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Homogeneous Catalysis

A Metalloenzyme-Like Catalytic System for the Chemoselective Oxidative Cross-Coupling of Primary Amines to Imines under Ambient Conditions

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Abstract: The direct oxidative cross-coupling of primary amines is a challenging transformation as homocoupling is usually preferred. We report herein the chemoselective preparation of cross-coupled imines through the synergistic combination of low loadings of Cu^{II} metal-catalyst and *o*-iminoquinone organocatalyst under ambient conditions. This homogeneous cooperative catalytic system has been inspired by the reaction of copper amine oxidases, a family of metalloenzymes with quinone organic cofactors that mediate the selective oxidation of primary amines to aldehydes. After optimization, the desired cross-coupled imines are obtained in high yields with broad substrate scope through a transamination process that leads to the homocoupled imine intermediate, followed by dynamic transimination. The ability to carry out the reactions at room temperature and with ambient air, rather than molecular oxygen as the oxidant, and equimolar amounts of each coupling partner is particularly attractive from an environmentally viewpoint.

Introduction

Imines, commonly known as Schiff bases, represent a very important class of N-containing intermediates widely utilized as electrophiles in many organic transformations, such as reduction, addition, condensation, and cyclization. They are also essential pharmacophores in numerous biologically active compounds. Imines have traditionally been prepared through condensation of amines with aldehydes or ketones, but new mild and practical catalytic methods,[1] including oxidative coupling of alcohols and amines[2] together with oxidation of secondary amines,[3] have also been developed. For a long time, little attention had been given to the oxidation of primary amines probably due to poor product selectivity.[4] The discovery of homogeneous and heterogeneous catalytic systems that operate effectively with molecular oxygen as the sole oxidant has contributed to revitalize interest in this area.[5] Recently, non-noble transition-metal catalysis,[6] metal-free catalysis,[7] and photocatalysis[8] have led to homocoupled imines in high yields and selectivity. However, save for a few exceptions,[6b,d] these catalytic systems require elevated temperature (70–130 °C) and/or oxygen pressure. In addition, the condensation of amines is not an efficient way to prepare cross-coupled imines due to the concomitant formation of self-coupling products.[6a,7a,9] To the best of our knowledge, only two highly efficient and selective (>95%) oxidative cross-coupling protocols for various amines have been reported to date, but they require high reaction temperatures (100 °C) together with oxygen pressure.[10]

The general interest in amine oxidation has also stimulated efforts to mimic the biological activity of metalloenzymes,[11] in particular copper amine oxidases (CuAOs) that promote selective aerobic oxidation of primary amines to aldehydes in nature through the cooperation between a quinone-based cofactor (topaquinone) and copper.[12] Recently, metalloenzyme-like catalytic systems have been developed for the aerobic oxidation of primary amines to imines under mild conditions.[13] In particular, the topaquinone analog 5-*tert*-butyl-2-hydroxy-1,4-benzoquinone has been described as an efficient biomimetic organocatalyst for the chemoselective aerobic oxidative self-coupling of primary amines to imines at room temperature and under 1 atm of molecular oxygen. The exclusive selectivity for primary benzylic amines allowed the preparation of various cross-coupled imines in high yields, from the oxidative condensation of benzylamine with anilines or with primary aliphatic amines.[13b]

We have ourselves described a biomimetic homogeneous catalytic system for the aerobic oxidation of primary amines to imines, based on the synergistic combination of copper and a topaquinone-like organocatalyst $\mathbf{1}_{ox}$, first discovered from electrochemical investigations.[14] Low catalyst loadings (2 mol% of $\mathbf{1}_{red}$ precursor of $\mathbf{1}_{ox}$ and 0.2 mol% of Cu^{I}) were sufficient to oxidize benzylic and aliphatic amines to self-coupled imines under ambient conditions. The oxidation process started with atmospheric oxygen and continued in a cascade-like manner by passing the oxidation potential of oxygen through the copper salt to the organic *o*-iminoquinone mediator $\mathbf{1}_{ox}$, which finally oxidized the amine substrate (Scheme 1). This cat-

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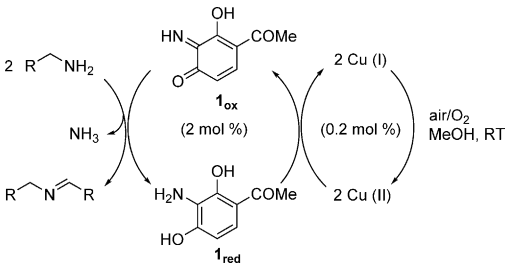


Scheme 1. Aerobic oxidation of primary amines to imines catalyzed by Cu^{II}/$\mathbf{1}_{ox}$ cooperative system.

alytic process combines two redox couples: the *o*-iminoquinone organocatalyst $\mathbf{1}_{ox}$ is the substrate-selective catalyst and the copper salt serves as an electron transfer mediator. This is reminiscent of other biomimetic catalytic systems that use transition metals as substrate-selective catalysts coupled with electron transfer mediators.[15]

Interestingly, the oxidative condensation of 4-methyl benzylamine with several aliphatic amines produced the corresponding cross-coupled imine in good yields, together with *N*-(4-methylbenzyl)-1-(*p*-tolyl)methanimine derived from homo condensation as the minor product (5–30%). This investigation of the performance of our bioinspired catalytic system led to a preliminary communication.[16] At this stage, only 4-methylbenzylamine or benzylamine[9,10,13b,d] had been engaged in the oxidative cross-coupling with alkylating amines. So, the development of a more general method that would operate effectively with complete selectivity, under ambient conditions, would be highly desirable but still challenging.

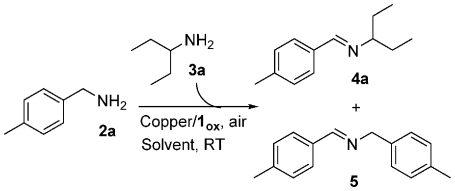
In this full paper, we have tried to achieve exclusive formation of cross-coupled imines and to expand the substrate scope. Diverse benzylic amines, including heterocyclic amines containing sulfur and oxygen atoms, could be converted with complete selectivity into the corresponding cross-coupled imines in high yields. The synthesis of aliphatic imines was inherently more challenging because of their instability due to subsequent tautomerization to the enamine form, which decomposed under ambient air. Although the cross-coupled aliphatic imine could be formed with complete selectivity as shown through monitoring the ^{1}H NMR spectrum, we were not able to isolate it as such. So, we decided to engage the generated alkylimine in situ in a Diels–Alder reaction with the Danishefsky's diene to produce *N*-alkylpyridin-4-one derivatives. Finally, all the results led us to revise the reaction pathway we had previously proposed for the oxidative cross-coupling of primary amines to imines.[16]

Results and Discussion

Choice of the optimal reaction conditions

First, we performed optimization studies of the Cu^{II}/$\mathbf{1}_{ox}$-mediated aerobic oxidative cross-coupling process by using 4-methylbenzylamine **2a** and 1-ethylpropylamine **3a** as the amine substrates. Only the copper source and solvent were varied, while the use of *o*-aminophenol $\mathbf{1}_{red}$ precursor of the *o*-iminoquinone cooperative organocatalyst $\mathbf{1}_{ox}$, room temperature, and ambient air as the source of oxidant was retained throughout. As shown in Table 1, the initial oxidation state of the copper catalyst had no significant impact on the reaction efficiency (entries 1–5). The reaction progressed in all of the solvents used (entries 5–8). But, after 10 h, complete conversion was observed only in MeOH probably because strong solvation of the *o*-iminoquinone $\mathbf{1}_{ox}$ by MeOH was required to enhance the electrophilicity of its quinonoid moiety, thereby favoring the nucleophilic attack of 4-methylbenzylamine **2a**.[14]

Table 1. Optimization of the Cu^{II}/$\mathbf{1}_{ox}$-catalyzed aerobic oxidative cross-coupling of 4-methylbenzylamine **2a** with 1-ethylpropylamine **3a**.[a]



Entry	Copper Catalyst	Solvent	Conversion [%]	Imine Selectivity **4a**:**5**[b]
1	CuMeSal	MeOH	100	95:5
2	CuI	MeOH	100	95:5
3	CuCN	MeOH	100	95:5
4	$CuBr_2$	MeOH	100	95:5
5	$Cu(OAc)_2$	MeOH	100	95:5 (100:0)[c]
6	$Cu(OAc)_2$	MeCN	90	92:8
7	$Cu(OAc)_2$	THF	83	84:16
8	$Cu(OAc)_2$	$CHCl_3$	60	52:48

[a] The reactions were carried out using equimolar amounts of amines **2a** and **3a** on a 2.5 mmol scale, in the presence of 4 mol% of $\mathbf{1}_{red}$ and 0.4 mol% of copper salt, in 10 mL of solvent, at room temperature, under ambient air for 10 h. [b] Molar ratio based on the ^{1}H NMR spectrum of the crude product. [c] After 6 h, an additional aliquot of $\mathbf{1}_{red}$ (1 mol%) was added. CuMeSal: copper(I) 3-methylsalicylate.

Optimization of the reaction parameters showed that mixing 4-methylbenzylamine **2a** and 1-ethylpropylamine **3a** in the ratio 1:1 with $Cu(OAc)_2$ (0.4 mol%) and *o*-aminophenol $\mathbf{1}_{red}$ (4 mol%), in MeOH under ambient conditions, afforded the desired cross-coupled product **4a** with 95% selectivity after 10 h (entry 5). In addition, exclusive formation of **4a** could be attained when an additional aliquot of *o*-aminophenol $\mathbf{1}_{red}$ (1 mol%) was introduced after 6 h (95% conversion). Probably, the in situ-generated *o*-iminoquinone organocatalyst $\mathbf{1}_{ox}$ polymerized slightly. Control studies revealed that copper catalyst and organocatalyst $\mathbf{1}_{ox}$ worked cooperatively to facilitate the aerobic oxidation of amines to imines under ambient conditions. In the absence of copper, the reaction proceeded very slowly owing to the spontaneous aerobic oxidation of $\mathbf{1}_{red}$ to $\mathbf{1}_{ox}$, whereas no reaction occurred at room temperature when a copper salt was used as the sole catalyst.

Scope and functional group tolerance of Cu^{II}/$\mathbf{1}_{ox}$-mediated oxidative cross-coupling of two primary amines

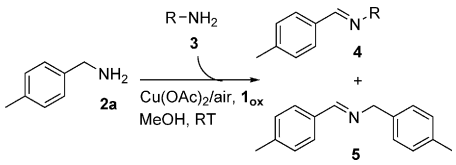
To explore potential applications of this method, the optimized reaction conditions (Table 1, entry 5) were first applied to the

catalytic oxidative cross-coupling of 4-methylbenzylamine **2a** with a range of primary amines **3** (Table 2). Both branched and linear aliphatic amines (entries 1–6) could be efficiently coupled with 4-methylbenzylamine **2a** in high yields, with complete selectivity, except for *n*-hexylamine **3e** and aminomethylcyclohexane **3f**, for which small amounts of homocoupled imines (4–5%) were also isolated (entries 5 and 6). 1-Phenylethan-1-amine **3g** (entry 7) together with 2,3-dihydro-1*H*-inden-2-amine **3h** (entry 8) reacted efficiently with **2a**, leading to cross-coupled imines that directly precipitated from the bulk solution. As has been observed earlier,[13b] anilines **3i**–**k** (entries 9–11) were less reactive, but afforded cross-coupled imines with good levels of conversion after 48 h, provided a second 2 mol% portion of *o*-aminophenol $\mathbf{1}_{red}$ was added after 24 h (entries 9 and 10), with the exception of *p*-chloroaniline **3k**, for which the conversion did not exceed 60% (entry 11). Interestingly, introduction of ether or alcohol groups (entries 12–14) allowed the synthesis of functionalized cross-coupled imines, notably without oxidation of the alcohol fragment (entry 14).

In a second series of experiments, a range of primary amine substrates **2** were screened in the presence of 1-ethylpropylamine **3a** (Table 3). High yields of cross-coupled imines were obtained from substituted benzylamines **2a**–**j** regardless of the electronic character and the position of the substituents (entries 1–10). The free amino group of *p*-aminobenzylamine **2g** did not affect the cross-coupling reaction although the yield slightly decreased (75%, entry 7). Likewise, a sterically bulky group, 1-naphthyl, was well tolerated (entry 11). Furthermore, heterocyclic amines **2l** and **2m**, containing sulfur and oxygen atoms, could be cross-coupled with **3a** in high yields with complete selectivity (entries 12 and 13).

Much more challenging, the possibility of expanding the reaction scope to the synthesis of scarcely stable aliphatic imines was also explored. The catalytic oxidative cross-coupling of aminomethylcyclopropane **6** and 4-methoxyaniline **3i** was chosen as the example and monitored by ^{1}H NMR spectroscopy. In the reaction of equimolar amounts of both amines **6** and **3i**, the time course revealed the formation of only heterocoupled product **7** at the early stages of the reaction. Although 1-cyclopropyl-*N*-(4-methoxyphenyl) methanimine **7** could be observed through monitoring the ^{1}H NMR spectrum (see the Supporting Information), its instability did not permit its isolation. Nevertheless, the mild conditions required for the generation of unstable cross-coupled aliphatic imine **7** proved to be useful for acting in situ as a dienophile in Diels–Alder reactions. After roughly 60% conversion of aminomethyl cyclopropane **6**, the reaction mixture was mixed with Danishefsky's diene **8** to form the dihydro-4-pyridone derivative **9** in 45% isolated yield (Scheme 2). Similar acid-free tandem oxidative aza Diels–Alder reactions have been previously reported for the synthesis of *N*-aryl and *N*-alkylbenzaldimines.[17] In addition to dihydro-4-pyridone **9**, (*Z*)-enaminone **10** was also isolated in 52% yield. The formation of **10** indicated that both 1-cyclopropyl-*N*-(4-methoxyphenyl) methanimine **7** and Danishefsky's diene **8** partially hydrolyzed under our experimental conditions, leading to benzaldehyde, 4-methoxyaniline **3i**, and (3*E*)-4-methoxybut-3-en-2-one. The latter further reacted with 4-methoxyaniline **3i** to generate the (*Z*)-enaminone **10** as previously reported.[18] As further proof of the partial hydrolysis of methanimine **7**, when the same reaction was performed using 4-methylbenzylamine **2a** as the amine substrate, which

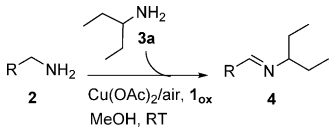
Table 2. $Cu(OAc)_2/\mathbf{1}_{ox}$-catalyzed aerobic oxidative cross-coupling of 4-methylbenzylamine **2a** with a range of primary aliphatic and aromatic amines **3**.[a]

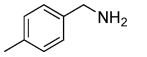
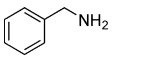
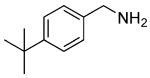
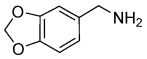
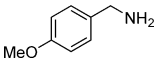
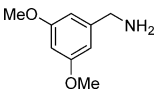
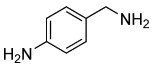
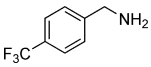
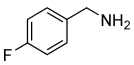
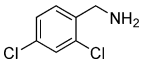
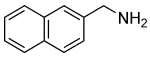
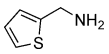
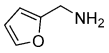


Entry	Alkylating Amine **3**	Imine Product **4**	Conversion [%]	Imine Selectivity **4**:**5**[b]	Yield [%][c]
1	**3a**	**4a**	100	100:0	97
2	**3b**	**4b**	100	100:0	97
3	**3c**	**4c**	100	100:0	96
4	**3d**	**4d**	100	100:0	95
5	**3e**	**4e**	100	95:5	90
6	**3f**	**4f**	100	96:4	90
7	**3g**	**4g**	100	100:0	90[d]
8	**3h**	**4h**	100	100:0	90[d]
9	**3i**	**4i**	95[e]	100:0	90[d]
10	**3j**	**4j**	90[e]	100:0	80[d]
11	**3k**	**4k**	60[e]	92:8	55[d]
12	**3l**	**4l**	100	93:7	90
13	**3m**	**4m**	100	100:0	95
14	**3n**	**4n**	100	94:6	85

[a] The reactions were carried out using equimolar amounts of amines **2a** and **3** on a 2.5 mmol scale, in the presence of 5 mol% of $\mathbf{1}_{red}$ (4 mol% + 1 mol% added after 6 h) and 0.4 mol% of $Cu(OAc)_2$, in 10 mL of methanol, at room temperature, under ambient air for 10 h. [b] Molar ratio based on the ^{1}H NMR spectrum of the crude product. [c] Yields of the cross-coupled imine refer to the isolated unpurified product, which, unless otherwise stated, was pure by ^{1}H NMR spectroscopy (see the Supporting Information). [d] Cross-coupled imine product directly precipitated from the bulk solution. [e] Conversion after 48 h, provided a second 2 mol% portion of *o*-aminophenol $\mathbf{1}_{red}$ was added after 24 h.

Table 3. $Cu(OAc)_2/\mathbf{1}_{ox}$-catalyzed aerobic oxidative cross-coupling of a range of primary amines **2** with 1-ethylpropylamine **3a**.[a]



Entry	Amine	Substrate **2**	Imine Product **4**	Conversion [%]	Yield [%][b]
1	**2a**		**4a**	100	97
2	**2b**		**4o**	100	96
3	**2c**		**4p**	100	97
4	**2d**		**4q**	100	94
5	**2e**		**4r**	100	95
6	**2f**		**4s**	100	92
7	**2g**		**4t**	95	75
8	**2h**		**4u**	100	94
9	**2i**		**4v**	100	92
10	**2j**		**4w**	100	96
11	**2k**		**4x**	100	94
12	**2l**		**4y**	100	94
13	**2m**		**4z**	100	95

[a] The reactions were carried out using equimolar amounts of amines **2** and **3a** on a 2.5 mmol scale, in the presence of 5 mol% of $\mathbf{1}_{red}$ (4 mol% + 1 mol% added after 6 h) and 0.4 mol% of $Cu(OAc)_2$, in 10 mL of methanol, at room temperature, under ambient air for 10 h. [b] Yields of the cross-coupled imine refer to the isolated unpurified product, which, unless otherwise stated, was pure by ^{1}H NMR spectroscopy (see the Supporting Information).

was oxidized to stable benzaldimine **4i**, dihydro-4-pyridone **11** was isolated in 80% yield at the exclusion of (*Z*)-enaminone byproduct **10** (Scheme 2).

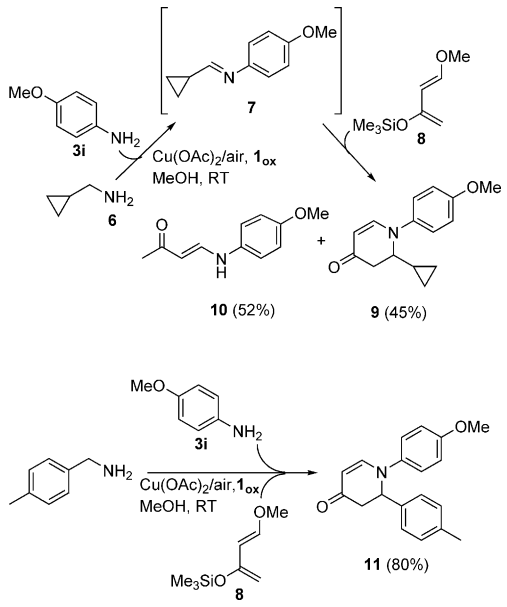
Mechanistic considerations

On the basis of our one previous example of the cross-coupling reaction, we had proposed that both homo- and cross-coupled products would be produced competitively through the ionic transamination mechanism described earlier.[16] Our present investigation into the substrate scope of the $Cu^{II}/\mathbf{1}_{ox}$-mediated cross-coupling of two primary amines led us to revise our original proposal to the one depicted in Scheme 3. Indeed, in almost all of the cases, the real-time monitoring of the cross-coupling reactions by ^{1}H NMR spectroscopy indicated that the homocoupled product was initially formed and accumulated at early stages of the reaction. After roughly 30 min, the homocoupled imine gradually converted into the cross-coupled product that finally became the exclusive product after ten hours. Of particular note, only the reaction of 4-methylbenzylamine **2a** with *n*-hexylamine **3e** (Table 2, entry 5) or aminomethylcyclohexane **3f** (Table 2, entry 6) revealed the simultaneous formation of homo- and cross-coupled products (**4e** or **4f**) from the outset of the reaction, but with a preference for the homocoupled product **5**. These observations indicated that the homocoupled product was first generated as the sole imine product through the transamination mechanism reported earlier.[14,16] The homocoupled product was further alkylated by the second primary amine $R'–NH_2$ through a transimination process[19] to give the cross-coupled product, the formation of which could be driven by continuous oxidation of the extruded primary amine $R–CH_2–NH_2$ (self-sorting step) as shown in Scheme 3. As a consequence, just one equivalent of each primary amine was sufficient to achieve exclusive formation of the cross-coupled imine product. This oxidative strategy, known as oxidative self-sorting, has previously been exploited to obtain thermodynamically disfavored products.[13b,20] We have further validated our mechanistic process by reacting the isolated homocoupled imine **5** with two equivalents of 1-ethylpropylamine **3a** under the standard conditions (Table 1, entry 5). Then, full conversion of the homocoupled imine **5** into the cross-coupled imine **4a** was observed after ten hours, providing support for the two-step mechanism.

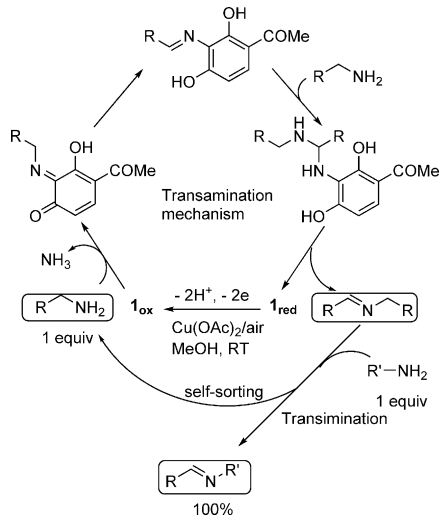
The synthesis of cross-coupled aliphatic imines was found to be troublesome because of their instability. The main problem associated with these imines is related to the formation of the tautomeric enamine form, which decomposed under ambient air.[21] Nevertheless, the fact that aliphatic imines can be engaged in situ for further reactions, leading to *N*-alkylpyridin-4-one derivatives, demonstrates that aliphatic amines are well oxidized to imines under our experimental conditions as previously reported.[16] Whereas transition-metal-catalyzed oxidations to dehydrogenate aliphatic amines to imines require vigorous reaction conditions, the synergistic action of our bioinspired homogeneous cooperative catalyst lowers the activation energy, enabling high reactivity that neither catalyst can accomplish alone.

Conclusion

New insights into the scope and mechanism of the bioinspired $Cu^{II}/\mathbf{1}_{ox}$-catalyzed aerobic oxidative cross-coupling of primary amines to imines have been delineated. Low loadings of biocompatible Cu^{II} metal-catalyst and topaquinone-like organocatalyst $\mathbf{1}_{ox}$ were sufficient to activate the α-C–H bond of various primary amines, which were converted to cross-coupled imines



Scheme 2. Tandem oxidative aza Diels–Alder reaction for the synthesis of dihydro-4-pyridones.



Scheme 3. Proposed overall two-step mechanism for the $Cu(OAc)_2/\mathbf{1}_{ox}$-mediated cross-coupling of primary amines.

through a transamination process, which leads to the homo-coupled imine intermediate, followed by dynamic transimination. This atom-economical process, which proceeds at room temperature, under ambient air, with equimolar amounts of each coupling partner, and tolerates diverse functional groups, generates with unprecedented selectivity cross-coupled imines, which have been previously shown to have broad use in organic synthesis. The mild reaction conditions used in this work should be particularly favorable for using unstable alkyl-imines in situ for further reactions.

Experimental Section

General considerations

^{1}H NMR and 1D proton decoupled ^{13}C NMR spectra were recorded in $CDCl_3$ on a Brucker AC-300 spectrometer operating at 300 MHz and 75 MHz, respectively. Chemical shifts, δ, are given in ppm relative to TMS and coupling constants, J, in Hz. The measurements were carried out using the standard pulse-sequences. The carbon type (methyl, methylene, methine, or quaternary) was determined by DEPT experiments. Mass spectra were recorded on a ZQ 2000 Waters spectrometer, equipped with the positive electrospray mode (ES+). Chemicals were commercial products of the highest available purity and were used as supplied. Reduced catalyst $\mathbf{1}_{red}$ was synthesized in two steps from commercially available 2-nitro-resorcinol.[22]

Representative experimental procedure for $Cu^{II}/\mathbf{1}_{ox}$-catalyzed aerobic oxidative cross-coupling of two primary amines

Equimolar amounts of 4-methylbenzylamine **2a** (2.5 mmol) and 1-ethylpropylamine **3a** (2.5 mmol), reduced organocatalyst $\mathbf{1}_{red}$ (0.1 mmol, 4 mol%), and copper (II) acetate (0.01 mmol, 0.4 mol%) were mixed in methanol (10 mL) in an air atmosphere. The reaction mixture was stirred at room temperature (25 °C) for six hours. Then, an additional aliquot of $\mathbf{1}_{red}$ (0.025 mmol, 1 mol%) was introduced into the reaction mixture and the reaction was stirred for roughly four hours. The progress of the reaction was monitored by ^{1}H NMR spectroscopy. After completion of the reaction, the solvent was evaporated at room temperature to give the cross-coupled imine product **4a** (97%) as an almost pure product as confirmed by ^{1}H and ^{13}C NMR spectroscopy (see the Supporting Information).

Imine 4a: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.88$ (t, $J = 8$ Hz, 6H, $2\times CH_3$), 1.70 (m, 4H, $2\times CH_2$), 2.43 (s, 3H, CH_3), 2.91 (m, 1H, CH), 7.25 (d, $J = 7$ Hz, 1H, $2\times$CH, Ar), 7.68 (d, $J = 7$ Hz, 1H, $2\times$CH, Ar), 8.24 ppm (s, 1H, CH=N); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 11.1$ ($2\times CH_3$), 21.5 (CH_3), 28.9 ($2\times CH_2$), 75.2 (CH), 128.1 ($2\times$CH, Ar), 129.3 ($2\times$CH, Ar), 133.8 (Cq), 140.5 (Cq), 159.4 ppm (*C*H=N); MS (ES+): $m/z = 190$ [MH^+].

The above procedure is generally representative for all the products shown in Tables 2 and 3. Any deviations from this protocol are specified in the footnotes of the tables.

Representative procedure for $Cu^{II}/\mathbf{1}_{ox}$-catalyzed aerobic oxidative synthesis of dihydro-4-pyridones derivatives

1-Cyclopropyl-*N*-(4-methoxyphenyl)methanimine **7** was prepared in situ by mixing equimolar amounts of aminomethylcyclopropane **6** (1.25 mmol) and 4-methoxyaniline **3i** (1.25 mmol), reduced organocatalyst $\mathbf{1}_{red}$ (0.05 mmol, 4 mol%), and copper(II) acetate (0.005 mmol, 0.4 mol%) in methanol (5 mL) under ambient conditions for six hours. Then, an additional aliquot of $\mathbf{1}_{red}$ (0.0125 mmol, 1 mol%) was introduced into the reaction mixture and the reaction was stirred for four hours. After roughly 60% of aminomethylcyclopropane **6** had been converted into the cross-coupled imine product **7** (see the NMR spectrum in the Supporting Information), 2 mL of the resulting solution (which corresponds to roughly 0.3 mmol of **7**) was removed and Danishefsky's diene **8** (0.6 mmol, 2 equiv) was added dropwise to it over 30 min. After stirring for 1 h at room temperature (25 °C), another equivalent of Danishefsky's diene **8** (0.3 mmol) was added dropwise over 15 min to the reaction mixture, which was stirred for 2 h at room temperature. The reaction mixture was then quenched with HCl (2 mL, 1.0 M). The product was extracted with diethyl ether and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography with dichloromethane/

ethyl acetate (4:1 v/v) as the eluent, leading to dihydro-4-pyridone **9** (45%) together with (*Z*)-enaminone **10** (52%).

Dihydro-4-pyridone 9: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.00 (m, 2H, CH_2), 0.40 (m, 2H, CH_2), 1.37 (m, 1H, CH), 2.62 (dd, J = 16 Hz, J = 4 Hz, 1H, CH), 2.98 (dd, J = 16 Hz, J = 6.7 Hz, 1H, CH), 3.24 (m, 1H, CH), 3.85 (s, 3H, CH_3), 5.16 (d, J = 7.6 Hz, 1H, CH), 6.93 (d, J = 8.9 Hz, 2H, 2×CH, Ar), 7.16 (d, J = 8.9 Hz, 2H, 2×CH, Ar), 7.27 ppm (d, J = 7.6 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.7 (CH_2), 5.6 (CH_2), 12.1 (CH), 41.6 (CH_2), 55.5 (CH_3), 65.4 (CH), 99.6 (*C*H=), 114.6 (2×CH, Ar), 125.2 (2×CH, Ar), 138.6 (Cq), 150.7 (*C*H=), 157.8 (Cq), 191.5 ppm (Cq, *C*=O); MS (ES+): m/z = 244 [MH$^+$]; elemental analysis calcd (%) for $C_{15}H_{17}NO_2$: C 74.07, H 6.99, N 5.76; found C 73.96, H 7.10, N 5.74.

(*Z*)-enaminone 10: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.18 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 5.30 (d, J = 7.6 Hz, 1H, CH), 6.93 (d, J = 9.0 Hz, 2H, 2×CH, Ar), 7.16 (d, J = 9.0 Hz, 2H, 2×CH, Ar), 7.20 (m, 1H, CH), 11.65 ppm (broad d, 1H, NH, D_2O exchanged); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 29.4 (CH_3), 55.6 (CH_3), 96.6 (*C*H=), 114.9 (2×CH, Ar), 117.7 (2×CH, Ar), 134.0 (Cq), 144.1 (*C*H=), 156.1 (Cq), 198.4 ppm (Cq, *C*=O). ^{1}H and ^{13}C NMR spectral data are in agreement with those previously reported in the literature.[23]

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Keywords: cross-coupling · cycloaddition · homogeneous catalysis · oxidation · primary amines

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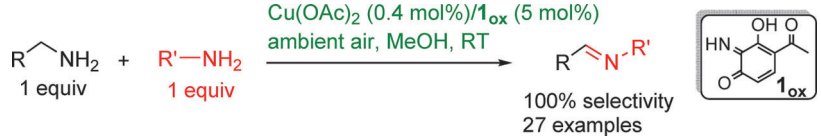

Synergistic action: The cooperative copper salt and topaquinone-like catalysts lower the activation energy, enabling high reactivity toward the chemoselective oxidative cross-coupling of primary amines to imines that neither catalyst can accomplish alone.

Homogeneous Catalysis

M. Largeron, M.-B. Fleury*

■■ – ■■

A Metalloenzyme-Like Catalytic System for the Chemoselective Oxidative Cross-Coupling of Primary Amines to Imines under Ambient Conditions