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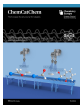

Synergistic One-pot Tandem Combination of Cu and Proline Catalysis: Stereodivergent Synthesis of Chiral Aldols from Primary Alcohols

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A new stereodivergent one-pot tandem protocol, which granted diastereo- and enantioselective access to chiral aldols by starting from simple primary alcohols, is presented as a proof-of-concept. The synergistic combination of a chemoselective Cu(II)-catalyzed oxidation of primary alcohols into the corresponding aldehydes (without the expected overoxidation into the corresponding carboxylic acids and using simple aerial O_2 as co-oxidant), followed by a concomitant organocatalyzed enantioselective aldol coupling promoted by the system (*S*)-proline/HTBD-BF_4 [TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene], was achieved after fine-tuning and compatibilizing the conditions required for the successful performance of both catalytic systems. Here, we demonstrated that selection and pairing of both catalysts needs to be extremely judicious to avoid orthogonality, kinetic, concentration or reciprocal poisoning issues. Refinement of the overall tandem protocol allowed us to design a synergistic and stereodivergent protocol which affords comparable or even better diastereoselective results than the organocatalytic system by itself. Finally, the following key factors (from a sustainable point of view) should be highlighted: *i*) no external *VOC* solvents are needed during our one-pot tandem synthetic protocol (by working under neat conditions); and *ii*) isolation/purification of any intermediate is not required, thus reducing the chemical waste and energy/time costs, simplifying the practical aspects of our synthetic methodology.

Introduction

The design of one-pot tandem reactions aimed to synergistically assemble the different synthetic organic protocols available in the catalysis tool-box (transition metals, organocatalysts and/or enzymes) is nowadays receiving great attention.[1] In addition to involving a proof of concept, it allows the straightforward preparation of complex molecular structures without requiring tedious and time/energy consuming multiple synthetic steps (including purifications and extractions).[2] In this sense, our research group has previously reported the fruitful combination of different transition-metal-catalyzed organic reactions, like isomerizations, cycloisomerizations or hydrations of several unsaturated organic substrates (ranging from olefins to alkynes or nitriles), with: *i*) a variety of biocatalyzed organic transformations (by using different enzymes, like ketoreductases, transaminases or laccases);[3] or *ii*) main-group mediated organic transformations (by using either organolithium or organomagnesium reagents).[4,5]

However, one of the most difficult challenges to solve in this chemistry is the design of the so-called *Asymmetric Organo/transition Metal combined Catalysis* (*AOMC*), which opens the door to the generation of single enantiomers starting from non-chiral or racemic substrates.[6] Interestingly, the *in-vivo* version of these protocols is already employed by nature when using the corresponding metalloenzyme/coenzyme combinations as cooperative catalytic systems for different metabolic transformations.[7] Despite the clear advanced features of *AOMC* in accessing enantiomerically enriched molecules, *via* design of one-pot tandem multicatalytic reactions, the careful selection of catalyst pairs from the two distinct categories (metal and organocatalyst) is crucial and needs to be extremely precise, as the assembly of these two catalytic worlds imposes several challenges, related with: *i*) catalyst compatibility and stability; *ii*) orthogonality and cross-reactivity; *iii*) kinetic, mechanism and thermodynamic factors of each catalytic reaction; and *iv*) use of different co-catalysts, solvents, temperatures or concentrations.

Despite having solved the aforementioned compatibility issues, a close look to the literature reveals that the vast majority of these *AOMC* processes rely on the use of sophisticated catalytic systems based on toxic, non-abundant

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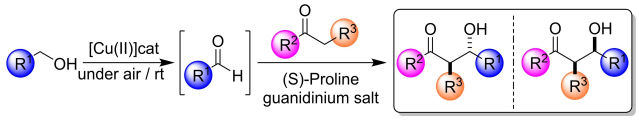
and expensive precious transition-metal-based compounds as catalysts (basically Au, Pd, Rh, Ru or Ir),[8] while the use of first-raw, abundant and cheap transitions metals (like Fe[9] or Cu[10]) as catalysts in *AOMC* is still in its infancy.

In the view of the scarcely studied catalytic performance of copper species in *AOMC* protocols and taking into account that we have previously reported the following two independent chemical approaches: *i*) chemoselective Cu(II)-catalyzed oxidations of primary alcohols into aldehydes;[4c] and *ii*) highly enantio- and diastereoselective cross aldol reactions catalyzed by a binary guanidium salt/(*S*)-proline system,[11] we decided to study (as a new proof of concept for *AOMC* methodologies), the successful marriage of these two synthetic procedures to design an unprecedented protocol capable of converting primary alcohols into densely-functionalized and highly elaborated chiral aldols,[12] thus improving the molecular complexity of the substrates used as starting materials (Scheme 1). Such a process is significantly demanding, as the organocatalyzed asymmetric aldol reaction has been identified as a rather sensitive transformation, prone to the occurrence of parasitic side reactions that jeopardize the selectivity of the aldol adducts or prevent their formation.[13] Also, the by-products generated in the first step should not risk the success of the later. Moreover, and for the sake of sustainability, we decided to design a global one-pot tandem protocol which should: *i*) proceed under aerobic conditions; *ii*) work under neat conditions (without requiring external *VOC* solvents during the synthetic protocol); *iii*) not need the isolation of any reaction intermediate (aldehydes in this case); and *iv*) get access to the desired final products with high yield and selectivity.

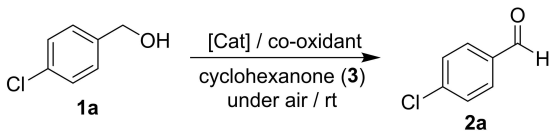


Scheme 1. Design of a stereodivergent one-pot tandem protocol through the successful combination of Cu(II)-catalyzed oxidation of primary alcohols with an organocatalyzed [(*S*)-proline/TBD] aldol protocol for the enantio- and regioselective synthesis of chiral aldols.

Results and Discussion

As previously commented, the first concern to settle for the design of a feasible *AOMC* one-pot tandem protocol is the compatibility of the different reaction conditions involved in both catalytic systems (organic and metallic in our case). Thus, we decided to start our investigations by testing the catalytic activity of our Cu(II)-based catalytic system in the selective oxidation of *p*-chlorobenzyl alcohol (**1 a**) into *p*-chlorobenzaldehyde (**2 a**), within a substrate required by the concomitant organocatalytic system, that is, using cyclohexanone (**3**) as solvent and working under bench-type reactions conditions (room temperature, in the presence of air/moisture, Table 1). By employing this set of conditions, we found that 7 mol% of the catalytic system $CuCl_2 \cdot 2H_2O$/TMEDA/TEMPO [TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl], is capable of promoting the oxidation of the alcohol **1 a** into the desired aldehyde **2 a** in high conversion and with total chemoselectivity (the formation of

Table 1. Oxidation of *p*-chlorobenzyl alcohol (**1 a**) into the corresponding *p*-chlorobenzaldehyde (**2 a**) using different catalytic oxidative systems, working at room temperature and under air.[a]



entry	[Cat.] (mol%)	Co–Ox. (mol%)	*t* (h)	*C* (%)[b]
1	$CuCl_2 \cdot 2H_2O$/TMEDA (7)	TEMPO (7)	16	91
2	$CuCl_2 \cdot 2H_2O$/TMEDA (1.3)	TEMPO (13)	20	88
3	$CuCl_2 \cdot 2H_2O$/TMEDA (1.3)	AZADO (13)	20	31[c]
4[d]	aq. NaOCl (160)	AZADO (1)	20	60
5	$Ca(OCl)_2$ (120)	–	20	44
6	$C_3Cl_3N_3O_3$ (105)	TEMPO (10)	0.2	42
7[e]	Laccase	TEMPO (10)	20	1
8	I_2 (200)	TEMPO (10)	20	73
9[f]	$CuCl_2 \cdot 2H_2O$/TMEDA (7)	TEMPO (7)	96	8
10[f]	$CuCl_2 \cdot 2H_2O$/TMEDA (1.3)	TEMPO (13)	96	0

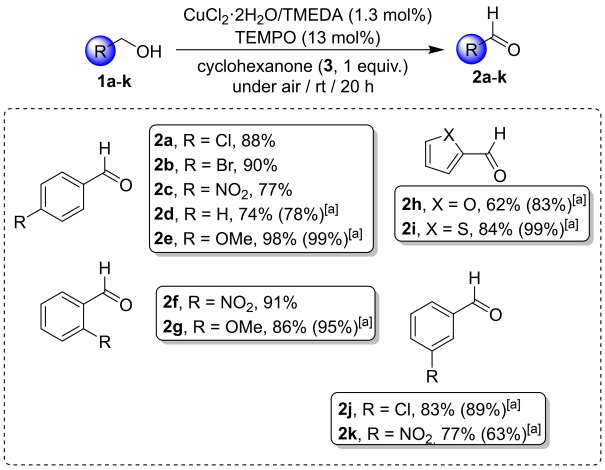
[a] General Conditions: Reactions performed under air, at room temperature using 1 mmol of the alcohol **1 a** and 1 mmol of cyclohexanone (**3**) as solvent. [b] Determined by ^{1}H NMR using $CHBr_3$ as an internal standard. [c] 7% of aldol adduct (resulting from the reaction of cyclohexanone and 4-chlorobenzaldehyde) was also detected, obviously in racemic form. [d] A 0.40 M aqueous solution of NaOCl (pH 7.9) was used. [e] 19.2 mg of Laccase from *T. versicolor* (10 U mg^{-1}) were employed (U mg^{-1} = units of activity per mg of enzyme). [f] (*S*)-proline (15 mol%), and the guanidinium salt HTBD-BF_4 (see Scheme 3, 10 mol%) were added at the beginning of the reaction.

the corresponding *p*-chlorobenzoic acid was not detected), employing 1 equivalent of cyclohexanone (**3**) as reaction media (entry 1, Table 1) and by using simple aerial O_2 as co-oxidant, thus being water the only by-product generated in the oxidation protocol.[4c]

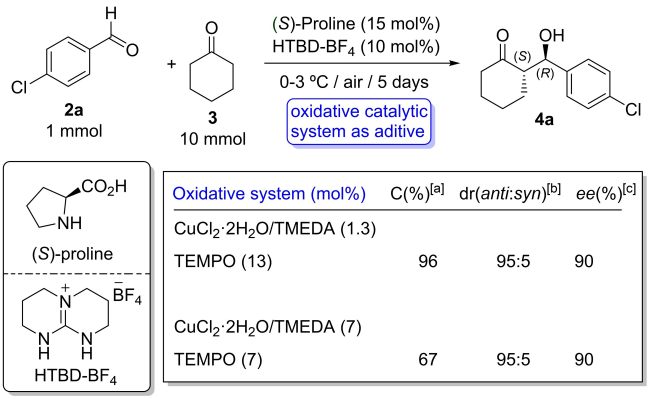
Interestingly, similar results could be also achieved by decreasing the catalyst loading of Cu and TMEDA to 1.3 mol%, while increasing the loading of TEMPO from 7 to 13 mol% (entry 2, Table 1). We also studied the use of other oxidizing systems such as Cu/AZADO (2-azaadamantane *N*-oxyl; entry 3, Table 1), AZADO/aq. NaOCl (entry 4, Table 1)[14] or trichloroisocyanuric acid/TEMPO (entry 6, Table 1);[15] biocatalytic oxidative systems based on the use of a Laccase from *Trameters Versicolor* (entry 7, Table 1);[16] or based on inorganic reagents: $Ca(OCl)_2$ (entry 5, Table 1), I_2 (entry 8, Table 1). In all these cases, lower conversions of the starting alcohol (**1a**) into benzaldehyde (**2a**) were registered. The sensitivity of the oxidizing systems based on Cu(II) species towards the subsequent organocatalytic reaction was tested by adding catalytic amounts of (*S*)-proline and a guanidinium salt to the reaction medium.[11] In principle, the later could promote a cross-aldol carboligation between cyclohexanone **3** and the generated aldehyde **2a**. All the attempts were unfruitful, as neither aldehyde **2a** nor aldol adducts were observed (entries 9 and 10, Table 1).

Trying to have a full picture of the influence of the substituents present in the primary alcohol used as the starting material, we decided to evaluate the catalytic activity of the oxidative system that employs smaller amounts of copper, $CuCl_2 \cdot 2H_2O$/TMEDA (1.3 mol%) and TEMPO (13 mol%), against a battery of benzyl alcohols decorated with various functional groups and substitution patterns (**1a–k**) always working under air, at room temperature, and using cyclohexanone (**3**), 1 equiv., as reaction media. In all the cases studied, good conversion of alcohols into the desired aldehydes **2a–k** were observed (62–98%; Scheme 2), with total chemoselectivity as no side products were observed in the crude reaction mixture (only unreacted starting alcohols **1a–k** were detected by ^{1}H NMR but not the corresponding aromatic/heteroaromatic carboxylic acids). Moreover, it is important to mention that when using liquid alcohols as substrates, *i.e.* thiophenyl alcohol (**1i**), the oxidative system is able to operate under neat (solvent free) conditions, affording quantitative conversion (99%) of the corresponding aldehyde **2i** after 20 h, employing the same loading of the catalysts but working under 1 atm of oxygen (external balloon, see Experimental Section for details).

Next, we decided to assess the feasibility of the cross-aldol carboligation in the presence of our oxidative Cu(II)-catalytic system. Accordingly, we studied the reaction of *p*-chlorobenzaldehyde (**2a**) and cyclohexanone (**3**) promoted by the binary catalytic system consisting of (*S*)-proline and a HTBD-BF_4 derived guanidinium salt [TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene], in the presence of the better oxidizing agents presented in the Table 1 (Scheme 3). We made use of our previously optimized reaction conditions, which simply imply mixing the reagents inside a closed-capped vial under air, without stirring, at a temperature around 3 °C for 5 days.[11a] To our delight, when the system $CuCl_2 \cdot 2H_2O$/TMEDA (1.3 mol%)-TEMPO



Scheme 2. Chemoselective oxidation of primary alcohols **1a–k** into aldehydes **2a–k** catalyzed by the system $CuCl_2 \cdot 2H_2O$/TEMPO/TMEDA, using cyclohexanone (**3**), 1 equiv., as reaction media. Conversion of **1a–k** into **2a–k** has been calculated by ^{1}H NMR from reaction crudes, using $CHBr_3$ as an internal standard.[a] In brackets, the conversion of alcohols **1d–e, g–k** into the corresponding aldehyde **2d–e, g–k** working under neat conditions under 1 atm of oxygen gas.



Oxidative system (mol%)	C(%)[a]	dr(*anti*:*syn*)[b]	*ee*(%)[c]
$CuCl_2 \cdot 2H_2O$/TMEDA (1.3)			
TEMPO (13)	96	95:5	90
$CuCl_2 \cdot 2H_2O$/TMEDA (7)			
TEMPO (7)	67	95:5	90

Scheme 3. Study of the impact of the Cu(II)-based oxidative system on the performance of the (*S*)-proline/guanidinium salt organocatalyzed aldol reaction between *p*-chlorobenzaldehyde (**2a**) and cyclohexanone (**3**).[a] Conversion of aldehyde **2a** into aldol adduct **4a**, as determined by ^{1}H NMR spectroscopy from crude reaction mixtures using $CHBr_3$ as an internal standard.[b] Determined by HPLC from crude reaction mixtures. *Anti* and *syn* diastereoisomers were unambiguously identified by comparison with similar compounds previously described in the literature.[c] Enantiomeric excess of the major diastereoisomer *anti*-**4a**, as determined by chiral HPLC from crude reaction mixtures.

(13 mol%) was added as an additive, the aldol **4a** was still obtained in high yield, with optimum diastereo and enantioselectivity, alike the one obtained in the absence of copper (see Ref. [11a]). This is a pivotal experimental observation which allows us to construct the desired *AOMC* protocol, as the organocatalyzed asymmetric aldol reaction is recognized as a highly delicate process, susceptible to be affected by undesired parasitic side reactions that puts under risk the selectivity of aldol adducts or hinder their formation. In this sense, increasing the catalyst loading of Cu(II), from 1.3 to 7 mol%, results in a rapid deterioration of the performance of the organocatalyst,

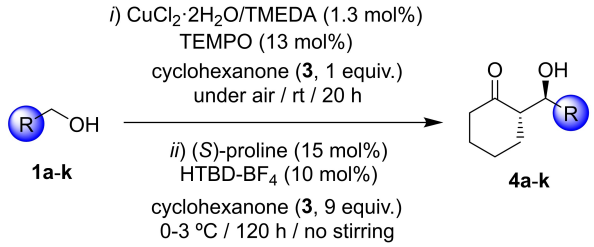
being the conversion of the benzyl alcohol (**1 a**) into the desired aldol (**4 a**) severely affected.

Having in hand the two optimized steps, and in order to build up an unprecedented metal-organocatalyzed combination (*AOMC*), we next planned their assembly in a one-pot tandem process. The concentration of the reagents in either subprocess was indicated as a critical parameter, since the optimized catalytic oxidative reaction requires a higher concentration than the organocatalytic protocol. In this regard, the oxidation conducted at lower concentration exhibited a significant lower conversion. Also, it is well known that the use of stoichiometric amounts (1 : 1) of aldehydes and enolizable ketones has a strong negative impact in the organocatalytic system.[11a] Satisfyingly, we were able to circumvent this problem by simple diluting the crude reaction mixtures rendered after the oxidation of alcohols **1** to aldehydes **2** with some extra cyclohexanone (9 equiv.), without any halfway isolation/purification of the aldehydes intermediates. As a proof of concept, we analyzed the performance and scope of the overall tandem protocol on the primary alcohols **1 a**–**k**, which were converted into the corresponding aldols **4 a**–**k** by the combined action of the Cu(II)-catalytic system and the organocatalytic set formed by (*S*)-proline and a TBD-based tetrafluoroborate guanidinium salt, using cyclohexanone (**3**) as reagent/solvent (see Table 2).

Gratifyingly, the overall tandem protocol worked well for alcohols **1 a**–**d**, **1 f**–**g** and **1 j**–**k**, decorated with different functional groups and exhibiting either substitution pattern on the aromatic ring. On these cases, conversions of primary alcohols **1** into aldols **4**, and particularly enantio/diastereoselectivites of the adducts **4**, is alike to those observed previously by us in the isolated organocatalytic methodology (see Ref. [11a]). 4-Methoxy benzyl alcohol (**1 e**) was not an optimum substrate, being reasoned this experimental observation by taking into account the poor electrophilic character exhibited by the intermediate aldehyde **2 e** (*p*-anisaldehyde). Finally, the reaction on heteroaromatic alcohols **1 h**–**i** produced modest results, being the corresponding aldehydes **2 h**–**i** identified as challenging substrates for the cross-aldol reaction.

One of the greatest virtues of our organocatalyzed cross-aldol reaction lies in the possibility of controlling the relative stereochemical disposition of the aldol products (diastereoselectivity) using a single chiral catalyst [(*S*)-proline]. In this regard, we have previously shown how the careful choice of the anion of our TBD-derived guanidinium salts allows preparing either *syn* or *anti*-aldol adducts, in demand.[11b] Going one step further and taking into account the scarce availability of sterodivergent *AOMC* protocols based on first-raw, cheap and abundant transition metals (*i.e.*, Cu),[10] we decided to explore this possibility within our tandem protocol. Thus, we chose to carry out some reactions replacing the salt HTBD-BF_4 by its analogue HTBD-BPh_4 (tetraphenylboric acid/1,5,7-triazabicyclo[4.4.0]dec-

Table 2. One-pot tandem protocol for the conversion of primary alcohols **1 a**–**k** into the corresponding *anti*-aldol adducts **4 a**–**k**.[a]



entry	R	**4 a**–**k** (%)[b,c]	dr (*anti*:*syn*)[d]	*ee* (%)[e]
1	**1 a**: 4-Cl-C_6H_4	73 (61)	94:6	98
2	**1 b**: 4-Br-C_6H_4	73 (58)	92:8	96
3	**1 c**: 4-NO_2-C_6H_4	71 (46)	83:17	92
4	**1 d**: C_6H_5	49 (41)	93:7	93
5	**1 e**: 4-OMe-C_6H_4	10 (3)	81:19	76
6	**1 f**: 2-NO_2-C_6H_4	73 (55)	96:4	92
7	**1 g**: 2-OMe-C_6H_4	63 (51)	92:8	87
8	**1 h**: 2-furyl	53 (31)	76:24	91
9	**1 i**: 2-thiophenyl	17 (13)	93:7	95
10	**1 j**: 3-Cl-C_6H_4	75 (65)	94:6	95
11	**1 k**: 3-NO_2-C_6H_4	73 (56)	94:6	96

[a] General Conditions: 1 mmol of alcohol (**1 a**–**k**), limiting reagent, was used in each reaction. The amount of catalysts and cyclohexanone was calculated accordingly. [b] Conversions determined by ^{1}H NMR from crude reaction mixtures, using $CHBr_3$ as an internal standard. [c] Isolated yields in brackets for *anti* products. [d] Diastereosisomeric ratios were determined by chiral HPLC from crude reaction mixtures. *Anti* and *syn* diastereoisomers were unambiguously identified by comparison with similar compounds previously described in the literature. [e] Enantiomeric excess of the major diastereoisomer (*anti*), as determined by chiral HPLC from crude reaction mixtures.

5-ene salt) a non-intimate ionic pair that features a bulkier anion (Table 3).

Here, it is important to signal out that in the particular case of adduct *syn*-**4f**, which could be obtained with almost complete diastereoselectivity (entry 2, Table 3), the combined tandem protocol affords significantly better results than the organocatalytic system by itself.[11b] We explain this experimental observation by taking into account that it is the whole reaction media (consisting of the metallic and the organocatalytic systems) which favors the formation of *syn*-**4f**, as we have previously concluded that this stereoisomer is not a kinetic but a thermodynamic product. In either case, it is to our knowledge the first occasion that *AOMC* one-pot protocol gives rise to a stereodivergent process, which are scarce.[17]

Conclusions

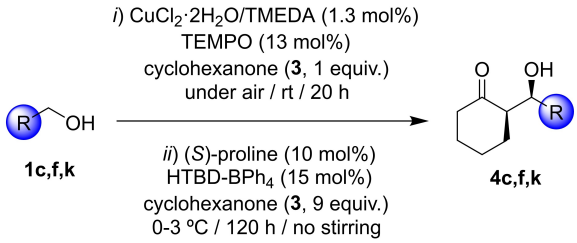
To conclude, we have evidenced the possibility of designing stereodivergent one-pot tandem-like protocols that imply the conflictive coexistence of metal species and asymmetric organocatalysts in the same reaction media. As a proof of concept, we have developed a procedure that marries a chemoselective Cu(II)-catalyzed oxidation of primary alcohols into aldehydes, and a subsequent diastereo-/enantioselective (*S*)-proline/guanidinium salt organocatalyzed cross-aldol reaction of the so formed aldehydes (which are not isolated). Its synergistic combination allows rendering aldol adducts in a straightforward manner, with good conversion and very high diastereo- and enantioselectivity, obtaining in some cases better results than the organocatalytic system by itself. Moreover, it is important to mention that our tandem protocol is based on the use of a first-raw, abundant and cheap transition metal (Cu) and not in toxic, non-abundant and expensive precious transition-metals (Au, Pd, Rh, Ru or Ir), which are usually employed in the design of *AOMC* protocols

Finally, we have demonstrated how the fine tuning of the organocatalytic system permits the design of a stereodivergent protocol, which are almost unexplored in the chemistry of one-pot tandem methodologies. This broadens the scope of the catalysis tool-box and fills up an existing gap in the chemical literature. Importantly, and from a sustainable point of view, no isolation/purification of any intermediate is required, thus reducing the chemical waste and energy/time costs, also simplifying the practical aspects of our synthetic methodology. We hope that our work will inspire the design of new stereodivergent one-pot tandem protocols employing combinations of non-precious metals and organocatalysts under bench-type and neat reaction conditions.

Experimental Section

All commercially available reagents and solvents were used without further purification unless otherwise stated. Liquid aldehydes, employed in the synthesis of racemic mixtures of adducts **4**, were distilled under reduced pressure before use. Flash chromatography of reaction products was carried out using Silica gel 60, particle size 400–630 micron (VWR). Analytical thin layer chromatography (TLC) was performed on DC-Alufolien Kieselgel 60F254 0.2 mm plates (Merck) and compounds were visualised by UV fluorescence or using an aqueous $KMnO_4$ solution followed by heating. ^{1}H-NMR and proton-decoupled ^{13}C-NMR spectra ($CDCl_3$) were obtained using a Bruker AV-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) spectrometer using the δ scale (ppm) for chemical shifts. Calibration was made on the signal of the solvent (^{13}C: $CDCl_3$, 77.16; ^{1}H: $CDCl_3$, 7.26).[18] The spectroscopic data for aldols **4a–k** is in fully agreement with that reported in the literature.

Table 3. One-pot tandem protocol for the conversion of primary alcohols **1c,f,k** into the corresponding *syn*-aldol adducts **4c,f,k**.[a]



entry	R	**4c,f,k** (%)[b,c]	dr (*anti*:*syn*)[d]	*ee* (%)[e]
1	**1c**: 4-NO_2-C_6H_4	64 (28)	43:57	88
2	**1f**: 2-NO_2-C_6H_4	40 (30)	2:98	83
3	**1k**: 3-NO_2-C_6H_4	37 (12)	43:57	88

[a] General Conditions: 1 mmol of alcohol (**1c,f,k**), limiting reagent, was used in each reaction. The amount of catalysts and cyclohexanone was calculated accordingly. [b] Conversions determined by ^{1}H NMR from crude reaction mixtures, using $CHBr_3$ as an internal standard. [c] Isolated yields in brackets for *syn* products. [d] Diastereosisomeric ratios were determined by chiral HPLC from crude reaction mixtures. *Anti* and *syn* diastereoisomers were unambiguously identified by comparison with similar compounds previously described in the literature. [e] Enantiomeric excess of the major diastereoisomer (*syn*), as determined by chiral HPLC from crude reaction mixtures.

General procedure for the oxidation of alcohols 1a–k into aldehydes 2a–k, using cyclohexanone as reaction medium

This method is based in an already procedure published by us.[4c] In a 12 mL vial were added copper(II) chloride dihydrate ($CuCl_2 \cdot 2H_2O$, 2.2 mg, 0.013 mmol), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 20.3 mg, 0.13 mmol), the corresponding alcohol **1** (1 mmol), cyclohexanone **3** (104 μL, 1 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 2 μL, 0.013 mmol). The mixture was gently stirred (300 rpm) opened to air at room temperature for 20 hours. Then, a saturated aqueous solution of NH_4Cl was added (10 mL) and the mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried with $MgSO_4$, filtered and the solvents were evaporated under vacuum. Conversions **1**→**2** were calculated from ^{1}H-NMR, dissolving the crude mixtures in $CDCl_3$ and adding bromoform (115.6 mg, 40 μL, 0.457 mmol) as an internal standard.

Standard procedure for the oxidation of alcohols 1d, e, g–k into aldehydes 2d, e, g–k under neat conditions

In a 12 mL vial were added copper(II) chloride dihydrate ($CuCl_2 \cdot 2H_2O$, 2.2 mg, 0.013 mmol), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 20.3 mg, 0.13 mmol), the corresponding liquid alcohol **1** (1 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 2 μL, 0.013 mmol). The vial was purged with oxygen gas for 30 seconds and then it was closed. The mixture was gently stirred (300 rpm) for 20 hours before it was allowed to stand for 30 minutes inside a standard laboratory freezer. Then, the mixture was quenched with 10 mL of NH_4Cl (aq. sat.) and extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried with $MgSO_4$, filtered and the solvents were evaporated under controlled vacuum. Conversions **1**→**2** were calculated from ^{1}H-NMR, dissolving the crude mixtures in $CDCl_3$ and adding bromoform (115.6 mg, 40 μL, 0.457 mmol) as an internal standard.

Standard procedure for the synthesis of *anti*-aldol adducts 4a–k

In a 12 mL vial were added copper(II) chloride dihydrate ($CuCl_2 \cdot 2H_2O$, 2.2 mg, 0.013 mmol), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 20.3 mg, 0.13 mmol), the corresponding alcohol **1 a-k** (1 mmol), cyclohexanone (104 μL, 1 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 2 μL, 0.013 mmol). The mixture was gently stirred (300 rpm) opened to air at room temperature for 20 hours. Then, (*S*)-proline (17.3 mg, 0.15 mmol), the tetrafluoroborate guanidium salt HTBD-BF_4 (TBD = 1,5,7-triazabicyclo[4.4.0]-dec-5-ene; 22.7 mg, 0.10 mmol) and cyclohexanone (936 μL, 9 mmol) were added to the vial. The resulting suspension was allowed to stay 5 days inside a standard laboratory fridge (temperature fixed at 0–3 °C) without agitation or mechanical stirring, obtaining a solution which showed the precipitation of a blue solid. The liquors were transferred to a funnel, quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried with $MgSO_4$ and filtered. Solvents and excess of cyclohexanone were eliminated under vacuum. Flash chromatography (hexane/EtOAc 4 : 1) of crude reaction mixtures was performed for all products.

Standard procedure for the synthesis of *syn*-aldol adduct 4c, f, k

An analogous experimental procedure to the aforementioned was carried out, excepting the addition of (*S*)-proline (11.5 mg, 0.10 mmol were added in this case) and the use of the tetraphenylborate guanidinium salt HTBD-BPh_4 (tetraphenylboric acid/1,5,7-triazabicyclo[4.4.0]dec-5-ene salt; 69.2 mg, 0.15 mmol) instead of HTBD-BF_4.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Asymmetric Organo/transition Metal combined Catalysis (*AOMC*) · One-pot Tandem · Organocatalysis · Transition Metals · Homogeneous Catalysis

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