3-phenoxymandelonitrile by asymmetric transcyanation reaction involving lipases.<sup>27</sup>

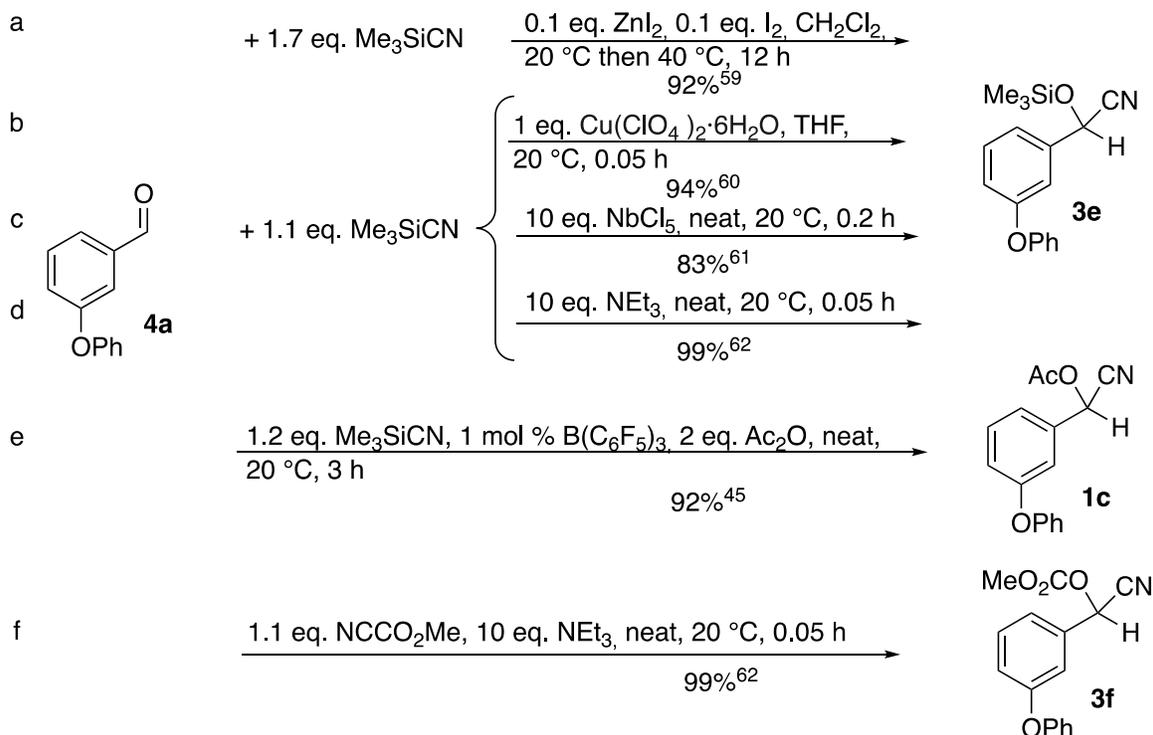
A more general and straightforward approach involves a transesterification reaction, in which an acid chloride is mixed with the  $\alpha$ -acetoxy nitrile catalyzed with titanium tetra-butoxide (0.5 mol. eq.) (Scheme 15, entry b).<sup>57</sup> The reaction has been extended to enantiopure 3-phenoxymandelonitrile acetate (**1c**) and chrysanthemoyl chloride that provides, after heating at reflux, the corresponding ester in modest yield but without epimerization at the asymmetric benzylic carbon (Scheme 17).<sup>57</sup>



**Scheme 17.** Synthesis of cyphenothrin by transesterification of (*S*)-acetyl 3-phenoxymandelonitrile.<sup>57</sup>

The synthesis of the 3-phenoxymandelonitrile (**3a**) has been also successfully achieved using acetone cyanohydrin (**13a**) in a process catalyzed by a base (Scheme 16).<sup>27,58</sup> Best results have been achieved using the solid 10% Amberlite IRA 904 in diisopropyl ether but has been often coupled with acetylation.<sup>27,58</sup>

Some conditions indicated for the synthesis of racemic trimethylsilyloxymandelonitrile (**12e**) from benzaldehyde (**11**) have been applied to the synthesis of racemic trimethylsilyloxy-3-phenoxymandelonitrile (**3e**) (Scheme 18, entry a-d).



**Scheme 18.** Selected reagents able to transfer the cyano group to benzaldehyde as model.<sup>45,59-62</sup>

Thus the synthesis of the trimethylsilyl 3-phenoxymandelonitrile (**3e**) has been carried out from 3-phenoxybenzaldehyde (**4a**) and trimethylsilyl cyanide in the presence of a catalytic amount of (0.1 eq.) of zinc diiodide in dichloromethane (Scheme 18, entry a),<sup>59</sup> an equimolar amount of hydrated copper perchlorate in THF (Scheme 18, entry b),<sup>60</sup> neat with excess of Lewis acids such as niobium pentachloride (Scheme 18, entry c),<sup>61</sup> or excess of base such as triethylamine (Scheme 18, entry d).<sup>62</sup>

The reaction carried out with trimethylsilyl cyanide and acetic anhydride in the presence of catalytic amounts of tris(pentafluorophenyl)borane provides very high yields of acetyl 3-phenoxymandelonitrile (**1c**) (Scheme 18, entry e). It is unclear whether the silylated (**3e**) is an intermediate in the process.<sup>45</sup>

Finally, triethylamine has been successfully used to catalyze the reaction of methyl cyanocarbonate with 3-phenoxybenzaldehyde (**4a**) leading to the related cyanocarbonate **3f** (Scheme 18, entry f).<sup>62</sup>

## 2.4. Synthesis of enantiopure (*S*)-3-phenoxymandelonitrile and protected species from 3-phenoxybenzaldehyde

Enantiopure cyanohydrins were known in nature long before 3-phenoxymandelonitrile (*S*)-(**3a**) was found to be a crucial partner for the synthesis of deltamethrin (**1b**). Unfortunately, most of the hydroxynitrile lyases that perform such synthesis on analogous benzaldehydes proved to produce the (*R*)-enantiomers.<sup>5,23,24</sup> Thus, intensive research had to be carried out to achieve the desired transformation as it will be reported below (Section 2.4.3.2.). In fact, many approaches to enantiopure cyanohydrins have been proposed since 1990 and almost all of them have been successfully applied to 3-phenoxymandelonitrile (*S*)-(**3a**). They are shown in the following sections and are summarized below.

### 2.4.1. Synthesis of enantiopure (*S*)-3-phenoxymandelonitrile by resolution of racemates

#### 2.4.1.1. Resolution of racemates chemical reagents

#### 2.4.1.2. Kinetic resolution of racemates using lipases

2.4.2. Chirality transfer in asymmetric synthesis of (*S*)-3-phenoxymandelonitrile

2.4.3. Catalytic asymmetric hydroxycyanation of aromatic aldehydes

2.4.3.1. Asymmetric hydroxycyanation of aromatic aldehydes using chemical catalysts

2.4.3.1.1. Metal catalyzed asymmetric hydroxycyanation of aromatic aldehydes

2.4.3.1.2. Organocatalysis for the enantioselective synthesis 3-phenoxymandelonitrile

2.4.3.2. Asymmetric hydroxycyanation of 3-phenoxybenzaldehyde using hydroxynitrile lyase

Note that although most of the method involve chemical reactions, the kinetic resolution of some racemates involving lipases (Section 2.4.1.) and the transformation of 3-phenoxybenzaldehyde (**4a**) to 3-phenoxymandelonitrile (*S*)-(**3a**) using chemical (Section 2.4.3.1.) or biochemical reactions (hydroxynitrile lyases, Section 2.4.3.2.) have been reported.

**2.4.1. Synthesis of 3-phenoxymandelonitrile (*S*)-(**3a**) by resolution of racemates. 2.4.1.1. Resolution of racemates involving chemical reagents.** Resolution of 3-phenoxymandelonitrile (*S*)-(**3a**) requires that the following steps are successfully achieved:

- (i) the synthesis of the racemate as reported above (Section 2.3.) and after derivatization leading to a diastereoisomeric mixture,
- (ii) an adequate method of separation of the diastereoisomers, and
- (iii) recovery of the 3-phenoxymandelonitrile (*S*)-(**3a**) without epimerization,
- (iv) recycling the unwanted stereoisomer/enantiomer that amount at least 50% that is otherwise lost. This recycling can either involve epimerization leading back to a mixture of diastereoisomers/enantiomers and repeating the separation/isolation processes or better inverting selectively their (*R*) to the (*S*) benzylic carbon either directly on the unwanted separated species or after adequate treatment.

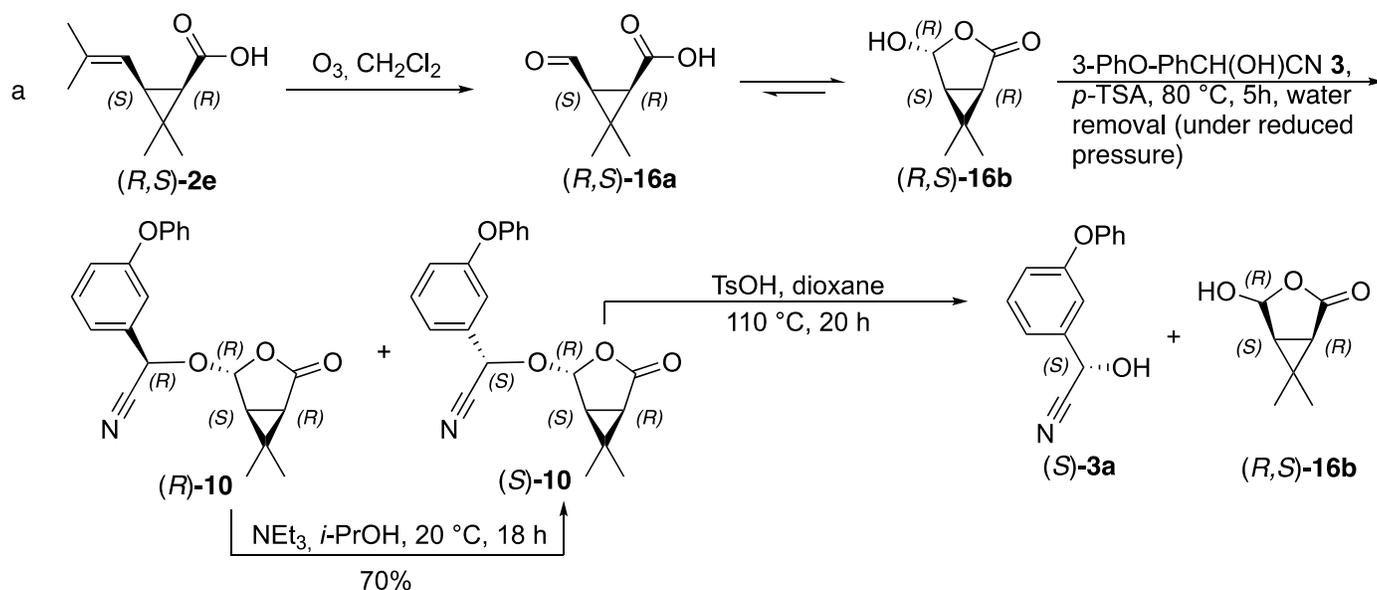
As already pointed out, epimerization of the cyanohydrin (*R*)-**3** easily takes place in basic media by equilibration involving the intermediate formation of the 3-phenoxybenzaldehyde-(**4a**) and hydrogen cyanide or through epimerization at the benzylic carbon of a suitably “protected” compound.

Thus, enantiopure biocartol (**16b**), from the ozonolysis of enantiopure (*1R*)-*cis*-chrysanthemic acid (**2e**),<sup>66</sup> has proven to be an extremely valuable reactant for the resolution of racemic 3-phenoxymandelonitrile (**3a**) (Scheme 19).<sup>63</sup> It offers the advantage to produce the conjugate diastereoisomeric mixture **10** in an acid medium, under conditions under which both the lactol **16b** and the cyanohydrin **3a** are stable. The reaction takes advantage of the easy substitution, after protonation, of its hydroxyl group by the alkoxy group of 3-phenoxymandelonitrile (**3a**) at its anomeric center on which a formal cation can be stabilized by the remaining carboxy oxygen.

This exceptional structural arrangement also allows the reverse reaction leading to biocartol and recovery of the alcohol (cyanohydrin) after resolution keeping untouched all chiral centers.<sup>63</sup> The “acetalization” takes place by removal of water under reduced pressure whereas the recovery of the cyanohydrin is carried out in the presence of an excess of water. Under these conditions, the enantiopure cyanohydrin (*S*)-**3a** is obtained from the enantiopure “acetal” (*S*)-(**10**) as the result of the resolution of the racemate (*R,S*)-**10** by crystallization of the later in iso-propanol (Scheme 19).<sup>63</sup>

Biocartol (**16b**)<sup>66</sup> is also extremely valuable for resolution of racemic mixtures of a wide variety of alcohols including allethrolone (Chapter 2)<sup>64,65,66</sup> and *trans*-chrysanthemol.<sup>64,65</sup>

Interestingly, if the crystallization is performed under suitable conditions in the presence of triethylamine, epimerization takes place at the benzylic carbon of **10** and crystallization of (*S*)-**10** shifts the equilibrium towards its formation (Scheme 19, entry b).<sup>63</sup>

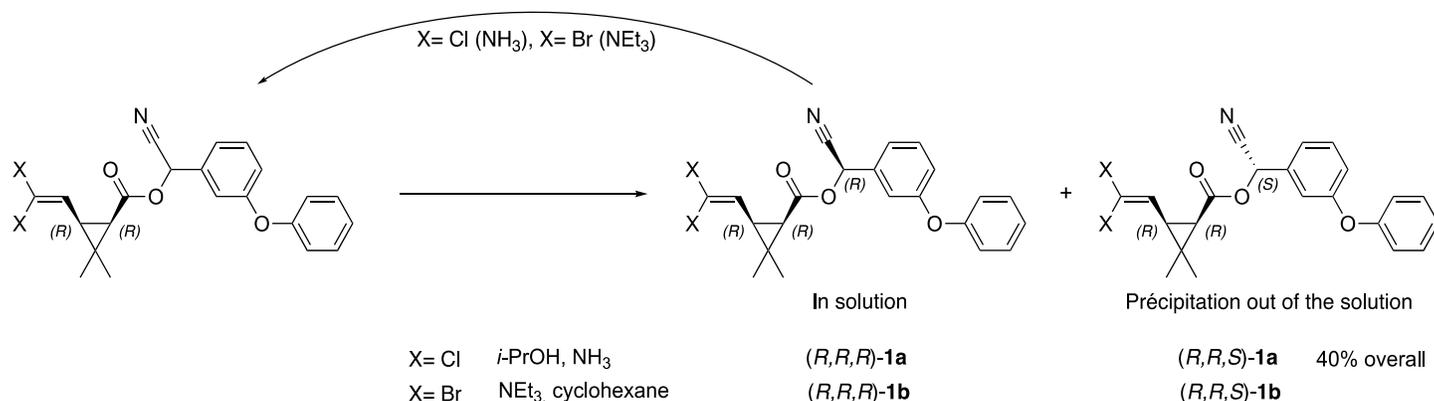


**Scheme 19.** Deracemization of a racemic cyanohydrin using biocartol.<sup>60</sup>

A related strategy, which was not designed to produce the enantiopure cyanohydrin (**S**)-**3a** but directly its enantiopure esters **1a**<sup>50</sup> and **1b**, has been successfully realized (Scheme 20). It involves the synthesis of 1:1 diastereoisomeric mixtures of (*S*,*1R*,*3R*)-*cis*- and (*R*,*1R*,*3R*)-*cis*-cypermethrin (**1a**) as well as (*S*,*1R*,*3R*)-*cis*- and (*R*,*1R*,*3R*)-*cis*-deltamethrin (**1b**) upon reaction of the related enantiopure (*1R*,*3R*)-*cis*-cypermethrinic acid (**2a**) and (*1R*,*3R*)-*cis*-deltamethrinic acid (**2b**) with racemic (*R*,*S*)-3-phenoxy mandelonitrile (**3a**) and the propensity of the (*S*,*1R*,*3R*)-stereoisomers **1a** and **1b** to crystallize from their solution in isopropanol<sup>50</sup> or cyclohexane,<sup>65-67</sup> respectively.

Performing the processes in the presence of ammonia<sup>50</sup> or triethylamine<sup>65-67</sup> allows at room temperature the *in situ* epimerization of the soluble (*R*,*1R*,*3R*)-(**1a**) and (**1b**) stereoisomers leading to increasing amounts of the crystalline (*S*,*1R*,*3R*)-(**1**) stereoisomers (Scheme 20).

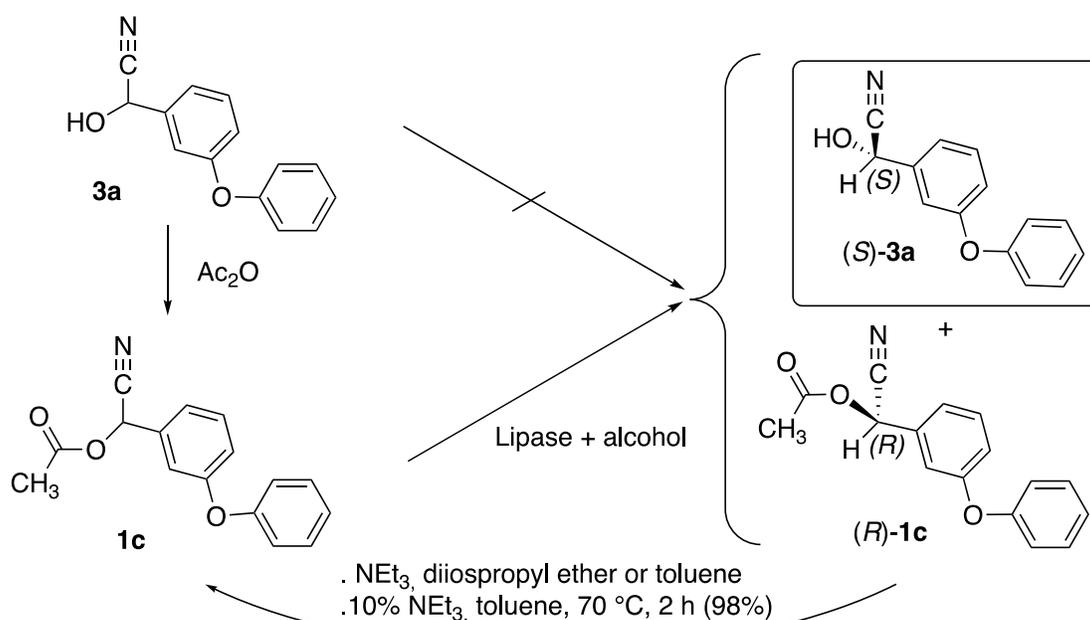
Otherwise separation of such diastereoisomeric mixture of deltamethrin has been performed, with mediocre success, by crystallization,<sup>68</sup> thin layer chromatography (TLC),<sup>68</sup> and high-pressure chromatography.<sup>68</sup>



**Scheme 20.** Synthesis of (*S*,*1R*,*3R*)-**1** permethrins from their mixture by epimerization at their benzylic carbon.<sup>50,65-67</sup>

**2.4.1.2 Kinetic resolution of racemates using lipases.** Lipases, the enzymes that catalyze the hydrolysis of carboxylic esters or esterification of carboxylic acid depending the conditions, have been used to produce the desired cyanohydrin (*S*)-**3a**.<sup>6</sup> Two strategies have been used for that purpose: (i) enantioselective hydrolysis of the racemic acetate **1c** (Scheme 21)<sup>52,53,55,56</sup> or (ii) enantioselective synthesis of the acetate **1c** from the racemic cyanohydrin (Scheme 22).<sup>27,58,59</sup>

The former process involves at first the synthesis of the racemic acetate **1c**. It has been achieved in many instances *in-situ*, in the same pot as the synthesis of the racemic cyanohydrin or after its purification and acetylation using acetic anhydride for example (Section 2.2 and 2.3). Its enantioselective hydrolysis, leading to (*S*)-**3a** takes place using *Arthrobacter* lipase,<sup>52</sup> *Pseudomonas sp.* lipase,<sup>53</sup> Amano lipase,<sup>56</sup> *Candida antarctica* lipase<sup>55</sup> in the presence of an excess of an added alcohol that keeps untouched its enantiomer (*R*)-**1c**. The latter has been recycled by racemization resulting from base-promoted epimerization at the benzylic carbon using triethylamine (Scheme 21).<sup>52,53</sup>



**Scheme 21.** Lipase monitored enantioselective hydrolysis of the racemic acetate **1c**: *Arthrobacter* lipase<sup>52</sup> *Pseudomonas sp* lipase,<sup>53</sup> Amano lipase,<sup>56</sup> *Candida antartica* lipase.<sup>55</sup>

A specific example that involves the lipase P (Amano, 30 units/mg) in the presence of n-butanol, is depicted in Scheme 22.<sup>56</sup> The enantiopure cyanohydrin (*S*)-**3a** that is produced besides butyl acetate is reacted with the cypermethrinic acid chloride (*1R,3R*)-*cis*-(**2a**) to produce the enantiomerically pure cypermethrin (*S,1R,3R*)-(**1a**).<sup>56</sup>

A similar process carried out on the same racemic acetate (*R,S*)-**1c** using instead *Candida cylindracea* lipase that provides the cyanohydrin (*R*)-**3a** and the acetate (*S*)-**1c** instead is less advantageous due to the difficulty to perform the transformation of acetate (*S*)-**1c** into for example cypermethrin (*S,1R,3R*)-**1a** (Scheme 23, entry b).<sup>52</sup>

Another process involves the enantioselective acylation of racemic cyanohydrin (*R,S*)-**3a** by vinyl acetate<sup>27,58,59</sup> or better isopropenyl acetate<sup>59</sup> using porcine pancreas lipase,<sup>59</sup> *Candida sp.* lipase,<sup>59</sup> *Alcaligenes sp.* lipase,<sup>58</sup> or *Pseudomonas cepacia* lipase<sup>27</sup> as the catalyst that also leads to the production of the acetate (*S*)-**1c**, leaving untouched the enantiomer (*R*)-**3a** (Scheme 23).



The resulting acetate (*S*)-**1c** can be directly used (Scheme 17)<sup>57</sup> or deprotected to the cyanohydrin then acylated with a permethrinic acid chloride (Scheme 14, entry a).<sup>50</sup>

The lipase selected and the conditions used are very important for the success of the process especially for industrial purposes. The key factors are: the accessibility of the lipase, the selectivity of the process, the nature of the enantiomers formed, the pH of the medium, the ease of recovery of the cyanohydrin and/or its acetate, the efficiency of the recycling of the compounds possessing the unwanted (*R*)-stereochemistry and the reuse of the lipase.

For example several lipases such as *Arthrobacter* lipase,<sup>52</sup> *Pseudomonas sp.* lipase,<sup>53</sup> lipase P (Amano),<sup>56</sup> and *Candida antartica* lipase,<sup>55</sup> hydrolyse efficiently (*S*)-3-phenoxymandelonitrile acetate (*S*)-**1c** to the corresponding (*S*)-3-phenoxymandelonitrile (*S*)-(**3a**) directly transformed to enantiopure deltamethrin (*S*,1*R*,3*R*)-(**1a**) on reaction with (1*R*,3*R*)-deltamethrinic acid chloride (**2a<sub>Cl</sub>**) while *Candida cylindracea* lipase hydrolyses its enantiomer (*R*)-**1c** instead of leading to (*R*)-3-phenoxymandelonitrile (*R*)-(**3a**) and acetyl (*S*)-3-phenoxy-mandelonitrile (*S*)-(**1c**) that cannot be conveniently use to produce enantiopure deltamethrin.<sup>52</sup>

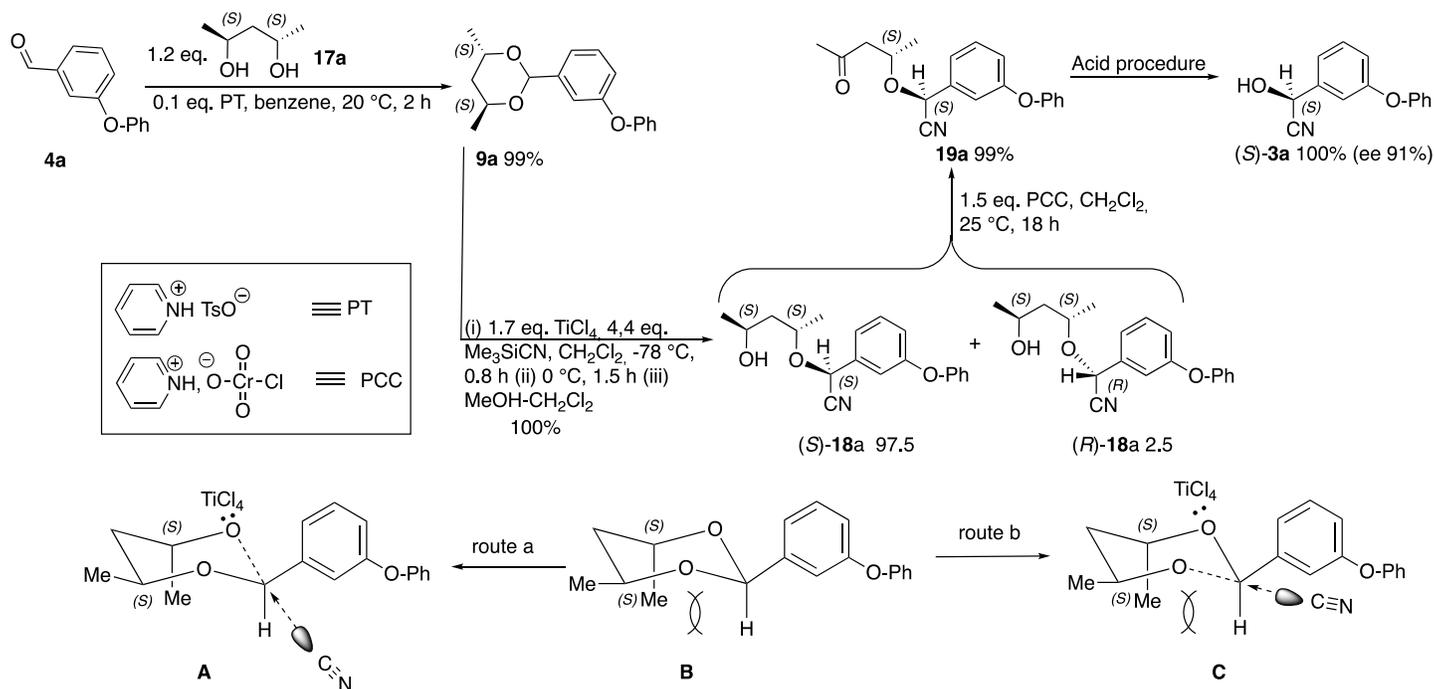
Enantioselective hydrolysis by *Arthrobacter* lipase gave the optically pure (*S*)-3-phenoxymandelonitrile (*S*)-(**3a**) at a particularly suitable pH of 4.0.<sup>52</sup> It has also been reported that the *Arthrobacter* lipase solution in the water/oil biphasic reaction system could be used repeatedly<sup>52</sup> whereas the same lipase immobilized to resins has insufficient activity and low operational stability for repeated batch reaction<sup>52</sup> (Scheme 21). However, in a study aimed at screening several enzymes,<sup>58</sup> immobilized *Alcaligenes sp.* lipase showed the highest activity, diisopropyl ether was found to be the best solvent, butanol the best reagent, higher substrate concentration proved to substantially increase the reaction rate at optimal temperature of 50 °C.<sup>58</sup>

Finally, 3-phenoxybenzaldehyde (**4a**) has been transformed into the corresponding acylated (*S*)-3-phenoxy-mandelonitrile **1c** in a two-steps process shown in Scheme 16<sup>27</sup> and Scheme 23<sup>27,58,59</sup> that involves a high yielding (95%) transhydrocyanation reaction using strongly basic anion exchange resin (Amberlite IRA 904) that leads to a racemic mixture of 3-phenoxymandelonitrile (**3a**), followed by a stereoselective enzymatic acylation involving isopropenyl acetate and leading to acylated (*S*)-3-phenoxymandelonitrile (*S*)-(**1c**) in good yield (88%), and good stereocontrol (ee 89%) in the presence of *Pseudomonas* M-12-33 lipase and molecular sieves.

**2.4.2. Chirality transfer in asymmetric synthesis of 3-phenoxymandelonitrile.** Another approach to of 3-phenoxymandelonitrile (*S*)-(**3a**) has been carried out by Johnson on 3-phenoxybenzaldehyde (**4a**) and enantiopure 1,3-propane diols (**17**) possessing at least one asymmetric center as reported in Scheme 24 and Scheme 25.<sup>70</sup>

The successful strategy<sup>70,71</sup> involves (i) the synthesis of the acetal **9** derived from 2,4-pentanediol (**17**) and 3-phenoxybenzaldehyde (**4a**) using pyridinium tosylate as catalyst,<sup>72</sup> (ii) the Lewis acid-assisted ring opening of acetal **9** by trimethylsilyl cyanide<sup>70,71</sup> leading to the β-benzyloxy alcohol **18a** (iii) its transformation to 3-phenoxymandelonitrile (**3a**) in good yield in a two-step process that involves the synthesis of β-benzyloxy methyl ketone **19a** on oxidation with pyridinium chlorochromate (PCC),<sup>73</sup> and its decomposition through a β-elimination reaction catalyzed by an acidic medium (Scheme 24).<sup>70</sup>

The whole process initiated by the prochiral (2*S*,4*S*)-pentane diol (**17a**) provides the (*S*)-mandelonitrile (*S*)-(**3a**) in almost quantitative yield and high stereocontrol (ee: 91%) but the chiral center is generated at the expense of the two chiral centers of the pentane diol (**17a**) that are both destroyed in the process!



**Scheme 24.** Chirality transfer in asymmetric synthesis of 3-phenoxymandelonitrile (*S*)-**3a** from 3-phenoxybenzaldehyde (**4a**) through its chiral dioxolane from enantiopure (*S,S*)-2,4-pentanediol.<sup>70</sup>

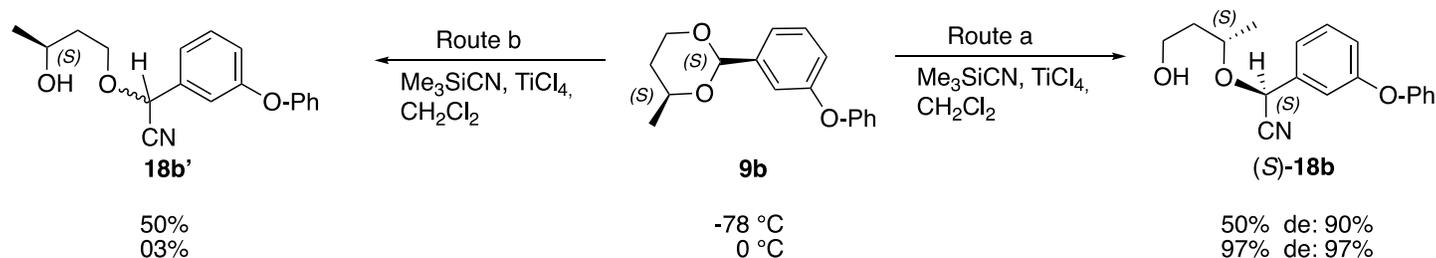
The key step of the process involves the titanium tetrachloride assisted ring opening of acetal **9a** using excess of trimethylsilyl cyanide. It is temperature-dependent with a de of 95% at -78 °C and only 84% at 0 °C.<sup>70</sup>

The reaction is believed to occur through an  $S_N2$ -like transition state A (Scheme 24, route a), stabilized by lengthening of the 2,3-bond of the ground state conformer **A** with consequential relief of the large 2,4-diaxial H/Me interaction.<sup>70</sup> As can be seen, the same is not operative if route b would have been instead involved (Scheme 24, route b).<sup>70</sup>

The reaction involving (*S*)-2,4-butanediol (**17b**), offers advantages of (i) its ready access from the related  $\beta$ -keto ester by yeast reduction,<sup>69</sup> and (ii) a 1/1 asymmetric center transfer, as compared to the one more being lost in the previous approach (Scheme 25, compare to Scheme 24).<sup>70</sup> Differences between the related approaches disclosed in Scheme 24 and Scheme 25 are listed below:

(i) the benzylic carbon of acetal **9b**<sup>69</sup> is chiral whereas that of **9a** is prochiral.<sup>70</sup> Therefore, **9b** can exist in two diastereoisomeric forms. Fortunately however, the *cis*-stereoisomer *cis*-**9b**, the more stable of all possible forms, is produced on equilibrating conditions involving for example pyridinium tosylate (97% yield).<sup>72</sup>

(ii) Titanium tetrachloride catalyzed ring opening can take place by cleavage of one the C-O bonds leading either to an aldehyde after oxidation of the primary alcohol (*S*)-**18b** (Scheme 25, Route a) or to a methyl ketone through the secondary alcohol **18b'** (Scheme 25, Route b).<sup>69</sup> It was indeed found that the cleavage leads to the primary alcohol (*S*)-**18b** (de: 90%) and to the secondary alcohol **18b'** (de: 0%) in identical amounts if the reaction is performed at -78 °C.<sup>69</sup> This ratio varies from 1/1 to 99/1 depending on the conditions. It has been however found that slow addition at 0 °C of  $\text{TiCl}_4$  to a mixture of *cis*-**9b** and 3 equivalents of TMSCN (**13e**) provides, after "deprotection", 3-phenoxymandelonitrile (*S*)-(**3a**) in good yields (97%) and high enantiomeric excess (ee 97%).<sup>70</sup> The preferential cleavage of the C-O bond leading to the primary alcohol can be rationalized by preferential  $\text{TiCl}_4$  complexation at the least hindered site on the acetal **9b**.<sup>70</sup>



**Scheme 25.** Chirality transfer in asymmetric synthesis of 3-phenoxymandelonitrile (*S*)-**3a** from 3-phenoxy benzaldehyde (**4a**) through its chiral dioxolane from enantiopure (*S*)-2,4-butanediol.<sup>70</sup>

**2.4.3. Catalytic asymmetric hydroxycyanation of aromatic aldehydes. 2.4.3.1. Asymmetric hydroxycyanation of aromatic aldehydes using chemical catalysts. 2.4.3.1.1. Metal catalyzed asymmetric hydroxycyanation of aromatic aldehydes.** Chemically catalyzed asymmetric cyanohydrin synthesis has been the subject of several publications including comprehensive reviews.<sup>6-9</sup> Over the past two decades, significant advances have been made towards developing asymmetric cyanohydrin synthesis of aldehydes possessing different structures including aliphatic aldehydes,<sup>6-8,113,114</sup> and ketones,<sup>6-9</sup> but relatively few have been performed on 3-phenoxybenzaldehyde (**4a**). The reviews, especially that of Holmes<sup>7</sup> and later North<sup>9</sup> efficiently cover the field, and we direct the reader's attention to them. We have restricted our contributions to two starting materials: (i)-3-phenoxybenzaldehyde (**4a**) (Scheme 28, Table 3, Scheme 29, table 4) the substance requested for the synthesis of cypermethrin and deltamethrin and (ii) benzaldehyde (**11**) (Scheme 27, table 2),<sup>36,74-100</sup> the parent aromatic compound that has been used as a model in almost all the researches published. We have gathered in Table 3<sup>35,36,75,77-80,85-90,97-99,101</sup> and Table 4<sup>102,103,104,105</sup> the reaction that leads directly to the chiral cyanohydrins **3a** and **12a**, respectively, or to their trimethylsilyl precursors **3e** and **12e**. We have gathered in Scheme 29 the reactions of **4a** that lead instead to the related chiral phosphonate **3g**, acetate **1c** or methoxy carbonate **3f**. Those are quite difficult to deprotect to the related cyanohydrins **3a** and **12a** and are moreover poorly enantioselective, that preclude their use for an industrial synthesis of **3a**.

The trimethylsilylated cyanohydrins occupy a special place since as already pointed out trimethylsilyl cyanide their precursor is easily prepared and commercially available, they are produced easily in high yield, they are stable and the enantiopure derivatives are stereoselectively desilylated in acidic media.

The synthesis of enantiopure cyanohydrins or their silyl-protected analogs have been thus carried out using a metal as pre-catalyst and a chiral-ligand that combines to produce the chiral catalyst that ideally should be reused. The different metals used are displayed on a periodic table of elements (Table 1): they include those belonging to the s-block (Li, Mg); p-block (B, Al, Sn, Bi); d-block (Sc, Ti, V, Mn, Co, Y, Zr, Re) and f-block (La, Sm, Eu, Yb, Lu) -metals.<sup>6-9</sup>

The nature of the metal (entry D), the structure of the related metallic compounds (entry E), the structure of the related ligands (entry B) and the postulated structure of the catalyst (entry F) are listed in Tables 2-4. We have also gathered succinct experimental details about each cyanation method (entry E). The yield (entry G) and the enantiomeric excess (entry H) in cyanohydrin or its protected form are shown in the Tables 2-4.

The following sections will discuss sequentially some of these parameters.

**2.4.3.1.1.1. The metal.** The metals belonging to the different blocks are gathered below:

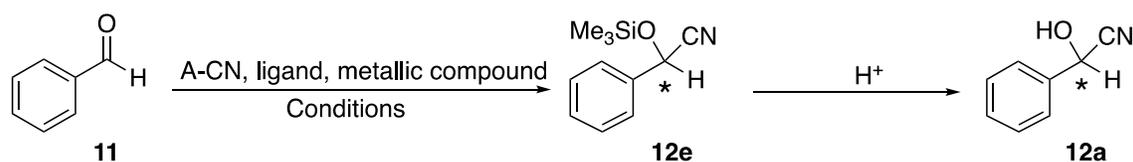
- (i) **s-block metals:** [**Li**]: Table 2, entries 8e, 17b; [**Na, K**]: Table 2, entries 17c,d; [**Mg**]: Table 2 entries 17e, 19e,
- (ii) **p-block metals:** [**B**]: Table 2, entry 22; [**Al**]: Table 2, entries 8f, 14a, 17f, 18b, 18c, 19a-c; Table 3, entry 5; Table 4, entries 3, 4; [**Bi**]: Table 2, entry 16; Table 3, entry 11),

**Table 1.** Location (in red) in the periodic table of elements of metals involved, as their salts or oxides, in the enantioselective synthesis of chiral cyanohydrins from aldehydes

|                      |                       |                       |                            |                      |                         |                        |                       |                         |                           |                          |                          |                       |                        |                        |                          |                         |                       |
|----------------------|-----------------------|-----------------------|----------------------------|----------------------|-------------------------|------------------------|-----------------------|-------------------------|---------------------------|--------------------------|--------------------------|-----------------------|------------------------|------------------------|--------------------------|-------------------------|-----------------------|
| 1<br>H<br>hydrogen   | 2/IIA                 | 3/IIIB                | 4/IVB                      | 5/VB                 | 6/VIB                   | 7/VII                  | 8/VII                 | 9/VII                   | 10/VII                    | 11/IB                    | 12/IIIB                  | 13/IIIA               | 14/IVA                 | 15/VA                  | 16/VIA                   | 18/VIIA                 | 19/0<br>He<br>helium  |
| 3<br>Li<br>lithium   | 4<br>Be<br>beryllium  |                       |                            |                      |                         |                        |                       |                         |                           |                          |                          | 5<br>B<br>bore        | 6<br>C<br>carbon       | 7<br>N<br>nitrogen     | 8<br>O<br>oxygen         | 9<br>F<br>fluorine      | 10<br>Ne<br>neon      |
| 11<br>Na<br>sodium   | 12<br>Mg<br>magnesium |                       |                            |                      |                         |                        |                       |                         |                           |                          |                          | 13<br>Al<br>aluminium | 14<br>Si<br>silicon    | 15<br>P<br>phosphorus  | 16<br>S<br>sulfur        | 17<br>Cl<br>chlorine    | 18<br>Xe<br>xenon     |
| 19<br>K<br>potassium | 20<br>Ca<br>calcium   | 21<br>Sc<br>scandium  | 22<br>Ti<br>titanium       | 23<br>V<br>vanadium  | 24<br>Cr<br>chromium    | 25<br>Mn<br>manganese  | 26<br>Fe<br>iron      | 27<br>Co<br>cobalt      | 28<br>Ni<br>nickel        | 29<br>Cu<br>copper       | 30<br>Zn<br>zinc         | 31<br>Ga<br>gallium   | 32<br>Ge<br>germanium  | 33<br>As<br>arsenic    | 34<br>Se<br>selenium     | 35<br>Br<br>bromine     | 36<br>Kr<br>krypton   |
| 37<br>Rb<br>rubidium | 38<br>Sr<br>calcium   | 39<br>Y<br>yttrium    | 40<br>Zr<br>zirconium      | 41<br>Nb<br>niobium  | 42<br>Mo<br>molybdenum  | 43<br>Tc<br>technetium | 44<br>Ru<br>ruthenium | 45<br>Rh<br>rhodium     | 46<br>Pd<br>palladium     | 47<br>Ag<br>silver       | 48<br>Cd<br>cadmium      | 49<br>In<br>indium    | 50<br>Sn<br>tin        | 51<br>Sb<br>antimony   | 52<br>Te<br>tellurium    | 53<br>I<br>iodine       | 54<br>Xe<br>xenon     |
| 55<br>Cs<br>caesium  | 56<br>Ba<br>calcium   | 57-71<br>lanthanoides | 72<br>Hf<br>hafnium        | 73<br>Ta<br>tantalum | 74<br>W<br>tungsten     | 75<br>Re<br>rhenium    | 76<br>Os<br>osmium    | 77<br>Ir<br>iridium     | 78<br>Pt<br>platinum      | 79<br>Au<br>gold         | 80<br>Hg<br>mercury      | 81<br>Tl<br>thallium  | 82<br>Pb<br>lead       | 83<br>Bi<br>bismuth    | 84<br>Po<br>polonium     | 85<br>At<br>astatine    | 86<br>Rn<br>radon     |
| 87<br>Fr<br>francium | 88<br>Ra<br>radium    | 89-103<br>actinoides  | 104<br>Rf<br>rutherfordium | 105<br>Db<br>dubnium | 106<br>Sg<br>seaborgium | 107<br>Bh<br>bohrium   | 108<br>Hs<br>hassium  | 109<br>Mt<br>meitnerium | 110<br>Ds<br>darmstadtium | 111<br>Rg<br>roentgenium | 112<br>Cn<br>copernicium | 113<br>Nh<br>nihonium | 114<br>Fl<br>flerovium | 115<br>Mc<br>moscovium | 116<br>Lv<br>livermorium | 117<br>Ts<br>tennessine | 118<br>Og<br>oganeson |

|                       |                     |                          |                       |                        |                       |                       |                        |                       |                         |                         |                      |                          |                       |                         |
|-----------------------|---------------------|--------------------------|-----------------------|------------------------|-----------------------|-----------------------|------------------------|-----------------------|-------------------------|-------------------------|----------------------|--------------------------|-----------------------|-------------------------|
| 57<br>La<br>lanthanum | 58<br>Ce<br>cerium  | 59<br>Pr<br>praseodymium | 60<br>Nd<br>neodymium | 61<br>Pm<br>promethium | 62<br>Sm<br>samarium  | 63<br>Eu<br>europium  | 64<br>Gd<br>gadolinium | 65<br>Tb<br>terbium   | 66<br>Dy<br>dysprosium  | 67<br>Ho<br>holmium     | 68<br>Er<br>erbium   | 69<br>Tm<br>thulium      | 70<br>Yb<br>ytterbium | 71<br>Lu<br>lutetium    |
| 89<br>Ac<br>actinium  | 90<br>Th<br>thorium | 91<br>Pa<br>protactinium | 92<br>U<br>uranium    | 93<br>Np<br>neptunium  | 94<br>Pu<br>plutonium | 95<br>Am<br>americium | 96<br>Cm<br>curium     | 97<br>Bk<br>berkelium | 98<br>Cf<br>californium | 99<br>Es<br>einsteinium | 100<br>Fm<br>fermium | 101<br>Md<br>mendelevium | 102<br>No<br>nobelium | 103<br>Lr<br>lawrencium |

- Titanium has been by far the most used metal providing the highest yields and enantiomeric excesses. It has been introduced as titanium tetra-ethoxide, -isopropoxide or -chloride,
- Vanadium introduced as oxovanadium sulfate has proven in rare cases to be superior (Table 2, compare entry 8d to entries 7, 8a, 8b),
- Aluminum as aluminum trichloride, dimethyl aluminum chloride, aluminum tetraisopropoxide and triethyl aluminum proved reasonably efficient, in particular when used in conjunction with lithium (Table 2, entries 14a, 17f; Table 3, entry 5; Table 4, entries 3, 4),
- Samarium as samarium trichloride (Table 2, entry 20) and yttrium as  $Y_5(O)(O-iPr)_{13}$  (Table 2, entry 21) with their related ligands have been much less frequently used.

**Scheme 26.** Catalytic enantioselective syntheses of mandelonitrile (**12a**), and its trimethylsilyl ether (**12e**).

**Table 2.** Presentation of selected catalyzed reactions that allow the enantioselective synthesis of mandelonitrile (**12a**) or its trimethylsilylated derivative **12e**

Columns: A: entry number, B: structure and number of the ligand, C: metal involved, D: experimental conditions, E: suspected catalyst structure, F: *stereochemistry of the major enantiomer*-reaction yield % (enantiomeric excess %)

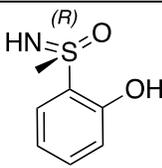
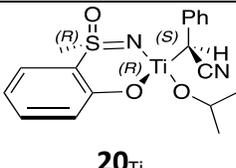
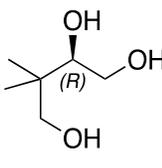
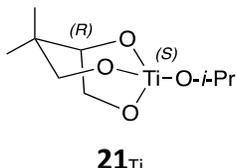
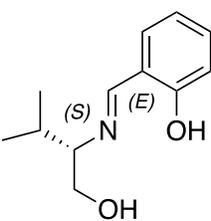
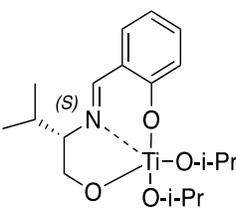
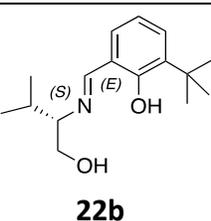
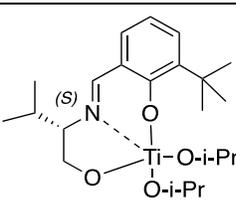
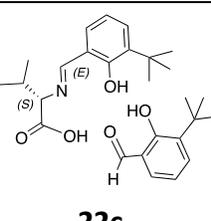
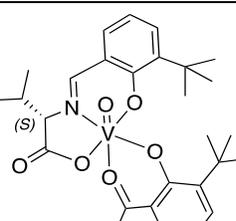
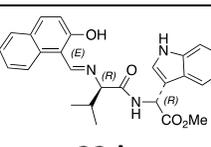
| A | B   | C  | D   | E  | F                             |
|---|---|----|---|--|-------------------------------|
| 1 |  <p><b>20</b></p>    | Ti | (i) 1 eq. <b>11</b> , TMSCN <b>13e</b> , 1.1 eq. <b>20</b> , 1 eq. Ti(O- <i>i</i> -Pr) <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , -50 °C, 24 h (ii) HF.   |  <p><b>20</b><sub>Ti</sub></p>    | S-72 (91) <sup>74,75</sup>    |
| 2 |  <p><b>21</b></p>    | Ti | (i) 0.1 eq. <b>21</b> , 0.1 eq. Ti(O- <i>i</i> -Pr) <sub>4</sub> CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 4 h (ii) 1 eq. ( <b>11</b> ), 2 eq. TMSCN <b>13e</b> , 4A MS (iii) H <sub>2</sub> SO <sub>4</sub> |  <p><b>21</b><sub>Ti</sub></p>    | S-92 (76) <sup>76</sup>       |
| 3 |  <p><b>22a</b></p>  | Ti | (i) 0.2 eq. <b>22a</b> , 0.1 eq. Ti(O- <i>i</i> -Pr) <sub>4</sub> CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h (ii) 2.25 eq. TMSCN <b>13e</b> , -80 °C, 36 h.   |  <p><b>22a</b><sub>Ti</sub></p>  | S-69 (22) <sup>77,78</sup>    |
| 4 |  <p><b>22b</b></p> | Ti | 0.2 eq. <b>22b</b> , 0.1 eq. Ti(O- <i>i</i> -Pr) <sub>4</sub> CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h (ii) 1 eq. <b>11</b> , 2.25 eq. TMSCN <b>13e</b> , -80 °C, 36 h.                                 |  <p><b>22b</b><sub>Ti</sub></p> | R-67 (85) <sup>75,77,78</sup> |
| 5 |  <p><b>22c</b></p> | V  | (i) 0.5 mol% VOSO <sub>4</sub> , 0.5% <b>22c</b> + <b>22cv</b> , (ii) 1 eq. <b>11</b> , 2eq. TMSCN <b>13e</b> , 0.5% TBAF, MeCN, -20 °C, 24 h   |  <p><b>22cv</b></p>             | S-94 (83) <sup>79</sup>       |
| 6 |  <p><b>22d</b></p> | Ti | (i) HCN, 10% <b>23</b> , 10% Ti(OEt) <sub>4</sub> , 1 eq. <b>11</b> , toluene, -40 °C, 11 h then -20 °C, 12 h (ii) H <sub>3</sub> O <sup>+</sup> .  |  | S-85 (84) <sup>80</sup>       |

Table 2. Continued

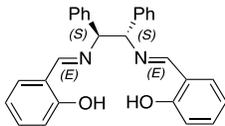
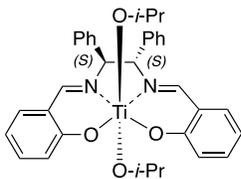
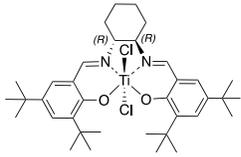
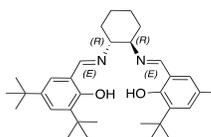
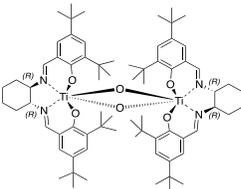
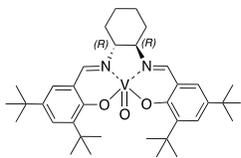
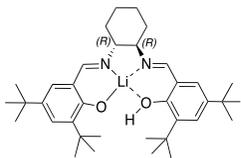
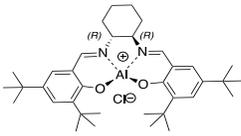
| A  | B   | C  | D   | E  | F                           |
|----|---|----|---|--|-----------------------------|
| 7  |  <p><b>23a (S,S)</b></p> | Ti | (i) 0.11 eq. <b>23a</b> , 0.1 eq. Ti(O <i>i</i> -Pr) <sub>4</sub><br>CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 2 h<br>(ii) 1 eq. <b>11</b> , 2. eq. TMSCN <b>13e</b> , -78 °C, 24 h.   |  <p><b>23a<sub>Ti</sub></b></p>   | R-72 (87) <sup>81</sup>     |
| 8a |   | Ti | (i) 0.001 eq. <b>23b</b> , 0.001 eq. TiCl <sub>4</sub> , 20 °C, 2 h, (ii) 1 eq. <b>11</b> , 2. eq. TMSCN <b>13e</b> , CH <sub>2</sub> Cl <sub>2</sub> , 24 h.   |  <p><b>23b<sub>Ti</sub></b></p>   | S-42 (40) <sup>82</sup>     |
| 8b |   | Ti | (i) 0.001 eq. <b>23b</b> , 0.001 eq. TiCl <sub>4</sub> , 20 °C, 2 h, (ii) 0.001 eq. H <sub>2</sub> O, 0.002 eq. NEt <sub>3</sub> , 20 °C, 3 h (iii) 1 eq. <b>11</b> , 2. eq. TMSCN <b>13e</b> , CH <sub>2</sub> Cl <sub>2</sub> , 24 h. |  | S-99 (86) <sup>82, 83</sup> |
| 8c |  <p><b>23b</b></p>       |    | or<br>(i) 0.001 eq. <b>23b</b> , 0.001 eq. Ti(OEt) <sub>4</sub> , 20 °C, 2 h, (ii) 0.001 eq. H <sub>2</sub> O, 20 °C, 3 h (iii) 1 eq. <b>11</b> , 2. eq. TMSCN <b>13e</b> , CH <sub>2</sub> Cl <sub>2</sub> , 24 h.                     |  <p><b>23b<sub>TiO</sub></b></p>  |                             |
| 8d |   | V  | (i) 1 eq. <b>23b</b> , 1.2 eq. VOSO <sub>4</sub> ·H <sub>2</sub> O, THF, reflux, 3 h: Catalyst <b>23b<sub>v</sub></b><br>(ii) 0.001 eq. <b>23b<sub>v</sub></b> , 1 eq. <b>11</b> , 2.2 eq. TMSCN <b>13e</b> , 20 °C, 24 h.              |  <p><b>23b<sub>v</sub></b></p>  | S-99 (94) <sup>83</sup>     |
| 8e |   | Li | (i) 0.5% BuLi, 1% eq. <b>23b</b> ether, -78 °C (ii) TMSCN <b>13e</b> , 1 eq. <b>11</b> , ether, -78 °C, 0.3 h   |  <p><b>23b<sub>Li</sub></b></p> | R-98 (86) <sup>84</sup>     |
| 8f |   | Al | (i) 1% <b>23b</b> , 1% AlCl <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> 10 °C (ii) 10% Ph <sub>3</sub> PO, 1 eq. <b>11</b> , 1.1 eq. TMSCN <b>13e</b> , -50 °C, 18 h, (iii) 2N HCl, 20 °C, 1 h.                                      |  <p><b>23b<sub>Al</sub></b></p> | R-94 (86) <sup>85</sup>     |

Table 2. Continued

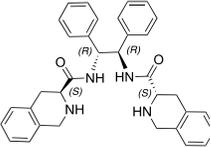
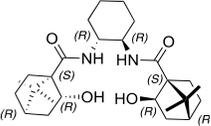
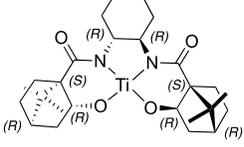
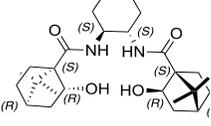
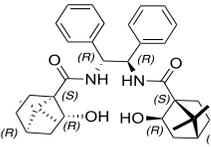
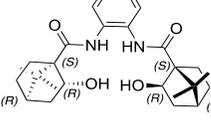
| A  | B   | C  | D   | E  | F                                  |
|----|---|----|---|--|------------------------------------|
| 9  |  <p><b>24a</b></p>         | Ti | (i) 0.06 eq. <b>24a</b> , 0.06 eq. Ti( <i>Oi</i> -Pr) <sub>4</sub> , 0.14 eq. 4-nitrobenzoic acid, CH <sub>2</sub> Cl <sub>2</sub> -toluene, 35 °C, 1 h (ii) 1 eq. <b>11</b> , 2.1 eq. TMSCN, 0 °C, 17 h.   |  | <i>S</i> -98 (88) <sup>86</sup>    |
| 10 |  <p><b>24b (R,R)</b></p>   | Ti | (i) 16.5 eq. ( <i>R,R</i> )- <b>24b</b> , 15% Ti( <i>Oi</i> -Pr) <sub>4</sub> , 4 Å MS, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h (ii) 1.8 eq. TMSCN <b>13e</b> , 0.5 h (iii) -78 °C, 48 h (iv) 1 eq. <b>11</b> , -78 °C (ii) 1M HCl, 20 °C, 6 h, 92% recovery of <b>25b</b> . |  <p><b>24b<sub>Ti</sub></b></p> | <i>S</i> -79 (94) <sup>75,87</sup> |
| 11 |  <p><b>24b (S,S)</b></p>  | Ti | (i) 16.5 eq. ( <i>S,S</i> )- <b>24b</b> , 15% Ti( <i>O-i</i> -Pr) <sub>4</sub> , 4 Å MS, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h (ii) 1.8 eq. TMSCN <b>13e</b> , 0.5 h (iii) -78 °C, 48 h (iv) 1 eq. <b>11</b> , -78 h (iv) 1M HCl, 20 °C, 6 h.                              |  | <i>R</i> -77 (04) <sup>87</sup>    |
| 12 |  <p><b>24c (R,R)</b></p> | Ti | (i) 16.5 eq. ( <i>R,R</i> )- <b>24c</b> , 15% Ti( <i>Oi</i> -Pr) <sub>4</sub> , 4A MS, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1h (ii) 1.8 eq. TMSCN <b>13e</b> , 0.5 h (iii) -78 °C, 48 h (iv) 1 eq. <b>11</b> , -78 h (iv) 1M HCl, 20 °C, 6 h.                                 |  | <i>S</i> -87 (93) <sup>87</sup>    |
| 13 |  <p><b>24d</b></p>       | Ti | (i) 16.5 eq. <b>24d</b> , 15% Ti( <i>O-i</i> -Pr) <sub>4</sub> , 4A MS, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h (ii) 1.8 eq. TMSCN <b>13e</b> , 0.5 h (iii) -78 °C, 60 h (iv) 1 eq. <b>11</b> , -78 h (vi) 1M HCl, 20 °C, 6 h.   |  | <i>S</i> -89 (61) <sup>87</sup>    |

Table 2. Continued

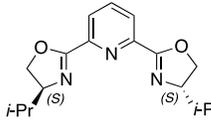
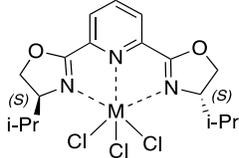
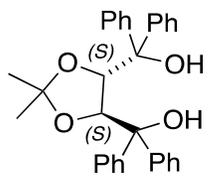
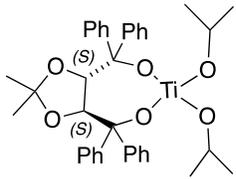
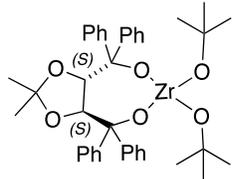
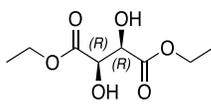
| A   | B   | C  | D   | E   | F                       |
|-----|---|----|---|---|-------------------------|
| 14a |   | Al | (i) 20% <b>25</b> , 20% AlCl <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> 10 °C (ii) 1 eq. <b>11</b> , 1.1 eq. TMSCN <b>13e</b> , 22 h.   |   | S-99 (96) <sup>88</sup> |
| 14b |   | Ln | (i) 0.2 eq. <b>25</b> , 0.1 eq. LnCl <sub>3</sub> , (ii) 1 eq. <b>11</b> , 1.2 eq. TMSCN <b>13e</b> , MeCN, 20 °C, n h (iii) 1M aq. HCl.  |   |                         |
| 14c |    | Y  | n: 1 h  |    | S-87 (67) <sup>89</sup> |
| 14d | <b>25</b>   | La | n: 3 h  | <b>25<sub>M</sub></b>   | R-96 (12) <sup>89</sup> |
| 14e |   | Eu | n: 16 h   |   | S-81 (32) <sup>89</sup> |
| 14f |   | Yb | n: 1 h  |   | S-94 (75) <sup>89</sup> |
| 15a |   | Ti | (i) 10% <b>26a</b> , 10% Ti (O- <i>i</i> -Pr) <sub>4</sub> , CHCl <sub>3</sub> , 20 °C, 1 h (ii) 1 eq. <b>11</b> , 2 eq. TMSCN <b>13e</b> , 10% Ph <sub>3</sub> P=O (iii) <b>4a</b> , -10° C, 20 h. |    | R-95 (50) <sup>90</sup> |
| 15b |   | Zr | (i) 20% Zr(Ot-Bu) <sub>4</sub> , 20% <b>26a</b> , 0.5 h (ii) Me <sub>2</sub> C(OH)CN, 1 eq. <b>11</b> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 18 h.  |  | R-45 (63) <sup>91</sup> |
| 16  |  | Bi | (i) 0.25 eq. <b>26b</b> , 2,6 eq. n-BuLi, 0.25 eq. BiCl <sub>3</sub> (ii) 1 eq. <b>11</b> , 2eq. TMSCN, CH <sub>2</sub> Cl <sub>2</sub> , -23 °C, 0.5 h (iii) 1M HCl.                               |   | S-99 (72) <sup>36</sup> |

Table 2. Continued

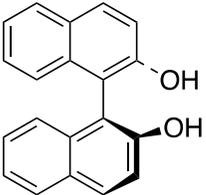
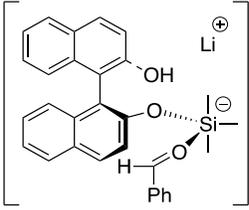
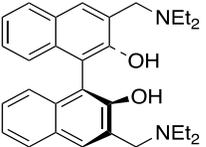
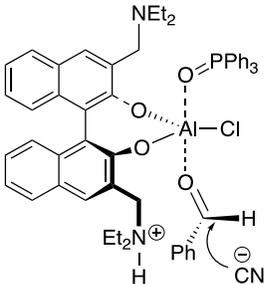
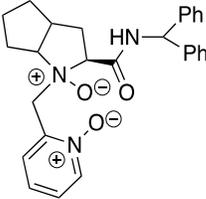
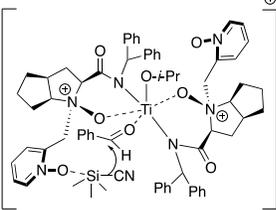
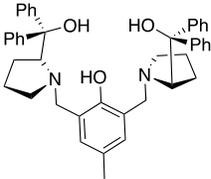
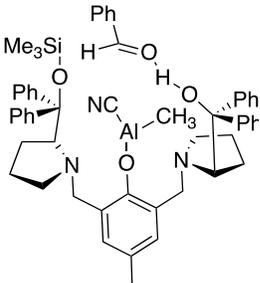
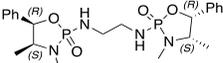
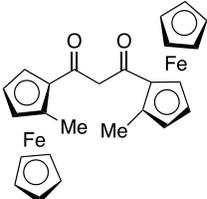
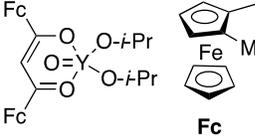
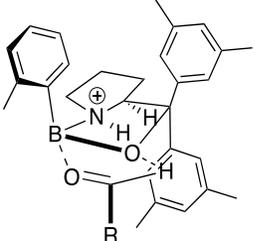
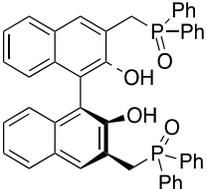
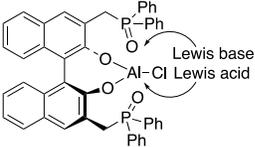
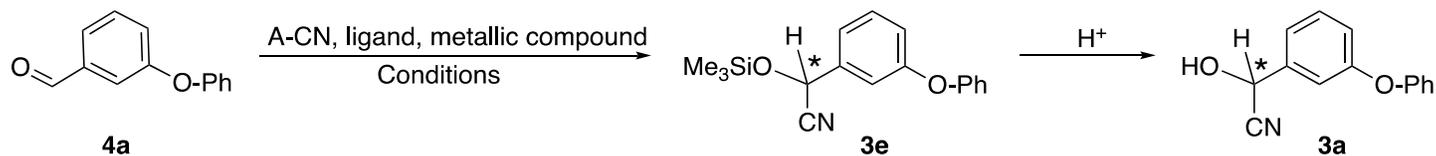
| A   | B   | C  | D   | E  | F  |
|-----|---|----|---|--|--|
| 17a |   | Ti | (i) <b>27a</b> , Ti(O <i>i</i> -Pr) <sub>4</sub> , 4 Å MS, CH <sub>2</sub> Cl <sub>2</sub> , 1 eq. <b>11</b> , TMSiCN <b>13e</b> , not specified  |  | S-90 (10) <sup>75</sup>  |
| 17b |    | Li | (i) 1% (S)- <b>27a</b> , 0.5 eq. BuLi, (ii) 1 eq. <b>11</b> , 1 eq. TMSiCN <b>13e</b> , (a,b or c):<br>(a) ether, -78 °C, 0.1 h or<br>(b) CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 0.1 h or<br>(c) Hexane, -78 °C, 0.1 h |   | S-96 (56) <sup>92</sup><br>96 (30) <sup>92</sup><br>67 (00) <sup>92</sup>                        |
| 17c |   | Na | (i) 1% (S)- <b>27a</b> , BM (M=Na,  |  | 0 (00) <sup>92</sup>   |
| 17d | (S)-BINOL   | K  | K, Mg), (ii) 1 eq. <b>11</b> , 1 eq.  |  | 0 (00) <sup>92</sup>   |
| 17e | <b>27a</b>  | Mg | TMSiCN ( <b>13e</b> ).  |  | 0 (00) <sup>92</sup>   |
| 17f |   | Al | 1 eq. <b>11</b> , 1 eq. <b>11</b> , TMSiCN ( <b>13e</b> ), 10% (R)- <b>27b</b> , Me <sub>2</sub> AlCl, 40% Ph <sub>3</sub> P=O, toluene, -20 °C, 6 h.   |   | S-99 (98) <sup>93,94</sup>   |
| 18a |  | Ti | 10% <b>28</b> , 5% MX, 1 eq. <b>11</b> , 1.5 eq. TMSiCN ( <b>13e</b> ), 20% <i>p</i> -MePhCO <sub>2</sub> H, CH <sub>2</sub> Cl <sub>2</sub> , -78 °C,  |  | 99 (80) <sup>95</sup><br>89 (69) <sup>95</sup><br>54 (36) <sup>95</sup><br>84 (55) <sup>95</sup> |
| 18b | <b>28</b>   | Al | MX: Ti(O <i>i</i> Pr) <sub>4</sub> , 20 h   |  |  |
| 18c |   | Al | MX: Al(O <i>i</i> Pr) <sub>4</sub> , 20 h   |  |  |
| 18d |   | Al | MX: AlEt <sub>3</sub> , 20 h  |  |  |
|     |   | Zr | MX: Zr(O <i>i</i> Pr) <sub>4</sub> , 20 h   |  |  |

Table 2. Continued

| A   | B   | C  | D  | E   | F                            |                              |
|-----|---|----|--|---|------------------------------|------------------------------|
| 19a | <br><b>29</b>    | Al | (i) n% MX- solvent, 11% <b>29</b> ,<br>(ii) 1 eq. TMSCN <b>13e</b> , 4 °C, 24 h<br>(iii) aq. phosphate buffer<br>n% MX: 10% AlMe <sub>3</sub> -PhCl  | <br><b>29Al</b>    | S-76 (86) <sup>96</sup>      |                              |
| 19b |   | Al | n% MX: 10% AlMe <sub>3</sub> -CH <sub>2</sub> Cl <sub>2</sub>  |   | S-60 (80) <sup>96</sup>      |                              |
| 19c |   | Al | n% MX: 10% Cl <sub>2</sub> AlMe-CH <sub>2</sub> Cl <sub>2</sub>  |   | S-20 (26) <sup>96</sup>      |                              |
| 19d |   | Zn | n% MX: 20% ZnCl <sub>2</sub> -CH <sub>2</sub> Cl <sub>2</sub>  |   | 04 (- -) <sup>96</sup>       |                              |
| 19e |   | Mg | n% MX: 10% MgBu <sub>2</sub> -CH <sub>2</sub> Cl <sub>2</sub>  |   | R-44 (15) <sup>96</sup>      |                              |
| 19f |   | Ti | n% MX: 10% Ti(O- <i>i</i> -Pr) <sub>4</sub> -CH <sub>2</sub> Cl <sub>2</sub>   |   | R-32 (21) <sup>96</sup>      |                              |
| 20  | <br><b>30</b>    | Sm | (i) 0,6% <b>30</b> , 0,2% eq. SmCl <sub>3</sub> ,<br>toluene, -78 °C (ii) 1 eq. <b>11</b> , 2 eq.<br>TMSCN <b>13e</b> , -78 °C (iii) -20 °C, 24 h  |   | R-99 (84) <sup>97</sup>      |                              |
| 21  | <br><b>31</b>   | Y  | (i) 1% Y5(O)(O- <i>i</i> Pr) <sub>3</sub> , 5% <b>31</b> ,<br>CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h (ii) 1 eq. <b>11</b> , 20 °C<br>(iii) -78 °C (iv) 7 eq. TMSCN <b>13e</b> , -78<br>°C, 2 h (v) aq. 1N HCl, THF.  | <br><b>31Y</b>    | S-95 (90) <sup>98,99</sup>   |                              |
| 22  | <br><b>32</b>  | B  | 0.1 eq. <b>32</b> , 0.2 eq. Ph <sub>3</sub> PO, 1 eq. <b>11</b> ,<br>1 eq. TMSCN <b>13e</b> , toluene, 0 °C, 40<br>h.  | <br><b>32C=O</b> | R-94 (95) <sup>100</sup>     |                              |
| 23a | <br><b>27c</b> | Al | (i) Phosphine oxide, 0.008 eq.<br>Et <sub>2</sub> AlCl, CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, (ii) 0.9 eq.<br><b>27c</b> , 20 °C (iii) -40 °C, additive, 1 eq.<br><b>11</b> , 1 h, 1.8 eq. TMSCN <b>13e</b> , 10 h<br>addition, (iv) -40 °C, final reaction<br>time | <br><b>27cAl</b> | S-91 (87) <sup>113,114</sup> |                              |
| 23b |   |    | Additive/final reaction time<br>None/36 h  |   |                              | S-98 (96) <sup>113,114</sup> |
| 23c |   |    | 3.6 eq. MeP(=O)Ph <sub>2</sub> / 96 h<br>3.6 eq. Bu <sub>3</sub> P=O/200 h   |   |                              | < 1 (- -) <sup>113,114</sup> |



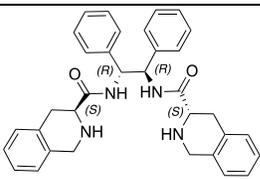
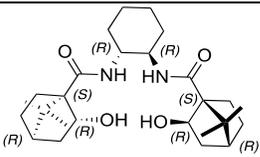
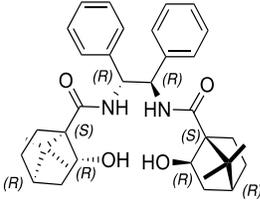
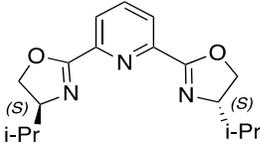
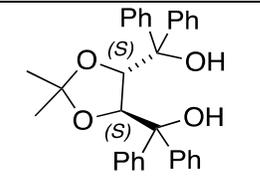
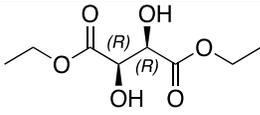
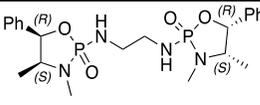
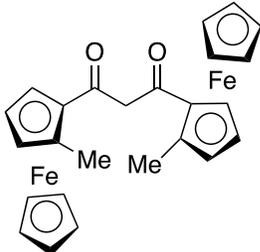
**Scheme 27.** Enantioselective synthesis of 3-phenoxymandelonitrile (**3a**), and its trimethylsilyl ether from 3-phenoxybenzaldehyde (**4a**) involving metallic species and chiral ligands.

**Table 3.** Presentation of selected catalyzed reactions that allow the enantioselective synthesis of 3-phenoxy mandelonitrile (**3a**) or its trimethylsilylated derivative (**3e**)

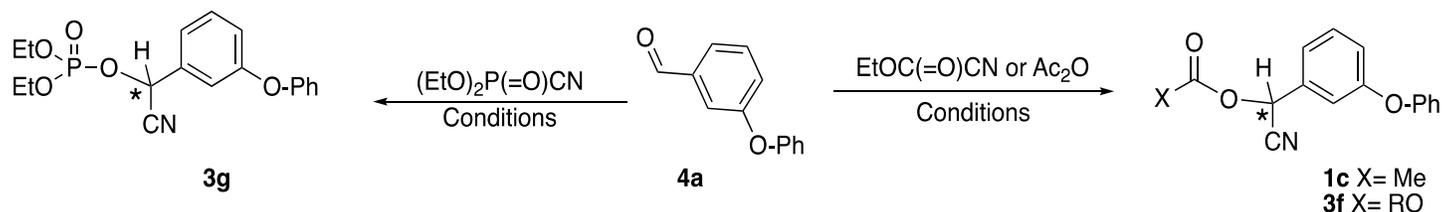
Columns: A: entry number, B: structure and number of the ligand, C: metal involved, D: experimental conditions, E: *stereochemistry of the major enantiomer*-reaction yield % (enantiomeric excess %)

| A | B                       | C  | D  | E                                  |
|---|-------------------------|----|--|------------------------------------|
| 1 | <p><b>22b</b></p>       | Ti | (i) 0.21 eq. <b>22b</b> CH <sub>2</sub> Cl <sub>2</sub> , 0.2 eq. Ti(O- <i>i</i> -Pr) <sub>4</sub> , 20 °C, 1 h (ii) -80 °C (iii) 1 eq. <b>4a</b> , 2.24 eq. TMSCN <b>3e</b> , -80 °C, 36 h, | <i>R</i> -67 (79) <sup>77,78</sup> |
| 2 | <p><b>22e</b></p>       | Ti | (i) 0.21 eq. <b>22b</b> CH <sub>2</sub> Cl <sub>2</sub> , 0.2 eq. Ti(O- <i>i</i> -Pr) <sub>4</sub> , 20 °C, 1 h (ii) -80 °C (iii) 1 eq. <b>4a</b> , 2.24 eq. TMSCN <b>3e</b> , -80 °C, 60 h. | <i>S</i> -58 (49) <sup>101</sup>   |
| 3 | <p><b>22c, 22cv</b></p> | V  | (i) 0.5% VOSO <sub>4</sub> , 0.5% <b>22c</b> + <b>22cv</b> , (ii) 1 eq. <b>4a</b> , 2 eq. TMSCN <b>3e</b> , 0.5% TBAF, MeCN, -20 °C, 24 h.   | <i>S</i> -94 (81) <sup>79</sup>    |
| 4 | <p><b>22d</b></p>       | Ti | (i) HCN, 10% <b>22d</b> , Ti(OEt) <sub>4</sub> , (ii) 1 eq. <b>4a</b> , 1 eq. TMSCN <b>3e</b> , toluene, -40 °C, 11 h then -20 °C, 11 h (iii) H <sub>3</sub> O <sup>+</sup> .                | <i>S</i> -85 (86) <sup>80</sup>    |
| 5 | <p><b>23d</b></p>       | Al | (i) 1% <b>23b</b> , 1% AlCl <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> 10 °C, (ii) 1 eq. <b>4a</b> , 1.1 eq. TMSCN <b>3e</b> , 22 h.   | <i>R</i> -93 (81) <sup>85</sup>    |

Table 3. Continued

| A  | B   | C  | D  | E                          |
|----|---|----|--|----------------------------|
| 6  | <br><b>24a</b>       | Ti | 2.1eq. TMSCN <b>13e</b> , 10% mol <b>24a</b> , 15% Ti(O- <i>i</i> -Pr) <sub>4</sub> , 0.075 eq. 4-nitro benzoic acid, 1 eq. <b>4a</b> , CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 17 h,  | S-73 (76) <sup>86</sup>    |
| 7  | <br><b>24b (R,R)</b> | Ti | (i) 16.5 eq. <b>24b</b> , 15% Ti(O <i>i</i> -Pr) <sub>4</sub> , 4 Å MS (65 mg/mmol), CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h (ii) 1.8 eq. TMSCN <b>13e</b> , 0.5 h (iii) -78 °C (iv) 1 eq. <b>4a</b> , -78 h, 120 h (iv) 1M HCl, 20 °C, 6 h; 92% recovery of <b>25d</b> . | S-57 (97) <sup>35,87</sup> |
| 8  | <br><b>24c (R,R)</b> | Ti | (i) 16.5 eq. <b>24c</b> , 15% Ti(O <i>i</i> -Pr) <sub>4</sub> , 4 Å MS (65 mg/mmol), CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h (ii) 1.8 eq. TMSCN <b>13e</b> , 0.5 h (iii) -78 °C (iv) 1 eq. <b>4a</b> , -78 h, 120 h (iv) 1 M HCl, 20 °C, 6 h.                             | S-54 (95) <sup>87</sup>    |
| 9  | <br><b>25</b>       | Yb | (i) 0.2 eq. <b>25</b> , 0.1 eq. YbCl <sub>3</sub> , (ii) 1 eq. <b>4a</b> , 2.5 mol. TMSCN <b>13e</b> , MeCN, 20 °C, 2 h.   | S-98 (68) <sup>89</sup>    |
| 10 | <br><b>26a</b>     | Ti | (i) 10% <b>26a</b> , 10% Ti (O- <i>i</i> -Pr) <sub>4</sub> , CHCl <sub>3</sub> , 20 °C, 1 h (ii) 2 eq. TMSCN <b>13e</b> , 10% Ph <sub>3</sub> P=O (iii) 1eq. <b>4a</b> , -10 °C, 20 h.   | R-92 (40) <sup>90</sup>    |
| 11 | <br><b>26b</b>     | Bi | (i) 0.25 eq. <b>26b</b> , 2,6 eq. <i>n</i> -BuLi, 0.25 eq. BiCl <sub>3</sub> (ii) 1 eq. <b>4a</b> , 2 eq. TMSCN <b>13e</b> , CH <sub>2</sub> Cl <sub>2</sub> , -23 °C, 0.5 h (iii) 1M HCl.   | S-99 (58) <sup>36</sup>    |
| 12 | <br><b>30</b>      | Sm | (i) 0.01% <b>30</b> , 0,2% SmCl <sub>3</sub> , toluene, 2 eq. TMSCN <b>13e</b> , -78 °C (ii) 1 eq. <b>4a</b> , -20 °C, 15 h (iii) 1N HCl, AcOEt, 27 °C, 4 h.   | R-92 (45) <sup>97</sup>    |
| 13 | <br><b>31</b>      | Y  | (i) 1% Y <sub>5</sub> (O)(O- <i>i</i> -Pr) <sub>13</sub> , 5% <b>31</b> , CH <sub>2</sub> Cl <sub>2</sub> , 20 °C, 1 h (ii) 1 eq. <b>4a</b> , 20 °C (iii) -78 °C (iv) 4 eq. <b>11</b> , 7 eq. TMSCN <b>13e</b> , -78 °C, 2 h (v) aq. 1N HCl, THF.                              | S-95 (79) <sup>98,99</sup> |

We have presented in a separate table (Scheme 28, Table 4) the results concerning differently “protected” 3-phenoxymandelonitriles **1c**, **3g**, **3f** that proved quite difficult to transform to 3-phenoxymandelonitrile (**3a**).



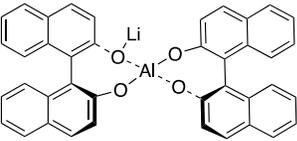
**Scheme 28.** Reactions that allow the enantioselective synthesis of 3-phenoxymandelonitrile-phosphonate **3g**, acetate **1c** and carbonate **3f** from 3-phenoxybenzaldehyde (**4a**).

**Table 4.** Presentation of selected catalyzed reactions that allow the enantioselective synthesis of 3-phenoxy-mandelonitrile-phosphonate **3g**, acetate **1c** and carbonate **3f**

A: entry number , B: structure and number of the ligand, C: metal involved, D: experimental conditions, E: *stereochemistry of the major enantiomer*-reaction yield % (enantiomeric excess %); reference

| A | B   | C  | D   | E                        |
|---|---|----|---|--------------------------|
| 1 | <p style="text-align: center;"><b>23b</b></p>               | Ti | 5% <b>23b</b> , 5% $\text{Ti}(\text{O-}i\text{-Pr})_4$ , 1 eq. <b>4a</b> , 1.5 eq. $\text{EtOC}(=\text{O})\text{-CN}$ , $i\text{-PrOH-CHCl}_3$ , $-20^\circ\text{C}$ , 10 h.  | 90 (90) <sup>102</sup>   |
| 2 | <p style="text-align: center;"><b>23b</b><sub>TiO</sub></p> | Ti | 1 eq. <b>4a</b> , 4 eq. KCN, 4 eq. $\text{Ac}_2\text{O}$ , 1% <b>23b</b> <sub>TiO</sub> , $\text{CH}_2\text{Cl}_2/t\text{-BuOH}/\text{H}_2\text{O}$ (2500/10/1), $-42^\circ\text{C}$ , 10 h, 280 rotations/min.                         | S-99 (90) <sup>103</sup> |
| 3 | <p style="text-align: center;"><b>(S)-BINOLAM 27b</b></p>   | Al | (i) 0.1 eq. $\text{Me}_2\text{AlCl}$ , 0.1 eq. <b>(S)-BINOLAM 27b</b> , hexane-toluene, $20^\circ\text{C}$ , 1 h (ii) 1 eq. <b>4a</b> , 3 eq. $(\text{EtO})_2\text{P}(=\text{O})\text{CN 13d}$ , $20^\circ\text{C}$ , 2 h (iii) 2M HCl. | R-90 (97) <sup>104</sup> |

Table 4. Continued

| A  | B   | C    | D   | E                        |
|----|---|------|---|--------------------------|
| 4  | <br>(S)-ALB<br><b>27a<sub>AlLi</sub></b> | AlLi | (i) 0.025 eq. (S)-BINOL, 0.0013 eq. AlEt <sub>3</sub> , 0.0013 eq. <i>n</i> -BuLi, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 1 h. Leads to <b>27a<sub>AlLi</sub></b> (ii) 1 eq. <b>4a</b> , 0.025 eq. cinchonine, CH <sub>2</sub> Cl <sub>2</sub> , 25 °C, 0.5 h (iii) 1.5 eq. EtOC(=O)CN <b>13c'</b> , -20 °C, 1.5 h: |                          |
| 4a |   |      | Reaction carried out in CH <sub>2</sub> Cl <sub>2</sub>   | S-99 (30) <sup>105</sup> |
| 4b |   |      | Reaction carried out in CHCl <sub>3</sub>   | 94 (30) <sup>105</sup>   |
| 4c |   |      | Reaction carried out in toluene   | 91 (00) <sup>105</sup>   |
| 4d |   |      | Reaction carried out in THF   | 90 (02) <sup>105</sup>   |

**2.4.3.1.1.2. The ligand.** Several types of ligands have been used (Tables 2, 3 and 4, entry B). They usually bear hydroxyl groups as alcohols or phenols and amino group that help to complex the metal. Among those are:

(1) Schiff's bases derived from:

(a)  $\alpha$ -formyl-phenols and (i) chiral  $\beta$ -amino alcohols **22a**, **22** introduced for asymmetric catalysis by Nozaki and Noyori (Table 2, entries 3, 4; Table 3, entries 1, 2)<sup>106</sup> or (ii) related chiral  $\alpha$ -amino acid **22c** (Table 2, entry 5; Table 3, entry 3). They are ligands for Ti(IV) and V(IV)

b)  $\alpha$ -formyl-phenols and chiral vicinal diamino compounds such as 1,2-diamino-1,2-diphenyl ethane (**23a**) or 1,2-diaminocyclohexane (**23b**) leading to salen-compounds, introduced by Jacobsen and Katsuki for asymmetric catalysis.<sup>107</sup> They proved to be particularly valuable for asymmetric hydrocyanation of aromatic aldehydes (Table 2, entries 7,8; Table 4, entries 1, 2). They are ligands among others for Ti(IV), Li(I), Al(III),

It has been reported that salen-Ti(IV) **23b** is only operative in anhydrous medium. Otherwise it is transformed to **23b<sub>TiO</sub>** that possesses a different catalytic profile.<sup>103</sup>

In the case of Schiff bases, it has been noticed that the presence of a hindered group such as a *t*-butyl group at the 6-position of the phenols dramatically favor the enantioselectivity (Table 2, compare entry 4 to entry 3). Many other ligands of the series possess this structural feature (Table 2, entries 5,8a,8b,8c,8d,8e,8f; Table 3, entries 1, 2, 3, 5; Table 4, entries 1, 2), It has however been found<sup>81</sup> that the ligand **23a** lacking the *t*-butyl group on the aromatic ring leads to a higher enantioselectivity as compared to the analogue possessing the *t*-butyl group in this position.

(2) The bis(oxazoline) (BOX) ligands such as (**25**) (PyBOX) introduced by Nishiyama<sup>108</sup> and popularized by Evans<sup>109</sup> for asymmetric catalysis. It complexes the metal of metal salts leading to **25<sub>M</sub>** without formation of a covalent bond (Table 2, entry 14b-14f, Table 3, entry 9) and have been used to complex Ti(IV), Al(III), Y(III), La(III), Eu(III) and Yb(III) compounds.

(3) The diamides **24** derived from ketopinic acid chloride and (i) ortho diamino benzene leading to **24d** or (ii) chiral vicinal diamino compounds involving 1,2-diamino-1,2-diphenylethane leading to **24c** and 1,2-diaminocyclohexanes leading to **24b**. The former combination leads to modest enantioselectivity (ee: 61%, Table 2 entry 13), whereas in the case of and 1,2-diaminocyclohexanes there is a very big difference of selectivity between the matched (*R,R*)-**24** and the mismatched (*S,S*)-**24b** pairs of diastereoisomers (Table 2, compare entry 10 to entry 11). It has been also incidentally found that the use of molecular sieves dramatically increases the enantioselectivity.<sup>87</sup>

(4) The chiral-1,4 diols such as 1,3-dioxolane-4,5-dimethanol (TADDOLs) **26a**(Table 2, entry 15; Table 3, entry 10) introduced by Seebach for asymmetric catalysis<sup>110</sup> that are ligands for Ti(IV), Zr(IV) as well as the binaphthols

(BINOLs) **27** introduced by Noyori for asymmetric catalysis<sup>111</sup> (Table 2, entries 17; Table 4, entries 3,4) that are ligands for Li(I), Na(I), K(I), Al(III). Although the ee proved to be quite modest when BINOL **26a** is used, dramatic increases of stereoselectivity have been observed with analogous enantiopure BINOL **27b** bearing a diethylaminomethylene group on each naphthalenyl units (Table 2, entry 17f; Table 4, entry 3).<sup>93,94,104</sup> Increased enantiomeric excesses have been also observed using the catalyst **27a**<sub>AILi</sub> heterobimetallic aluminum lithium compound that includes two BINOL units,<sup>105</sup> a type of catalyst invented by Shibasaki (Table 4, entry 4).<sup>112</sup>

In few cases comparisons of the results related to different metals using the same ligands have been shown (Table 2, compare entries 8a to 8d-8f; entry 14a to 14b-f; entry 15a to 15b; entry 17a to 17b-e; entry 18a to 18b-d; entries 19a-f).

In some cases, it has been noticed that the ligand has been easily separated from the other compounds after the reaction, recovered in up to 95% yield and successfully recycled.<sup>100</sup>

**2.4.3.1.1.3. The catalyst.** The catalyst produced by reaction between the “metal salt” and the ligand has been in some case prepared then introduced in the reaction mixture whereas in other case it has been prepared *in situ*. Although at the early time, stoichiometric amount of catalyst has been used (Table 2, entry a), catalysts have been later designed that leads to the cyanohydrins in high enantiomeric excess when used in only 10-20% (Table 2, entries 2, 3, 4, 6, 7, 11, 12, 13, 14a-f, 15a, 15b, 16, 17f, 18, 19, 22; Table 3, entry, 1, 2, 4, 6, 7, 8, 9, 10, 11; Table 4, entry 3) and even 1-5% (Table 2, entry 5, 8a, 8b, 8c, 8d, 8e, 8f, 17b, 20, 21; Table 3, 5, 12, 13; Table 4, entry 1, 2, 4).

**2.4.3.1.1.4. The cyanide donor.** Most of the reactions presented in Tables 2 and 3 have been carried out with trimethylsilyl cyanide. Other reagents that have been only scarcely used are acetone cyanohydrin (**13a**) and potassium cyanide in the presence of a trapping agent such as acetic anhydride or ethoxycarbonyl cyanide or cyanodiethylphosphonate (Scheme 28, Table 4).

Reactions have been usually performed in chlorinated solvents such as dichloromethane or chloroform. In some cases, dramatic differences have been observed between those closely related solvents (Table 4, compare entries 4a and 4b).<sup>105</sup> However, toluene, ether, THF, ethanol, acetonitrile, have been from time to time used (Tables 2, 3, 4). Some striking differences have been in some cases noticed (Table 2, compare entry 17c to 17d,e; entry 19a to 19b; Table 4, entry 4a to entries 4b-d). See also ref. 103.

The reactions have often been carried out in the presence of additives, that either increase the yield or the enantioselectivity but the mechanistic implications of which have rarely been elucidated. We can cite among others (i) tetrabutyl ammonium fluoride (Table 2, entry 5; Table 3, entry 3); (ii) triethylamine (Table 2, entry 8b); benzoic acids (Table 2, entries 9,18; Table 3, entry 6); molecular sieves (Table 2, entries 10, 11, 12, 13, 17a; Table 3, entries 7, 8), cinchonine (Table 4, entry 4) and *t*-butanol (Table 4, entry 2).

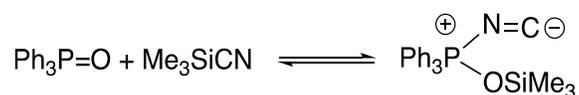
In the last case, for example, several additives have been tested with little success in the reaction of potassium cyanide, acetic anhydride and 1% catalyst **23b**<sub>TiO</sub> with benzaldehyde:<sup>103</sup> For example, the addition of acids generally and acetic acid in particular decreases the rate of the reaction, and addition of hydrogen cyanide leads to dramatic loss of enantioselectivity.<sup>103</sup> Water, *t*-butanol, mineral acids, N-bases, thiols, thiourea, CS<sub>2</sub>, Ph<sub>4</sub>BNa, mineral carbonates, surfactants, phosphines, and phosphine oxides have improved greatly the reaction rate, but the most successful additives proved to be either 1H-imidazole (10 mol-% rel. to benzaldehyde) or the mixture of H<sub>2</sub>O/*t*-BuOH (10 and 100 mol-% rel. to benzaldehyde, resp.) added to the reaction mixture (see Table 4, entry 2 for application of those conditions to 3-phenoxybenzaldehyde (**4a**)).<sup>103</sup>

The role of water (Table 2, compare entries 8a to 8b)<sup>103</sup> and triphenylphosphine<sup>100</sup> (Table 2, entries 8f,15a,17f,22; Table 3, entry 10), has been however identified in some cases. As already discussed above, it has been found that salen-Ti(IV) **23b**<sub>TiO</sub> rapidly reacts with water, even with trace of moisture, to produce, *in situ*,

the dimer **23b**<sub>TiO</sub> that possesses a different catalytic profile and changes the course of the reaction.<sup>103</sup> Since (**23b**<sub>TiO</sub>) is a better catalyst than **23b**, the later has been voluntarily reacted with an equivalent amount of water prior introduction of the reactants in the medium for the next step (Table 2, compare entries 8; Table 4, entry 2).<sup>82,83,103</sup>

It was originally noticed by Shibasaki<sup>113-115</sup> and Najera<sup>93,94</sup> that increased enantioselectivity is observed in reactions carried out in the presence of Bu<sub>3</sub>P=O,<sup>113,114</sup> MeP(=O)Ph<sub>2</sub><sup>113,114</sup> or Ph<sub>3</sub>P=O.<sup>93,94,100</sup> Those results have triggered the incorporation of the phosphine oxide moiety into the ligands<sup>113,114</sup> (Table 2, entry 23/F)<sup>115</sup> and has been at the root of the concept of “two-center catalysis”.

Corey also found that addition of triphenylphosphine (20 mol%) to the reaction containing the boron catalyst **32** (10 mol%), improved dramatically the enantioselectivity of the reaction.<sup>100</sup> Basic NMR and infrared studies suggested that triphenylphosphine oxide reacts with trimethylsilyl cyanide to produce the new and more reactive species, whose structure are shown on Scheme 29, that exhibits an isocyanato structure and is suspected to be responsible of the observed increased selectivity.<sup>100</sup>



**Scheme 29.** Cyanide-to-isocyanide transformation.<sup>100</sup>

**2.4.3.1.2. Organocatalysis in asymmetric synthesis of 3-phenoxymandelonitrile.** Catalysis implying metals presented above although it allows the synthesis of cyanohydrins in good yields and with high stereocontrol, suffers from (i) the loss of the metal involved in the catalyst, (ii) low temperature (<-30°C) often required, and long reaction times (>24h) that are not compatible with industrial requirements.

On the contrary, organocatalysis proved to be efficient for the enantioselective synthesis of mandelonitriles especially that of 3-phenoxymandelonitrile (**3a**). This is in particular the case when the cyclic dipeptides: cyclo[(*R*)-phenylalanyl-(*R*)-histidyl]diketopiperazide (*R,R*)-(**33**) or its enantiomer cyclo[(*S*)-phenylalanyl-(*S*)-histidyl] diketo piperazide (*S,S*)-(**33**)<sup>4,116-122</sup> that to a certain extent mimic the nitrile lyase enzymes, are used as catalyst.<sup>4</sup>

It was found that (*S*)-**3a** is produced in about 4h in high yield (94%) and high enantiomeric excess (ee > 92%, Table 5, entry 2d) on reaction of **4a** with two equivalents of hydrogen cyanide (from NaCN and H<sub>2</sub>SO<sub>4</sub>)<sup>121</sup> and only 0.2% equivalents of (*R,R*)-**33** as a catalyst in a suitable solvent at 5°C (Scheme 30, Table 5, entry 2d).<sup>120</sup> Lower yields are obtained if the aldehyde **4a** is subjected to a transcyanation using instead acetone cyanohydrin (**13a**) in the presence of the same catalyst that requires to be carried out at higher temperature (Table 5, compare entry 1a to 2a).<sup>116</sup>

Poor results are observed when DMSO is used as the solvent<sup>119,120</sup> whereas very good results have been observed with **33** in toluene,<sup>120</sup> that exhibits thixotropic behavior. Increased enantioselectivity is observed upon increasing the stirring rate that concomitantly decreases the viscosity.<sup>119,121</sup> Otherwise, good results are obtained when the reactions are performed in a gel or when the catalyst is present in the medium as an amorphous solid (by precipitation from methanol, spray drying, supercritical CO<sub>2</sub> drying, lyophilization).<sup>121</sup> The presence of an alcohol at early stage of the process besides the aprotic inert solvent is especially useful in reducing the induction period,<sup>122</sup> increasing the reaction rate, and the enantiomeric excess of the cyanohydrin.<sup>122</sup>

Higher enantioselectivity is observed when the solution is extracted with acid (aq. H<sub>2</sub>SO<sub>4</sub>) prior to the addition of the catalyst since this treatment allows the removal of trace of amines, if any, that could compete with the catalyst to produce racemic **3a**.<sup>117</sup>

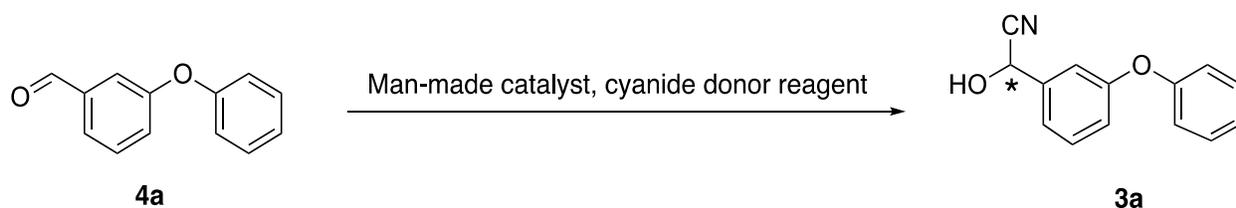
It was also found<sup>120</sup> that the enantioselectivity of the transformation of 3-phenoxybenzaldehyde (**4a**) to 3-phenoxymandelonitrile (**3a**) increases by increasing the reaction time (Scheme 30, Table 5, entries 2g,2h; Compare entry 2d to entries 2a,2b,2c). This implies that the product **3a** formed interacts with the original catalyst **33** to form a more enantioselective one! This behavior named “enantioselective autoinduction” has been observed and defined previously by Alberts and Wynberg.<sup>123</sup>

It has been thus reported that addition, at the early stage of the reaction, of small amount of:

(i) (*S*)-3-phenoxymandelonitrile (*S*)-(**3a**) (0.09 eq.), the enantiomer expected to be formed,<sup>121</sup> generates<sup>121</sup> (*S*)-3-phenoxymandelonitrile (*S*)-(**3a**) more rapidly and with higher enantioselectivity compared to the original reaction (Table 5, compare entry 2h to entries,2e,2f,2g; Compare entry 2e to entry 2a especially entry H),

(ii) (*R*)-3-phenoxymandelonitrile (*R*)-(**3a**) (0.09 eq.), the mismatched enantiomer, generates<sup>121</sup> (*S*)-3-phenoxymandelonitrile (*S*)-(**3a**) more rapidly but with lower enantioselectivity compared to the original reaction (Table 5, compare entries 2l, 2h and 2d),

(iii) (*S*)-mandelonitrile (*S*)-(**12a**) (0.04 eq.) leads<sup>116</sup> to (*S*)-3-phenoxymandelonitrile (*S*)-(**3a**) with a slightly higher enantioselectivity compared to the original reaction (Table 5, entry 3b compare to entry 3a). This enantioselectivity proved to be lower than the one generated by addition of the same seed amount (0.04 eq.) of (*S*)-3-phenoxymandelonitrile (*S*)-(**3a**) (Table 5, entry 3c compare to 3a, b).<sup>116</sup>



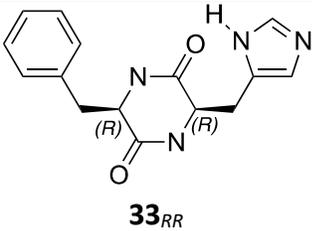
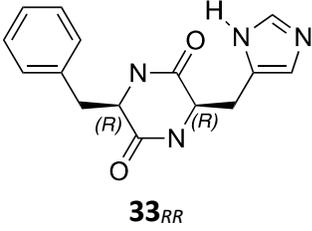
**Scheme 30.** Enantioselective synthesis of a cyanohydrin from an aromatic aldehyde using enantiopure man-made catalysts.

**Table 5.** Presentation of selected catalyzed reactions that allow the enantioselective synthesis of 3-phenoxymandelonitrile-phosphonate (**3g**), acetate **1c** and carbonate **3f**

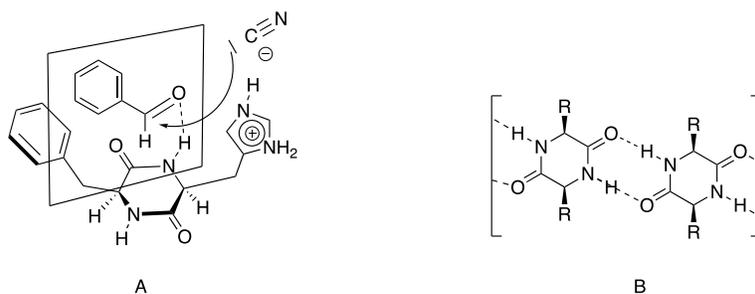
Columns: A: entry number, B: structure and number ligand, C: additive, D: Experimental conditions, E: *major enantiomer generated*-reaction yield % (enantiomeric excess %)

| A  | B                          | C | D  | E                                |
|----|----------------------------|---|--|----------------------------------|
| 1a | <br><b>33<sub>ss</sub></b> | - | (i) 1 eq. <b>4a</b> , 1eq. Me <sub>2</sub> C(OH)CN, 0.04 eq. <b>33</b> , benzene, 50 °C, 1 h (ii) HCl, MeOH. | <i>R</i> -25 (46) <sup>116</sup> |
| 1b |                            | - | (i) 1 eq. <b>4a</b> , 0.02 eq. <b>33</b> , 2 eq. HCN, toluene, -20 °C, 8 h                                   | <i>R</i> -97 (92) <sup>118</sup> |

Table 5. Continued

| A  | B  | C                        | D  | E                          |
|----|--|--------------------------|--|----------------------------|
|    |   |                          | 1 eq. <b>4a</b> , 0.02 eq. ( <i>R</i> )- <b>33</b> , 2 eq. HCN, n eq. <b>3a</b> , toluene, 5 °C, t h   |                            |
| 2a |  | -                        | 0.5 h  | S-21 (34.4) <sup>120</sup> |
| 2b |  | -                        | 1 h  | S-39 (66.2) <sup>120</sup> |
| 2c |  | -                        | 2 h  | S-92 (91.6) <sup>120</sup> |
| 2d |  | -                        | 4 h  | S-94 (92.0) <sup>120</sup> |
| 2e |  | ( <i>S</i> )- <b>3a</b>  | n = 0.09 eq., 0.5 h  | S-55 (95.8) <sup>120</sup> |
| 2f |  | ( <i>S</i> )- <b>3a</b>  | n = 0.09 eq., 1 h  | S-79 (96.4) <sup>120</sup> |
| 2g |  | ( <i>S</i> )- <b>3a</b>  | n = 0.09 eq., 2 h  | S-92 (96.8) <sup>120</sup> |
| 2h |  | ( <i>S</i> )- <b>3a</b>  | n = 0.09 eq., 4 h  | S-95 (96.6) <sup>120</sup> |
| 2i |  | ( <i>R</i> )- <b>3a</b>  | n = 0.09 eq., 0.5 h  | S-17 (34.8) <sup>120</sup> |
| 2j |  | ( <i>R</i> )- <b>3a</b>  | n = 0.09 eq., 1 h  | S-38 (66.2) <sup>120</sup> |
| 2k |  | ( <i>R</i> )- <b>3a</b>  | n = 0.09 eq., 2 h  | S-92 (92.2) <sup>120</sup> |
| 2l |  | ( <i>R</i> )- <b>3a</b>  | = 0.09 eq., 4 h  | S-95 (92.4) <sup>120</sup> |
|    |  |                          | (i) 0.02 eq. solid <b>33</b> , n eq. ( <i>S</i> )-RCH(OH)CN, toluene, 20 °C, 0.8 h (ii) 1 eq. ( <b>4a</b> ), -25 °C, 4 h (iii) 2.5 eq. HCN (iv) 0.1N HCl |                            |
| 3a |  | -                        | n= 0   | S-92 (85) <sup>116</sup>   |
| 3b |  | ( <i>S</i> )- <b>12a</b> | n= 0.04  | S-94 (87) <sup>116</sup>   |
| 3c |  | ( <i>S</i> )- <b>3</b>   | n= 0.04  | S-87 (89) <sup>116</sup>   |

Although some studies have been carried out in solution and mechanisms have been proposed (Scheme 31),<sup>4,118,121</sup> they do not account for all the experimental observations and therefore the precise structure of the transition state of the reaction, and its intimate mechanism remain unresolved.<sup>121</sup>



**Scheme 31.** A: Simplified model of the transition state of the enantioselective organocatalyzed hydrocyanation of benzaldehyde, B: model of the interactions in solution between structures of cyclic dipeptides involved in the process shown in A.

**2.4.3.2. Asymmetric hydroxycyanation of 3-phenoxybenzaldehyde using hydroxynitrile lyase.** Enantiopure cyanohydrins<sup>4,23,24,124</sup> are known in nature where they play the role of chiral building block or alternatively as a stock of ammunition by producing on request the deadly hydrogen cyanide for leaving system that possess a

respiratory system such as mammals. This field has been investigated in plants more than a century ago by Rosenthaler.<sup>125</sup>

Hydroxynitrile lyases are responsible of the transformation of carbonyl compounds to the corresponding cyanohydrins.<sup>23,24,126-134, 139-143</sup> Applying successfully this process to the enantioselective organic synthesis request that the enzymatic process is favored over the non-enzymatic reaction that could compete leading to racemic cyanohydrins.

It has been calculated<sup>126</sup> that to achieve an enantiomeric excess of 99% a ratio of 100:1 catalyzed / uncatalyzed process is required whereas to reach an ee of 99.9% a ratio of 1,000:1 is obligatory and therefore, the non-enzymatic must be significantly reduced.<sup>131</sup> This has been usually accomplished:<sup>126</sup>

(a) by decreasing the pH-value in the aqueous phase and the reaction temperature. For example, at 5 °C and pH 5.5, the non-enzymatic reaction involving benzaldehyde is drastically inhibited over that of hydroxynitrile lyase from *Prunus amygdalus* (for which the rate determining step seems to be the conversion of the ternary complex into the free enzyme and mandelonitrile) although its rate is also lowered,<sup>127</sup>

(b) by introducing a chemical shunt in the transformation of carbonyl compounds to their cyanohydrins that could divert the flux of reactants away from the nonenzymatic direction that favors the enzymic pathway.<sup>132</sup> This strategy has been originally successfully applied by Kyler<sup>132</sup> on phenylacetaldehyde using acetone cyanohydrin (**13a**) as a cyanide donor in water-immiscible solvent [1.3 eq. **13a**, acetate buffer (pH 5.0), *R*-oxynitrilase, ether, 23 °C; 83% yield, ee 88%; in absence of the oxynitrilase; 8% yield, ee 0%].<sup>132</sup> It has been successfully applied to 3-phenoxybenzaldehyde (**3a**) using (*R*)-hydroxynitrile lyase from *Prunus mume* (Table 6, compare entry 2 to entry 1).<sup>133</sup>

Although crude enzymes are available and often used, genes encoding HNL's enable the heterologous production of HNL's in industrially relevant expression system such as *Escherichia coli* so sufficient quantities of proteins can be produced with constant quality and batch-to -batch reproducibility at low cost.<sup>124</sup>

It has been also described by Effenberger<sup>128</sup> that immobilized hydroxynitrile lyase (*e.g.* on nitrocellulose) in an organic solvent offers a definite advantage over biocatalysis in aqueous media.<sup>129</sup> The use of organic solvents greatly enhances the solubility of the substrate and suppresses the non-enzymatic reaction. Recovery of product is easier and substrate and/or product inhibition is reduced. However, limitations arise from limited stability and lower activity of the enzymes.

Immobilization has been successfully applied to the synthesis of 3-phenoxymandelonitrile (**3a**) out of a solution of 3-phenoxybenzaldehyde (**4a**) and hydrogen cyanide is passed through a porous membrane comprising a polymeric resinous binder having finely divided filler particles dispersed through-out the binder to which the (*S*)-hydroxynitrile lyase from *sorghum shoots* enzyme has been chemically bound (Table 6).<sup>142</sup> It can be observed that di-*n*-butyl ether was the best solvent, the higher yield being achieved at 20 °C (Table 6, entry 6a) and the higher ee obtained when the reaction is performed at lower temperature (6 °C, Table 6, entry 6b).<sup>142</sup>

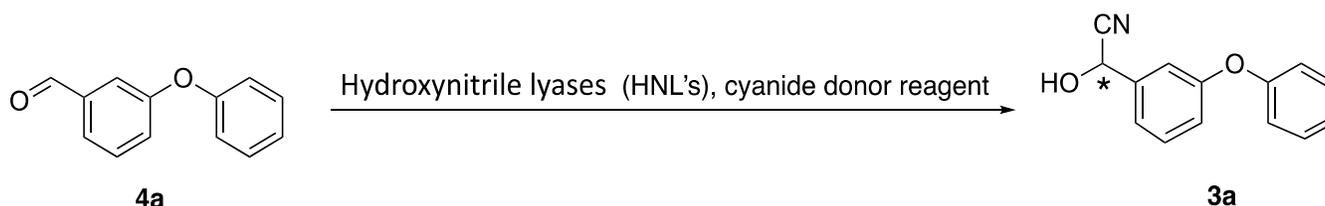
Reactions have even been also successfully carried out in "dry" organic solvents.<sup>141</sup>

Homogeneous pure organic systems wherein the substrates and products are dissolved afford high degrees of conversion even at low hydrogen cyanide-substrate ratios.<sup>126,130</sup> Hydrogen cyanide<sup>131</sup> and more efficiently acetone cyanohydrin (**13a**)<sup>132</sup> in an ether-aqueous-buffered biphasic solvent system, proved to be valuable although in the latter case the solubility properties of the substrate have a pronounced effect on the enantiomeric purity of the mandelonitrile and although exchanging ether by ethanol still generates mandelonitrile in high yield it takes place with poor enantioselectivity.<sup>132</sup>

Several hydroxynitrile lyases belong to the(*R*)-selective series.<sup>4</sup> This is among others the case of those related to the following species: *Prunus amygdalus* (almond, nuts),<sup>126</sup> *Prunus laurocerasus* (cherry laurel, seeds),

*Prunus lyonii* (California cherry, seeds), *Prunus serotina* (black cherry, seeds), *Linum usitatissimum* (linseed, seedling),<sup>126</sup> *Phlebodeum aureum* (fern, leaves) and *Arabidopsis thaliana*. They have been the first to be discovered. (See Table 6, entries 1-3 for results involving 3-phenoxybenzaldehyde (**4a**))

Others belong to (*S*)-selective series.<sup>4</sup> This is among others the case of those related to the following species: *Manihot esculenta* (manioc, leaves; Table 6, entry 5), *Hevea brasiliensis* (rubber tree, leaves; Table 6, entry 4), *Sorghum bicolor* (millet, seedlings), *Sorghum vulgare* (millet, seedlings), *Ximenia americana* (sandalweed, leaves). The hydroxynitrile lyase from *Manihot esculenta* (MeHNL), transforms a broad spectrum of aldehydes and ketones and some variants such as MeHNL–W128A expands the substrate range to more bulky substrates (Table 6, entry 5a, compare with entry 5b).<sup>131</sup> The synthesis of the (*S*)-enantiomers is hampered by the limited availability of the required biocatalyst (*S*-oxynitrilase from *Sorghum*) and its narrow substrate specificity. (See Table 6, entries 4-6 for results involving 3-phenoxybenzaldehyde (**4a**)).



**Scheme 32.** Hydroxynitrile lyases: cyanohydrin syntheses under conditions shown in Table 6.

**Table 6.** Enantioselective syntheses of 3-phenoxymandelonitrile (**3a**) using hydroxynitrile lyases<sup>131</sup>

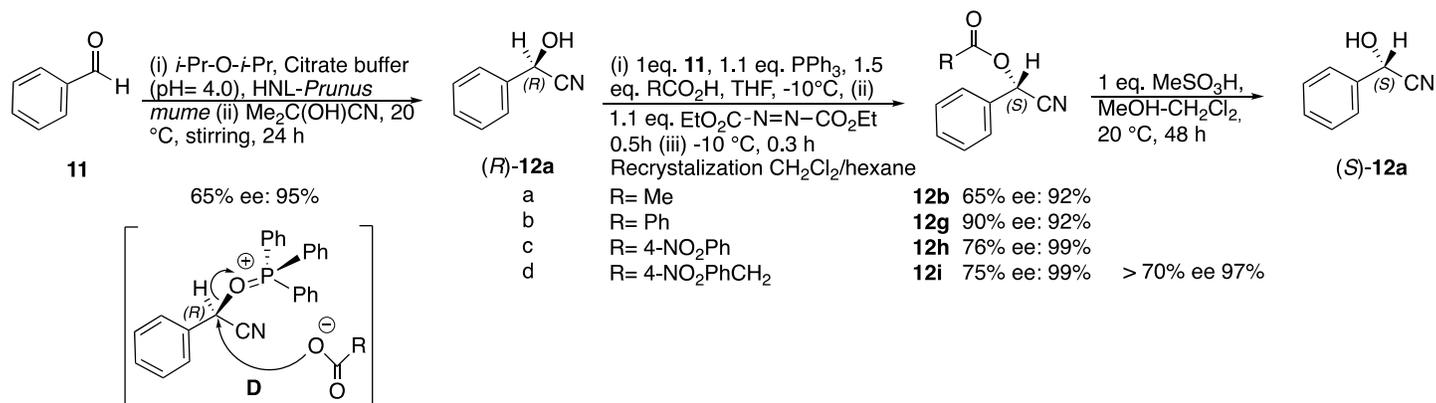
Columns: A: entry number, B: enzyme used, C: cyanide delivering species, D: number of phases, E: experimental conditions, F: *stereochemistry of the major enantiomer generated*-reaction yield % (enantiomeric excess %)

| A  | B  | C              | D | E  | F                 |
|----|--|----------------|---|--|-------------------|
| 1  | ( <i>R</i> )-hydroxynitrile lyase from <i>Prunus mume</i>              | HCN            | 1 | 1 eq. <b>4a</b> , 1.25 eq. KCN, citric acid buffer aqueous solution pH 4.5, enzyme, 0 °C, 0.5 h.   | <i>R</i> -42 (99) |
| 2  | ( <i>R</i> )-hydroxynitrile lyase from <i>Prunus mume</i>              | ( <b>13a</b> ) | 2 | 1 eq. <b>4a</b> , vigorously stirred biphasic solution aqueous citrate buffer (pH: 4.5) / diisopropyl ether (1/10), 1.5 eq. <b>13a</b> , 36 h.             | <i>R</i> -68 (98) |
| 3  | ( <i>R</i> )-hydroxynitrile lyase from <i>Prunus armeniaca</i> ParsHNL | HCN            | 2 | (i) 1 eq. <b>4a</b> , biphasic reaction media diisopropyl ether/aq. Na-citrate buffer, (pH 4.0) 1/1, (ii) 2 eq. HCN (from NaCN + aq. 33% HCl), 10 °C, 6 h. | <i>R</i> -82 (99) |
| 4a | ( <i>S</i> )-hydroxynitrile lyase from <i>Hevea brasiliensis</i>       | HCN            | 1 | 1 eq. <b>4a</b> , 2 eq. KCN, citric acid buffer aqueous solution pH 4.0, Enzyme, 0 °C, 0.7 h   | <i>S</i> -99 (99) |
| 4b |  | HCNg           | 2 | 5 eq. anhydrous HCN added to 1 eq. <b>4a</b> , aqueous / <i>t</i> -BuOMe vigorous stirring 0.3 h leading to emulsion (pH 5.0)                              | <i>S</i> -99 (99) |

Table 6. Continued

| A  | B  | C   | D | E   | F         |
|----|--|-----|---|---|-----------|
| 5a | (S)-hydroxynitrile lyase from <i>Manihot esculenta</i> MeHNL-W128A, type | HCN | 2 | 1 eq. <b>4a</b> solution aqueous phosphate buffer (pH: 7) /diisopropyl ether (1/1), 1.5 eq. HCN, 10 °C: MeHNL-W128A, 6 h (high enzyme load)                 | S-99 (90) |
| 5b | MeHNL-wild type  |     |   | MeHNL-wild type, 24 h   | S-99 (75) |
| 6a | (S)-hydroxynitrile lyase from <i>sorghum shoots</i>                      | HCN | 2 | ACTI-DISK supported (S)-hydroxynitrile lyase, AcONa (i) 1 eq. <b>4a</b> in solvent (ii) HCN, circulation, 24 h, 5mL/min: <i>n</i> -Bu <sub>2</sub> O, 20 °C | S-92 (83) |
| 6b |  |     |   | <i>n</i> -Bu <sub>2</sub> O, 6 °C   | S-70 (90) |
| 6c |  |     |   | <i>t</i> -BuOMe, 20 °C  | S-74 (16) |
| 6d |  |     |   | <i>i</i> -Pr <sub>2</sub> O, 20 °C  | S-80 (32) |
| 6e |  |     |   | THF, 20 °C  | R-82 (04) |
| 6f |  |     |   | HCN, 20 °C  | S-97 (16) |
| 6g |  |     |   | MeCN  | S-88 (04) |

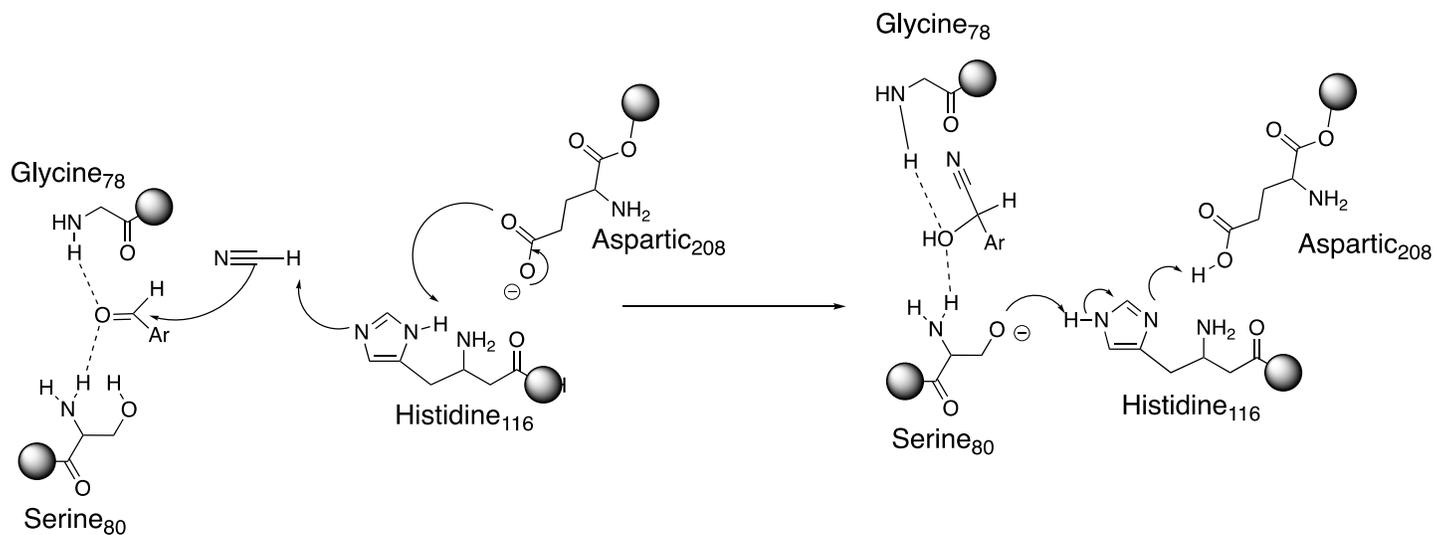
Most of the hydroxynitrile lyases known earlier were related to that of bitter almond (*Prunus amygdalus*)<sup>24</sup> promoting the addition of KCN in buffered solution (pH: 4.5) to produce the (*R*)-mandelonitrile (**12a**) from benzaldehyde (**11**). This is also the case of the seeds of the Japanese apricot (*Prunus mume*, Table 6, entry 1)<sup>133</sup> or that of the white apricot of the Indian Himalaya (*Prunus armeniaca*, Table 6, entry 2).<sup>134</sup> They allow, among others, the enantioselective synthesis of (*R*)-3-phenoxymandelonitrile (*R*)-(**3a**) from 3-phenoxybenzaldehyde (**4a**). Its (*S*)-enantiomer required for the synthesis of deltamethrin for example, needs therefore an inversion of configuration that could be achieved using a subsequent Mitsunobu reaction, a substitution reaction of the hydroxyl group using ethyl azodicarboxylate, triphenylphosphine and a carboxylate nucleophile (Scheme 32).<sup>13</sup> This reaction leads usually to an ester whose configuration is inverted as compared to that of the starting alcohols.<sup>136,137</sup> In the case of the cyanohydrin derived from benzaldehyde relatively poor results have been obtained when acetic acid was used (ee: 92%).<sup>135</sup> Better results have been observed using instead benzoic acids or arylacetic acids.<sup>135</sup> 4-nitrophenyl acetic acid has been finally selected because (i) it provides the corresponding ester in good yield and high enantioselection (ee: 99%) (ii) the resulting ester can be easily purified by recrystallization and (ii) transformed in high yield and excellent stereocontrol to (*S*)-mandelonitrile in acidic media (MeSO<sub>3</sub>H/MeOH, 20 °C, 48 h, Scheme 33).<sup>135</sup> Use of at least one equivalent of methane or para-toluenesulfonic acid and methanol as the solvent was crucial since dilute hydrochloric or sulfuric acid caused no reaction at all and stronger aqueous acidic conditions, such as concentrated hydrochloric acid or 20% sulfuric acid, resulted in partial hydrolysis of the cyano group.<sup>135</sup> The whole transformation of benzaldehyde sequentially to (*R*)- then (*S*)-mandelonitrile is presented in Scheme 33.<sup>133,135</sup> It should be noticed that many other esters require a basic media for saponification that is incompatible with the stability of cyanohydrins.



**Scheme 33.** Stereoselective epimerization of mandelonitrile.<sup>133,135</sup>

Effenberger<sup>138</sup> also attempted to accomplish the same conversion but through  $\alpha$ -sulfonyloxynitriles. As it turned out, these compounds proved to be rather unstable and satisfactory results have been obtained only in the case the cyanohydrins derived from saturated aliphatic aldehydes.<sup>135,138</sup>

Successful cloning of HNLs and structure determinations<sup>23,143</sup> have been achieved and models have been proposed using site directed mutagenesis (Scheme 34).<sup>4,144</sup>

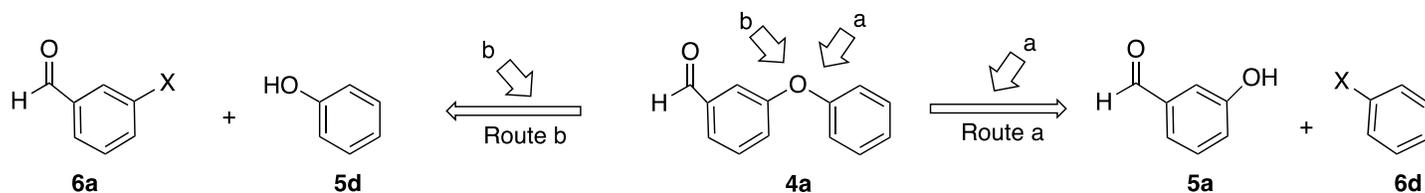


**Scheme 34.** Adapted<sup>4</sup> key steps in the mechanism of cyanohydrin biosynthesis derived from site-directed mutagenesis of hydroxynitrile lyase from *Manihot esculenta*.<sup>144</sup>

### 3. Syntheses of 3-Phenoxybenzaldehyde

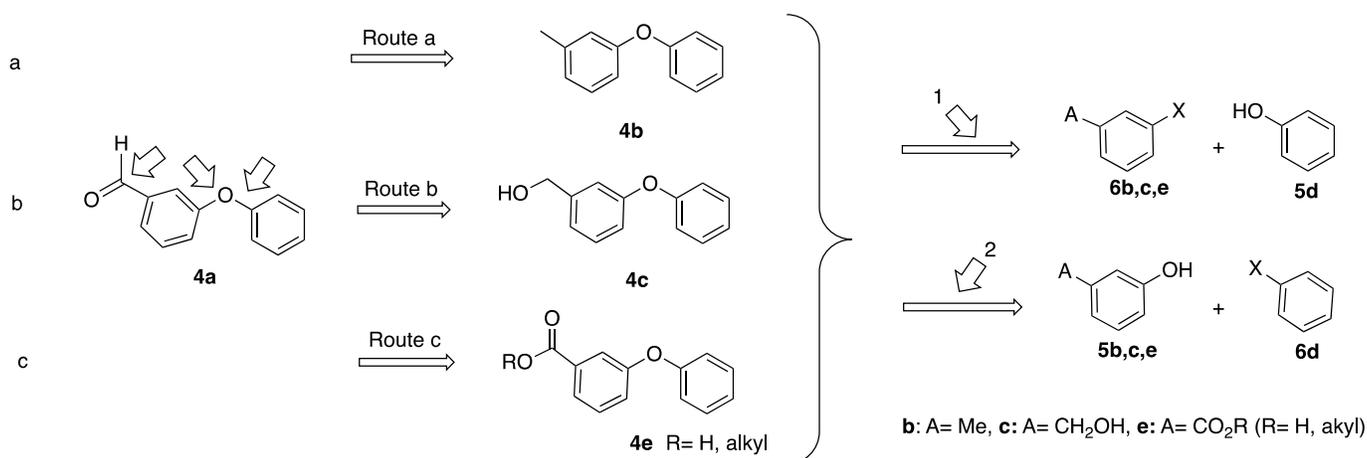
#### 3.1. Generalities, strategies and retrosynthetic approaches to 3-phenoxybenzaldehyde

The shortest and most convergent synthesis of 3-phenoxybenzaldehyde (**4a**) involves the formation of the ether from a benzaldehyde suitably functionalized at its 3-position so that the oxygen atom can be either present on the aromatic aldehyde (**5a**) (3-hydroxybenzaldehyde, Scheme 35, Route a) or on its partner the (**5d**) (phenol, Scheme 35, Route b).



**Scheme 35.** Retrosynthetic approach to 3-phenoxybenzaldehyde (**4a**) from related 3-substituted benzaldehydes.

3-Phenoxybenzaldehyde (**4a**) is also accessible from (i) 3-phenoxytoluene (**4b**) (Scheme 36 route a), 3-phenoxybenzyl alcohol (**4c**) (Scheme 36 route b) or (ii) 3-phenoxybenzoates **4e<sub>R</sub>** or 3-phenoxybenzoic acid (**4e<sub>H</sub>**) (Scheme 36 route c). The synthesis of **4a** from **4b** and **4c** involves an oxidation whereas that from the **4d** involves a reduction.

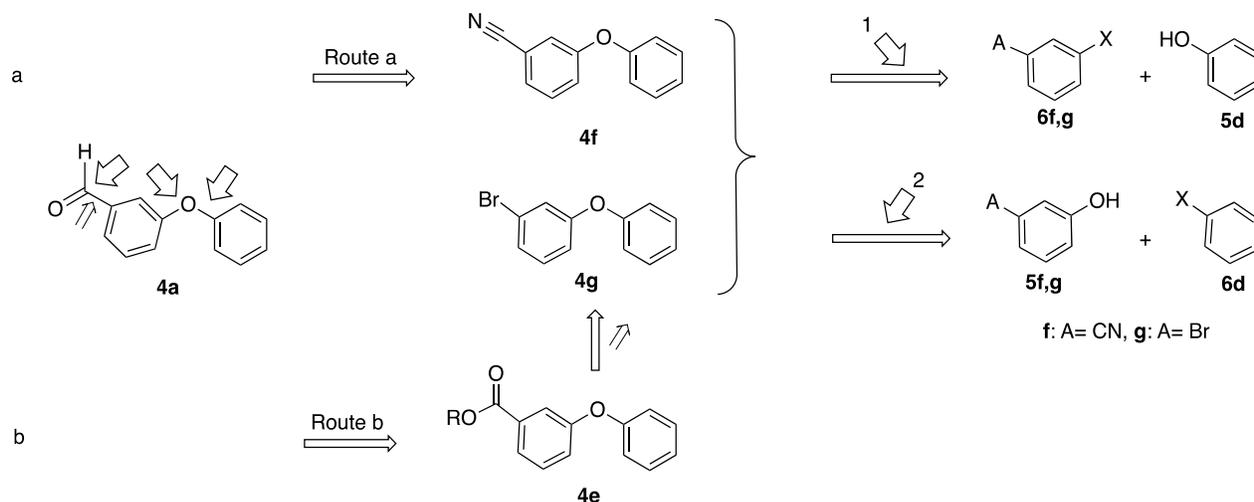


**Scheme 36.** Retrosynthetic approaches to 3-phenoxybenzaldehyde (**4a**) involving 3-phenoxytoluene (**4b**), 3-phenoxybenzyl alcohol (**4c**), 3-phenoxybenzoates **4e<sub>R</sub>** and 3-phenoxybenzoic acid (**4e<sub>H</sub>**).

The transformation of 3-phenoxytoluene (**4b**) into 3-phenoxybenzaldehyde (**4a**) can be achieved (i) directly by substitution of two hydrogens by oxygen or (ii) in two steps that involve as the first step a halogenation reaction. Both routes are far from regioselective. Oxidation of 3-phenoxytoluene (**4b**) to 3-phenoxybenzaldehyde (**4a**) is not an easy task due to competing formation of the 3-phenoxybenzyl alcohol (**4c**) and 3-phenoxybenzoic acid (**4e<sub>H</sub>**). Lateral halogenation is not an easy task since not only mono and polyhalogenation coexist but also ring halogenation compete.

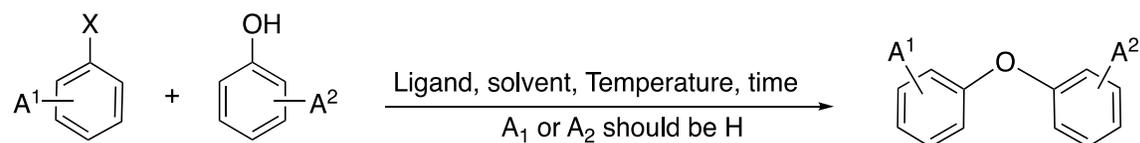
Anyhow the synthesis of **4b**, **4c**, or **4e** the potential precursors of **4a** (Scheme 36) uses the same approaches as the ones proposed for the direct synthesis of **4a** (Scheme 35) that involves the formation of an oxygen aryl bond but involves one different partner in each case **5b**, **5c**, (**5d**) instead of **5a**; **6b**, **6c**, **6d** instead of (**6a**).

We have also briefly included the case of 3-phenoxybenzotrile (**4f**) whose transformation to **4a** has been partially achieved and that of 3-phenoxybromo-benzene (**4g**) that involves a strategy different to that of used to synthesize **4b**, **4c**, or **4e** and has been used for the synthesis of the <sup>14</sup>C labelled **4a** required for biochemical tracing (Scheme 37).



**Scheme 37.** Retrosynthetic approaches to 3-phenoxybenzaldehyde (**4a**) involving 3-phenoxybenzonitrile (**4e**), 3-phenoxybromobenzene (**4f**), and 3-phenoxybenzoic esters/acid (**4e**).

The formation of the ether linkage relies on the reaction originally published in 1905 by Ullmann<sup>145</sup> (known as the Ullmann condensation) on potassium phenoxide and bromobenzene, who demonstrated the important effect of copper (as a powder originally) on the rate of the reaction. This reaction shown in Scheme 38, entry a, has been the subject of constant interest since then.<sup>10-14,146,147</sup> Variants use (i) Soluble copper complexes or supported copper catalysts,<sup>148</sup> (ii) better leaving group by replacing the halogen on the aryl group by a iodonio group,<sup>149-151</sup> (iii) nickel or palladium as replacement for the copper pre-catalyst as in the Buchwald-Hartwig condensation reaction (Scheme, 38 entry b)<sup>152-154</sup> and offers, by using the adequate ligand, substantial advantages over the Ullmann condensation reaction although being substantially more expensive. (iv) Replacement of aryl halides by arylboronic acids in the Evans-Lam coupling reaction (Scheme 38, entry c),<sup>155-157</sup> or by arylbismuth Bi(III or V) in the Barton-Gagnon arylation reaction (Scheme 38, entry d).<sup>158-160</sup> Parallels between Ullmann,<sup>10-14,146,147</sup> and Buchwald-Hartwig<sup>152-154</sup> condensations that applies to ether synthesis and the Goldberg<sup>161,162</sup> condensation that applies to amines, have been discussed in the related references.



|   |   |                                      |                               |
|---|---|--------------------------------------|-------------------------------|
| a | X= Cl, Br, I, +I-Ph   | Cu or Cu <sub>n</sub> Y <sub>m</sub> | Ullmann condensation          |
| b | X= Cl, Br, I  | Pd <sub>n</sub> Y <sub>m</sub>       | Buchwald-Hartwig condensation |
| c | X= B(OH) <sub>2</sub>                                       | Cu <sub>n</sub> Y <sub>m</sub>       | Lam-Evans coupling            |
| d | X= BiAr <sub>2</sub> , BiAr <sub>2</sub> (OAc) <sub>2</sub> | Cu <sub>n</sub> Y <sub>m</sub>       | Barton-Gagnon coupling        |

**Scheme 38.** Familiar reactions allowing diaryl ether synthesis by forming a O-C-aryl bond.

Most of the reactions shown in Scheme 38 have been applied to the coupling leading to **4a**, **4b**, **4c**, **4e** and **4f**. We have gathered (i) related examples in Schemes 78, 81, 82, 84, 85 and 86.

We have gathered before discussing the related specific examples, some recent knowledge about (i) the Ullmann reaction that was not available at the time the industrial transformations have been carried out and (ii) Buchwald-Hartwig condensation that use the more expensive palladium catalyst and was unknown at that time. We have purposefully selected the more judicious examples that do not rely on the specific topic of interest and we have included the more recent advances about their mechanisms.

**3.1.1. The copper-catalyzed Ullmann condensation reaction.** The copper-catalyzed Ullmann condensation reaction involves the coupling of aryl halides and phenols and delivers diaryl ethers by copper catalysis.<sup>145</sup> It originally took place with excess of phenol in pyridine or polar solvents, at high temperature (120-250°C), in the presence of strong bases and stoichiometric amounts of copper powder, salts or oxides as the catalyst, and delivered, after long reaction time (12-48h), the diaryl ether in low to moderate yields that furthermore is difficult to isolate from the inorganic brownish sludge.<sup>10-14,146,147</sup>

In the context of pyrethrin synthesis that require to be carried out at large industrial scale, it offers the advantage of using a cheap pre-catalyst but suffers from the drastic conditions required, the low yields obtained, the better reactivity of more expensive aryl iodides and the poorer reactivity of those reactants that possess electron-withdrawing group (such as the formyl group). Such behavior has triggered the synthesis of the **4b** or **4c** that are easier to produce but require an extra step to produce **4a**.

As a general trend the reaction:

(i) *Proceeds faster* with the aryl bromides or iodides than with the corresponding chlorides (the cheaper reagent) or fluorides (F<Cl<Br<I) but still requires high temperatures.<sup>163</sup> It has been however found that the arylation of phenols, including 3-hydroxybenzaldehyde (**5a**) can be conveniently carried out at room temperature without the need of copper catalyst if performed, in THF, with diphenyl iodonium triflates or tetrafluoroborates **6d**,<sup>+</sup> in the presence of stoichiometric amount of potassium *t*-butoxide (see below, Scheme 84, Scheme 85),<sup>149,151</sup>

(ii) *Does not generally work* with aryl halides possessing strong electron-donating groups and phenols with electron-withdrawing. In such cases the reduction of aryl halides to arenes (Ar-Br to Ar-H), usually the major side reaction in Ullmann ether synthesis, takes place to a large extent.<sup>164</sup>

It has been also found that bulky substituents *at ortho*-position of the reactants lower the reaction rate, in particular that of phenols with *ortho* methoxy or acetoxy groups, whereas the presence of an additional halogen on the aryl halide increases the reaction rate.<sup>163</sup>

More recently however, some of those restrictions seem to have been overcome using an original process performed in toluene as the solvent at 110 °C for 12-26h with aryl bromides and iodides, that uses an excess of phenol (1.4-2 eq.) as a reactant, cesium carbonate as the base, copper triflate (CuOTf, 0.25-2.5% eq.) as pre-catalyst, small amount of ethyl acetate (5% eq.) and eventually naphthoic acid (1 eq.) as an additive.<sup>165</sup>

(iii) *Tolerates a variety of functional groups*<sup>10-14,146,147</sup> either on (a) the aryl halide, which include alkyl, alkoxy, hydroxymethyl, amino, halogeno including fluoro, nitro, carbonyl, amido, sulfonamido and cyano group or on (b) the phenol:<sup>10-14,146,147</sup> such as halogeno including fluoro, alkoxy, hydroxymethyl, carbonyl, carboxy, nitro, trifluoromethyl groups.

(iv) *Has been carried out with a large variety of bases* such as Et<sub>3</sub>N, DIPEA, DBU, 1,2,2,6,6-pentamethyl piperidine, dicyclohexylamine, as well as K<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, Li<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, BaCO<sub>3</sub>, but cesium carbonate (2 eq. Cs<sub>2</sub>CO<sub>3</sub>) has often been preferred.<sup>165</sup>

(v) *Use copper*<sup>145</sup> *or copper compounds as the catalyst/pre-catalyst in the presence of additives or ligands* in stoichiometric or catalytic amounts (Scheme 38, entry a, Table 7).<sup>10-14,146,147</sup> It includes (Table 7) copper chlorides (CuCl, CuCl<sub>2</sub>), copper iodide (CuI),<sup>165</sup> copper bromide (CuBr,<sup>165</sup> CuBr<sub>2</sub>), copper triflate (CuOTf),<sup>165</sup> copper acetate

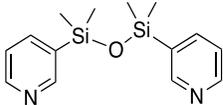
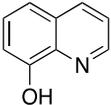
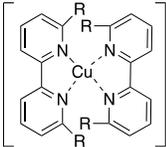
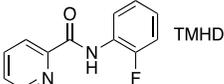
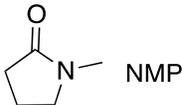
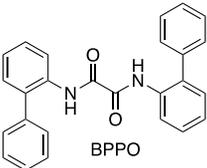
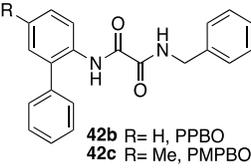
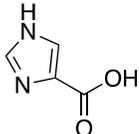
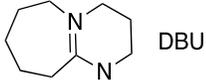
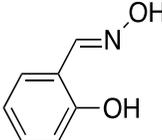
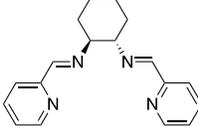
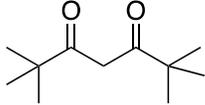
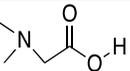
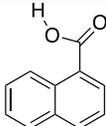
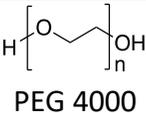
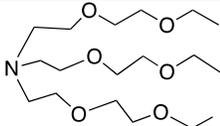
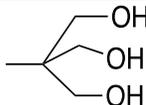
(Cu(OAc<sub>2</sub>))<sup>165</sup> and copper sulfate (CuSO<sub>4</sub>) as well as copper oxide (CuO, Cu<sub>2</sub>O) that includes reusable Cu<sub>2</sub>O-nanocubes<sup>195</sup> and copper fluoroapatite<sup>166</sup> or Cu/CNFs nanofiber composite.<sup>167</sup> Although the choice of the copper salt did not appear to be critical,<sup>165</sup> the use of the more soluble copper triflate (CuOTf) or its complex with benzene has been suggested.<sup>165</sup>

(vi) *Is improved:*

- Under sonication<sup>168</sup> or photo-assistance<sup>169</sup> that allows a copper assisted coupling of phenols and aryl iodides at room temperature;
- With Microwave assistance that offers the advantage<sup>170</sup> of about 15% increased yields over the same unirradiated process. Microwave irradiation has also been used in the synthesis of diaryl ethers in the absence of copper catalyst,<sup>171</sup> but seems almost exclusively limited to halogeno-benzenes substituted in 2- and 4-position by an electron withdrawing group that usually involves a two steps mechanism (aromatic substitution by addition/elimination).

The structure of some of the ligands as well as the related copper compound and the solvent used in the modified Ullmann reactions are depicted in Table 7.

**Table 7.** Additives/ligands or catalysts used in the Ullmann reaction (Scheme 38, entry a)

|   |   |   |   |   |
|---|---|---|---|---|
|    |    |    |    |    |
| <b>35</b> , CuCl, pyridine <sup>173</sup>   | <b>36</b> , CuI, DMF <sup>174</sup>   | <b>37</b> , CuCl, DMI <sup>175</sup>  | <b>38<sub>Cu</sub></b> , CuCl, DMF <sup>176</sup>                                     | <b>39</b> , CuCl, DMF <sup>177</sup>  |
|  |  |  |   |  |
| <b>40a</b> , CuCl, DMF <sup>178</sup>   | <b>41</b> , Cu-apatite, NMP <sup>166</sup>  | <b>42a</b> CuI, MeCN <sup>179</sup>   | <b>42b,c</b> , CuI, DMSO <sup>179,180</sup>   | <b>43</b> , Cu <sub>2</sub> O, MeCN <sup>181</sup>                                    |
|  |  |  |  |  |
| <b>44</b> , Cu <sub>2</sub> O, MeCN <sup>169</sup>                                  | <b>45</b> , Cu <sub>2</sub> O, MeCN <sup>182</sup>                                  | <b>46</b> , Cu <sub>2</sub> O, MeCN <sup>182</sup>                                  | <b>47</b> , Cu <sub>2</sub> O, MeCN <sup>182</sup>                                    | <b>48</b> , CuCl, NMP <sup>183</sup>  |
|  |  |  |   |  |
| <b>49</b> , CuI, dioxane <sup>164</sup>   | <b>50</b> , CuTf, PhMe-AcOEt <sup>165</sup>   | <b>51</b> , CuCl, PEG 4000 <sup>178</sup>   | <b>52</b> , CuCl, anisole <sup>184</sup>  | <b>53</b> , CuI, dioxane <sup>185</sup>   |

In fact, the copper compounds act as pre-catalyst since except in rare cases where the effective catalyst is produced *in situ* on interaction with a ligand also named additive (Scheme 38, Table 7)<sup>147</sup> and in some cases with the solvent that plays a similar role. The proper use of ligand/additive and the copper pre-catalyst increases the rate of the reaction and allow to perform the reaction at lower temperature probably by increasing in conjunction with the solvent the solubility of the copper catalyst and that of the copper phenolate responsible of the substitution leading to the diaryl ethers.

Many more additives/ligands have been tested under different conditions.<sup>10-14,146,147</sup> They involve compounds that possess a nitrogen atom known for their aptitude to complex copper compounds such as:

(a) pyridine (**35**) or compounds that include that motif **36-39**, especially the 8-hydroxyquinoline (**37**) and the 2,2'-bipyridine (**38a**) precursor of **38a<sub>Cu</sub>**;

(b) Compounds possessing an amido-group that include N,N-dimethyl formamide (DMF) (**40**) and N-methyl pyrrolidone (NMP) (**41**) often also used as solvents and especially oxalamides derived from glyoxal such as N,N'-bis(2-phenylphenyl) oxalamide (BPPO) (**42a**) or N-(2-phenylphenyl)-N'-benzyl oxalamide (PPBO) (**42b**) and its methylated derivative **42c** which represent one of the lowest loadings for a general Cu/ligand-catalyzed diaryl ether formation;

(c) Imidates such as diazabicyclooctane (DBU) (**44**) and ureas such as 1,3-dimethyl-2-imidazolidinone (DMI) that proved to be one of the best solvent used for the synthesis of diaryl ethers;

(d) Schiff bases such as **45**, **46** and diimides well known for their aptitude to complex copper compounds as well as:

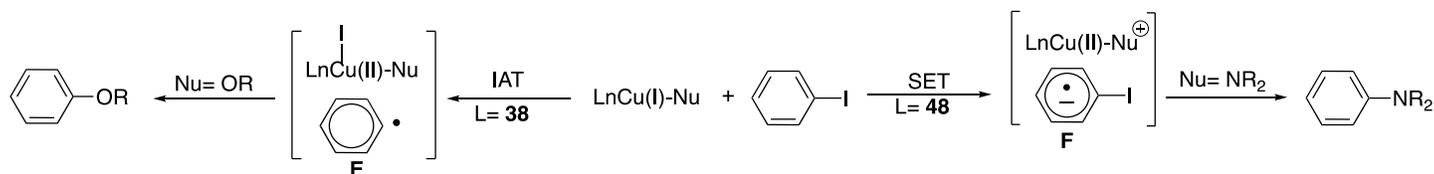
(e) oxo- and oxy-compounds such as 1,3-dicarbonyl compounds such as 2,2,6,6-tetramethylheptane-3,5-dione **48** known for its chelating property;

(f) carboxylic acids such as **50** and especially  $\alpha$ -amino-acids **43**, **49**;

(g) Polyethers such as the commercially available PEG 4000 **51**, tridentate ligand **52** and the tripodal triol 2-methyl-2, hydroxymethyl-1,4-diol (**53**) have also been successfully used in promoting the Ullmann coupling.

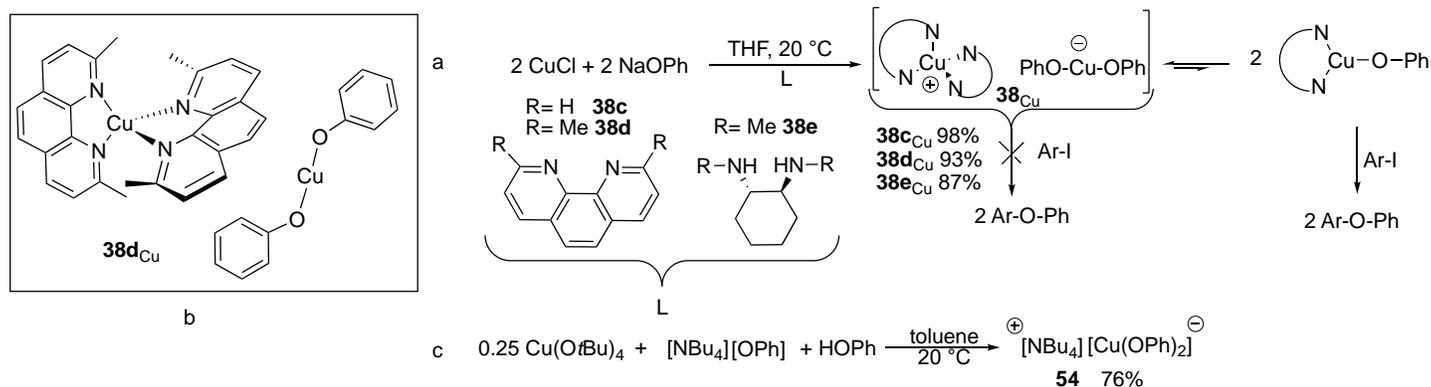
The crucial role of the ligand/ and the solvent on the course of the Ullmann condensation has been further investigated.<sup>15,16</sup>

A ligand-directed selectivity in *N*- versus *O*-arylation reactions of ambident nucleophiles has been observed and rationalized.<sup>15</sup> It has been suggested<sup>15</sup> that it does not derive from initial "Cu(I) (nucleophile)" complex formation but from the subsequent steps involving aryl halide activation leading to *O*-arylation via an iodine atom transfer (IAT) process whereas *N*-arylation takes place via a single-electron transfer (SET) process that depends on the electron-donating abilities of the ligand and the nucleophile (Scheme 39).



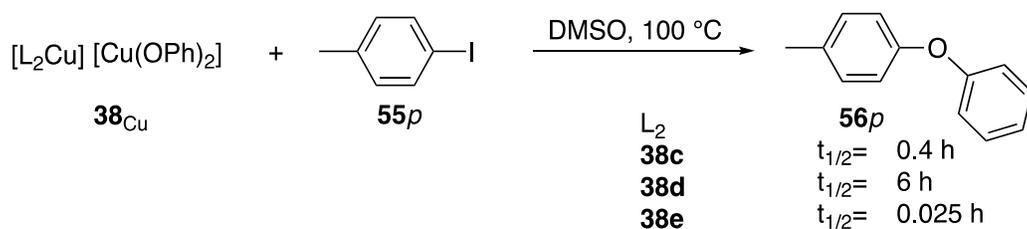
**Scheme 39.** IAT versus SET mechanism potentially involved in the Ullmann condensation reaction.<sup>15</sup>

Detailed study on the intimate mechanism of Ullmann condensation, has been carried out by Hartwig who investigated the nature of the reactive phenolate species.<sup>16</sup> For that purpose neutral **38<sub>Cu</sub>** (Scheme 40, entry a),<sup>16</sup> and ionic **54** copper alkoxides (Scheme 40, entry c),<sup>16</sup> have been synthesized unambiguously characterized even by X-ray crystallography in the case of **38d<sub>Cu</sub>** (Scheme 40, entry b) and reacted with a few aryl halides.<sup>16</sup>



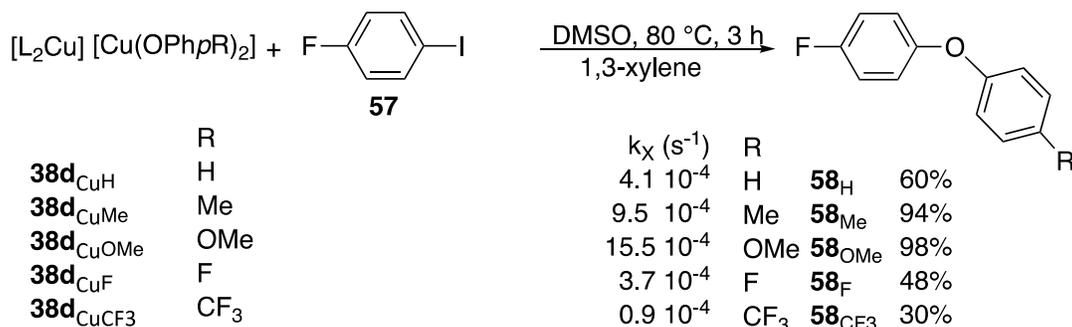
**Scheme 40.** Reactivity of suspected intermediates involved in the Ullmann condensation reaction.<sup>16</sup>

It has been found that the neutral species **38**<sub>Cu</sub> efficiently reacts with 4-iodotoluene (**55p**) in DMSO with the highest reactivity being observed for the species derived from 1,2-diaminocyclohexane (**38e**) and the lower for the species derived from the 9,10-dimethylphenanthroline (**38d**), hindered at the two *ortho* positions (Scheme 41).<sup>16</sup>



**Scheme 41.** Comparative reactivity of differently liganded copper phenolates in the Ullmann condensation reaction.<sup>16</sup>

The reaction of reagents **38d**<sub>Cu</sub> with different ligands, in which the embedded phenoxy group bears electron donating- or electron withdrawing groups in *para*-position, with 4-fluoro iodobenzene (**57**), provides interesting information about the relative reactivity of related phenolates (Scheme 42):<sup>16</sup> the reaction is faster when the reactive ligand is more electron rich, most likely because it helps make the metal more electron rich and thereby accelerates oxidative addition of the aryl halide.<sup>16</sup>

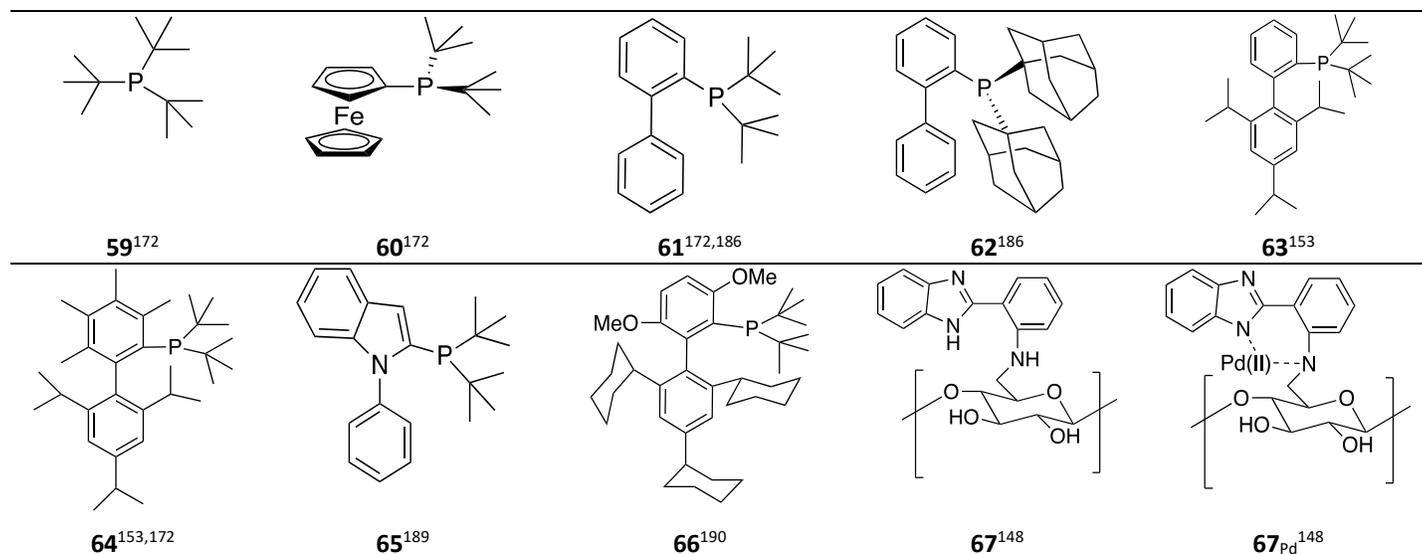


**Scheme 42.** Comparative rates of reaction of a series of aryloxy copper reagents toward 4-fluoro iodobenzene.<sup>16</sup>

### 3.1.2. The palladium catalyzed Buchwald-Hartwig condensation reaction

It has been demonstrated that the cross-coupling of electron-deficient, electron-neutral, and electron-rich aryl halides and sulfonates with a variety of phenols could be conducted in high yield under relatively mild conditions using palladium as a pre-catalyst (Scheme 38, entry b) and electron-rich, bulky phosphines ligands ((**59**)-(66), Table 8).<sup>153,172,186,189,190</sup> The coupling has been also successfully achieved using supported palladium catalyst (**67**<sub>Pd</sub>, Table 8)<sup>148</sup> crafted onto cellulose whose ligand (**79**, Table 8) is devoid of phosphorus.<sup>148</sup>

**Table 8.** Selected characteristic ligands used in the Buchwald-Hartwig condensation reaction (Scheme 38, entry b)



The reaction is very dependent upon the nature of the catalyst, especially the ligand. The Buchwald-Hartwig reaction has been continuously elaborated since its discovery in 1999<sup>172,186</sup> to expand its scope and to get some insight about its intimate mechanism.<sup>153,189-191</sup>

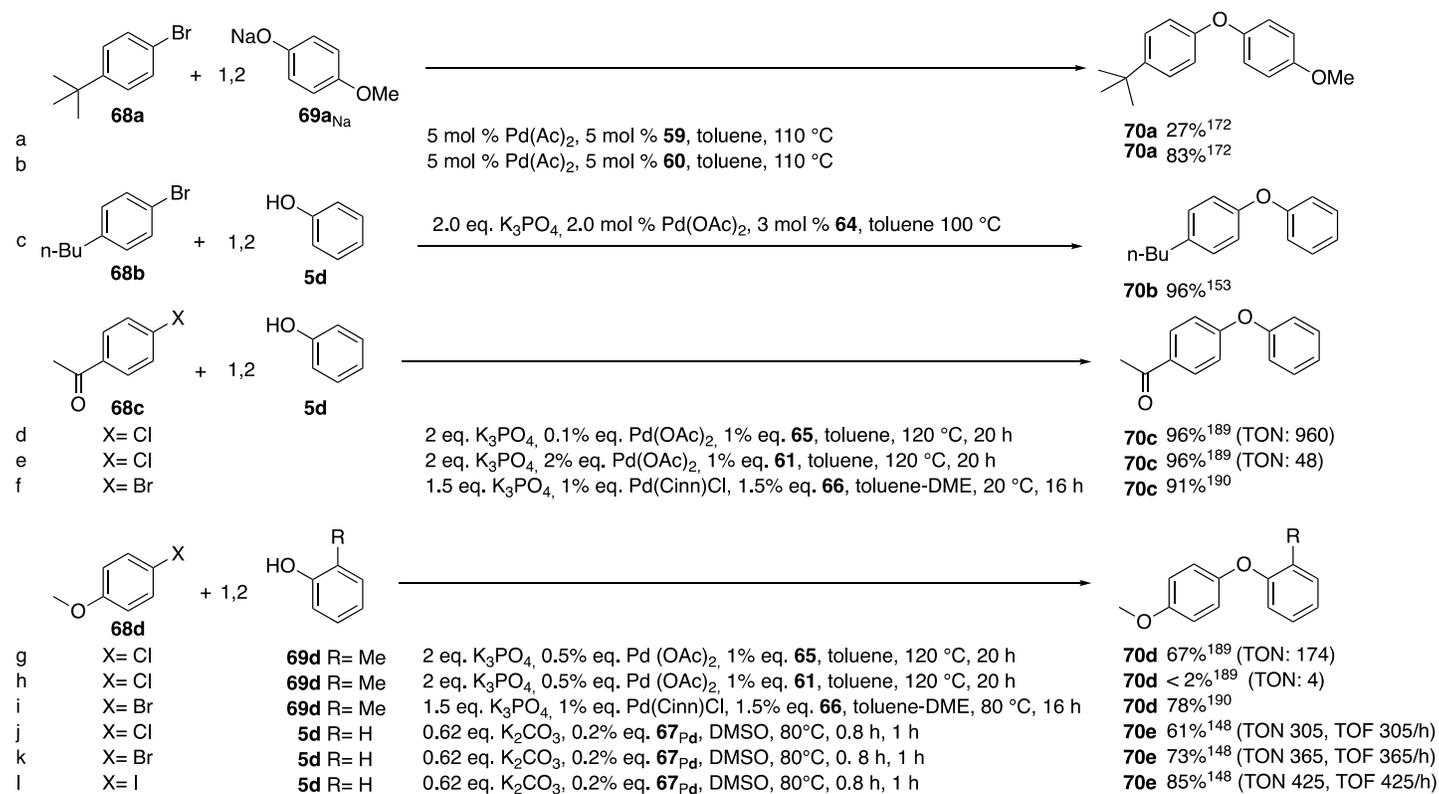
As general trends the limitations are often orthogonal to that of the copper mediated Ullmann reaction discussed above since for example phenols missing a substituent in *ortho* position pose problems, and except one case (Scheme 43, entry l, compare to entries j,k),<sup>148</sup> aryl bromides and eventually aryl chlorides are far better substrates than aryl iodides (Scheme 43).<sup>153,172,186,189,191</sup>

Limitations have been observed with little or no product from reactions of:

- (i) Phenols with aryl halides that possess either strongly electron-withdrawing or electron-donating *ortho* substituents. 2-bromo-acetophenone for example is reluctant to couple,
- (ii) electron-deficient phenols and phenols that did not possess an *ortho* substituent at least as large as a methyl group and especially the first member of the series, the phenol as already pointed out.

The coupling proceeds equally well with various source of Pd such as palladium diacetate [Pd(OAc)<sub>2</sub>], or palladium(0) bis(dibenzylideneacetone) [Pd(dba)<sub>2</sub>]. The latter has been nevertheless in some instances preferred,<sup>172</sup> and in the case of reaction carried out at room temperature, the liganded (cinnamyl)PdCl<sub>2</sub> proved by far the best pre-catalyst,<sup>190</sup> accounting for its exceptional aptitude to generate the active Pd(0) species at low temperatures as compared to the other commonly used precursors.<sup>190</sup>

It has been also once noticed<sup>186</sup> that the amount of ligand compared to the palladium pre-catalyst (1/1 to 5/1) does not affect the course of the reaction.



**Scheme 43.** Selected examples of the Buchwald-Hartwig condensation reaction.<sup>148,153,172,189,190,192</sup>

In fact, over the years, following the discovery of new ligands (Table 8), many of the original limitations have been overcome.

The first reports involve (i) phosphines **59-62** whose phosphorus atom is surrounded by at least two bulky groups such as *t*-butyl, adamantyl groups, and a ferrocenyl or biphenyl group as the third substituent, (ii) quite large amount of non-recoverable palladium species (2-5% molar equivalent), (iii) various bases such as NaOH as K<sub>3</sub>PO<sub>4</sub> (Scheme 43 entries a,b,e,h).<sup>172,186</sup>, (iv) toluene as solvent and (v) heating at 80-110°C for several hours (14-48 h).

The next improvement involves increasing substitution on each of the two aryl groups of the biphenyl moiety of the ligand (**63**, **64**).<sup>153</sup> It dramatically increases the type of phenols and aryl halides that can couple (Scheme 43 entry c).<sup>153</sup>

The latter generation of ligands (**65,66**, Table 8, Scheme 43, entries d,f,g,i) includes **65** that instead bears an 1-arylidole moiety and **66** that still belongs to the biphenyl series but possesses larger substituents on the biphenyl group. It extends the scope of the reaction to *o*-unsubstituted phenols, lowers the amount of palladium and ligand used and offers exceptional TON. These ligands allow in some specific case to carry out the reaction at room temperature (**66**, Table 8, Scheme 43, entry f).<sup>189,190</sup>

The final improvement uses palladium grafted on cellulose and liganded by two nitrogen atoms. It still allows low loading of the catalyst, but also allows its reuse, couples a large spectrum of aryl halides including aryl iodides that usually pose problems, involves benign bases such as potassium carbonate, short reaction times and offers remarkable TON and TOF performances (Table 8, Scheme 43, entries j,k,l).<sup>148</sup>

The ligand has been prepared stepwise from filter paper (i) acidic hydrolysis (2.5M HBr) of filter paper under ultrasonication (100 °C, 3h) (ii) isolation of the residue after washing with deionized and centrifugation (12.000 RPM) (iii) reaction with tosyl chloride in pyridine, leading to tosylated cellulose nanocrystals “CNC-Tos” (iv)

grafting “CNC-Tos” with 2-(1*H*-benzo[d]imidazol-2-yl) aniline “BIA” (DMF, 100 °C, 24 h) leading to “CNC-BIA” (**67**) (v) reaction of **67** with palladium dichloride in the same solvent (60°C, 24h). The resulting “CNC-BIA-Pd” (**67**<sub>Pd</sub>) (Table 8) accounts 0.047g Pd/ 1g **67**<sub>Pd</sub> (4.7%) and is used in 0.4 g amount for 1 mmol of aryl halide.<sup>148</sup>

K<sub>2</sub>CO<sub>3</sub> proved a better base than Na<sub>2</sub>CO<sub>3</sub>, NaOH or KOH; DMSO proved to be better than MeCN, DMF, dioxane or ethanol.<sup>148</sup> The coupling is efficient even with phenols with withdrawing group and aryl halides with electron donor groups. The yields were in the order of *para* > *ortho* > *meta*, the catalytic performance of the substrates is I > Br > Cl and the CNC-BIA-Pd **67**<sub>Pd</sub> catalyst could be reused even eight times without losing its effectiveness with very low Pd leaching (5%).<sup>148</sup>

Successful coupling has been also achieved using recyclable nano-particles implying graphene oxide grafted with a Pd compound.<sup>192</sup>

Little is known about the molecular basis of the catalysis and although X-ray crystallographic data of some postulated intermediates are available, the rationale about the request of bulky ligands for successful catalysis is still missing. It has been for example proposed<sup>153</sup> that the better performance of ligand **64** compared to that of **63** (Table 8) could be due to restricted rotation around the C-aryl, P bond in catalyst **67**<sub>Pd</sub> (compared to its des-tetra-methyl analogue **64**<sub>Pd</sub>) that fixes, for steric reasons, the location of the palladium-containing entity in **64**' as shown in Scheme 44.

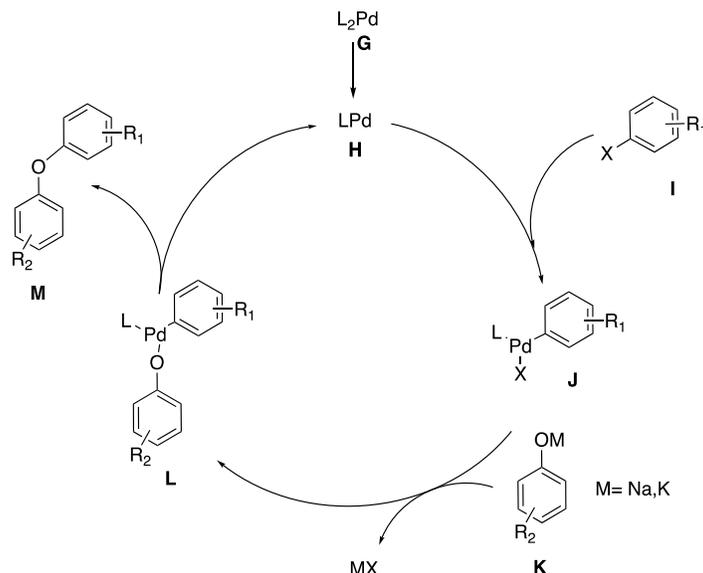


**Scheme 44.** Modelling the reactivity of related postulated catalyst in the Buchwald-Hartwig condensation.<sup>153</sup>

The mechanism of the reaction has been at several occasions discussed<sup>172,186</sup> and is admitted to consist of three distinct steps depicted in Scheme 45:

- (1) oxidative addition of aryl halide **I** to the ligand–palladium complex L<sub>n</sub>Pd(0) to give **J**;
- (2) formation of the Pd-aryloxy complex **L** from the Pd–halide adduct via transmetalation of metal phenolate **K**; and
- (3) reductive elimination leading to the diaryl ether product **M** with concomitant regeneration of the active L<sub>n</sub>Pd(0) species **H**.

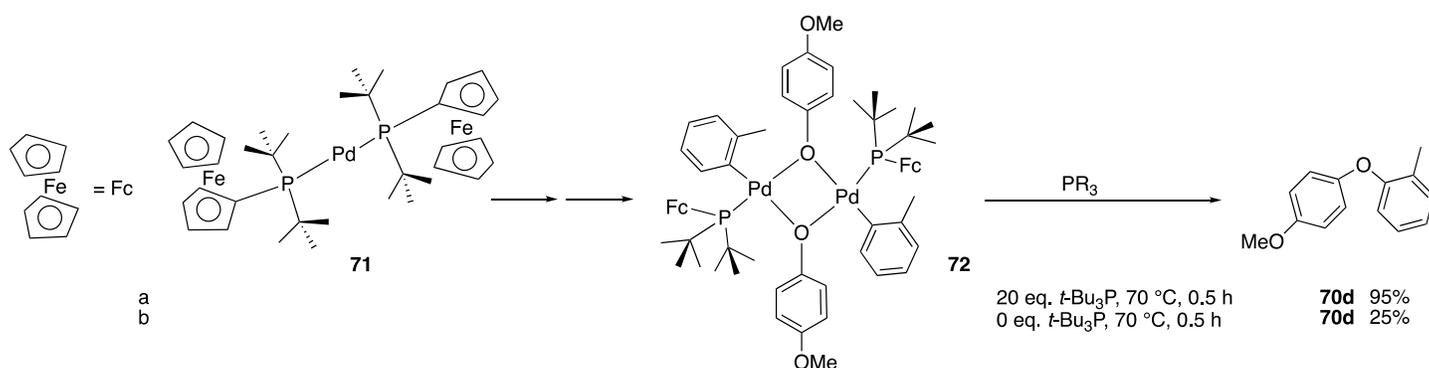
While the oxidative addition and transmetalation may be expected to be relatively facile, the reductive elimination to form the C–O bond is disfavored due to the Pd,C (LUMO) and Pd,O (HOMO) energy gap.



**Scheme 45.** Suggested mechanism of the Buchwald-Hartwig condensation reaction.<sup>172,186</sup>

The nature of the intermediate **L** (Scheme 45), its formation and its decomposition have been the subject of intensive work.<sup>172,186</sup>

Thus, Hartwig<sup>172</sup> has synthesized palladium-containing potential linear intermediate **71** containing the ligand and palladium and both Hartwig<sup>172</sup> and Buchwald,<sup>186</sup> have synthesized more elaborate species that include palladium, a ligand, one of the aryl group (the one expected to arise from the aryl halide) and the aryloxy such as **72** (Scheme 46)<sup>172</sup> or **73** (Scheme 47, entry a)<sup>186</sup> and have subjected them to thermolysis to produce the diaryl ether **70d** or the alkyl aryl ether **75a**. The potential square planar intermediate **72**, whose structure has been attested by X-ray,<sup>172</sup> produces the diaryl ether **70d** in very high yield (95%) on thermolysis at 70°C in the presence of 20 equivalents of tri-*t*-butylphosphine (**59**) (Scheme 46, entry a), but leads to the same compound in very modest yield in its absence (25%, Scheme 46, entry b).

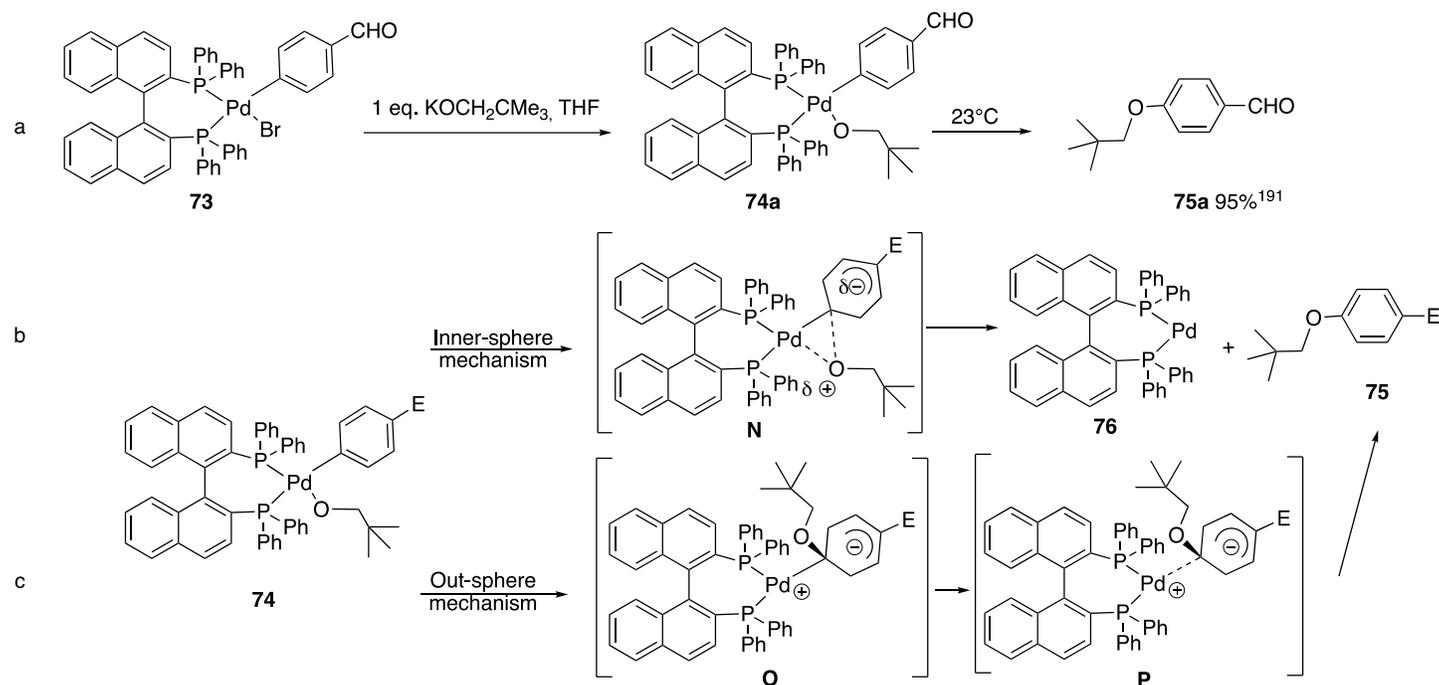


**Scheme 46.** Synthesis of diaryl ethers from palladium containing reagents in stoichiometric amounts.<sup>172</sup>

The authors have proposed that “The contrast between the modest yield of ether from the stoichiometric reductive eliminations without added  $P(t\text{-Bu})_3$  (**59**) and the excellent yields of catalytic reactions with only ferrocenyl di-tertbutylphosphine as the ligand, indicates that the dimeric species (**72**) is not the precise intermediates on the catalytic cycle”<sup>172</sup> and among others the higher yields of the catalytic chemistry observed

at lower concentrations (82% at 0.2 M aryl halide vs 23% at 1 M aryl halide), lead to the suggestion that monomeric complexes are almost certainly the real intermediates.<sup>172</sup> The authors have also proposed that “coordination of ligand  $P(t\text{-Bu})_3$  (**59**) to arylpalladium phenoxides makes reductive elimination of ethers much faster than it is from complexes containing more conventional arylphosphine ligands “.<sup>172</sup>

Thermolysis of aryl alkoxide complex **74** (Scheme 47, entry a) carried out by raising the temperature from  $-50$  to  $23$  °C in THF, leads to the C-O reductive elimination producing the *p*-neopentoxybenzaldehyde (**75a**) in excellent yield.<sup>191</sup>



**Scheme 47.** Modelling the reactivity of palladium species as an insight about the mechanism of the Buchwald-Hartwig condensation reaction.<sup>191</sup>

Decomposition of **74a** at  $23$  °C obeys first-order kinetics and the rate of C-O reductive elimination from (**1b**) is nearly an order of magnitude faster than decomposition of *p*-cyanophenyl derivatives **74** (E= CN). It has also been found that the rate of reductive elimination decreases in the order E=  $\text{NO}_2$  > CHO > CPh (**74**, Scheme 47).<sup>191</sup>

It was found that C-O reductive elimination from aryl(neopentoxide) complexes occurs far more readily than that of aryl(aryloxide) complexes and is facilitated by the presence of substituents on the palladium-bound aryl group capable of delocalizing negative charge.

These observations are consistent with the buildup of negative charge in the palladium-bound aryl group in the transition state for C-O reductive elimination.

This charge accumulation can be accounted for by a mechanism initiated by inner-sphere nucleophilic attack of the alkoxide ligand at the ipso-carbon atom of the palladium-bound aryl group to form a zwitterionic Meisenheimer intermediate or transition state (Scheme 47, entry b). However, the proposed mechanism does not appear to be the only mechanism available for C-O reductive elimination.

In an effort to further probe the intimate mechanism of palladium-mediated C-O reductive elimination, the rate and efficiency of the thermal decomposition of palladium (aryl) neopentoxide complexes has been

investigated as a function of the electronic nature of the palladium-bound aryl group. Kinetics are consistent with rapid and reversible generation of intermediate **O** followed by rate-limiting Pd,C heterolysis to form the liganded palladium **74** and the aryl ethers **75** via a charge-separated transition state such as **P** (Scheme 51, entry c). Alternatively, kinetic results are consistent with rate-limiting alkoxide migration via a transition state such as **N** followed by rapid Pd,C bond cleavage (Scheme 47, entry b).

Using these informations, it could be suggested that:<sup>186</sup>

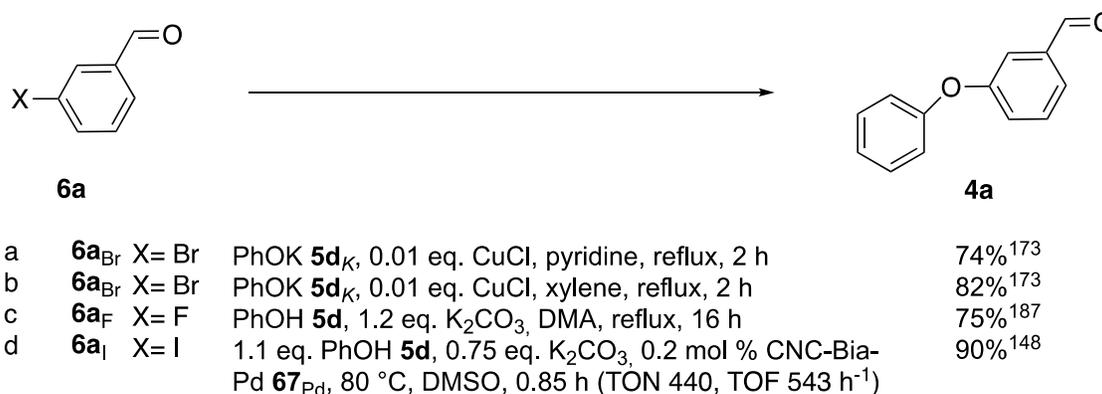
(1) For electron-deficient aryl halides, a mechanism involving transfer of the phenolate from the palladium to the ipso-carbon of the aryl halide to form a zwitterionic intermediate such as **O** then **P** is suggested which then converts to the diaryl ether and a palladium(0) complex,

(2) For electronically neutral and electron-rich aryl halides, a different mechanism is proposed for reductive elimination to form the C-O bond that most likely involves a three-centered transition state such as **N**. In these cases, the bulkier ligands are necessary to destabilize the ground state of the LnPd(OAr)Ar' complex, forcing the palladium-bound aryl and aryloxy groups to be closer, favoring a distorted complex and a three-centered transition state.<sup>186</sup>

### 3.2. Syntheses of 3-phenoxybenzaldehyde from 3-halogenobenzaldehydes and 3-hydroxybenzaldehyde

This approach takes advantage of the fact that one of the two partners, the phenol (**5d**), is a basic compound and the fact that the coupling proceeds efficiently from the 3-bromobenzaldehyde (**6a<sub>Br</sub>**) catalyzed by copper chloride under the classical Ullmann reaction (Scheme 48, entries a,b).<sup>173</sup>

**3.2.1. Syntheses of 3-phenoxybenzaldehyde from 3-halogenobenzaldehydes.** The approaches to 3-phenoxybenzaldehyde (**4a**) from 3-halogenobenzaldehydes **6a** and 3-hydroxybenzaldehyde (**5a**) are apparently the most straightforward ones. They have been achieved in the first case by coupling 3-halogenobenzaldehydes **6a** with the parent phenol in the presence of a base or with pre-generated sodium or potassium phenoxide in the presence of a transition metal (Section 3.2.1) or 3-hydroxybenzaldehyde (**5a**) and a diphenyliodonium salt or triphenylbismuth diacetate (Section 3.2.2.).



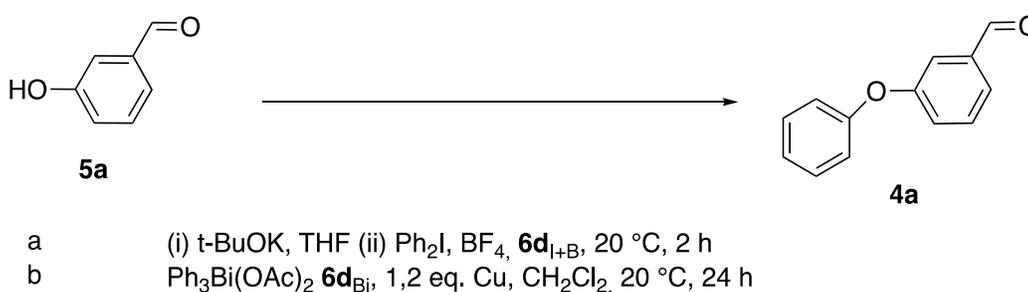
**Scheme 48.** Syntheses of 3-phenoxybenzaldehyde from 3-halogenobenzaldehydes.<sup>148,173,187</sup>

These results do not seem to align with the admitted knowledge that (i) aromatic halides react poorly when they bear electron withdrawing groups, the fact that (ii) contrary to what is believed, the reaction carried out in pyridine does not perform better than that performed in xylene (Scheme 48; compare entries a,b) and that (iii) the fluoro derivative **6a<sub>F</sub>**, which is believed to be the least reactive perform so well and even does not require the presence of copper (Scheme 48, entry c).<sup>187</sup> This suggests a process that involves an addition-elimination

reaction through a Meisenheimer intermediate<sup>188</sup> that does not usually proceed with fluoro derivatives that bears an electron attractive group in *meta*-position but rather in *ortho/para*.

The reaction catalyzed by palladium supported on cellulose nanocrystals (CNC-Bia-Pd (**67**<sub>Pd</sub>), Table 8) according to a modified Buchwald-Hartwig process, provides an exceptionally high yield of 3-phenoxybenzaldehyde under mild conditions (DMSO, 80 °C, <1h), profiling reasonably good catalytic performances (TON 440, TOF 543 h<sup>-1</sup>, Scheme 52, entry d) and efficient reuse of the catalyst.<sup>148</sup> This reaction however proceeds on the aryl iodide that is the most expensive and the heaviest of the series.

**3.2.2. Syntheses of 3-phenoxybenzaldehyde from 3-hydroxybenzaldehyde.** Arylation of 3-hydroxybenzaldehyde does not seem to have been carried out using the Ullmann or Buchwald-Hartwig reactions. It has been however successfully achieved at room temperature and in high yield using the particularly reactive diphenyliodonium tetrafluoroborate (Scheme 49).<sup>151</sup> Furthermore it does not require the presence of a metal catalyst (Scheme 49, entry a).<sup>151</sup>



**Scheme 49.** Syntheses of 3-phenoxybenzaldehyde from 3-hydroxybenzaldehyde.<sup>151,158</sup>

The other successful synthesis involves arylation of 3-hydroxybenzaldehyde (**5a**) using triphenylbismuth diacetate.<sup>193</sup> This reaction also takes place at room temperature but requires longer time (24 h) and uses copper powder as catalyst (Scheme 49, entry b).<sup>158</sup>

### 3.3. Multistep syntheses of 3-phenoxybenzaldehyde from 3-halogenotoluenes and 3-hydroxytoluene

This approach requires first the synthesis of 3-phenoxytoluene (**4b**) then its selective oxidation to 3-phenoxybenzaldehyde (**4a**).

**3.3.1. Synthesis of 3-phenoxytoluene from 3-halogenotoluene or 3-hydroxytoluene. 3.3.1.1. Synthesis of 3-phenoxytoluene from 3-halogenotoluenes and phenol.** The results concerning the synthesis of 3-phenoxytoluene (**4b**) from 3-halogeno-toluenes **6b** and phenol (**5d**) are gathered in Scheme 50. They all involve the Ullmann reaction using copper salts as the pre-catalysts, cesium carbonate as the base or already prepared potassium phenate, are usually carried out in aprotic polar solvents such as *N,N*-dimethyl formamide (DMF), *N,N*-dimethyl acetamide (DMAC), *N*-methyl-2-pyrrolidone (NMP) or acetonitrile and provides 3-phenoxytoluene (**4b**) in medium to high yields.<sup>166,168,169,181,194,195</sup>

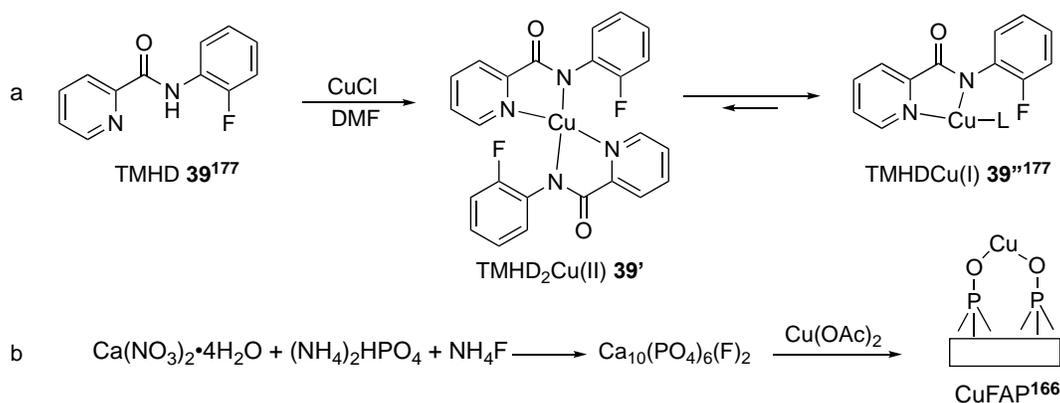


- |   |   |                    |
|---|---|--------------------|
| a | X= Br; 1.5 eq PhOH <b>5d</b> , 2 eq. Cs <sub>2</sub> CO <sub>3</sub> , 0.5 eq. CuCl, 0.1 eq. TMHD <b>39</b> , DMF <b>40a</b> , 120°C, 24h | 58% <sup>194</sup> |
| b | X= Br: 1.5 eq. PhOH <b>5d</b> , 2 eq. Cs <sub>2</sub> CO <sub>3</sub> , Cu/CNFs catalyst, 140° C, DMAC <b>40b</b> , 24 h                  | 58% <sup>167</sup> |
| c | X= Br: 1.1 eq. PhOK <b>5d<sub>K</sub></b> , cat CuFAP, NMP <b>41</b> , 120°C, 5h,   | 90% <sup>166</sup> |
| d | X= Br: 2 eq. PhOH <b>5d</b> , K <sub>2</sub> CO <sub>3</sub> , 0.05 CuI, 140°C, 5h, neat, sonication                                      | 97% <sup>168</sup> |
| e | X= I: 0.8 eq. PhOH <b>5d</b> , 0.1 eq CuI, 1 eq. DBU <b>44</b> , 0.5 equiv KOT-Bu, MeCN, hv (254 nm), 20°C, 12 h                          | 80% <sup>169</sup> |
| f | X= I: 1.2 eq. PhOH <b>5d</b> , 0.01 eq. Cu <sub>2</sub> O, 0.02 <b>43</b> , 2 eq. Cs <sub>2</sub> CO <sub>3</sub> , MeCN, 80°C, 24 h, air | 92% <sup>181</sup> |
| g | X= I: 1 eq. PhOH, Cs <sub>2</sub> CO <sub>3</sub> 2 eq., 0.1 eq. Cu <sub>2</sub> O-nanocubes, THF, 150°C, 3h                              | 98% <sup>195</sup> |

**Scheme 50.** Synthesis of 3-phenoxytoluene from 3-halogenotoluenes.<sup>166-181,195</sup>

They are however striking differences in conditions and yields depending on the catalytic system used. The reaction has usually been carried out with 3-bromotoluene (**6b<sub>Br</sub>**) (Scheme 50, entries a-d) and its iodo analogue **6b<sub>I</sub>** (Scheme 50, entries e-g) usually at temperature of 120-150 °C for 3 to 24 h. In one case, the transformation has been performed on **6b<sub>Br</sub>** without solvent under sonication at 120 °C with extremely low copper iodide loading (0.05%, Scheme 50, entry d)<sup>168</sup> or even at room temperature under light irradiation (254 nm, Scheme 50, entry e).<sup>169</sup>

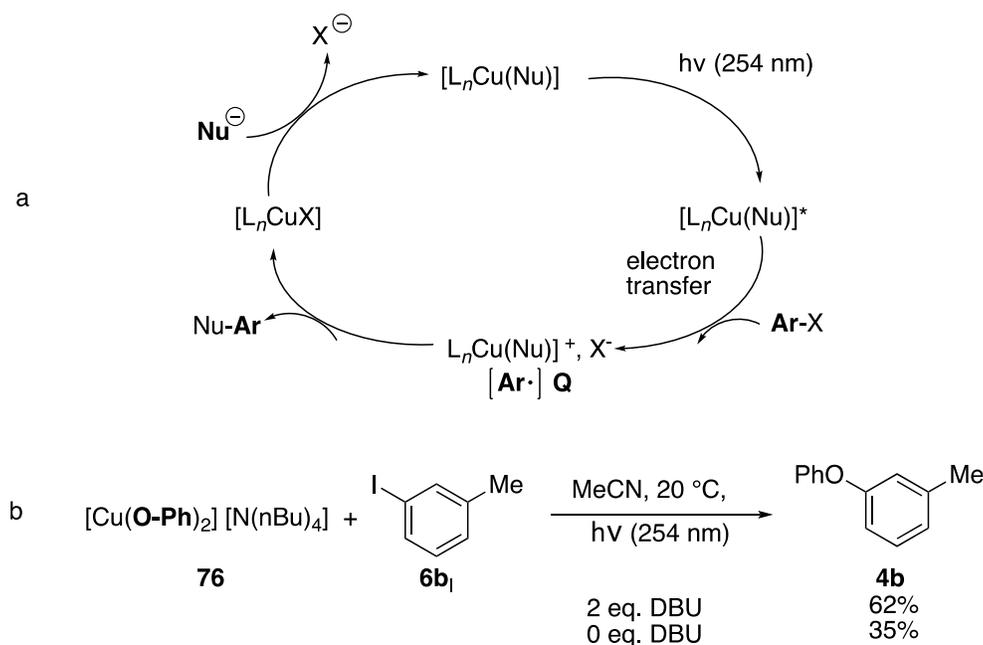
The reaction performed using a more elaborated copper chloride catalyst (Cu/CNFs) deposited on carbon nanofibers, resulting from a carbonization process, delivers **4b** in similar modest yield (Scheme 54, entry b, compare to entry a).<sup>167</sup> It nevertheless offers the advantage of easy recovery of the catalyst that is usually cumbersome to achieve, and its easy recycling.<sup>167</sup> It was noticed<sup>167</sup> that regioisomeric bromotoluenes behave similarly, generating the isomeric phenoxytoluenes in similar modest yield although under similar conditions diphenyl ether is produced in almost quantitative yield.<sup>167</sup>



**Scheme 51.** Synthesis of copper deposited on fluorapatite (CuFAP) and complexed copper catalysts.<sup>166,177</sup>

Higher yields have been observed using copper deposited on fluorapatite (CuFAP) solid support that requires a high loading and no ligand (100 mg/mmol, Scheme 50, entry c),<sup>166</sup> or Cu<sub>2</sub>O-nanocubes (Scheme 50, entry g)<sup>195</sup> that similarly allow the easy isolation of the product from the inorganic phase. Note that the former reaction that use (CuFAP) has been successfully extended to the whole series of halogeno-benzenes, except the

fluoro (> 90% yield; I, Br, Cl: 4 h, 5 h, 15 h).<sup>166</sup> Excellent yield of **4a** have been obtained from the reactions carried out neat under sonication (Scheme 54, entry d),<sup>168</sup> or induced by light (Scheme 50, entry e).<sup>169</sup>



**Scheme 52.** Possible pathway for photoinduced copper catalyzed cross-coupling between 3-halogeno-toluenes and phenol.<sup>169</sup>

The latter reaction merits further comments. It has been established<sup>169</sup> that:

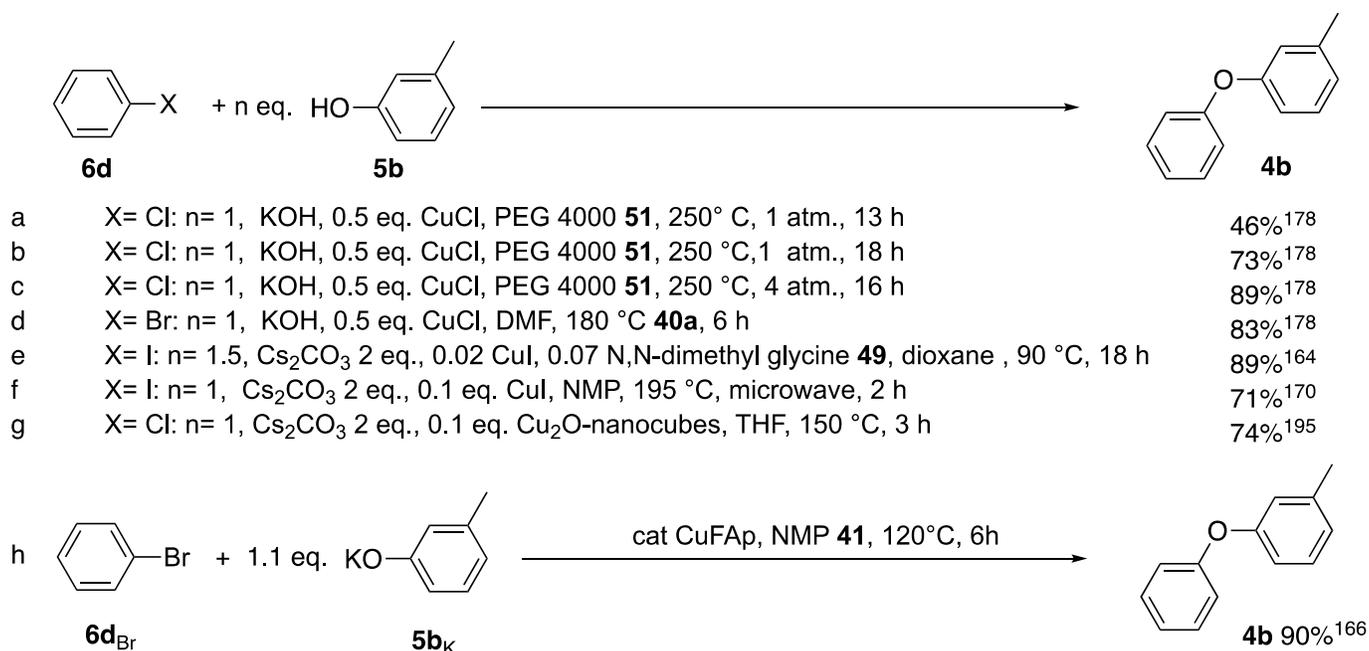
- (i) Use of longer-wavelength light result in less efficient C–O bond formation (300 nm: 64%),
- (ii) Combination of DBU and *t*-BuOK provides a better yield (80%), than each one alone (DBU: 70% ; *t*-BuOK: 74%),
- (iii) Excess *t*-BuOK is detrimental,
- (iv) the alkali-metal cation associated with the *t*-butoxide base has a significant impact on the coupling efficiency (*t*-BuOLi: 18%),
- (v) the use of a lower quantity of CuI (5%: 42% yield instead of 80%) or replacement of CuI with CuCl (78% yield), CuCl<sub>2</sub> (65% yield) or Cu (22% yield) leads to diminished yields in the diaryl ether **4b**.

A mechanism that involves the intermediate formation of the aryl radical **Q** has been postulated to account for this process (Scheme 52, entry a)<sup>169</sup> and interestingly 3-phenoxytoluene (**4b**) has been successfully synthesized on reacting on 3-iodo-toluene (**6b<sub>1</sub>**) with **76**, a postulated intermediate in the process, even in the absence of copper iodide (Scheme 52, entry b).<sup>169</sup>

**3.3.1.2. Synthesis of 3-phenoxytoluene from 3-hydroxytoluene and halogenobenzenes.** 3-phenoxytoluene (**4b**) has also been synthesized from *m*-cresol (**5b**) and halogenobenzenes **6d** using the Ullman procedure as shown in Scheme 53,<sup>164,170,166,178,197</sup> the reaction employing the stannyl derivative **6d<sub>Sn</sub>** instead is reported in Scheme 54.<sup>155</sup>

The reaction has been carried on almost the whole family of halogenobenzenes with the exclusion of fluorobenzene and involves in most of the cases *in situ* formation of a cresolate on reaction with potassium hydroxide or cesium carbonate (Scheme 52, entries a-f).<sup>178,164,170</sup> In other cases, the phenolate is prepared separately and introduced in the reaction mixture (Scheme 57, entries h,i).<sup>166,197</sup>

It has been observed, as expected, that bromobenzene (**6d<sub>Br</sub>**) in PEG 4000 as the solvent and ligand (Table 7) is far more reactive than the related chloride **6d<sub>Cl</sub>** (Scheme 53, compare entries a,d) and that in the latter case performing the reaction under pressure has a favorable impact on the yield of **4b** (Scheme 57, compare entries a-c).



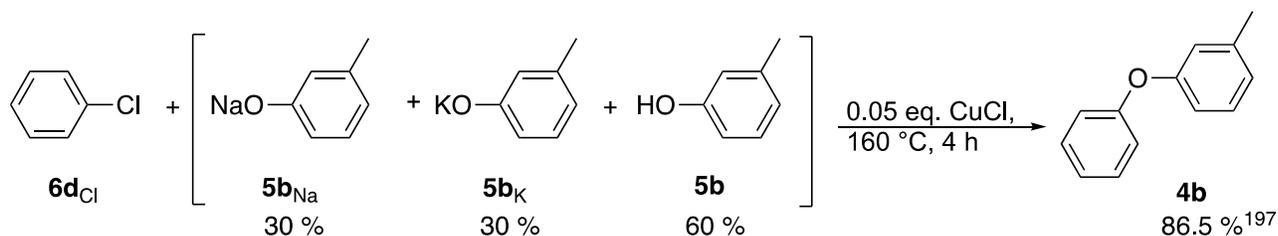
**Scheme 53.** Copper-catalyzed synthesis of 3-phenoxytoluene from metal cresolates and aryl halides.<sup>166,178,170,195,197</sup>

Successful coupling has been performed on iodo-benzene (**6d<sub>I</sub>**) in the presence of *N,N*-dimethylglycine (Table 7) as the ligand (Scheme 53, entry e),<sup>164</sup> under microwave irradiation in NMP, although it proceeded at very high temperature (Scheme 53, entry f),<sup>170</sup> or using copper deposited on fluorapatite (CuFap) in NMP (Scheme 51, entry b, Scheme 53, entry h).<sup>166</sup>

Apparently, the process implying Cu<sub>2</sub>O-nanocubes in THF was very attractive since it proceeds<sup>195</sup> rapidly (3 h) with chlorobenzene (**6d<sub>Cl</sub>**) (Scheme 53, entry g). It does not seem to be impacted by the halophilicity that follows the bond reactivity order of C–I > C–Br > C–Cl. It requires an extremely low loading (0.1 mol%), allows easy isolation of the product and provides the product in high yield and the catalyst can be recycled at least 3 times without losing of its activity and furthermore these Cu(I)] particles are easily produced at 240 °C by a one-pot process from Cu(II)(acac)<sub>2</sub>, in the presence of poly-(vinyl pyrrolidone) (PVP) as a surfactant and 1,5-pentane-diol (PD) as both reductant and solvent.<sup>195</sup> Nevertheless this process requires 2 equivalents of Cs<sub>2</sub>CO<sub>3</sub> as base (Scheme 57, entry g) that precludes its industrialization due to its high cost and to the fact that cesium is genotoxic. This topic is discussed below (Scheme 54).

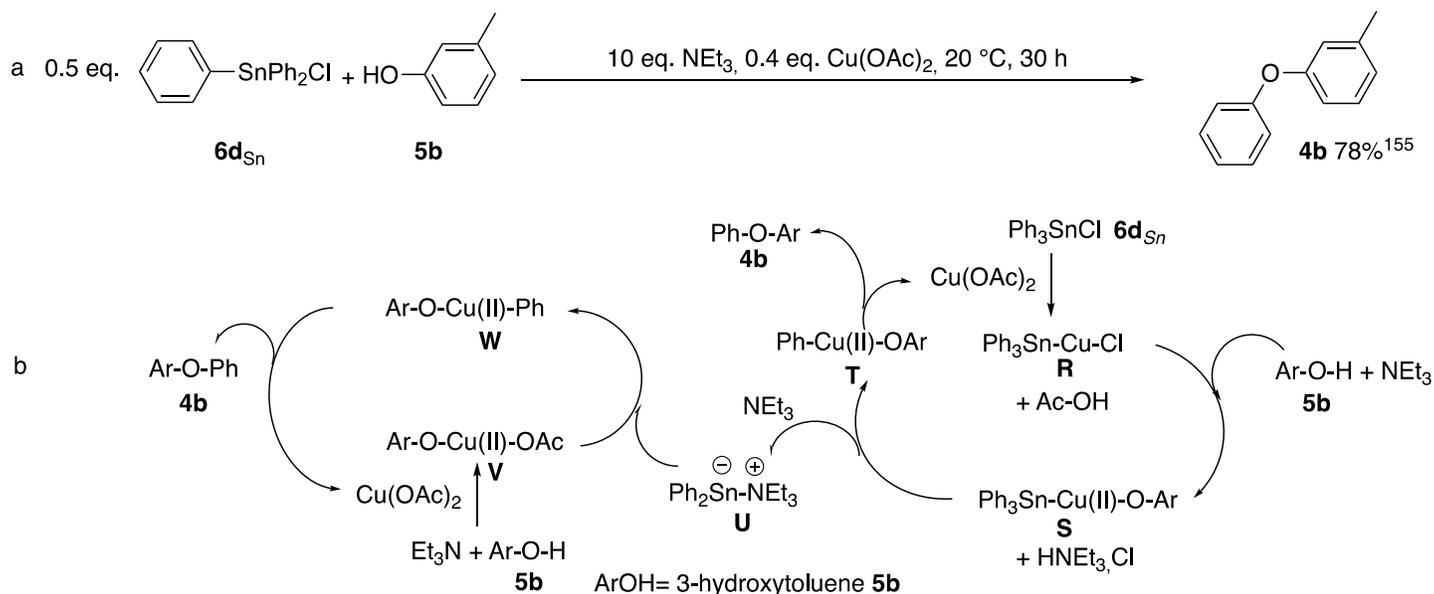
According to a patent, the most convenient industrial route to 3-phenoxytoluene (**4a**) should use the cheapest chlorobenzene (**6d<sub>Cl</sub>**), sodium cresolate (**5b<sub>Na</sub>**) and the smallest possible amount of copper chloride catalyst. Although the reaction takes place at 160 °C with an amount of copper chloride as low as 0.05 eq. with the more expensive potassium cresolate, it does not work with its sodium analogue.<sup>197</sup> In order to perform the reaction at the lowest cost, it has been found that the reaction proceeds under similar conditions (160 °C, 5 mol% CuCl), neat under anhydrous conditions when sodium cresolate is mixed with at least 40% of the related

potassium salt or if chlorobenzene (**6d<sub>Cl</sub>**) is reacted neat with a mixture of sodium cresolate / potassium cresolate / cresol (1/1/2) (Scheme 54).<sup>197</sup> It has also been reported that: (i) the catalytic activity of copper chloride is limited to about four hours and (ii) the red-brown solid resulting from the coupling dissolves in aqueous acidic media allowing extraction of the coupling product (**4b**) with chlorobenzene that can be reused as starting material for another run.<sup>197</sup>



**Scheme 54.** Industrial synthesis of 3-phenoxytoluene from chlorobenzene.<sup>197</sup>

The synthesis of 3-phenoxybenzaldehyde (**4b**) has also been achieved from *m*-cresol and triphenylstannyl chloride (**6d<sub>Sn</sub>**) and 3-hydroxytoluene (**5b**) in the presence of copper acetate. The reaction occurs at room temperature and proceeds with 0.5 equivalents of reagent suggesting that the triphenyltin chloride is able to transfer more than one phenyl group in the process (Scheme 55, entry a).<sup>155</sup> Since tetraphenyltin does not provide **4b**, it has been suggested that the presence of the Sn-Cl bond in triphenyl chlorostannane (**6d<sub>Sn</sub>**) provides the site of insertion for copper to produce the postulated intermediate **R** that on reaction with cresol (**5b**) leads, in the presence of triethylamine, to **S** by phenyl migration, then to intermediates **T** and **U** (Scheme 58, entry b).<sup>155</sup> interestingly, **U** has still the capability to transfer one more phenyl group to (**5b**) to produce **4b**.<sup>155</sup>

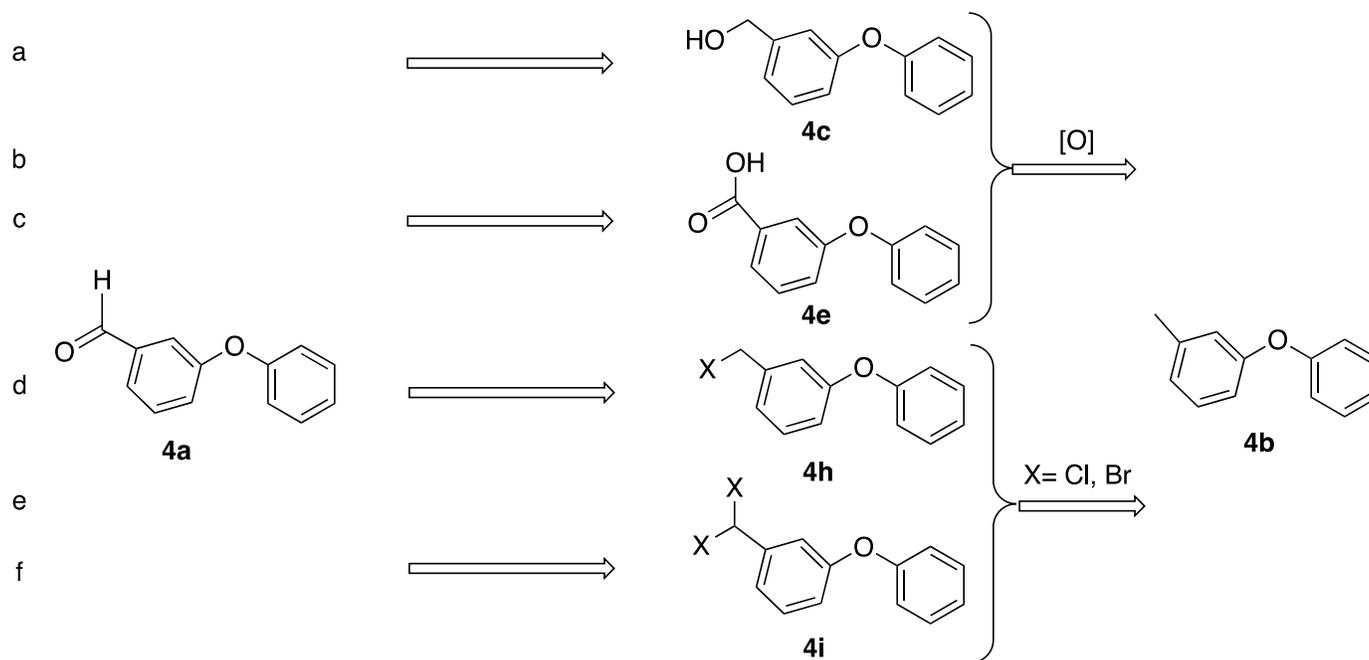


**Scheme 55.** Copper-catalyzed synthesis of 3-phenoxytoluene from *meta*-cresol and arylstannanes and a proposed mechanism.<sup>155</sup>

**3.3.2. Syntheses of 3-phenoxybenzaldehyde from 3-phenoxytoluene.** The strategies involved for the transformation of 3-phenoxytoluene (**4b**) to 3-phenoxybenzaldehyde (**4a**) are summarized in Scheme 56.

Oxidation of 3-phenoxytoluene (**4b**) to produce 3-phenoxybenzaldehyde (**4a**) (Scheme 56, entry b) is not an easy task since the removal of the first benzylic hydrogen leading formally to the benzyl alcohol (**4c**) is the most difficult task (Scheme 59, entry a) and over-oxidation competes (Scheme 56, entry c).

Oxidation by oxygen is without context the cheapest but the synthesis of 3-phenoxybenzaldehyde (**4a**) request fine tuning since the formation of the intermediate 3-phenoxybenzyl alcohol (**4c**) is difficult (Scheme 56, entry b then a) and overoxidation leading to 3-phenoxybenzoic acid (**4e**) particularly easy (Scheme 56, entry c).



**Scheme 56.** Alternative approaches to 3-phenoxybenzaldehyde from 3-phenoxytoluene.

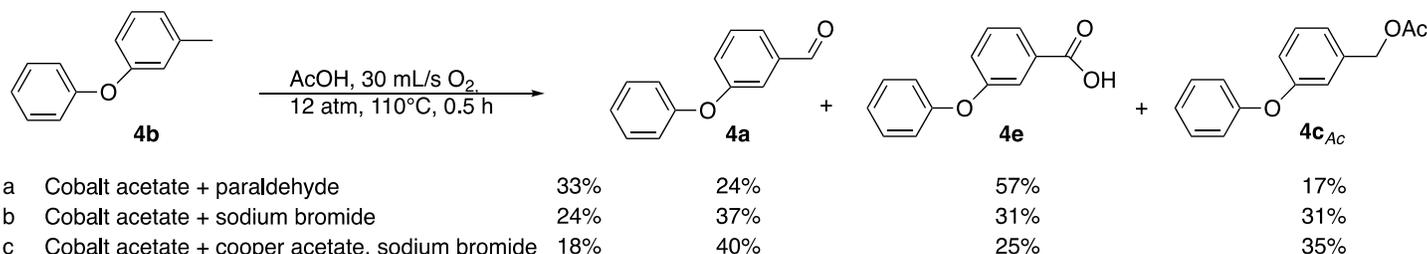
Oxidation using metal oxides offers the advantage of tuning their reactivity by selection of the metal.

Oxidation has been also carried out with halogens (Scheme 56, entries c,d) and again the first exchange leading to 3-phenoxybenzyl halides **4h** is usually the most difficult and polyhalogenation that can either occur laterally leading to **4i** (Scheme 56, entry d) or on the ring. Furthermore, use of halogens is not only more expensive than use of oxygen but it also requires an extra step to deliver the required aldehyde **4a**.

The syntheses of 3-phenoxybenzaldehyde (**4a**) involving the oxidation of 3-phenoxytoluene (**4b**) by direct H/O exchange are summarized in Section 3.3.2.1 and those involving the intermediate H/Cl or H/Br exchange in Section 3.3.2.2.

**3.3.2.1. Transformation of 3-phenoxytoluene to 3-phenoxybenzaldehyde.** Oxidation of benzylic hydrogen of 3-phenoxytoluene (**4b**) by dioxygen in the presence metal catalyst does not go to completion and is not usually chemoselective.<sup>178,198-204,205</sup> It provides besides the required aldehyde (**4a**) a mixture of 3-phenoxybenzyl alcohol (**4c**) and in some case the carboxylic acid **4e**. These have been then transformed to 3-phenoxybenzaldehyde (**4a**) on chemoselective oxidation of the benzyl alcohol **4c** (Chapter 3.3.) or by reduction of the carboxylic acid **4e** that has been achieved among others through the corresponding benzoyl chloride **4j** using usually the Rosenmund reaction.<sup>206</sup>

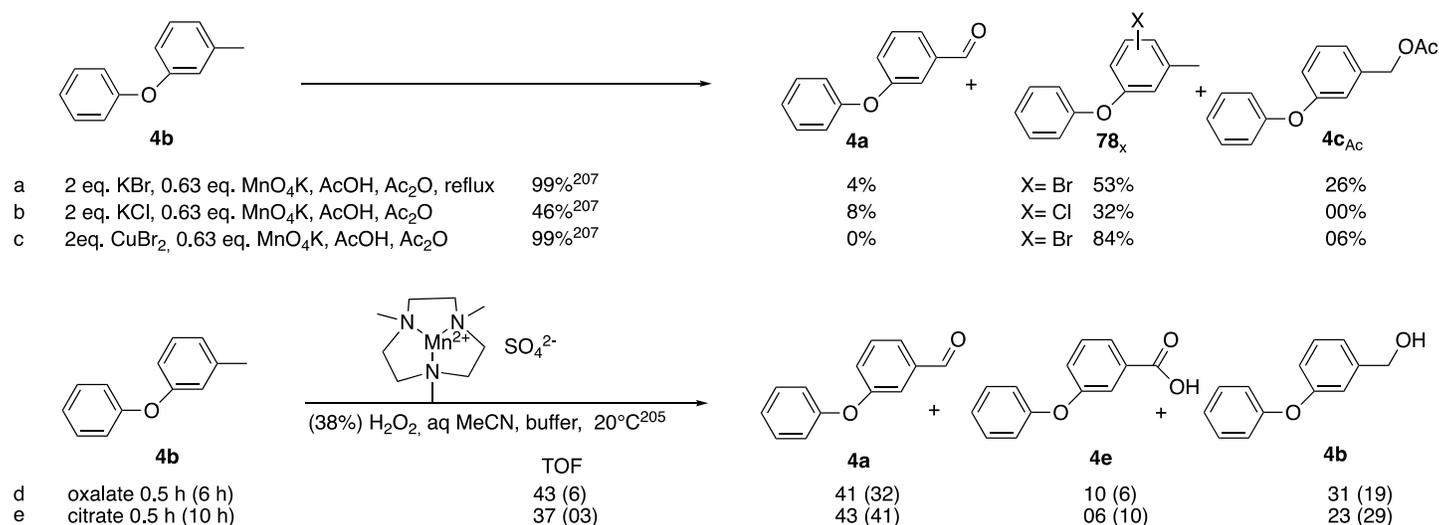
The direct oxidation of 3-phenoxytoluene (**4b**) using dioxygen as oxidant and cobalt diacetate as catalyst [Co(OAc)<sub>2</sub>/O<sub>2</sub>] has been reported in the patent literature (see references quoted in refs 178, 207) to provide 3-phenoxybenzaldehyde (**4a**) (29% yield), the corresponding benzyl alcohol (**4c**) or its acetate **4c<sub>Ac</sub>** (21% yield) beside a large amount of by-products (21-50%).<sup>207</sup>



**Scheme 57.** Oxidation of 3-phenoxytoluene by air catalyzed by cobalt acetate.<sup>178</sup>

More recent results using the same catalyst are shown in Scheme 57.<sup>178</sup> The reaction is best achieved by dioxygen at quite high temperature (110 °C) and under high pressure (12 bar), in the presence of cobalt acetate (Co(OAc)<sub>4</sub>) as a catalyst and an additive such as paraldehyde, sodium bromide alone or mixed with copper acetate. These reactions deliver in all the cases 3-phenoxybenzaldehyde (**4a**), the corresponding carboxylic acid **4e** and the corresponding benzyl acetate **4c<sub>Ac</sub>** in low overall yield (18-33%).<sup>178</sup>

Oxidation of 3-phenoxytoluene has been also performed by stoichiometric amounts of potassium permanganate (KMnO<sub>4</sub>) and added potassium or copper halides. It delivers a small number of compounds resulting from side-chain oxidation, besides larger amounts of compounds **78<sub>x</sub>** resulting from ring halogenation (Scheme 58, entries a-c).<sup>207</sup> These poor results have been ascribed to the detrimental role of the phenoxy group attached in *meta* position to the methyl group.<sup>207</sup>

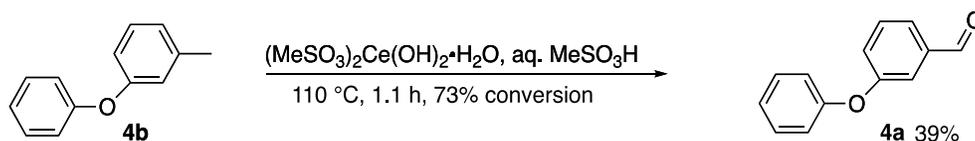


**Scheme 58.** Oxidation of 3-phenoxytoluene with manganese compounds.<sup>205,207</sup>

Oxidation has also been achieved by hydrogen peroxide in the presence of *N,N',N''*-trimethyl-1,4,7-triazacyclononane (Mn-tmtacn) sulfate and oxalic acid in the presence of a buffer. It leads to a mixture of the

desired aldehyde **4a** along with the alcohol **4c** and the acid **4e** (Scheme 58, entries d,e).<sup>205</sup> Replacement of oxalic by a citric acid or increasing the reaction time, does not dramatically change the figure.<sup>205</sup>

Among the various reagent tested<sup>207,178</sup> cerium(IV) in aqueous methanesulfonic acid proved to be an excellent reagent for benzylic oxidation.<sup>204</sup> This medium offers the advantages of low nucleophilicity, high solubility of Ce(III) and Ce(IV) ions and ideal for electrochemical regeneration.<sup>204</sup> The reaction is usually fast (0.5-2 h) except for compounds possessing electron-withdrawing groups on the aromatic ring that are less reactive and require high acid concentration.<sup>204</sup>

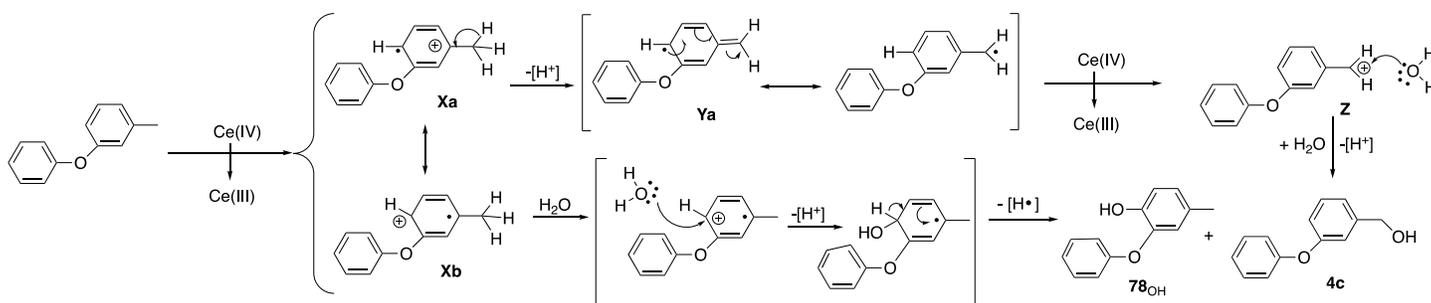


**Scheme 59.** Oxidation of 3-phenoxytoluene by “solid” ceric methanesulfonate.<sup>204</sup>

Oxidation of 3-phenoxytoluene takes place with solid ceric methanesulfonate  $[\text{Ce}(\text{MeSO}_3)_2(\text{OH})_2\cdot\text{H}_2\text{O}]$  in methanesulfonic acid (110°C, 1.10 h) and produces the aldehyde **4a** in around 40% (Scheme 59).<sup>204</sup> Performing the same reaction with fully dissolved ceric reagent does not produce the aldehyde **4a** but leads to substantial loss of the 3-phenoxytoluene (**4b**), the latter being recovered in less than 27 % after the same reaction time.<sup>204</sup>

It has been found<sup>208</sup> that ceric trifluoroacetate in aqueous trifluoroacetic acid is particularly effective for the oxidation of activated toluenes including (**4b**) to the corresponding aldehydes such as (**4a**), but unfortunately aromatic ring oxidation compete with benzylic oxidation (Scheme 60).<sup>208</sup> These competitive processes have been rationalized by the involvement of the ring centered radical cation **X** as shown in Scheme 63.<sup>208</sup>

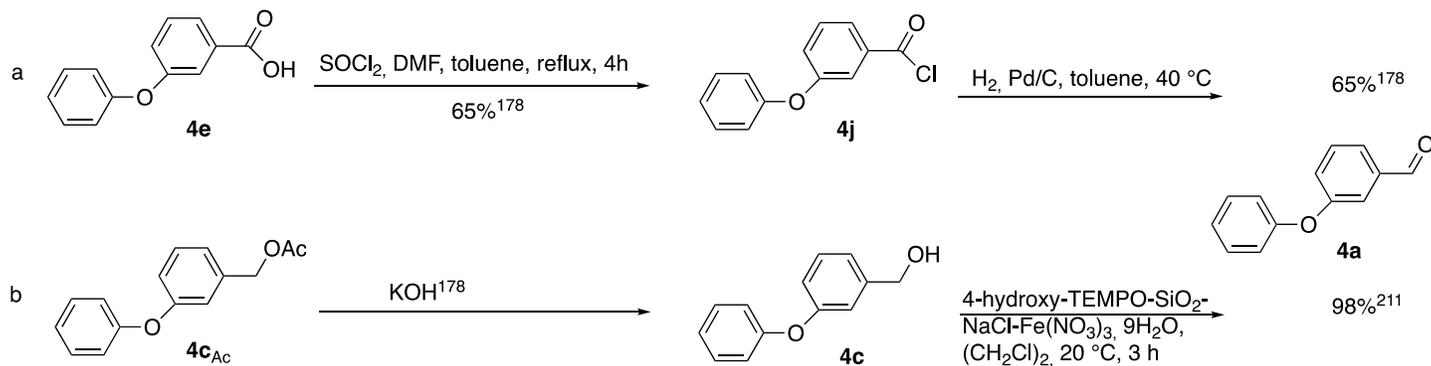
Finally, since the ceric ion is consumed in stoichiometric amounts in these process, its electrochemical regeneration at high current efficiencies (95%) allows to achieve the oxidation using catalytic amounts of cerium.<sup>208</sup>



**Scheme 60.** Oxidation of 3-phenoxytoluene by cerium(IV) and rationalization.<sup>208</sup>

As already pointed out, only few oxidants have been found selectively to transform 3-phenoxytoluene (**4b**) into 3-phenoxybenzaldehyde (**4a**). At best, this oxidation delivers besides **4a** the benzyl alcohol **4c** or/and the carboxylic acid **4e**. Separation and recycling **4c** by selective oxidation and **4e** by selective reduction allows the production of the desired aldehyde **4a** in fair yield.

Otherwise,<sup>178</sup> the mixture can either be reduced by for example by lithium aluminum hydride<sup>209</sup> to 3-phenoxybenzyl alcohol (**4c**) or oxidized to the carboxylic acid **4e** by the Jones reagent for example,<sup>210</sup> then selectively oxidized or reduced to the corresponding 3-phenoxybenzaldehyde (**4a**) (Scheme 61).



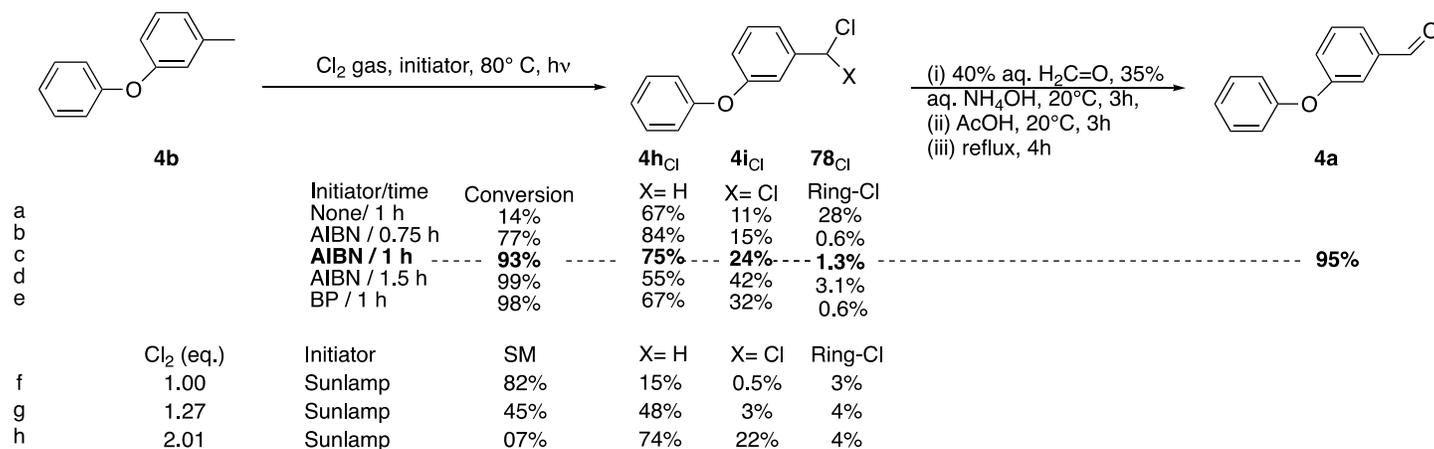
**Scheme 61.** Synthesis of 4-phenoxybenzaldehydes.<sup>178,211</sup>

Thus, the carboxylic acid **4e** has been successfully transformed to 3-phenoxybenzaldehyde **4a** using the Rosenmund reduction<sup>206</sup> that involves the transformation to the corresponding acid chloride **4j** on reaction of thionyl chloride in DMF at reflux and its reduction with hydrogen in the presence of palladium on charcoal as catalyst (Scheme 61, entry a).<sup>178</sup> The transformation of 3-phenoxybenzyl alcohol (**4c**) to 3-phenoxybenzaldehyde (**4a**) discussed in Section 3.4.2.

**3.3.2.2. Transformations of 3-phenoxytoluene to 3-phenoxybenzaldehyde involving its side-chain halogenation.** Transformation of 3-phenoxytoluene (**4b**) to 3-phenoxybenzaldehyde (**4a**) has been achieved by side chain halogenation of the starting material and subsequent substitution. Halogenation usually involves the intermediate formation of a radical and provides benzyl halides **4h** and subsequently benzal halides **4i**. Although both are good precursors of 3-phenoxybenzaldehyde (**4a**), there is an economical advantage to produce the former since a single halogen is consumed and although both 3-phenoxybenzyl bromide (**4h<sub>Br</sub>**) and the 3-phenoxybenzyl chloride (**4h<sub>Cl</sub>**) are able to generate **4a** the latter has to be preferred due to lower cost.

**3.3.2.2.1. Side-chain chlorination of 3-phenoxytoluene.** The results involving the chlorination of 3-phenoxytoluene (**4b**) are gathered in Schemes 62 and 63. Chlorination has been performed with chlorine gas (Section 3.3.2.2.1.1.) without a radical initiator (Scheme 62, entry a),<sup>202</sup> in its presence (Scheme 63, entries a-e),<sup>202</sup> under sunlamp irradiation,<sup>212</sup> or otherwise with sulfuryl chloride (Section 3.3.2.2.1.2., Scheme 64).<sup>212</sup>

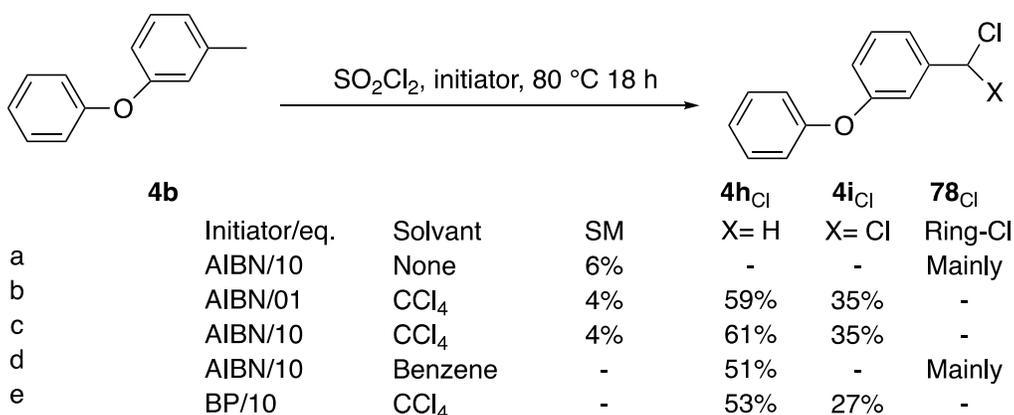
**3.3.2.2.1.1. Chlorination of 3-phenoxytoluene with chlorine gas.** The reaction performed for 1 h in a flow of chlorine gas at 80 °C in CCl<sub>4</sub>, in the absence of radical initiator, takes place with a very low conversion (14%, Scheme 62, entry a) and provides compounds resulting from lateral chlorination as a mixture of benzyl **4h<sub>Cl</sub>** and benzal (**4i<sub>Cl</sub>**) derivatives in a 85/15 ratio and ring chlorinated compounds **78<sub>Cl</sub>** in (**4h<sub>Cl</sub>** + **4i<sub>Cl</sub>**/**78<sub>Cl</sub>**: 74/26) ratio.<sup>202</sup> Performing the reaction under similar conditions in the presence of a radical initiator as azobisisobutyronitrile (AIBN, Scheme 65, entry c)<sup>202</sup> or benzoyl peroxide (BP, Scheme 62, entry e)<sup>202</sup> substantially improves the conversion and the amount of chlorination. AIBN proved to be more selective than BP providing the benzyl derivative **4h<sub>Cl</sub>** in higher yield (Scheme 65, entry c, compare to entries a,e).<sup>202</sup> It has been found that the amount of benzal chloride is highly dependent on the reaction time and increases by increasing it since the amount of gas is dependent on the reaction time (Scheme 62, compare entries b-d).<sup>202</sup> Under sunlamp irradiation that also favor the radical process (Scheme 65, entries f-h) chlorination is more efficient by increasing the amount of chlorine gas involved but this at the same time substantially favors the formation of benzal chloride (**4i<sub>Cl</sub>**) produced (Scheme 62, entries f,g,h: 1/1.27/2.1 eq.; **4h<sub>Cl</sub>**: 15/48/74% yield; **4i<sub>Cl</sub>**/**4h<sub>Cl</sub>**/**4i<sub>Cl</sub>**: 3/6/23 ratio).<sup>212</sup>



**Scheme 62.** Oxidation of 3-phenoxytoluene to 3-phenoxybenzaldehyde involving chlorine.<sup>202,212</sup>

**3.3.2.2.1.2. Chlorination of 3-phenoxytoluene by sulfuryl chloride or phosphorus oxychloride.** The reaction of 3-phenoxytoluene (**4b**) with sulfuryl chloride at 80 °C (Scheme 63)<sup>212</sup> or phosphorus oxychloride at 220 °C<sup>213</sup> proved less efficient (compare Scheme 63 to Scheme 62). Ring chlorination almost exclusively takes place even in the presence of a large amount of radical initiator when the reaction is performed in the absence of solvent (AIBN, 10%, Scheme 63, entry a),<sup>212</sup> and mixture of compounds that include 3-phenoxybenzyl chloride (**4h<sub>Cl</sub>**) is formed when the reaction is performed with AIBN in different solvents (CCl<sub>4</sub>, 1,2-dichloroethane, chlorobenzene)<sup>212</sup> or in the presence of different radical initiator such as lauryl or benzoyl peroxide (low conversion).<sup>212</sup>

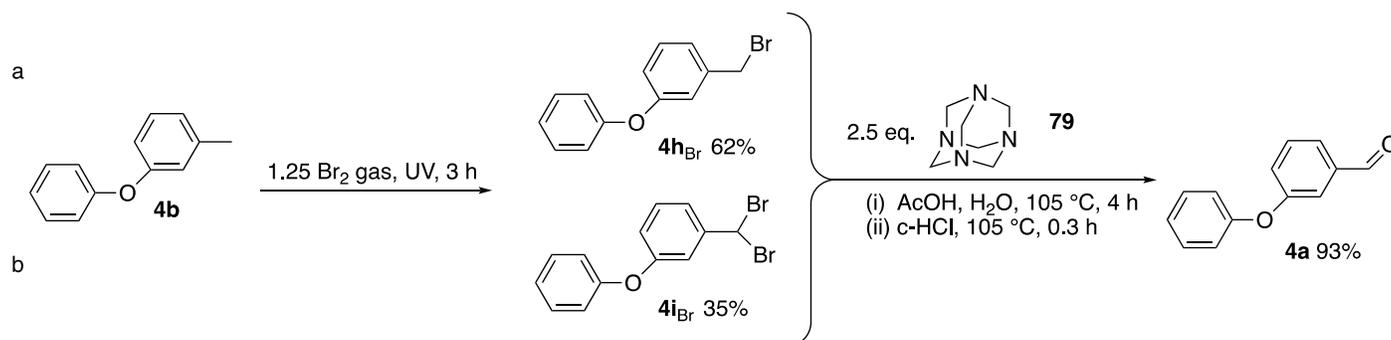
As a general rule and in order to avoid the formation of ring chlorinated compounds, the chlorination reaction must be performed, whatever is the reagent (i) at low concentration (5-50%),<sup>202</sup> in a solvent and therefore not neat<sup>212</sup> (ii) in non-polar solvent,<sup>202</sup> and (iii) should be prevented from going to completion and should be stopped at 95-98% conversion.<sup>202</sup>



**Scheme 63.**<sup>212</sup> Oxidation of 3-phenoxytoluene to 3-phenoxybenzylchloride using sulfuryl chloride.<sup>212</sup>

**3.3.2.2.2. Side-chain bromination of 3-phenoxytoluene.** Bromination of 3-phenoxytoluene (**4b**) has been carried out in a stream of excess of bromine (1.25 eq.) under ultraviolet irradiation close to the place the bromine is introduced in the reactant and vigorously circulated (Scheme 64).<sup>202</sup> After cooling for more than 12 h and flushing with nitrogen to remove the unreacted bromine, the resulting mixture

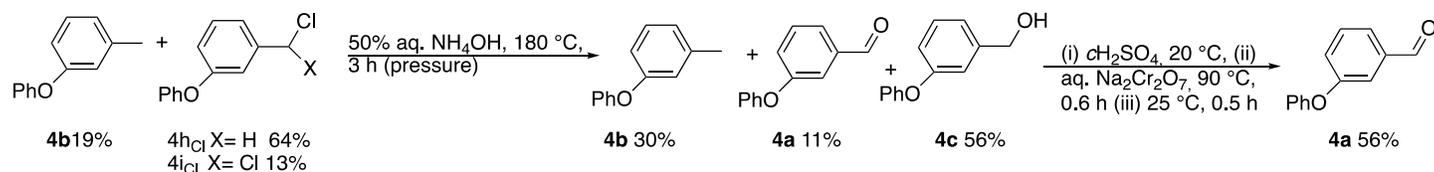
(**4b**/**4h<sub>Br</sub>**/**4i<sub>Br</sub>**:2.1/61.5/36.4%) is not purified but instead directly engaged for the next step leading to **4a** as will be discussed in the forthcoming paragraph.<sup>202</sup>



**Scheme 64.** Oxidation of 3-phenoxytoluene to 3-phenoxybenzylbromide and transformation to 3-phenoxybenzaldehyde.<sup>202</sup>

### 3.3.2.2.3. Transformation of 3-phenoxybenzyl halides and benzal halides to 3-phenoxybenzaldehyde.

**3.3.2.2.3.1. By oxidation of the transient 3-phenoxybenzyl alcohol.** The transformation of 3-phenoxybenzyl-**4h** and benzal-**4i** halides to 3-phenoxybenzaldehyde (**4a**) has been carried out on the mixture of 3-phenoxytoluene (**4b**), 3-phenoxybenzyl chloride (**4h<sub>Cl</sub>**) and 3-phenoxybenzal chloride (**4i<sub>Cl</sub>**) generated as described above, in two steps. The first one is performed with sodium or calcium hydroxide under harsh conditions (180 °C, pressure) and allows the substitution of the chloro by the hydroxyl-group (Scheme 65).<sup>214</sup> The presence of the aldehyde **4a** besides 3-phenoxybenzyl alcohol (**4c**) that results from the expected substitution of 3-phenoxybenzylchloride (**4h<sub>Cl</sub>**), let suggest that substitution also occurs also on the benzal chloride **4i<sub>Cl</sub>**.<sup>214</sup> Anyhow the resulting mixture, after acidification, is then oxidized to the corresponding aldehyde **4a** using sodium dichromate in concentrated sulfuric acid (Scheme 65).<sup>214</sup>

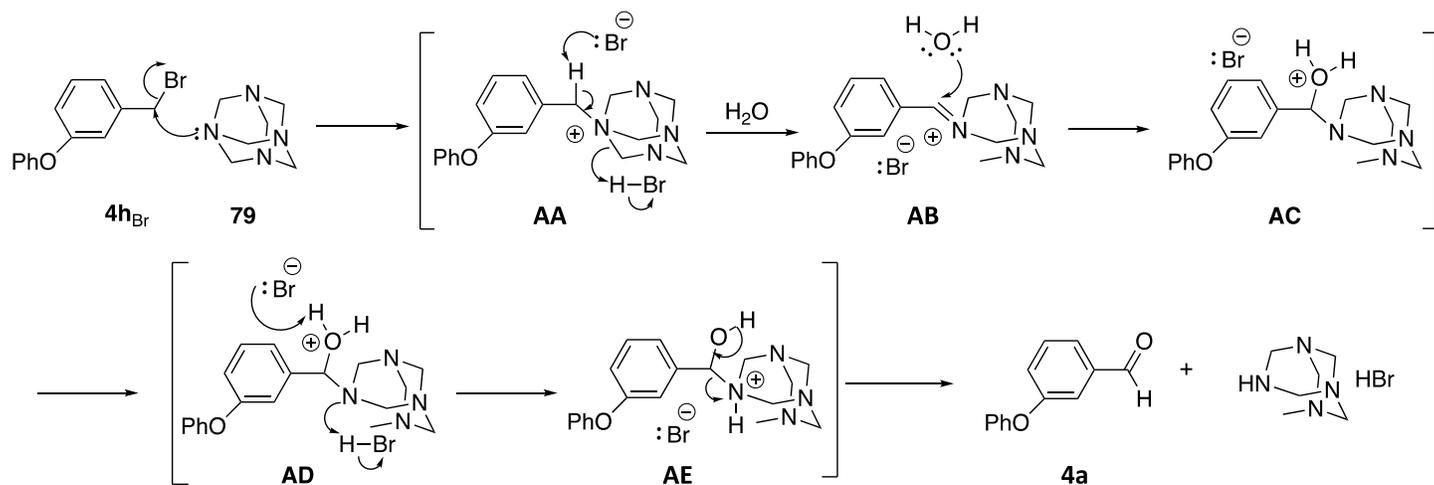


**Scheme 65.** Transformation of 3-phenoxybenzylchloride to 3-phenoxybenzyl alcohol and 3-phenoxybenzaldehyde.<sup>214</sup>

**3.3.2.2.3.2. Using the Sommelet reaction.** The synthesis of 3-phenoxybenzaldehyde (**4a**) has been more conveniently achieved from 3-phenoxybenzyl chloride (**4h<sub>Cl</sub>**) and formimine (**80**) formed *in situ*, on reaction of formaldehyde with ammonium hydroxide (Scheme 65),<sup>202</sup> corresponding bromide **4h<sub>Br</sub>** using aqueous hexamethylenetetramine (urotropine) (**79**) (Scheme 67)<sup>202</sup> in processes related to the Sommelet reaction.<sup>202,215,216</sup>

The extremely high yields in 3-phenoxybenzaldehyde (**4a**) observed when hexamethylenetetramine (urotropine) (**79**) or formimine (**80**) are used on the mixture of benzyl **4h** and benzal **4i** halides suggest that both families of substrates possessing benzylic carbons at different oxidation level react through a different mechanisms to produce the same compound **4a**.

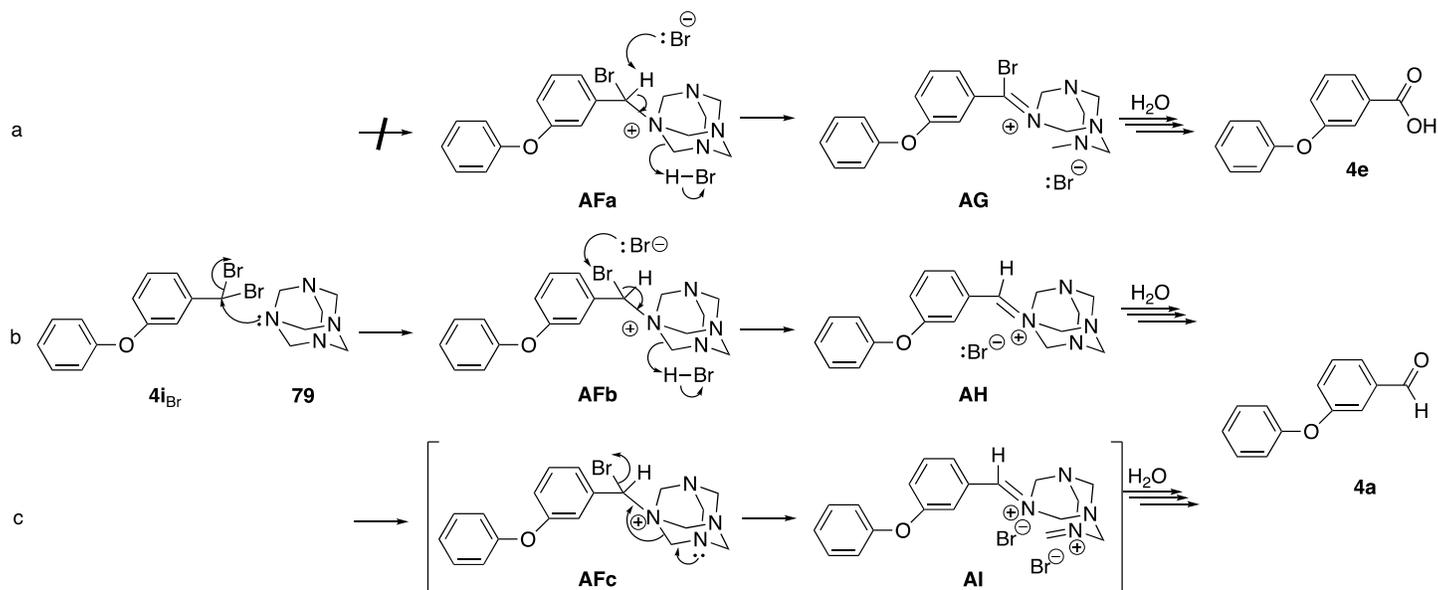
Those results are tentatively rationalized as follows (Schemes 66, 67 and 68): hexamethylene tetramine (urotropine) (**79**) (Scheme 66) is expected to react on the benzylic carbon through a nucleophilic substitution to produce the corresponding quaternary ammonium bromide **AA** that generates the iminium **AB** by subsequent  $\beta$ -elimination reaction. It takes advantage of the high acidity of one of the benzylic hydrogens and the cleavage of the adjacent C-N bond. Addition of water on the iminium carbon and release of the ammonium moiety on **AE** leads in one pot to 3-phenoxybenzaldehyde (**4a**).



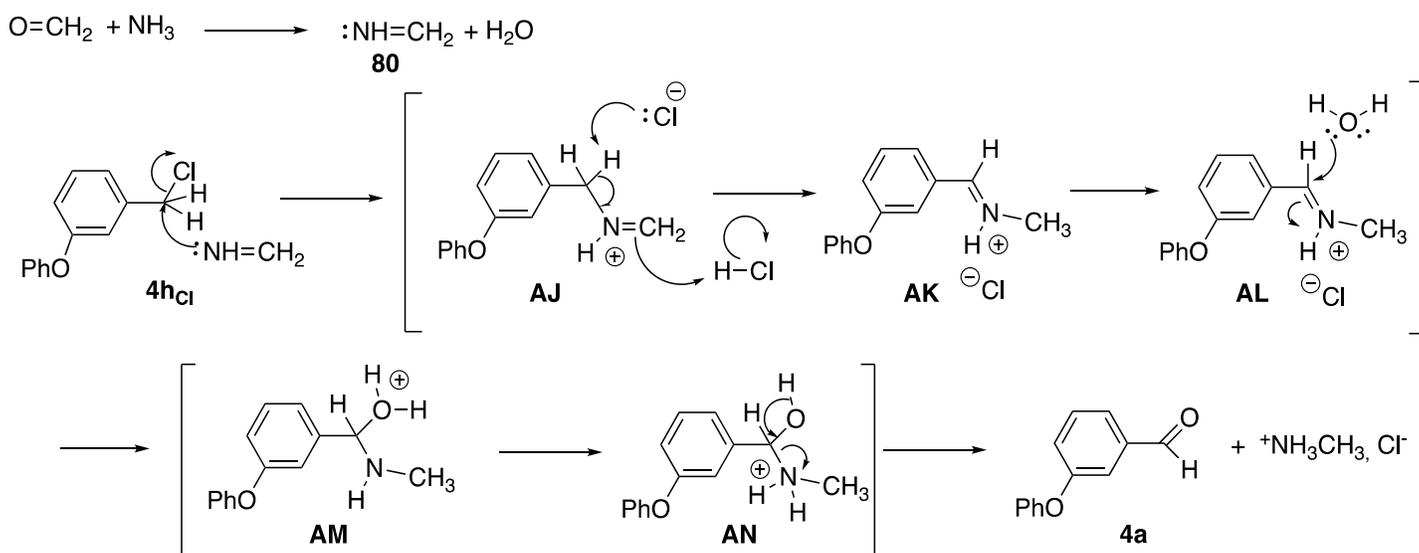
**Scheme 66.** Tentative mechanism about the oxidation of 3-phenoxybenzyl bromide to 3-phenoxybenzaldehyde involving hexamethylenetetramine.

The same mechanism is not expected to take place on the 3-phenoxybenzal bromide since it would have produced 3-phenoxybenzoic acid (**4e**) instead of 3-phenoxybenzaldehyde (**4a**) that is instead formed (Scheme 67, entry a).<sup>202</sup> Removal of the remaining bromine on the  $\alpha$ -bromo ammonium **AF** instead of hydrogen, through the processes depicted in route b (attack of the soft bromine by the soft bromide ion at a benzylic position) or more probably in route c (that take advantage of the leaving group ability of the bromine at the benzylic position), would produce the iminiums **AH** or **AI** precursors of 3-phenoxybenzaldehyde (**4a**) (Scheme 67).

An alternative mechanism, proposed by a referee, might be that urotropine (**79**) is decomposed to ammonia by hydrolysis that then reacts with 3-phenoxybenzal bromide to finally produce 3-phenoxybenzaldehyde (**4a**).



**Scheme 67.** Tentative mechanism for the oxidation of 3-phenoxybenzal bromide to 3-phenoxybenzaldehyde involving hexamethylenetetramine.



**Scheme 68.** Tentative mechanism for the oxidation of 3-phenoxybenzylchloride to 3-phenoxybenzaldehyde involving formimine.

The reaction involving the formimine (**80**) is expected to proceed through the formation of iminium **AJ** resulting from substitution of chlorine at the benzylic carbon (Scheme 68) followed by a prototropy generating the isomeric iminium **AK**. Hydrolysis of **AK** would lead then to 3-phenoxybenzaldehyde **4a** (Scheme 71).

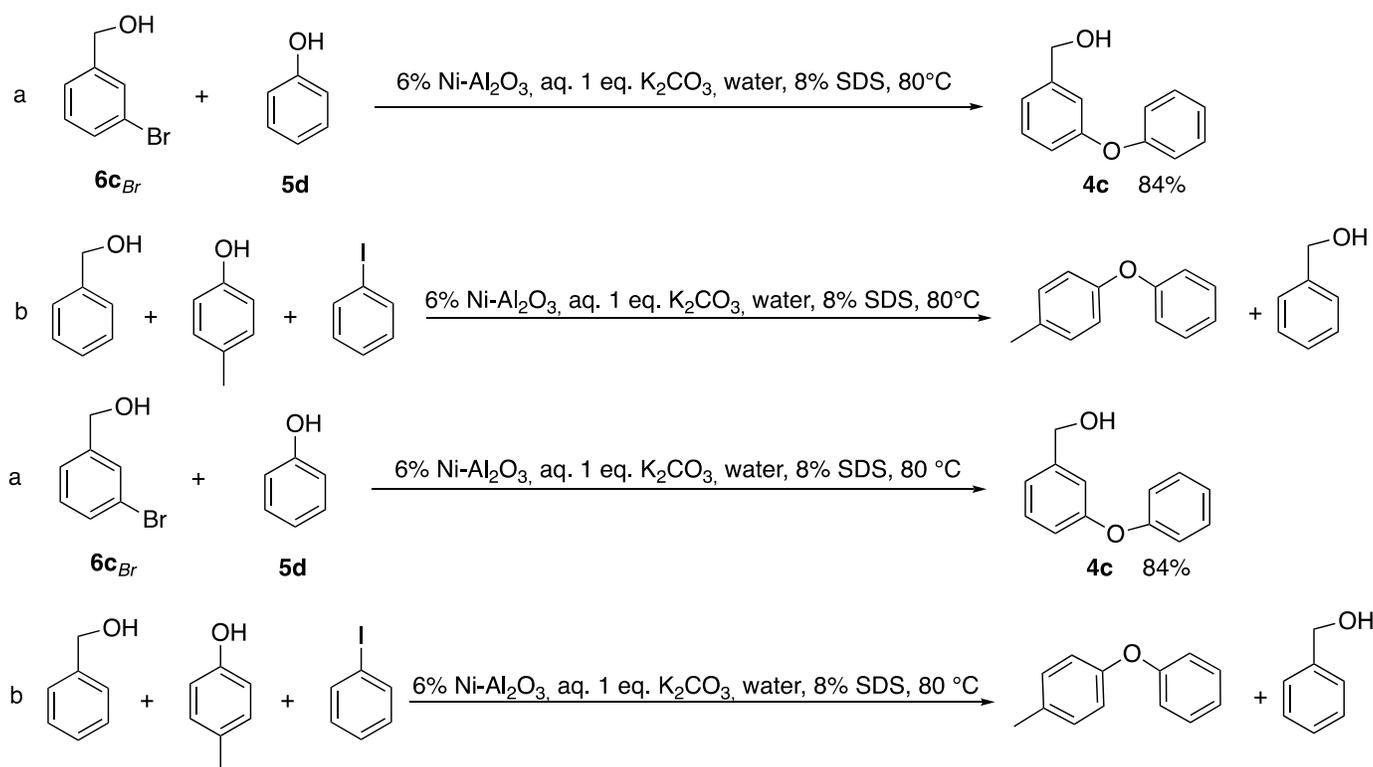
### 3.4. Multistep syntheses of 3-phenoxybenzaldehyde from 3-halogenobenzyl alcohols and 3-hydroxybenzyl alcohol

The synthesis of 3-phenoxybenzaldehyde (**4a**) from 3-halogeno-benzyl alcohols **6c** and 3-hydroxybenzyl alcohol (**5c**) involves the intermediate formation of 3-phenoxybenzyl alcohol (**4c**) that has been then oxidized to the

aldehyde without overoxidation to the corresponding acid **4e**. It offers therefore a net advantage over the transformation that instead involve the intermediate formation of 3-phenoxytoluene (**4b**) discussed above since selective oxidation of benzylic primary alcohol is much easier and selective compared to that of the methyl group of 3-phenoxytoluene (**4b**) (See above).

**3.4.1. Synthesis of 3-phenoxybenzyl alcohol from 3-halogenobenzyl alcohols and 3-hydroxytoluene.** In the two approaches that involves the 3-halogeno-benzyl alcohols **6c** and phenol (**5d**) (Section 3.4.1.1.), or the 3-hydroxybenzyl alcohol (**5c**) and halogenobenzenes **5d** (Section 3.4.1.2.), remains the possibility that the alcohol moiety competes with the phenol in the coupling process forming competitively the unwanted phenyl benzyl ether instead of the diaryl ether and potentially a polymer from **6c**. It has been interestingly found that such possibility does not occur under the conditions used (Scheme 69a, Scheme 70).<sup>175,179,180, 217</sup>

**3.4.1.1. Synthesis of 3-phenoxybenzyl alcohol from 3-halogenobenzyl alcohols and phenol.** The former coupling that is not so easy to achieve when using copper catalyst<sup>176</sup> that has been successfully carried out with a nickel catalyst.<sup>217</sup> This method offers the advantage to occur under mild conditions (80 °C), in the presence of a mild base (K<sub>2</sub>CO<sub>3</sub>) in aqueous medium along with a surfactant such as sodium dodecyl sulfate (SDS), catalyzed by alumina-supported nickel nanoparticles as a stable recyclable heterogeneous catalyst (Scheme 69, entry a).



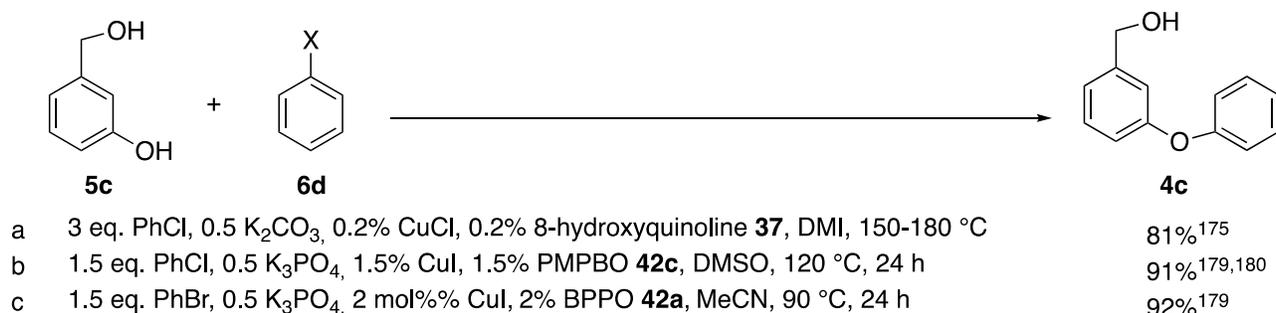
**Scheme 69.** Synthesis of 3-phenoxybenzyl alcohol from 3-bromo-benzyl alcohol and phenol. Aryl versus alkyl coupling.<sup>217</sup>

A control experiment carried out using a 1/1/1 mixture of *p*-cresol, iodobenzene and benzyl alcohol showed explicitly that the diaryl ether is produced selectively and the benzyl alcohol fully recovered at the end of the process (Scheme 72, entry b).<sup>217</sup>

**3.4.1.2. Synthesis of 3-phenoxybenzyl alcohol from 3-hydroxybenzyl alcohol and halogenobenzenes.** The synthesis of 3-phenoxybenzyl alcohol (**4c**) from 3-hydroxybenzyl alcohol (**6c**) and chlorobenzene (**5c<sub>Cl</sub>**) has been successfully achieved in high yield (> 80%) in 3-dimethyl-2-imidazolidinone (DMI) using copper chloride complexed by 8-hydroxyquinoline (**37**) (Table 7) as catalyst. The reaction is carried out at high temperature (150-

180 °C) in chlorobenzene, as one of the reagent and as the solvent, so the excess of chloro-benzene can be distilled off during the process to allow, by azeotropic distillation, the removal of the water produced on reaction of the phenol with potassium carbonate (Scheme 70, entry a).<sup>175</sup>

Interestingly, the coupling chemoselectively occurs to produce the diaryl ether and not to the alkyl aryl ether.<sup>175</sup>



**Scheme 70.** Synthesis of 3-phenoxybenzyl alcohol from 3-hydroxybenzyl alcohol and chloro- and bromobenzenes.<sup>175,179,180</sup>

Even better results (91 % yield) have been obtained from 1.5 eq. of chlorobenzene (half the amount used in the previous process) with less than 2% of copper iodide and *N*-aryl,*N'*-alkyl oxalamines (PMPBO) **42c** as ligand (Table 7) in DMSO at 120 °C for 24 h (Scheme 70, entry b).<sup>179,180</sup>

The reaction can be achieved at lower temperature when performed<sup>179</sup> on bromobenzene (90 °C, instead of 120 °C, Scheme 70, entry c, compare to entry b) but requires a slightly different *N*-aryl,*N'*-alkyl oxalimine ligand (BPPO **42b** instead of PMPBO **42c**, Table 7).<sup>179</sup> Apparently, the proper selection of the ligand and the solvent proved to be crucial for the success of the reaction.

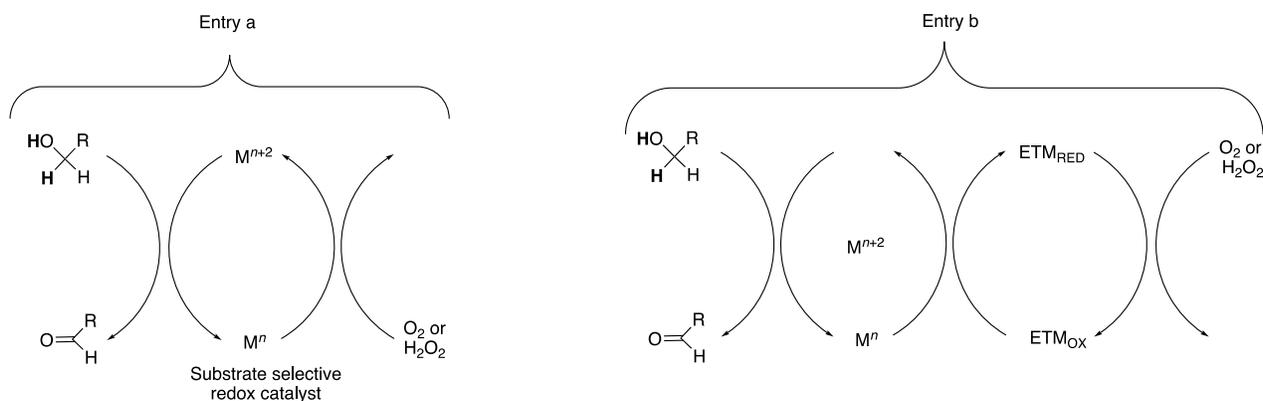
Those conditions allow the efficient coupling of ortho- and meta-substituted aryl bromides using a 1 mol% loading of the catalyst-ligand mixture and proceed well with electron-rich phenols but requires a higher loading (2 mol%) with the less reactive electron-poor phenols.<sup>179</sup>

### 3.4.2. Synthesis of 3-phenoxybenzaldehyde by chemoselective oxidation of 3-phenoxybenzyl alcohol.

Selective oxidation of alcohols to the corresponding aldehydes is a ubiquitous transformation in organic chemistry<sup>196,198-222</sup> that include several named reactions such as Swern oxidation, Moffat oxidation, Jones oxidation, Corey-Suggs oxidation, Dess-Martin oxidation (references cited).<sup>211</sup> It has been traditionally achieved by numerous stoichiometric oxidants, often involving transition metals, that lead to the release of quantities of toxic by-products into the environment. Molecular oxygen as a pure substance or diluted in air and hydrogen peroxide offer several advantages since they are environmentally friendly and exhibit a high efficiency per weight of oxidant. Molecular oxygen is inexpensive but difficult to handle whereas hydrogen peroxide is easy to handle as a water miscible liquid.<sup>196,218</sup>

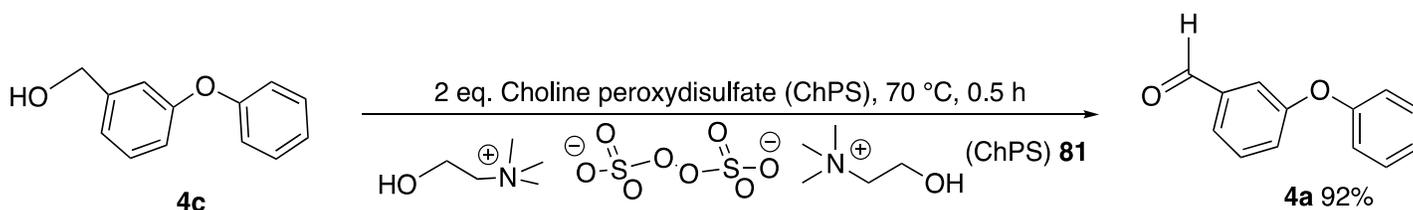
The direct oxidation of organic substrates by either O<sub>2</sub> or H<sub>2</sub>O<sub>2</sub> is rare as the energy barrier for electron transfer from the organic substrate to the oxidant is usually high. For molecular oxygen, which has a triplet ground state, this high energy barrier is nature's way of protecting organic compounds from destructive oxidation".<sup>218</sup> For a catalytic oxidation reaction, the substrate-selective catalyst, which may often be a transition metal (M<sup>n+2</sup>/M<sup>n</sup>), oxidizes the substrate to the desired product. The reduced form of the catalyst is subsequently reoxidized by the stoichiometric oxidant that could be ideally oxygen or hydrogen peroxide.<sup>218</sup>

In several cases however this process fails because the electron transfer between  $M^n$  and  $O_2$  or  $H_2O_2$  is too slow compared to the decomposition of the reduced metal; that can be circumvented by use of a (i) ligand to stabilize the species (Scheme 71, entry a) or (ii) an extra electron-transfer mediator (ETM) (Scheme 71, entry b).<sup>218</sup>



**Scheme 71.** Oxidation with a substrate-selective redox catalyst b. Electron transfer facilitated by an electron-transfer mediator (ETM).

We have selected a few examples of oxidation that cover the field of oxidation of 3-phenoxybenzyl alcohol (**4c**) to 3-phenoxybenzaldehyde (**4a**). It has been for example reported<sup>223</sup> that choline peroxydisulfate (ChPS) (**81**), easily generated from the commercially available related potassium salt, performs efficiently neat at 70 °C and in a short time the reagent playing also the role of an ionic liquid (Scheme 72).

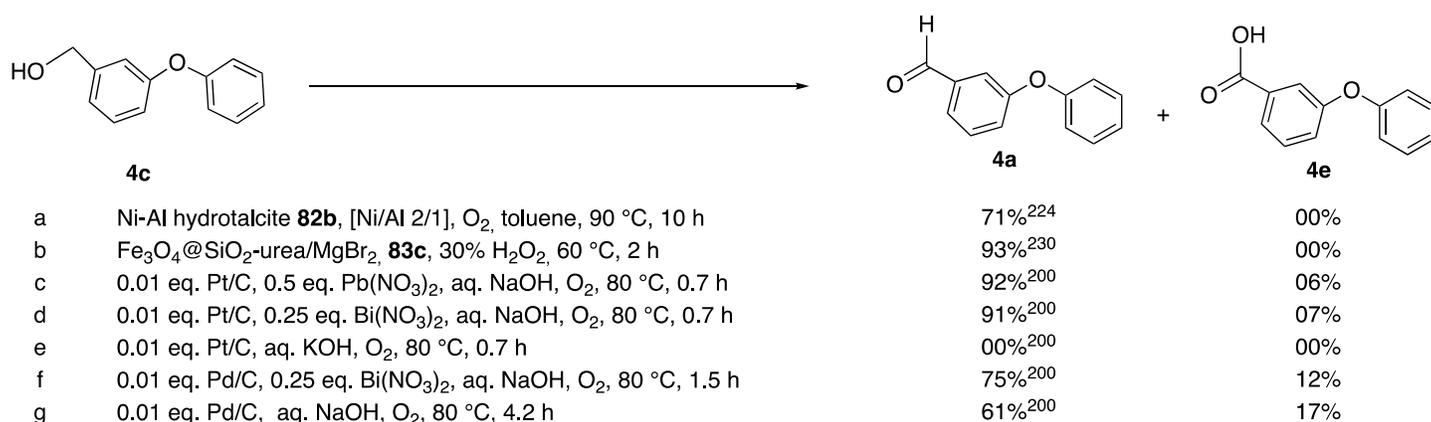


**Scheme 72.** Oxidation of 3-phenoxybenzyl alcohol (**4c**) to 3-phenoxybenzaldehyde (**4a**) involving choline peroxydisulfate (ChPS).<sup>223</sup>

Otherwise, oxidation of 3-phenoxybenzyl alcohol (**4c**) to 3-phenoxybenzaldehyde (**4a**) has been carried out using benign reagents such as (1) dioxygen, eventually air in the presence of nickel (Scheme 73, entry a), platinum (Scheme 73, entries c-e), palladium (Scheme 73, entries f,g, Scheme 75, entry a) or tetramethylpiperidin-1-yl)oxyl (TEMPO) in the presence of copper (Scheme 75, entry i) or in its absence (Scheme 75, entries f-h); (2) hydrogen peroxide in the presence of an iron catalyst (Scheme 75, entry b), (3) iodosyl benzene in the presence of a ruthenium catalyst (Scheme 75, entries c-e). These reactions have been carried out in heterogeneous (3.4.2.1.) or homogeneous (3.4.2.2.) medium.

**3.4.2.1. Heterogeneous oxidations of 3-phenoxybenzyl alcohol.** Oxidation in a heterogeneous medium offers the advantages of an easy separation of the catalyst once the reaction is over and allow the easy recycling of the catalyst but are usually less efficient due to difficult contact between the starting material and the catalyst. In some cases the oxidant has been inserted in a nickel-alumina matrix **82a** to produce the reagent **82b** (Scheme 73, entry a; Scheme 74, entry a),<sup>224</sup> or complexed through an organic linker to a magnetic end of a silicon coated

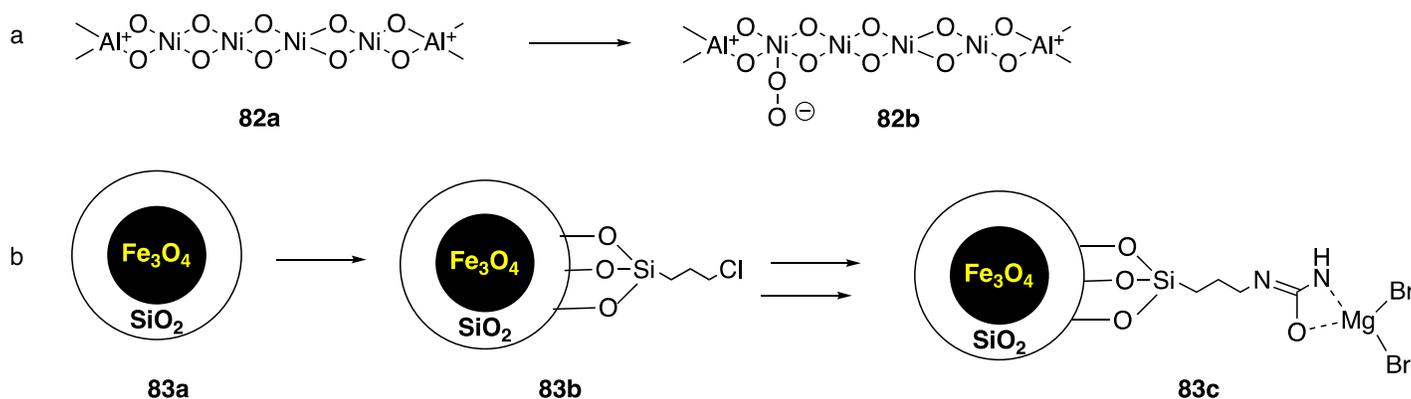
magnetite as in the case of **83c** ( $\text{Fe}_3\text{O}_4$ ; Scheme 73, entry b, Scheme 74, entry b).<sup>230</sup> In other cases, the metal (Pt, Pd) supported on pulverulent carbon is directly used.



**Scheme 73.** Aerobic oxidation of 3-phenoxybenzyl alcohol (**4c**) to 3-phenoxybenzaldehyde (**4a**) using Ni, Pt and Pd containing catalysts.<sup>200,224,230</sup>

**3.4.2.1.1. Nickel-promoted oxidation of 3-phenoxybenzyl alcohol.** The nickel-hydrotalcite **82a** allows the oxidation of 3-phenoxybenzyl alcohol (**4c**) to 3-phenoxybenzaldehyde (**4a**) in 71% yield on bubbling molecular oxygen in toluene at 90 °C for 10 h (Scheme 73, entry a) probably through the intermediate formation of the catalyst **82b** (Scheme 74a).<sup>224</sup> The reaction is best achieved in non-polar solvents such as benzene, hexane, cyclohexane, and toluene and does not proceed in the polar ones such as acetonitrile or methanol.<sup>224</sup>

The required catalyst has been synthesized by co-precipitation of nickel and aluminum compounds employing NaOH/ $\text{Na}_2\text{CO}_3$  (Scheme 74, entry a).<sup>224</sup>



**Scheme 74.** Heterogeneous Ni/Al catalyst,<sup>224</sup> and magnesium bromide complex to a silicon coated magnetite<sup>230</sup> for activation of molecular oxygen.

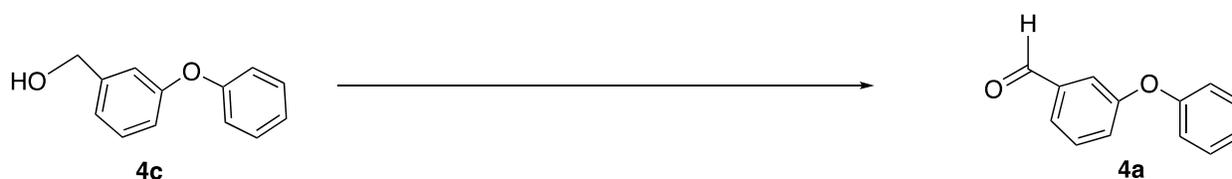
**3.4.2.1.2. Magnesium-promoted oxidation of 3-phenoxybenzyl alcohol.** The branched urea complexed magnesium bromide (**83c**), that usually allows the efficient formylation of phenols in *ortho* position, proved even more efficient to oxidize benzyl alcohols to the corresponding aldehydes without overreduction.<sup>230</sup> The transformation of 3-phenoxybenzyl alcohol (**4c**) to the aldehyde (**4a**) takes place in less than 2 h at 60 °C with 30% hydrogen peroxide and 0.02 mg of catalyst **83c** per mmole of alcohol (Scheme 73, entry b).<sup>230</sup> Furthermore

the catalyst **83c** is easily extracted from the medium using a magnet and has been recycled for at least five times without affecting its catalytic activity.<sup>230</sup>

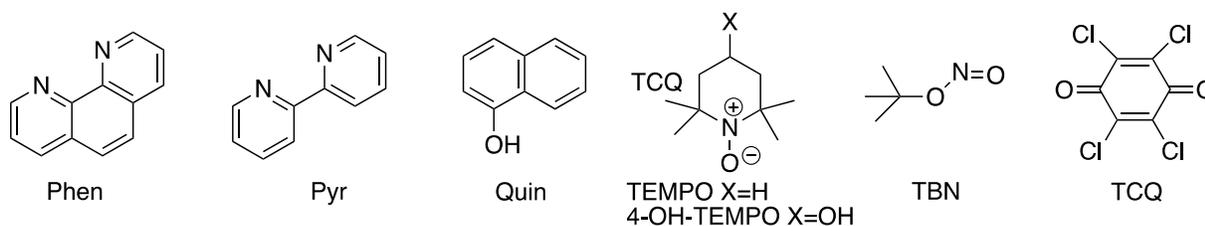
**3.4.2.1.3. Platinum/palladium-promoted oxidation of 3-phenoxybenzyl alcohol.** Platinum and palladium (1 wt-% and 5 wt-% respectively) deposited on pulverised carbon proved extremely valuable for promoting the oxidation of 3-phenoxybenzyl alcohol (**4c**) to 3-phenoxybenzaldehyde (**4a**).<sup>200</sup> Best conditions involve bubbling dioxygen on a heated mixture (80 °C) of the alcohol **4c** in the presence of 0.1 equivalents of a 1 wt-% Pt on carbon, 0.5% of lead nitrate in an aqueous solution of sodium hydroxide leading to **4a** in up to 90% yield besides 7% of the carboxylic acid **4e** resulting from an overoxidation that is easily removed by alkali (Scheme 73, entry c). Each ingredient is essential for the success of the reaction although interchanging lead- by bismuth-nitrate does not affect too much the process.<sup>200</sup>

Similar results are obtained by replacing platinum by palladium (Scheme 73, entries f,g).<sup>200</sup> However, the percentage of **4e** arising from overoxidation of **4a** is higher (12% instead of 7%; Scheme 73, entry f compare to entry d).<sup>200</sup> The palladium catalyzed reaction does not strictly require the use of an additive as it is the case in the platinum catalyzed reaction (Scheme 73, compare entry g to entry e) but in its absence the reaction time increases substantially as well as the overoxidation.<sup>200</sup>

**3.4.2.2. Homogeneous oxidation of 3-phenoxybenzyl alcohol.** Specific examples of oxidation of 3-phenoxybenzyl alcohol (**4c**) in a homogeneous solution are gathered in Scheme 75.



|   |  |                     |
|---|--|---------------------|
| a | 0.05 eq. Pd(OAc) <sub>2</sub> , 1 eq. pyridine, MS3A, toluene, O <sub>2</sub> , 90 °C, 5 h                                     | 92% <sup>225</sup>  |
| b | 3.2% Phen-Ru-Phen, 2.5 eq. PhIO, MeCN, 25 °C, 4 h (TON 32)   | 100% <sup>229</sup> |
| c | 6% Phen-Ru-Quin, 2.5 eq. PhIO, MeCN, 25 °C, 0.5 h (TON 17)   | 100% <sup>229</sup> |
| d | 5.5% Quin-Ru-Quin, 2.5 eq. PhIO, MeCN, 25 °C, 0.5 h (TON 18)   | 100% <sup>229</sup> |
| e | PS-Phen-Ru(III), 2.5 eq. PhIO, MeCN, 25 °C, 2 h  | 100% <sup>213</sup> |
| f | 1% eq. 4-HO-TEMPO, 2% eq. TCQ, 5% eq. TBN, 1% HCl, O <sub>2</sub> , 20 °C, 6 h   | 98% <sup>226</sup>  |
| g | 5% eq. TEMPO, 5% eq. NaNO <sub>2</sub> , 10% eq. HCl, CH <sub>2</sub> Cl <sub>2</sub> (8.0 mL), air, 20 °C, 11 h               | 99% <sup>228</sup>  |
| h | 5% eq. HO-TEMPO, 5% eq. NaCl on SiO <sub>2</sub> , 5% eq. FeNO <sub>3</sub> ·9H <sub>2</sub> O, 20°C, air, dichloroethane, 3 h | 92% <sup>211</sup>  |
| i | 1% eq. TEMPO, 1% eq. Cu(OAc) <sub>2</sub> , air, MeCN-H <sub>2</sub> O (1-2), 3 h  | 91% <sup>227</sup>  |



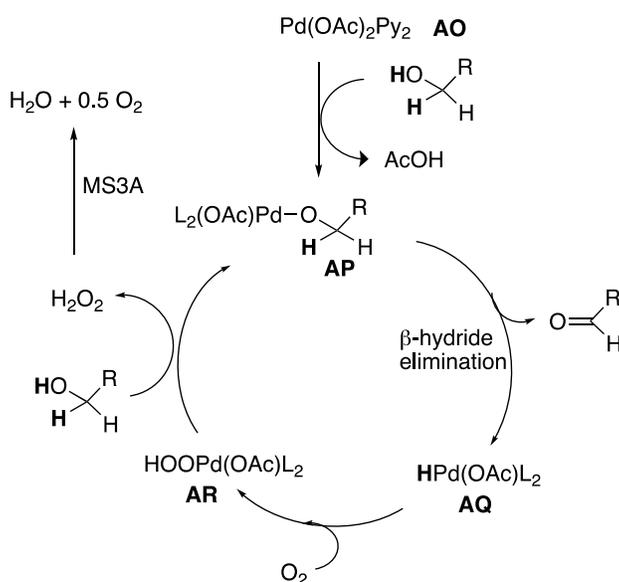
**Scheme 75.** Aerobic oxidation of 3-phenoxybenzyl alcohol (**4c**) to 3-phenoxybenzaldehyde (**4a**), involving metal catalysis and iodosyl benzene, TEMPO or TCQ as oxidant.<sup>211,213, 225-229</sup>

**3.4.2.2.1. Palladium-promoted oxidation of 3-phenoxybenzyl alcohol.** The oxidation of 3-phenoxybenzyl alcohol (**4c**) to 3-phenoxybenzaldehyde (**4a**) by dioxygen or even by air, has been achieved also in homogeneous solution, in toluene at 90 °C<sup>225</sup> using Pd(OAc)<sub>2</sub> (5 mol%), pyridine (1 eq.) and molecular sieve (MS 3 Å). The role of the latter proved to be essential for the success of the reaction since it catalyzes the decomposition of the

hydrogen peroxide, formed in the process, to water and oxygen (Scheme 75, entry a).<sup>225</sup> The process can be advantageously compared to the heterogeneous process that uses the same transition metal catalyst (Scheme 73, entries f,g).<sup>200,222,225</sup>

The oxidation takes place with lower loading of catalyst (1 mol%) for benzylic alcohols but the rate of the reaction is slower. Air can be replaced by oxygen as already disclosed but the reaction rate is much slower. The reaction does not take place<sup>225</sup> with (i) other palladium compounds such as PdCl<sub>2</sub>, Pd(dba)<sub>3</sub> or Pd(PPh<sub>3</sub>)<sub>4</sub> (ii) 2,6-dimethylpyridine whose nitrogen atom is unable properly to complex the metal, as pyridine does, (iii) If the reaction is carried out in toluene but at reflux of the solvent instead of 80 °C since palladium black is released rapidly and its catalytic activity lost. It has been also mentioned that the yield of **4a** greatly diminishes when methylene dichloride, THF, ether or 1,4-dioxane are replacing toluene as the solvent.<sup>225</sup>

A tentative mechanism in which Pd(II) species work all along the process is shown in Scheme 76.<sup>225</sup> The reaction is expected to take place via the formation of the Pd(II) alcoholate **AP**, from the Pd(II)pyridine complex **AO**, to provide by β-elimination the aldehyde and the Pd(II)-hydride species **AQ** that reacts with dioxygen to provide the Pd(II)-hydroperoxide species **AR**. The latter exchanges its ligand with the alkyl group to produce hydrogen peroxide that is decomposed to water and dioxygen by the MS 3 Å molecular sieves at 80 °C (Scheme 76).<sup>225</sup>



**Scheme 76.** Postulated mechanism of the Pd(II) catalyzed aerobic oxidation of alcohols to aldehydes.<sup>225</sup>

**3.4.2.2.2. Ruthenium-promoted oxidation of 3-phenoxybenzyl alcohol.** Complexed ruthenium compounds have been successfully used for the same purpose with iodosylbenzene as oxidant (Scheme 75, entries b-e).<sup>213,229</sup> The required complexes (Phen-Ru-Phen, Pyr-Ru-Pyr, Quin-Ru-Quin, (Scheme 75) have been synthesized, in a straightforward way, by mixing, at 20 °C for 4 h, stoichiometric amounts of ruthenium trichloride hydrates (1-3) and 1,10-phenanthroline (Phen), 8-hydroxyquinoline (Quin) or 2,2'-bipyridine (Pyr) or their mixture in acetonitrile. Although all exhibit catalytic activities, those containing 8-hydroxyquinoline (Quin) possesses the highest aptitude to oxidize alcohols and offers the advantage of possessing the lower molecular weight and to do not perform overoxidation (Scheme 75, entry d).<sup>229</sup>

Related oxidation of benzyl alcohol delivers benzaldehyde in lower yields when using lower amounts of iodosylbenzene or when acetonitrile (100%) is replaced by toluene (18%), THF (31%), or dichloromethane (58%).<sup>229</sup>

A related polymer supported catalyst (PS) has also been used for the same purpose (Scheme 75, entry e).<sup>213</sup> The polymeric ligand has been prepared from chloromethyl polystyrene (Merrifield resin) and 5-amino-1,10-phenanthroline then reacted with ruthenium trichloride in THF (20 °C, 12 h). The best conditions and solvent proved to be similar to those selected in the homogeneous version (Scheme 78, compare entry e to entries b,c) and similarly no overoxidation is taking place.<sup>213</sup> This supported ruthenium complex can also be reused for at least three time with benzyl alcohol as substrate before its activity decreases (40 mg/mmol benzyl alcohol: 1-3rd recycling: 100%; 4, 5th recycling 71, 55% yield) but using a larger amount of supported catalyst (60 mg instead of 40 mg/mmol) allows an overuse of at least 7 runs.<sup>213</sup>

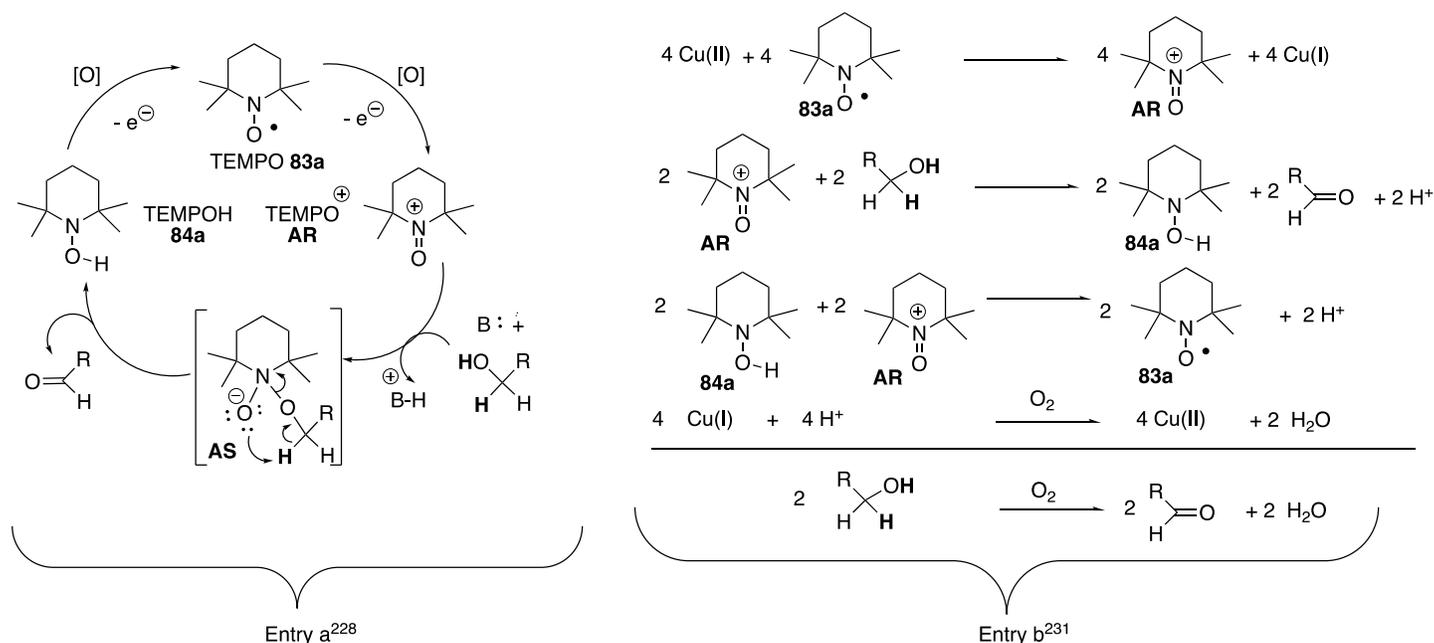
**3.4.2.2.3. TEMPO-promoted oxidation of 3-phenoxybenzyl alcohol.** Oxidation of 3-phenoxybenzyl alcohol (**4c**) to 3-phenoxybenzaldehyde (**4a**) has been advantageously carried out using 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) (**83a**) or its 4hydroxy-TEMPO (**83b**) analog (easier to separate by chromatography, cheap, highly reactive) under a large number of conditions (Scheme 75, entries f-i). Most of the conditions use catalytic amount of TEMPO and therefore require the *in situ* oxidation of the resulting TEMPOH (**84a**) by-product. This has been effectively achieved by dioxygen (Scheme 75, entry f)<sup>226</sup> or air (Scheme 78, entries g-i)<sup>211,227,228</sup> in some cases in the presence of transition metal catalysts (iron or copper, Scheme 75, entries h,i).<sup>211,227</sup> Originally the oxidation of TEMPO required the presence of a transition metal catalyst and several conditions have been tested in order to perform the aerobic oxidation reaction under mild metal-free conditions. Among the various combinations tested,<sup>226,228</sup> two high yielding conditions have been selected for the oxidation of 3-phenoxybenzyl alcohol (**4c**).

The first one is carried out neat, without solvent and uses gaseous dioxygen (1 atmosphere), in the presence of a small amount of 4-hydroxyTEMPO (**83b**) (1%), as well as tetrachlorobenzophenone (TCQ, 2%), *tert*-butyl nitrite (TBN, 5%) and hydrochloric acid (HCl) generates **4a** in extremely high yield at room temperature (98%, Scheme 75, entry f).<sup>226</sup>

The other involves a slightly higher amount of TEMPO (5%) but uses air in place of dioxygen, sodium nitrite (NaNO<sub>2</sub>) instead of TBN and hydrochloric acid to promote the catalytic oxidation that takes place for a little longer time (overnight) at room temperature (Scheme 78, entry g) but minimizes the waste produced.<sup>228</sup> The choice of sodium nitrite and hydrochloric acid takes advantage of the intimate mechanism of the TEMPO oxidation that is presented in Scheme 77, entry a.<sup>228</sup>

The processes shown above could be rationalized in terms of the positive halogen species being able to oxidize TEMPO (**83a**)/TEMPOH (**84a**) to the oxoammonium cation TEMPO<sup>+</sup> **AR** (Scheme 77).<sup>231</sup> It was found that, HCl for example, in combination with TEMPO and NaNO<sub>2</sub>, is effective in promoting the catalytic aerobic oxidation of the alcohol to the corresponding aldehyde under mild conditions.

The role of the acid was assumed to be the donation of a proton (H<sup>+</sup>) to NaNO<sub>2</sub> to generate NO/NO<sub>2</sub>. The effect of the halide anion on the catalysis may stem from its reaction with NO<sub>2</sub> to generate oxidizing species such as NOCl, which is known to oxidize TEMPO (**83a**)/TEMPOH (**84a**) to TEMPO (**83a**). These preliminary studies revealed that acidic conditions and chloride or bromide anions have beneficial impacts on the catalytic oxidation.<sup>228</sup> Importantly, the results clearly demonstrated that oxidizing halogen-containing compounds are not essential to drive the TEMPO/NaNO<sub>2</sub>-based catalytic system. The TEMPO/HCl/NaNO<sub>2</sub> system, efficiently achieves in a wide range of solvents, such as ClCH<sub>2</sub>CH<sub>2</sub>Cl, EtOAc, CH<sub>3</sub>CN, HOAc, and PhF, the conversions of benzyl alcohols at atmospheric pressure and ambient temperature (without dioxygen or air bubbling).<sup>228</sup>



**Scheme 77.** Mechanism for the TEMPO mediated process that imply any oxidant such as dioxygen as the co-oxidant (Scheme 77, entry a) and a related one that includes copper acetate (Scheme 77, entry b).<sup>228,231</sup>

It was also found that silica gel adsorbed 4-hydroxyTEMPO, smoothly catalyzed the aerobic oxidation of 3-phenoxybenzyl alcohol (**4c**) in the presence of  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  and NaCl (1/1) in a nonpolar solvent (Scheme 75, entry h).<sup>211</sup> The reaction proceeds at room temperature in six hours and the resulting 3-phenoxybenzaldehyde (**4a**) is obtained in excellent yield just after filtration and moreover the recovered the catalyst can be reused at least six times without loss of catalytic activity.<sup>211</sup>

It has been reported that 4-hydroxyTEMPO possess a much higher propensity (x8) than TEMPO to be absorbed on silica gel and that the mixture of sodium chloride and iron nitrate cannot be replaced by ferric chloride ( $\text{FeCl}_3$ ). Although ferric chloride proved in some cases to be more efficient than the sodium chloride, iron nitrate combination, its high Lewis acid acidity often promotes unwanted competing reactions.<sup>211</sup> The requirement of chlorine for successful result could be related to the comment discussed in the previous transformation.<sup>228</sup>

Finally, 3-phenoxybenzyl alcohol (**4c**) has been oxidized by “ligand- and additive-free” process involving the couple  $\text{Cu}(\text{OAc})_2/\text{TEMPO}$  as catalyst that enables efficient and selective aerobic oxidation, at low catalyst loading, of a broad range of primary and secondary benzylic and aliphatic alcohols to the corresponding aldehydes and ketones.<sup>227</sup>

This ambient temperature oxidation protocol is of practical features like aqueous acetonitrile as solvent, ambient air as the terminal oxidant, and low catalyst loading, presenting a potential value in terms of both economical and environmental considerations.<sup>227</sup> Based on the experimental observations, a plausible reaction mechanism was proposed that originates from the original work of Semmelhack on TEMPO (Scheme 77, entry b).<sup>231</sup> Accordingly cupric ion effects one-electron oxidation of TEMPO (**83a**) to the nitrosonium ion **AR** that in turn is able to oxidize the alcohol to the aldehyde and return the hydroxyl amine TEMPOH (**84a**) (Scheme 77, entry b). Rapid symproportionation of **84** with **AR** regenerates TEMPO (**83a**). Finally, Cu(I) is regenerated by dioxygen in a process that consume protons and gives Cu(II) and water in a well know process. The net reaction is the oxidation of the alcohol to the aldehyde and water (Scheme 77, entry b)” with (i) no formation of the

carboxylic acid resulting from an over-oxidation and (ii) no requirement of an added base in the nitrosonium **AR** oxidation.<sup>211, 231</sup>

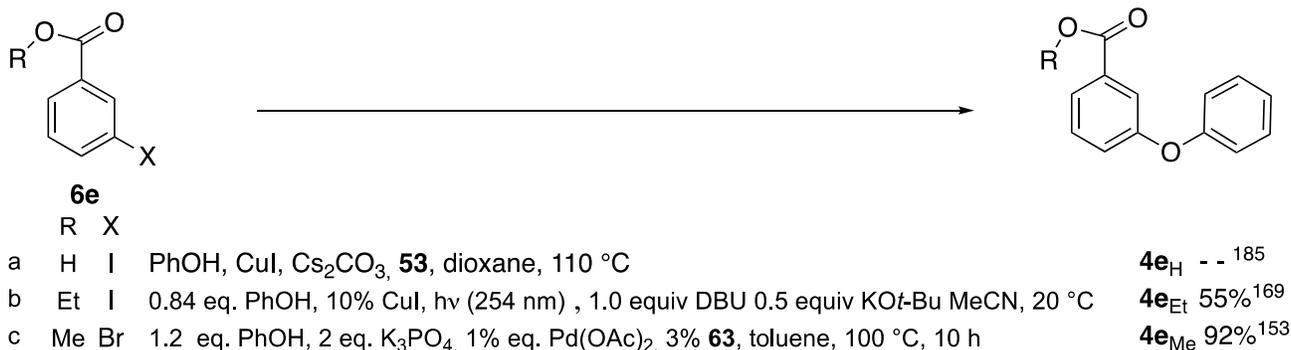
### 3.5. Multistep syntheses of 3-phenoxybenzaldehyde from 3-phenoxybenzoic acid/esters

**3.5.1 Synthesis of 3-phenoxybenzoic acid/esters.** Those syntheses have been achieved either by forming the ether function from 3-halogeno-benzoic acid/ esters **6e** or from 3-hydroxybenzoic acid/ esters (**5e**) (as already pointed out in Scheme 36, Route c) or from 3-phenoxybromobenzene (**4g**) by halogen-metal exchange followed by carbonation of the resulting organometallic (Scheme 37, route b). These syntheses will be reported in Sections 3.5.1.1. and 3.5.1.2. respectively. Note that we have already presented one synthetic route to **4e**<sup>210</sup> from 3-phenoxytoluene (**4b**) as well as its transformation to **4a** in Section 3.3.2.1.

#### 3.5.1.1. Synthesis of 3-phenoxybenzoic acid/esters from 3-halogenobenzoic acid/ esters or from

##### 3-hydroxybenzoic acid/ esters. 3.5.1.1.1. Synthesis of 3-phenoxybenzoic acid/esters from 3-

halogenobenzoic acid/ esters .The direct synthesis of 3-phenoxybenzoic acid (**4e<sub>H</sub>**) from 3-iodo-benzoic acid (**4e<sub>I</sub>**) and phenol has been performed in the presence of copper iodide and the triol (**53**) (Table 7)<sup>185</sup> but details and yield are missing (Scheme 78, entry a).<sup>185</sup>

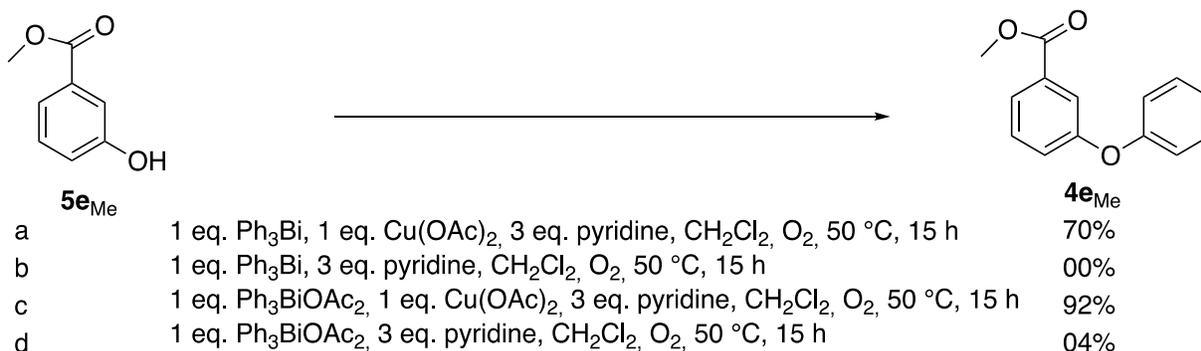


**Scheme 78.** Transformation of 3-halogenobenzoic acid/ esters to 3-phenoxybenzoic acid/esters.<sup>153,169,185</sup>

The same copper catalyst has been used with the related iodo-ester **6e<sub>Et</sub>** in a reaction promoted by light and delivers ethyl 3-phenoxybenzoate in modest yield (55%) (Scheme 78, entry b).<sup>169</sup> It extends to aryl iodides possessing the unfavorable electron withdrawing group, the reaction originally published for the synthesis of 3-phenoxytoluene (**4b**) from 3-iodo-toluene (**6c**), already discussed in Section 3.3.2.1. <sup>169</sup>

This transformation has been more efficiently achieved from methyl 3-bromo-benzoate (**6e<sub>Me</sub>**) using instead a palladium catalyst and the hindered phosphine ligand (**63**) (Table 8) at reflux of toluene for 10 h (Scheme 78, entry c)<sup>153</sup> as suggested in the Buchwald-Hartwig protocol (Section 3.1.2.)

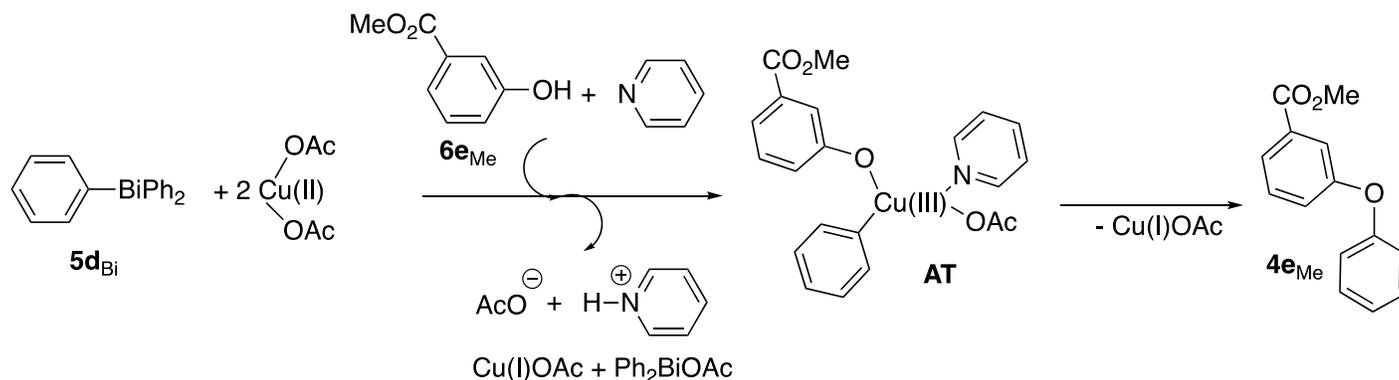
**3.5.1.1.2. Synthesis of 3-phenoxybenzoic esters from 3-hydroxybenzoic esters.** The synthesis of methyl 3-phenoxybenzoate (**4e<sub>Me</sub>**) from methyl 3-hydroxybenzoate (**5e<sub>Me</sub>**) completely relies on the Barton-Gagnon arylation reaction (Scheme 38, entry d)<sup>158-160</sup> already presented for direct synthesis of 3-phenoxybenzaldehyde (**4a**) (Scheme 49, entry b).<sup>158</sup> Although the direct synthesis of **4a** has been achieved with copper powder as the catalyst, the synthesis of methyl 3-phenoxybenzoate (**4e<sub>Me</sub>**) has been successfully carried out from methyl 3-hydroxybenzoate (**5e<sub>Me</sub>**), triphenylbismuth and copper diacetate instead and excess of pyridine as base and ligand (Scheme 79, entry a).<sup>160</sup> An even better yield has been observed when triphenylbismuth diacetate is instead used (Scheme 79, entry c)<sup>160</sup>



**Scheme 79.** Transformation of methyl 3-hydroxybenzoate to methyl 3-phenoxybenzoate (**4e<sub>Me</sub>**).<sup>160</sup>

It has been observed that the presence of copper is mandatory since the reaction does not take place or almost does not take place in its absence (Scheme 79, entries b,d, compare to entries a,b respectively).<sup>160</sup>

The intimate mechanism of this O-arylation of methyl 3-hydroxybenzoate is shown below (Scheme 80) and suggest that the Cu(III) intermediate **AT** generated from Cu(II) diacetate is produced.<sup>160</sup>

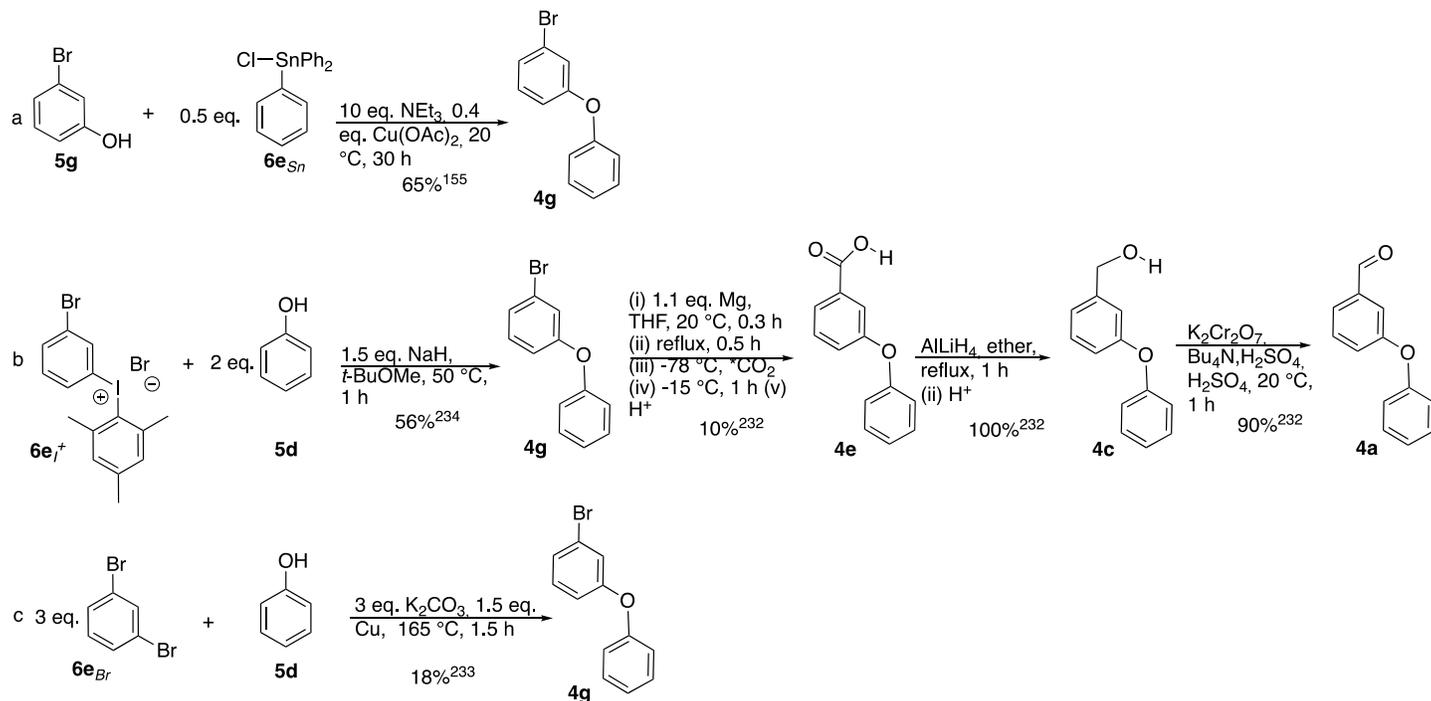


**Scheme 80.** Proposed mechanism for the copper-catalyzed O-phenylation of methyl 3-hydroxybenzoate using triphenylbismuthine.

**3.5.1.2. Synthesis of 3-phenoxybenzoic acid from 3-phenoxybromobenzene.** The synthesis of 3-phenoxybenzoic acid (**4e<sub>H</sub>**) has been also achieved using a different strategy that involves the bromine/magnesium exchange on 3-phenoxybromo-benzene (**4g**). The later on reaction with magnesium, leads to the Grignard reagent 3-phenoxyphenyl magnesium bromide that is then sequentially carbonated and protonated (Scheme 81).

The sequence of reactions in Scheme 81 has allowed the synthesis of <sup>14</sup>C-radiolabelled 3-phenoxybenzoic acid <sup>14</sup>C(**4e<sub>H</sub>**) as well as <sup>14</sup>C-radiolabelled 3-phenoxybenzyl alcohol <sup>14</sup>C(**4c**) and <sup>14</sup>C-radiolabelled 3-phenoxybenzaldehyde <sup>14</sup>C(**4a**).<sup>232</sup>

The synthesis of the required 3-phenoxybromobenzene (**4g**) has been achieved in poor yield from the bifunctional 1,3-dibromobenzene (**6e<sub>Br</sub>**), excess of phenol (**5d**) and copper metal as catalyst that requires harsh conditions (Scheme 81, entry c).<sup>233</sup>



**Scheme 81.** Synthesis of 3-phenoxybromo-benzene from bromobenzene substituted at C-3 by a hydroxy, an iodonio- or a bromo-group.<sup>155,232,233</sup>

Better results have been obtained on coupling phenol (**5d**) with the 3-bromo-iodoniums **6e<sub>I</sub><sup>+</sup>** that possess two leaving groups exhibiting different reactivity (Scheme 81, entry b) in a reaction that takes place,<sup>234</sup> as already discussed, under milder conditions and does not require a copper catalyst (Scheme 53, entry a).<sup>151</sup> The choice of the mesityl iodonium among different other iodonium is documented.<sup>234</sup> The selected one offers the advantage (i) to react selectively on the phenyl instead of the 2,4,6-methyl phenyl group and (ii) to be recyclable.<sup>234</sup>

Even better results have been obtained from 3-bromo-phenol (**5g**) as starting material and triphenyl tin chloride **6e<sub>Sn</sub>** that requires a copper catalyst (Scheme 81, entry a)<sup>155</sup> in a reaction that has been also used for the synthesis of 3-phenoxytoluene (**4b**) (Scheme 58, entry a),<sup>155</sup> and for which a mechanism has been proposed (shown in Scheme 55, entry b).<sup>155</sup>

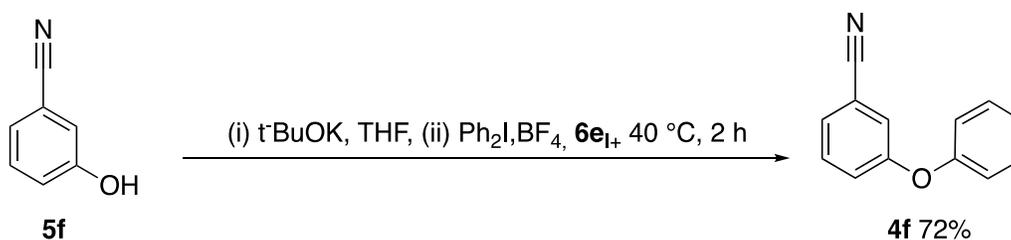
**3.5.2. Synthesis of 3-phenoxybenzaldehyde from 3-phenoxybenzoic acid/ esters.** The transformation of 3-phenoxybenzoic acid/ esters **4e** to 3-phenoxybenzaldehyde (**4a**) is shown in two different approaches (Scheme 61, entry a; Scheme 81, entry b). The Rosenmund reduction, that involves the transformation of the carboxylic acid **4e** to its acid chloride **4j** using thionyl chloride and the catalytic hydrogenation of the latter to the aldehyde **4a**, is probably the most efficient large-scale transformation especially in the industrial context (Scheme 61, entry a). The strategy used to produce the tiny amount of <sup>14</sup>C-radiolabelled 3-phenoxybenzaldehyde <sup>14</sup>C (**4a**) has been achieved in two steps that involves the reduction of the aldehyde using lithium aluminum hydride<sup>209</sup> leading to <sup>14</sup>C-radiolabelled 3-phenoxybenzyl alcohol <sup>14</sup>C (**4c**) and selective oxidation to the aldehyde <sup>14</sup>C **4a** using chromium oxidant<sup>210</sup> (Scheme 81, entry b). This transformation is unsuitable for industrial purpose.

### 3.6. Multistep syntheses of 3-phenoxybenzaldehyde from 3-phenoxybenzotrile

This approach has not been documented; nevertheless the synthesis of 3-phenoxybenzotrile (**4f**) according to the two strategies traditionally used to produce the ether linkage from phenol or from a 3-functionalized phenol

have been reported as presented below. Furthermore, the transformation of aromatic nitriles to the corresponding aldehydes directly or after transformation to the corresponding carboxylic acids is a well-established route.

**3.6.1. Syntheses of 3-phenoxybenzonitrile.** **3.6.1.1. Synthesis of 3-phenoxybenzonitrile from 3-hydroxybenzonitrile.** The synthesis of 3-phenoxybenzonitrile (**4f**) from 3-hydroxybenzonitrile (**5f**) has been achieved on reaction of diphenyliodonium tetrafluoroborate **6e**<sub>I</sub><sup>+</sup> in the presence of potassium *t*-butoxide (Scheme 82),<sup>151,149</sup> in a process similar to the one involved in the synthesis of 3-phenoxybenzaldehyde (**4a**) from 3-hydroxybenzaldehyde **5a** (Scheme 57),<sup>151</sup> or the synthesis of 3-phenoxybromobenzene (**4g**) from phenol (**5e**) (Scheme 81, entry b).<sup>234</sup>



**Scheme 82.** Transformation of 3-hydroxybenzonitrile to 3-phenoxybenzonitrile.<sup>149,151</sup>

**3.6.1.2. Synthesis of 3-phenoxybenzonitrile from 3-halogenobenzonitrile.** The second approach that involves 3-halogenobenzonitriles **6f**, phenol (**5d**) and a base or a preformed phenate, is better documented (Scheme 83).<sup>169,176,184,235</sup> All the reactions involve copper as the pre-catalyst and belong to the category of coupling with a poorly reactive aryl halide since they bear an electron withdrawing group. Therefore, the ligand plays a key role to favor the coupling.

Thus, in 3-phenoxybenzonitrile (**4f**) is produced in no more than 15% yield on reaction at 155 °C of 3-chlorobenzonitrile (**6f**<sub>Cl</sub>), potassium phenate in the presence of copper chloride in anisole as the solvent (Scheme 83, entry a),<sup>184</sup> and a dramatic increase in the yield, up to 85%, is observed by performing the reaction under the same conditions but in the presence of no more than 1 mol% of the tridentate ligand **52** (Table 7, Scheme 83; compare entries a,b).<sup>184</sup>

Similarly: performing the reaction in the presence of no more than 1.25 mol% of “Nano-Cu” (from sodium citrate-assisted generated CuI nanoparticles) in DMF not only increases the reaction yield (+8%) but at the same time allow to perform coupling at lower temperature (by -45 °C) and reaction time (-2 h) compared to use liganded copper catalyst (Scheme 83, entry c).<sup>235</sup> It also offers the possibility to recycle, after ethyl acetate washing and drying at 65 °C, the catalyst isolated by centrifugation.<sup>235</sup>

Finally, using the air stable Cu(I)-bipyridyl complex **38**<sub>M</sub> offers the advantage of an extremely low loading of the catalyst and lowering the reaction temperature (Scheme 83, entry d).<sup>176</sup> It however suffers from a much longer reaction time (24 h), use of the more expensive aryl bromide and of lower yield in **6f** (Scheme 83, entry d).<sup>176</sup> Similarly, the photochemically promoted Ullmann reaction, requires the even more expensive 3-iodobenzonitrile but offers the advantage to carry the coupling at room temperature.<sup>169</sup>



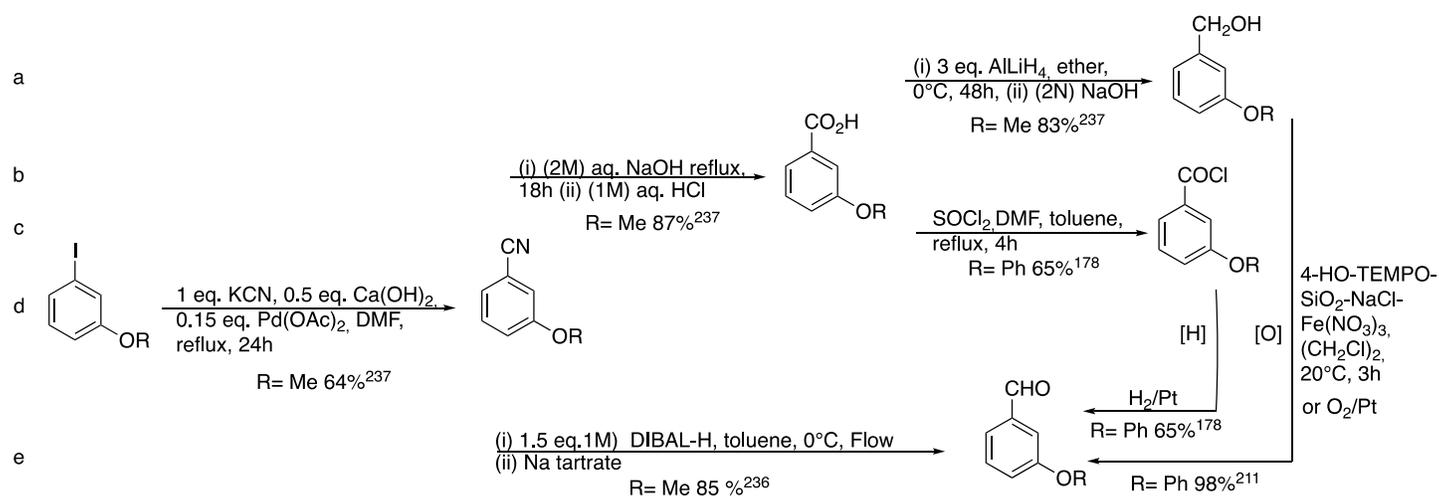
- |   |  |                    |
|---|--|--------------------|
| a | X= Cl, 1.15 eq. PhOK, 1% eq. CuCl, anisole, 155 °C, 6 h  | 15% <sup>184</sup> |
| b | X= Cl, 1.15 eq. PhOK, 1% eq. CuCl, 1% eq. <b>52</b> , anisole, 155 °C, 6 h                                   | 85% <sup>184</sup> |
| c | X= Cl, 1.2 eq. PhOH, 1.2 eq. K <sub>2</sub> CO <sub>3</sub> , 1.25 nano-Cu (from CuI), DMF, 110 °C, air, 4 h | 93% <sup>235</sup> |
| d | X= Br, 1.5 eq. PhOH, 2 eq. K <sub>3</sub> PO <sub>4</sub> , 0.5 % eq. <b>38'</b> , DMF, 90 °C, 24 h          | 80% <sup>176</sup> |
| e | X= I, 1 eq. PhOH, 20% eq. CuI, hv (254 nm), 1.0 eq. DBU, 0.5 eq. <i>t</i> -BuOK, MeCN, 20 °C                 | 77% <sup>169</sup> |

**Scheme 83.** Transformation of 3-halogenobenzonitrile to 3-phenoxybenzonitrile.<sup>169,176,184,235</sup>

**3.6.2. Synthesis of 3-phenoxybenzaldehyde from 3-phenoxybenzonitrile.** We have not found the in the literature the desired transformations of **4f** to **4a**. The transformation of the related 3-methoxybenzonitrile however has been reported<sup>236</sup> especially in the context of synthesis of <sup>13</sup>C-labelled 3-methoxybenzaldehyde and can be used as model to achieve the desired transformations of **4f** to **4a**. The chemical equations shown in Scheme 84 mix, on purpose, reactions carried out either on the 3-methoxybenzonitrile and on the 3-phenoxybenzonitrile. Thus 3-methoxy or aryloxybenzonitriles have been transformed into the corresponding aldehydes:

(i) in the multistep sequence presented in Scheme 87, entry a, that involves its easy transformation to 3-methoxybenzoic acid on refluxing the aqueous solution of the benzonitrile with sodium hydroxide (100 °C, 18 h) followed by an acidic treatment (Scheme 87, entry b). The latter has been transformed either to: (a) the corresponding benzyl alcohol on reaction with an excess of using lithium aluminum hydride (Scheme 84 entry a)<sup>237</sup> that has been then oxidized to the corresponding 3-substituted benzaldehyde by oxygen using a supported TEMPO reagent (Scheme 84, entry e)<sup>211</sup> or catalyzed by Pt or Pd as discussed in the Chapter 3.4.2. or (b) the corresponding aromatic carboxylic acid chloride using thionyl chloride<sup>178</sup> (Scheme 84, entry c) followed by its hydrogenation<sup>178</sup> using dihydrogen in the presence of platinum catalyst (Scheme 84, entry e) as proposed in the Rosenmund protocol already discussed in this review, or:

(ii) directly to the required benzaldehyde on reduction with DIBAL-H followed by hydrolysis (Scheme 84, entry e). Interestingly the transformation selected has been achieved in a flow system.<sup>236</sup>

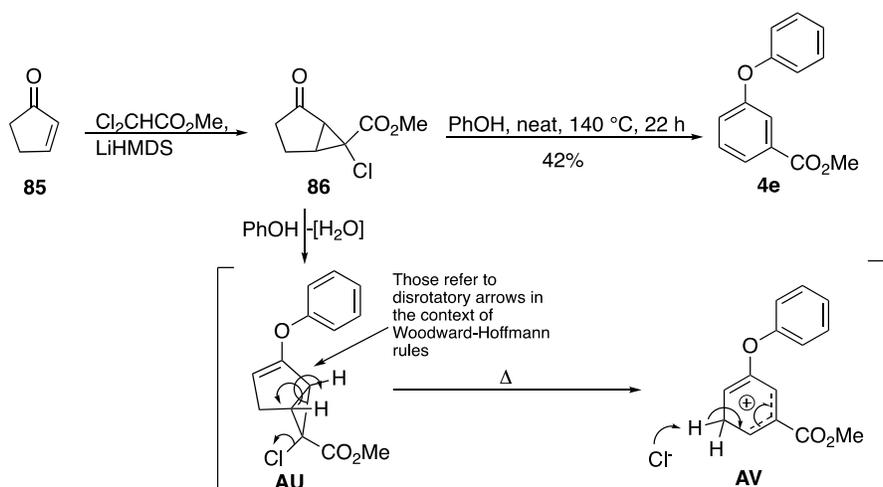


**Scheme 84.** Synthesis and transformation 3-methoxy and 3-phenoxybenzonitriles to 3-methoxy- and 3-phenoxybenzaldehyde.<sup>178,211,236,237</sup>

### 3.7. Strategies to approach 3-phenoxybenzoates *in route* to 3-phenoxybenzaldehyde

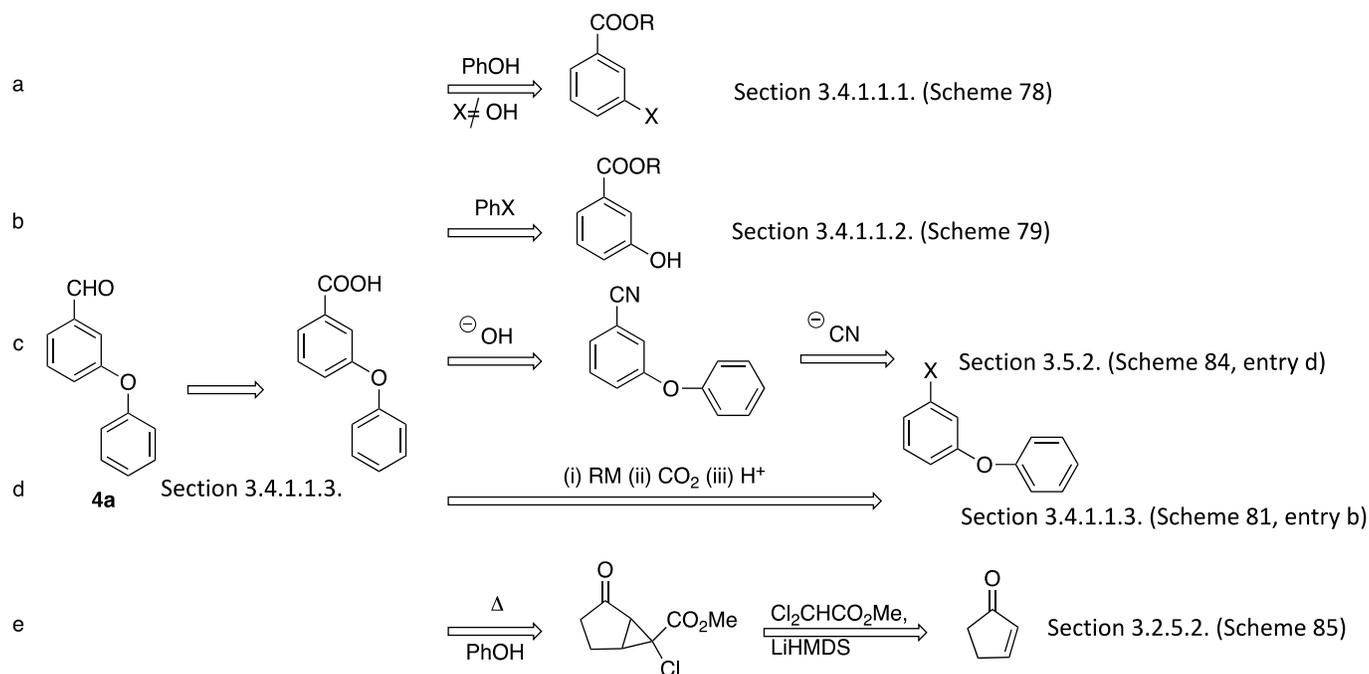
Since the industrial interest on 3-phenoxybenzaldehyde and related compounds such as 3-phenoxytoluene, 3-phenoxybenzyl alcohol, 3-phenoxybenzoic acid and alkyl 3-phenoxybenzoates in relation with the synthesis of cypermethrin and deltamethrin insecticides, that mainly rely on the Ullmann or the Buchwald-Hartwig reactions, other methods have appeared that will not be discussed in this review.

As an example, we briefly report in Scheme 85<sup>238</sup> on an original regioselective synthesis of methyl 3-phenoxybenzoate (**4e<sub>Me</sub>**), a known precursor of 3-phenoxybenzaldehyde (**4a**) that does not rely in the Ullmann or Buchwald-Hartwig reaction. This synthesis uses the easily available cyclopentenone (**85**), methyl dichloroacetate (**86**), and phenol and involves sequential formation of a [3.1.0]bicyclic derivative **87** and its ring opening to generate in an original way the aromatic ring and the diaryl ether in a single pot (Scheme 85).<sup>238</sup>



**Scheme 85.** Two-step synthesis of methyl 3-phenoxybenzoate from cyclopenten-2-one and phenol.

We have gathered in Scheme 86 different approaches to 3-phenoxybenzaldehyde that involve the intermediate formation of 3-phenoxybenzoic acid.<sup>238</sup>



**Scheme 86.** Approaches to 3-phenoxybenzoic acid *en route* to the 3-phenoxybenzaldehyde.

## 4. Conclusions

We have discussed in this chapter several syntheses of 3-phenoxymandelonitrile involved in the synthesis of cypermethrin and deltamethrin, one of the most active man-made but nature-inspired pyrethroid insecticides.

We have presented the strategy and methods specifically devoted to the synthesis of diaryl ethers bearing a formyl group and one of its precursors, especially the original Ullmann coupling that uses copper catalysis and its modifications that use copper ligands and the more recent Buchwald-Hartwig coupling that instead use palladium catalysts. Alternative methods such as Barton-Gagnon are also presented.

We have also extensively reviewed the different methods to synthesize cyanohydrins from aldehydes especially that derived from 3-phenoxybenzaldehyde. Methods for separation of the enantiomers, recycling the unwanted enantiomer as well as their enantioselective synthesis, including enzymic ones, are reported.

We have only reported the methods and conditions that specifically refer to the synthesis of the selected products. Several have not been invented to specifically allow such synthesis but have been used as model to generalize those methods. Other methods could apply to the synthesis of such compounds and there are rooms to test them.

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