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Oxidation

Reactions Catalysed by a Binuclear Copper Complex: Relay Aerobic Oxidation of *N*-Aryl Tetrahydroisoquinolines to Dihydroisoquinolones with a Vitamin B1 Analogue

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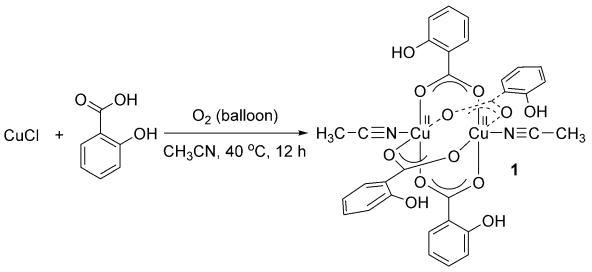
Abstract: *N*-Aryl tetrahydroisoquinolines were oxidised to dihydroisoquinolones through the relay catalysis of a binuclear paddle-wheel copper complex and a vitamin B1 analogue with oxygen as oxidant. Mechanistic studies revealed that the copper catalyst oxidises amines to the corresponding iminium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

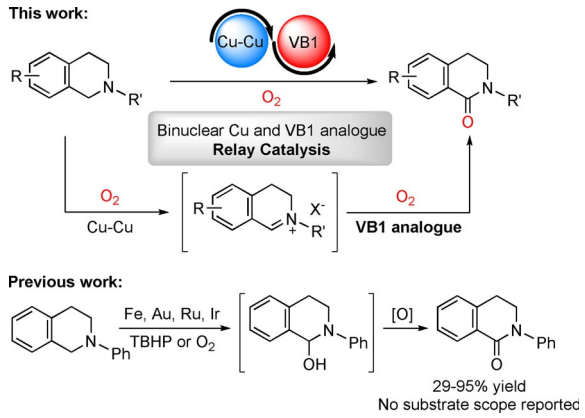
Introduction

Paddle-wheel 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 in which Cu^{II} salts react 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 treating CuCl with cheap salicylic acid under oxygen (Scheme 1). Previously, we have shown that **1** is a powerful catalyst for the oxidative coupling of *N*-aryl tetrahydroisoquinolines with various nucleophiles.[4] Herein, we disclose that **1** forms a novel relay catalytic system with a vitamin B1 analogue that allows for the oxidation of *N*-aryl tetrahydroisoquinolines to lactams via iminium intermediates with oxygen (1 bar) as oxidant under mild conditions (Scheme 2).

Relay or cooperative catalysis offers the potential for more environmentally friendly processes and novel activity and selectivity patterns compared to single-catalyst 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, whereby 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 by 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.



Scheme 1. Synthesis of binuclear copper complex [{Cu(Sal)$_2$(NCMe)}$_2$] (**1**).



Scheme 2. Oxidation of *N*-aryl tetrahydroisoquinolines to dihydroisoquinolones.

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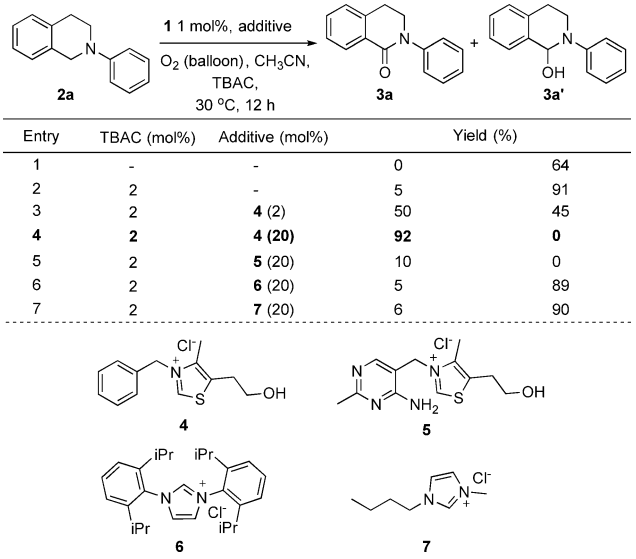
The direct α oxidation of amines to lactams is an appealing transformation, but examples are rare.[7] Dihydroisoquinolones and their derivatives are important examples of lactams, which exist as core structures in many natural and biologically active compounds.[8] Traditional methods for the synthesis of dihydroisoquinolones generally rely on multiple-step synthesis.[8c,9] 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

Relay oxidation of amines to lactams

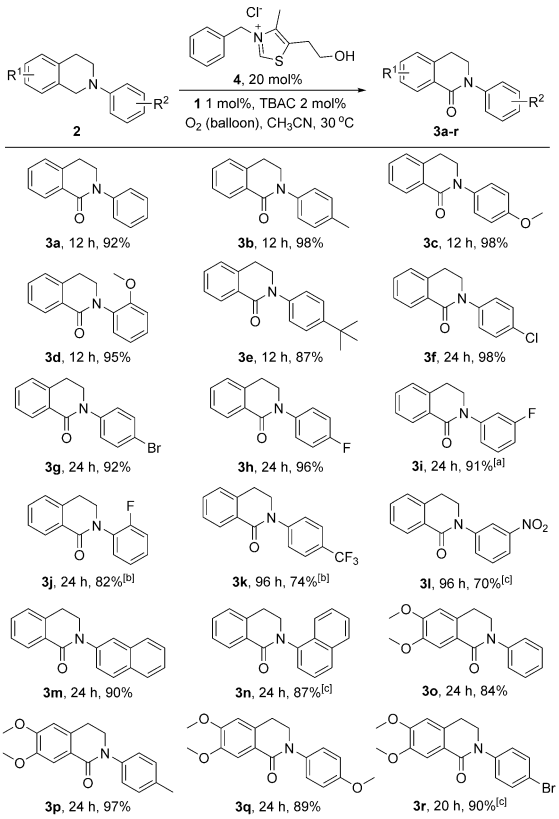
Complex **1** was tested for the oxidation of *N*-phenyltetrahydroisoquinoline (**2a**) to the target lactam product **3a** (Scheme 3). Initially, hemiaminal product **3a′** was formed exclusively when **2a** was subjected to the aerobic catalysis of **1** in CH_3CN for 12 h (Scheme 3, entry 1). Interestingly, with the addition of 2 mol% of *n*-tetrabutylammonium chloride (TBAC), a higher yield of **3a′** was detected, accompanied by 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] Surprisingly, when a catalytic amount of thiazolium salt **4**,[12] a vitamin B1 (VB1) analogue, was introduced, the yield of **3a** was boosted remarkably (Scheme 3, entries 3 and 4). VB1 **5** could also promote the formation of **3a**, albeit with much lower activity (Scheme 3, entry 5). In this case, the majority of **2a** did not react and no **3a′** was observed, possibly because of the amino group in VB1 deactivating **1**. Although **4** may function by carbene formation, as in the case of organocatalysis (see below), commonly used carbene catalyst precursors such as **6** and **7** did not promote the formation of **3a** (Scheme 3, entries 6 and 7).



Entry	TBAC (mol%)	Additive (mol%)	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

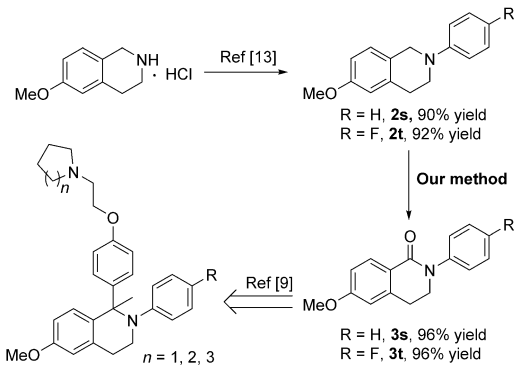
Scheme 3. Catalytic oxidation of *N*-phenyltetrahydroisoquinoline (see the Supporting Information for experimental details).

The substrate scope for the oxidation of **2** to amides with the **1**/**4** binary catalyst was next examined (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 higher activity than electron-withdrawing ones (e.g., **3b** and **3c** versus **3h** and **3k**). The sterically bulky naphthyl substrate reacted efficiently (**3m**), and so did 6,7-dimethoxyl *N*-aryl tetrahydroisoquinolines (**3o**–**r**), but the sterically more demanding substrate **3n** was less reactive and required a higher catalyst loading and higher reaction temperature, probably due to difficulty in coordinating to the catalyst.



Scheme 4. Cu-catalysed aerobic oxidation of *N*-aryl tetrahydroisoquinolines. See the Supporting Information for experimental details. Yields of isolated products. [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.

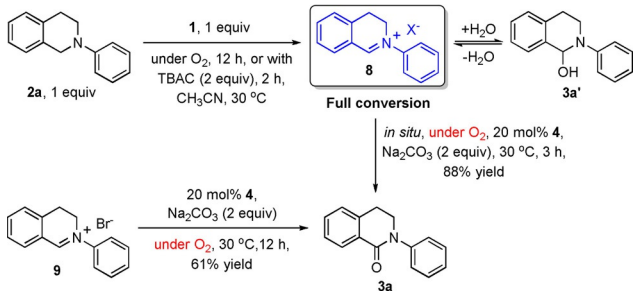
To demonstrate the potential application of the reaction, tetrahydroisoquinolines **2s** and **2t** were oxidized under the relay catalysis of **1**/**4** to furnish lactams **3s** and **3t** in excellent yield, which could be transformed into potent oestrogen receptor modulators by established methods (Scheme 5).[9,13]



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

Mechanistic observations

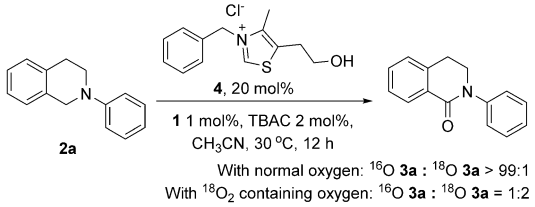
Mechanistic studies were carried out to probe how the amines were oxidised to amides. In the catalytic reaction, **2a** was converted to **3a** under the joint catalysis of **1**/**4**. As presented before,[4] on stirring an equal amount of **2a** and **1** under O_2, iminium salt **8** was observed (Scheme 6).[14] The broad ^{1}H NMR



Scheme 6. Observation of iminium formation and transformation.

spectrum of **8** indicates that the anion in **8** forms an ion pairs with the cation and is paramagnetic, in contrast to that observed in the CDC reactions reported by Klussmann and coworkers.[14b] However, the structure of the anion remains unclear (denoted X^-), and efforts to grow single crystals of **8** have failed so far.[4] Treating the in-situ-formed **8** with a catalytic amount of **4** and Na_2CO_3 (2 equiv) under 1 bar of O_2 afforded amide **3a** in 88% yield in 3 h. However, this reaction could not take place under Ar or without **4**, and in both cases the hemiaminal intermediate **3a′** was observed.[14b,15] The base, Na_2CO_3, is also essential for a high yield of **3a** under these conditions. In its absence, only 46% of **3a** was observed in 12 h, along with 54% of **3a′**. These observations show that amide **3** is formed from **2** by oxidation of the iminium intermediate, and it is the VB1 analogue that catalyses the oxygenation of the iminium cation, by forming a relay catalyst with **1**.

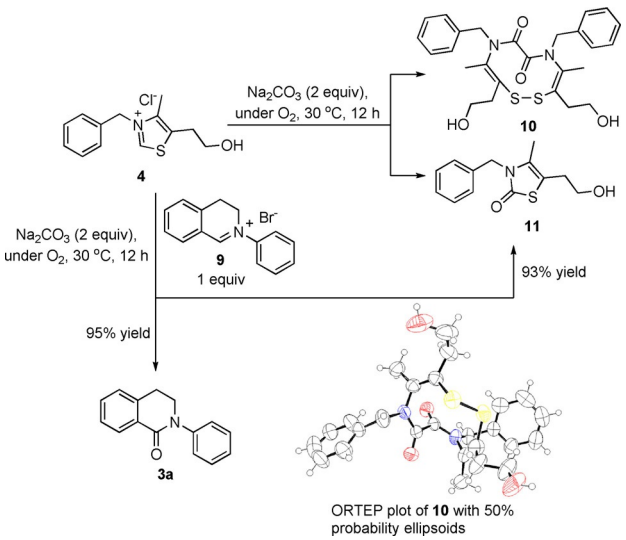
Compound **3a′** was proposed to be an intermediate for amide formation.[11e] However, it may only serve as a reservoir of the iminium salt[14b,15a] in our system. Indeed, **3a′** could be isolated and characterized, and it is interconvertible with the corresponding iminium salt **9**[16] upon acid and base treatment (see Supporting Information for details). Further, **3a′** showed a similar reactivity to **8**. The formation of **3a′** is likely to be due to the reaction of **8** with residual water in the solvent. If **3a′** were an intermediate for **3a**, the oxygen of the amide product would come from H_2O rather than O_2. However, isotopic labelling showed that the oxygen atom in the amide originates from O_2, 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 is almost exclusively ^{16}O-containing **3a**. However, with oxygen gas containing $^{18}O_2$, the major part of the product became ^{18}O-labeled [Eq. (1); see Supporting Information for details):.



(1)

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 equiv of Na_2CO_3 in CH_3CN (1 mL) under an O_2 atmosphere afforded **3a** in 61% yield in 12 h, and thus **4** was shown to be a catalyst for the iminium oxygenation. The slower rate of formation of **3a** from **9** compared to **8** may stem from **9** existing as a contact ion pair in solution.[14b] Interestingly, replacing Na_2CO_3 with substrate **2a** in the reaction of **9** afforded the amide product in a higher yield of 92%, which suggests that **2a** could act as an effective base in the catalytic reactions in which no extra base was added (Scheme 4).

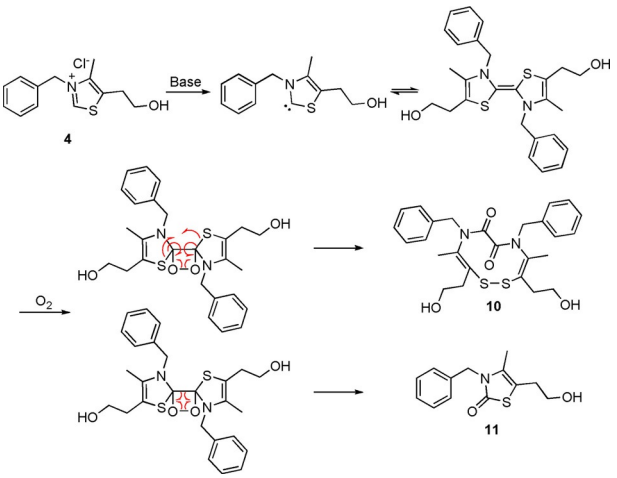
To understand further this unprecedented thiazolium-catalysed conversion of iminium salts to amides, stoichiometric reactions were carried out (Scheme 7). When 1 equiv of **4** was



Scheme 7. Reaction of **4** with O_2 with or without **9**.

treated with 2 equiv of Na_2CO_3 under an atmosphere of O_2 in MeCN, cyclcodithiadiazecinedione **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 interconverted 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 compound was believed to be converted to a carbene, which dimerizes to afford a fulvalene, which reacts with O_2 to give the disulfide heterocycle and thiazolinone.

The formation of carbenes from thiazolium salts and their dimerization to 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



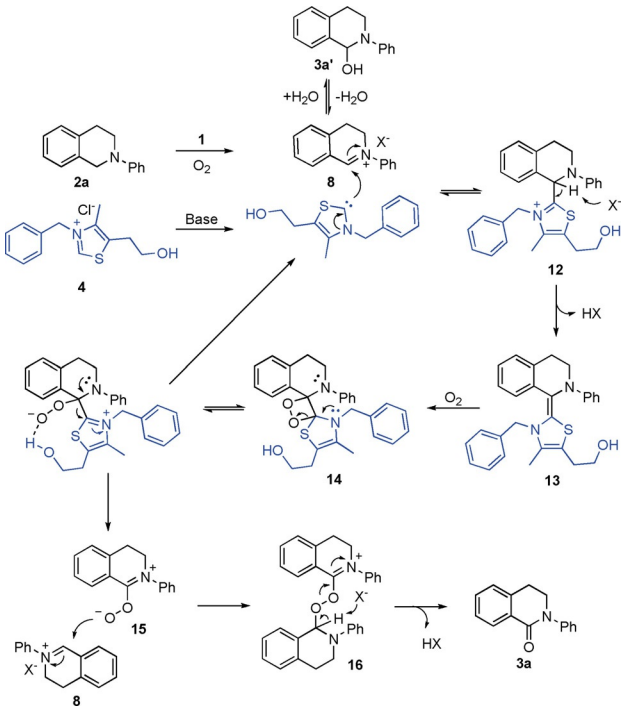
Scheme 8. Possible pathways for the formation of **10** and **11** from **4**.

intermediates are known to react with O_2, forming reactive dioxetane 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 Na_2CO_3 under Ar in CH_3CN led to a complex mixture, as revealed by ^1H NMR spectroscopy. This may be a result of carbene dimerization followed by rearrangements.[18a]

When the above reaction was conducted in the presence of 1 equiv of **9**, the expected amide **3a** was obtained in 95% yield, alongside **11** in 93% yield. Na_2CO_3 was found to be 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.

Suggested mechanism for the relay oxidation

On the basis of the evidence above and the literature (see below), 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



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

8.[4] Under the catalytic conditions, **4** is deprotonated by **2a** to give 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 dioxetane **14** and an equilibrating peroxide. The latter may readily decompose into the carbene catalyst and 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 catalytic activity between **4** and **6** or **7** may be due to the hydroxyl group in **4**, which could stabilize the peroxide anion through hydrogen bonding and thus promote the oxidation of **13** by O_2.[21] Whilst evidence for the formation of 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]

Conclusion

We have disclosed a mild and efficient method for the oxidation of *N*-aryl tetrahydroisoquinolines 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 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**: To 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 flushed with oxygen gas (3×) 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 dichloromethane (3× 15 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the crude product purified by column chromatography on silica gel with ethyl acetate/petroleum ether to afford the desired product.

Acknowledgements

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Keywords: amides · copper · homogeneous catalysis · oxidation · relay catalysis

[1] a) A. L. Abuhijleh, J. Khalaf, *Eur. J. Med. Chem.* **2010**, *45*, 3811 – 3817; b) V. Paredes-García, R. C. Santana, R. Madrid, A. Vega, E. Spodine, D. Venegas-Yazigi, *Inorg. Chem.* **2013**, *52*, 8369 – 8377.

[2] M. O'Connor, A. Kellett, M. McCann, G. Rosair, M. McNamara, O. Howe, B. S. Creaven, S. McClean, A. Foltyn-Arfa Kia, D. O'Shea, M. Devereux, *J. Med. Chem.* **2012**, *55*, 1957 – 1968.

[3] a) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062 – 11087; *Angew. Chem.* **2011**, *123*, 11256 – 11283; b) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 6234 – 6458.

[4] See the proceeding paper: Reactions Catalysed by a Dicopper Complex: Aerobic Cross Dehydrogenative Coupling of *N*-Aryl Tetrahydroisoquinolines.

[5] a) N. T. Patil, V. S. Shinde, B. Gajula, *Org. Biomol. Chem.* **2012**, *10*, 211 – 224; b) Z. Du, Z. Shao, *Chem. Soc. Rev.* **2013**, *42*, 1337 – 1378; c) H. Pellissier, *Tetrahedron* **2013**, *69*, 7171 – 7210; d) X.-P. Yin, X.-P. Zeng, Y.-L. Liu, F.-M. Liao, J.-S. Yu, F. Zhou, J. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 13740 – 13745; *Angew. Chem.* **2014**, *126*, 13960 – 13965.

[6] a) I. Ibrahem, J. S. M. Samec, J. E. Bäckvall, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 3965 – 3968; b) A. Sud, D. Sureshkumar, M. Klussmann, *Chem. Commun.* **2009**, 3169 – 3171; c) J. Xie, Z.-Z. Huang, *Angew. Chem. Int. Ed.* **2010**, *49*, 10181 – 10185; *Angew. Chem.* **2010**, *122*, 10379 – 10383; d) D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094 – 8097; e) G. Zhang, Y. Ma, S. Wang, Y. Zhang, R. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 12334 – 12337; f) J. Zhang, B. Tiwari, C. Xing, X. Chen, Y. R. Chi, *Angew. Chem. Int. Ed.* **2012**, *51*, 3649 – 3652; *Angew. Chem.* **2012**, *124*, 3709 – 3712; g) G. Zhang, Y. Ma, S. Wang, W. Kong, R. Wang, *Chem. Sci.* **2013**, *4*, 2645 – 2651; h) G. Bergonzini, C. S. Schindler, C.-J. Wallentin, E. N. Jacobsen, C. R. J. Stephenson, *Chem. Sci.* **2014**, *5*, 112 – 116.

[7] a) M.-H. So, Y. Liu, C.-M. Ho, C.-M. Che, *Chem. Asian J.* **2009**, *4*, 1551 – 1561; b) E. R. Klobukowski, M. L. Mueller, R. J. Angelici, L. K. Woo, *ACS Catal.* **2011**, *1*, 703 – 708; c) P. Preedasuriyachai, W. Chavasiri, H. Sakurai, *Synlett* **2011**, *2011*, 1121 – 1124; d) J. R. Khusnutdinova, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2014**, *136*, 2998 – 3001; e) X. Jin, K. Kataoka, T. Yatabe, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2016**, *55*, 7212 – 7217; *Angew. Chem.* **2016**, *128*, 7328 – 7333; f) T. O. Dairo, N. C. Nelson, I. I. Slowing, R. J. Angelici, L. K. Woo, *Catal. Lett.* **2016**, *146*, 2278 – 2291.

[8] a) M. J. Fisher, B. P. Gunn, C. S. Harms, A. D. Kline, J. T. Mullaney, R. M. Scarborough, M. A. Skelton, S. L. Um, B. G. Utterback, J. A. Jakubowski, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2537 – 2542; b) Y. Asano, S. Kitamura, T. Ohra, K. Aso, H. Igata, T. Tamura, T. Kawamoto, T. Tanaka, S. Sogabe, S.-I. Matsumoto, M. Yamaguchi, H. Kimura, F. Itoh, *Bioorg. Med. Chem.* **2008**, *16*, 4715 – 4732; c) R. Jin, F. W. Patureau, *Chemcatchem* **2015**, *7*, 223 – 225.

[9] J. Renaud, S. F. Bischoff, T. Buhl, P. Floersheim, B. Fournier, C. Halleux, J. Kallen, H. Keller, J.-M. Schlaeppi, W. Stark, *J. Med. Chem.* **2003**, *46*, 2945 – 2957.

[10] a) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335 – 344; b) M. Klussmann, D. Sureshkumar, *Synthesis* **2011**, *2011*, 353 – 369; c) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215 – 1292; d) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, *Chem. Rev.* **2015**, *115*, 12138 – 12204; e) H. M. L. Davies, D. Morton, *J. Org. Chem.* **2016**, *81*, 343 – 350.

[11] a) M. O. Ratnikov, X. Xu, M. P. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 9475 – 9479; b) W. Han, P. Mayer, A. R. Ofial, *Adv. Synth. Catal.* **2010**, *352*, 1667 – 1676; c) P. Liu, C. Y. Zhou, S. Xiang, C. M. Che, *Chem. Commun.* **2010**, *46*, 2739 – 2741; d) H. Miyamura, M. Morita, T. Inasaki, S. Kobayashi, *Bull. Chem. Soc. Jpn.* **2011**, *84*, 588 – 599; e) T. Hirao, T. Amaya, T. Ito, *Heterocycles* **2012**, *86*, 927; f) P. Kohls, D. Jadhav, G. Pandey, O. Reiser, *Org. Lett.* **2012**, *14*, 672 – 675.

[12] C. E. I. Knappke, A. Imami, A. Jacobi von Wangelin, *Chemcatchem* **2012**, *4*, 937 – 941.

[13] F. Y. Kwong, A. Klapars, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 581 – 584.

[14] a) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928 – 8933; b) E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317 – 5325; c) M. O. Ratnikov, M. P. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 1549 – 1557.

[15] a) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Farès, M. Klussmann, *J. Am. Chem. Soc.* **2011**, *133*, 8106 – 8109; b) M. Scott, A. Sud, E. Boess, M. Klussmann, *J. Org. Chem.* **2014**, *79*, 12033 – 12040.

[16] P. C. B. Page, G. A. Rassias, D. Barros, A. Ardakani, B. Buckley, D. Bethell, T. A. D. Smith, A. M. Z. Slawin, *J. Org. Chem.* **2001**, *66*, 6926 – 6931.

[17] G. Morel, G. Gachot, D. Lorcy, *Synlett* **2005**, *2005*, 1117 – 1120.

[18] a) M. B. Doughty, G. E. Risinger, *Bioorg. Chem.* **1987**, *15*, 1 – 14; b) F. G. Bordwell, A. V. Satish, *J. Am. Chem. Soc.* **1991**, *113*, 985 – 990.

[19] R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719 – 3726.

[20] R. A. W. Frank, F. J. Leeper, B. F. Luisi, *Cell. Mol. Life Sci.* **2007**, *64*, 892 – 905.

[21] R. Orru, H. M. Dudek, C. Martinoli, D. E. Torres Pazmiño, A. Royant, M. Weik, M. W. Fraaije, A. Mattevi, *J. Biol. Chem.* **2011**, *286*, 29284 – 29291.

[22] a) R. A. W. Frank, C. W. M. Kay, J. Hirst, B. F. Luisi, *J. Am. Chem. Soc.* **2008**, *130*, 1662 – 1668; b) N. S. Nemeria, A. Ambrus, H. Patel, G. Gerfen, V. Adam-Vizi, L. Tretter, J. Zhou, J. Wang, F. Jordan, *J. Biol. Chem.* **2014**, *289*, 29859 – 29873.

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