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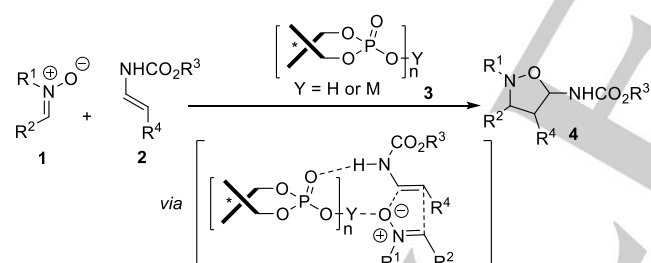
# Chiral Cu(II) Phosphate-Catalyzed Enantioselective Tandem Deoxygenation / [4+2] Cycloaddition of Nitrones with Enecarbamates

Coralie Gelis, Guillaume Levitre, Vincent Guérineau, David Touboul, Luc Neuville, and Géraldine Masson\*

**Abstract:** A new catalytic enantioselective tandem deoxygenation / aza-Diels-Alder reaction of nitrones with enecarbamates was serendipitously discovered in the presence of chiral copper(II) diphosphate complexes. This process affords a wide range of 4-aminotetrahydroquinolines in respectable yields under mild conditions with good to excellent ee values.

## Introduction

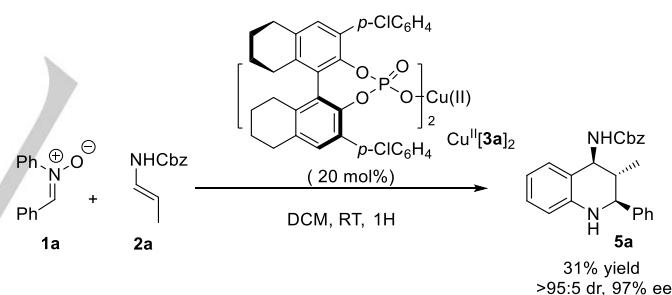
Nitrones are valuable and versatile building blocks in organic synthesis because of their ready accessibility and high reactivity in various transformations.<sup>[1]</sup> In particular, 1,3-dipolar cycloaddition reaction of nitrones with various dipolarophiles, has been extensively investigated especially in its catalytic asymmetric version.<sup>[2,3]</sup> Surprisingly, enamides and enecarbamates, which commonly served as dienophiles in cycloadditions,<sup>[4]</sup> have been rarely used as dipolarophiles in the inverse electron demand [3+2]-cycloaddition.<sup>[2b,5]</sup> To the best of our knowledge, no catalytic enantioselective version has been reported yet.



**Scheme 1.** Catalytic enantioselective [3+2]-cycloaddition synthesis of trisubstituted isoxazolidines.

In continuation of our research program in catalytic asymmetric cycloadditions with enecarbamates,<sup>[6]</sup> we became interested in exploring their reactivity in connection with nitrones. We speculated that chiral phosphoric acid catalysts<sup>[7]</sup> or their corresponding metal salts<sup>[7b,8]</sup> could promote enantioselective

[3+2] cycloaddition to deliver valuable isoxazolidines. Indeed, as the nitrones and enecarbamates can be activated by these catalysts via hydrogen bonding<sup>[3b]</sup> and/or metal chelation, reactivity and high stereoselectivity might be achieved (Scheme 1). However, our first attempts with chiral phosphoric acids were totally unsuccessful, the starting materials being mainly recovered. Therefore, we turned our attention to their corresponding more active phosphate metal salts as viable catalysts for this cycloaddition. Alkali or alkaline earth metal-phosphoric acid complexes were not more effective as catalysts.<sup>[7b]</sup> But to our surprise, when copper(II) phosphate salt  $\text{Cu}^{\text{II}}[\mathbf{3a}]_2$  was used, the reaction took a completely different course.<sup>[9]</sup> No isoxazolidine was observed but instead a 4-amino-tetrahydroquinoline **5a** was isolated in low yield albeit with excellent diastereo- and enantioselectivity (Scheme 2). To explain this, we reasoned that product arose from two events, namely a copper promoted deoxygenation<sup>[10]</sup> and copper phosphate catalyzed inverse electron demand aza-Diels-Alder (IEDADA) reaction (also called Povarov reaction)<sup>[6c,g,i,k, 11, 12]</sup> to give a 1,2,3,4-tetrahydroquinoline.



**Scheme 2.** Copper phosphate catalyzed deoxygenation and enantioselective IEDADA reaction.

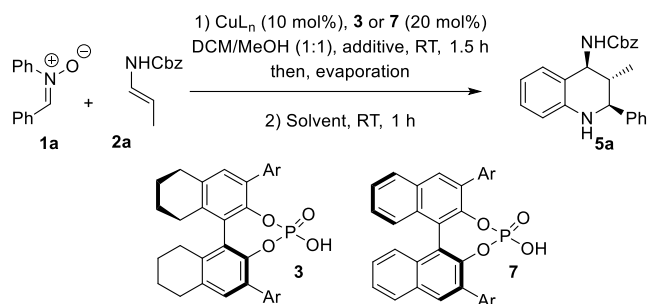
## Results and Discussion

Being interested in this unexpected<sup>[13]</sup> enantioselective tandem deoxygenation/IEDADA reaction, we decided to optimize the reaction conditions, with the aim of increasing the yield to a synthetically-useful level while maintaining the high levels of stereocontrol. The catalytic asymmetric methods do not require isolation and prior purification of copper complex; catalyst freshly prepared, can be utilized directly (entry 1, Table 1). Initial experiments showed that the catalysts formation is sensitive to a number of parameters. Presence of water during the copper(II) phosphate complex preparation was crucial for obtaining the 4-amino-tetrahydroquinoline **5a**. Only starting materials were isolated when the reaction was performed in dry solvents (entry 2). We hypothesized that water can hydrolyze  $\text{Cu}(\text{OMe})_2$  to

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**Table 1.** Synthesis of 4-aminotetrahydroquinoline: a survey of reaction conditions.<sup>[a]</sup>

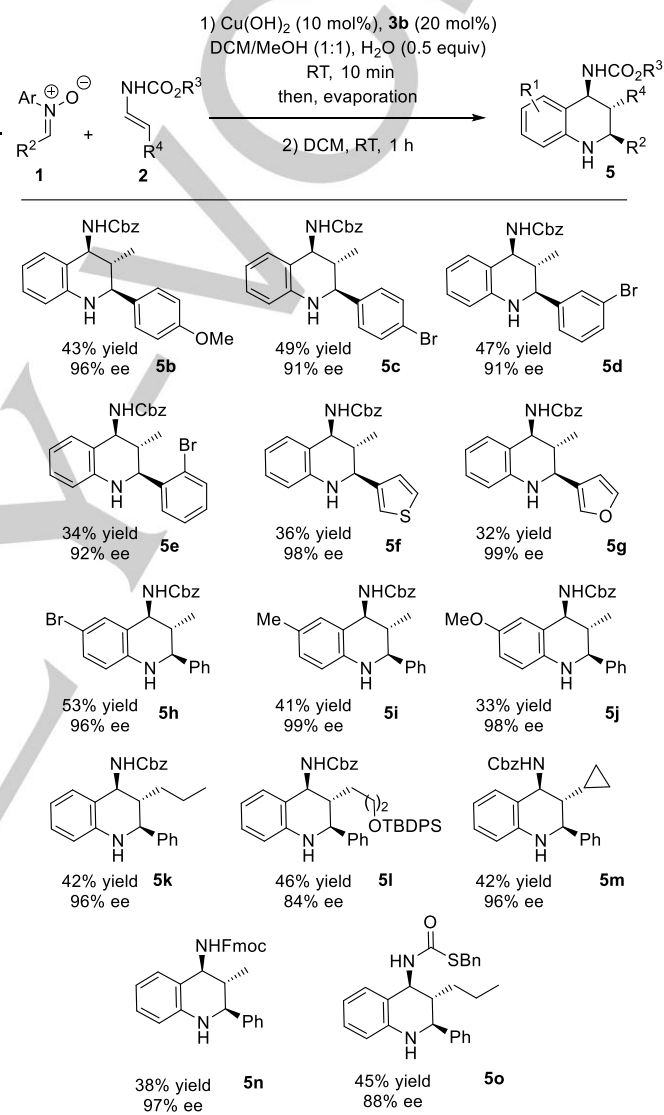
Entry	Cu <sub>L<sub>n</sub></sub>	Ar	Additive	Solvent	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	Cu(OMe) <sub>2</sub>	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>3a</b> )	-	DCM	31	97
2	Cu(OMe) <sub>2</sub>	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>3a</b> )	-	DCM <sup>[d]</sup>	0	-
3	Cu(OH) <sub>2</sub>	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>3a</b> )	-	DCM	28	94
4	Cu(OH) <sub>2</sub>	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>3a</b> )	H <sub>2</sub> O <sup>[e]</sup>	DCM	38	92
5	CuCl <sub>2</sub>	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>3a</b> )	H <sub>2</sub> O <sup>[e]</sup>	DCM	17	61
6	CuO	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>3a</b> )	H <sub>2</sub> O <sup>[e]</sup>	DCM	28	93
7	Cu(OH) <sub>2</sub>	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>3a</b> )	H <sub>2</sub> O <sup>[e]</sup>	DCM	56 <sup>[f]</sup>	96
8	Cu(OH) <sub>2</sub>	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>3a</b> )	H <sub>2</sub> O <sup>[e]</sup>	Toluene	57	96
9	Cu(OH) <sub>2</sub>	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>3a</b> )	H <sub>2</sub> O <sup>[e]</sup>	CHCl <sub>3</sub>	54	91
10	Cu(OH) <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> ( <b>3b</b> )	H <sub>2</sub> O <sup>[e]</sup>	DCM	59	98
11	Cu(OH) <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> ( <b>7a</b> )	H <sub>2</sub> O <sup>[e]</sup>	DCM	48	95
12	Cu(OH) <sub>2</sub>	2,4,6-( <i>i</i> Pr) <sub>3</sub> C <sub>6</sub> H <sub>5</sub> ( <b>7b</b> )	H <sub>2</sub> O <sup>[e]</sup>	DCM	39	96
13	Cu(OH) <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> ( <b>3b</b> ) <sup>[g]</sup>	H <sub>2</sub> O <sup>[e]</sup>	DCM	59	98

[a] General conditions: Cu<sub>L<sub>n</sub></sub> (0.01 mmol), **3** (0.02 mmol) in DCM/MeOH (1/1, 2 mL), RT, 1.5 h and evaporation followed by addition of **1** (0.2 mmol), **3** (0.1 mmol) in DCM (2 mL), RT, 1 h. [b] Yields refer to chromatographically pure products. The d.r. were determined by <sup>1</sup>H NMR analysis to be higher than 98:2 in all cases. [c] Enantiomeric excess was determined by HPLC on a chiral stationary phase: see the Supporting Information for details. [d] Freshly distilled DCM. [e] With 0.5 equiv of H<sub>2</sub>O. [f] With 0.3 mmol of **1a**. [g] Cu<sup>I</sup>[**3b**]<sub>2</sub> prepared in 10 min.

Cu(OH)<sub>2</sub>, a copper source subsequently able to allow copper phosphate complex formation.<sup>[14]</sup> Indeed, when the complex was prepared from Cu(OH)<sub>2</sub> in the absence of H<sub>2</sub>O in dry DCM/MeOH,

the desired product was formed (entry 3). However, the yield was further improved by adding 0.5 eq of water as a protic additive (entry 4).<sup>[15]</sup> Then, other copper salts were screened and showed lower activity compare to Cu(OH)<sub>2</sub> (entry 5 and 6). The yield increased from 38% to 56% when 3 equiv. of nitrene **1a** was used as the partner of enecarbamate **2a** (entry 7). Next, we studied the reactivity in different solvents, and no improvement was observed when toluene, or CHCl<sub>3</sub> were used (entry 8 and 9).

**Table 2.** Scope of the organocatalytic enantioselective [3+2] cyclization.<sup>[a]</sup>



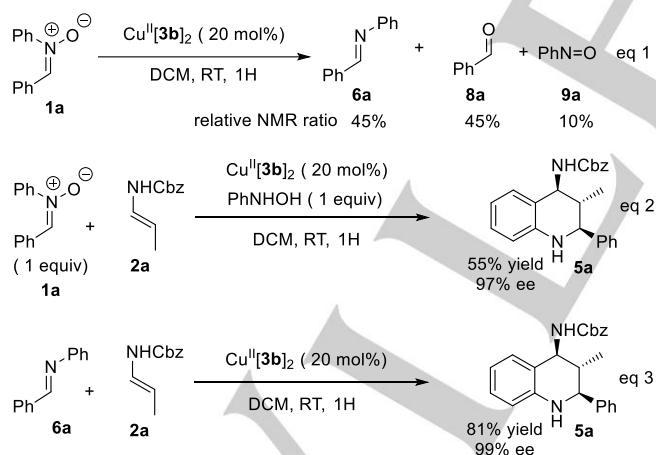
[a] General conditions: Cu(OH)<sub>2</sub> (0.01 mmol), **3b** (0.02 mmol) in DCM/MeOH (1/1, 2 mL), RT, 10 min and evaporation followed by addition of **1** (0.3 mmol), **3** (0.1 mmol) in DCM (2 mL), RT, 1 h. [b] Yields refer to chromatographically pure products. The d.r. were determined by <sup>1</sup>H NMR analysis to be higher than 98:2 in all cases. [c] Enantiomeric excess was determined by HPLC on a chiral stationary phase.

Phosphate screening revealed that the 3,3'-substituent on the octahydrogenated-BINOL scaffold had a little effect on the chemical yield, but did impact the enantioselectivity (entry 7 vs 10-

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12). Indeed, the catalyst bearing less-hindered 3,3'-substituents on the BINOL such as phenyl group gave best result (entry 10). The same effect was observed when BINOL **7a** and **7b** were used as a ligand (entry 10 vs 11). However, these phosphates led to lower yield and enantioselectivity than **3a** and **3b** (entry 9-12). Although the yield remained moderate, we deemed it respectable in light of this complex tandem process. Finally, the reaction time for the Cu(II) complex formation was reduced to 10 min without affecting the overall process (entry 13).

With the optimal reaction conditions established (Table 1, entry 14), we next investigated the substrate scope of the reaction by employing a variety of *N*-aryl nitrones **1**. The reaction proceeded well with decent yields and enantioselectivity in almost all cases when nitrones derived from electron poor or electron rich aromatic aldehydes were employed (**5b** to **5e**). However, the reaction gave a lower yield in the case of nitron substituted at the ortho-position **5e**, possibly due to steric effects. Remarkably, nitrones derived from heteroaldehydes such as thiophene-3-aldehyde and 3-furaldehyde were successfully engaged in this tandem deoxygenation/IEDADA process. Next, the *N*-substituent effect of **1** was also examined and it was found that its electronic property had little yield effect. For instance, nitrones bearing both electron-withdrawing (**5h**) and weak electron-donating (**5i**) substituents afforded the desired products in better yield than strong electron-donating (**5j**) substituent such as MeO group. An array of  $\beta$ -substituted enecarbamates **2** including linear and branched ones, were tested, resulting in the formation of the expected 4-amino-tetrahydroquinolines (**5k** to **5m**) with excellent enantioselectivities. It is also noteworthy that the silyl ether group was untouched in this process. *N*-Fmoc carbamate and benzylthiocarbamate were tolerated giving rise to the final cycloadducts **5n** and **5o**, respectively, with slightly lower yields.

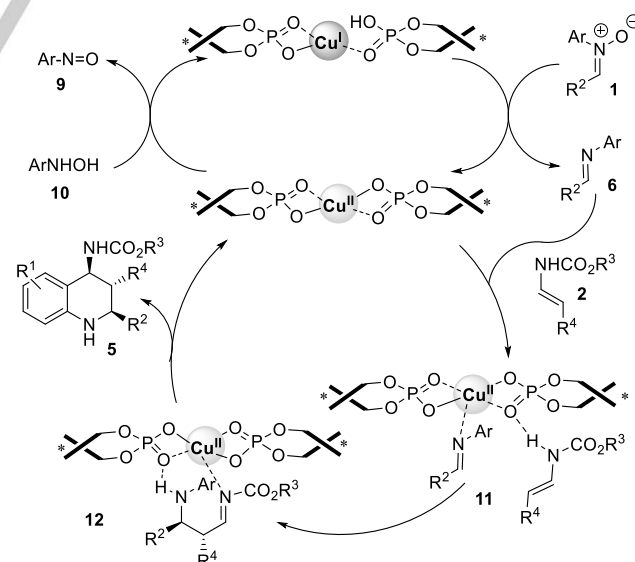


**Scheme 3.** Control experiments.

In order to gain some mechanistic insight, control experiments were carried out. No reaction took place with only Cu(OH)<sub>2</sub> hence indicating the crucial role of phosphates ligands on the deoxygenation step of nitrones. To clarify which species participates in the deoxygenation of product, the reaction of nitron **1a** with Cu(II)-phosphate Cu<sup>II</sup>[**3b**]<sub>2</sub> was performed in DCM at RT. After 1h, nitron **1a** totally disappeared, revealing the

presence of *N*-arylimine **6a**, benzaldehyde and nitroso compound **9a** in the following 45/45/10 ratio, respectively (eq 1). Partial hydrolysis of the nitron **6a** would account for the presence of aldehyde. By that, *N*-arylhydroxylamine could be released and subsequent oxidation by Cu(II) would to furnish **9a**. The resulting Cu(I) complex produce during this last event is next suitable in promoting the deoxygenation of nitron to imine.<sup>[16,17]</sup> Possible implication of *N*-arylhydroxylamine **10** was established by control experiment showed in eq 2. Indeed, when one equivalent of *N*-arylhydroxylamine was added to the reaction mixture, the number of nitron equivalent could be reduced in this cycloaddition keeping overall yield constant. Moreover, when *N*-arylimine **6a** was used as the reactant in place of nitron **1a**, under otherwise identical conditions, the same desired enantiomer tetrahydroquinolines **5a** was obtained (eq 3). The fact that this enantiomer has an opposite configuration to the one obtained in our previous work with chiral phosphoric acid derived from the same axially chiral (*S*)-BINOL<sup>[6k,18]</sup> suggest that a chiral copper(II) phosphate complex rather than free phosphoric acid acts as active catalyst in this IEDADA reaction.

On the basis of the results obtained above and the previous literature,<sup>[15]</sup> a plausible mechanism is proposed in Scheme 4. In the initial step, Cu(II) is probably reduced by the *N*-arylhydroxylamine generated, during a partial hydrolysis of **1** to form Cu(I) complex. This latter is able to reductively deoxygenate the nitron **2** to the corresponding *N*-arylimine **6** and gives the catalytically active Cu(II) phosphate complex.<sup>[10]</sup> While its exact structure awaits further study, the MS spectra of complex show a peak at *m/z* 1214.93 which indicates the formation of copper bis(phosphate) complex.<sup>[19]</sup> Then, Cu<sup>II</sup>[**3b**]<sub>2</sub> could simultaneously activate both *N*-arylimine **9** and enecarbamate **2** via metal ion coordination and hydrogen bonding. Finally, an enantioselective Mannich reaction would occur to form a transient imine **12**, which would further undergo an intramolecular Friedel–Crafts reaction to deliver the (2*S*,3*R*,4*S*)-4-amino-tetrahydroquinoline **5**.<sup>[6i-k,11]</sup>



**Scheme 5.** Assumed mechanism for the enantioselective tandem deoxygenation/IEDADA reaction.

## Conclusions

In conclusion, we have developed a highly efficient asymmetric synthesis of chiral 4-aminotetrahydroquinolines through the copper(II)/phosphate-catalyzed tandem deoxygenation/IEDADA reaction of nitrones with enecarbamates. This process allows the synthesis of various tetrasubstituted 4-amino-tetrahydroquinolines bearing 3 contiguous stereocenters with excellent diastereo and enantioselectivities. Further investigation of the mechanistic insights is currently underway in our laboratory.

## Experimental Section

Experimental Details.

## Acknowledgments ((optional))

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**Keywords:** Copper phosphate • deoxygenation • aza-Diels-Alder reaction • enecarbamate • heterocycle

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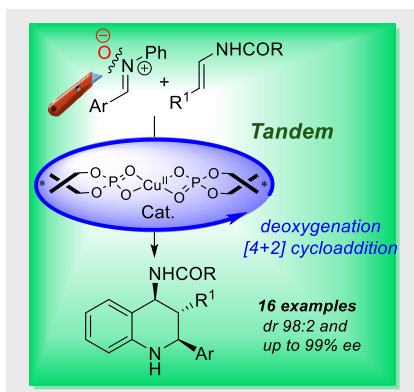
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**Chiral Cu(II) Phosphate-Catalyzed Enantioselective Tandem Deoxygenation / [4+2] Cycloaddition of Nitrones with Encarbamates**

\* Cut and joint together: double role of copper phosphate in tandem deoxygenation/[4+2] cycloaddition

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