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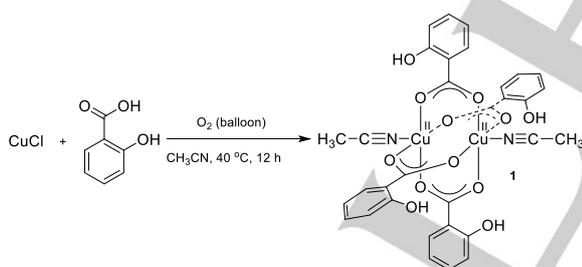
Binuclear Copper Complex Catalysed Reactions: Relay Aerobic Oxidation of *N*-Aryltetrahydroisoquinolines to Dihydroisoquinolones with a VB1 Analogue

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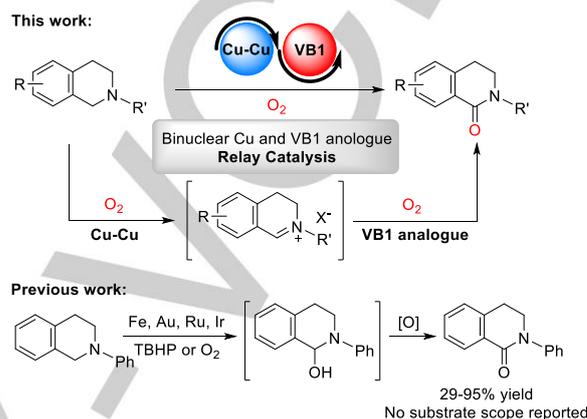
Abstract: *N*-aryltetrahydroisoquinolines were oxidised to dihydroisoquinolones through the relay catalysis of a binuclear paddle-wheel copper complex and a vitamin B1 analogue with oxygen as oxidant. Mechanistic studies revealed that the copper catalyst oxidises amines to the corresponding iminium salts, which were then oxygenated to lactam products by the catalysis of the vitamin B1 analogue.

Introduction

The paddle-wheel type Cu(II)-carboxylate dimers are well-known binuclear copper complexes.^[1] Although they have been extensively studied as superoxide dismutase mimetics in bioinorganic and medicinal chemistry,^[1a, 2] their potential as catalysts for organic synthesis has rarely been explored thus far.^[3] Traditional methods of reacting Cu(II) salts with carboxylic acids may lead to copper complexes of various structures depending on the synthetic conditions. However, the binuclear Cu(II)-salicylate complex **1** can be prepared easily and reproducibly by reacting CuCl with cheap salicylic acid under oxygen (Scheme 1). In the previous study,^[4] we have shown that **1** is a powerful catalyst for the oxidative coupling of *N*-aryltetrahydroisoquinolines with various nucleophiles. Herein, we disclose that **1** forms a novel relay catalytic system with a



Scheme 1. Synthesis of binuclear copper complex Cu(Sal)₂(NCMe)₂ **1**.



Scheme 2. Oxidation of *N*-aryltetrahydroisoquinolines to dihydroisoquinolones

vitamin B1 analogue that allows for the oxidation of *N*-aryltetrahydroisoquinolines to lactams via iminium intermediates with oxygen (1 bar) as oxidant under mild conditions (Scheme 2)

Relay or cooperative catalysis has been actively pursued by chemists, offering the potential of more environmental friendly processes and novel activity and selectivity patterns than single catalytic systems. Great progress has been made in this area in recent years.^[5] For example, relay catalysis has been applied to the selective transformation of amines, where the amine substrates are catalytically oxidised to iminium salts often with stoichiometric organic oxidants, followed by organocatalytic nucleophilic addition.^[6] We envisioned that in the absence of a nucleophile the iminium salts generated via the catalysis of **1**^[4] might be trapped by oxygen with a suitable catalyst to form amides or lactams, an important class of organic compounds.

The direct α -oxidation of amines to lactams is an appealing transformation but examples are rare.^[7] Dihydroisoquinolones and their derivatives are important examples of lactams, which exist as core structures in many natural and biologically active compounds.^[8] Traditional methods for the synthesis of dihydroisoquinolones generally rely on multiple-step synthesis.^[8c] The direct oxidation of tetrahydroisoquinolines to lactams is one of the most direct ways for accessing these compounds. The formation of dihydroisoquinolone from *N*-phenyltetrahydroisoquinoline in cross-dehydrogenative-coupling (CDC) reactions^[10] has been observed sporadically, often as a byproduct.^[11] However, neither the substrate scope nor the reaction mechanism of these oxidation processes has ever been reported. A hemiaminal was believed to be the intermediate for the lactam product (Scheme 2).^[11e]

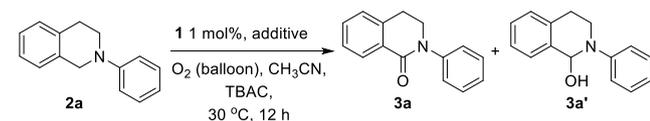
Results and Discussion

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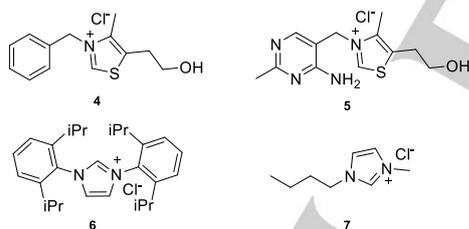
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1. Relay oxidation of amines to lactams

Complex **1** was tested for the oxidation of *N*-phenyltetrahydroisoquinoline (**2a**), aiming for the lactam product **3a** (Scheme 3). Initially, a hemiaminal product **3a'** was formed exclusively when **2a** was subjected to the aerobic catalysis of **1** in CH₃CN for 12 h (Scheme 3, entry 1). Interestingly, with the addition of 2 mol% of *n*-tetrabutyl ammonium chloride (TBAC), a higher yield of **3a'** was detected, accompanied with a trace amount of the amide product **3a** (Scheme 3, entry 2). This is in line with the accelerating effect of chloride anion on the oxidation of **2a** noted before.^[4] Much to our surprise, when a catalytic amount of a thiazolium salt **4**,^[12] a vitamin B1 (VB1) analogue, was introduced, the yield of **3a** was boosted remarkably (Scheme 3, entries 3-4). VB1 (**5**) could also promote the formation of **3a**, albeit with a much lower activity (Scheme 3, entry 5). In this case, the majority of **2a** remained unreacted and no **3a'** was observed, possibly because of the amino group in VB1 deactivating **1**. Although **4** may function via carbene formation as in the case of organocatalysis (vide infra), the commonly-used carbene catalyst precursors, such as **6** and **7**, did not promote the formation of **3a** (Scheme 3, entries 6-7).



Entry	TBAC (mol%)	Additive (mol%)	Yield (%)	Yield (%)
1	-	-	0	64
2	2	-	5	91
3	2	4 (2)	50	45
4	2	4 (20)	92	0
5	2	5 (20)	10	0
6	2	6 (20)	5	89
7	2	7 (20)	6	90

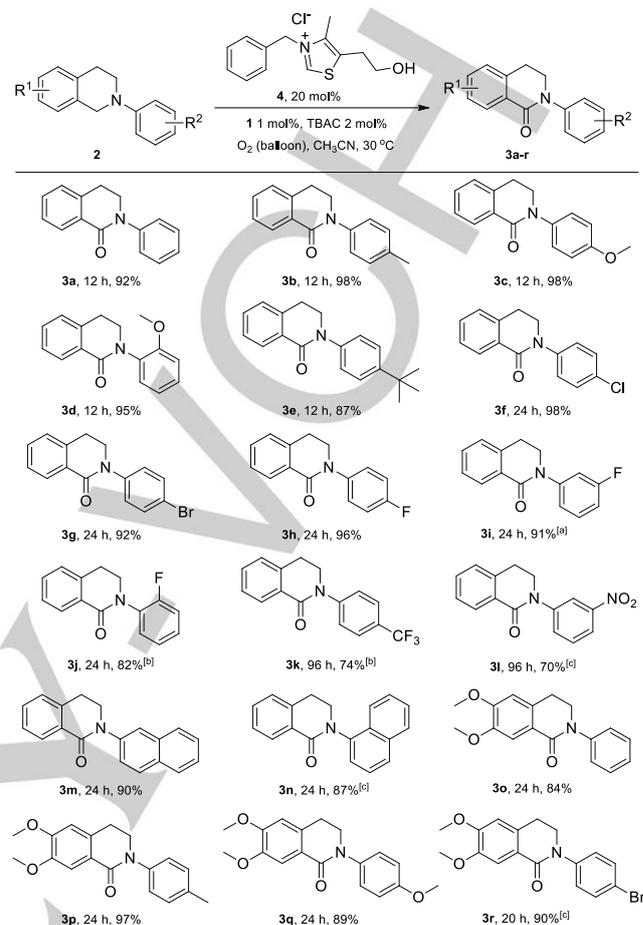


Scheme 3. Catalytic oxidation of *N*-phenyltetrahydroisoquinoline (See the SI for experimental details).

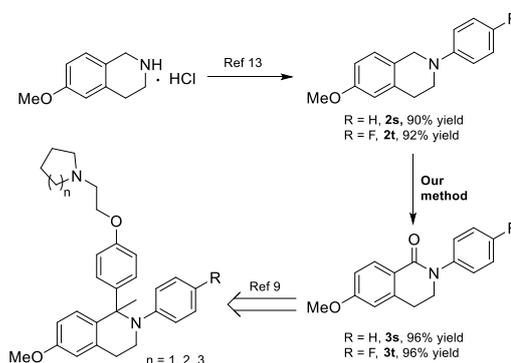
Having found the effect of this 1/4 binary catalyst, the substrate scope for the oxidation of **2** to amides was next examined and the results are shown in Scheme 4. Both electron donating and electron withdrawing groups on the *N*-phenyl ring could be tolerated (**3a-l**). In general, electron donating substituents brought about a higher activity than electron withdrawing ones (e.g. **3b-3c** vs **3h** and **3k**). The sterically bulky naphthyl substrate reacted efficiently (**3m**), so did 6,7-dimethoxyl *N*-aryltetrahydroisoquinolines (**3o-r**); but the sterically more demanding substrate **3n** was less reactive, necessitating a higher catalyst loading and higher reaction temperature, probably due to difficulty in coordinating to the catalyst.

To demonstrate the potential application of the chemistry, the tetrahydroisoquinolines **2s** and **2t** were oxidized under the relay catalysis of **1** and **4**, furnishing the lactams **3s** and **3t** in excellent

isolated yield, which could be turned into the potent estrogen receptor modulators using established methods (Scheme 5).^[9, 13]



Scheme 4. Cu-catalysed aerobic oxidation of *N*-aryltetrahydroisoquinolines. See the SI for experimental details. Isolated yield. [a] 5 mol% **1**, 10 mol% TBAC. [b] 10 mol% **1**, 20 mol% TBAC, 60 °C. [c] 5 mol% **1**, 10 mol% TBAC, 60 °C.

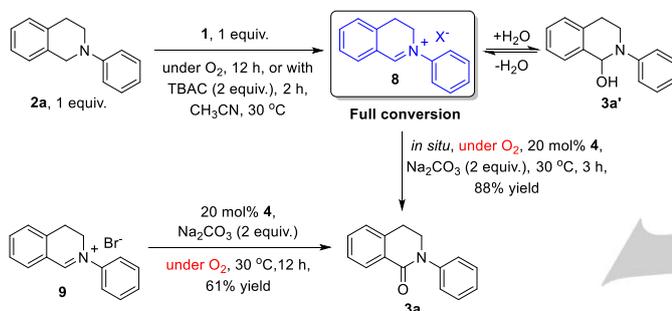


Scheme 5. Potential application of 1/4 catalysed aerobic oxidation.

2. Mechanistic observations

Mechanistic studies were carried out to probe how the amines were oxidized to amides. In the catalytic reaction, **2a** was converted to **3a** under the joint catalysis of **1/4**. As presented before,^[4] on stirring an equal amount of **2a** and **1** under O₂, an

iminium salt **8** was observed (Scheme 6).^[14] The ¹H NMR spectrum of **8** is broad, which indicates that the anion in **8** ion-pairs with the cation and is paramagnetic, differing from that observed in the CDC reactions reported by Klussmann and co-workers.^[14b] However, the structure of the anion remains unclear (denoted as X⁻), and efforts to grow single crystals of **8** have failed so far.^[4] Treating the *in situ* formed **8** with catalytic amount of **4** and Na₂CO₃ (2 equiv.) under 1 bar of O₂ afforded the amide **3a** in 88% yield in 3 h. However, this latter reaction could not take place under Ar or without **4**, and in both cases, the hemiaminal intermediate **3a'** was observed.^[14b, 15] The base, Na₂CO₃, is also essential for a high yield of **3a** under this condition. In its absence, only 46% of **3a** was observed in 12 h, along with 54% of **3a'**. These observations show that *the amide 3 is formed from 2 via the oxidation of the iminium intermediate, and it is the VB1 analogue that catalyses the oxygenation of the iminium cation, forming a relay catalyst with 1.*

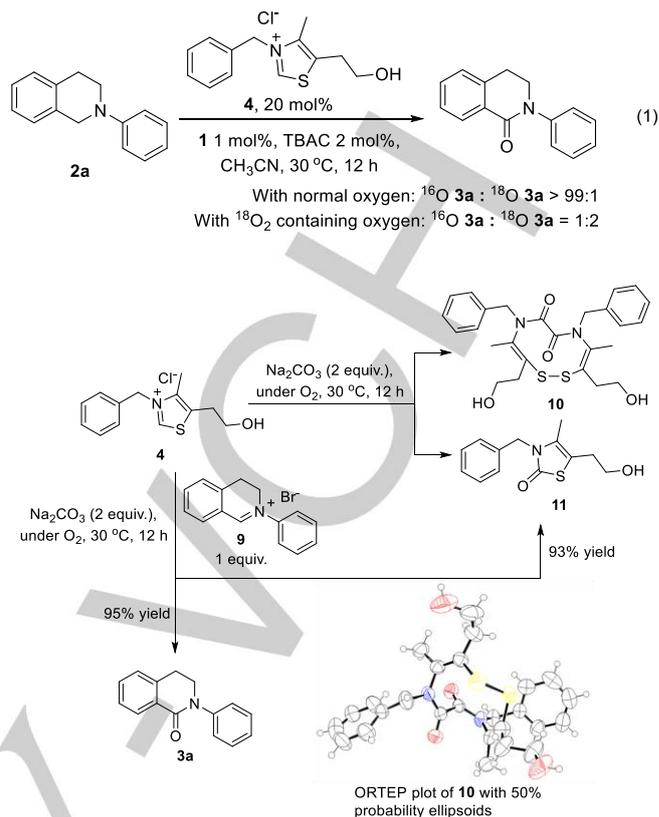


Scheme 6. Observation of iminium formation and transformation.

As noted, **3a'** was proposed to be an intermediate for amide formation.^[11e] However, it may only serve as a reservoir of the iminium salt^[14b, 15a] in our system. Indeed, **3a'** could be isolated and characterized and it is inter-convertible with the corresponding iminium salt **9**^[16] upon acid and base treatment (See SI for details). Further, **3a'** showed a similar reactivity to that of **8**. The formation of **3a'** is likely to be due to the reaction of **8** with residual water in the solvent. If **3a'** was an intermediate for **3a**, the oxygen of the amide product would come from H₂O rather than O₂. However, isotope labeling showed that the oxygen atom in the amide originates from O₂, which supports **8** rather than **3a'** as the intermediate for the product **3a**. Thus, in the oxygenation of **2a** catalysed by **1/4** with normal oxygen gas, the product formed constitutes almost exclusively ¹⁶O-containing **3a**. However, with oxygen gas containing ¹⁸O₂, the major part of the product became ¹⁸O labeled (Eq 1, See SI for details).

To gain more evidence that **4** catalyses the oxygenation of **8**, the reactivity of iminium salt **9** was studied (Scheme 6). Stirring **9** with 20 mol% of **4** and 2 equivalents of Na₂CO₃ in CH₃CN (1 mL) under an O₂ atmosphere afforded **3a** in 61% yield in 12 h, thus showing **4** to be a catalyst for the iminium oxygenation. The slower rate in forming **3a** from **9** than **8** may stem from **9** existing as a contact ion pair in solution.^[14b]

Interestingly, replacing Na₂CO₃ with the substrate **2a** in the



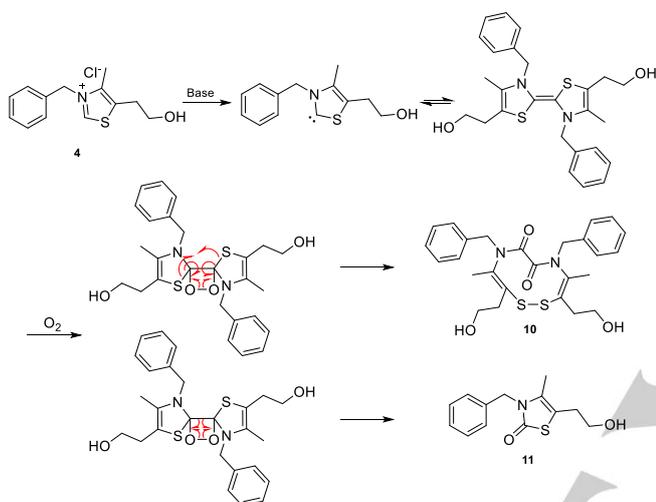
Scheme 7. Reaction of **4** with O₂ with or without **9**.

reaction of **9** afforded the amide product in a higher yield of 92% suggesting that **2a** could act as an effective base in the catalytic reactions (Scheme 4), in which no extra base was added.

To understand further this unprecedented thiazolium-catalysed conversion of iminium salts to amides, stoichiometric reactions were carried out (Scheme 7). When 1 equivalent of **4** was treated with 2 equivalents of Na₂CO₃ under an atmosphere of O₂ in MeCN, cyclodithiadiazecinedion **10** and thiazolinone **11** were isolated in 15 and 65% yield, respectively. The structure of **10** was confirmed by X-ray diffraction analysis. However, neither **10** nor **11** was catalytically active in the oxidation of iminium ions. In addition, they could not be inter-converted under the reaction conditions. Similar products were obtained by Morel et al when a thiazolium iodide was treated with KOH.^[17] Under such conditions, the thiazolium was believed to be converted into a carbene, which dimerizes, affording a filvalene that reacts with O₂ to give the disulfide heterocycle and thiazolinone.

The formation of carbenes from thiazolium salts and their dimerization into ethylenic species and reactions with electrophiles have long been known^[18] since Breslow's seminal work^[19] and studied in the context of thiamine or VB1 catalysis.^[20] In the current case, **10** and **11** could be generated via the pathways shown in Scheme 8. Carbene dimers and the related Breslow intermediates are known to react with O₂, forming reactive dioxentane species that readily decompose to oxygenation products.^[12, 17-18] However, attempts to detect and isolate the thiazolyl carbene were not successful. Treating **4** with Na₂CO₃ under Ar in CH₃CN led to a complex mixture, as revealed by ¹H NMR. This may be a result of carbene dimerization followed by rearrangements.^[18a]

Insightfully, when the above reaction was conducted in the presence of 1 equivalent of **9**, the expected amide **3a** was obtained in 95% yield, alongside **11** in 93% yield. Na_2CO_3 was found indispensable for all these reactions that afford **10**, **11** and **3a** (Scheme 7). Without it, no reaction was noted. These observations support the hypothesis that **4** is deprotonated in the oxygenation, affording a carbene intermediate that attacks the iminium cation and triggers the reaction with O_2 . Although *N*-heterocyclic carbenes (NHCs), generated from imidazolium or thiazolium salts, have been shown to catalyse oxidative coupling reactions with oxidants generally stronger than O_2 ,^[12] *there appears to be no example of oxidation of imines or iminium ions to an amide by such carbene catalysts.*

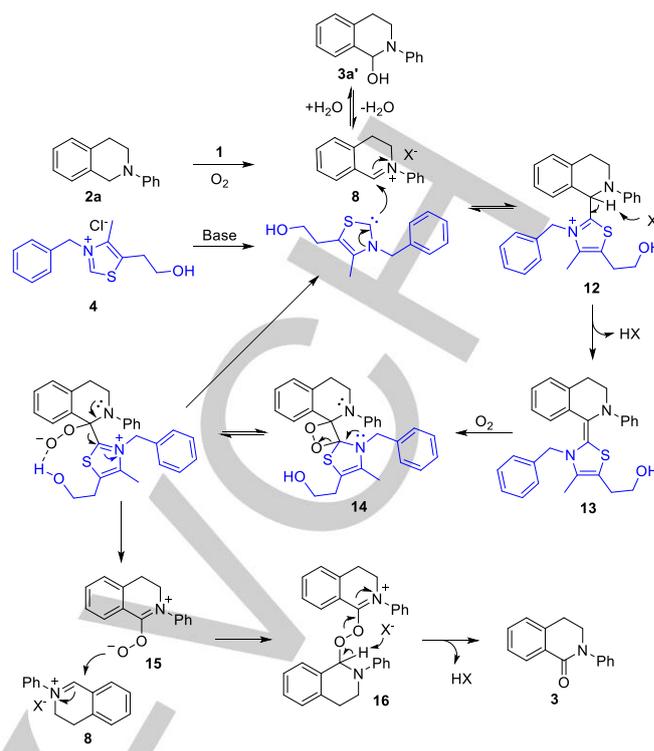


Scheme 8. Possible pathways for the formation of **10** and **11** from **4**.

3. Suggested mechanism for the relay oxidation

Based on the evidence above and literature (*vide infra*), a mechanistic scenario for the relay catalysis of **1/4** is presented in Scheme 9. In the presence of O_2 , **1** converts **2a** to **8**.^[4] Under the catalytic conditions, **4** is deprotonated by **2a** to a carbene intermediate, which attacks the iminium cation of **8** to generate **12**. Deprotonation of this leads to the electron-rich ethylenic Breslow-type intermediate^[19] **13**, which could react with O_2 to form the dioxentane **14** and an equilibrating peroxide. The latter may readily decompose into the carbene catalyst and the peroxide **15**, which then attacks another iminium cation, forming the peroxo dimer **16**, decomposition of which leads to the lactam product.

The striking difference in the catalytic activity between **4** and **6** or **7** may be due to the hydroxyl group in **4**, which could stabilize the peroxide anion via hydrogen bonding and thus promote the oxidation of **13** by O_2 .^[21] Whilst evidence for the formation of the intermediates **12-16** is lacking in this study, literature examples of carbene nucleophilic addition, formation of enamine compounds and their reaction with O_2 to form oxygenation products are well known.^[12] In particular, species similar to **13** have been shown to form and react with O_2 in bioprocesses, such as the Krebs cycle.^[22]



Scheme 9. Proposed mechanism for the relay catalysis of **1-4** (The nature of X^- is not defined; for a suggestion, see reference 4. However, the deprotonation could be effected with any base present in the system).

Conclusions

This paper discloses a mild and efficient method for the oxidation of *N*-aryltetrahydroisoquinolines to dihydroisoquinolones, which is enabled by the relay catalysis of a binuclear Cu catalyst and a VB1 analogue. Mechanistic studies revealed that the Cu catalyst converts the amine to an iminium intermediate, which is then oxygenated by the catalysis of the VB1 analogue. The oxygenation of iminium salts to amides catalysed by NHCs appears unprecedented in the literature.

Experimental Section

General procedure for the oxygenation of **2**: In a Schlenk tube equipped with a magnetic stir bar, **2** (0.25 mmol), **1** (0.0025 mmol, 3 mg), TBAC (0.005 mmol, 2.8 mg), and **4** (0.05 mmol, 13.4 mg) were added. MeCN (1.0 mL) was then introduced with a syringe. The reaction tube was degassed with oxygen gas (3 times), and kept under an oxygen atmosphere by using a balloon. After stirring at 30 °C or 60 °C for the time indicated, the reaction mixture was diluted with water, and then extracted with DCM (3 x 15 mL). The organic layers were combined, washed with brine, and dried over Na_2SO_4 . The solvent was removed via rotary evaporation and the crude product purified by column chromatography on silica gel using ethyl acetate/petroleum ether to afford the desired product.

Acknowledgements

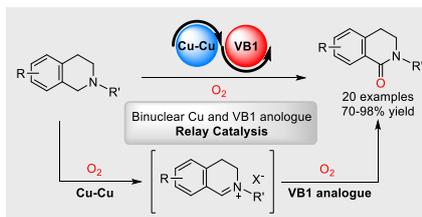
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Keywords: oxidation • relay catalysis • copper • amide • binuclear metal complex

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COMMUNICATION

A novel relay catalytic system consisting of a binuclear copper and a vitamin B1 analogue is disclosed, which allows for the aerobic oxidation of *N*-aryltetrahydroisoquinolines to dihydroisoquinolones under mild conditions.



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Binuclear Copper Complex Catalysed Reactions: Relay Aerobic Oxidation of *N*-Aryltetrahydroisoquinolines to Dihydroisoquinolones with a VB1 Analogue

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