EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: Tandem Chiral Cu(II) Phosphate-Catalyzed Deoxygenation of Nitrones/ Enantioselective Povarov Reaction with Encarbamates

Authors: Coralie Gelis, Guillaume Levitre, Vincent Guerineau, David Touboul, Luc Neuville, and Géraldine Masson

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900547

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900547

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

WILEY-VCH

COMMUNICATION

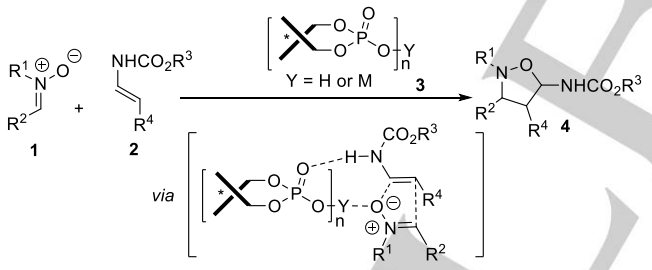
Tandem Chiral Cu(II) Phosphate-Catalyzed Deoxygenation of Nitrones/ Enantioselective Povarov Reaction with Encarbamates

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.

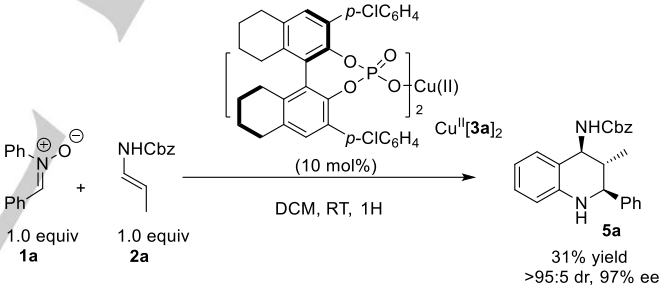
Introduction

Nitones are valuable and versatile building blocks in organic synthesis because of their ready accessibility and high reactivity in various transformations.[1] While a large amount of work has been dealing with rearrangements, nucleophilic or radical additions and CH functionalization among others,[1c] nitrones are probably best known for their cycloaddition reactivity.[1d] In particular, 1,3-dipolar cycloaddition reaction of nitrones with various dipolarophiles, has been extensively investigated especially in its catalytic asymmetric version.[2,3] Surprisingly, enamides and enecarbamates, which commonly served as dienophiles in cycloadditions,[4] have been rarely used as dipolarophiles in the inverse electron demand (3+2) cycloaddition.[2b,5] 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,[6] we became interested in exploring their reactivity in connection with nitrones. We speculated that chiral phosphoric acid catalysts[7] or their corresponding metal salts[7b,8] could promote enantioselective (3+2) cycloaddition to deliver valuable isoxazolidines **4**. Indeed, as the nitrones and enecarbamates can be activated by these catalysts via hydrogen bonding[3b] 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.[7b] But to our surprise, when copper(II) phosphate salt Cu^{II}**[3a]**$_2$ was used, the reaction took a completely different course.[9] No isoxazolidine **4** was observed but instead a 4-amino-tetrahydroquinoleine **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[10] and a copper phosphate catalyzed inverse electron demand aza-Diels-Alder (IEDADA) reaction (also called Povarov reaction)[6c,g,i-k, 11, 12] to give a 1,2,3,4-tetrahydroquinoline.



Scheme 2. Copper phosphate catalyzed deoxygenation and enantioselective Povarov reaction.

Results and Discussion

Being interested in this unexpected[13] enantioselective tandem deoxygenation/Povarov 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**. As such, starting materials were essentially recovered when the reaction was performed in dry solvents or in the presence in molecular sieves from $Cu(OMe)_2$ (entry 2 and 3).

[a] Dr. C. Gelis, Mr. G. Levitre, Mr V. Guérineau, Dr D. Touboul, Dr. L. Neuville, Dr. G. Masson
Institut de Chimie des Substances Naturelles CNRS UPR 2301, Université Paris-Sud, Université Paris-Saclay, 1, av. de la Terrasse, 91198 Gif-sur-Yvette Cedex, France
Fax: (+33)1-6907-7247
E-mail: Geraldine.masson@cnrs.fr
Homepage: http://www.icsn.cnrs-gif.fr/spip.php?article848

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

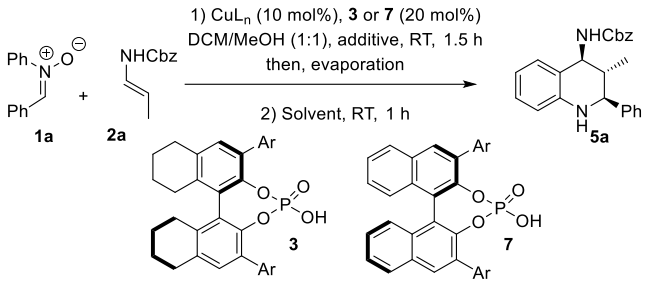


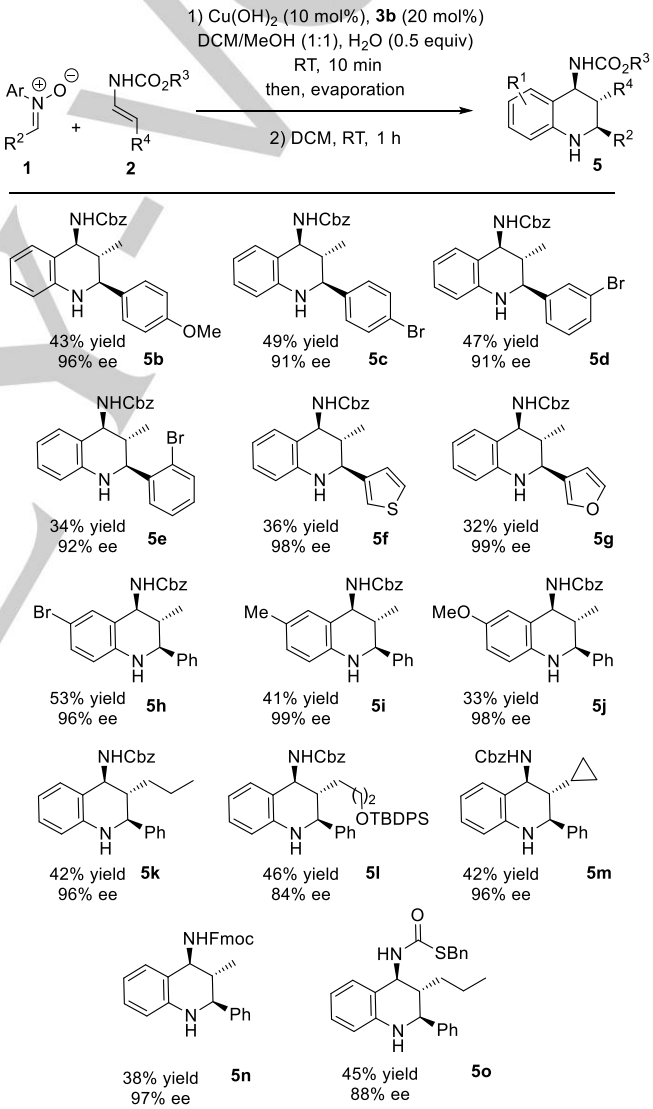
Table 1. Synthesis of 4-aminotetrahydroquinoline: a survey of reaction conditions.[a]

Entry	CuL_n	Ar	Additive	Solvent	Yield [%][b]	ee [%][c]
1	$Cu(OMe)_2$	4-ClC_6H_4 (**3a**)	-	DCM	31	97
2	$Cu(OMe)_2$	4-ClC_6H_4 (**3a**)	3 Å MS	DCM[d]	5%	-
3	$Cu(OMe)_2$	4-ClC_6H_4 (**3a**)	-	DCM[d]	0	-
4	$Cu(OH)_2$	4-ClC_6H_4 (**3a**)	-	DCM[d]	28	94
5	$Cu(OH)_2$	4-ClC_6H_4 (**3a**)	H_2O[e]	DCM	38	92
6	$CuCl_2$	4-ClC_6H_4 (**3a**)	H_2O[e]	DCM	17	61
7	CuO	4-ClC_6H_4 (**3a**)	H_2O[e]	DCM	28	93
8[f]	$Cu(OH)_2$	4-ClC_6H_4 (**3a**)	H_2O[e]	DCM	56	96
9[f]	$Cu(OH)_2$	4-ClC_6H_4 (**3a**)	H_2O[e]	Toluene	57	96
10[f]	$Cu(OH)_2$	4-ClC_6H_4 (**3a**)	H_2O[e]	$CHCl_3$	54	91
11[f]	$Cu(OH)_2$	C_6H_5 (**3b**)	H_2O[e]	DCM	59	98
12[f]	$Cu(OH)_2$	C_6H_5 (**7a**)	H_2O[e]	DCM	48	95
13[f]	$Cu(OH)_2$	2,4,6-(iPr)$_3C_6H_5$ (**7b**)	H_2O[e]	DCM	39	96
14[f]	$Cu(OH)_2$	C_6H_5 (**3b**)[g]	H_2O[e]	DCM	59	98
15[f]	$Cu(OH)_2$	C_6H_5 (**3b**)[h]	H_2O[e]	DCM	49	98

[a] General conditions: CuL_n (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), **2a** (0.1 mmol) in DCM (2 mL), RT, 1 h. [b] Yields refer to chromatographically pure products. The d.r. were determined by ^{1}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_2O. [f] With 0.3 equiv of **1a**. [g] Cu^{II}[**3b**]$_2$ prepared in 10 min. [h] 1 mmol scale relative to **2a.**

On the contrary, $Cu(OH)_2$, probably also generated upon water hydrolysis of $Cu(OMe)_2$, proved to be a suitable precursor for effective copper phosphate complex formation in the absence of H_2O.[14] Indeed, when the complex was prepared from $Cu(OH)_2$ in the absence of H_2O in dry DCM/MeOH, the desired product was formed (entry 4). However, the yield was further improved by adding 0.5 eq of water as a protic additive (entry 5).[15] Then, other copper salts were screened and showed lower activity compare to $Cu(OH)_2$ (entry 6 and 7). The yield increased from 38% to 56% when 3 equiv. of nitrone **1a** was used as the partner of enecarbamate **2a** (entry 8). Next, we studied the reactivity in different solvents, and no improvement was observed when toluene, or $CHCl_3$ were used (entry 9 and 10).

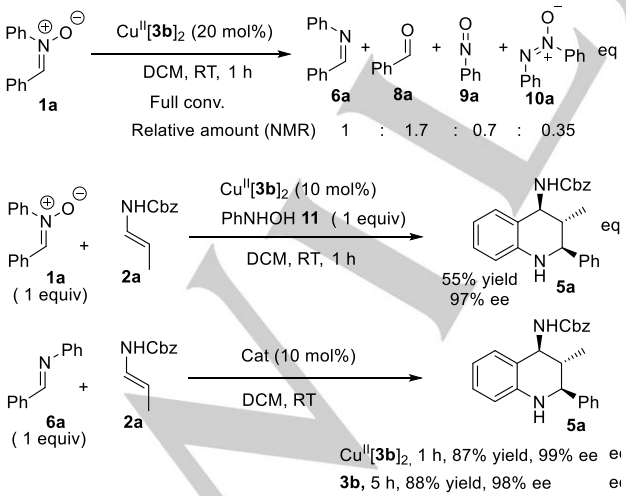
Table 2. Scope of the organocatalytic enantioselective (3+2) cyclization.[a]



[a] General conditions: $Cu(OH)_2$ (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 ^{1}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 BINOL scaffold had a little effect on enantioselectivity, but did impact the chemical yield (entry 8 vs 11-13). Indeed, the catalyst bearing less-hindered 3,3'-substituents on the octahydrogenated-BINOL such as phenyl group gave best result (entry 11). The same effect was observed when BINOL **7a** and **7b** were used as a ligand (entry 11 *vs* 12). However, these phosphates led to lower yield and enantioselectivity than **3a** and **3b** (entry 10-13). Although the yield remained moderate, we deemed it respectable in light of this complex tandem process. The reaction time for the Cu(II) complex formation could be reduced to 10 min without affecting the overall process (entry 14). Finally, the reaction was scaled up without affecting enantioselectivity, even if isolated yield were somewhat reduced (entry 15).

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 nitrone 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/Povarov 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 *β*-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.

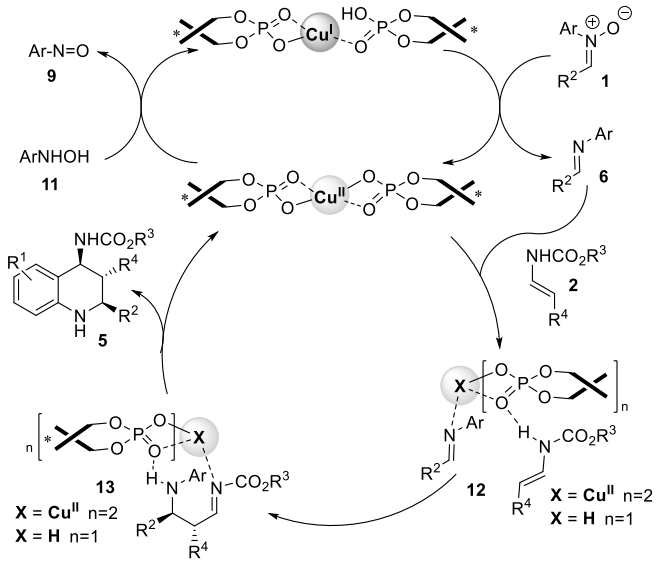


Scheme 3. Control experiments.

In order to gain some mechanistic insight, control experiments were carried out (Scheme 3). No reaction took place with only $Cu(OH)_2$ 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 nitrone **1a** with Cu(II)-phosphate Cu^{II}[**3b**]$_2$ was performed in DCM at RT. After 1h, nitrone **1a** totally disappeared, reveling the presence of *N*-arylimine **6a**, benzaldehyde, nitroso compound **9a** and azobenzene **10a** in the following 1/1.7/0.7/0.35 ratio, respectively (eq 1). Partial hydrolysis of the nitrone **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 nitrone to imine.[16,17] Possible implication of *N*-arylhydroxylamine **11** 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 nitrone equivalent could be reduced in this cycloaddition keeping overall yield constant. Moreover, when *N*-arylimine **6a** was used as the reactant in place of nitrone **1a**, under otherwise identical conditions, the same desired enantiomer tetrahydroquinolines **5a** was obtained (eq 3).[18] Omitting copper and performing the reaction with phosphoric acid **3b** furnished the cycloadduct **5a** in similar yield and ee albeit with longer reaction times (eq 4, 5 h vs. 1 h).[19] This indicated that the chiral copper(II) phosphate complex might be the active catalyst in the cycloaddition process. Nevertheless, at the present stage of the development, we cannot exclude the possibility that phosphoric acid is involved in catalytic cycle.

On the basis of the results obtained above and the previous literature,[15]**Erreur ! Signet non défini.** 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 nitrone **2** to the corresponding *N*-arylimine **6** and gives the catalytically active Cu(II) phosphate complex.[10] 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.[20] Then, Cu^{II}[**3b**]$_2$ 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 **13**, which would further undergo an intramolecular Friedel–Crafts reaction to deliver the (2*S*,3*R*,4*S*)-4-aminotetrahydroquinoline **5**.[6i-k,11]

10.1002/ejoc.201900547



Scheme 4. Assumed mechanism for the enantioselective tandem deoxygenation/Povarov reaction.

Conclusions

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

Experimental Section

Typical procedure for the synthesis of compound **5**: In a flame dried schlenk under argon were added copper(II) hydroxide (0.01 mmol), phosphoric acid 3b (0.02 mmol) and degassed solvents (dichlormethane 1mL and methanol 1 mL). The mixture was stirred at room temperature for 10 minutes and concentrated under vacuum. After introduction of 2 mL of degassed dichloromethane, Nitrone 1 (0.3 mmol) and enecarbamate 2 (0.1 mmol) were added and the reaction was stirred at room temperature until complete consumption of starting materials. Reaction was concentrated under reduced pressure to give a residue which was purified by flash chromatography (SiO_2, eluent: Petroleum ether: Ethyl Acetate) to afford the desired product.

Acknowledgments ((optional))

We thank ICSN and CNRS for financial support; C.G. and G.L. thank Saclay University for the doctoral fellowships;

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

[1] a) Breuer, E., In Nitrones, Nitronates and Nitroxides, (Eds S. Patai, Z.; Rappoport), Wiley: Chichester, **1989**, p 139-312; b) I. A.Grigor'ev, in *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*; Second Edition, (Ed H. Feuer), John Wiley & Sons, Inc., Hoboken, New Jersey, **2007**, pp 129-434; c) For a recent review, see: S.-I. Murahashi, Y. Imada, *Chem. Rev.* **2019**, DOI: 10.1021/acs.chemrev.8b00476; d) L. L. Anderson, *Asian J. Org. Chem.* **2016**, *5*, 9.

[2] a) A. Brandi, F. Cardona, S. Cicchi, F. M. Cordero, A. Goti, *Org. React.* **2017**, *94*, 1; b) M. Berthet, T. Cheviet, G. Dujardin, I. Parrot, J. Martinez, *Chem. Rev.* **2016**, *116*, 15235; c) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366; d) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887; e) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863.

[3] For selected examples, see: a) P. Jakubec, M. E. Muratore, I. Aillaud, A. L. Thompson, D. J. Dixon, *Tetrahedron Asymm.* **2015**, *26*, 251; b) P. Jiao, D. Nakashima, H. Yamamoto, *Angew. Chem. Int. Ed.* **2008**, *47*, 2411; *Angew. Chem.* **2008**, *120*, 2445; c) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2000**, *122*, 9874; d) K. B. Simonsen, P. Bayón, R. G. Hazell, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **1999**, *121*, 3845; e) K. B.Jensen; R. G. Hazell; K. A. Jørgensen, *J. Org. Chem.* **1999**, *64*, 2353; f) J. P. G. Seerden, M. M. M. Boeren, H. W. Scheeren, *Tetrahedron*, **1997**, 53, 11843; g) J. P. G. Seerden, M. M. M. Kuypers, H. W. Scheeren, *Tetrahedron Asymm.* **1995**, *6*, 1441; h) J. P. G. Seerden, A. W. A. Schotte op Reimer, H. W. Scheeren, *Tetrahedron Lett.,* **1994**, *35*, 4419.

[4] For representative reviews, see: a) T. Courant, G. Dagousset, G. Masson, *Synthesis* **2015**, *13*, 1799; b) K. Gopalaiah, H. B. Kagan, *Chem. Rev.* **2011**, *111,* 4599; c), R. Matsubara, S. Kobayashi, *Acc. Chem. Res.* **2008**, *41*, 292; d) D. R. Carbery*, Org. Biomol. Chem.* **2008**, *6*, 3455.

[5] a) T. B.Nguyen, A. Martel, R. Dhal, G. Dujardin, *J. Org. Chem.* **2008**, *73*, 2621; b) T. B. Nguyen, C. Gaulon, T. Chapin, S. Tardy, A. Tatibouet, P. Rollin, R. Dhal, A. Martel, G. Dujardin, *Synlett*, **2006**, 3255.

[6] a) L. Jarrige, D. Glavač, G. Levitre, P. Retailleau, G. Bernadat, L. Neuville, G. Masson, *Chem. Sci.* **2019**, *10*, 3765; b) C. Gelis, G. Levitre, J. Merad, P.Retailleau, L. Neuville, G. Masson, *Angew. Chem. Int. Ed.* **2018**, *57*, 12121; *Angew. Chem.* **2018**, *130*, 12297; c) L. Jarrige, F. Blanchard, G. Masson, *Angew. Chem. Int. Ed.* **2017**, *56*, 10573; *Angew. Chem.* **2017**, *129*, 10709; d) C. Gelis, M. Bekkaye, C. Lebée, F. Blanchard, G. Masson, *Org. Lett.* **2016**, *18*, 3422; e) J. Pous, T. Courant, G. Bernadat, B. I. Iorga, F. Blanchard, G. Masson, *J. Am. Chem. Soc.* **2015**, *137*, 11950; f) C. Lebée, A. Kataja, F.Blanchard, G. Masson, *Chem. Eur. J.* **2015**, *21*, 8399; g) J. Brioche, T. Courant, L. Alcaraz, M. Stocks, M. Furber, J. Zhu, G. Masson, *Adv. Synth. Catal.* **2014**, *356*, 1719; h) L. He, G. Laurent, P. Retailleau, B. Folléas, J.-L. Brayer, G. Masson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11088; *Angew. Chem.* **2013**, *125*, 11294; i) G. Dagousset, P. Retailleau, G. Masson, J. Zhu, *Chem. Eur. J.* **2012**, *18*, 5869; j) G. Dagousset, J. Zhu, G. Masson, *J. Am. Chem. Soc.* **2011**, *133*, 14804; k) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598.

[7] For recent reviews on phosphoric acid catalysis, see: a) J. Merad, C. Lalli, G. Bernadat, J. Maury, G. Masson, *Chem. Eur. J.* **2018**, *24*, 3925; b) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2017**, *117*, 10608; *Chem. Rev.* **2014**, *114*, 9047*;* c) S. Schenker, A. Zamfir, M. Freund, S. B. Tsogoeva, *Eur. J. Org. Chem*. **2011**, 2209; d) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev*. **2011**, *40*, 4539; e) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem*. **2010**, *291*, 395; f) M. Terada, *Bull. Chem. Soc. Jpn*. **2010**, *83*, 101; g) M. Terada, *Synthesis* **2010**, 1929; h) M. Terada, *Chem. Commun*. **2008**, *0*, 4097; i) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; j) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal*. **2006**, *348*, 999.

[8] For selected reviews combining metals and Brønsted acids, see: a) Z.-P. Yang, W. Zhang, S.-L. You, *J. Org. Chem*. **2014**, *79*, 7785; b) D.-F. Chen, Z.-Y. Han, X.-L. Zhou, L.-Z. Gong, *Acc. Chem. Res.* **2014**, *47*, 2365; c) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518; *Angew. Chem.* 2013, *125*, 540; d) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534; *Angew. Chem.* **2013**, *125*, 558; e) A. Parra, S.

Reboredo, A. M. Martín Castro, J. Aleman, *Org. Biomol. Chem.* **2012**, *10*, 5001; f) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603; g) A. S. K. Hashmi, C. Hubbert, *Angew. Chem. Int. Ed.* **2010**, *49*, 1010; *Angew. Chem.* **2010**, *122*, 1026; h) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350; i) Z. H. Shao, H. B. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745; j) J. Lacour, D. Moraleda, *Chem. Commun.* **2009**, 7073.

[9] For selected example using chiral copper(II) phosphate catalyst, see: a) K. Saito, Y. Kajiwara, T. Akiyama, *Angew. Chem. Int. Ed*. **2013**, *52*, 13284; *Angew. Chem.* **2013**, *125*, 13526; b) V. Rauniyar, Z. J. Wang, H. E. Burks, F. D. Toste, *J. Am. Chem. Soc.*, **2011**, *133,* 8486; For selected example using chiral copper(I) phosphate catalyst, see: c) J.-S. Lin, T.-T. Li, J.-R. Liu, G.-Y. Jiao, Q.-S. Gu, J.-T. Cheng, Y.-L. Guo, X. Hong, X.-Y. Liu, *J. Am. Chem. Soc.* **2019**, *141,* 1074; d) J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan, X.-Y. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 9357; e) Y.-F. Cheng, X.-Y. Dong, Q.-S. Gu, Z.-L. Yu, X.-Y. Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 8883; f) J.-S. Lin, F.-L. Wang, X.-Y. Dong, W.-W. He, Y. Yuan, S. Chen, X.-Y. Liu, *Nat. Commun.* **2017**, *8*, 14841.

[10] For selected examples of copper catalyzed-deoxygenation *N*-oxides, see: a) A. Saini, S. Kumar, J. S. Sandhu, *Synlett*, **2006**, 395; b) S. K. Singh, M.; Mangle, M. Srinivasa Reddy, K. Ravi Ganesh, *Tetrahedron*, **2007**, *63*, 126; c) J. Jeong, D. Lee, S. Chang, *Chem. Commun.* **2015**, *51*, 7035; d) Y. Kong, Y. Liu, B. Wang, S. Li, L. Liu, W. Chang, J., Li, *Adv. Synth. Catal.* **2018**, *360*, 1240; e) O. V. Larionov, D. Stephens, A. Mfuh, G. Chavez, *Org. Lett.* **2014**, *16,* 864; f) Y. Shen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang, H. Wu, *Chem. Commun.* **2014**, *50*, 4292; g) R. Odani, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2015**, *80*, 2384; h) B. Du, P. Qian, Y. Wang, H. Mei, J. Han, Y. Pan, *Org. Lett.* **2016**, *18*, 4144; h) C. S. Wang, T. Roisnel, P. H. Dixneuf, J. F. Soulé, *Org. Lett.* **2017**, *19*, 6720; i) S. Yu, H. L. Sang, S. Ge, *Angew. Chem. Int. Ed.* **2017**, *56*, 15896; *Angew. Chem.* **2013**, *129*, 10691.

[11] Selected recent reviews on the Povarov reaction: a) V. A. Glushkov, A. G. Tolstikov, *Russ. Chem. Rev*. **2008**, *77*, 137; b) V. V. Kouznetsov, *Tetrahedron*, **2009**, *65*, 2721; c) D. Bello, R. Ramón, R. Lavilla, *Curr. Org. Chem.* **2010**, *14*, 332; d) V. Sridharan, P. A. Suryavanshi, J. C. Menendez, *Chem. Rev.* **2011**, *111*, 7157; e) X. X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515; d) G. Masson, C. Lalli, M. Benohoud, G. Dagousset, *Chem. Soc. Rev.* **2013**, *42*, 902; e) X. X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515; f) M. Fochi, L. Caruana, L. Bernardi, *Synthesis*, **2014**, *46*, 135; G) V. Eschenbrenner-Lux, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 11146; *Angew. Chem.* **2014**, *126*, 11326.

[12] For recent selected examples on catalytic enantioselective Povarov reaction: a) W. Dai, X.-L. Jiang, J.-Y. Tao, F. Shi, *J. Org. Chem.* **2016**, *81*, 185; b) X.-L. Yu, L. Kuang, S. Chen, X.-L. Zhu, Z.-L. Li, B. Tan, X.-Y. Liu, *ACS Catal.* **2016**, *6,* 6182; c) J. Yu, H.-J. Jiang, Y. Zhou, S.-W. Luo, L.-Z Gong, *Angew. Chem. Int. Ed.* **2015**, 54, 11209; *Angew. Chem.* **2015**, *127*, 11361; d) C. S. Luo, Y. Huang, *J. Am. Chem. Soc.* **2013**, *135*, 8193; e) Z. L. Chen, B. L. Wang, Z. B. Wang, G. Y. Zhu, J. W. Sun, *Angew. Chem. Int. Ed.* **2013**, *52*, 2027; *Angew. Chem.* **2013**, *125*, 2081; f) L. Caruana, M. Fochi, S. Ranieri, A. Mazzanti, L. Bernardi, *Chem. Commun.* **2013**, *49*, 880; g) C. Min, N. Mittal, D. X. Sun, D. Seidel, *Angew. Chem. Int. Ed.* **2013**, *52*, 14084; *Angew. Chem.* **2013**, *125*, 14334; h) F. Shi, G. J. Xing, R. Y. Zhu, W. Tan, S. J. Tu, *Org. Lett.* **2013**, *15*, 128; i) F. Shi, G.-J. Xing, Z.-L. Tao, S.-W. Luo, S.-J. Tu, L.-Z. Gong, *J. Org. Chem.* **2012**, *77*, 6970; j) L. He, M. Bekkaye, P. Retailleau, G. Masson, *Org. Lett.* **2012**, *14*, 3158; k) J. H. Lin, G. Q. Zong, R. B. Du, J. C. Xiao, S. B. Liu, *Chem. Commun.* **2012**, *48*, 7738.

[13] H.-G. Imrich, J. Conrad, U. Beifuss *Eur. J. Org. Chem.* **2016**, 5706.

[14] a) K. J. Nelson, I. A. Guzei, G. S. Lund, R. W. Mcgaff, *Polyhedron*, **2002**, *21*, 2017; b) K. J. Tubbs, A. L. Fuller, B. Bennett, A. M. Arif, L. M. Berreau, *Inorg. Chem.* **2003**, *42*, 4790.

[15] Reducing or increasing the amount of H_2O resulted in lower yield of **5a**.

[16] For a review, see S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113,* 6234.

[17] For copper shuttle between Cu(II) and Cu(I) in catalyzed disproportionation of PhNHOH to PhNO and $PhNH_2$ see: Ho, C.-M.; Lau, T.-C. *New J. Chem.* **2000**, *24*, 859; b) R. S. Srivastava, N. R. Tarver, K. M. Nicholas *J. Am. Chem. Soc.* **2007**, *129*, 15250.

[18] Absolute configuration determined by comparison of the specific rotation and HPLC peak intensities with our previous work reported, see ref 5k.

[19] We thank one referee for suggesting and highlighting this point.

[20] Cu(I) complex was seen in MS (MALDI-TOF), but matrice could be responsible for reduction (See supporting information).

WILEY-VCH

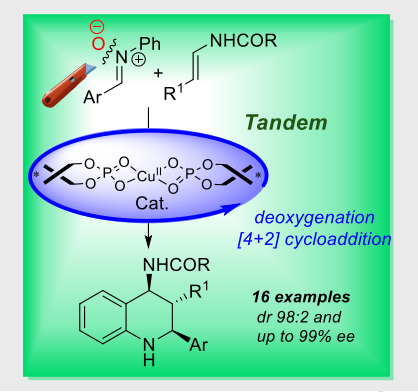
COMMUNICATION

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Cut and joint together: Chiral Copper phosphate complexes efficiently promoted a tandem sequence of deoxygenation/ [4+2] cycloaddition reactions. This process gives access to various tetrahydroquinolines with three consecutive stereogenic centers in good yields with excellent diastereo- and enantioselectivity.



Tandem catalysis*

*Coralie Gelis, Guillaume Levitre, Vincent Guérineau, David Touboul, Luc Neuville, Geraldine Masson**

Page No. – Page No.

Tandem Chiral Cu(II) Phosphate-Catalyzed Deoxygenation of Nitrones/ Enantioselective Povarov Reaction with Encarbamates

*one or two words that highlight the emphasis of the paper or the field of the study

Layout 2:

COMMUNICATION

((Insert TOC Graphic here; max. width: 11.5 cm; max. height: 2.5 cm; NOTE: the final letter height should not be less than 2 mm.))

Key Topic*

*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

Text for Table of Contents (about 350 characters)

*one or two words that highlight the emphasis of the paper or the field of the study